RSSDI Textbook - A Comprehensive Review of Diabetes in Women, First Edition

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Pre-Print Proof Copy

ISBN: X-XX-XXXXX-X

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List of Abbreviations

25(OH)D:	25-Hydroxyvitamin D

A

A1c/ Hba1c:	Glycated Hemoglobin
AACE:	American Association of Clinical Endocrinologists
AAO:	American Academy of Otolaryngology
AASLD:	American Association for the Study of Liver Diseases
ACE:	Angiotensin-Converting-Enzyme
ACEi:	Angiotensin-Converting-Enzyme Inhibitors
ACIP:	Advisory Committee On Immunization Practices
ACOG:	American College Of Obstetricians And Gynecologists
ACR:	Albumin To Creatinine Ratio
ADA:	American Diabetes Association
ADIPS:	The Australian Diabetes In Pregnancy Society
AGE:	Advanced Glycation End Product
AGI:	Alpha Glucosidase Inhibitor
ALT:	Alanine Aminotransferase
AMH:	Anti-Müllerian Hormone
AMP:	Adenosine Monophosphate
AMPK:	Adenosine Mono Phosphate Activated Protein Kinase
ANOVA:	Analysis of Variance
Anti-TPO:	Anti-Thyroid Peroxidase Antibodies
APGAR:	Appearance (Skin Color), Pulse (Heart Rate), Grimace (Reflex Irritability), Activity (Muscle Tone), and Respiration
APRI:	AST to Platelet Ratio Index
ARB:	Angiotensin II Receptor Blocker
aRR:	Adjusted Risk Ratio
AST:	Aspartate Aminotransferase
ATP:	Adenosine Triphosphate

B

BAT:	Brown Adipose Tissue
BGMS:	Blood Glucose Monitoring Systems
BMD:	Bone Mineral Density
BMI:	Body Mass Index
BMR:	Basal Metabolic Rate
BP:	Blood Pressure
BSSC-W:	Brief Sexual Symptom Checklist for Women
BU:	Bupropion

C

CAD:	Coronary Artery Disease
CASM:	Computer Assisted Self-Management
CDA:	Canadian Diabetes Association
CDC:	Center for Disease Control and Prevention
CGM:	Continuous Glucose Monitoring
CHC:	Combined Hormonal Contraceptive
CHD:	Chronic Heart Disease
CI:	Confidence Interval
CKD:	Chronic Kidney Disease
cm:	Centimeter
CO_2:	Carbon Di-Oxide
COC:	Combined Oral Contraceptive
CRP:	C-Reactive Protein
CT:	Computed Tomography
CTX:	C-Terminal Telopeptide Of Type I Collagen
CVD:	Cardiovascular Disease

D

DALYs:	Diabetes Adjusted Life Years
DASH:	Dietary Approaches to Stop Hypertension
DCCT:	Diabetes Control and Complication Trial
D-CLIP:	Diabetes Community Lifestyle Improvement Program
DD:	Diabetes Distress
DDS:	Diabetes Distress Scale
DEPS-R:	Diabetes Eating Problems Survey-Revised
DEXA:	Dual-Energy X-Ray Absorptiometry
DIPSI:	Diabetes In Pregnancy Study Group Of India
DKA:	Diabetic Ketoacidosis
DKK-1:	Dickkopf-Related Protein-1
DM:	Diabetes Mellitus
DME:	Diabetic Macular Edema
DNA:	Deoxyribonucleic Acid
DPP4:	Dipeptidyl Peptidase-4
DPP4i:	Dipeptidyl Peptidase-4 Inhibitors
DR:	Diabetic Retinopathy

List of Abbreviations

E

EASL-EASD-EASO:	European Association for the Study of the Liver-European Association for The Study of Diabetes-European Association for the Study of Obesity
ECG:	Electrocardiogram
EGFR:	Estimated Glomerular Filtration Rate
EMEA:	European Medicines Agency
ESI:	Endocrine Society of India

F

FDA:	Food And Drug Administration
FGF:	Fibroblast Growth Factor
FIB-4:	Fibrosis-4
FPG:	Fasting Plasma Glucose
FRAX:	Fracture Risk Assessment Tool
FREEDOM:	Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months
FSD:	Female Sexual Dysfunction
FSDI:	Female Sexual Dysfunction Index
FSFI:	Female Sexual Function Index
FSH:	Follicle Stimulating Hormone

G

g:	Grams
GDM:	Gestational Diabetes Mellitus
GFR:	Glomerular Filtration Rate
GH:	Growth Hormone
GLP-1:	Glucagon-Like Peptide-1
GLP-1R:	Glucagon-Like Peptide 1 Receptor
GLP-1RA:	Glucagon-Like Peptide-1 Receptor Agonist
GnRH:	Gonadotropin Releasing Hormone

H

h:	Hours
HAPO:	Hyperglycemia and Adverse Pregnancy Outcomes
Hba1c:	Glycated Hemoglobin
HBV:	Hepatitis B Virus
HCP:	Healthcare Provider
HCV:	Hepatitis C Virus
HDL:	High Density Lipoprotein
HDP:	Hypertensive Disorders of Pregnancy
HFCS:	High Fructose Corn Syrup
HIIT:	High Intensity Interval Training
HIP:	Hyperglycemia In Pregnancy
HIV:	Human Immunodeficiency Virus
HLA:	Human Leukocyte Antigen
HOMA	Homeostatic Model Assessment
HPLC:	High Performance Liquid Chromatography
HR:	Heart Rate
HR-pQCT:	High-Resolution Peripheral Quantitative Computed Tomography
HRSA:	Hamilton Rating Scale For Anxiety
HRT:	Hormone Replacement Therapy
HSD:	Hydroxysteroid Dehydrogenase
HSDD:	Hypoactive Sexual Desire Disorder

I

IADPSG:	International Association of Diabetes and Pregnancy Study Groups
ICMR:	Indian Council of Medical Research
ICR:	Insulin to Carbohydrate Ratio
ICU:	Intensive Care Unit
IDF:	International Diabetes Federation
IDQS:	Indian Diet Quality Score
IFG:	Impaired Fasting Glucose
IGF:	Insulin-Like Growth Factor
IGT:	Impaired Glucose Tolerance
IL:	Interleukin
INDIAB:	India Diabetes
IR:	Insulin Resistance/Resistant
IRR:	Incidence Rate Ratios
IUD:	Intrauterine Device

K

KASL:	Korean Association for the Study of the Liver
Kg:	Kilograms

L

LAM:	Lactational Amenorrhea Method
LARC:	Long-Acting Reversible Form of Contraception
LDL:	Low Density Lipoprotein
LH:	Luteinizing Hormone
LNG-IUD:	Levonorgestrel Intrauterine Devices
LPIR:	Lipoprotein Insulin Resistance Score
LSM:	Lifestyle Modification

List of Abbreviations

M

MDD:	Major Depressive Disorder
MERS:	Middle East Respiratory Syndrome
MET:	Metabolic Equivalent Minutes
MHC:	Major Histocompatibility Complex
MHP:	Mental Health Professional
MHT:	Menopausal Hormone Therapy
mins:	Minutes
MiRNA:	Micro Ribonucleic Acid
MMP:	Metalloproteinases
MNT:	Medical Nutrition Therapy
MRI:	Magnetic Resonance Imaging

N

NAFLD:	Nonalcoholic Fatty Liver Disease
NASH:	Nonalcoholic Steatohepatitis
NCAC:	Non-C. *Albicans Candida*
NCD:	Non Communicable Disease
NF-kb:	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NFS:	NAFLD Fibrosis Score
NGSP:	National Glycohemoglobin Standardization Program
NHANES:	National Health And Nutrition Examination Surveys
NICE:	National Institute For Health And Care Excellence
NIDDM:	Non-Insulin Dependent Diabetes Mellitus
NPDR:	Non- Proliferative Diabetic Retinopathy
NPH:	Neutral Protamine Hagedorn

O

OC:	Oral Contraceptives
OGTT:	Oral Glucose Tolerance Test
OR:	Odds Ratio
OSA:	Obstructive Sleep Apnea

P

P1NP:	Procollagen Type 1 N-Peptide
PAID:	Problem Area In Diabetes
PARp:	Partial Population Attributable Risk
PCOS:	Polycystic Ovary Syndrome
PCR:	Polymerase Chain Reaction
PCV:	Pneumococcal Conjugate Vaccine
PDE5:	Phosphodiesterase Type 5
PDR:	Proliferative Diabetic Retinopathy
PHQ-9:	Patient Health Questionnaire-9
PIIINP:	Procollagen Type III Amino-Terminal Peptide
PLISSIT:	Permission, Limited Information, Specific Suggestions and Intensive Therapy
POC:	Process of Care
PPAR:	Peroxisome Proliferator- Activated Receptor
PPV:	Pneumococcal Polysaccharide Vaccine
PRESIDE:	Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking
PRR:	Prevalence Rate Ratio

Q

QCT:	Quantitative Computed Tomography

R

RADIEL:	The Finnish Gestational Diabetes Prevention Study
RANKL:	Receptor Activator ff Nuclear Factor-Kb Ligand
RDA:	Recommended Dietary Allowance
RNA:	Ribonucleic Acid
RR:	Relative Risk
RSSDI:	Research Society For The Study of Diabetes In India
RVVC:	Recurrent Vulvovaginitis Candidiasis

S

SARS:	Severe Acute Respiratory Syndrome or
SD:	Standard Deviation
SGLT:	Sodium-Glucose Co-transporter
SGLT1i:	Sodium-Glucose Co-transporter-1 Inhibitor
SGLT2i:	Sodium-Glucose Co-transporter-2 Inhibitor
SHBG:	Sex Hormone-Binding Globulin
SIGN:	Scottish Intercollegiate Guidelines Network
SMBG:	Self-Monitoring of Blood Glucose
SNP:	Single Nucleotide Polymorphism
SPPARM:	Selective Peroxisome Proliferator Activated Receptor Modulator
SU:	Sulfonylurea
SVR:	Skeletal-to-Visceral Ratio
SWAN:	Study of Women's Health Across The Nation
SWIFT:	The Study of Women, Infant Feeding, and Type 2 Diabetes

List of Abbreviations

T

T1D:	Type 1 Diabetes
T2D:	Type 2 Diabetes
TGF-β:	Transforming Growth Factor-β
THANDAV:	Taking High-Intensity Interval Training and Dance to Adolescents for Victory Over Non-Communicable Diseases
TIR:	Time in Range
TNF:	Tumor Necrosis Factor
TSH:	Thyroid Stimulating Hormone
TZD:	Thiazolidinediones

U

UDCA:	Ursodeoxycholic Acid
UK:	United Kingdom
US:	United States
USG:	Ultrasonography
USPSTF:	United States Preventive Services Task Force
UTI:	Urinary Tract Infections

V

VEGF:	Vascular Endothelial Growth Factor
VLDL:	Very Low Density Lipoprotein
VLED:	Very Low Energy Diet
VPP:	Vaginal Photoplethysmography
VVC:	Vulvovaginitis Candidiasis

W

WBC:	White Blood Cell
WHO:	World Health Organization
WINGS-MOC:	Women in India with Gestational Diabetes Mellitus Strategy-Model of Care

Preface to the First Edition

Management of diabetes is a major concern worldwide. Its increasing prevalence, especially in developing countries becomes a challenging situation for the health-care system. According to the International Diabetes Federation, more than 285 million people are suffering from diabetes globally and the figure is expected to be 435 million by 2030. India is at second position, right behind China with 65.1 million cases of diabetes estimated in 2013, which is expected to grow to 109 million by 2035.

Diabetes has a wide variety of ramifications on patient's physiology and psychology that sometimes progresses to co-morbid conditions and results in mortality. The number of female patients with diabetes has increased currently in many districts belonging to several states such as, Tamil Nadu, Kerala, Andhra Pradesh and Odisha, especially among women in their late reproductive age. In addition, young population is at higher risk to develop associated co-morbid illnesses as well as early predisposition to age related disorders. Estimates of prevalence suggest a 55.5% lifetime risk of diabetes in 20 years old men and 64.6% in women without diabetes. The lifetime risk is consistently higher among women compared to men and declined with age. Despite such alarming state, women with diabetes, their family members and the society still lack the understanding of diabetes-mediated complications and its management.

Diabetes in women is more prevalent due to several factors, like reproductive hormone profile, fat distribution, tendency to gain weight, polycystic ovary syndrome, pregnancy, bone mineral metabolism, use of contraception, lifestyle, socio-economic and psychosocial issues. Furthermore, diabetes advances to development of hypertension, cardiovascular disease, infections, complications during pregnancy, impaired muscle and bone structure, renal dysfunction and poor sexual health in women.

Being the pillar of the family, a diabetic woman has to fight an internal battle with the disease while managing the family at the same time. Therefore, diabetes associated with nonalcoholic fatty liver disease, polycystic ovary syndrome, gestational diabetes, obesity, vaginal infection, depressive symptoms etc. needs to be diagnosed at an early stage to prevent any form of maladies. Different advanced diagnostic approaches and process of regular screening of the disease is included in the chapters. Suggestions on diabetes management by means of lifestyle changes, pharmacological or surgical interventions and counseling for both patient and family members are well documented in this book.

This is our first publication in hope to reach health care professionals with the knowledge of rapid advances in diabetes. Fortunately, in the current advanced digital era building resources containing current information, trends and research in the field of diabetes in women has been made available to a large number of health care professionals treating diabetes. There has been a lot of hard work put in by the authors to bring information in easy readable format. Excellent flow diagrams, charts, figures and pictures have been put in for better understanding of the subject. We are grateful to all authors, who despite having their busy schedule, managed to spare time to contribute in this book. Our appreciation also goes to the designing, publication and production team to compile this book in line with international standards. We hope you enjoy reading this book as much as we did while compiling it.

November 2021

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Foreword

The increasing burden of diabetes on the health-care sector and the rise in death rate needs to be addressed and managed. Scientific research is a platform for new inventions and a book is the medium to reach health care professionals with updated knowledge. This book gives a comprehensive overview on diabetes as it presents in women and includes a series of up to date chapters with well referenced articles covering risk of diabetes, treatment and care, associated complications and challenges specific to women.

This book begins with the epidemiological spectrum of diabetes in women and presents the global scenario of diabetes in both genders and where our country stands today. Prevalence of diabetes in all phases of woman's life, such as, adolescence, young adults, pregnant and menopausal women are well documented in this book along with its management. Other risks associated with diabetes, like cardiovascular and other macro-vascular complications, micro-vascular complications, nonalcoholic steatohepatitis, gestational diabetes mellitus, hypertension, infection, sexual health, bone health, and psychosocial complications are covered extensively in the following chapters. Care for diabetes and other associated maladies by lifestyle modification, use of oral medications, use of insulin therapy and gender specific counselling to address changes in psychosocial behavior, are splendidly discussed in the respective chapters. The book finishes with socio-economic aspect and public health need, which are thought provoking and informative.

This book evaluated studies from various countries and their approaches towards diabetes care and management, knowledge of which can be implemented by healthcare professionals in the Indian population. As women have a tendency to neglect their own care, it is necessary for their family members to become well-aware about the disease prevalence to avoid any bitter experience. Reading this book gave me an immense understanding of gender specific issues of diabetes related to women and how we need to address them. I hope this book will be of major help to all those who read it and I recommend this book to be a part of your library.

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Section 1

Diabetes in Women: Overview

Editor: Dr. Mala Dharmalingam

CHAPTER 1 DIABETES IN WOMEN: EPIDEMIOLOGICAL SPECTRUM

Dr. Nanditha Arun, Dr. Jyothi Idiculla

Global burden of diabetes and projections

Diabetes is a serious, chronic disease with significant influence on the lives and well-being of individuals, families and society across the world. It is among the top ten causes of death in adults.

T2D accounts for nearly 90% of all cases. This upward trend can be attributed to ageing, increased urbanization and obesogenic settings. An additional factor contributing to the increase in prevalence is longer survival of people with diabetes as a result of early detection, improved diabetes management and resulting reduction in premature mortality. Finally, the rising prevalence of T2D among younger adults in recent years contributes to the overall increase in T2D prevalence[1]. Increased morbidity, mortality and economic burden of diabetes make it an important public health condition[1].

Estimates of diabetes and prediabetes for 2019 and projections to 2030 and 2045

According to the IDF, DM affected more than 463 million individuals worldwide in 2019, accounting for 9.3% of the global adult population aged 20–79 years[2] (Figure 1). This figure is projected to grow to 578 million (10.2%) in 2030 and 700 million 10.9% in 2045[2]. Diabetes prevalence is reported to be 9% in women and 9.6% in men in 2019[2]. Estimates have shown an increase in the prevalence with age, reaching 19.9% (111.2 million) in adults aged 65–79 years. The data provided by the World Bank income category was different from these figures and estimated a higher prevalence in high-income (10.4%) and middle-income countries (9.5%) in comparison to low-income countries (4%). Diabetes is projected to reach 11.9% in high-income nations, 11.8% in middle-income countries and 4.7% in low-income countries by 2045, with 67% living in an urban setting[2].

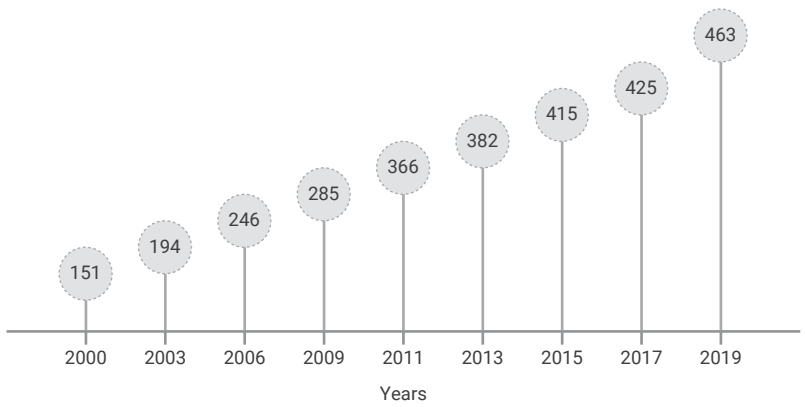
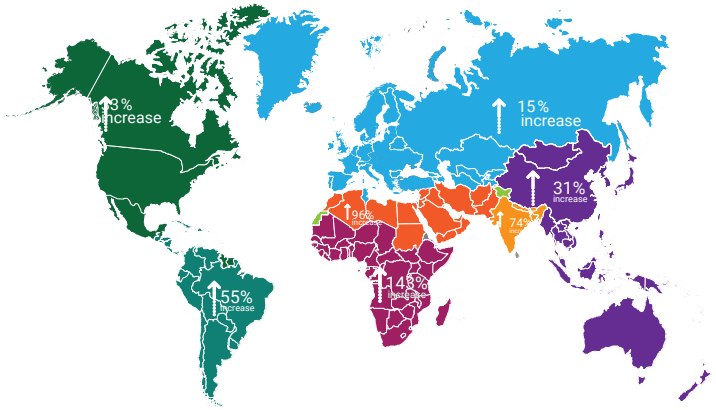


Figure 1: Estimates and projections of the global prevalence of diabetes (millions) in the 20–79 years age group
Source: Federation ID, 2019[3]

The IDF Diabetes Atlas (Figure 2) presented the global picture of diabetes, including estimates for each of the seven IDF regions based on the current literature[3].

Estimates of IGT for 2019 and projections to 2030 and 2045

In 2019, the global prevalence of IGT was expected to be 7.5% or 373.9 million people (Figure 3). By 2030, 8% (453.8 million) and by 2045, 8.6% (548.4 million) people are expected to have IGT. The majority of patients with IGT (72.2%) live in low - and middle-income countries. Overall, there are no variations in IGT prevalence between males (7.5%) and females (7.5%). Nearly



Year	World	North America & Caribbean	South & Central America	Africa	Middle East & North Africa	Western Pacific	South-East Asia	Europe
2019	463	48	32	19	55	163	88	59
2030	578	56	40	29	76	197	115	66
2045	700	73	49	47	108	212	153	68

Figure 2: Global picture of diabetes, including estimates for each of the seven IDF regions
Source: Federation ID, 2019[3]

half (48.1%) of persons aged 20–79 years with IGT are under the age of 50 years (180 million). This number is projected to rise to 204.1 million in 2030 and to 231.8 million in 2045. Over one third (28.3%) of all those with IGT, who are between the ages of 20 and 39 years, are likely to spend many years at increased risk of developing diabetes and CVD[2].

The Global Burden of Disease Study 2017 (Figure 4) presented a comprehensive picture of the numbers, rates and increased trends of the burden of diabetes in 195 countries and territories over the past 28 years. The study showed that the global burden of diabetes increased significantly between 1990 and 2017[4]. The prevalence and DALYs associated with diabetes reached 476 million and 67.9 million, with a 129.7% and 116.7% increase respectively. The study projected the prevalence to be 570.9 million causing 1.59 million deaths and 79.3 million DALYs in 2025 without effective interventions[4].

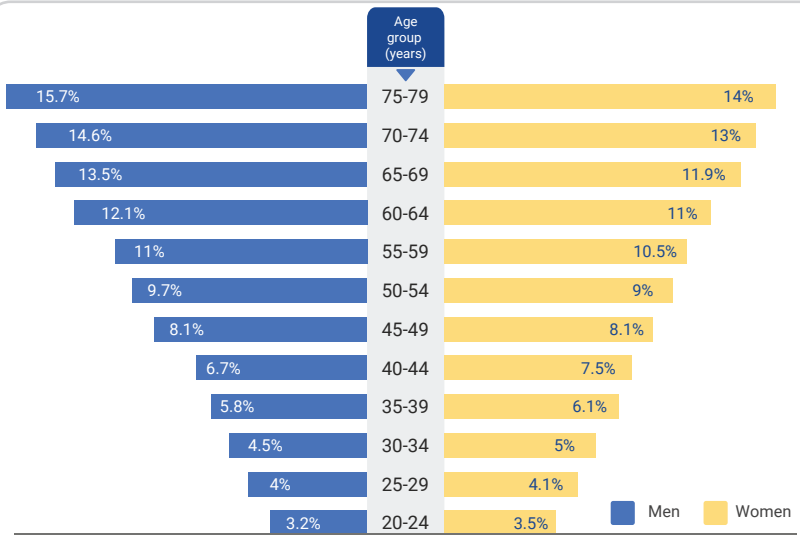
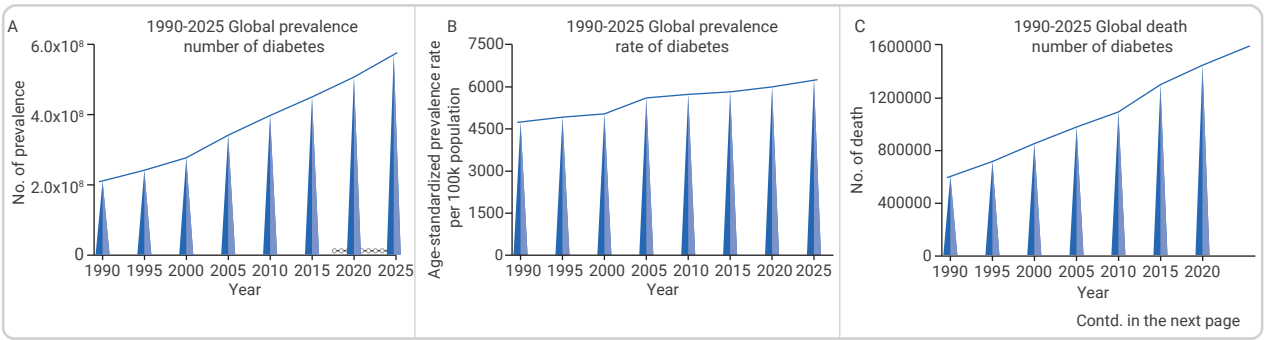


Figure 3: Prevalence of IGT in adults (20-79 years) by age and sex in 2019
Source: Federation ID, 2019[3]



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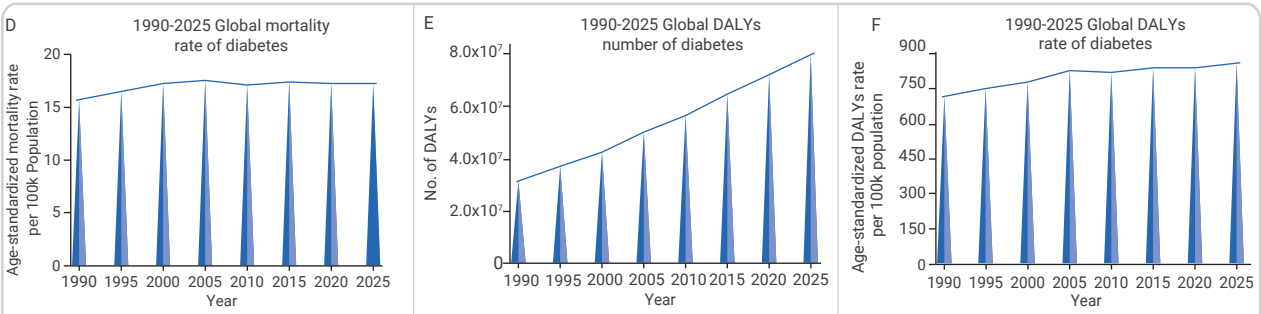


Figure 4: Global burden of diabetes mellitus from 1990 to 2025: (A) Prevalence number; (B) Age-standardized prevalence rate; (C) Death number; (D) Age-standardized mortality rate; (E) DALYs number; (F) Age-standardized DALYs rate

Source: Lin et al., 2020[4]

Geographic distribution of diabetic burden

In 2019, the IDF region with the highest world-age-standardized diabetes prevalence was the middle East & North Africa or MENA, where diabetes was predicted to affect 12.2% of the population. The Africa region had the lowest diabetes prevalence, with 4.7% of people aged 20–79 years estimated to have diabetes. China (116 million), India (77 million) and the US (31 million) had the greatest diabetes prevalence. China with 140 million, India with 101 million and the US with 34 million people with diabetes will continue to lead the list in 2030. China, India and Pakistan are predicted to have the highest rates of diabetes in 2045, with 147, 134 and 37 million affected people respectively[2].

Table 1 represents top 10 countries or territories for number of adults (20-79 years) with diabetes in 2019, 2030 and 2045[3].

Table 1: Top 10 countries or territories for number of adults (20-79 years) with diabetes in 2019, 2030 and 2045

2019					
China	1	116.4 (108.6–145.7)[i]	Mexico	6	12.8 (7.2–15.4)
India	2	77.0 (62.4–96.4)	Indonesia	7	10.7 (9.2–11.5)
USA	3	31.0 (26.7–35.8)	Germany	8	9.5 (7.8–10.6)
Pakistan	4	19.4 (7.9–30.4)	Egypt	9	8.9 (4.8–10.1)
Brazil	5	16.8 (15.0–18.7)	Bangladesh	10	8.4 (7.0–10.7)
2030					
China	1	140.5 (130.3–172.3)	Mexico	6	17.2 (9.7–20.6)
India	2	101.0 (81.6–125.6)	Indonesia	7	13.7 (11.9–14.9)
USA	3	34.4 (29.7–39.8)	Egypt	8	11.9 (6.4–13.5)
Pakistan	4	26.2 (10.9–41.4)	Bangladesh	9	11.4 (9.4–14.4)
Brazil	5	21.5 (19.3–24.0)	Germany	10	10.1 (8.4–11.3)
2045					
China	1	147.2 (134.7–176.2)	Mexico	6	22.3 (12.7–26.8)
India	2	134.2 (108.5–165.7)	Egypt	7	16.9 (9.0–19.4)
Pakistan	3	37.1 (15.8–58.5)	Indonesia	8	16.6 (14.6–18.2)
USA	4	36 (31–41.6)	Bangladesh	9	15.0 (12.4–18.9)
Brazil	5	26 (23.2–28.7)	Turkey	10	10.4 (7.4–13.3)

Note: Figures in millions, 95% CI are reported in brackets

Source: Federation ID, 2019[3]

The Indian perspective

Country-wise distribution by IDF showed that India, with 77 million, had the second highest number of people in the age group of 20–79 years with diabetes in 2019 and this number was expected to almost double to 134 million by 2045[3] (Figure 5). Adults with diabetes in India, Bangladesh and Sri Lanka make up 98.9% of the total adult population with diabetes in the South-East Asia region. Adults aged 50–70 years have the highest diabetes prevalence among all age groups[3].

The report from National Diabetes and Diabetic Retinopathy Survey conducted during 2015-2019, estimated that the prevalence of diabetes in India to be 11.8% in people aged above 50 years[5]. The survey also showed that the prevalence of known diabetes cases was 8% and new diabetes cases was 3.8%. According to the survey, prevalence of diabetes in male and female was estimated to be 12% and 11.7% respectively[5].

The study also reported the lifetime risk of diabetes and diabetes-free life expectancy in metropolitan cities in India among the population aged ≥ 20 years and their variation by sex, age and BMI. Estimates of prevalence suggest a 55.5% (51.6, 59.7%) lifetime risk of diabetes in 20 year old men and 64.6% (60, 69.5%) in women without diabetes. The lifetime risk was consistently higher among women compared to men and declined with age. Remaining lifetime risk declined with age to 37.7% (30.1, 46.7%) at the age of 60 years among women and 27.5% (23.1, 32.4%) in men (Table 2)[5]. Findings also revealed a positive association between BMI and lifetime risk, which was highest among obese Indians, 86% (76.6, 91.5%) among women and 86.9% (75.4, 93.8%) among men (Figure 6)[6].

A study identified a group of districts in India with the highest prevalence of diabetes among women[7]. The researchers used data from the National Family Health Survey-4 (2015-2016) to determine women's health indicators at the district level. The demographic characteristics of 2,35,056 women from 36 States/Union territories were analyzed to determine the prevalence of disease and the association between disease and socio-economic status, location, number of children, obesity and hypertension, among other variables. Districts in Tamil Nadu, Kerala, Andhra Pradesh and Odisha had the highest prevalence. All 254 districts have a "very high level" (> 10.7%) of diabetes bur-

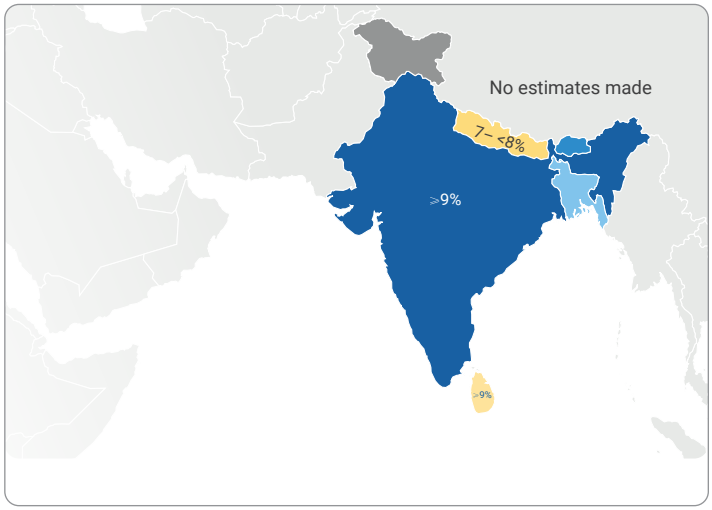


Figure 5: Age adjusted comparative prevalence (%) of diabetes (20-79 years) in IDF South-East Asia Region, 2019

Source: Federation ID, 2019[3]

Table 2: Age- and gender-wise prevalence of diabetes in population aged ≥ 50 years

	Male	Female	Total (%)
All ages	12	11.7	11.8
80 years and above	9.7	9.8	9.7
70-79 years	13.9	12.5	13.2
60-69 years	13.1	13.1	13.1
50-59 years	10.5	10.8	10.7

Source: Sharma NC, 2019[5]

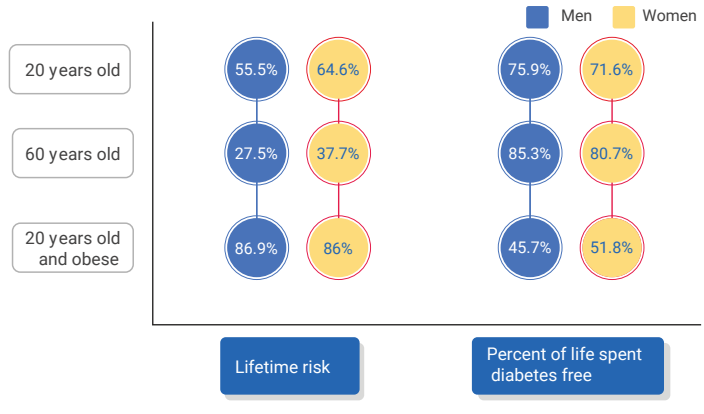


Figure 6: Lifetime risks of developing diabetes in urban metropolitan Indian adults

Source: Luhar et al., 2021[6]

den and 130 have a moderately high (8.7-10.6%) burden. The prevalence was highest in the southern and eastern parts of the country and lowest in central India[7] (Figure 7).

The findings indicate that diabetes prevalence is more among women in their late reproductive years with two or fewer children, who are educated, belonging to economically stable households, living in urban areas with increased access to high-energy (refined and processed) foods and an evolving lifestyle[7].

Another study investigated the prevalence of IFG and IGT in urban Indians and found higher prevalence of IFG in women (9.8%) than in men (7.4%), while the gender differences in IGT (men 8.4%, women 7.9%) and diabetes (men 13.3%, women 14.3%) were not significant. Prevalence of diabetes, IGT and IFG + IGT was increased with age[8].

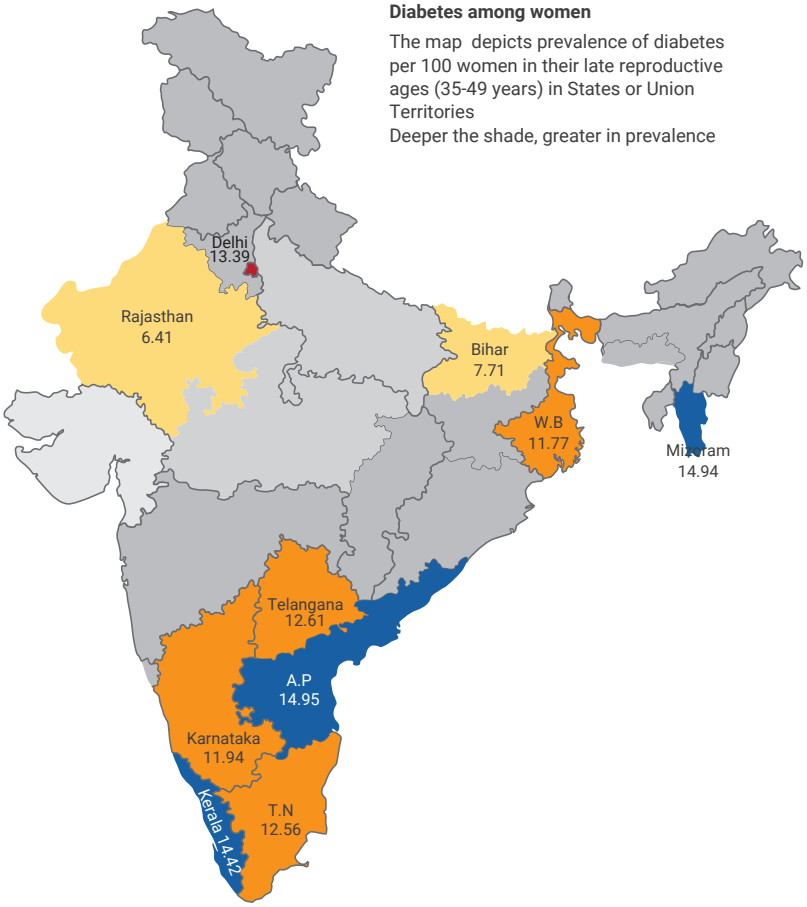


Figure 7: Prevalence of diabetes per 100 women in the reproductive age group.W.B: West Bengal, A.P: Andhra Pradesh, T.N: Tamil Nadu

Source: Singh et al., 2020[7]

A recent study analyzed data from two epidemiological surveys done 10 years apart (2006 and 2016) in three different geographic and socioeconomic backgrounds in Tamil Nadu, India. The results showed that the prevalence of diabetes increased from 18.6% (95% CI 16.6–20.5) to 21.9% (20.5–23.3) in the city, 16.4% (14.1–18.6) to 20.3% (18.9–21.6) in the town and 9.2% (8–10.5) to 13.4% (11.9–14.8) in the periurban villages ($p < 0.0001$ in all). When comparing the two time periods, the rise in prevalence was non-significant (8%) in the city, while significant increases had occurred in the town (39%) and in the periurban villages (34%). Prevalence of prediabetes also increased significantly in these three locations. Age, family history of diabetes, increased waist circumference and obesity were the common risk factors. The incidence of diabetes was also reported to have increased in these three locations; however, the rise was more pronounced in the city and town when compared with the villages[9].

Types of diabetes and dysglycemia in women

Hyperglycemia in pregnancy

According to IDF, 2019, for an estimated 20.4 million (15.8% of live births), women had some form of HIP. GDM accounted for 83.6% of these, while 7.9% and 8.5% were attributable to diabetes diagnosed prior to pregnancy and diabetes (including T1D and T2D) first detected in pregnancy respectively[3].

It is projected that an estimated 18.3 million of live births in 2030 and 18 million of live births in 2045 will be affected by HIP. About half (50.1%) of all HIP (10.2 million) cases occur in women under the age of 30 years due to higher fertility rate. However, the highest prevalence of HIP (37%) is in 45-49 year old women[3].

Diabetes following GDM

Women with GDM are at greater risk of developing T2D due to common diabetic risk alleles, similar insulin secretory defects and risk factors. A meta-analysis involving 20 studies and over 600,000 women showed increased risk of T2D in women with a history of GDM compared with those who had a normoglycemic pregnancy. Failure to attend postpartum follow-up increased the risk of progression from GDM to T2D. In the Diabetes Prevention Programme, 38% of the women with previous GDM developed diabetes within 3 years of randomization, compared to 25.7% of the women with no previous GDM, despite being at equivalent risk of developing IGT[10].

Obesity and prevalence of diabetes

T2D risk increases dramatically with BMI above 25 kg/m². The risk of T2D increases 2-8 fold at BMI 25, 10-40 fold at BMI > 30 and > 40 fold at BMI > 35, depending on age, gender, duration and distribution of adiposity and ethnicity. A BMI of 30–35 increased the prevalence of T2D > 20 fold in women and > 10 fold in men. Obesity significantly increases the incidence of T2D among South Asians with BMI 27.5 being associated with similar morbidity as BMI 30 in Europids. The accumulation of abdominal fat ('central' obesity), as evidenced by an elevated waist-to-hip ratio, is usually considered as an independent risk factor for T2D due to increased visceral (intra-abdominal) obesity[11].

Indians develop metabolic syndrome, hypertension and T2D earlier than whites, regardless of BMI. Obesity has doubled in males and tripled in women in India over the last two decades (1970-1990). Obesity has risen dramatically in India during the last few decades. Urban India's adult population is currently projected to be 30% overweight or obese leading to an exponential increase in the number of people with T2D[12].

Women are more obese than men, possibly due to the effect of estrogen on fat metabolism. Obesity was reported to be more common in women than men in a study of 13,662 NIDDM patients, which found 13.2% of men to be obese with BMI > 27, while 55% of women had BMI > men. Women with NIDDM also had a higher waist-to-hip ratio than men[13]. A cohort sample of 1,100 women in South Delhi showed that an increase in BMI was statistically associated with an increase in diabetes among married women[14].

Metabolic syndrome is becoming increasingly common in India due to urbanization, high calorie diet and sedentary lifestyle. Metabolic syndrome is also highly prevalent in female patients globally. A hospital-based, cross-sectional study found a 40.9% overall prevalence of metabolic syndrome. Female patients had a higher prevalence of metabolic syndrome (59% vs. 26.2%) along with significantly higher rates of hyperglycemia, obesity and triglycerides[15].

Diabetes in premenopausal women

Midlife women are at elevated risk of diabetes due to excess adiposity, IR and disorders like sleep disturbances and depression[16]. Specific reproductive hormones are known to be associated with CVD risk factors in premenopausal and postmenopausal Caucasian women. An increase in testosterone and a decrease in SHBG are substantially related with central adiposity, higher triglycerides and lower HDL cholesterol in Caucasian women and in a diverse ethnic population[17].

The SWAN found that the prevalence of metabolic syndrome increases dramatically during the perimenopausal and early postmenopausal years, regardless of ageing and other recognised CVD risk factors including weight gain and smoking. Met-

abolic syndrome incidence increased from 6 years before to 6 years after the final menstrual period. By the final menstrual period, 13.7% of the women had newly onset metabolic syndrome. Odds of developing the metabolic syndrome per year in perimenopause were 1.45 and in postmenopause were 1.24. Levels of bioavailable testosterone and, alternatively, SHBG emerged as an independent predictors, after controlling for ageing and CVD risk factors[17]. A report from the Atherosclerosis Risk in Communities cohort found that the metabolic syndrome progressed and became more severe during late premenopausal and perimenopausal years rather than postmenopausal years[18].

Gender-specific epidemiology of diabetes

Gender differences exist in epidemiology, pathophysiology, treatment and outcomes of many diseases, particularly NCDs. Women show more pronounced changes in sex hormones and their effects on organ systems during their lifetime. Genetic background, lifestyle and environmental factors contribute to an alarming increase in T2D and its associated complications[19].

Socio-cultural factors, such as difference in behaviours among women and men, social roles, specific influences of the environment, nutritional differences, lifestyles or stress, mental health or attitudes towards treatments and prevention, educational level and interplay between genetic and endocrine results in clinical differences in the prevalence of diabetes[19].

There is also a significant disparity in educational level among women and men. This has been corroborated by various studies showing an inverse relationship between educational level and diabetes prevalence. Compared with individuals having ≥ 13 years of education, those with ≤ 6 years of education (OR 2.10, 95% CI, 1.27–3.48) or with 7–12 years of education (OR 1.62, 95% CI, 1.04–2.52) had higher risks of developing T2D. This trend was not observed in men[20].

Gender differences in T2D incidence across the life span have also been observed with females having significantly higher rates of T2D in youth and males more likely to develop T2D in midlife. These rates however become almost similar in later life. T2D incidence has considerably in adolescents and young adults aged 18 years due to concurrent increases in obesity and inadequate diet and physical activity behaviours. Studies have also shown that approximately 2/3rd of children and adolescents diagnosed with T2D were female. Time trends indicate that this disparity may be worsening, as suggested by the British Paediatric Surveillance Unit that reported an increase in the incidence of T2D by 58% in girls and only by 7% in boys between 2005 and 2015[21].

The global age-standardized prevalence of diabetes was estimated to have increased from about 4% in 1980 to 9% in 2014 in men and from 5% to almost 8% in women with substantial differences in the prevalence of diabetes across regions (Figure 9)[22].

The data suggested that if the post-2000 trends continue, the age-standardized prevalence of diabetes in 2025 will rise to over 10% in women and by 13% in men[22].

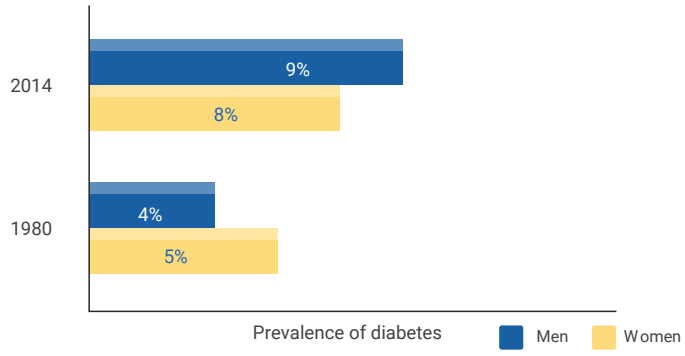


Figure 8: Comparison of prevalence of diabetes in men and women in 1980 and 2014
Source: Luhar et al., 2021[6]

The IDF estimated that global prevalence of diabetes in women aged 20–79 years in 2019 was 222.9 million, which is 9% of the world's population in this age group. This figure is predicted to rise to 281.8 million (10%) by 2030 and to 342.5 million (10.8%) by 2045[3] (Table 3).

Gender differences in complications of diabetes

Table 3: Number of men and women (20-79 years) with diabetes in 2019, 2030 and 2045

	2019		2030		2045	
	Number of people with diabetes (millions)	Prevalence (%)	Number of people with diabetes (millions)	Prevalence (%)	Number of people with diabetes (millions)	Prevalence (%)
Men	240.1	9.6	296.7	10.4	357.7	11.1
Women	222.9	9	281.8	10	342.5	10.8

Source: Federation ID, 2019[3]

Diabetes is associated with an increased risk of stroke, heart failure, ophthalmic disease, end-stage renal disease, birth complications, sexual dysfunction and other chronic conditions. Diabetes patients have more than 10 fold risk of having CVD as compared to non-diabetic persons younger than 45 years of age. Patients with diabetes often have associated CVD risk factors, including hypertension, dyslipidemia and obesity and are at a greatly increased risk for morbidity and mortality from diabetes related complications[23].

DR is a significant NCD disease leading to ocular morbidity. In 2015, DR accounted for 1.06% of blindness and 1.16% of visual impairment globally. The National Diabetes and DR Survey report estimated the prevalence of any form of DR in diabetic population aged up to 50 years to be 16.9%, in the 50-59 years age group to be 14.3%, 60-69 years age group to be 18.6%, 70-79 years to be 18.3% and in the > 80 years group to be 18.4%. The prevalence of DR was similar among men (17%) and women (16.7%). Prevalence of blindness among diabetics was 2.1% and of visual impairment was 13.7%[5]. Systematic reviews have suggested a RR for CVDs between 1.6 and 2.6, which is higher among those of younger age and slightly higher in women[3] (Table 4).

Table 4: Global estimates of the association and impact of diabetes on CVD

Outcome	Impact	Data systems/study	References
Prevalence of CVDs	• **Any CVD:** 32% • **CHD:** 21% • **Myocardial infarction:** 10% • **Stroke:** 7.6%	57 cross-sectional studies	Einarson et al., 2018
CHD	160% increased risk	102 prospective studies	Emerging Risk Factors Collaboration, 2010
Ischaemic heart disease	127% increased risk	102 prospective studies	Emerging Risk Factors Collaboration, 2011
Hemorrhagic stroke	56% increases risk	102 prospective studies	
CVDs death	132% increased risk	97 prospective studies	
Years of life lost	5.8 years for men age 50 years 6.4 years for women age 50 years	97 prospective studies	

Source: Federation ID, 2019[3]

Diabetes has contributed to an increase in prevalence of CAD (21%) and CVD (32%) in adults living in high and middle-income countries. About 15% of all deaths due to CVD, kidney disease and diabetes are attributed to excess glucose (Table 4)[3].

Studies have shown poorer glycemic control in women, with lesser percentage achieving glycemic targets for HbA1c in women with T2D[24,25].

The mortality rate in CVD has decreased among non-diabetic women, but the risk has remained nearly 4 fold higher in women with diabetes[26] (Figure 9).

Women with diabetes have increased risk of CHD as compared to men. The greater risk of CHD in women with diabetes can be attributed to increased prevalence of cardiovascular risk factors, such as HDL cholesterol, triglycerides, LDL particle size and BP in women as compared to men. It has also been proposed that gender may alter the effect of some cardiovascular risk factors in subjects with diabetes, leading to a stronger risk effect in women. Further, diabetes can enhance atherogenesis and/or thrombogenesis by interfering with protective mechanisms in the vascular wall[27].

This was affirmed by a study that showed a considerably higher diabetes-related RR for a major CHD event in women with diabetes (hazard ratio 14.7) than in men (hazard ratio 3.8). Major CHD event rate per 1,000 person-years was found to be 11.6 in non-diabetic men, 1.8 in non-diabetic women, 36.3 in men with diabetes and 31.6 in women with diabetes[27].

Large-scale meta-analysis have provided compelling evidence that diabetes confers a 44% greater risk of CHD and a 27% greater risk of stroke in women than in men, independent of sex differences in other major risk factors. Similar results were reported even among patients with T1D where women greater risk of premature death than men. These gender differences in vascular outcomes occured beyond CHD and stroke, the major components of CVD[22] (Table 5).

Women have poorer risk factor profiles and evidence suggests that women are less likely to receive proper cardiovascular care than men. These healthcare differences in the prevention and management of diabetes and its complications contribute to greater risks in women of diabetes complications. Moreover, lack of awareness among women about their CVD risk makes them less likely to adhere to treatment recommendations[22].

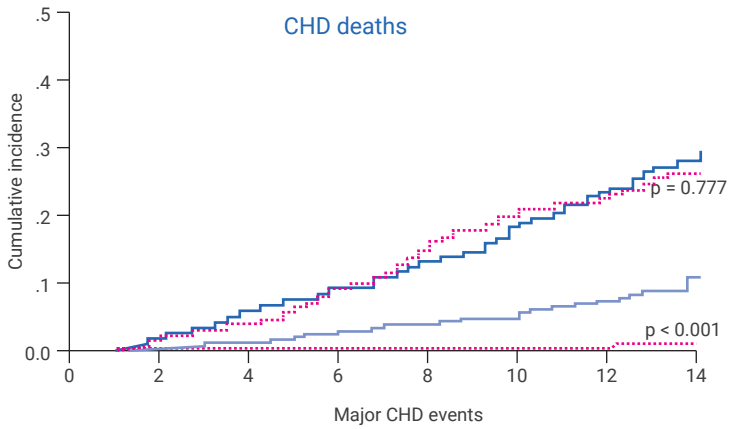
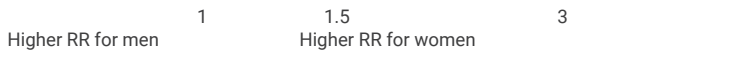


Figure 9: Kaplan-Meier curves for cumulative incidence (proportion with event) of CHD mortality and major CHD events according to gender and diabetes status during 13 years of follow-up. The curves with small dashes indicate women: the lowest curve is for non-diabetic women and the upper curve is for women with diabetes. The lower continuous line denotes non-diabetic men and the bold continuous line denotes men with diabetes. p values denote log-rank test statistics for gender differences in non-diabetic and subjects with diabetes

Source: Juutilainen et al., 2004[27]

Table 5: Results from prior meta-analysis of sex differences in the effects of diabetes on vascular outcomes, summarized through the ratios of women-to-men adjusted RR (and 95% CI) pooled across cohort studies

Type of diabetes and outcome analyzed	Ratio of RR (95% CI)
All diabetes	
CHD	1.44 (1.27, 1.63)
Stroke	1.27 (1.10, 1.46)
End-stage renal disease	1.37 (1.23, 1.52)
Vascular dementia	1.19 (1.08, 1.30)
T1D only	
CHD	2.54 (1.80, 3.60)
Stroke	1.37 (1.21, 1.56)
End-stage renal disease	1.97 (1.10, 3.53)



Source: Peters and Woodward, 2018[22]

Gender and diabetes related mortality

South-East Asian region recorded 1.2 million deaths in 2019 (14.1% of all-cause mortality), second highest number of deaths attributable to diabetes in adults (20–79 years) among the IDF Regions. Diabetes related mortality was higher in women (643,400) than in men (507,000) and India was the largest contributor to regional diabetes mortality with more than 1 million estimated deaths attributable to diabetes and related complications (Figure 10)[3].

In 2019, approximately 4.2 million adults aged 20–79 years were estimated to die due to diabetes and its complications. This is equivalent to one death every 8 seconds. About 11.3% of global deaths from all-causes are attributable to diabetes in this age group. Almost half (46.2%) of these deaths occur in people under the age of 60 years. Globally, there are more deaths associated with diabetes in women (2.3 million) than in men (1.9 million) (Figure 11)[3].

A study examined the decline in all-cause and CVD mortality rates among the US population with and without self-reported diabetes. The results suggested a decrease in all-cause mortality by 18.2 annual deaths per 1,000 persons (from 42.6 to 24.4 annual deaths per 1,000 persons, p = 0.03) among men with diabetes between 1971-1986 and 1988-2000. Trends for CVD mortality paralleled those of all-cause mortality, with 26.4 annual deaths per 1,000 persons in 1971-1986 and 12.8 annual deaths per 1,000 persons in 1988-2000 (p = 0.06). However, neither all-cause nor CVD mortality declined between 1971-1986 and 1988-2000 among women with diabetes and the all-cause mortality rate difference between women with diabetes and non-diabetic women more than doubled (from a difference of 8.3-18.2 annual deaths per 1,000 persons). This study highlighted the continuing increase of mortality among women with diabetes (Figure 12)[28].

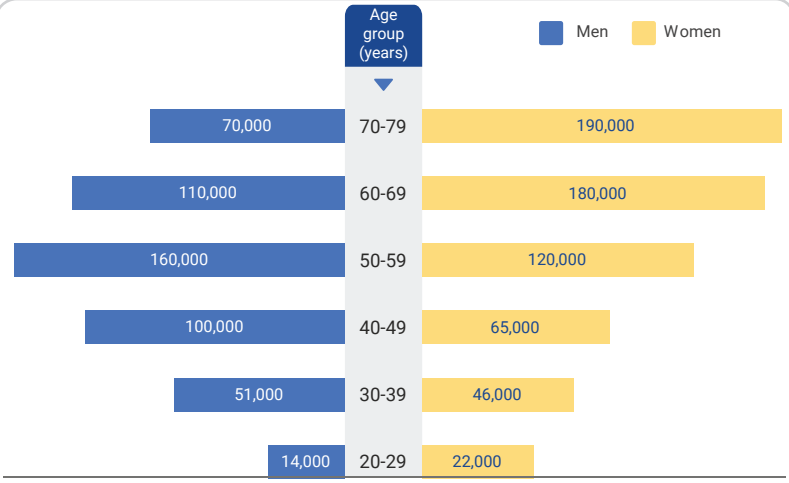


Figure 10: Mortality due to diabetes by age and sex, IDF South-East Asia Region, 2019
Source: Federation ID, 2019[3]

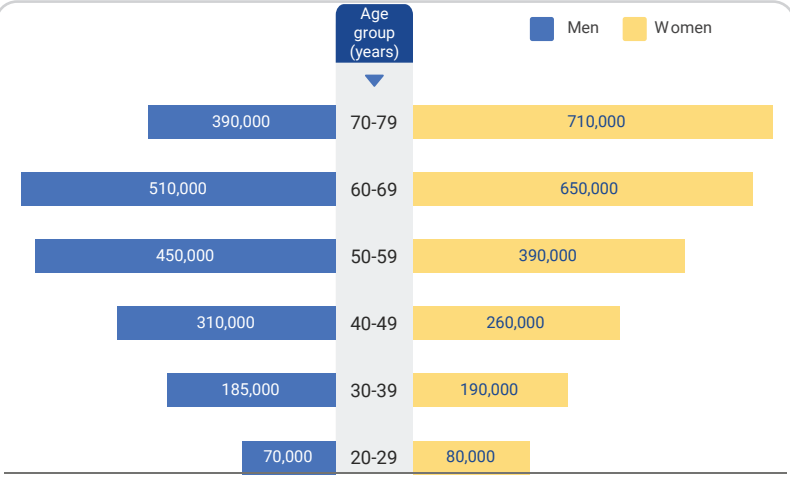


Figure 11: Number of deaths due to diabetes in adults (20-79 years) by age and sex in 2019
Source: Federation ID, 2019[3]

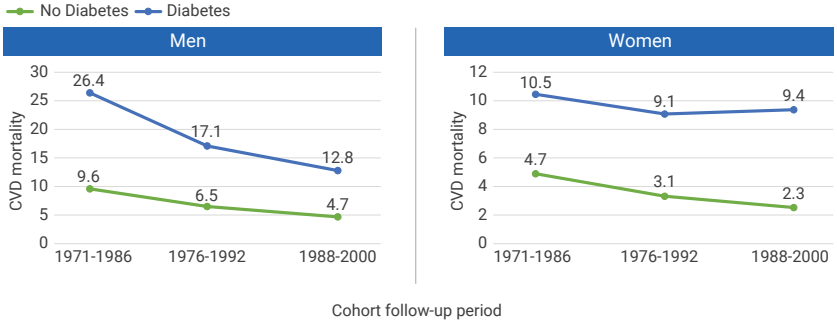


Figure 12: Age-adjusted CVD mortality rates among the US population aged 35-74 years with and without diabetes, by cohort and sex
Source: Gregg et al., 2007[28]

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CHAPTER 2 ANTHROPOLOGY AND PATHOPHYSIOLOGY OF DIABETES IN WOMEN

Dr. Purvi Chawla, Dr. Lotika Purohit

Medical anthropology and diabetes

Over the last century, tremendous changes in lifestyles and eating patterns due to industrialization, urbanization, economic development and globalization have negatively impacted people's health. A decline in fertility and mortality rate has resulted in an older population in the background of this economic transformation. Diabetes, hypertension, CVD and certain cancers are among the chronic NCDs that have increased with this epidemiological change[1].

The nutritional transition has varied between regions, but the global tendency to abandon traditional nutrition patterns in favour of foods high in saturated fats, sugar and processed carbohydrates and low in fiber and polyunsaturated fats with accompanying decline in physical activity[1].

According to anthropological and epidemiological studies, diabetes is a "disease of modernization" that closely correlates with economic progress within countries[2].

According to epidemiological research, people in developing countries who have adopted western or similar modern urbanized lifestyles are at an increased risk of chronic degenerative diseases[3].

South Asia is also experiencing rapid urbanization, economic growth and rural-to-urban migration. South Asian food is generally high in carbohydrates, especially simple carbohydrates and saturated fats. Females from this region may not be particularly encouraged to participate in social activities, including outdoor physical activities, thus enhancing a sedentary lifestyle among them. Diabetes is a chronic condition requiring anti-diabetic medications, including insulin and often lifelong impacting the adoption and adherence to anti-diabetic medications, as it affects both genders and is considered as a stigma[4].

Important physiological and pathophysiological sex differences of anthropometric, metabolic and endocrine parameters are summarized in Figure 1.

Figure 1: Overview of physiological and pathological sex differences in metabolism and energy homeostasis in men (left) and women (right). HPA: hypothalamus-pituitaryadrenal; ARC: Arcuate nucleus; POMC: Proopiomelanocortin; FFA: Free fatty acid; TG: Triglyceride; ↑= Increase, ↓= Decrease = Increase/decrease

Source: Kautzky-Willer et al., 2016[5]

Role of obesity in pathophysiology of diabetes

IR is commonly present in overweight and obese individuals, but diabetes develops when insulin secretion is not adequate to normalize hyperglycemia in these individuals. Pancreatic β-cell dysfunction is a major contributor in the progression from prediabetes to diabetes[6].

At the start of this century, 171 million people were estimated to have T2D and projected to increase to 360 million by 2030[6].

There are 3 main hypothesis described to explain the molecular links between obesity and diabetes (Figure 2).

The "Inflammation hypothesis"

Obesity is a state of chronic, underlying inflammation caused by invading macrophages in the adipose tissue that further trigger pathological alterations in insulin-sensitive tissues as well as β-cells. However, studies have also shown that people with T2D can have IR with no significant changes in inflammatory markers. Inflammation alone cannot therefore explain the effect of obesity on insulin sensitivity or the development of T2D in a subset of obese people[7].

The "Lipid overflow hypothesis "or "Adipose tissue expandability hypothesis"

This predicts that obesity may increase 'ectopic' lipid stores in glucose-metabolizing organs such as muscle, liver and pancreas due to reduced capacity of adipose tissue to store fat in obese patients. Recent research shows that hyperglycemia contributes to lipid-induced β-cell dysfunction and diabetes. Thus, T2D is also considered as a lipid metabolism disorder[7].

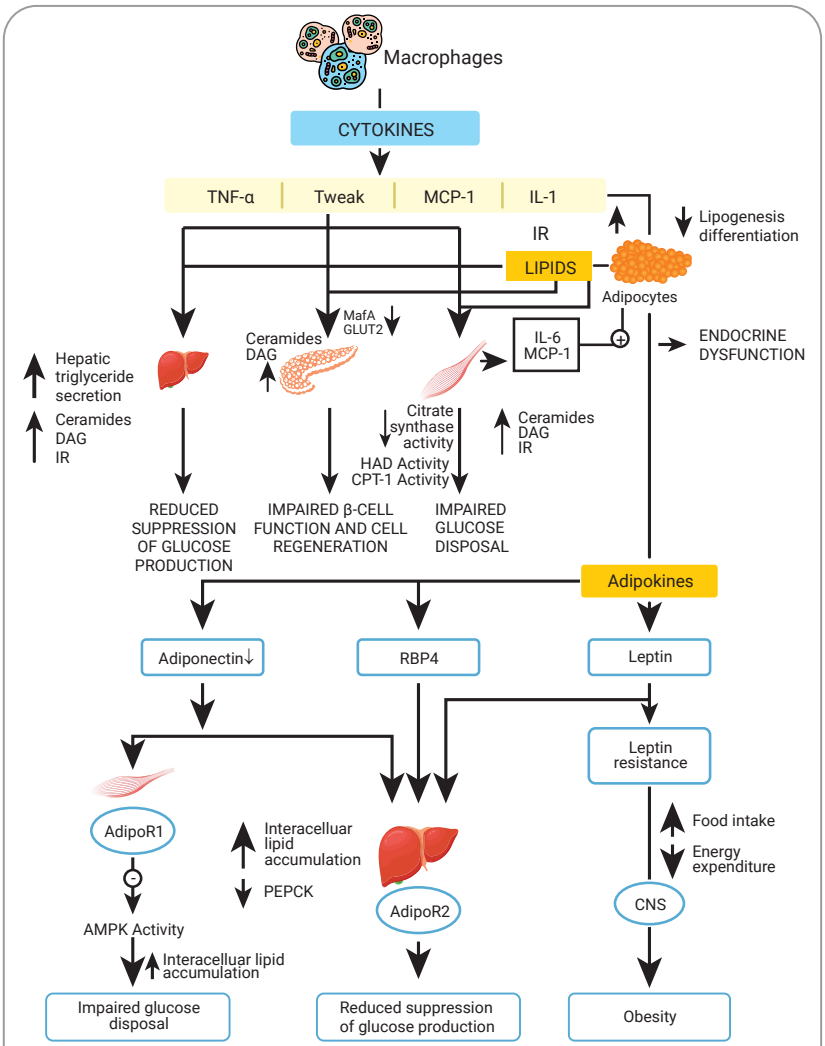

Figure 2: Pathophysiology of obesity-induced chronic inflammation and peripheral IR, ectopic lipid stores that cause peripheral IR and impaired β-cell function, dysfunction of adipokines in adipose cells contributing to peripheral IR. MCP-1: Monocyte chemotactic protein-1, DAG: Diacylglycerol, GLUT2: Glucose transporter 2, HAD: Hydroxyacyl-CoA dehydrogenase, CPT-1: Carnitine palmitoyltransferase 1, RBP4: Retinol binding protein 4, AdipoR: Adiponectin receptor, PEPCK: Phosphoenolpyruvate carboxykinase, CNS: Central nervous system, ↑= Increase, ↓= Decrease

Source: Chadt et al., 2018[7]

The "Adipokine hypothesis"

The "Adipokine hypothesis" states the white adipose tissue serves as an endocrine organ, secreting several autocrine and paracrine hormones and the dysfunctional release of endocrine components result in the metabolic impairment of insulin target tissues and eventual failure of insulin producing β-cells[7].

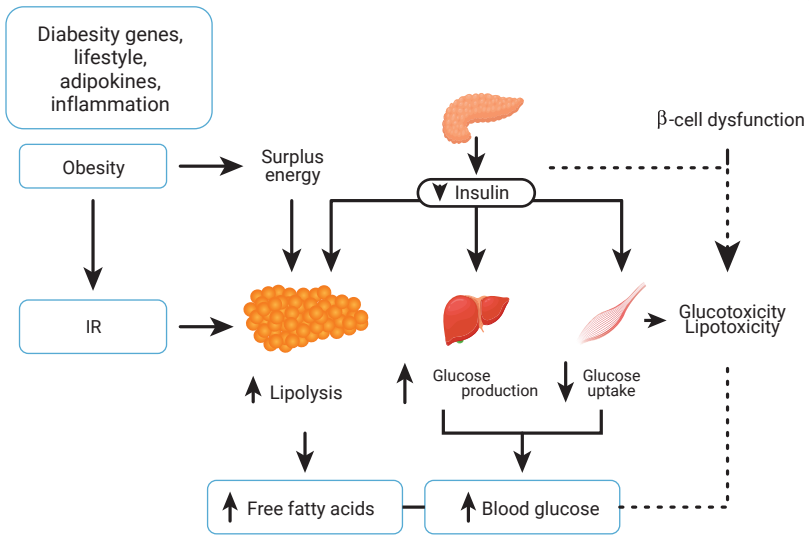

Figure 3: Pathogenesis of T2D, IR and β-cell dysfunction. ↑= Increase, ↓= Decrease
Source: Day and Bailey, 2011[8]

Obesity and β-cell dysfunction

In individuals with normal BMI, the β-cells produce insulin proportionally in response to increased demands by the adipose tissue liver, or muscles. Changes in insulin sensitivity are usually accompanied by changes in level of circulating insulin. The efficiency of hepatic and muscle glucose uptake is reduced in absence or incomplete inhibition of hepatic glucose production. Long-term insulin secretion abnormalities, coupled with chronically elevated blood glucose levels, eventually lead to complete β-cell failure[6] (Figure 3).

Biology of sex differences in diabetes

BMI and body fat distribution

Anthropometric parameters including BMI and waist-to-hip ratio tend to differ between the two sexes in people with diabetes. Obesity is more prevalent in women than in men as seen in a study including 13,662 NIDDM or T2D patients that reported 13.2% of men with a BMI > 27 kg/m², while 55% of women with a BMI > 25 kg/m². Women with T2D also had a higher waist-to-hip ratio than men with T2D[9]. These sex disparities in anthropometric parameters may be attributed to differences in fat storage patterns in the adipose tissue in both women and men[10] (Figure 4).

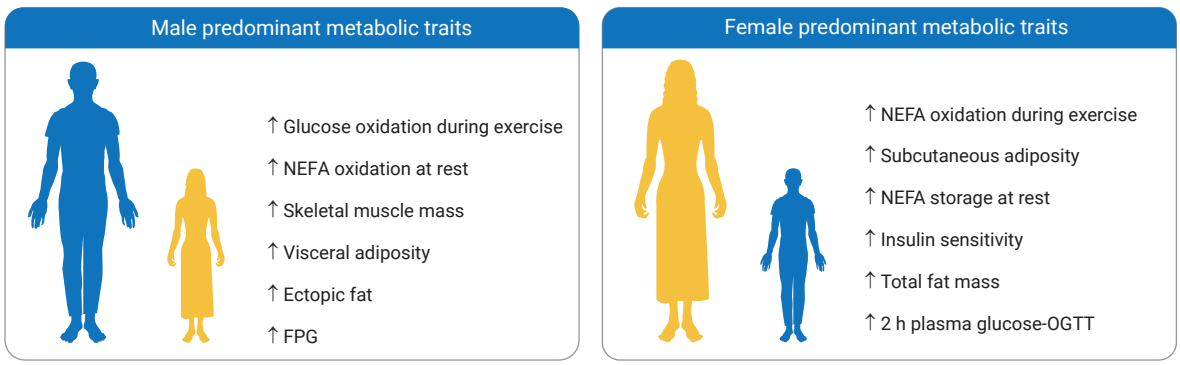

Figure 4: Main sex dimorphisms in body composition and metabolic homeostasis in humans (premenopausal women vs. age-matched men).
NEFA : Non-esterified fatty acids
Source: Tramunt et al., 2020[11]

Despite a curvilinear correlation between increasing BMI and the risk of developing diabetes in both sexes being comparable, women with diabetes are more obese than men with diabetes. However, men have more fat-free muscle than women, so BMI may not be an accurate measure of the body fat mass[5]. The main sexually dimorphic body composition and metabolic traits in humans are summarized in Figure 4.

In general, men have greater visceral and ectopic fat than premenopausal women, regardless of BMI or total body fat.

Men usually have a characteristic "android" body fat distribution pattern, with greater adipose tissue accumulation in the abdominal region, whereas women have a "gynoid" body fat distribution pattern, with adipose tissue accumulation in the gluteal and femoral regions[1].

Abdominal visceral adipose tissue is more strongly associated with IR in women than in men, suggesting a stronger link between excess visceral adipose tissue and diabetes in women than in men. This is in line with the findings from the UK Biobank analysis that showed a greater risk of myocardial infarction with higher waist circumferences and waist-to-hip ratio in women than in men. Obesity and metabolic dysfunction in women decrease the inherent protection from CVD by sex hormones[10] (Figure 5).

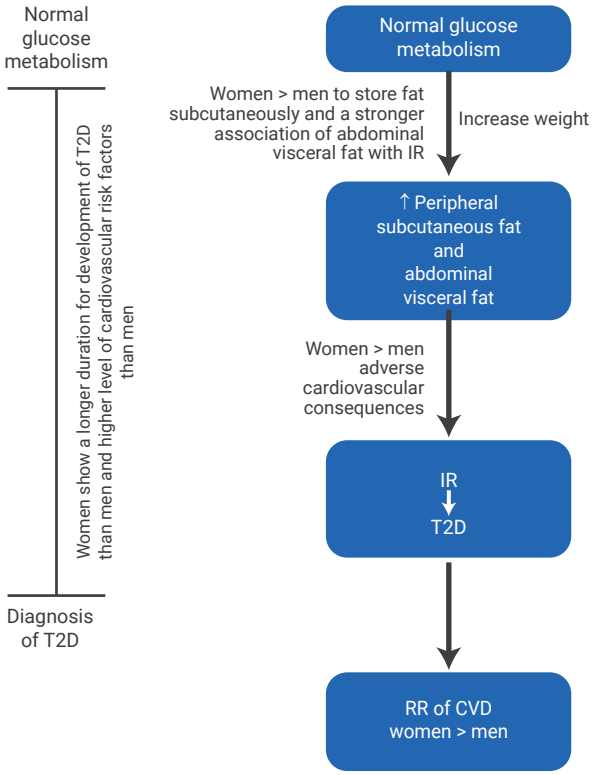

Figure 5: Impact of adiposity in women in association with diabetes and CVD

Source: de Ritter et al., 2020[10]

Women have greater body fat percentages and develop peripheral adiposity, whereas men gain fat centrally. One third of overweight women develop the android phenotype. Postmenopausal women are also more prone to male-type obesity and lipid characteristics. Among those withT2D, 40% of men and 70% of women are found to have abdominal obesity, indicating a strong link between T2D and abdominal obesity, especially in women[12].

Brown adipose tissue

The total mass and activity of BAT impact the whole body energy metabolism, IR and obesity-related T2D. Women have much higher proportion and activity of BAT presence of BAT has been found to be independently and inversely related to age in both sexes, but only BMI in males and visceral fat in females, in a large population-based study. Ovaries and estrogens have a positive influence on the production of BAT related factors including FGFs in mice. Thus, stronger BAT impact may help to reduce the risk of diabetes in women.

Adipokines

Leptin regulates satiety, food intake and energy expenditure and also modulates the insulin-glucose axis and IR. Similarly, adiponectin improves insulin sensitivity in the target tissues and improves lipid and glucose metabolism. Adiponectin and its receptor expression are both increased in the female abdominal adipose tissue, presumably contributing to lower cardio-met-

abolic risk in women. Overall, higher levels of leptin and adiponectin in women as compared to age and BMI-matched men, appears to be due to sex hormones. In people with diabetes, there is an inverse relationship between plasma adiponectin and insulin sensitivity, particularly prominent in women. Androgens may also decrease the adiponectin secretion[5].

Metabolic syndrome

The metabolic syndrome is a combination of risk factors for CVD, including IR, hypertension, dyslipidemia and abdominal obesity. Metabolic syndrome is increasingly more common in women as compared to men, driven by rising obesity, especially, abdominal obesity and other risk factors in women. After menopause, there is an increase in metabolic syndrome, with a greater atherogenic lipid profile and hypertension[12].

New biomarkers

There are a number of biomarkers reporting sexual dimorphism and differential the risk for diabetes, such as the hepatokine fetuin-A, shown to be related to T2D development, only in women. In the Prevention of Renal and Vascular Endstage Disease Study, copeptin was shown to be associated with the risk of future diabetes in women but not in men[5].

Another novel hormone biomarker is proneurotensin, which acts as a neurotransmitter in the central nervous system while also stimulating the pancreatic and biliary secretion, inhibiting gastric motility and facilitating fatty acid translocation. Women have lower fasting proneurotensin levels than men. During a 13 year follow-up study, each SD increase in baseline proneurotensin was related with a 41% greater risk of new-onset diabetes in women[5].

Low cholecalciferol or vitamin D3 levels were found to be related with T2D in women but not in men in a cross-sectional study. Women with vitamin D3 levels below 15 ng/mL were more than twice as likely to have developed diabetes[5].

T2D was associated with elevated liver enzymes (ALT, AST and γ-glutamyl transferase) in both sexes in a large, community-based, prospective cohort study. Premenopausal women have lower enzyme levels and less liver fat and BMI than age-matched men, attributable to their estrogen levels. Overall, men and elderly women have a higher prevalence of increased liver fat[5].

Imbalance of sex hormones

Estrogens and androgens regulate the bidirectional control of glucose and lipid homeostasis and their receptor activation in the central and peripheral targets in both sexes. Higher levels of androgens lead to increased body weight and visceral fat in women as well as in men, who have transitioned to being transsexuals. Diabetes is linked to higher testosterone levels in women but lower testosterone levels in males. The PCOS is a female-specific state of androgen excess and hyperinsulinemia associated with obesity, T2D and higher cardiometabolic risk.

GDM

GDM serves as an independent and strong risk factor for eventual progression to T2D in women. GDM predominantly affects IR in overweight/obese women with increased age at the time of conception, however normal weight women may also be impacted due to thier genetic and physiologically exaggerated IR during pregnancy. Women with GDM have a 70% greater risk to develop T2D than women with prediabetes of devoloping T2D[5].

Impact and interaction between sex and gender on development and outcomes of T2D

Apart from biological factors, gender differences in the uptake and provision of health care contribute to women's higher RR of developing vascular complications associated with diabetes[10] (Figure 6).

Differences in health care provision

Gender disparities in health care can occur at three levels: evaluation and monitoring of risk factors, control of risk factors among those identified at risk and pharmacological and lifestyle interventions. Two recent studies indicated that women were less likely than men to receive cardiovascular risk factor screening[10]. Another study of 10,000 people with CHD indicated that risk factor management for secondary prevention was worse in women than men[10]. While women are less likely than men to achieve risk factor control for LDL cholesterol, HbA1c has been observed to be equivalent in both the sexes. Another study found that despite pharmacological interventions, women had higher HbA1c and LDL cholesterol than men[10].

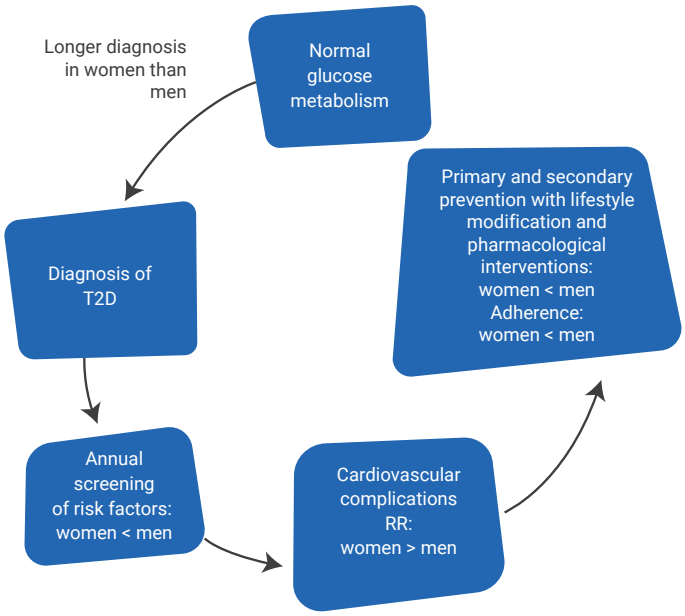

Figure 6: Disparities in the uptake and provision of health care of women compared to men
Source: de Ritter et al., 2020[10]

Differences in drug adherence

Inadequate drug adherence is associated with adverse cardiovascular outcomes, including premature mortality. A large meta-analysis of 53 trials from varied demographics found that 50% of men and 47% of women were adherent to statins, with women being additionally, at least 10% more likely to be non-adherent than men[10].

Differences in socio-cultural aspects

The gender disparities affect illness manifestation, treatment seeking behaviour, nature of treatment and care and support of family and caregivers[13].

A study found that women's access to health care is limited due to domestic duties and cultural limitations. Encouraging men to participate and share responsibilities in child-rearing and domestic duties may help support women. The health care system is less accessible, comprehensive and responsive to women. The primary financial obstacles include cost of therapy, medications, consultations and tests. Women's denial of disease status and severity due to fear of stigmatization are among other identified psychological barriers[14].

Sex hormones and pathophysiology of glucose homeostasis disorder

Sex hormones also regulate glycemic control in both sexes and body type. These differences are described in this section:

Cortisol

High cortisol levels are associated with an increase in IR, gluconeogenesis, visceral adipose tissue accumulation, hypertension and dyslipidemia.The enzyme, 11β-HSD1 may enhance reduction of cortisone to cortisol, increasing the cortisol levels in visceral adipose tissue.

Testosterone

Low testosterone levels are linked to male abdominal obesity and IR, thus posing as a risk factor for T2D. Testosterone substitution improves insulin sensitivity, visceral fat mass, BP and plasma lipids. The risk of developing T2D was reduced by 42% in

men having their testosterone levels between 15.6–21 nmol/L. Increased androgen levels cause IR in women, thereby increasing the risk of T2D and CVD.

SHBG

SHBG regulates the free (active) testosterone levels. Insulin regulates SHBG by inhibiting its synthesis and thus hyperinsulinemia results in low SHBG. Low SHBG levels are seen in men and women with abdominal obesity; and contribute to hyperandrogenemia in women. High insulin levels stimulate ovarian androgen production while low SHBG, resulting in hyperandrogenemia and IR in PCOS. High SHBG levels protect against T2D independent of gender, probably because low SHBG is a marker of hyperinsulinemia; however, it is more protective in women than in men[12].

Estrogen

Estrogen may have beneficial effects on insulin sensitivity via direct effects on insulin and glucose homeostasis, involvement in adipose tissue metabolism and body composition and effects on proinflammatory markers[15] (Figure 7).

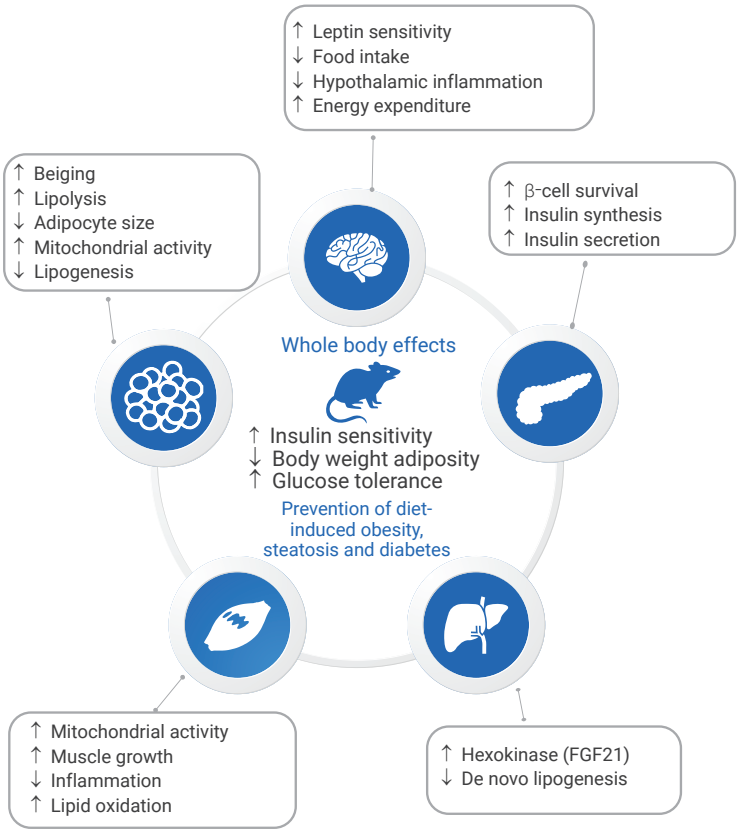

Figure 7: Tissue-specific actions of estrogens on energy balance and metabolic regulation in rodent models, ↑= Increase, ↓= Decrease

Source: Tramunt et al., 2020[11]

GH and IGF-1

Although GH exerts anabolic effects, it is also lipolytic and causes IR in fasting or starvation states. Women have greater mean GH levels and GH pulse amplitudes than men.

Adiponectin

Adiponectin increases the insulin sensitivity of the liver and skeletal muscle. Women have greater adiponectin levels than men as adiponectin decreases with IR and obesity and vice versa. Low levels of adiponectin are associated with IR, while higher levels of adiponectin are associated with a lower risk of T2D and CVD[15].

Leptin

Leptin is an adipokine produced in the adipose tissue that regulates food intake. Obesity reduces signalling through leptin receptors causing leptin resistance. Women have higher leptin levels than men, indicating greater overall fat mass. Free estrogen in postmenopausal women and free testosterone in men are positively associated with leptin levels. Increased leptin levels are related to CVD in men but may be protective in women[12].

IR in women

In most women with obesity, IR and compensatory hyperinsulinemia precede the development of T2D and increase the risk of CVD[1].

IR may develop as early as *in utero stage*. Scientific evidence suggests that sex-specific genes affecting insulin sensitivity are responsible for the weight disparity at birth, with girl infants weighing less at birth than the male counterparts. These genes also appear to make women more prone to developing T2D, corroborating the predominant prevalence of diabetes in the female population, especially in the younger age group populations. Thus, the sex-specific genes influencing prenatal growth and future development of IR, may be responsible for the smaller size of female neonates as compared to the male counterparts. The greater insulin concentrations, indicate innate IR in girls. Another study reported that Caucasian girls aged 5 years are more IR than age-matched boys and that this difference persists through puberty and adolescence. In one study, there was a higher fasting glucose-stimulated insulin, insulin-to-glucose ratio and lower insulin-stimulated glucose utilization in women than in men and these metabolic changes were associated with greater androgenicity in women[1].

Heredity

The risk of IR transmission is hereditary (approximately 2-3 times the risks compared to no family history of diabetes), further magnified in women, especially in those with a history of diabetes on the maternal side, whereas in men, both the maternal as well as the paternal side contribute equally to the risk[16].

Lifestyle

Physical inactivity and poor diet remain important contributors to increased IR. Television time is a strong predictor of metabolic syndrome, especially in women. In comparison to subjects who viewed television < 14 h/week, those who viewed television > 20 h/week had a 1.5 folds risk for men and a 1.93 folds risk for women for developing metabolic syndrome. Eating at irregularly times relates to increased risk of developing IR and metabolic syndrome risk, while eating regular meals reduces that risk by 60–70%.

Work culture

Work culture also influences the risk preferentially in women. Metabolic syndrome has been observed to be more common among female blue-collar employees than white-collar workers, but not among male workers.

Menopause

During the menopausal transition, there is associated risk of IR and metabolic syndrome. According to the study from SWAN, the odds of developing metabolic syndrome per year were higher in the perimenopause (OR 1.45) period than postmenopause (OR 1.24) women. Higher bioavailable testosterone and lower SHBG levels improved the odds. The risk of developing metabolic syndrome also increases after surgical menopause[17]. Another study indicated that women aged between 45-54 years with normal glucose tolerance had higher fasting insulin and homeostasis model assessment of IR or HOMA-IR levels than those in other age groups and men of the same age. In normal women aged between 45-54 years, the increased plasma insulin and HOMA-IR levels suggest an impairment of insulin homeostasis during the perimenopausal period.

Insulin sensitivity in perimenopausal women differs from age-matched men. During menopause, a major metabolic change may contribute to the rapid rise in CVD[18].

IR and PCOS

PCOS is a complex, heterogeneous condition characterized by hyperandrogenism (clinical and biochemical), ovarian dysfunction (manifesting as menstrual irregularities) and polycystic ovarian morphology. Globally, the incidence of this syndrome varies from 6-20% depending on the diagnostic criteria applied, with greater prevalence among overweight/obese women and in certain ethnic groups[19].

Insulin-mediated glucose uptake is reduced by 35–40% in women with PCOS as compared to age and weight-matched women. Despite increased insulin secretion, the hepatic insulin extraction is decreased. Obesity and age significantly enhance the risk of developing PCOS; both non-obese and younger women may also be affected by PCOS. The risk for impaired glucose tolerance is 2-3-folds greater with PCOS and the rate of conversion to T2D may be rapid[20].

IR is the most prevalent metabolic impairment in women with PCOS, affecting 65–70% of all patients. IR is frequently associated with compensatory hyperinsulinemia[19].

IR is a recognized risk factor in the development of T2D, which itself is 5-10 folds higher in women with PCOS than in healthy controls[21].

Hyperinsulinemic women with PCOS have 5 folds higher incidence of CVD than the normoinsulinemic ones[22].

The association between IR and hyperandrogenism in PCOS is based mainly on two underlying pathophysiological reasons (Figure 8):

- Hyperinsulinism acts as a true gonadotropic hormone and acts synergistically with LH through the CYP17a enzymatic system, increasing the ovarian synthesis of the androgens.
- Hyperinsulinism increases androgenic production by reduction of hepatic synthesis of the SHBG[24].

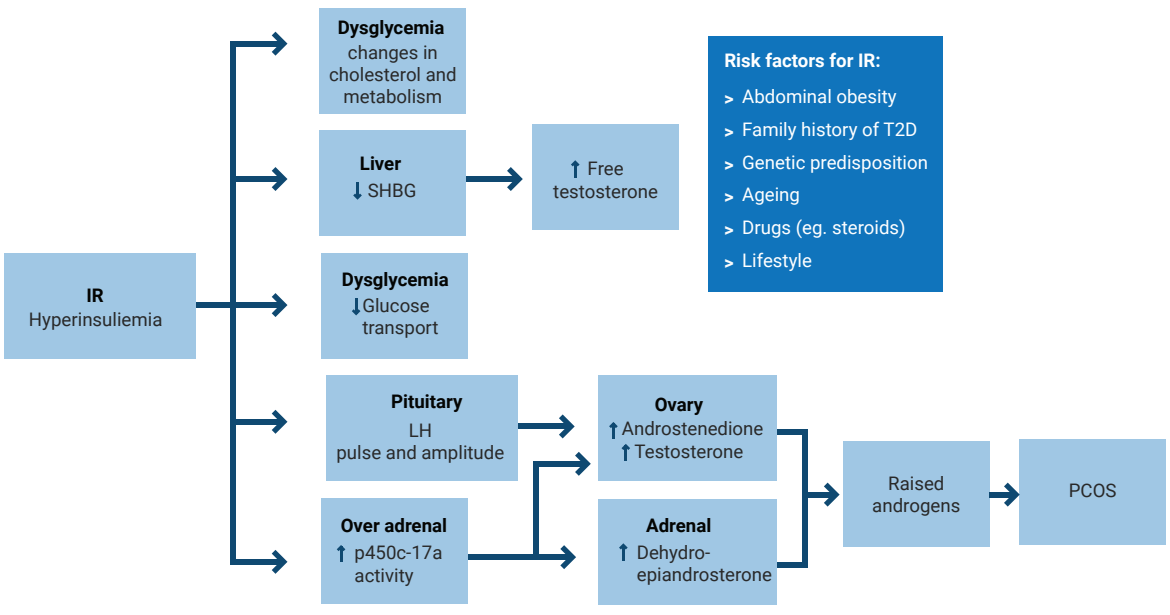

Figure 8: Overview of peripheral IR in PCOS, ↑ = Increase, ↓ = Decrease

Source: Barber et al., 2016[23]

Metabolic dysfunction in PCOS: role of androgen excess

Androgen excess is regarded as the cardinal feature capital PCOS. Hyperandrogenism plays a prominent role in the development of metabolic disturbances associated with PCOS, acting on peripheral tissues as well as at the central level[19] (Figure 9).

PCOS has metabolic implications that cause dyslipidemia in many women, independent of the diabetes or hypertension. Studies have reported higher triglycerides, non-HDL levels and lower HDL in women with PCOS as compared to age and weight-matched controls[25].

Pathophysiology of T1D and T2D

Factors involved in the pathogenesis of T1D and T2D (Figure 10):

T1D

T1D is a chronic autoimmune disease associated with selective destruction of the pancreatic β-cells. The autoimmune destruction of pancreatic β-cells is associated with insulin deficiency leading to metabolic derangements. It was formerly called insulin dependent DM. Additionally, there is an abnormality in the functioning of the pancreatic α-cells leading to excessive secretion of the counter-regulatory hormone glucagon in these patients. Hyperglycemia normally reduces glucagon secretion; however, in people with T1D, hyperglycemia does not inhibit glucagon secretion, further aggravating metabolic abnormalities caused by insulin insufficiency[27].

T2D

T2D is a heterogeneous disorder characterized by a variety of genetic factors associated with decreased insulin production, environmental factors and lifestyle-related factors such as obesity, physical inactivity, stress as well as increasing age. Plasma glucose concentrations are maintained within the normal physiological range through a tightly regulated yet dynamic interplay between tissue insulin sensitivity (particularly liver) and secretion of insulin by the pancreas, besides other synchronously working processes. These pathways fail in T2D, resulting in two major clinical defects: impaired insulin secretion due to pancreatic β-cells dysfunction and impaired insulin action due to IR[27].

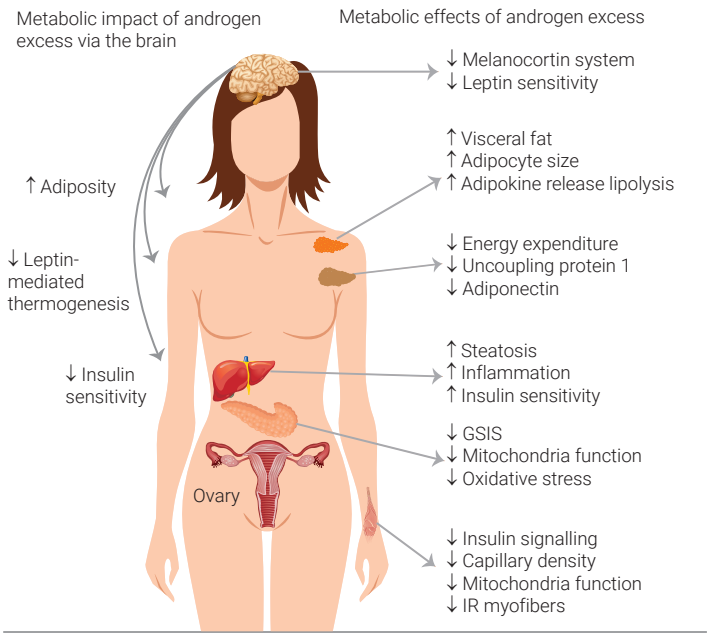

Figure 9: Metabolic impact of androgen excess in PCOS. GSIS: Glucose-stimulated insulin secretion, ↑ = Increase, ↓ = Decrease

Source: Sanchez-Garrido MA, Tena-Sempere, 2020[19]

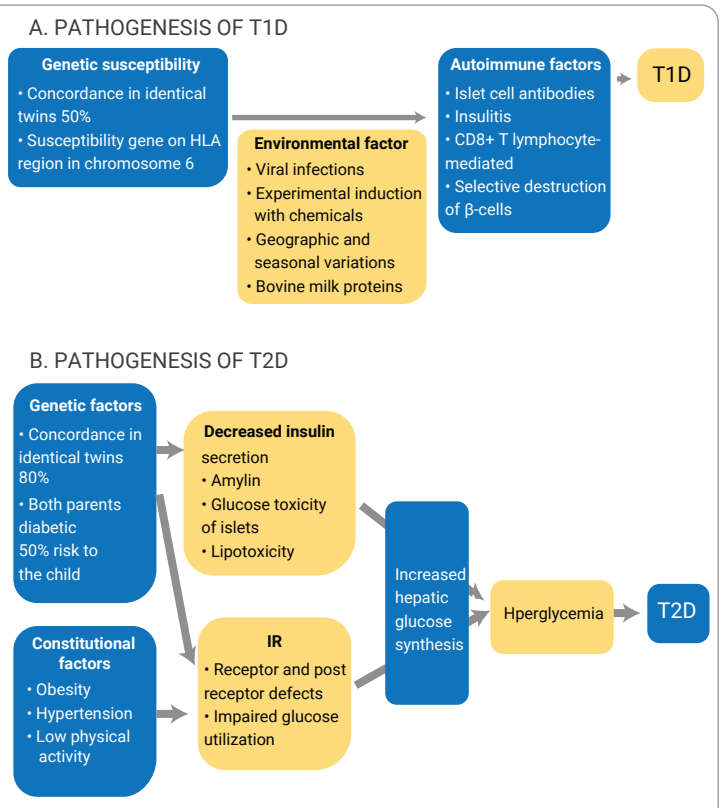

Figure 10: Schematic mechanism underlying the pathogenesis of T1D and T2D

Sorce: Praveen., et al 2017[26]

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CHAPTER 3 INTERPOSE DIABETES CARE FROM ADOLESCENT GIRLS TO YOUNG ADULTHOOD

Dr. Mala Dharmalingam, Dr. Pramila Kalpa

Hormonal adaptations during puberty

Puberty is a phase of substantial physiologic change involving the activation of the reproductive system and the secretion of sex hormones, acceleration of growth and the accumulation of both lean and fat mass. There is also a physiologic reduction in insulin sensitivity during puberty. Adolescence is characterized by the stimulating action of hypothalamic GnRH that increases the concentrations of LH over FSH, leading to release of estradiol in females and testosterone in males, development of secondary sexual characteristics and increase in lean and fat mass. A physiological decrease in insulin sensitivity occurs during this period that resolves after completion of puberty[1]. Adolescents are vulnerable to impaired glucose metabolism due to these hormonal variations of puberty (Figure 1)[1]. Furthermore, the onset of T2D in adolescents is strongly correlated with puberty[2].

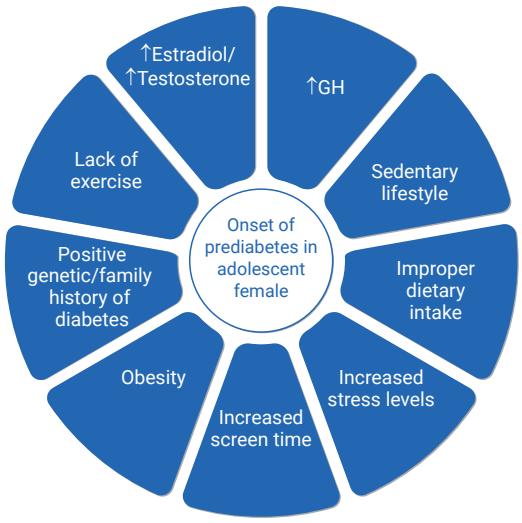

Figure 1: The pathogenesis of prediabetes in adolescence

Source: Stefanaki et al., 2016[1]

In a study of non-diabetic children, insulin sensitivity dropped between the ages of 12-14 for both sexes and across ethnic groups, before returning to almost prepubertal levels in those over 16 years. Insulin action declines by 30-50% during puberty, contributing to poor glycemic control in adolescents (Figure 2)[3]. According to the Hvidore Study Group on Childhood Diabetes, insulin requirements grow dramatically during puberty, especially in girls with T1D. Another study corroborated this fact by showing decreased sensitivity to insulin in puberty and an approximately 30% increase in insulin dosage in patients with insulin dependent DM with the onset of puberty[3].

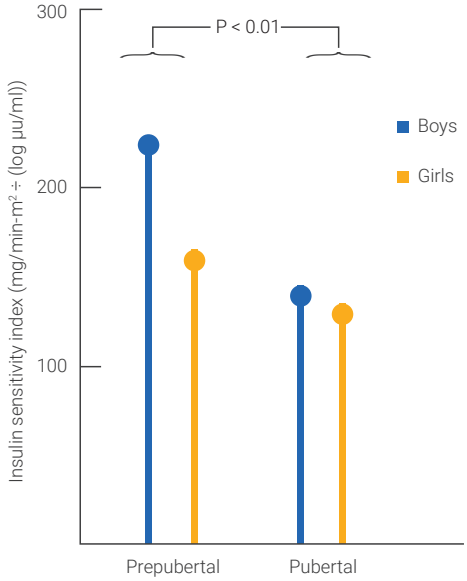

Figure 2: Insulin sensitivity index, calculated as glucose utilization rate (mg/m².min) divided by log insulin concentration (µU/mL) in prepubertal and pubertal children. (Mean ± SEM)

Source: Source: Bloch et al., 1987[3]

Additionally, HbA1c, which is a predictor of glycemic control, is often worse in boys during early puberty and in girls during later puberty due to predisposition of girls in late adolescence to gain excessive weight[4].The DCCT revealed 1% higher average long-term blood glucose levels (measured by HbA1c) in adolescents as compared with the adults, despite similar therapeutic approaches and despite receiving higher doses of insulin[5].

Adolescence alters the physiology of the GH/IGF-1 axis. GH secretion increases with the onset of adolescence (Figure 3)[1]. GH in excess is diabetogenic, causing IR due to increased endogenous glucose production, and decreased glucose disposal in muscle. Normal IGF-1 protect from the diabetogenic effects of GH, while low and high-normal IGF-1 concentrations are both associated with IR. The association of IGF-1 with fasting insulin differs between the sexes, and appears to be related to adiposity in girls[1]. SHBG regulates biological activity of sex steroids. Serum SHBG levels rise from birth to early childhood, fall during puberty, and then rise again until early adulthood. Low serum SHBG level is associated with increased adiposity and IR in children and adolescents and acts as a biomarker for cardiometabolic risk[6]. GnRH resides under the control of kisspeptin, its permissive neurokinin B, and it's opposing dynorphin signals. GnRH does not seem to be implicated in glucose homeostasis derangement[1].

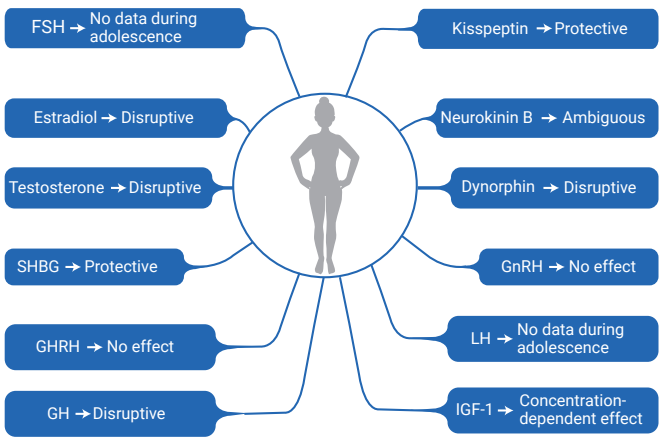

Figure 3: Hormones, proteins in adolescence, and their effect on glucose metabolism

Source: Stefanaki et al., 2016[1]

Psychosocial considerations of adolescent girl

Psychosocial issues are common in young adults with diabetes than without. Living with diabetes typically involves a variety of diabetes related concerns that interfere with effective self-care including unclear diabetes goals, feeling of discouragement and issues with diabetes regimen, uncomfortable interactions with non-diabetic family, friends, or co-workers, and guilt or anxiety with diabetes self-care and possible complications[7]. Adolescence is characterized by defiance, autonomy and privacy issues, increased social pressure, and eating disorders in certain girls. Diabetes causes and impacts such altered behavior[5].

Girls have shown a 0.92% increase in HbA1c compared to boys from pre- to post-puberty. Diabetes mismanagement is more common in girls with low adherence to diet plans during stressful times, more depressive symptoms and eating disorders[8]. Obese girls with T1D have shown significantly worse psychosocial (self-worth, close friendships, perceived stress, and depressive symptomatology), self-management, quality of life and family functioning than normal-weight girls with T1D in a study[9]. This was reaffirmed by another study showing poorer overall treatment compliance and metabolic control, lower self-esteem, less self-efficacy, and more depressive symptoms in girls as compared to boys[8].

Alcohol and substance abuse

Young adults, with or without diabetes, are known to engage in alcohol and tobacco use. In a sample of 117 youth with diabetes, 47% reported alcohol consumption, 29.9% reported binge drinking, and 34.7% reported smoking[10]. A study highlighted greater burden of diabetes related distress in females as compared to males (44% vs. 19%). Females reported twice the fear of hypoglycemia and had a higher HbA1c value than males. Females were also more likely than males to smoke during adolescence, affecting metabolic regulation and increasing the risk of future vascular complications[11].

Monitoring blood glucose levels, staying hydrated, and consuming carbohydrates should be advised to patients to reduce the risk of delayed hypoglycemia from alcohol intake[10].

Depression and anxiety

As the most common psychiatric condition, anxiety disorders can complicate management of diabetes with fear of injections provoking panic attacks and hypoglycemia. Depression is a common comorbid disorder in patients of diabetes which is associated with poor glycemic control and diabetes complications[7].

Depression, anxiety and poor self-esteem have been linked to chronic illness in adolescents. Depression is 2-3 fold more likely in youth with diabetes than in non-diabetics. Diabetes is also related to increased risk of suicide and suicidal tendencies in children and adolescents, rendering diabetes management and self-care even more challenging[3]. A national survey found that adolescents with T2D experience high rates of depression, with 19% reporting mild levels and 19% reporting moderate/severe levels of depressive symptoms. According to a study, the most common psychiatric conditions in T1D adolescents were depressive disorders (26%), anxiety disorders (20%) and behaviour disorders (16%). Each unit increase in HbA1c raised the risk of depression by 27%[12].

Another study found that depression and anxiety to be more common in girls with diabetes than boys, even when controlling differential levels of metabolic control. Social and academic pressures in adolescent girls' lives also contribute to their feelings of anxiety and depression[13]. Treatment Options for T2D in Adolescents and Youth or TODAY study found similar levels of depressive symptoms in adolescents with T2D, with clinically significant depression symptoms exceeding 20% in older adolescent females. Additionally, symptoms of depression were associated with lower quality of life[7]. A statistical report revealed that anxiety is considerably overrepresented among young women aged 16-24 years compared to young men (25% vs. 14%)[11].

Depressive symptoms can intensify as older teens enter young adulthood, affecting physical and psychological well-being. It is crucial to monitor and refer older adolescents and young adults with T1D or T2D to appropriate mental health resources[7].

Eating disorders

Disordered eating behaviours are much more common in women than men. About 30% of all women taking insulin struggle with subclinical symptoms of disordered eating, such as restrictive eating, obsession over weight and shape, feelings of guilt after eating, and strategic misuse of insulin for weight control. Approximately 60% of teenagers and young adults with diabetes engage in unhealthy weight loss practices, with almost 57% going for intentional insulin mismanagement for weight loss[7]. Girls with T1D are at a 2-fold greater risk of developing eating disorders than their non-diabetic peers[14].

Binge eating and insulin under dosing for weight control are common in adolescent girls with diabetes[15]. Disturbed eating attitudes and behaviours such as omitting insulin to control weight can be seen in 12–40% girls and binge eating in 60–80% girls[14]. Acute weight gain, dietary restriction and insulin omission to 'purge' through induced glycosuria may trigger an eating disorder. Eating disorders should be suspected in adolescent girls with persistently poor metabolic control[15]. Dieting for weight management, binge eating and purging, exercising to lose weight and/or unrealistic attitudes regarding weight are commonly seen in adolescent girls with diabetes. Insulin restriction has been reported by 31%-36% of women with T1D[12]. Clinical diagnosis of eating disorders can be made in 10% of girls with diabetes and an additional 10%-15% girls meet the criteria for subclinical eating disorders[15].

Eating disorders including anorexia and bulimia, as well as subclinical disordered eating attitudes and behaviours, pose substantial health risks to emerging adults with diabetes, including other risks such as poor metabolic control, lower adherence, depression, increased risk of DKA and microvascular consequences[7].

Insights into the transition experience

This transition from pediatric to adult care, defined as a 'purposeful, planned process that addresses the medical, psychosocial, educational and vocational needs of adolescents and young adults as they grow up learning to live with their lifelong me-

dical condition', occurs over time and include the adolescents gradually assuming responsibility for independently accomplishing diabetes care[16].

Transitioning care for adolescents with diabetes from a pediatric, family-centered paradigm to an adult, patient-centered model marks a critical period in the life trajectory of persons with diabetes. The physical aspects are linked to the hormonal changes of puberty that impact body shape and size, particularly the development of IR, necessitating increased self-monitoring and insulin adjustments. The psychological elements include sexual awakening, alcohol intake and poor monitoring of blood glucose to detect hypoglycemia, especially during certain critical times like before driving. These psychological changes occur along with the eventual assumption of independent decision making over years. During this time, there may be decreased dependence and increased defiance at parental or other authority figures. To maintain or improve metabolic control and avoid acute metabolic complications such as hypoglycemia or DKA, these factors must be integrated into a comprehensive, realistic, and personalized diabetes care plan[10].

In addition to the psychological aspects of transition (e.g. potential anxiety or sense of loss), the transition process may include communication with diabetes care providers, employers or educational institutions, informed decision making associated with driving, sex, alcohol consumption, prescription and illicit drugs, roommate interactions, safety at parties and diagnosis disclosure to peers. Relocating, relationships, educational and/or career responsibilities, financial freedom, and other life changes connected with obtaining independence also complicate the transition process even further. The process of transition includes informing and educating youth about adult-oriented issues related to general health and specific to T1D[16].

Transitional healthcare should be coordinated and seamless, without disruptions that compromise health outcomes. However, most youth (60%) report not getting recommended consultations with their pediatrician about healthcare transition. Additionally, a marked decline in clinic attendance has been observed for youth during the transfer of care. Moreover, around 24% of youth with T1D have reported a gap of more than 1 year between their last pediatric visit and first adult visit, while over 14% experienced a lapse of greater than 2 years. Also, young adults are more likely to experience care interruptions when transitioning to an adult environment, with over half transferring adult providers at least once. Poor health outcomes for transitioning youth are likely due to care gaps, missed appointments, and frequent changes in providers. Youth with T1D show reduced adherence while transitioning to adult care, putting them at risk for poor glycemic control and medical complications. Approximately 65% of adolescents in transition report at least one negative medical event inaccessibility to medical care[16]. The T1D exchange reported that only 21% of adolescents aged 13 to < 20 years of age met the HbA1c criteria of 7.5% recommended by ADA[10]. Moreover, individuals transferring to an adult provider have a 2.46 fold increased risk of poor glycemic management, with HbA1c rising from 7.5% to 9.2% from their final pediatric visit to their first adult visit[17]. The Society for Adolescent Medicine outlined 5 primary areas of focus in their 'General Principles for Successful Transition' (Table 1)[16]. These recommendations are further supported by a consensus statement published by the American academy of pediatrics, the American academy of family physicians, the American college of physicians–American society of internal medicine, and the ADA[16].

Issues in the transition between pediatric and adult diabetes care

Differences between pediatric and adult care

Diabetes care for pediatric and adult patients differs in several ways. Successful pediatric diabetes care requires family involvement as young children lack the cognitive ability to manage diabetes, and adolescents lack the emotional maturity to maintain daily therapy. Visits are usually family-centered, holistic, and centered on approaches in accordance with the child's and family's lifestyle[7].

Table 1: Transition recommendations of the Society for Adolescent Medicine

Recommendations from the Society of Adolescent Medicine for Transition

1. Appropriate transition is recommended as per the patient's chronological and developmental age
2. Common concerns in the adolescent age group must be addressed by the Health authorities
   - Growth
   - Development
   - Security
   - Mood
   - Mental health outcomes
   - Substance use and other health promoting and damaging behaviour
3. The patient's autonomy, personal responsibility must be enhanced by the transition and it must also facilitate reliance on self
4. Individualized transfer of care should take place as per the patient and the family
5. A designed professional such as a coordinator or advocate should be included in the transition taking responsibility for the process in collaboration with the family and the patient

Source: Wagner et al., 2015[16]

Adult patients are expected to make their own decisions about their own behaviour and treatments. Adult visits are usually shorter and more focused on medical issues. Adult patients are considered to be independent with access to their health information. The change in HCPs can be abrupt and unsettling making a gradual transition more preferable[7]. However, in countries like India the family involvement and support are present throughout ones journey with diabetes so it makes it more easier for the transition.

Poor control of glycemia and other risk factors

The gap between recommended and actual glycemic control levels remains large, especially for older teens and younger adults. The SEARCH for Diabetes in Youth study found that only 32% of T1D aged 13-18 and 18% of those aged ≥ 19 years achieved ADA-recommended A1c targets. Conversely, National Health and Nutrition Examination Survey suggested that 56% of adults maintain A1C levels < 7%. One in four teenagers with T1D, and T2D, aged 12 years or above had the worst glycemic control (A1c ≥ 9.5%), with one in four patients aged 12 or older having this condition[7].

Regardless of ethnicity, youth with T2D have more cardiovascular risk factors than those with T1D. However, with increasing obesity, adolescents with T1D experience similar cardiovascular risk. Obese children and adolescents with T2D have greater prevalence of dyslipidemia and hypertension. Fatty liver disease is more common in obese children with IR and diabetes, and has also been linked to T1D. These risk factors must be addressed in adolescence and young adulthood[7].

Loss to follow-up

Inappropriate follow-up diabetes care put transitioning older teens and young adults at greater risk of disengagement from health care and undiscovered complications. There are short-term (hypoglycemia, hyperglycemia or DKA) and long-term nephropathy and retinopathy consequences of such loss to follow-up. Poor glycemic management increases hospitalization, emergency use and healthcare expenses. Patients, who do not understand or engage in their care have worse glycemic control and outcomes. Young adults with diabetes have a higher RR of death than non-diabetics. Better access to care is essential for older teens and young adults with diabetes, especially those from racial/ethnic minorities or poor socioeconomic backgrounds. This prevents acute hospitalizations and allows early intervention for chronic issues and improves long-term health and function[7].

Increased risk for acute complications

Loss of parental supervision, reduced clinical attendance, challenges of work and/or school, other lifestyle changes including alcohol consumption, reduced physical activity, varying motivation for self-care, and varying dietary patterns increase the risk of hypoglycemia and severe hyperglycemia or DKA in transitioning youth. In the DCCT adolescents aged 13–17 years at study entry and 20–24 years at study's end had a higher rate of severe hypoglycemia than adults. Rates of DKA in older adolescents are associated with nonadherence and poorer glycemic control[7].

Sexual and reproductive health issues

To reduce unwanted pregnancies and sexually transmitted illnesses, pediatric and adult care professionals should discuss sexual behaviour and reproductive health. Adolescents and young women with diabetes need to be educated about contraception to avoid unwanted pregnancies and enhance diabetic pregnancy outcomes. Only 16% of youth with diabetes aged 13–19 years used birth control. The relevance of preconception counselling and care for individuals with T1D and T2D is evident given the highest pregnancy and birth rates among those aged 18-30 years. Less than one in four young women aged 16–20 years with diabetes were aware of the maternal and fetal risks of pregnancy and the necessity for adequate glycemic control to conceive and deliver a healthy baby[7].

Alcohol, smoking and drug abuse

Young adults with diabetes may jeopardize their health by drinking alcohol or smoking cigarettes. Alcohol and tobacco usage among teenagers and young adults with diabetes appears to be comparable to non-diabetics. Alcohol consumption decreases glycemic control and raises the risk of severe hypoglycemia, while smoking elevates cardiovascular risk and microalbuminuria risk in young adults with diabetes. Involvement in such high risk practices puts young people at risk for immediate and long term diabetes complications. The dangers of these actions, as well as associated hypoglycemia risk should be discussed. Adequate blood glucose monitoring and prevention and treatment of hypoglycemia should be implemented, especially before and during driving[7].

Chronic complications

The prevalence of diabetic complications in adolescence is low. However atherosclerotic vascular changes have been reported to develop in early adolescence. High LDL cholesterol, low HDL, smoking and higher HbA1c levels heighten the cardiovascular risk[18]. The SEARCH study has verified a 3-fold higher rate of microalbuminuria in youth with T2D compared to those with T1D[7].

Since diabetes management guidelines in adults are based mostly on T2D, these guidelines must be individualized for the adult patient with T1D. Preparations for the transition of care must be discussed prior to the actual transition[18].

Practical clinical aspects of transition to adult care/recommendations for diabetes care

Effective transitional care involves collaboration between pediatric and adult diabetologists. Best self-management relies on behavioural change provided by the multidisciplinary team and a realistic medical model of care[19]. To maximize short term well being and health and prevent long-term complications, it is critical to develop effective and translatable transition process from pediatric to adult providers. These young adults must also attain glycemic goal to avoid long-term complications and enhance lifelong well-being[7].

ADA recommendations for care transition of emerging adults with diabetes "Diabetes care for emerging adults: Recommendations for transition from pediatric to adult diabetes care systems"-2011[7].

- Pediatricians, in collaboration with patients and families, should prepare the development of the teen for the approaching health care transition at least a year in advance, if not earlier.
- Diabetes self-management skills for the teen/emerging adult and their parents should be emphasized during preparation. The parent or guardian should gradually hand over diabetes care responsibilities to the teen. Beyond diabetes management tasks like glucose self-monitoring and insulin administration, organizing appointments and ensuring adequate medicine and supplies should be taught. Diabetes education should target the teen rather than just the parents.
- Education on difference between pediatric and adult care, as well as health insurance options should be included in preparation.
- A written summary including an active problem list, prescription list, assessment of diabetic self-care skills, prior glycemic control and diabetes related comorbidities, as well as any mental health concerns and referrals during pediatric care should be prepared by pediatric provider.
- Competing psychosocial, educational, and vocational changes may cause emerging adults with diabetes to lose consistent health care, resulting in poor glycemic control. Both pediatric and adult caregivers should offer assistance and referrals to patient friendly services.

- The transferring HCP should provide emerging adults with particular referrals to adult care providers educated in intense diabetes management strategies.
- The transferring providers should provide access to resources that might help emerging adults reconnect to care if they become lost to follow-up. A care ambassador or patient navigator can help the transitioning young adult schedule the first appointment with the adult care provider within 3–4 months of the final pediatric visit.
- The focus of diabetes care must be on adherence to diabetic self management and regular use of glucose-lowering drugs to prevent acute and long term complications.
- Adolescents with diabetes should be assessed and treated for eating disorders and mood issues. The diabetes provider should provide a mental health referral source with basic understanding of working with diabetics.
- The ADA recommends ongoing visits every 3 months for insulin users and every 3-6 months for non-insulin users.
- Screening for microvascular and macrovascular complications in children with diabetes and adults should be done.
- Lipid screening, BP monitoring, and weight management should begin in childhood. Lipid and hypertension management should follow pediatric and adult recommendations.
- Both pediatric and adult clinicians should discuss birth control, pregnancy planning and risks, prevention of sexually transmitted diseases, alcohol and drug use, smoking, and driving with older teens and emerging adults, emphasizing the relevance with diabetes.
- The emerging adult should feel that he/she is receiving accessible, patient-centered, coordinated, comprehensive, continuous, compassionate, and culturally effective treatment[7].

Conclusion

The combination of pubertal hormonal changes, adolescent psychosocial challenges, pediatric along with conventional age constraints of pediatric and internal medicine makes it difficult to have well-controlled diabetes for both patient and practitioner. Early planning and open communication among pediatric and adult physicians, patients and families is advised to ensure a seamless transition from pediatric to adult health care[10].

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CHAPTER 4 PREVENTION OF DIABETES IN WOMEN

Dr. RM Anjana, Dr. Neelaveni.K, Dr. Ranjani Harish

Effect of dietary pattern on incidence of diabetes in women

NCDs account for approximately 41 million deaths each year[1]. 85% of these deaths occur in low and middle-income countries[2]. In India, NCDs contribute to 62% of total deaths and 48% of these are preventable[3]. Also, the progression from prediabetes to diabetes occurs much faster in Asian Indians than in other ethnic groups[4].

Two major factors solely responsible for this rapid rise in the incidence of diabetes in developing countries are dietary habits and sedentary lifestyle[5]. There is substantial evidence that lifestyle modifications and/or pharmacological therapies can prevent or delay 25-40% of incident diabetes in high risk individuals[6-8].

Dietary interventions can prevent and control T2D by improving energy balance, IR and blood glucose control. There is evidence linking high calorie intake and high glycemic index diets to increased risk of T2D. The quality of diet components corresponds with T2D risk, progression and consequences[9]. In particular, a diet low in whole grains and high in glycemic load[10] and processed meats appears to increase the risk, especially in women[11]. In the Framingham Offspring Study, women with the "empty calorie" dietary pattern had higher and those with "wine and moderate eating" dietary habits had lower prevalence of the metabolic syndrome. In the Malmö Diet and Cancer Cohort, the metabolic syndrome was more prevalent in women with the "white-bread" dietary pattern and less prevalent in women with the "milk-fat" pattern[12].

A consensus report on nutrition therapy for diabetes concluded that people with diabetes consume same proportion of macronutrients as the general public, which is ~ 45% of their calories from carbohydrate, ~ 36-40% of calories from fat and the remainder (~ 16-18%) from protein[13].

A study on Japanese women found that eating white rice increased their risk of T2D by 1.65 times[14]. The prevention with mediterranean diet or PREDIMED trial showed that a Mediterranean style diet resulted in a 30% lower RR of T2D onset compared to a low fat eating pattern[15]. Another study on Caucasian women aged 40-60 years, found that a healthy diet pattern was related with decreased odds of IR and the metabolic syndrome, while a western diet pattern was associated with increased risks[16]. Many Indian studies have also highlighted that the dietary carbohydrates especially refined grains are positively associated with T2D. Polished white rice was noted to be the major contributor. Also, it was noticed that those who eat more rice, also eat less of virtually all other foods such as legumes, tubers, fruits and vegetables and dairy products[17].

A prospective cohort study of 35,988 older American women from Iowa State showed an inverse association between a healthy dietary pattern and metabolic syndrome. This was attributed to a diet that included whole grains, fiber, fruit and vegetables and high dietary magnesium[18]. Based on the DASH programme, the healthy dietary pattern helped to lower BP and improves symptoms of metabolic syndrome[19]. Higher intakes of these foods may also reduce insulin demand. A study from Chennai, India showed that a higher intake of fruit and vegetables contributed to 48% of the protective effect against CVD risk factors, including diabetes[20]. Furthermore, low glycemic load foods are associated with lower risk of IR.

An Indian study[21] sought to evaluate the contribution of various modifiable risk factors to the PARp for diabetes in an Asian Indian population. Of a cohort of 3,589 individuals, representative of Chennai, followed up after a period of 10 years, data from 1,376 individuals, who were free of diabetes at baseline, was analyzed.

The combination of risk factors like obesity, physical inactivity, unfavourable diet risk score, hypertriglyceridemia and low HDL cholesterol was found to explain 80.7% of all incident diabetes. Of these modifying diet and physical inactivity alone could (at least theoretically) prevent 50% of incident diabetes in the Asian Indian population[21] and this was more so in women (59.3% vs. 54% in men).

The PARp for the diet score was 29.8 (-2.0, 56.1) and 42.6 (10.7, 66.6) in males and females respectively. Thus, overall a low risk diet score could prevent 30% of cases of diabetes. The diet risk score in this study was computed incorporating intake of refined cereals, fruits and vegetables, dairy products and monounsaturated fatty acid[21]. Refined cereals showed the highest risk for diabetes (Figure 1).

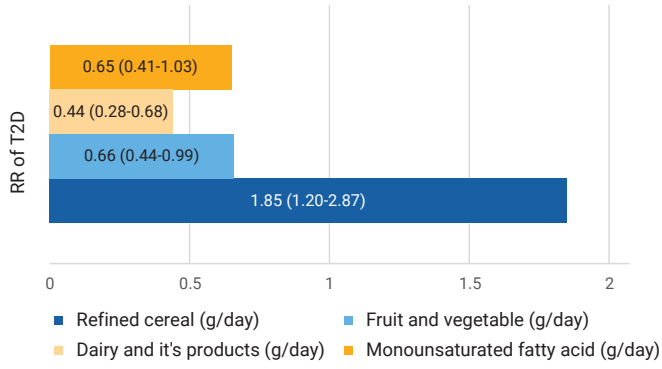


Figure 1: Diet risk score components and RR for T2D
Source: Anjana et al., 2015[21]

In another large nationwide trial, Indian dietary data collected from 12,500 individuals (46% females) was analyzed. The results showed that the consumption of milk, meat, junk food and less vegetables and fruits (Table 1) had a significant effect on the glycemic status and cholesterol levels of the participants[22].

A unique population-specific food-based diet score called the IDQS was developed with the aim to assess the independent association of diet with incidence of diabetes among Asian Indian adults. The association between diet score and the incidence of diabetes was prominent among both gender, older adults (> 30 years), overweight and obese individuals and those with higher physical activity. Higher IDQS was associated with a lower risk of T2D among South Indian adults[23].

Table 1: Association between dietary factors with categories of diabetes, prediabetes and normoglycemia

Milk

	PPBG	FBG
Diabetes OR	17.19*	7.18*
Prediabetes OR	3.44	2.74*
Normoglycemia OR	2.56*	2.31

Meat

	PPBG	FBG
Diabetes OR	22.82*	6.81*
Prediabetes OR	3.90	2.63*
Normoglycemia OR	1.64	1.51*

Less fiber

	PPBG	FBG
Diabetes OR	17.77*	9.17*
Prediabetes OR	2.78	2.87*
Normoglycemia OR	2.80*	1.95*

Less fruit

	PPBG	FBG
Diabetes OR	14.71*	8.99*
Prediabetes OR	3.51*	1.95*
Normoglycemia OR	1.21*	1.18*

Skipping of breakfast

	PPBG	FBG
Diabetes OR	5.63	4.14
Prediabetes OR	1.33	1.69*
Normoglycemia OR	1.72*	1.45*

Note: There was a highly significant association between blood glucose (Fasting blood glucose and postprandial blood glucose) values and consumption of milk, meat, less fruits and less fiber, but not with skipping of breakfast in individuals with diabetes.*Significance $p < 0.001$. FBG: Fasting blood glucose, PPBG: Postprandial blood glucose

Source: Nagarathna et al., 2020[22]

Similarly, another Indian study highlighted the role of food choices and frequency of intake in diabetes prevention. The cross-sectional data of 99,574 women and 61,361 men aged 20-49 years, who participated in India's third National Family Health Survey conducted during 2005-2006 were used for this study. In women, daily or weekly consumption of pulses/beans and fruits was associated with a lower likelihood of diabetes[24]. The impact of a diabetes prevention intervention on diet and risk of diabetes in South Asians at high risk showed that decreasing total energy intake and increasing intakes of fruits and vegetables, could reduce the 1 year incidence of diabetes by half[25].

Dietary intake was assessed in 133 women with GDM enrolled under the WINGS-MOC[26], from 6 maternity centers in Chennai, in South India. The WINGS-MOC dietary intervention included one-on-one monthly antenatal diet counselling, providing a dietary guideline booklet and healthy recipe demonstrations. A 'healthy diet score' was derived from the reported intake of whole grains, dairy products and dietary fiber. The effect of healthy diet score on neonatal outcomes (macrosomia, hyperbilirubinemia, congenital anomalies and neonatal ICU admissions) was evaluated. Higher consumption of whole grain, dairy products and dietary fiber was inversely associated with adverse neonatal outcomes. Those with the highest healthy diet score had lower risk for adverse neonatal outcomes even after adjusting for potential confounders[26].

Nutritional factors and approaches in diabetes

There may not be a single ideal percentage of carbohydrate, protein and fat for all people with or at risk of diabetes, therefore, macronutrient distribution should be based on existing eating patterns, preferences and metabolic goals. An assessment and review of current dietary intake should be followed by tailored advice on self-monitoring carbohydrate intake to optimizing meal timing and food choices as well as medication and physical activity[13,27].

The rapid nutritional transition in India has led to increased intake of calories, saturated fats, trans fatty acids, simple sugars, salt and low intake of fiber. Therefore, the consensus guidelines for Asian Indians recommends decrease in the overall intake of carbohydrates, increased intake of complex carbohydrates, fiber and low glycemic index foods, reduction in intake of saturated fats, maintaining ideal ratio of essential fatty acids, reduction in trans fatty acids, moderate increase in protein intake, decrease in salt intake and controlled intake of sugar[28,29](Table 2).

Table 2: Currently available recommendations for medical nutrition therapy for the management of DM

Carbohydrates		
Indian guidelines		**ADA guidelines**
RSSDI	**Recommended intake:** 45-65% of total daily calories (minimum intake 130 g/day)	No specified recommended intake
	High fiber diet: Increased intake of soluble and insoluble fibers	High fiber and low glycemic index diet
	Preferred sources: Pulses, legumes, coarse grains, sprouted grams, unprocessed vegetables and fruits	**Preferred sources:** Fruits, vegetables, whole, grains, legumes and dairy products (milk and yoghurt)
	Substitution of polished white rice with millets and brown rice	
ICMR	**Recommended intake:** 55-60% of total daily calories	
	Intake of fiber-rich foods	
	Preferred sources: Cereals, mixed coarse grains, whole grains (e.g. ragi, oats, barley, jowar), whole pulses, whole fruits, salads and soybeans, leafy vegetables, fenugreek seeds	
	Restricted intake of all-purpose flour (maida)-based products	

Proteins		
Indian guidelines		**ADA guidelines**
RSSDI	**Recommended intake:** 10-15% of total daily calories	Typically 15-20% of total energy in individuals without diabetic kidney disease
		Recommended daily allowance in individuals with T2D and compromised renal function: 0.8 g/kg body weight/day
	Preferred sources: Not mentioned	**Preferred sources:** Not mentioned
ICMR	**Recommended intake:** 10-15% of total daily calories	
	Preferred sources: Vegetable sources, low-fat milk and milk products, fish and lean meat	

Contd. in the next page

For Indians who currently consume about 65-75% of calories from carbohydrates, reducing this to 50-55% and adding enough protein (20-25%), especially from vegetable sources and deriving the remaining calories from fat (20-30%) by including monounsaturated fats (e.g. groundnut or mustard oil, nuts and seeds) along with plenty of green leafy vegetables, would be the best diet prescription for the prevention and management of NCDs such as T2D and CVD[30].

Also, studies have shown that substituting brown rice for white rice has potential benefit on glycemic control among individuals with metabolic syndrome[31,32]. Regular consumption of dietary fiber is associated with decrease in all-cause mortality in diabetes. Therefore, people with diabetes should consume at least 25-40 g of dietary fiber/day. Daily consumption of 3 g of soluble fiber from 70 g of oats lead to beneficial effects on the lipid parameters, specifically total cholesterol and LDL cholesterol in hypercholesterolemic Asian Indians[33].

A large epidemiological study found that consumption of polyunsaturated fat is associated with lower risk of T2D[34]. Supplementation with Omega-3 fatty acids in individuals with prediabetes has demonstrated some efficacy in surrogate outcomes beyond serum triglyceride levels[35]. The PREDIMED study found that a Mediterranean style eating pattern supplemented either with extra virgin olive oil or with nuts, reduced incidence of T2D among people without diabetes with high cardiovascular risk at baseline[15]. Hence, it may be prudent to advocate these healthy dietary habits to help prevent and/or delay onset of diabetes.

Weight management, physical activity and glycemic control

The risk for diabetes significantly increases with age, obesity and physical inactivity[34]. Physical inactivity has been shown to be a major risk factor leading to NCDs like diabetes[35]. Globally women are physically less active than men[36]. This holds true for India as well. ICMR-INDIAB study showed that physical inactivity was higher in Indian women (67.2%) than in men (54.9%)[37] (Figure 2).

Fats		
Indian guidelines		**ADA guidelines**
RSSDI	**Recommended calorie intake:** No specified ideal intake	**Recommended calorie intake:** No specified ideal intake
	Restricted intake of saturated fats: <10% of total daily calories	**Restricted intake of saturated fats:** <10% total daily calories
	Minimal intake of trans fats	Minimal intake of trans fats
	Restricted intake of dietary cholesterol: < 300 mg/day	**Restricted intake of dietary cholesterol:** < 300 mg/day
	Preferred sources of MUFA/PUFA: Moderate intake of fish/seafood, chicken without skin and red meat as a source of PUFA	**Preferred sources of MUFA/PUFA:** Fatty fish, nuts and seeds
	Not recommended: Sunflower oil	
ICMR	**Recommended calorie intake:** 20–25% total daily calories	
	Restricted intake of saturated fats: < 7% total daily calories	
	Minimal intake of trans fats (hydrogenated vegetable fats)	
	Restricted intake of dietary cholesterol: < 300 mg/day	
	Preferred sources of MUFA/PUFA: Groundnut, sesame, cotton seed, rice bran or safflower along with soybean, mustard, canola, etc. as preferred choices for edible oils containing MUFA and PUFA	

Sugars and sweeteners		
Indian guidelines		**ADA guidelines**
RSSDI	Reduced intake of refined sugars	Reduced intake of HFCS and sucrose
	Moderate intake of non-nutritive artificial sweeteners	Substitute nutritive sweeteners with non-nutritive sweetener
	Avoid consumption of HFCS	Natural fructose/free fructose from fruits (3–4% of energy intake and not < 12) is permissible
ICMR	Avoidance of sugar, honey, jaggery	
	Restricted use of artificial sweeteners and avoidance in pregnant/lactating women with diabetes	
	Avoidance of very sweet fruits and fruit juices	

Micronutrients and other dietary recommendations		
Indian guidelines		**ADA guidelines**
RSSDI	Inclusion of micronutrients (chromium, α-lipoic acid, magnesium and zinc) as adjunct to standard care[b]	Not recommended
	Restricted intake of dietary salt: < 5 g/day[c]	**Restricted sodium intake:** < 2300 mg/day[c]
	Avoidance of alcohol consumption	Moderate alcohol consumption
	Cessation of tobacco use	
ICMR	Not recommended	
	Restricted intake of dietary salt: < 6 g/day	
	Moderate of alcohol consumption	
	Cessation of any form of tobacco use	

Note: a Particularly in patients with established CVD
b Insufficient evidence available
c Further restriction in patients with diabetes and hypertension
MUFA Mono-unsaturated fatty acids, PUFA Poly-unsaturated fatty acids
Source: Viswanathan et al., 2019[29]

Recent studies have showed an extremely strong positive relation between level of BMI and the risk of diabetes in women[6]. Conversely, weight loss appears to be highly effective in preventing prediabetes progression to T2D and managing cardiometabolic health in T2D[6,8]. Regular physical activity contributes to both weight loss and prevention of weight regain. Structured weight loss programmes and meal replacements have been found to help weight loss in people with diabetes. Metabolic surgery, weight loss drugs and glucose lowering therapies can be used in conjunction with lifestyle modifications to achieve greater weight loss that is maintained for a longer period of time[39].

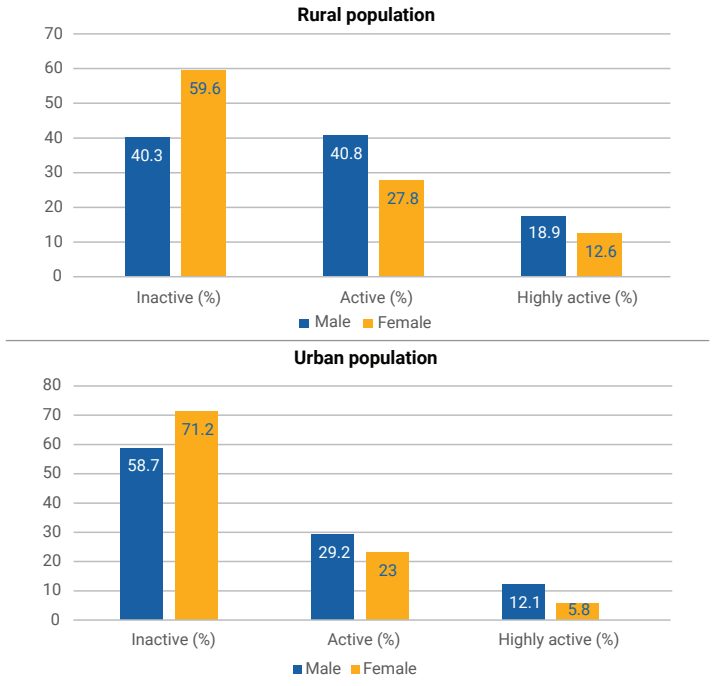


Figure 2: Physical activity levels in the study population
Source: Anjana et al., 2014[38]

In T2D, 5% weight loss is recommended to achieve clinical benefit and the benefits are progressive. The goal for optimal outcomes is loss of 15% or more weight when needed and whenever it can be feasibly and safely accomplished. In prediabetes, the goal is 7-10% weight loss for preventing progression to T2D[6,8].

Laboratory and clinical studies suggest that physical activity can enhance insulin sensitivity and glucose tolerance, thus reducing the risk of T2D. This effect can last up to 72 h after exercising even in people with T2D[38]. Exercise independently affects glucose metabolism by increasing both insulin-mediated and non-insulin mediated glucose disposal. A single exercise session increases insulin-mediated glucose uptake for more than 24 h. The increased insulin sensitivity occurs because of increased number and activity of glucose transport proteins (especially the glucose transporter 4 isoform), both in muscle and adipose tissue. Glycogen synthase activity leads to increased glycogen synthesis and non-oxidative glucose disposal[40]. Exercise also reduces adipose tissue mass and preserves or increases lean body mass, which increases insulin sensitivity[41] (Figure 3).

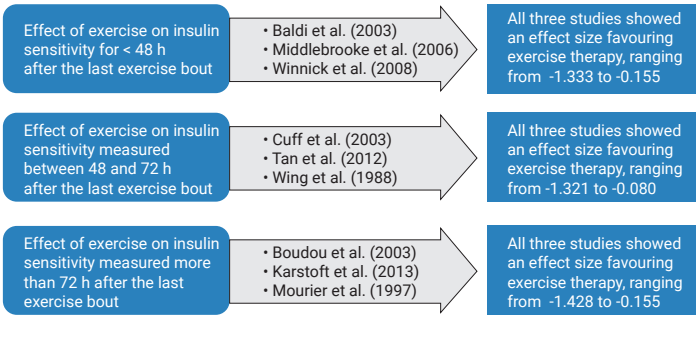
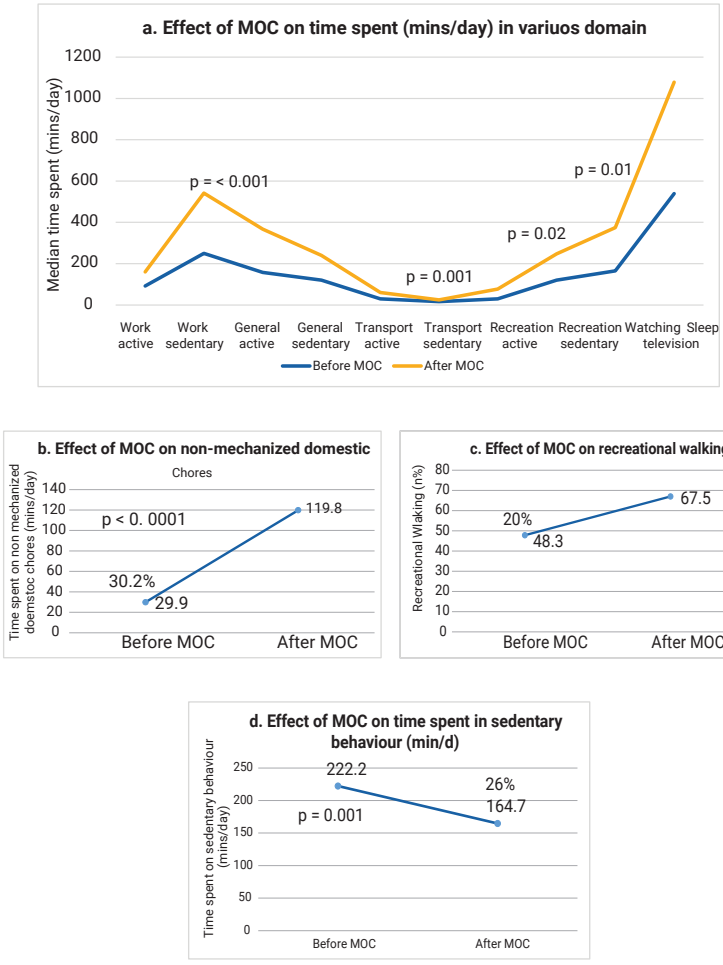


Figure 3: The effect of exercise on insulin sensitivity at < 48 h, at 48-72 h, and at > 72 h after the last bout of exercise. ES: Effect size
Source: Way et al., 2016[41]

Among people who do not have diabetes, research show that strategically adding exercise to diet therapy facilitate and helps maintain weight loss, mediated by reducing the adipose tissue and increasing muscle mass and strength[10]. Thus, physical activity is important in the prevention of T2D in women through its independent effects on body weight, IR/sensitivity and glucose tolerance[42].

A prospective cohort study of women with diabetes showed that greater leisure-time physical activity was associated with substantially reduced risk for cardiovascular complications. Women with diabetes who exercised for at least 4 h/week had a 40% lower risk of CVD. The reduction in risk was similar for CHD and ischemic stroke and the dose-response relationship was consistent in subgroup analyses according to cardiovascular risk factors[43].

Indian studies have also shown that women with diabetes are at particularly high risk against CVDs and diabetes eliminates the usual female advantage for death from coronary disease[44,45].



*p < 0.05 considered as significant using Wilcoxon signed rank test

Figure 4: Effect of WINGS MOC on physical activity patterns of GDM women (n = 151). (a) Effect of WINGS MOC on time spent (mins/day) in various domains, (b) Effect of WINGS MOC on non-mechanized domestic chores, (c) Effect of WINGS MOC on recreational walking, (d) Effect of WINGS MOC on the time spent in sedentary behaviour (mins/day)

Source: Anjana et al., 2016[47]

A randomized controlled translation trial D-CLIP of 578 overweight/obese Asian Indian adults with prediabetes, compared standard care to a culturally tailored lifestyle education curriculum, based on the US diabetes prevention programme plus stepwise addition of metformin (500 mg, twice daily). Three year follow-up showed that the RR reduction in diabetes incidence was 9.8 (34.9% in the control group and 25.7% in the intervention group developed diabetes)[8]. The D-CLIP-step-wise diabetes prevention programme besides resulting in a 32% lower 3 year diabetes risk, also showed an almost 50% reduction of diabetes incidence in participants who had a BMI of ≥ 27 at baseline, thus showing weight loss is an important risk factor in diabetes prevention.

In the WINGS study, physical activity patterns were studied in 795 pregnant women with and without GDM, and WINGS-MOC intervention was evaluated. It was found that physical activity levels were inadequate amongst this group of pregnant women studied. However, a low-cost, culturally appropriate MOC could bring about significant improvements in physical activity in women with GDM. These changes were associated with improved glycemic control and reduction in adverse neonatal outcomes[46] (Figure 4).

However, as this chapter specifically addresses diabetes prevention in women it also imperative to recognise the challenges to making lifestyle changes especially exercise among women. Low level physical activity is known to contribute to poor health outcomes for women, with cultural barriers being a major factor in discouraging women from participation.

Reasons for higher physical inactivity in women include time constraints, self-consciousness, lack of confidence, physical inability, lack of encouragement from family members, discomfort with the attire, expensive club and gym memberships, inability to access exercise facilities, unfavourable weather conditions and exercise not being considered 'culturally acceptable'[47,48].

The D-CLIP study data revealed gender differences in the perceived barriers to exercise showing women having many socio-cultural barriers compared to their male counterparts[49] (Figure 5).

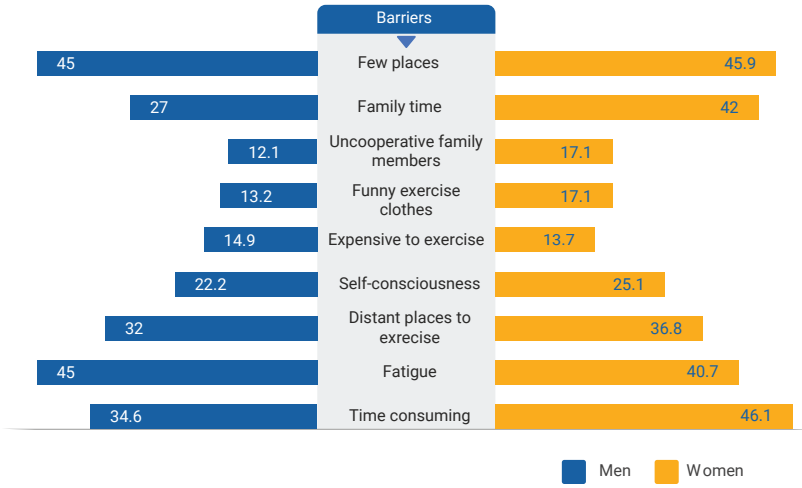


Figure 5: Perceived barriers to exercise among the non-exercisers

Source: Anjana et al., 2015[50]

Future research should therefore devise and test lifestyle interventions specific for women. One such novel intervention called THANDAV (over NCDs) was designed specifically for adolescent girls and women and a pilot study testing the intervention showed that THANDAV, which fused HIIT with a culturally accepted form of physical activity namely dance helped improve the fitness of adolescent girls[51,52]. We need more such targeted interventions that focus on improving both dietary habits and physical activity behaviour specifically among women, thereby helping to prevent diabetes and improve metabolic outcomes.

Conclusion

To prevent diabetes in women, interventions should target the two main modifiable risk factors namely diet and exercise that cause the disease. However, these lifestyle behaviours are the most difficult to change and hence designing gender specific strategies that promote healthy eating and regular physical activity is of considerable public health importance.

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CHAPTER 5 LIFESTYLE MANAGEMENT FOR WOMEN WITH DIABETES

Dr. Vaishali Deshmukh, Dr. Vedavati Purandaret

Introduction

Lifestyle interventions for prevention of prediabetes and T2D in women have been discussed in Chapter 4. This chapter will focus on two main aspects of LSM programmes for women with diabetes:

- Lifestyle goals and recommendations.
- Barriers and strategies to lifestyle and dietary pattern interventions.

Women with a family history of diabetes or those with obesity are known to be at increased risk of T2D. The risk of diabetes increases with obesity and consumption of energy-dense food[1,2]. The lifestyle goals and recommendations for women with diabetes are same as general diabetes goals and recommendations.

Lifestyle goals

Lifestyle goals for women with diabetes should be aimed at[3]:

- Improving health through optimum nutrition.
- Providing energy for optimum body weight, growth and development.
- Maintaining euglycemia.
- Achieving optimum serum lipid levels.
- Individualization of the diet plan according to complications and comorbidities.
- Achieving optimal physical activity.
- Bringing positive behavioural changes to avoid smoking, use of other tobacco products and alcohol.
- Managing stress.
- Delaying and preventing complications.

Lifestyle recommendations

LSM aims at improving diet quality and quantity, increasing physical exercise, preventing weight gain and ensuring weight control should form the backbone of diabetes prevention and management[4,5]. The Look AHEAD trial showed that intensive lifestyle intervention showed good results for weight loss and blood glucose control[6]. Hence women with diabetes, obesity (diabesity) are likely to benefit from LSM. However, without continued monitoring and motivation, most patients lose sight of their goals and do not adhere to LSM[7,8].

Physical activity alone causes modest weight reduction, but helps in preserving fat-free mass, maintaining weight, promoting cardio-respiratory fitness and reducing cardiovascular risk[9]. Therefore, structured lifestyle interventions to prevent or delay the onset of T2D in women with prediabetes or at risk of T2D should include[5,7,8,10,11]

- At least 150 mins/week of physical activity.
- Diet modifications resulting in 5-7% weight loss.

- Continued monitoring of glycemic and weight loss goals.
- Continued motivation and counselling.
- Psychological support and counselling for stress eating, eating disorders and other factors that result in binge eating.
- Patient education should be an important aspect of diabesity care. This should be reinforced at diagnosis, then annually, at the time of complications/change in treatment and when there is change in care[12].

General recommendations for physical activity in women with or at risk of diabetes

Increased physical activity and structured exercise programs supervised by a registered HCP should be an integral part of LSM [9-11,13].

- Physical activity required for weight maintenance is higher than that recommended for the general population.
- Physical activity counselling should provide ways/options for increasing physical activity in daily life.
- Physical activity counselling should include structured exercise programme supervised and guided by a trained HCP. Exercise programme should include aerobic exercises, yoga, stretch and flexibility, resistance training and strength training.
- 10 mins for aerobic activity bouts; total ~ 30 mins/day or more of aerobic activity as per capacity, done on most days of the week. Exercise programme should be individualized, stepped up and designed according to patient's health and capability to exercise.

General dietary recommendations for women with or at risk of diabetes

Dietary counselling or MNT that aims at weight and glycemic control through healthy eating patterns should be an integral part of LSM [7,9,13–18].

- Healthy dietary patterns should be encouraged through education.
- A balanced hypocaloric diet should be individualized by a registered HCP to patient's need, culinary practices, local food diversity, lifestyle, affordability and acceptability. Appendix I can serve as a guide for calorie planning.
  - Ensure inclusion of high quality complex carbohydrates; limit refined carbohydrates.
  - Ensure use of poly/mono-unsaturated fats; limit use of saturated fats.
  - Ensure 1-1.2 g/kg of protein intake daily unless contraindicated.
  - Include right micronutrient balance.
  - Encourage healthy cooking practices such as baking, steaming and low fat cooking over deep frying.
  - Dieting and other diet fads should be strongly discouraged, pros and cons to be explained to patients.
- While reducing food portions, care should be taken to avoid drastic reduction. Figure 1 gives the plate method as a guide for calorie distribution and portion size.
- Patients should be encouraged to maintain food diaries to track their eating patterns and behaviours.
- Every effort should be made to understand and address emotional eating patterns, eating disorders, food perceptions and behaviours.
- Weight loss targets and glycemic control goals should be periodically monitored and adjusted according to patient's needs.
- Patients should be counselled on the amount and sources of protein to be taken to ensure proper muscle metabolism for exercising.
- Some patients not responding to dietary modifications may need supplementation through formula MNTs.

A summary of dietary recommendations by various societies are covered in Table 1.

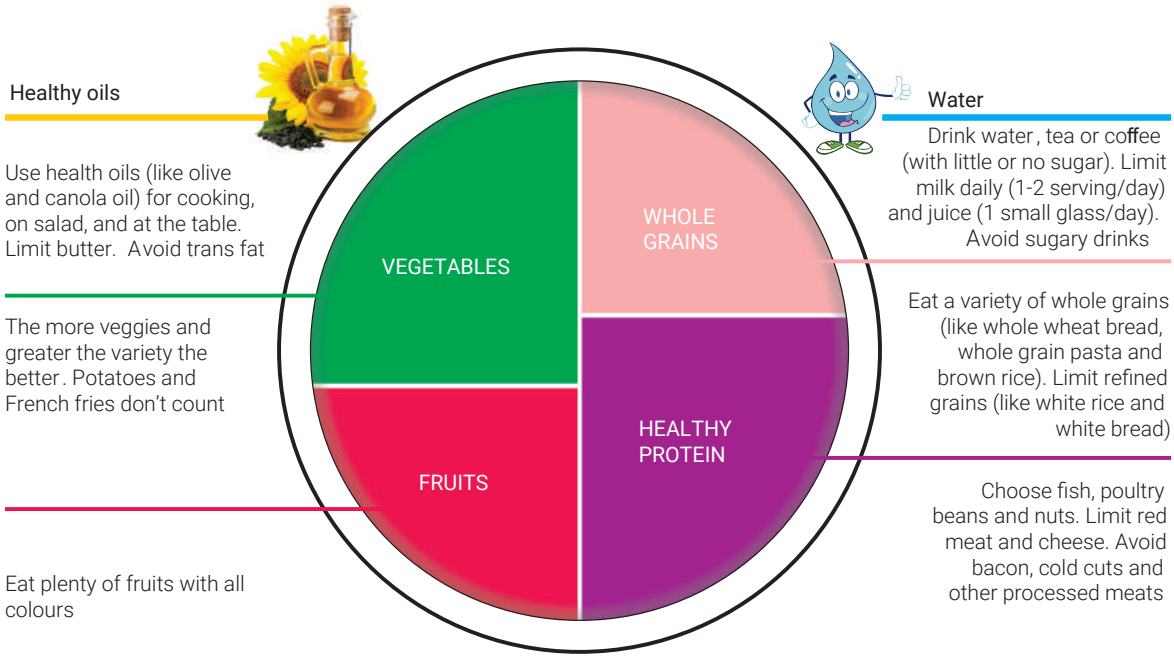

Figure 1: Plate method of portion control
Source: Kapoor et al., 2021[4]

Table 1: Dietary recommendations for women with diabetes

	ICMR	RSSDI	ADA
Carbohydrates	55-60% of total daily calories	45-65% of total daily calories (Minimum intake: 130 g/day)	No recommendations provided due to lack of clinical evidence. Low glycemic index diet encouraged
Fibers	Intake of fiber rich foods 40 g for 2000 calories	**High-fiber diet:** increase intake of soluble and insoluble fibers	High fiber diet
Sugars and sweeteners	• Avoid sugar, honey, jaggery, sweetened beverages • Restrict artificial sweeteners • Avoid artificial sweeteners in pregnant/lactating women	• Reduce refined sugars intake • Moderate intake of artificial sweeteners • Avoid HFCS	• Reduce HFCS and sucrose • **Substitute high calorie sweeteners with non-nutritive sweetener. Fructose from fruits:** 3-4% of energy intake is permissible
Proteins	10-15% of total daily calories	10-15% of total daily calories	15-20% of total energy (reduces in kidney disease to 0.8 g/kg body weight/day)
Fats	20-25% total daily calories **Restrictions:** • **Saturated fats:** < 7% total daily calories • Minimize hydrogenated vegetable fats (trans fats) • **Dietary cholesterol:** < 300 mg/day	No specific recommendations **Restrictions:** • **Saturated fats:** < 10% total daily calories • Minimize trans fats • **Dietary cholesterol:** < 300 mg/day	No specific recommendations **Restrictions:** • **Saturated fats:** < 10% total daily calories • Minimize trans fats • **Dietary cholesterol:** < 300 mg/day
Micronutrients	No specific recommendations	Chromium, α-lipoic acid, magnesium and zinc	No specific recommendations
Salt	**Restricted intake of dietary salt:** ≤ 6 g/day	**Restricted intake of dietary salt:** < 5 g/day	**Restricted sodium intake:** < 2,300 mg/day
Alcohol/tobacco	Moderate alcohol consumption; cessation of tobacco use	Avoid alcohol; cessation of tobacco use	Alcohol in moderation

Source: ICMR, 2018[3]; Chawla et al., 2020[19]; American Diabetes Association, 2019[20]

Lunch plate: One cup salad, vegetables, egg omelettes with one egg white, half cup dal in a bowl, one phulka and half cup watermelon

Breakfast plate: One cup vegetable upma with low starch vegetables, four small paneer cubes, one table spoon curd and three slices of orange

Special considerations in women

Women are also at increased risk of diabetes if they have PCOS, are obese, are pregnant or are in postmenopausal age group.

PCOS

PCOS is one of the most prevalent endocrinopathies of the reproductive age group[21]. A European study found that in overweight/obese (BMI ≥ 25.0 kg/m^2) women, presence of PCOS significantly increased the risk of T2D compared to controls without PCOS (OR 2.45, 95% CI, 1.28–4.67)[1]. The risk of pre diabetes and T2D did not increase in normal weight women with PCOS. Women with PCOS who developed T2D had significantly greater increase in weight between ages 14, 31 and 46 years, compared to women with PCOS and without T2D. The increase in weight in women with PCOS and T2D was significant during early adulthood (14-31 years; $p < 0.001$)[1]. The study showed obesity was strongly associated with pre diabetes and diabetes.

Recommendations:

Recommended LSM programs to delay onset of T2D, and overcome IR and IGT includes[21]:

- *General:*
  - Low carbohydrate diet.
  - **Combination of aerobic and resistance exercise:** High intensity training 150-175 mins/week + resistance exercise 2-3 days/week.
  - Weight loss (5-14%) improves metabolic profile and reproductive function; reduces cardiovascular risk factors.
- *Women with IGT:*
  - Limiting dietary calorie to achieve 5-7% weight loss associated with 40-70% decline in T2D risk[22].
  - High intensity exercise (HR > 80%)[23].
- Giving insulin sensitizers such as metformin along with LSM programmes improves metabolic profile and reproductive function; reduces cardiovascular risk factors[24,25].

Pregnancy

Pregnancy related DM can be explained in four situations:

(i) Women with diabetes who become pregnant.

(ii) New onset GDM.

(ii) Pregnant women with history of GDM in previous pregnancy.

(iv) Postpartum diabetes.

High blood sugar during pregnancy is associated with adverse fetal and maternal outcomes[26]. Hence, a comprehensive pregnancy management in women with T2D or at risk of GDM should include a multi-target approach that focuses on regulating blood glucose level (using insulin if required), weight gain, BP and provides the required dietary advice and outreach patient education[26].

Lifestyle interventions help in preventing excess weight gain during pregnancy and therefore prevent GDM[27]. The RADIEL randomized controlled trial (n=269) found that individualized moderate lifestyle intervention reduced GDM risk by 39% in high risk pregnant women[27]. The multicenter Diabetes Prevention Program showed that intensive LSM reduced diabetes incidence by 58% during a follow-up of 2.8 years[28]. The beneficial effect was maintained during the 10 years of follow-up. An effective reduction in diabetes by 34% was seen during the 10 years[29].

In pregnant women with history of GDM in previous pregnancy, lifestyle interventions such as diet, exercise and breastfeeding that are aimed at ameliorating modifiable risk factors are successful in reducing the incidence of postpartum obesity related morbidities including diabetes[30]. A systematic review (14 reports) and meta-analysis (n=5) concluded that exclusive breastfeeding during first 6-9 weeks postpartum and longer duration of continued lactation for 4-12 weeks significantly reduces the risk of T2D in the coming years (2 to > 5 years)[31].

Pregnant women irrespective of their GDM status are considered to be highly motivated about health[32].Therefore, pregnancy offers a critical window of opportunity for improving their health[32]. A study from India looked at the impact of an educational intervention programme on the blood glucose, weight, obesity and metabolic parameters in women with GDM in pregnancy who had postpartum normoglycemia or prediabetes[33]. The intervention comprised of six 2 h session given to small groups (n=10-15). which included information and problem solving skills on nutrition, eating behaviour, physical activity, motivation and barriers to lifestyle change. About 80% of women attended ≥ 4 sessions with significant reduction in weight, BMR, waist circumference, fasting and postprandial blood glucose, systolic BP and triglycerides[33].

Recommendations:

- Women planning to become pregnant should start the dietary modifications before pregnancy[34,35].
- Pregnant women should be encouraged to eat healthy with focus on carbohydrate quantity and quality, especially if they have a history of GDM[26,34,36,37]. Diets such as the Mediterranean diet (rich in fruits and vegetables, high quality carbohydrates and proteins and micronutrients such as magnesium and vitamin C)[37–39], reducing intake of following foods can reduce GDM incidence in high risk women[35,37,40–45]:
  - High sugar content/glycemic index (e.g. sweetened beverages, sweets, cakes, pastries, etc.).
  - High heme iron content (e.g. red meat).
  - High fat content.
- Apart from usual recommendations for diet, probiotics and myo-inositol supplementation may be given to pregnant women with obesity[46-48]. Incidence of GDM significantly decreases with probiotic supplementation and diet control as compared to those only on diet control (13% vs. 36%, p = 0.003)[49]. Myo-inositol supplements appear to work as insulin sensitizers and significantly reduce GDM risk (p = 0.001)[47,50].
- Pregnant women should be encouraged to breastfeed. Lactation reduces the risk of postpartum diabetes, especially in women who had GDM in previous pregnancy[30,31,51,52].
- Postpartum progression of IGT, GDM to T2D should be prevented through weight loss followed by maintaining a healthy body weight achieved through increased physical activity and improved diet quality.[36,39,53–55]. A meta-analysis (n = 34,929 prepregnancy and n = 4,401 early pregnancy) showed that level of physical activity before and during early pregnancy directly correlates with 24% lower risk of developing GDM[56] .

- Pregnant women with or at risk for GDM should be advised 20–30 mins of moderate intensity exercise on most or all days of the week[10,11].
- LSM education programmes should be built for all women in child bearing age group, pregnant women, women at risk of developing GDM and postpartum women with GDM during pregnancy[33,57]. This will prevent or delay progression to T2D[58]. Interventions may be planned prior to delivery in pregnant women with GDM.
- The LSM behavioural programmes for weight-management should last a minimum of 12-15 weeks[32].
- Women with diabetes, who become pregnant and those with GDM on pharmacological treatment. The usual diabetes education on glucose monitoring, including identifying and acting on signs of hypoglycemia should be part of education programme[26].

- Dietary advice for pregnant women with diabetes (diabetes before pregnancy and GDM) [26]:
  - A registered dietician should develop an individualized nutrition plan in early pregnancy to minimize glycemic excursions and ensure appropriate gestational weight gain. The plan should encourage:
    - Carbohydrate counting at each meal and snack.
    - Low-glycemic-index carbohydrates; limit sweets and sweetened beverages.
    - A minimum total daily carbohydrate intake of 175 g (150 g from a combination of bread, rice, whole grain, dairy products, potatoes, fruits, pasta and sweets; 25 g from vegetables or other sources).
    - Carbohydrate breakup: breakfast 20 g, lunch 40 g, dinner 40 g and 10-20 g for each in-between snack (2-4).
  - Dietary advice should cater to other co-morbidites as well (e.g. low protein in kidney disease, low salt in hypertension).

Menopause

A US study looked at the association between baseline dietary energy density and incident diabetes in 143,204 post menopausal women without self-reported diabetes[2]. Participants were followed up for 12.7 ± 4.6 years. The study found that women in the highest dietary energy density quintile had a 24% higher risk of developing diabetes than those in the lowest quintile (95% CI, 1.17-1.32)[2]. In women, who were in dietary energy density quintiles 2-5, those with waist circumference > 88 cm had 9-12% higher risk of developing diabetes than women with waist circumference < 88 cm[2]. The study showed that high dietary energy density and obesity was strongly associated with diabetes. Thus, lifestyle interventions aimed at reducing weight and consuming balanced nutrition could prevent or delay diabetes.

Another US study found a strong association between LPIR, a metabolic marker and incident of T2D in 25,925 healthy women aged ≥ 45 years, followed prospectively for > 20 years[59]. The study showed that pre-clinical insulin resistance and β-cell dysfunction preceded clinical diabetes for several years. Lifestyle interventions initiated during this period could help delay or prevent diabetes.

Recommendations:

The general LSM recommendations for women with diabetes or at risk of diabetes should be followed with special considerations for the age and comorbidities.

Barriers to lifestyle interventions and strategies to mitigate them

Barriers to LSM can be general barriers or they can be women specific.

General barriers and their solutions

General barriers inhibiting LSM are usually related to food preferences and increased sedentary behaviour due to modernization[14,17,60–62]:

- Preference for refined carbohydrates, sweets, sweetened beverages and saturated fats.
- Preference for deep fried and calorie dense food.

- Low fruit and vegetable intake resulting in low fiber intake.
- Increased intake of calorie-dense food.

These preferences for calorie-dense high glycemic index food is because these food types stimulate serotonin secretion, which result in a feeling of well-being and craving for carbohydrates[63]. Another barrier to LSM uptake in low middle income countries like India is that MNT and exercise training are not covered by insurance[4]. Additionally, most physicians are not sensitized or trained in providing MNT and exercise training. Many regions are lacking trained dieticians and physical therapists[64]. Most diet charts used in hospitals and clinics are pre-printed with little scope for individualization and modification[64]. Another problem is that different diets provide varied effects on different individuals making individualization tedious. Also, different types of low calorie diets vary in components and therefore, have different benefits, making it difficult to choose the best option for the individual[65–68].

MNT, exercise and weight management given by a registered HCP should be integrated into the primary care of a woman with diabetes or at risk of diabetes during any phase of her lifecycle. Every effort should be made for continued medical education of HCPs to promote healthy lifestyle in their patients. Smartphone technology should be used where possible to increase the reach of education programmes and ensure continued education[26] .

Women specific barriers and their solutions

Women specific barriers that influence their LSM uptake and adherence (based on a study on postpartum women) include mother's priorities, demands in life and her role in family and childcare, social support, personal experiences and preferences, education level to assess risk and information and available finances and resources[69]. The various women specific barriers and their mitigation strategies are shown in Figure 2.

National Diabetes Prevention Program are reliable ways to addressing barriers of care. However, women in child bearing age are less likely to enroll in National Diabetes Prevention Programs than older women but equally likely to benefit from the programme[70]. Hence, women in child bearing age who have obesity or IGT, IR or prediabetes/diabetes, or any metabolic disorder likely to increase T2D risk should be encouraged to participate in National Diabetes Prevention Programs.

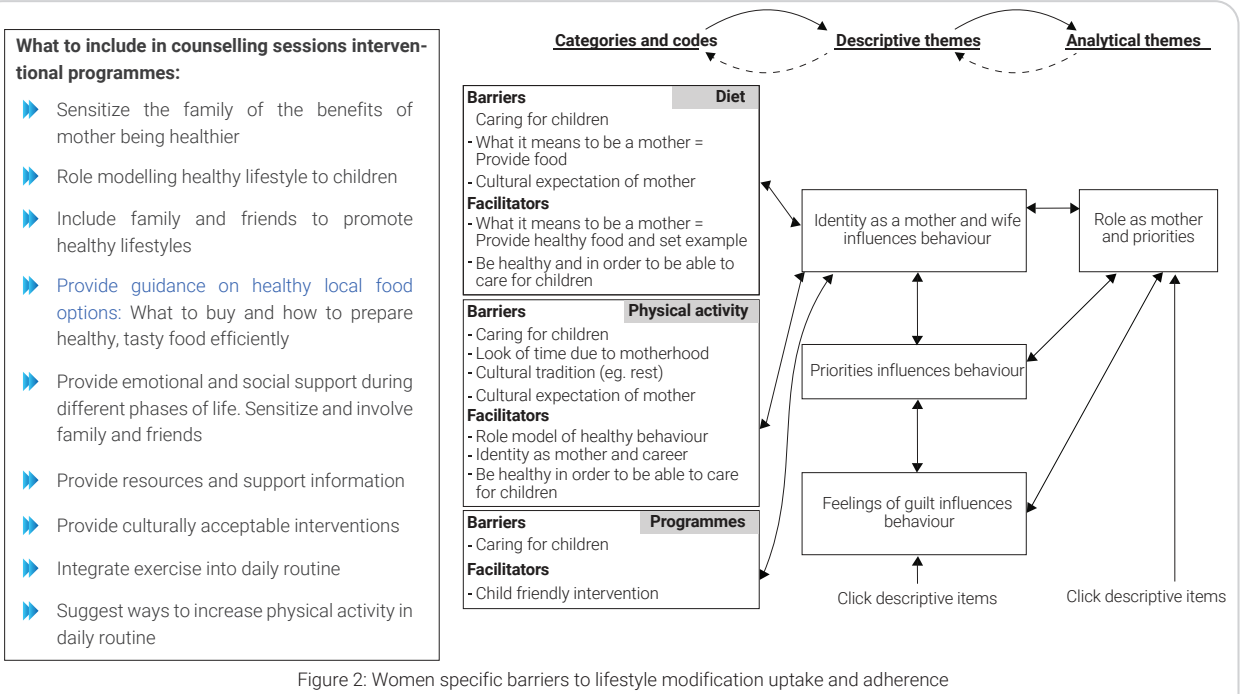

Figure 2: Women specific barriers to lifestyle modification uptake and adherence

Source: Dennison et al., 2019[69]

Appendix

Appendix I: Approximate calorific value of some cooked food preparations[4,71]

Preparation	Quantity for one serving	Calories (Kcal)
Cereals		
Rice	1 cup	170
Phulka	1 piece	80
Parantha	1 piece	150
Puri	1 piece	80
Bread	2 slices	170
Poha	1 cup	270
Upma	1 cup	270
Idli	2 pieces	150
Dosa	1 piece	125
Khichdi	1 cup	200
Wheat porridge	1 cup	220
Semolina porridge	1 cup	220
Cereal flakes with milk (corn/wheat/rice)	1 cup	220
Pulse		
Plain dal	1/2 cup	100
Sambhar	1/2 cup	100
Vegetables		
With gravy	1 cup	170
Dry	1 cup	150
Non-Vegetarian		
Boiled egg	1 piece	90
Omelette	1 piece	160
Fried egg	1 piece	160
Mutton curry	14 cup	260
Chicken curry	3/4 cup	240
Fish fry	2 big pieces	190
Fish cutlet	2 pieces	190
Prawn curry	3/4 cup	220
Savoury snacks		
Bajji or pakora	8 pieces	280
Besan ka puda	1 piece	220
Chat (dahi-pakora)	5 pieces	80
Cheese balls	2 pieces	250
Dahi vada	2 pieces	180
Vada	2 pieces	140

Contd. in the next page

Masala vada	2 pieces	150
Masala dosa	1 piece	200
Peas kachori	2 pieces	380
Sago vada	2 pieces	210
Samosa	1 piece	200
Sandwiches (butter 2 tsp)	2 pieces	200
Vegetable puff	1 piece	200
Pizza (cheese and tomato)	1 slice	220
Chutneys		
Coconut/groundnut/til	2 tbsp	100
Tomato	1 tbsp	10
Tamarind (with jaggery)	1 tbsp	60
Sweets and desserts		
Besan barfi	2 small pieces	400
Chikki	2 pieces	290
Fruit cake	1 piece	270
Rice puttu	1/2 cup	280
Sandesh	2 pieces	140
Halwa (kesari)	1/2 cup	280
Jelly/jam	1 tbsp	20
Custard (caramel)	1/2 cup	160
Srikhand	1/2 cup	380
Milk chocolate	25 g	140
Ice cream	1/2 cup	200
Beverages		
Tea (2 tsp sugar + 50 ml toned milk)	1 cup	75
Coffee (2 tsp sugar + 100 ml)	1 cup	110
Cow's milk (2 tsp sugar)	1 cup	180
Buffalo's milk (2 tsp sugar)	1 cup	320
Lassi (2 tsp sugar) Squash Squash	1 cup/glass (200 ml) 1 cup/glass	110 75
Syrups (sharbats)	1 cup/glass	200
Cold drinks	1 bottle (200 ml)	150
Fresh lime juice	1 glass	60

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Section 2

Management of Diabetes & Complications of Diabetes in Women

Editor: Dr. Neeta Deshpande

CHAPTER 6 OPTIMIZING THE MEDICAL MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN WOMEN

Dr. Sarita Bajaj, Dr. Sonali Patange

Optimal management of diabetes in women should aim at reducing the incidence and progression of macrovascular and microvascular disease associated with diabetes. This involves addressing CVD risk factors, screening and treatment for end organ damage as well as management of blood glucose[1].

Treatment options for T2D are now focusing on a patient-centric and evidence-based approach that may take into account all the metabolic derailments accompanying T2D. Associated factors beyond glycemic control, such as cardiovascular risks, weight management along with improvement in quality of life should be taken into account while deciding treatment strategies. Several guidelines/recommendations provide treatment algorithms on ways in which glucose-lowering agents can be used either alone or in combination. Ideally, treatment decisions should be directed, based on glycemic efficacy and safety profiles along with impact on weight and hypoglycemia risk, comorbidities, route of administration, patient preference as well as treatment costs[2].

Targets for metabolic control in diabetes

Recommended glycemic targets for nonpregnant adults

Recommended glycemic targets for nonpregnant women are presented in Table 1.

Table 1: Recommended glycemic targets for nonpregnant adults

A1c	
AACE	Individualize on the basis of age, comorbidities and duration of disease
	≤ 6.5% for most
	Closer to normal for healthy
	Less stringent for "less healthy"
ADA	< 6.5% for patients, who meet the following criteria: Short duration of diabetes
	Long life expectancy
	No concurrent illness
	Goal can be achieved without significant hypoglycemia or other adverse effects of treatment
	< 7%, a reasonable goal for many patients
	< 8% for patients who meet the following criteria: · History of severe hypoglycemia · Limited life expectancy advanced microvascular or macrovascular complications · Extensive comorbid conditions long-standing T2D in which A1c goal has been difficult to obtain despite intensive efforts
RSSDI-ESI clinical practice recommendations, 2020	5.7-6.4%
FPG	
AACE	< 110 mg/dL
ADA	80-130 mg/dL
RSSDI-ESI clinical practice recommendations, 2020	100-125 mg/dL
2 h postprandial glucose	
AACE	<140 mg/dL
ADA	<180 mg/dL
RSSDI-ESI clinical practice recommendations, 2020	140-199 mg/dL

Source: Tsatsoulis et al., 2009[1]; Chawla et al., 2020[2]

Glycemic targets in pregnancy

Glycemic targets during pregnancy by ACOG, ADA and RSSDI-ESI is presented in the Table 2.

Table 2: Glycemic targets in pregnancy

FPG	
ACOG and ADA	70–95 mg/dL (3.9–5.3 mmol/L)
RSSDI-ESI clinical practice recommendations, 2020	95 mg/dL (5.3 mmol/L)
1 h postprandial glucose	
ACOG and ADA	110–140 mg/dL (6.1–7.8 mmol/L)
RSSDI-ESI clinical practice recommendations, 2020	140 mg/dL (7.8 mmol/L)
2 h postprandial glucose	
ACOG and ADA	100–120 mg/dL (5.6–6.7 mmol/L)
RSSDI-ESI clinical practice recommendations, 2020	120 mg/dL (6.7 mmol/L)

Source: Chawla et al., 2020[2]; American Diabetes Association, 2021[3]

Targets for lipid control in diabetes

AACE and the ADA both recommended annual dyslipidemia screening by means of a fasting lipid profile[4] for all adults with diabetes and is summarized in Table 3. Therapeutic lifestyle modification along with pharmacologic therapy should be used to achieve the targets dIscussed in Table 3[4].

Table 3: Target goals to control dyslipidemia

Total cholesterol	**LDL cholesterol**
Recommended goal: < 200 mg/dL	**Recommended goal:** < 100 mg/dL; < 70 mg/dL (all very high risk patients)
Non-HDL cholesterol	**Apolipoprotein B**
Recommended goal: 30 mg/dL above LDL cholesterol goal	**Recommended goal:** < 80 mg/dL very high risk, < 90 mg/dL high risk
HDL cholesterol	**Triglycerides**
Recommended goal: As high as possible but at least > 40 mg/dL in both men and women	**Recommended goal:** < 150 mg/dL

Source: American Association of Clinical Endocrinologists[4]

Pharmacological management of diabetes

Eight core defects, collectively known as "the ominous octet," including decreased insulin secretion, decreased incretin effect, increased lipolysis, increased glucose reabsorption, decreased glucose uptake, neurotransmitter dysfunction, increased hepatic glucose production and increased glucagon secretion, contribute to the pathophysiology of T2D. Therapeutic choices should target these established pathophysiologic defects in T2D, while following a patient-centered approach guided by glycemic efficacy, safety profiles, particularly effects on weight and hypoglycemia risk, tolerability, patient comorbidities, route of administration, patient preference and cost[5].

The main sites of action of present and possible future glucose-lowering treatments are summarized in Table 4.

Table 4: Intervention sites for glucose-lowering, showing available treatments and possible new treatments

Available treatments	
Site of intervention for glucose lowering	
α-glucosidase inhibitors slow the progression of carbohydrates	Intestine and brain
Bromocriptine is dopamine D2 agonist	Brain
GLP-1RA and DPP4i enhance the effect of incretin	Brain and pancreas
SU and meglitinides stimulate the secretion of insulin	Pancreas
Metformin causes a reduction in the production of glucose, increases the use of glucose and counters IR	Liver
Insulin injections, inhalers and pumps cause an increased uptake of glucose, storage and metabolism. It also suppresses glucose production and decrease in lipolysis	Liver, muscles and adipose tissue
TZDs: Insulin sensitivity is increased	Adipose tissue
SGLT2i is glucosuric	Kidney

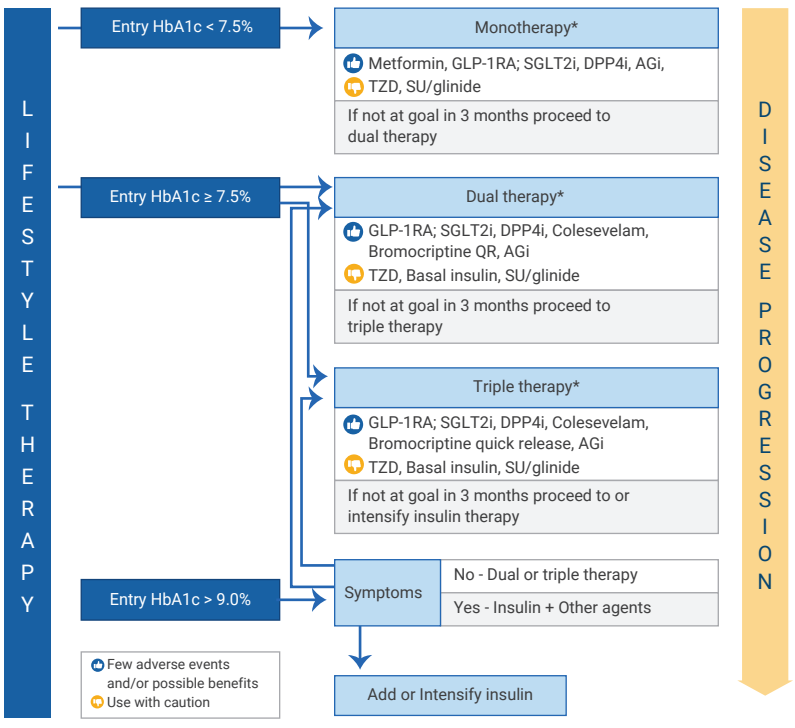
Contd. in the next page

Possible future treatments	
Site of intervention for glucose lowering	
SGLT1i inhibitors cause a delay in absorption of glucose	Intestine
Satiety inducing agents cause a reduction in adiposity	Brain
Incretin analogue peptides and small molecule receptor agonists enhance the effect of incretin	Brain
Glucokinase activators, fatty acid receptor agonists, imeglimin enhance the effect of insulin	Pancreas
Inhibitors of glucagon secretion and glucagon action suppressing counter regulation	Pancreas and liver
Stimulants of muscle glucose uptake and metabolism and direct inhibitors of hepatic glucose production	Liver and muscles
Small molecule insulin mimetics that enhance action of insulin	Muscles
Adipokine analogues/agonists/inhibitors, FGF21 analogues, SPPARMs, 11β HSD1 inhibitors- all of these counter IR in various ways	Adipose tissues
Novel insulin analogues, formulations and routes of delivery like oral, buccal, skin-smart insulins, all enhance action of insulin	Blood glucose
Further SGLT2i glucosuric	Kidney

Source: Bailey et al., 2016[6]

The AACE/The American College of Endocrionology and the ADA support a stepwise, progressive approach to pharmacotherapy and is summarized in Figure 1 and Figure 2. This includes the individualization of A1c goals based on patient specific variables and the adverse effects of therapy, especially hypoglycemia[5].

General recommendations of glucose-lowering therapy in T2D from the ADA are given in Figure 2. The order in the chart was determined by historical availability and route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of glucose-lowering therapy for patients with T2D are displayed with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is possible, depending on the circumstances).



Note: Order of medications represents a suggested hierachy of usage; length of line reflects strength of recommendation

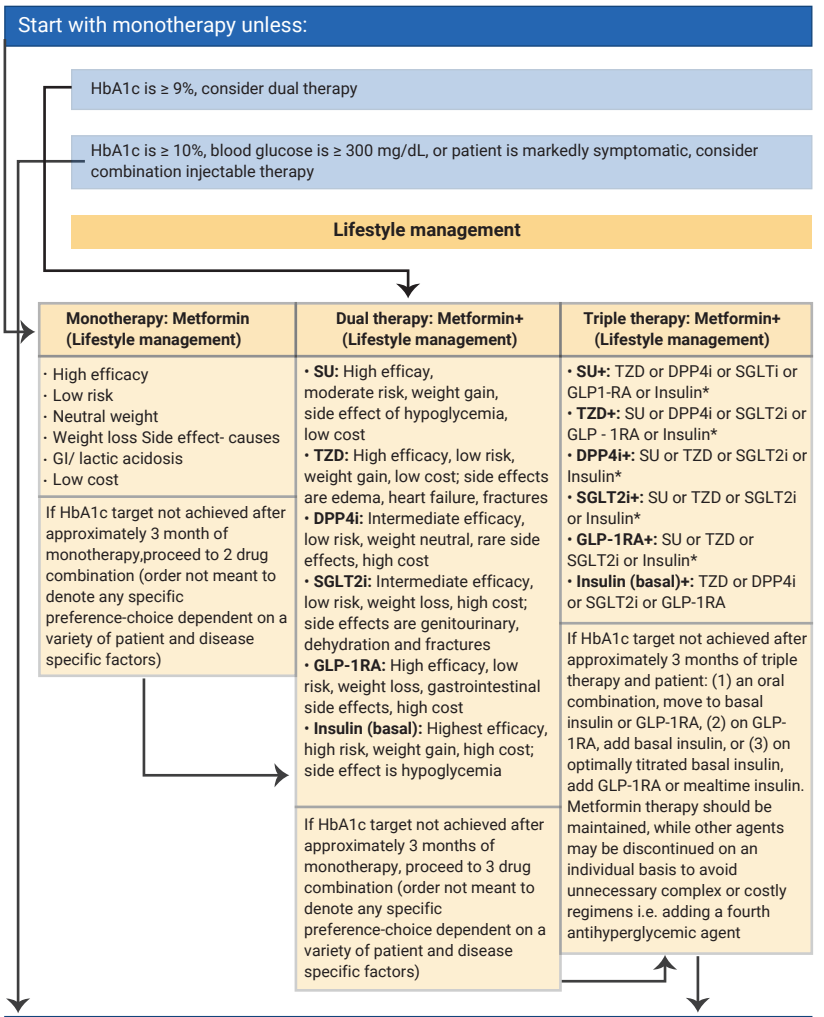
Figure 1: Glycemic control algorithm from the AACE/American College of Endocrionology

Source: Thrasher J, 2016[5]

Management of diabetes in young women

Recommendations from International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2018 include:

- Caregivers should be educated to recognize the signs of mental health problems (depression, eating disorders, illicit drug usage, etc.) and cognitive issues such as attention deficit and personality disorders and need for psychiatric treatment.
- Adolescents and young adults should be educated on employment, driving, alcohol, drugs, sexual health and contraception, taking into account the background, cultural and religious influences.
- In order to increase awareness of the risks of unplanned pregnancy and poor metabolic control preconceptional counselling should begin in puberty in all girls.
- All adolescents should be advised on methods of avoiding pregnancy and sexually transmitted infections, prevention of hypoglycemia during or after intercourse and maintenance of genital hygiene[7].



Note: *Usually a basal insulin (NPH, glargine, detemir, degludec)

Figure 2: Glucose-lowering therapy in T2D: general recommendations from the ADA

Source: Thrasher J, 2016[5]

Pharmacological treatment of T2D in adolescents

Table 5 presents treatment option of T2D in children and adolescents according to US-FDA and EMEA[8].

Multidisciplinary approach incorporating specific skills in pediatrics, DM, nutrition, psychology, social work and DM education should be employed to maximize compliance and treatment adherence services for children with T2D[8].

Management of diabetes in young women contemplating pregnancy/ women of reproductive age

Preconception planning and care

Preconception care aimed at optimizing social, biomedical and psychological aspects, can minimize the diabetic pregnancy complications and to control congenital malformation in women with child bearing potential. The elements of preconception plan are discussed in Table 6.

RSSDI-ESI recommends that women with T2D, who are actively trying to become pregnant should be switched from oral or non-insulin injectable hypoglycemic agents to insulin prior to conception if possible during preconception and the first trimester of women with pre-GDM the primary goal is to maintain optimum glycemic level, while minimizing the risk of hypoglycemia. For example, SU has three compounds, namely, glimepiride, glipizide and glibenclamide with distinct effects during pregnancy, like, intrauterine death, skeletal deformities, fetal growth retardation and permeability through placental barrier. Glibenclamide is associated with decreased rate of morbidity and mortality in fetus and infants. Metformin crosses the barrier of placenta, depicts minor congenital malformation. But the effect is insignificant in comparison to those not on metformin medication. α-glucosidase inhibitors are responsible for congenital malformation in some cases. Meglitinides (nateglinide and repaglinide) may risk the fetus by developing toxicity. TZDs crosses placenta, delays fetal development, reduces fetal weight, postimplantation losses and placental toxicity. Insulin rapid acting analogs, like, aspart, lispro and gluisine, glargine or detemir are also used. Aspart is considered as most efficacious to manage glycemia and it reduces the risk of hypoglycemia during preconception and throughout pregnancy. Lispro is also efficacious and safe in maintaining blood glucose level. However, lack of data and evidence is found on use of detemir, glargine and glusine during pregnancy[2].

Table 5: Treatment option of T2D in children and adolescents by US-FDA and EMEA

Modality	Glycemia reduction	Enhance insulin secretion	IR lowering	FDA/EMEA approved for children	Notes
Diet and exercise	✓	x	✓	✓	First-line approach Efficacy depends on successful lifestyle change
Insulin	✓	x	x	✓	Weight gain discussed Risk of hypoglycemia
Metformin	✓	x	✓	✓	Good safety record Minimal weight loss
SU	✓	✓	x	x	Good safety record in adults Risk of hypoglycemia
Meglitinide analogues	✓	✓	x	x	Sparse data on their use
TZD	✓	?	✓	x	Weight gain Lack of long-term data
DPP4/GLP-1 mimetics	✓	x	x	x	Moderate weight loss Carcinoma of the pancreas discussed Lack of long-term data
SGLT2i	✓	x	x	x	Minimal weight loss Urinary and genital tract infections Risk of hypoglycemia Sparse data on their use Lack of long-term data
Acarbose	?	x	x	x	Side effects may be unacceptable
Orlistat	?	x	x	x	Side effects may be unacceptable
Surgical treatment of obesity	✓	x	✓	x	Some anecdotal evidence

Note: ✓ = yes, x = No, ? = Unknown

Source: Reinehr T, 2013[8]

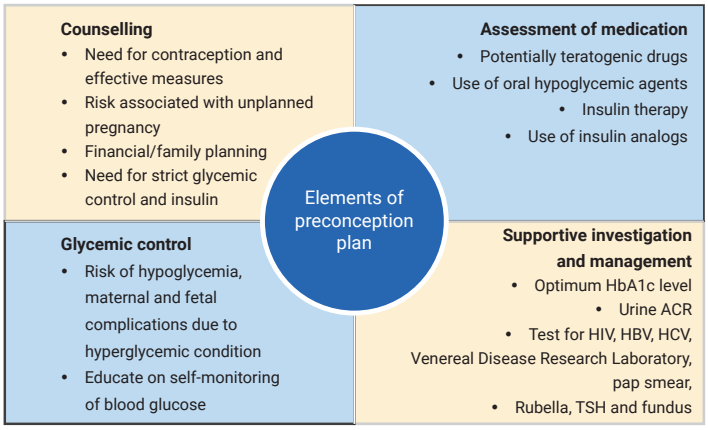
Management of diabetes in elderly women

Older patients have an increased risk of adverse events related to drugs due to pharmacokinetic changes as decreased renal elimination and age related pharmacodynamics changes, such as increased sensitivity to certain medications, which can affect at their disposal. These changes may result in an increased risk of hypoglycemia, the need to reduce the dose of certain medicines and monitor renal function to minimize adverse effects. Figure 3 shows the IDF global guidelines for managing older people with T2D[9].

Why gender specific diabetes management need to be considered?

Between 1971 and 2000, men with diabetes experienced a 43% relative reduction in age-adjusted mortality (including cardiovascular mortality), which is comparable to men without diabetes. In comparison, women with diabetes experienced no reduction in total or cardiovascular mortality and the gap in all-cause mortality rates between women with and without diabetes nearly doubled[10].

Table 6: Elements of preconception plan



Source: Chawla et al., 2020[2]

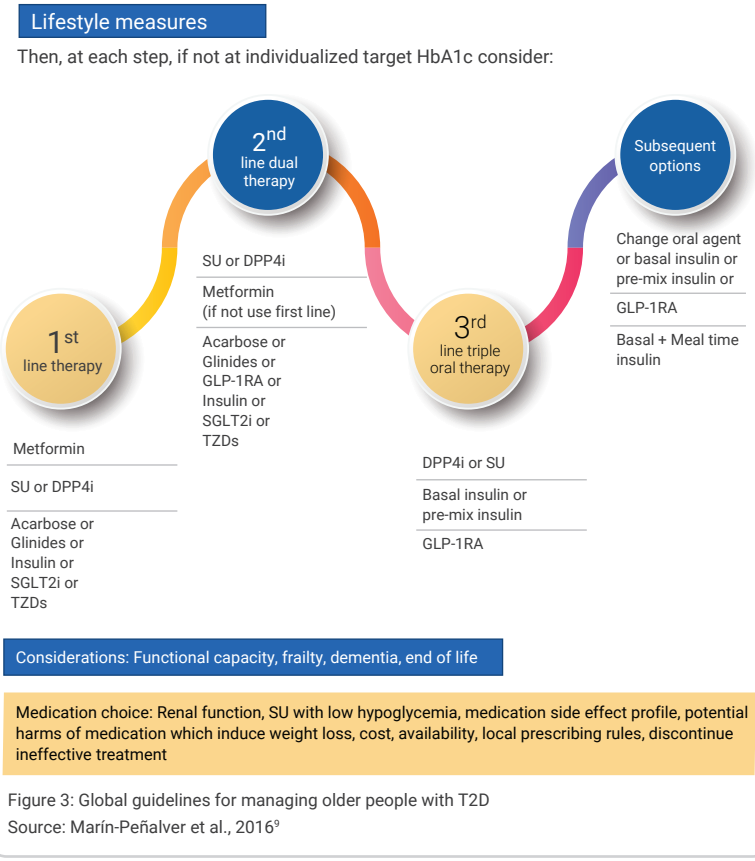


Figure 3: Global guidelines for managing older people with T2D
Source: Marín-Peñalver et al., 2016[9]

Women with diabetes have worse control of cardiovascular risk factors despite comparable or even greater treatment intensity, including antihyperglycemic, antihypertensive or lipid-lowering combination therapies and use of antiplatelet agents and anticoagulants. Some studies shows that women are more likely to be on medication but less likely to be on targets for lipids, A1c and BP. Therefore, additional factors for potential differences in intensity of pharmacological management or control must be considered[11].

Worse quality of care in women with diabetes could be ascribed to both biological factors and patient or physician attitudes. Women have shown a 10% greater likelihood of non-adherence to statin therapy than men. In a study population of 30 million US adults, women were prescribed more drugs than men but showed less drug adherence. Women also received less antihypertensive, lipid-lowering and coronary heart disease and heart failure drugs than men. Lower drug adherence in women could be due to multiple medications and higher frequency of side effects[12].

Most studies found no sex differences in patients with diabetes using antihypertensive or other cardiovascular pharmacological therapies. Side effects of certain β-blockers or ACEi are more frequent in women. Potentially teratogenic antihypertensive or lipid-lowering drugs, particularly renin-angiotensin-system blockers or statins should be cautiously used in women with diabetes of child-bearing age[11].

Pharmacological considerations in women with DM to reduce the cardiovascular mortality

Women are less aggressively treated than men for therapeutic goals of hypertension, A1c for DM, LDL cholesterol and triglycerides levels for dyslipidemia[10].

Dyslipidemia

- A low fat diet improves lipid profiles and cardiovascular outcomes in men but not in women.
- Statins lower cardiovascular events in both men and women, although women see a smaller reduction in total mortality and stroke events.
- Recommended HDL levels in women is 50 mg/dL and in men is 40 mg/dL. Increasing HDL drugs might reduce the more harmful effect of low HDL in women with diabetes[10].

Hypertension

- Recommended therapeutic goals for hypertension by the ADA are similar (130/80 mm Hg) for men and women with DM. However, women with DM would benefit more from aggressive treatment and lower targets for BP.
- CRP reducing antihypertensive drugs might be of particular benefit to women as inflammation and endothelial dysfunction are more strongly involved in the pathophysiology of CVD and metabolic syndrome in women with diabetes than in men. Women with DM and the metabolic syndrome should be closely monitored for ischemic heart disease.
- Low dose aspirin primary prevention is recommended to both men and women with DM, although prothrombotic status is worse in women than in men.
- Men and women with DM should stop smoking; alcohol consumption should be limited to one daily drink in women and two in men[10].

Gender difference in glycemic control

A study showed that women with T2D had worse glycemic control than men, with significantly higher A1c levels than men. In addition, sex modified factors associated with glycemic control suggest that treatment guidelines for men and women should be developed separately. This was consistent with previous studies. In 2002, a study of 21,277 patients with diabetes aged 45-64 years found that men had better glycemic control while using less healthcare services. Another study of 9,375 patients with diabetes indicated better glycemic control (A1c ≤ 6.5% or 48 mmol/mol) in men than women. A cross-sectional study of 3,849 patients with diabetes indicated that women were less likely to have A1c < 7% (53 mmol/mol) than men. In 2010, the Health and Retirement Study found that women had worse glycemic control than men, despite higher adherence to diet and self-monitoring than males[12].

Women may have poorer glycemic control due to differences in glucose homeostasis regulation, therapeutic response and psychological factors. Women are also suggested to be constrained by several social and economic disadvantages such as lower education, lower participation in paid work and reduced wages or economic dependence that create further difficulties in achieving glycemic control[12].

Sex hormones are vital in maintaining glucose homeostasis and are responsible for the underlying biological variations between men and women. Low testosterone levels are linked to abdominal obesity and IR in men. In women, postmenopausal estrogen decline is associated with increasing blood glucose levels, but in men, high estrogen levels may be associated with IR. Sex affects the relationship between BMI and glycemic control. Differences in body fat distribution between men and women influence glycemic control outcomes[12].

Psychological factors, such as depression, stress and anxiety affect men and women differently and potentially contribute to poor glycemic control. A cross-sectional study of 8,871 subjects showed that social class and psychosocial stress were stronger predictors of T2D in women than in men. A study showed that men with T2D were more satisfied with their disease management and had less depression and anxiety than women with T2D. Women with T2D had higher rates of depression than women without T2D[12].

Gender specific clinical trials for antidiabetic drugs

Glucose-lowering therapy

Metformin

Metformin has more beneficial effects on myocardial fatty acid and glucose metabolism in men, compared to women. Women treated with metformin to prevent T2D experienced greater adverse events than men (15% vs. 10%) and were also less adherent to treatment[13].

Metformin should be cautiously used in women to prevent lactic acidosis as it increases plasma lactate levels significantly higher in women than men. Females seem to be more responsive than males to cardiovascular protection by metformin and greater protective effect from breast cancer[16].

A systematic review also reported that greater percentage of males, Caucasian race, higher age, lower BMI and shorter duration of diabetes were all associated with higher success rates in regard to glycemic control[11].

Sulfonylureas

Intensive glucose control with gliclazide in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial patients showed overall risk reduction of 46% in end stage kidney disease as compared to standard glucose control, after 10 years of follow-up. However, subgroup analysis by sex showed that the risk reduction was only significant in males[11].

Another analysis of data from 9,108 patients with T2D demonstrated higher body weight reductions in women during lifestyle, metformin or SU treatment, while men showed higher HbA1c reductions during lifestyle or metformin treatment[15]. The gender specific effects of treatment with metformin and SU on glycemic control and body weight is shown in Figure 4.

Thiazolidinediones

TZDs are more effective at lowering CRP and leptin in women than in men. However, women may be more susceptible to side effects, including hypoglycemia and fractures, than men using TZDs. Pioglitazone has been observed to raise basal serum cortisol in women but not in men. Women treated with rosiglitazone had higher mortality than men, although no difference in mortality was observed with other therapies, such as metformin[13].

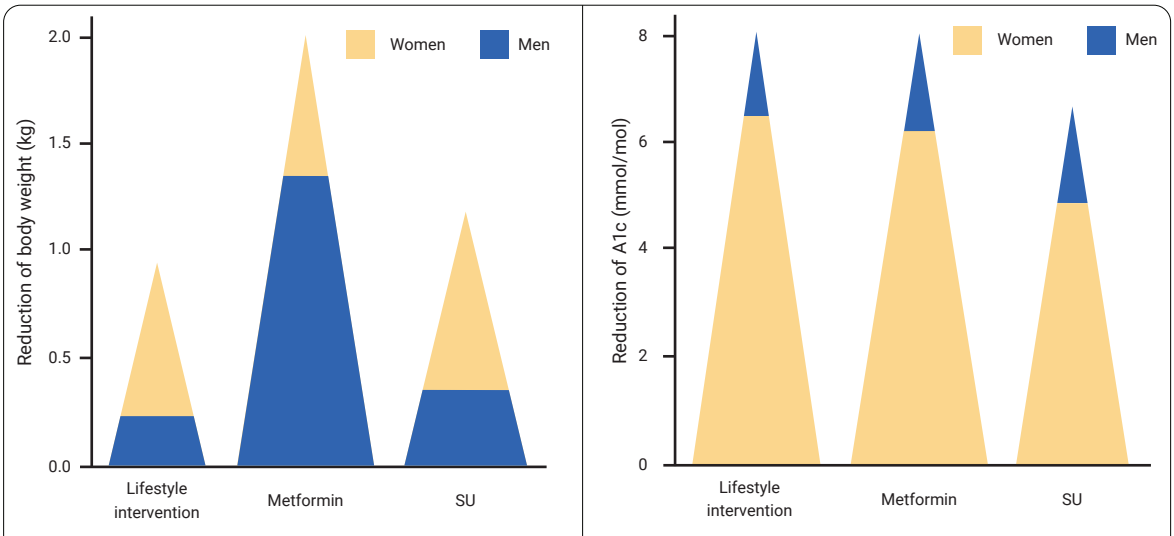


Figure 4: Treatment-related effects on body weight (left) and on A1c (right)

Source: Schütt et al., 2015[15]

Medications affecting the incretin system

A study showed more frequent hypoglycemia in women treated with sitagliptin or alogliptin[9]. Subgroup analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial showed a greater cardio-protective effects of GLP-1 in men than women. In another trial in patients with T2D at high cardiovascular risk receiving semaglutide, only males had a significantly lower rate of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke than among those receiving placebo. In both studies risk reductions was lower and insignificant for women[11].

An evaluation of the effectiveness and tolerability of exenatide showed that women had more gastrointestinal side effects, but also lost more weight and had lower FPG and BP[11].

The Researching Cardiovascular Events with a Weekly Incretin in Diabetes trial included 9,901 participants (mean age 66.2 years [SD 6·5], median HbA1c 7.2%, 4,589 [46.3%] women) showed that dulaglutide was associated with greater reduction in the incidence rate of major adverse cardiovascular events (including non fatal myocardial infarction, non fatal stroke or death from cardiovascular causes) in patients with T2D as compared to the placebo group (12% vs. 13.4%)[16].

Insulin therapy

In a meta-analysis, men on insulin glargine or NPH insulin were more likely to reach HbA1c targets, despite women having a greater reduction in FPG and higher weight-adjusted insulin doses. Hypoglycemic events are both more common and more severe in women, probably due to lower counter-regulatory responses to hypoglycemia in women[14].

Sodium-glucose cotransporter 2 inhibitors

In the post hoc analysis of Empagliflozin Cardiovascular Outcome Event Trial in T2D Patients-Removing Excess Glucose outcome trial, lower rate of cardiovascular death or non fatal myocardial infarction or stroke and lower overall mortality in patients receiving empagliflozin was observed only in males[11].

Incidence of UTI, VVC and balanitis and related genital infections have been reported to be higher among women[11].

Aspirin

In a meta-analysis, aspirin reduced major adverse cardiovascular events in men by 20% but no significant impact was found in women. A subgroup analysis of another meta-analysis concluded that the risk of major adverse cardiovascular events in

patients with diabetes on aspirin therapy was significantly reduced in men, but not in women. Increased platelet reactivity or higher frequency of aspirin resistance of women, could contribute to the sex-dimorph findings regarding protective effects of aspirin use[11].

Recommendation for future research in pharmacotherapy of T2D in women

The sex disparities in drug efficacy and tolerance must be acknowledged. Clinical trials should include pre and postmenopausal women, pregnant women with diabetes and both elderly men and women for high quality research. Future research should focus on protective mechanisms of sex against cardiometabolic, renal and psychological disorders. Research should elucidate on sex dimorphism in central insulin action that may aid in treating obesity related T2D. Sex-specific genetic and epigenetic research could allow for primary and secondary prevention that prioritizes infant and parental behaviour factors[17].

Preventive strategies that are sex-sensitive and culturally appropriate require more research. Preventive trials using glucose-lowering drugs also need to identify adverse events and gender-specific differences[18].

Other recommendations

- Focus on sex analysis in study design including appropriate sample size calculations including hormonal status of participants (pre or postmenopausal, OCs, HRT etc.) and sex-specific reporting of baseline characteristics and results of trials.
- A balanced sex ratio in weight loss programmes and randomized controlled trials with weight loss drugs and in randomized controlled trials including early phases of clinical trials with cardiovascular and antihyperglycemic drugs.
- Analysis of gender differences in drug metabolism, glycemic control, lipid goals, BP, comorbidities and treatment modalities.
- Monitor development of cancers as well as fractures in relation to sex, BMI, diabetes duration and drug therapy.
- Clarify the causes of cardio and cerebrovascular risk in women with diabetes with development of new sex-specific concepts regarding diagnosis and therapy of diabetes and its complications to improve long-term outcome in both sexes[11].

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CHAPTER 7 CARDIOVASCULAR RISKS IN WOMEN WITH DIABETES MELLITUS AND THEIR MANAGEMENT

Dr. Sudha Vidyasagar, Dr. Archana Sarda

Trends of CVD in women with diabetes

CVD is a well-recognized complication of T2D in both men and women. Numerous studies have indicated that people with T2D have a higher risk of CVD than the general population, with women having a significantly higher risk than men[1] (Figure 1).

There were an estimated 6-10 million deaths from CVD in women in 1990, rising to 8-94 million in 2019[3].

The San Antonio Heart Study found that women had a hazard ratio of 4.65 and men had 1.82 for cadiovascular mortality with metabolic syndrome[4].

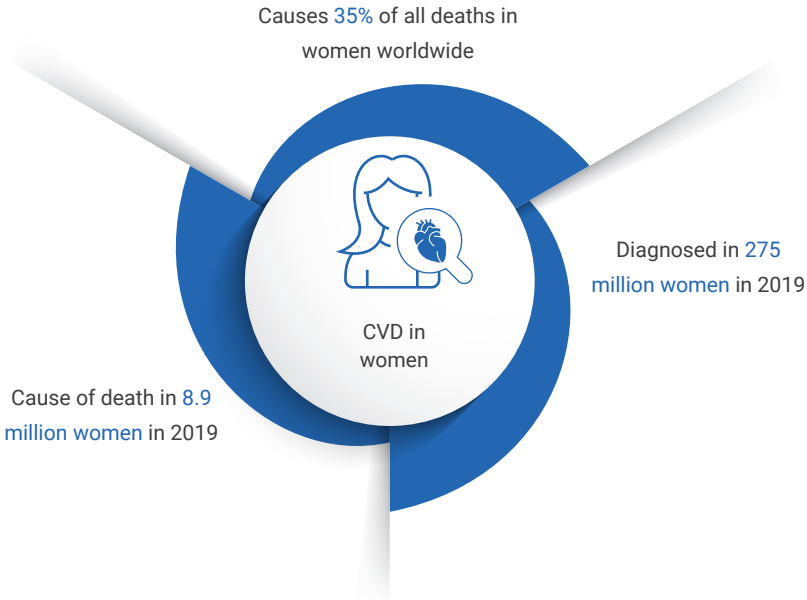


Figure 1: According to the Lancet women and CVD commission

Source: Women and cardiovascular disease[2]

Globally, mortality due to diabetes is higher in women than in men (2.1 vs. 1.8 million annually). Excess risk is mainly due to the higher risk of cardiovascular death in women[5].

Women are 1.8 times more likely than men to develop peripheral artery disease, which is the most common initial manifestation of CVD in patients with diabetes[5].

Women with diabetes are 5 times more likely than women without diabetes to develop heart failure, while men with diabetes are 2 times more likely to get heart failure than men without diabetes[5].

In a meta-analysis of over 800,000 people, women with T2D had a 44% greater RR of CVD than men. Women with T2D have a 3 fold increased risk of fatal CAD, compared to women without diabetes. Women with diabetes have a 5 fold higher risk of fatal CAD than men with T2D. According to an international meta-analysis, a 50 year old man with diabetes has a 5.8 year shorter life expectancy and a 60 year old man with diabetes has a 4.5 year shorter life expectancy than a man of the same age without diabetes. The corresponding estimates for a woman are 6.4 and 5.4 years, respectively. In the Monitoring Trends and Determinants in CVD/Cooperative Health Research in the Region Augsburg study, the risk of myocardial infarction was 4 times higher in men and 6 times higher in women. Notably, women with diabetes have twice the risk of ischemic heart disease as men[6].

Pathogenesis of CVD in diabetes

Multiple cellular and molecular pathophysiologic factors participate in atherosclerotic CVD, creating the "perfect storm" for atherosclerosis. The development and progression of atherosclerosis in DM is presented in Figure 2. Patients with T2D have greater atherosclerotic plaque burden, higher atheroma volume and smaller coronary artery lumen diameter than persons without DM. Numerous processes may contribute to atherosclerotic CVD in DM: like, hyperglycemia, IR or hyperinsulinemia, dyslipidemia, inflammation, reactive oxygen species, endothelial dysfunction, hypercoagulability and vascular calcification (Figure 2)[7].

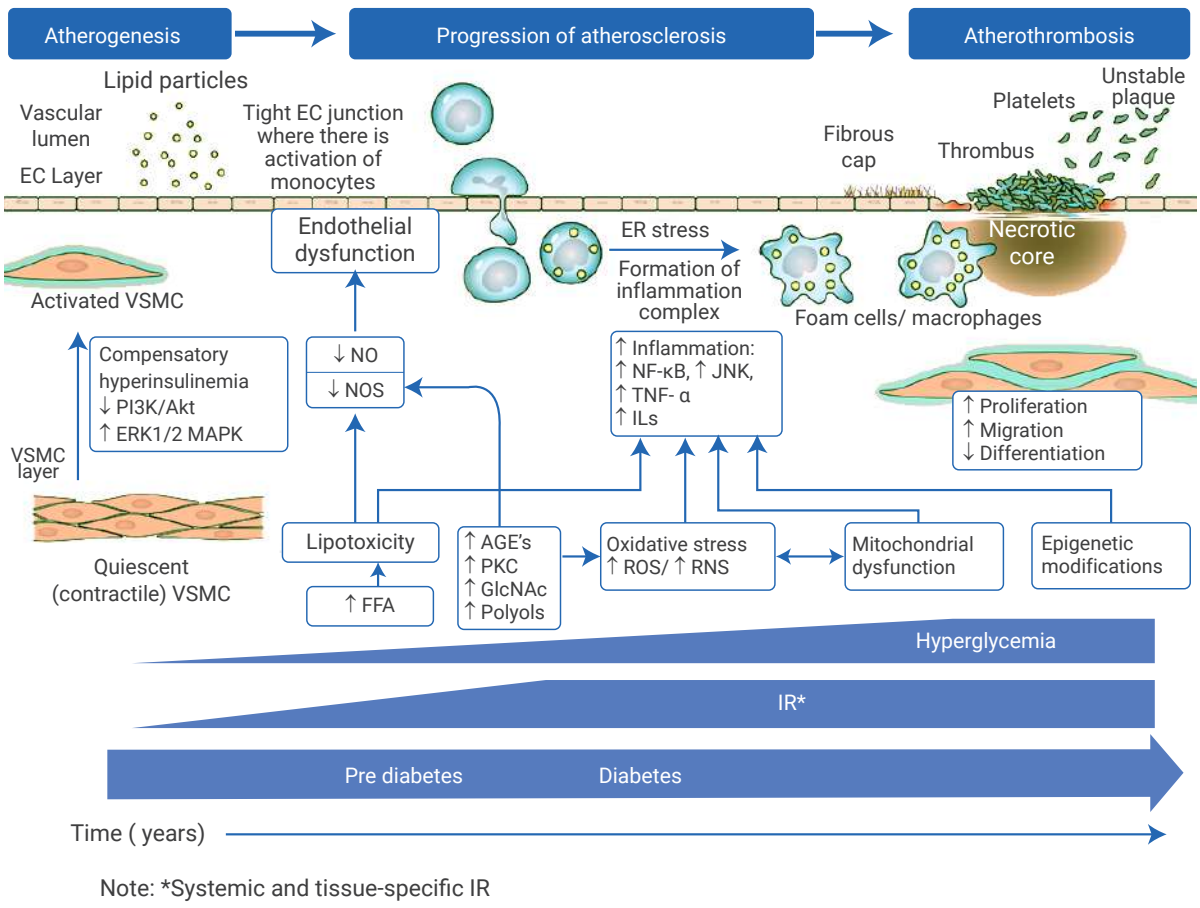


Figure 2: Development and progression of atherosclerosis in DM. IR with impairment of insulin signalling, hyperinsulinemia and hyperglycemia contribute to multiple processes including elevated free fatty acids (FFA), AGE production, protein kinase C (PKC) activation, oxidative stress, mitochondrial dysfunction and epigenetic modifications, which together contribute to endothelial dysfunction and inflammation resulting in activation of vascular smooth muscle cells (VSMC), endothelial cells (EC) and monocytes. Akt: Protein kinase B, ERK: Extracellular signal-regulated kinase, GlcNAc: N-Acetylglucosamine, JNK: c-Jun N-terminal kinase, MAPK: Mitogen-activated protein kinase, NO: Nitric oxide, NOS: Nitric oxide synthase, PI3K: Phosphoinositide 3-kinase; RNS: Reactive nitrogen species ROS: Reactive oxygen species

Source: Low Wang et al., 2016[7]

Cardiovascular risk in women with diabetes: Possible causes

The causes of cardiovascular risk in women with diabetes is presented in Figure 3.

Diabetes increases coronary heart disease risk by 4-6 fold in women with diabetes, compared to 2-3 fold in men with diabetes[8].

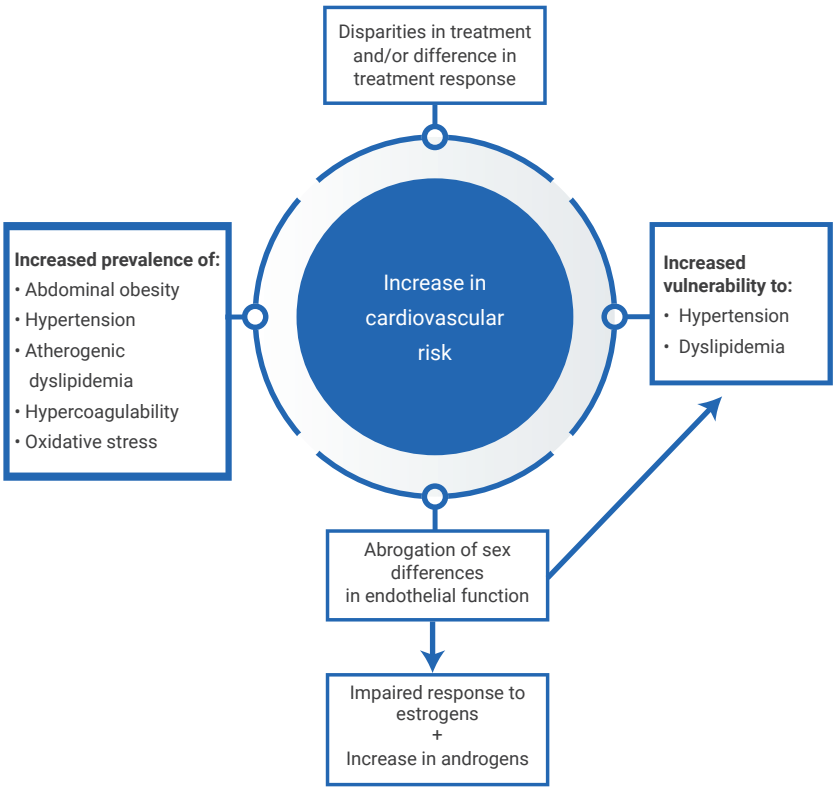


Figure 3: Possible causes of the high cardiovascular risk in women with diabetes

Source: Rivellese et al., 2010[8]

Obesity

Obesity affects women more than men and is rapidly rising globally. Abdominal obesity is higher in women (24.4%) than men (15.6%) that raise cardiovascular risk directly or by clustering with other risk factors such as hypertension, dyslipidemia, IR, subclinical inflammation and physical inactivity[8]. The CVD manifestations and risk factors in obese women is given in Figure 4[9]. A study from South India showed that the prevalence of generalized, abdominal and combined obesity was significantly higher in women and individuals in the age group of 41-50 years[10].

Hypertension

Hypertension is a significant cardiovascular risk factor, prevalence of which is higher in women as compared to men. Several studies have shown higher incidence and prevalence of hypertension in women with diabetes compared to men with diabetes. In the UK Prospective Diabetes Study, 35% of men and 46% of women with diabetes were hypertensive, across all age groups. In the Mind It Study, women with diabetes had significantly greater systolic BP than men. Higher prevalence of hypertension in women with diabetes may be associated with increased prevalence of abdominal obesity (Figure 4). A 10% increase in systolic BP increases the risk of CVD by 30% in women and by 14% in men[8].

Dyslipidemia

The impact of triglycerides and HDL cholesterol on cardiovascular events seems to be greater in women. Almost all studies comparing lipoprotein abnormalities in women and men with diabetes found that regardless of disease duration, medication or ethnicity, women with diabetes have: (1) greater triglyceride values than men with diabetes compared to controls, ranging from 33 to 58% in women and -2 to 27% in men according to a study (Figure 5), a similar trend is seen for VLDL triglycerides;

(2) lower HDL cholesterol and apolipoprotein A1 levels compared to women without diabetes and men with diabetes, with an HDL cholesterol reduction ranging from 13 to 26% in women with diabetes and 2 to 17% in men with diabetes; (3) higher apolipoprotein B levels; (4) a greater decrease in LDL size and a predominance of the LDL B pattern on electrophoresis[8].

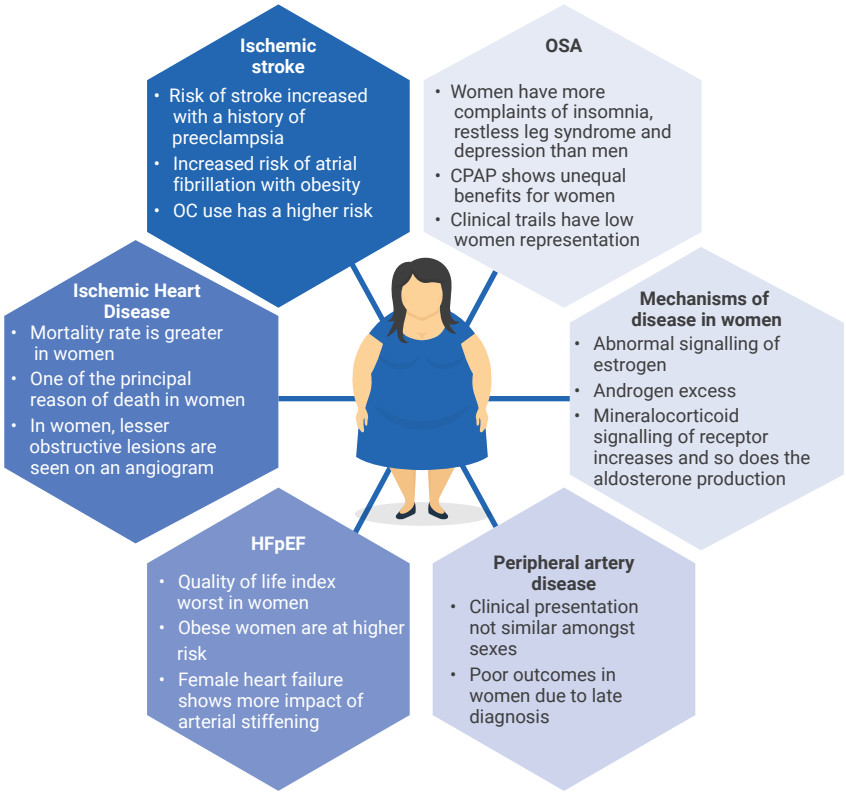


Figure 4: CVD manifestations and risk factors in obese women. CPAP: Continuous positive airway pressure, HFpEF: Heart failure with preserved ejection fraction

Source: Manrique-Acevedo et al., 2020[9]

Women have greater adipose tissue stores and heightened free fatty acid mobilization during fasting leading to a larger supply of substrates to the liver, where uptake, esterification to triglycerides and VLDL secretion appear to be also increased and estrogen-driven. This higher hepatic VLDL secretion together with an equivalent defect in their removal may result in higher VLDL concentrations in women with diabetes compared to men. The reduced removal of VLDL from the circulation may also account for the lower increase in HDL cholesterol levels that occurs in T2D women. Studies have suggested that greater frequency of these lipid abnormalities in women with diabetes compared with men may be due, at least in part, to the higher prevalence of abdominal obesity and, therefore, greater IR in women with diabetes[8].

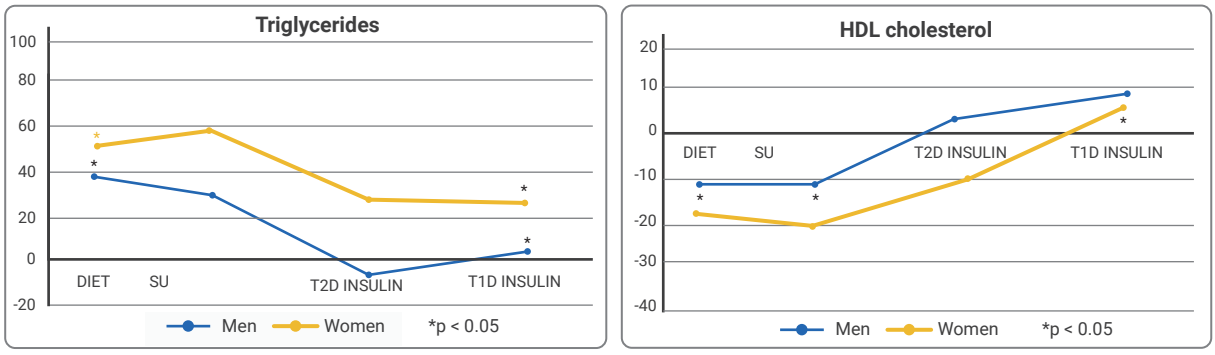


Figure 5: The diabetes-associated change in triglyceride and DL cholesterol levels from a healthy comparison group. Changes in women are consistently greater than in men

Source: Rivellese et al., 2010[8]

Factors modulating gender difference in CVD in diabetes

The possible causes of the gender differences in CVD is presented in Figure 6[11].

Cardiovascular risk factors

The prevalence of cardiovascular risk factors is generally higher in women with diabetes than in those without it. These risk factors include waist-to-hip ratio, obesity, IR, dyslipidemia, hypertension, coagulation factors, endothelial dysfunction and systemic inflammation (Figure 6). Endothelial function has been shown to be impaired to a greater extent in premenopausal women with T2D than in men with T2D. Furthermore, low grade inflammation can disturb insulin action in women and inflammatory factors may interact with female sex hormones, reducing the protective effects of estrogens on body fat distribution and insulin action[11]. Greater prevalence of CVD risk factors in urban middle-aged women is explained by greater income and literacy, dietary fat, low physical activity and obesity[12].

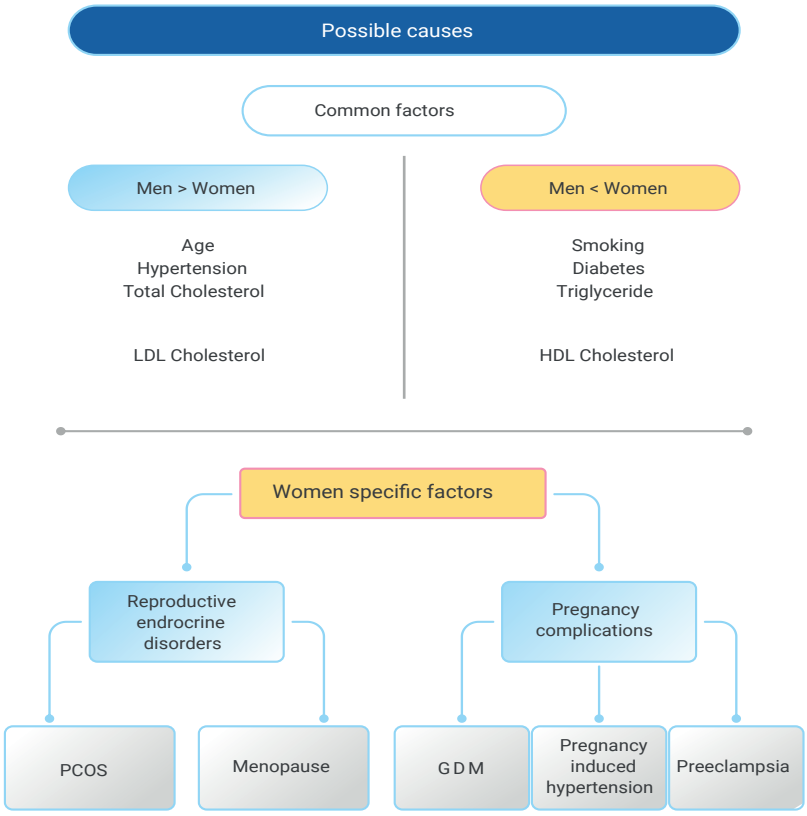


Figure 6: Possible causes of the gender differences in CVD

Source: Gao et al., 2019[11]

Sex hormones and diabetes

Endogenous sex hormones may play a role in the development of T2D. Association between endogenous testosterone and risk of T2D show significant sex differences. Testosterone levels are related to increased risk of developing T2D in postmenopausal women. Androgen excess in women likely impairs insulin action as seen in women with PCOS. Increased cardiovascular risk in postmenopausal women may be due to loss of endogenous estrogen protection[13]. The reduction of testosterone and estrogen is associated with higher cardiac risk in both males and females[14] (Figure 7).

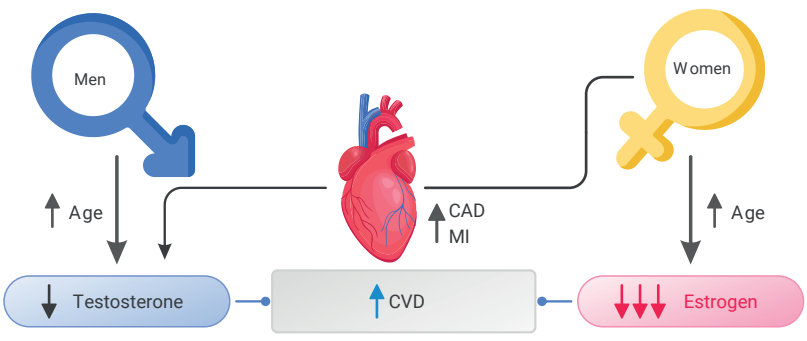


Figure 7: Schematic diagram of the influence of sex hormones on CVD.
↑ indicates upregulation and ↓ indicates downregulation. MI: Myocardial infarction

Source: Rodgers et al., 2019[14]

The relationship of female-specific risk factors with CVD is given in the Table 1.

Table 1: Female-specific risk factors associated with CVD

	Weak association	Moderate association	Strong association
PCOS	CVD, hypertension	-	T2D
Primary ovarian insufficiency	-	CVD, coronary heart disease	-
Pregnancy-induced hypertension	Coronary heart disease, stroke	CVD, T2D	Hypertension
Preeclampsia	-	CVD, Coronary heart disease, stroke, T2D	Hypertension
GDM	-	CVD, Coronary heart disease	Hypertension, T2D
Preterm birth < 37 weeks	Coronary heart disease, hypertension	CVD, stroke, T2D	-

Source: Gao et al., 2019[11]

Polycystic ovarian syndrome

PCOS affects 5-10% of women of reproductive age and is the most common endocrine disease in women. A women's ischemic syndrome assessment study showed that postmenopausal women with PCOS have higher clustering of coronary heart disease risk factors and higher coronary heart disease event rates. T2D, chronic hypertension and dyslipidemia are common in PCOS women. A meta-analysis indicated that PCOS tripled the risk of metabolic syndrome[11].

Menopause

Menopause marks a transition from reproductive to non-reproductive life that is associated with changes in the endocrine system associated with cardiovascular health. The age of menopause affects changes in estrogen and androgen and is associated with differences in the risk of CVD. A meta-analysis showed that early menopause (< 50 years) was independently correlated with coronary heart disease (RR 1.38) and the early menopause caused by surgical removal of ovaries (RR 4.55). Very early menopause (< 40 years old) or primary ovarian insufficiency, occurs in 1-2% of women is also associated with increased risk of coronary heart disease and total CVD[11].

Pregnancy complications

Planned pregnancies along with risk factor reduction prior to pregnancy can reduce women's CVD risk in long term. Preeclampsia confers a 4 fold increased risk of hypertension later in a woman's life, triples the risk of a CVD event in her lifet-

me and doubles her future stroke risk. A reduction of 10 or more pounds reduces the risk of GDM by 40% and a gain of 10 or more pounds, increases the risk by 50%. Within 5-15 years after pregnancy, 15-60% of women with GDM develop diabetes[15]. The complications from prepregnancy obesity is presented in Figure 8.

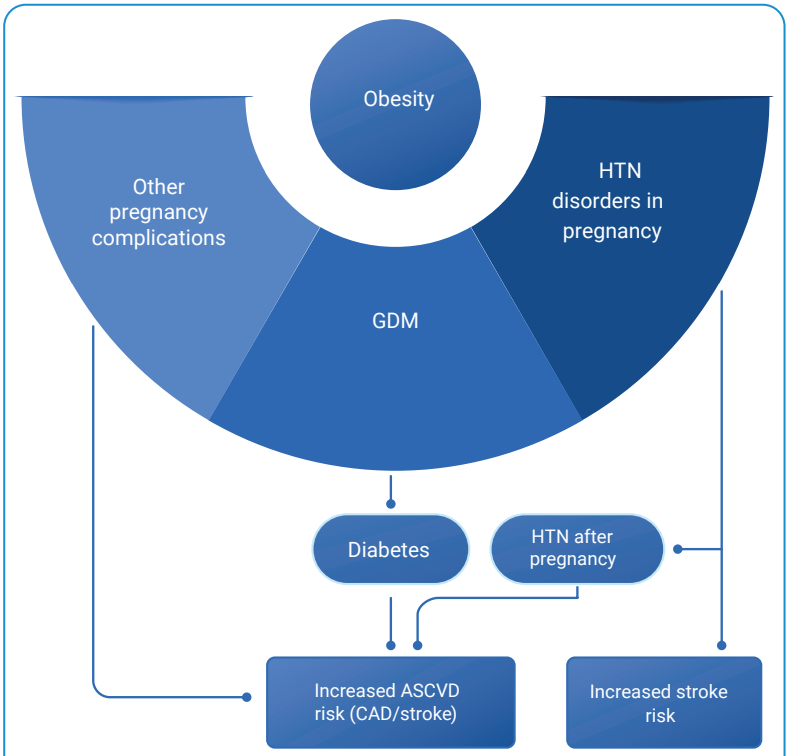


Figure 8 : Cascade of complications from pre pregnancy obesity. HTN: Hypertension; ASCVD: Atherosclerotic cardiovascular disease

Source: Gill SK, 2015[15]

Stroke

Data from the 2019 US Heart Disease and Stroke Statistics showed that 58.2% of total stroke deaths occurred in women. Stroke incidence has been found to be high in women aged 25-34 years compared with similarly aged men[2].

A European study found that women were less likely to receive brain imaging, carotid ultrasound and ECG than men[2].

The International Stroke Outcomes Study indicated that women had inferior health related quality of life after stroke than men. Women are more likely to have pre-existing depression, which raises stroke risk and morbidity and mortality after stroke than men. Data from the UK Biobank showed that hypertension was more strongly associated with the risk of any stroke and stroke subtypes in women than in men[2].

In a pooled analysis of 64 cohorts, with data for more than three quarters of a million individuals and more than 12,000 fatal and non-fatal stroke events, diabetes was a stronger risk factor for stroke in women than in men. Compared with men with diabetes, women with diabetes have been found to have a 27% greater RR for stroke[16].

Pregnancy and the use of OCs may increase the risk of stroke in women in their mid 30s to mid 40s, whereas their relative longevity may increase the risk in older women. Diabetes is a well-established independent risk factor for stroke, conferring a 2-3 times increase in RR. The UK Prospective Diabetes Study found that women with diabetes had twice the risk of stroke fatality as men with diabetes. Factors such as pregnancy and the use of OCs are believed to contribute to the increased risk of stroke in women in their mid 30s to mid 40s and their relative longevity contributes to the higher risk of stroke in older women. It has also been hypothesized that greater elevation of risk factors in the pre-diabetic state in women (compared with men) could also contribute to the increased risk of stroke in women with diabetes[17].

Pathophysiology

There are several possible mechanisms in diabetes including vascular endothelial dysfunction, increased early age arterial stiffness, systemic inflammation and thickening of the capillary basal membrane that leads to stroke[18]. The mechanisms of stroke in individuals with diabetes is given in Figure 9.

Heart failure

Women and men have the same overall incidence of heart failure, but women are associated with increased prevalence of heart failure with preserved ejection fraction, especially in the older age groups. In patients with incident heart failure with preserved ejection fraction, women outnumber men by almost 2:1. Heart failure has a significant morbidity due to high symptom burden and frequent hospitalizations and 5 year survival was 44% according to a UK analysis published in 2019. Women with heart failure also have lower quality of life, higher incidence of depression, or both, compared with men[2].

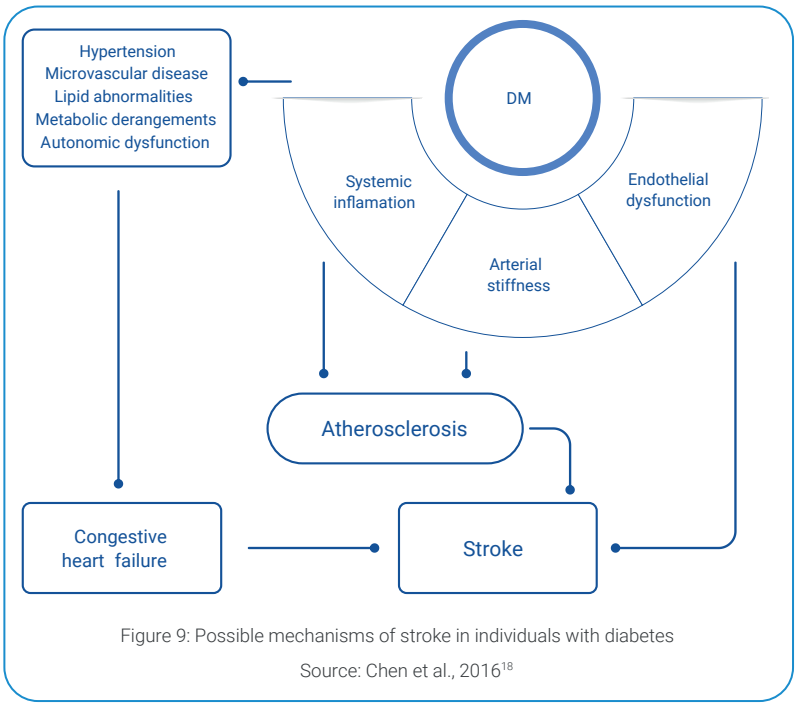


Figure 9: Possible mechanisms of stroke in individuals with diabetes

Source: Chen et al., 2016[18]

Inflammation is suggested to be crucial in heart failure with preserved ejection fraction progression. Noncardiac comorbidities such as hypertension, diabetes, CKD, obesity, iron deficiency and preeclampsia may contribute to inflammation in the myocardium. Combined with the increased immune function in women, inflammation is a major factor in the female predominance in heart failure with preserved ejection fraction. These factors that determine cardiac structure and function, along with underlying differences in diastolic function, are represented in the Figure 10[19].

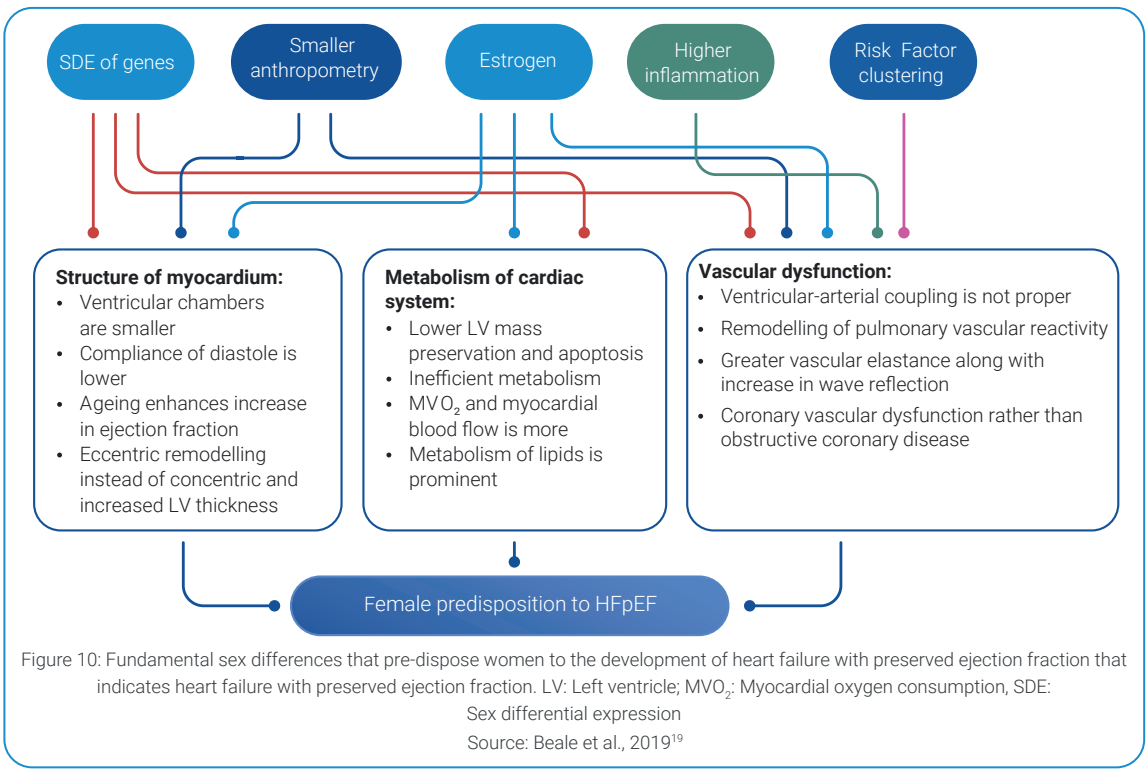


Figure 10: Fundamental sex differences that pre-dispose women to the development of heart failure with preserved ejection fraction that indicates heart failure with preserved ejection fraction. LV: Left ventricle; MVO_2: Myocardial oxygen consumption, SDE: Sex differential expression

Source: Beale et al., 2019[19]

There is also an increasing trend towards rising numbers of ischemic heart disease in women in India, with the constellation of risk factors of atherosclerosis including diabetes. Kiran et al. found that ischemic heart disease is increasing more in women than in men in the Indian population based on a registry based analysis[20].

Noncardiac comorbidities

Comorbidities including iron deficiency, DM, obesity, preeclampsia, hypertension and autoimmune diseases contribute to heart failure with preserved ejection fraction risk through cardiac structural and functional changes and systemic inflammation. Comorbidities that have a pronounced effect on cardiac remodelling in women, further predisposing them to heart failure with preserved ejection fraction are demonstrated in in Figure 11[19].

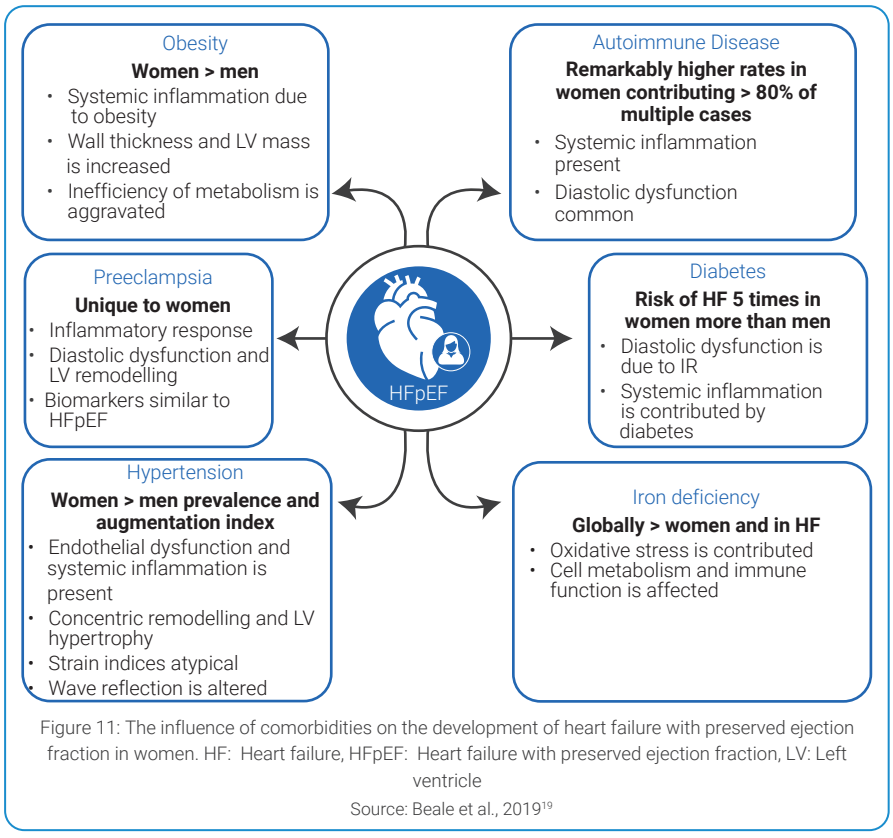


Figure 11: The influence of comorbidities on the development of heart failure with preserved ejection fraction in women. HF: Heart failure, HFpEF: Heart failure with preserved ejection fraction, LV: Left ventricle

Source: Beale et al., 2019[19]

Recommendations for future cardiovascular trials in women

Female exclusion from CVD trials is a recognized barrier in making clinical recommendations for prevention of CVD in women. Among randomized controlled trials, cited by the women's guidelines, 87% included both women and men. A review of randomized controlled trials indicated that women made up only 37% of participants. Only 35% of studies presented analyses by sex, 11% did not offer sex analyses but provided an explanation and 64% did not present sex analyses, did not provide an explanation or both[21].

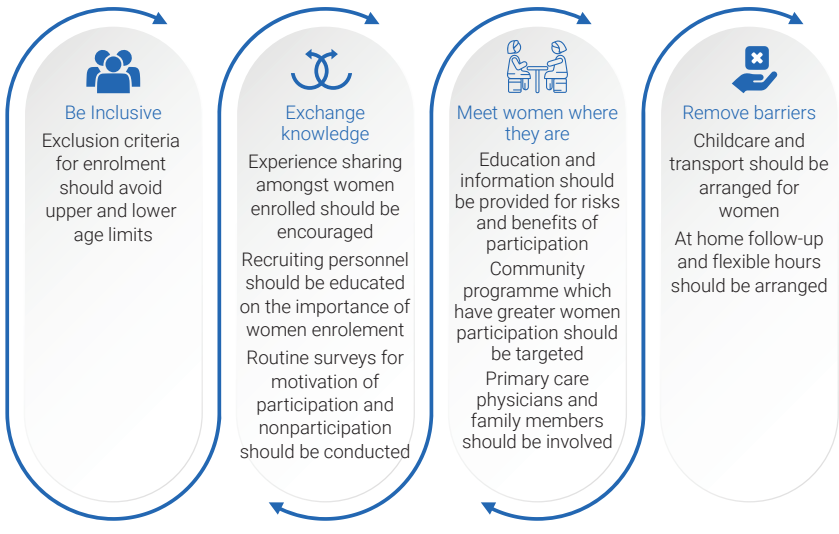


Figure 12: Strategies to increase the proportion of women in cardiovascular trials

Source: Women and cardiovascular disease[2]

The Lancet women and CVD commission lays out recommendations for increasing the proportion of women in cardiovascular trials[22] and is presented in Figure 12.

Other recommendations:

- Cardiovascular endpoints should encompass all acute coronary syndromes, fatal coronary heart disease, stroke (thromboembolic and hemorrhagic) and heart failure for women.
- Reasons for non-adherence to interventions should be documented according to gender.
- Dissemination of results should include gender disparities in efficacy and adverse effects[21].
- Early phase trials should include pre and postmenopausal women, pregnant women with diabetes and elderly men and women.
- Potential sex disparities in medication efficacy and tolerance should be explored.
- Future research should focus on the causes of loss of female vascular protection in women with diabetes and possible solutions and better understanding of sex protection against cardiometabolic, renal and psychological disorders.
- Individualized sex specific screening programme and therapies must be implemented and assessed for their efficacy.
- Future T2D management guidelines should incorporate sex and gender disparities.
- Future guidelines for the management of T2D, as well as its complications should consider sex and gender differences[22].

Management recommendations from guidelines

Recommendations for the management of BP in patients with diabetes and prediabetes

- A renin-angiotensin-aldosterone system blocker ACEi or ARB is recommended in the treatment of hypertension in patient with DM, particularly in the presence of microalbuminuria, albuminuria, proteinuria or left ventricular hypertrophy[23].

Recommendations for the management of dyslipidemia with lipid-lowering drugs

- Statins are recommended as the first choice lipid-lowering treatment in patients with DM and high LDL cholesterol levels.
- Statins are not recommended in women of childbearing potential[23].

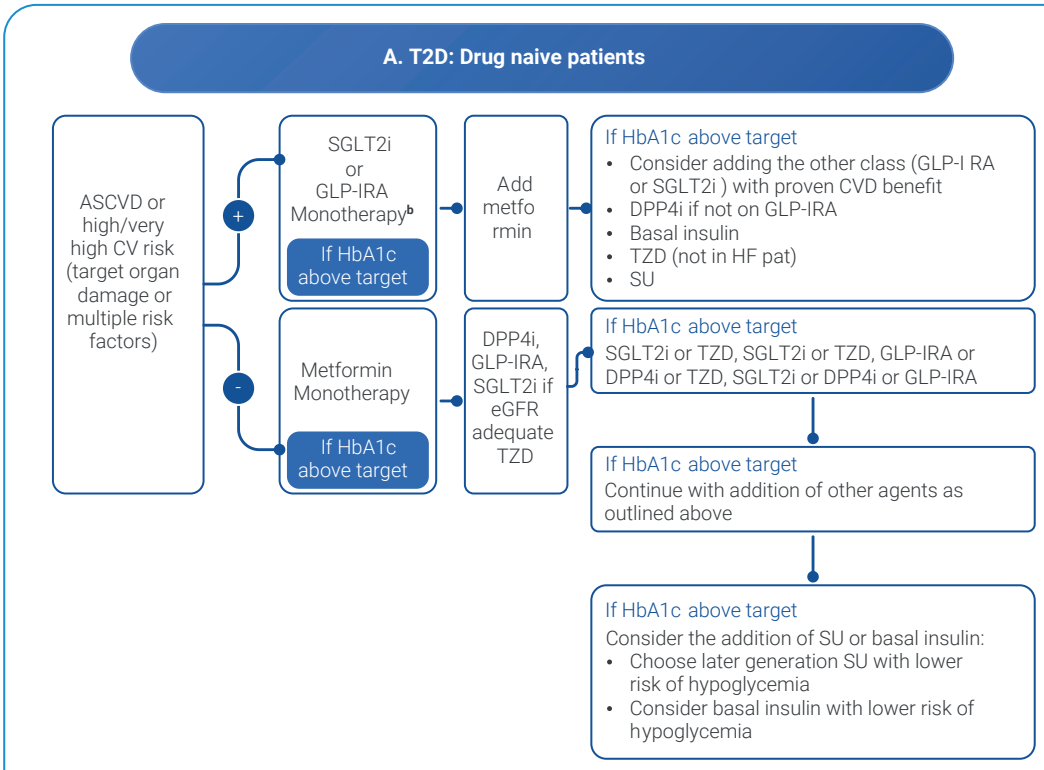
Lifestyle intervention (with a focus on weight reduction and decreased consumption of fast absorbed carbohydrates and alcohol) and fibrates should be considered in patients with DM and pre-DM with hypertension and low HDL cholesterol and high triglyceride levels[23].

Recommendations for the use of antiplatelet agents from the ADA 2021

- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic CVD[24].

Treatment algorithm in patients with T2D and atherosclerotic CVD or high/very high cardiovascular risk

Treatment algorithm in patients with T2D and atherosclerotic CVD, or high/very high cardiovascular risk is presented in Figure 13.



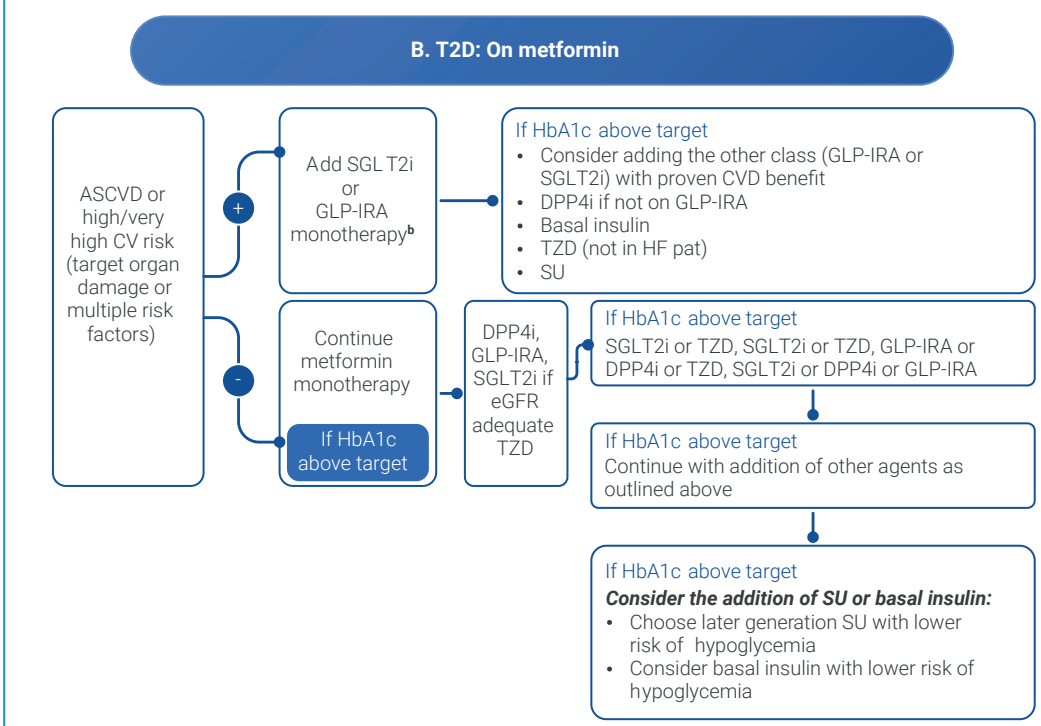


Figure 13: Treatment algorithm in patients with T2D and atherosclerotic CVD or high/very high cardiovascular risk
Treatment algorithms for (A) drug-naïve and (B) metformin-treated patients with DM. ASCVD: Atherosclerotic CVD, CV: Cardiovascular, HF: Heart failure

Source: Cosentino et al., 2020[23]

Among patients with T2D who have established atherosclerotic CVD or established kidney disease, a SGLT2i or GLP-1RA with demonstrated CVD benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens[24].

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CHAPTER 8 MICROVASCULAR COMPLICATIONS IN WOMEN WITH DIABETES AND THEIR MANAGEMENT

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Vascular complications, both microvascular and macrovascular, are a leading cause of morbidity and mortality in men and women with T1D and T2D[1]. Macrovascular complications of diabetes are covered in Chapter 7. This chapter will discuss the microvascular complications in diabetes and their management.

Microvascular complications in women with diabetes

The prevalence rates of diabetes related microvascular complications reported from cross-sectional studies across India range from 13 to 52.1% in T2D[2–8]. Indian data on microvascular complications in T1D is scarce and covered in Table 1.

Asian Indians with T2D have a lower risk of microvascular complications as compared to white population[9]. The prevalence of DR in India is lower compared with western populations[9]. The prevalence of diabetic nephropathy in migrant Asian Indians is higher than that of native populations of the concerned countries[9]. Asian Indians have significantly lower rates of neuropathy compared with Europeans ($p < 0.02$)[10].

Table 1: Incidence and prevalence of diabetic microvascular complications in India

Publication (Year) (Number of subjects)	Type of diabetes	Geographical region	Retinopathy	Neuropathy	Nephropathy
Age adjusted incidence (per 1,000 person years)					
Amutha et al, (2021) (n= 4,555)[11]	T1D (childhood and adolescent-onset)	South India	52.9 (CI, 42.9-62.8)	8.8 (CI, 3.6-14)	6.2 (CI, 3.3-9)
Amutha et al (2021) (n= 4,555)[11]	T2D (childhood and adolescent-onset)	South India	49.8 (CI, 30.8-68.8)	24.0 (CI, 9.8-38.2)	13.8 (CI, 5.6-22)
Publication (Year) (Number of subjects)	**Type of diabetes**	**Geographical region**	**Retinopathy (%)**	**Neuropathy (%)**	**Nephropathy (%)**
Govindarajan et al, (2020) (n=390)[8]	T2D	South India (rural set-up)	-	44.9%	12.1%
			Overall prevalence of microvascular complications: 52.1%		
Sinha and Kishore (2019) (n=100)[5]	Newly diagnosed T2D	North India	-	-	Male: 21.66% Female: 15%
Sudhanshu et al, (2019) (n=164)[12]	T1D	North India	3.6	-	3
Agrawal et al, (2017) (n=11,157)[7]	T2D	Northwest India	32.5	26.8	30.2
Bansal et al, (2014) (n=449)[2]	T2D	North India	9.5	8.2	2.8
Gill et al, (2014) (n=195)[4]	Newly diagnosed T2D	North India	-	29.2	-
Raman et al (2012) (n=1,414)[3]	T2D (both known and newly diagnosed)	South India	4.8	10.5	10.5
			Any microvascular complication: 30.2%		
Pradeepa et al, (2010) (n = 1,736)[6]	T2D	Urban South India	17.5	25.7	26.5
Sudhanshu et al, (2019) (n=164)[12]	T1D	North India	3.6	-	3
Agrawal et al, (2017) (n=11,157)[7]	T2D	Northwest India	32.5	26.8	30.2

Bansal et al (2014) (n=449)[2]	T2D	North India	9.5	8.2	2.8
Gill et al. (2014) (n=195)[4]	Newly diagnosed T2D	North India	-	29.2	-

Microvascular complications of diabetes include in the following Box[11,13,14]:

Box 1

Microvascular complications
DR
Diabetic neuropathy, diabetic autonomic neuropathy, diabetic peripheral neuropathy (mononeuropathy, plexopathy, radiculopathy, polyneuropathy, food disease)
Diabetic nephropathy

Diabetic nephropathy

The treatment of diabetic nephropathy in women is same as in men and includes[15]:

1. Optimizing glucose control.
2. Optimizing BP control.
3. Managing protein intake.
    - For women with non-dialysis dependent CKD, dietary protein intake should be as per RDA.
    - Approximately 0.8 g/kg body weight/day.
    - For women on dialysis, consider higher dietary protein intake in malnutrition cases.

Women with T2D

1. Consider SGLT2i if eGFR ≥ 30 mL/min/1.73 m^2 and urinary albumin > 300 mg/g creatinine.
2. In women with CKD at increased risk for cardiovascular events, use of a GLP-1RA reduces progression of albuminuria, and cardiovascular events[15].

Women with hypertension

1. Treat with ACEi or ARB[15]:
    - Recommended in modestly elevated urinary ACR (30–299 mg/g creatinine).
    - Strongly recommended for urinary ACR ≥ 300 mg/g creatinine and/or eGFR < 60 mL/min/1.73 m^2.
    - ARB need not be discontinued for minor serum creatinine increases (< 30%) in the absence of volume depletion.
    - ACEi/ARB is not recommended for primary CKD prevention in women with normal BP, normal urinary ACR (< 30 mg/g creatinine), and normal eGFR.
2. Periodically monitor serum creatinine and potassium levels when ACEi/ARB/diuretics are used.

Women with diabetic nephropathy should be referred to a nephrologist if eGFR < 30 mL/min/1.73 m^2 or if unsure of management or progressive disease[15].

Prenatal counselling

Diabetic nephropathy is associated with adverse pregnancy outcomes. Eclampsia and preeclampsia results in deterioration of kidney function (serum creatinine >176 µmol/L) in the mother and preterm delivery, and placental dysfunction which causes fetal intrauterine growth restriction and fetal distress[16]. Women with diabetic nephropathy have a higher prevalence of severe congenital malformations than women with diabetes and normal kidney function[16]. Hence, women with diabetic nephropathy, planning to become pregnant should receive prepregnancy counselling regarding adverse maternal and fetal outcomes and need for strict glycemic control and regular follow-ups[16].

Pre-pregnancy ACE inhibitors combined with strict metabolic control given for ≥ 6months until reduced albumin excretion is associated with higher chances of successful pregnancy outcome[16].

Medical management

ACEi not recommended during pregnancy

ACEi are stopped as soon as pregnancy test comes positive due to increased risk of congenital malformation with their use in first trimester[16]. Also, ACEi use in last trimester is associated with abnormal fetal renal development and renal failure[16]. Hence, other antihypertensive medications regarded safe in pregnancy, such as methyldopa, β-blockers (labetalol) or calcium antagonists should be used[16].

Pregnancy monitoring in pregnant women with diabetic nephropathy

Pregnant women with diabetic nephropathy require more frequent monitoring than pregnant women without diabetic nephropathy[16].

Throughout pregnancy (frequency dependent on severity) monitoring is required to assess[16]:

- Clinical control, including BP and protein excretion.
- Intrauterine growth restriction.
- Monitor serum urate, serum creatinine and thrombocyte if preeclampsia is detected.

In late pregnancy monitoring is required to[16]:

- Diagnose complications.
- Assess flow profile in the umbilical artery or the uterine artery if required.
- Prevent stillbirths: cardiotocography may be performed once or twice weekly to detect cardial morbidity and prevent stillbirth.
- Give glucocorticoid treatment for preterm delivery before 34 gestational weeks.
- Plan the time of delivery.

Diabetic retinopathy

DR is the most common microvascular complication of diabetes[17]. DR is mainly of two types: NPDR and PDR. Of the two, PDR is the more advanced disease characterized by neovascularization, which leads to increased risk for vision loss due to development of neovascular glaucoma, or by tractional retinal detachment, or occurrence of vitreous hemorrhage[18]. DME is a major cause of vision loss in diabetes, especially in India[17]. Disruption of blood retina barrier can occur at any stage in diabetes and results in fluid accumulation at or near the macula. This affects the structural arrangement of the photoreceptors in the foveola, resulting in vision loss[18].

Treatment of DR in women is same as in men and includes[15]:

1. Optimizing glucose control.
2. Optimizing BP and serum lipid control.
3. Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk PDR and in some severe NPDR cases.
4. Intravitreous anti-VEGF injections are not inferior to panretinal laser photocoagulation and are also indicated in PDR to reduce the risk of vision loss.
5. Intravitreous anti-VEGF injections are indicated for central (occurs beneath the foveal center) involved DME that may threaten reading vision.
6. Aspirin therapy for cardioprotection can be continued in women with retinopathy, as aspirin does not increase the risk of retinal hemorrhage. Patients with any level of macular edema, severe NPDR should be immediately referred to an ophthalmologist experienced in DR management[15].

Special considerations: DR and pregnancy

Prenatal counselling

The management of DR should begin before conception in the form of preconception counselling. Most DR management guidelines (AAO, ADA, Canadian, and SIGN) stress that this time period should be used to address all issues related to glycemic control, hypertension and the retinopathy treatment[15,19–22].

Medical management

The usual treatment advocated for glycemic control during pregnancy should be followed.

Laser photocoagulation (recommended)

Pregnant women with PDR can be safely treated with pan retinal laser photocoagulation[19,22] .The procedure is as effective as in non-pregnant women; however, it may need to be performed at an earlier stage as compared to non-pregnant women[19,23]. Scatter laser photocoagulation at an earlier stage than non-pregnant women is recommended for severe NPDR or worse[19,20,22]. Photocoagulation should be done prior to conception in women with severe NPDR or worse.

Anti-VEGF agents (not-recommended)

Sight threatening DME can occur during pregnancy[24]. Earlier, the primary goal of treating DR was to prevent severe vision loss. However, with the advent of anti-VEGF agents, there has been a paradigm shift in the goal towards preservation or even improvement of vision[25]. However, given the short duration of pregnancy, and embryo–fetal developmental risk of intra-vitreal anti-VEGF[26,27], the treatment should be delayed until postpartum[25]. Also, women taking anti-VEGF agents should wait for at least 3 months after last dose before conceiving[25].

Monitoring of DR in pregnant women

There is no evidence-based consensus on the frequency of monitoring DR during pregnancy. Despite this, all guidelines recommend a first trimester eye examination to be done as soon as possible where preconception screening was missed; that may be delayed if screening was done within 3-6 months prior to pregnancy[25]. Most guidelines recommend a second and third trimester retinal exam based on level of DR detected in first trimester and on the presence of diabetic risk factors[19–22,28,29]. Additional need-based exams may be done during pregnancy based on the level of clinical and retinopathy deterioration[25]. ADA, Canadian and NICE guidelines recommend a postpartum follow-up at 6-12 months[20,22,29].

Diabetic neuropathy

Specific treatment for the underlying nerve damage in diabetic neuropathy is currently not available[15]. Symptomatic management of diabetic neuropathy in women is same as in men and includes[15]:

1. Optimizing glucose control; however this will not reverse sensory loss.
2. Autonomic neuropathy recognition and treatment is important as it improves symptoms, reduces sequelae, and improves quality of life.
3. Treatment of autonomic neuropathies is symptomatic.
5. Pain relief strategies (pharmacologic and non-pharmacologic) may bring pain relief.

Special considerations: Diabetic neuropathy and pregnancy

Pregnancy does not appear to alter the course of autonomic neuropathy[30]. However, women may develop mononeuropathy, plexopathy, radiculopathy or polyneuropathy during pregnancy or postpartum. Therefore, careful monitoring of glycemic control is required. Treatment is symptomatic; pain relief drugs safe in pregnancy should be used. Early referral to foot care clinics may prevent foot ulcers in high risk cases[14,30].

Risk factors of microvascular complications in diabetes

The general risk factors for diabetes related microvascular complications are covered in Table 2. Also, as shown in Table 2, presence of one microvascular complication increases the risk for another.

Table 2: Risk factors for diabetes related microvascular complications

Risk factor	Diabetic microvascular association	Level of association
	General risk factors	
Early age at onset	Multiple microvascular	Significant (p = 0.003)[31]
	Complications	
Older age	Multiple microvascular complictations	Significant (p < 0.001)[2]
Age	Retinopathy, neuropathy	Significant[7]
Family History	Retinopathy	Significant (p = 0.016)[32]
	Neuropathy	Significant (p < 0.001)[33]
	Nephropathy	Significant (p = 0.005)[33]
High HbA1c	At least one microvascular complication	Significant (p < 0.01)[2]
	Neuropathy	Significant (p < 0.01)[2]
	Multiple microvascular complications	Significant (p < 0.001)[2]
	At least one microvascular complication	Significant (p = 0.047)[2]
	Neuropathy and nephropathy	Increased risk[7]
	NPDR	Significant (p = 0.045)[2]
	PDR	Significant (p = 0.03)[2]
High triglyceride	Multiple microvascular complications	Significant (p = 0.005)[2]
	At least one microvascular complication	Significant (p = 0.011)[2]
	Neuropathy	Significant (p = 0.05)[2]
	NPDR	Significant (p = 0.02)[2]
	Nephropathy	Significant (p = 0.032)[2]

Duration of diabetes	Neuropathy, nephropathy	Significant[7]
Hypertension	Nephropathy	Hypertension is associated with nephropathy[7]

Risk relationship between microvascular complications

- Nephropathy was dependent on retinopathy[2]
- The risk of nephropathy and neuropathy was significantly higher ($p < 0.0001$ for both) in patients with sight-threatening retinopathy compared to those without DR[6]
- The risk of nephropathy and neuropathy was significantly higher ($p < 0.0001$ for both) in patients with sight-threatening retinopathy compared to those without DR[6]
- Diabetic neuropathy is associated with the development of diabetic retinopathy and nephropathy[34]
- Diabetic cardiac autonomic neuropathy has a strong correlation with DR and diabetic neuropathy[34]

Women with diabetes have a 13% greater risk of diabetes related all-cause mortality as compared to men (pooled RR 1.13, 95% CI. 1.07 - 1.19, $p < 0.001$)[35]. Hence, it is very important to identify the risk factors specific to women. These women-specific risk factors increase the risk of microvascular complications throughout the life cycle of women with diabetes, starting at menarche and continuing through the child bearing age and menopause. Women-specific risk factors for diabetic microvascular complications are enumerated in Table 3.

Table 3: Women-specific risk factors for diabetes related microvascular complications

Risk factor	Diabetic microvascular association	Level of association
Female gender	Overall risk for any microvascular complications	Significantly more women with diabetes have any microvascular complication than men with diabetes ($p < 0\ 0001$)[31]
	Neuropathy	• Negative association ($p = 0.01$)[2] • Renoprotective effect is lost in diabetes (both T1D and T2D)[36,37]
Delayed menarche (> mean age + 2 years) (FinnDiane Study)	Microvascular complications	Increased risk[38]
	Nephropathy	• 2.3 times higher risk than women with normal age menarche ($p < 0.006$)[38] • Each annual increase in age at menarche increased overt nephropathy by 1.24 times ($p = 0.02$)[39] • Delayed menarche increased overt nephropathy by 3.2 times ($p = 0.009$) as compared with women with normal onset menarche[39]
	Retinopathy	• Increased risk[38] • Age at menarche not associated with proliferative retinopathy or confirmed distal symmetric polyneuropathy[39]
Pregnancy	Retinopathy	• Independent risk factor for worsening of diabetic retinopathy[25] • Progression in pregnant women occurs at double the rate compared to non-pregnant women[40] • Presence of other risk factors such as poor glycemic control, longer duration of diabetes, hypertension, and higher baseline retinopathy level further increases the risk in pregnant women[25]

Inter-relationships between microvascular and macrovascular complications

Though micro- and macro-vascular complications have their distinct mechanism, pathophysiology, risk factors and management, they have several intersecting pathways that connect them[34].

Retinal and cerebral vasculatures have an inter relationship because of common embryologic and anatomic characteristics[34]. Hence, retinal microvascular abnormalities and retinopathy have been found to be associated with increased incidence of clinical stroke, combined stroke events, CVD, myocardial infarction and death due to CVD[41–45]. The level of association became stronger with severity of retinopathy[43,45].

Evidence shows that microalbuminuria (as seen in nephropathy) is directly associated with macrovascular complications[34]. Both abnormalities are associated with presence of reactive oxygen species, advanced glycation end products, and activated intracellular signaling molecules[34]. Apart from severe DR, nephropathy has also been found to be linked to increased risk of all stroke types and cardiovascular events[45–47].

Even though the precise nature of injury in diabetic neuropathy is unknown, a significant association exists between diabetic neuropathy and one or more macrovascular complications[34]. Patients with diabetes and peripheral neuropathy have significantly higher rates of peripheral vascular disease and cardiac events, and numerically higher number of strokes than patients with diabetes but no neuropathy[48].

Mechanism underlying sex differences in diabetic microvascular complications

The prevalence, progression and pathophysiology of diabetic microvascular complications differ in males and females (Table 4).

Table 4: Sex differences in diabetic microvascular disease

	T1D	T2D
Microvascular complications		
Neuropathy	Cardiac autonomic neuropathy more prevalent in men than women[49,50]	• **Asian population:** Higher prevalence in women than men[51] • **Caucasian**: Prevalence of peripheral neuropathy in women and men (46.2 and 52.6%, respectively)[52]
Retinopathy	• **Diabetes diagnosed before 9 years of age:** Males at higher risk than females[53] • **Early disease:** Either no sex differences or mixed reports of higher risk in one sex than other[54–56] • **Advanced disease:** More prevalent in men than women[54,57] • Age at menarche not associated with proliferative retinopathy or confirmed distal symmetric polyneuropathy[39]	**Advanced disease:** • Male sex independent risk factor; sex difference weakens with duration of diabetes[18,58,59] • Higher prevalence in Japanese women than men[60]
Nephropathy	• Male sex risk factor for macro and micro-albuminuria[61,62] • Female sex a risk factor for microalbuminuria only for shorter term diabetes[63] • **Men with established diabetic nephropathy:** More rapid decline in renal function than women[64] • Higher percentage of women exhibit another end-organ complication than in men[65]	• Male sex risk factor for persistent microalbuminuria (incipient) and macroalbuminuria (overt)[66,67] • African American, Hispanic and Pima Indian women are at a higher risk than men[68–70] • **Incidence of diabetes related end-stage renal disease:** Marginally greater in white men; greater in black women[1] • White, Caucasian postmenopausal women may have a faster decline in renal function than age-matched men[71,72]

Male sex is an independent risk factor for diabetic nephropathy, while the protective effect of female sex seen in non-diabetic nephropathy is lost in women with diabetes[36,37]. Experimental and clinical data suggest that T1D may be associated with reduced circulating estradiol levels, most likely to be due to dysregulation of sex hormone biosynthesis[48–53] .

Several other findings during the life cycle of woman with diabetes, especially those with T1D, show that dysregulation of sex hormones are likely to be associated with microvascular complications. These women are more likely to have delayed menarche, delayed puberty, impaired ovarian function, menstrual irregularities, hyperandrogenism, adverse pregnancy outcomes (e.g., spontaneous abortions, stillbirths, and congenital anomalies), and premature menopause than age-matched women without diabetes. They are also less likely to conceive[73-81].

Data regarding association of sex hormones with T2D is a little confusing. A meta-analysis of data on endogenous sex hormone levels in postmenopausal women, controlled for BMI, showed that elevated plasma estradiol and decreased SHBG were associated with an increased risk for T2D[82]. This observation, contrary to popular belief, reflects a potential detrimental effect of estrogen in diabetes. In contrast, another study showed non-obese premenopausal women with T2D had decreased plasma estradiol concentrations[83]. Despite the controversies, most clinical and experimental studies report beneficial effects of estrogens in diabetes and the preventive effect of hormone therapy on the onset of diabetes[36].

The Finnish Diabetic Nephropathy (FinnDiane) Study showed that sex steroids influence the progression of microvascular complications[38]. Diabetic microvascular complications are rarely seen before puberty but they increase with the onset of puberty[75,84-87]. Delayed menarche, but not early menarche, correlated with an increased risk of diabetic nephropathy and retinopathy[38]. Prepubertal diabetes duration is a key determinant for the development of DR and nephropathy[36,37]. Though, an imbalance in sex hormones is postulated as a theory for the progression of microvascular disease at puberty, its precise mechanism is not well understood[37] .

The GH-IGF-1 axis regulates the sex differences in nephropathy and retinopathy during puberty[37]. However, disturbed sex hormone levels are likely to be involved in progression of diabetic microvascular complications, even after puberty. Females with diabetic microalbuminuria and males with DPR have increased testosterone levels[37]. In men with T1D, decreased testosterone levels are associated with the development of albuminuria, whereas, increased levels of both free testosterone and estradiol are associated with the progression of end stage renal disease[88]. Testosterone is one of the activators for the renin-angiotensin system. Treatment with ACEi results in reduction in glomerular filtration rate only in females[37].

In vivo interventional studies with sex hormones changed the progression of diabetic nephropathy depending on the hormone used[37]. Testosterone administration in prepubertal male streptozotocin-induced diabetic rats led to tubulointerstitial kidney damage, along with increased TGF-β expression; whereas 17β-estradiol treatment reduced the expression of TGF-β and increased matrix MMP, resulting in reduced albuminuria, glomerulosclerosis and tubulointerstitial fibrosis (Figure 1)[37,89]. DR animal models have been difficult to develop because animal models either do not develop the retinopathy related changes seen in human beings or die before proliferative DR develops[18].

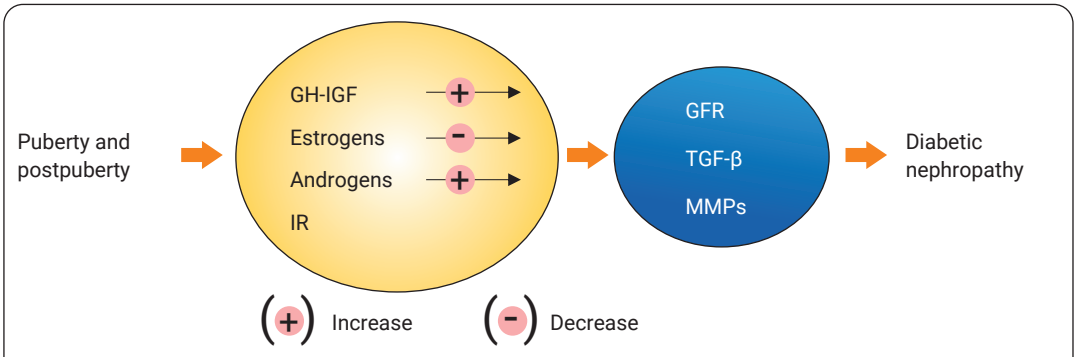

Figure 1: Sex hormones in diabetic nephropathy as an example of sex differences in microvascular complications

Source: Jia W, 2012[37]

Gender related considerations for managing diabetic microvascular complications

The biological/psychosocial gender differences influence the management of diabetic microvascular complications[1]. Lifestyle, environment, nutrition and outlook towards prevention and treatment affect the management of these complications in women. In general, women have a poor outlook towards preventive programmes[1]. A survey of 1,230 people with diabetes who had been fitted with therapeutic shoes to prevent diabetic foot ulceration found that women are less likely to adhere due to negative attitude towards appearance and high price[90]. The study cautioned the physicians to pay more attention towards addressing their concern for ensuring adherence[90].

Hence, there is a need to educate women about prevention and management of diabetic microvascular complications. A randomized controlled trial compared the effect of a 1 month supportive educational programme with 3 months of follow-up in 120 women with T2D and mild to moderate peripheral neuropathy (60 received the intervention and 60 served as controls[91]. The intervention significantly decreased mean diabetic neuropathy symptoms score ($p = 0.001$), severity of neuropathy ($p = 0.001$), fasting blood sugar ($p = 0.001$), and HbA1c ($p = 0.004$)[91]. This shows that an educational programme for women is effective in improving glycemic control and reducing symptom severity of microvascular complications.

Screening for microvascular disease in diabetes

Diabetic microvascular complications are common and evidence shows that early detection and identification of risk factors for retinopathy, nephropathy, and neuropathy may prevent or delay the progression to blindness, end stage renal disease, and diabetic foot ulcers, respectively[15]. The general screening principles adopted for DR[15,92], nephropathy[15] and neuropathy[15] should be used for women with diabetes (Table 5). Diabetic neuropathy is the most difficult to diagnose due to varied presentations and because diagnosis is achieved by excluding non-diabetic neuropathies[15].

Table 5: Screening for microvascular complications in women with diabetes

Microvascular Complication	Screening
Retinopathy	**Screening**
	1. Women with T1D • An initial dilated and comprehensive eye examination including visual acuity by an ophthalmologist or optometrist within 5 years of diagnosis 2. Women with T2D • Initial comprehensive eye examination including visual acuity (by ophthalmologist or optometrists) at time of diagnosis
	Monitoring
	1. Follow-up every 1-2 years, if no evidence of retinopathy at initial screening and good glycemic control 2. Annual monitoring if retinopathy detected at initial screening or poor glycemic control 2. Frequent monitoring in progressive cases
	Screening tool
	Mydriatic fundus photography
Nephropathy	Women with T1D duration of ≥ 5 years and all women with T2D Annual screening • Urinary albumin (e.g., spot urinary ACR, urine microalbumin) • eGFR Twice annual monitoring if • Urinary albumin > 300 mg/g creatinine and/or • eGFR 30–60 mL/min/1.73 m²

Neuropathy	Monofilament testing for peripheral neuropathy • **Small fiber function:** Pinprick and temperature sensation • **Large fiber function:** Vibration perception and 10g monofilament • **Protective sensation:** 10g monofilament Careful history and physical exam to capture symptoms and signs of autonomic neuropathy • **Cardiac autonomic neuropathy:** Resting tachycardia, orthostatic hypotension • **Gastrointestinal:** Gastroparesis, constipation, diarrhea, fecal incontinence • Sudomotor dysfunction with either hyperhidrosis or hypohidrosis • **Others:** Hypoglycemia unawareness, erectile dysfunction, neurogenic bladder

Special considerations

Screening for microvascular complications at menarche

Age at menarche is significantly associated with development of overt nephropathy in T1D[38,39]. Also, if diabetes is diagnosed before the age for menarche, then menarche is expected to be delayed. Estrogen is believed to have a reno-protective action. Delayed menarche is associated with delayed exposure of the renal system to higher estrogen level, which could be the reason for nephropathy[39]. Therefore, early screening and timely interventions, in women with delayed menarche, are necessary to prevent the development of nephropathy[39].

There is mixed evidence of age at menarche and its relation with DR. The FinnDiane Study found an increased risk of retinopathy in women with delayed menarche[38]. However, another cross-sectional and prospective study found no association between age at menarche and proliferative retinopathy or confirmed distal symmetric polyneuropathy[39]. Since, the evidence of association between age at menarche and retinopathy and neuropathy is not conclusive, strict screening may not be required. However, all women with delayed menarche should be assessed for retinopathy and neuropathy as per usual guidelines for screening.

Screening for microvascular complications in pregnant women

Diabetic retinopathy

Pregnant women with diabetes are at 2 fold increased risk of DR than nonpregnant women[25]. Evidence from case-control and cohort studies in pregnant women with T1D has shown that the progression of DR during pregnancy occurs mainly during the first and second trimesters; is likely to peak at the end of the second trimester, and then regresses during the third trimester[93–95].

Screening for DR should be carried out in all pregnant women with diabetes and pre-diabetes[25]. However, there is no global consensus on the preferred method for screening that fulfills the recommended requirement of minimum sensitivity, specificity and technical failure rate of 60–80%, 92–95% and 5–10%, respectively[21,96]. The sensitivity and specificity of slit-lamp biomicroscopy is 87% and 95% respectively[28]. The sensitivity and specificity of using mydriatic fundus photography to detect referable DR (moderate NPDR and above with or without DME)[92] depends on the method of imaging and ranges from 73-96% and from 68-99%[28,96] .

Retinal photography, in general, meets the acceptability criteria as a screening modality for DR and has the added benefit of generating a permanent record[25,92]. Though retinal photography compares well with slit-lamp biomicroscopy, the process faces issues of technical failure[25].

Fundus fluorescein angiography is generally not recommended during pregnancy as fluorescein crosses the placenta and likely to cause harm to fetus. The test should be particularly avoided during the first trimester[25] .

The pregnancy-specific guidelines by the AAO[19], ADA[20], Canadian Diabetes Association[22], NICE-UK[29], Ministry of Health Malaysia[28] and SIGN [21] recommend either a comprehensive eye examination (by ophthalmologist/optometrists) or mydriatic fundus photography to assess DR risk in the pregnancy period. National DR screening programs prefer retinal photography[25].

Retinal screening guidelines do not apply to women with GDM as DR rarely occurs during pregnancy in these patients[10,41,48]. However, some of these patients may have undiagnosed pre GDM and hence proper follow-up is necessary[25].

Diabetic neuropathy

Women with pre-existing diabetes should be screened for autonomic neuropathy as gastroparesis, impaired hypoglycemia awareness and orthostatic hypotension associated with autonomic neuropathy can become problematic during pregnancy[30]. Women should be counselled to recognize and report these. Severe gastroparesis is considered a relative contraindication to pregnancy[30]. Women should be screened for diabetic foot disease, including peripheral neuropathy and peripheral vascular disease. They should be referred to a podiatrist or foot care clinics if necessary[30].

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CHAPTER 9 RISK OF NONALCOHOLIC STEATOHEPATITIS IN WOMEN WITH DIABETES

Dr. Neeta Deshpande, Dr. Ami Sanghvi

Introduction

NAFLD and NASH is a spectrum of liver disorders that includes uncomplicated steatosis (fat deposition in cells), steatohepatitis (i.e., steatosis accompanied by hepatocyte damage and inflammation), cirrhosis (inflammation or degeneration of cells) and hepatocellular carcinoma[1]. Individuals with no prior history of excessive alcohol consumption also develop NAFLD, with identical histology to that of alcoholic liver disease, caused by triglyceride accumulation in liver. The prevalence of NAFLD in European population is about 5-33%, of which 43-70% are patients with T2D[2,3]. In fact, diabetes is considered to be an associated abnormality with NAFLD, on the basis of a previous study that reported higher prevalence of prediabetes and T2D as well as abnormal glucose metabolism in patients with NAFLD[4]. A meta-analysis reported global prevalence of NAFLD to be 25.24%, with highest in the Middle East and in South America and lowest in Africa with associated metabolic comorbidities like obesity (51.34%), T2D (22.51%), hyperlipidemia (69.16%), hypertension (39.34%) and metabolic syndrome (42.54%)[5]. The future predictions indicate that the NAFLD prevalence and the consequent liver transplantation as well as mortality will dramatically rise by the end of this decade[6].

Gender wise prevalence of NAFLD/NASH

Earlier, the prevalence of NAFLD was considered to be higher among males, but current reports depict an increasing trend in women, with a higher susceptibility in postmenopausal women, compared to premenopausal women[7–9]. According to a report of NHANES, prevalence of NAFLD in women has increased from 18.54% in the year 1988-1994 to 21.36% in 1999-2006 and 24.86% in 2007-2014, along with a higher risk of CVD and subsequent mortality[8]. Furthermore, a 12 year study (1989-2000) demonstrated prevalence of fatty liver in 26% males and 12.7% females with increased chances of NAFLD every year in both sexes and with a higher prevalence of age-related increase in the females, especially, in the 60-69 year age group[10]. Another study also observed higher age related increase in NAFLD prevalence in women with 3.9% in the age group of 21-39 years, 7.6% in 40-49 years, 14% in 50-59 years and 18.9% in 60-69 years group[11]. Generally, the increasing prevalence of NAFLD is age dependent as 39% and 40% cases were noted in the age group of 40-50 years and above 70 years, respectively[12]. Another study observed that age standardized death rate was increased by 2.99% in women, compared to 1.16% in men and 5% higher death rate from cirrhosis in women with NAFLD compared to men[13]. In NAFLD patients, the prevalence of stage 3 or 4 fibrosis was seen to be higher in postmenopausal women (36.1%), compared to men (17.7%)[14]. Similarly, another study reported advanced fibrosis in postmenopausal NAFLD women (27.6%), compared to men (22.2%)[15]. Kojima and group found higher BMI (8.7 vs. 5.5), triglyceride (5.6 vs. 3.3) and FPG (5.9 vs. 2.6) levels in women compared to men[10].

Risk factors for NAFLD/NASH in women

PCOS

The most common hormonal disorder that occurs during the reproductive age of a woman is PCOS, characterized by clinical features like anovulation, hirsutism, menstrual dysfunction, acne and infertility; and metabolic aberrations like IR, obesity, dyslipidemia, poor glucose tolerance, T2D and NAFLD[2,16]. It is already established that women with PCOS are more prone to developing NAFLD than healthy women[17]. 51% of Caucasian women of Greece with PCOS were reported to have NAFLD along with larger waist circumference, lipid accumulation product (i.e., an index of steatosis), IR, cholesterol and triglycerides in comparison to women in the control group[18]. Prevalence of PCOS was found to be 9.13% in a study on a South Indian adoles-

cent population[19], while the chances of fatty liver development was reported to be 38.3% in another study on South Indian females[2]. Anthropometric parameters are of great importance as both obese and lean women with PCOS can develop NAFLD[2]. The common reason for NAFLD in women with PCOS is IR caused by obesity that further leads to hepatic fat accumulation and ovarian dysfunction, like arrested follicle and anovulation along with increased androgen synthesis[17]. The PCOS mediated IR and hyperinsulinemia were reported to be higher (65%) in women with NAFLD in the above-mentioned study, compared to women without NAFLD. In addition, PCOS women with NAFLD showed elevated hyperandrogenemia and testosterone level that together with IR acted as independent predictors of NAFLD among these women[2]. Hyperandrogenic PCOS females were found to have higher liver fat in comparison to normoandrogenic PCOS females. This hyperandrogenism might be associated with hepatic low density lipoprotein receptor and lower concentrations of serum adiponectin and therefore, these women were more susceptible to developing dyslipidemia. Apart from this, leptin and resistin might also interfere with the metabolic functions and could be responsible for the development of NAFLD in women with PCOS[20].

Genetic influences are also considered to be responsible for association between NAFLD and PCOS that involves genes responsible for the action and secretion of androgen, cytokines and insulin[21,22]. Many diagnostic approaches like measurement of ALT, AST, USG, biopsy, NAFLD liver fat score index, fatty liver index, visceral adiposity index and fibrosis index consisting of BMI, AST/ALT ratio and NAFLD fibrosis score are used nowadays to diagnose NAFLD in PCOS patients [20,22]. Various biomarkers like caspase-generated cytokeratin-18, osteopontin, type IV collagen, matrix metalloproteinase and hyaluronic acid are also measured[20].

GDM

Women have a higher risk of developing GDM-mediated NAFLD due to higher incidence of obesity, PCOS, hypothyroidism, IR, dyslipidemia and T2D[23]. In Europe, 2-6% of pregnant women suffer from glucose intolerance, indicating development of GDM[24], which can further progress to T2D[25] and these women are more susceptible to developing NAFLD, compared to women with T2D alone. One of the reasons for this progression to T2D in later life is failure to adapt to complex metabolic needs during gestation, resulting in GDM and related metabolic syndrome[23,26]. Development of GDM in women itself highlights poor metabolic health that explains prevalence of NAFLD in women with GDM, compared to women without GDM[23]. In one study, a likely increased risk of NAFLD in the follow-up period was reported in women with GDM, especially, in those with a history of PCOS or hypothyroidism[23]. An Indian study on GDM showed a comparatively higher prevalence (19.19%) of cases[27]. Another Indian study from All India Institute of Medical Sciences, New Delhi reported a comparatively higher prevalence of grade 2 and 3 NAFLD in women with GDM (USG: 62.7%, fibroscan: 50.3%) vs. women without GDM (USG: 50%, fibroscan: 28%), which was thought to be associated with higher IR and poorer β-cell function along with a high risk of CVD at young age[28]. A previous study reported NAFLD as seen in the first trimester USG, which indicated dysglycemia during mid-pregnancy and possibility of T2D development in these patients in future[29]. Another study reported that women with NAFLD-GDM had abnormal glucose tolerance, but not pre-diabetes[3]. Probably, a higher fasting C-peptide concentration in these women indicative of better insulin secretion was the reason for glucose tolerance and subsequent absence of diabetes. However, the reason for NAFLD development was the increased peripheral and hepatic IR that facilitated hepatic lipogenic mechanisms and fat accumulation in the liver[3].

Other risks associated with NAFLD/NASH in women

Besides the liver, NAFLD can cause significant damage in other organs as well (Figure 1). Sarcopenia, i.e., loss of muscle mass and strength, is increasingly being observed in patients with NAFLD[30]. Conversion of glucose to glycogen takes place in skeletal muscle with the help of insulin and the reduced muscle mass in obese patients with NAFLD may cause IR[31] that is marked by low SVR tertile. 60% Chinese women with T2D in the lowest tertile and 30.4% in the highest tertile showed decreased SVR and thus a higher chance to develop NAFLD[30].

Change in bone turnover is another associated risk factor of NAFLD as its markers, such as, C-terminal telopeptide, N-terminal/midregion fragment of osteocalcin or N-MID osteocalcin and P1NP are found to be linked to liver injury, fibrosis and inflammation[32]. P1NP is released from bone osteoblasts or hepatic stellate cells and can be measured in patient's arterial, hepatic or

venous blood[33]. Both osteocalcin and C-terminal telopeptide are bone turnover markers and indicate changes with fatty liver disease progression. A study on postmenopausal Chinese women with diabetes showed negative association of N-MID osteocalcin with NASH, but positive association of C-terminal telopeptide and P1NP with fibrosis[32]. Another study on postmenopausal diabetic women with NAFLD reported higher serum sclerostin along with fibrosis but decreased DKK-1, RANKL, serum carboxy-terminal collagen I and 25(OH)D levels, though the patients consumed daily dose of oral vitamin D3[34]. DKK-1 is a protein that acts as an antagonist of Wnt/b-catenin pathway, which mainly regulates bone osteoblastic and osteoclastic activity, by regulating RANKL and osteoprotegerin (a member of TNF). However, in NAFLD with clinically significant fibrosis, the hepatocytes cannot release DKK-1, resulting in a lower DKK-1 level and hence, low RANKL was recorded along with low serum 25(OH)D, which is an indicator of NAFLD progression[34]. Moreover, BMD was found to be independently associated with NAFLD related fibrosis in postmenopausal women with T2D[35]. An increase in parathormone along with bone formation markers like osteocalcin and P1NP and bone resorption marker like procollagen type-I carboxy terminal peptide β special sequence in these patients, compared to patients without fibrosis, indicates high risk of developing osteoporosis in postmenopausal females with T2D or impaired glucose regulation[35].

Hypothyroidism or underactive thyroid that produces lower than normal levels of thyroid hormone can also be linked to NAFLD. A 21% higher prevalence of hypothyroidism was found among patients with NAFLD, reason of which was assumed to be because of IR, dyslipidemia and obesity in these patients[36]. In another study on patients from hepatology clinics at Indiana University Hospital, US reported a 15% prevalence of hypothyroidism in patients with NASH[37]. A study from Mayo Clinic in Rochester, US showed higher prevalence of thyroid dysfunction (25%) in NAFLD patients[38]. Women with NAFLD are at a higher risk of developing hypothyroidism[36]. The hypothyroidism is responsible for increased dyslipidemia in NAFLD patients as it elevates cholesterol and LDL and reduces HDL, resulting in dyslipidemia[36].

Another chronic condition that is associated with NAFLD is hypopituitarism, in which the pituitary gland fails to produce optimum level of one or more hormones. Similar to hypothyroidism, hypopituitarism also lowers the HDL level and increases LDL/HDL ratio leading to lipid imbalance and fat accumulation, resulting in NAFLD development and progression[39]. Patients with pituitary disease, gain excessive weight and tend to have impaired glucose tolerance that result in dyslipidemia and progression to NAFLD[40]. Clinical data of patients with anterior hypopituitarism showed link with rapidly progressive NAFLD and required hormonal therapy[41]. OSA is thought to induce liver fibrosis which is associated with NAFLD[42]. Elevated aminotransferase levels, evidence of NASH along with advanced NASH histology were reported in patients undergoing weight loss surgery and had OSA[43]. In fact, multivariate analysis showed that absence of OSA protects NAFLD patients from fibrosis and treatment for OSA improves enzyme activity involved in liver function and subsequently metabolic syndrome[42,43].

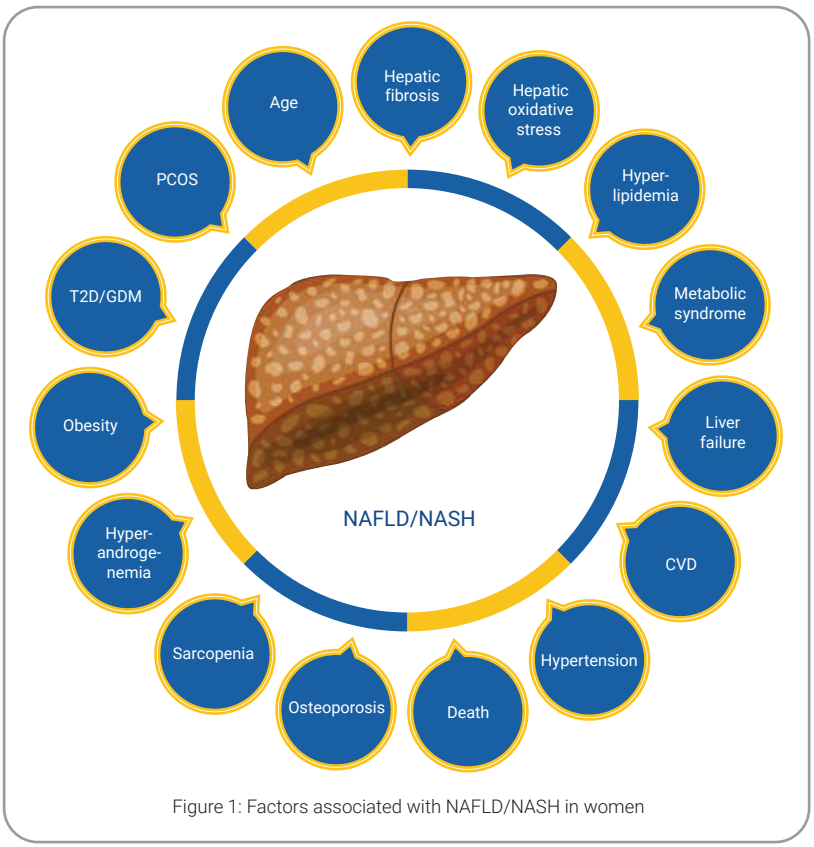

Figure 1: Factors associated with NAFLD/NASH in women

NAFLD/NASH and T2D in women

Obese female patients with IR and PCOS are at higher risk of developing T2D[44] and study suggest that about 70% of patients with T2D develop NAFLD simultaneously, resulting in impaired glucolipid metabolism along with risk of progression to macro or microvascular complications[30]. Risk factors of NAFLD in T2D patients include CVDs and a proatherogenic lipid profile, in which the LDL increases as a result of increased fatty acid influx, increased VLDL production and decreased HDL level[3,45]. This leads to excessive fat mass and decreased muscle mass, subsequently increasing the waist-to-calf circumference index in T2D patients[46].

Pathogenesis of NAFLD/NASH

Development of NAFLD is associated with increased BMI, waist circumference and visceral fat mass[3,45]. In NAFLD, fat accumulates in the liver and leads to low-grade chronic inflammation by means of increased adipokines, cytokines, chemokines as well as activation and recruitment of leukocytes at the inflammatory site[17]. In NAFLD, an imbalance in lipid uptake, its metabolism and clearance occurs that results in accumulation of triglycerides in the cytoplasm of hepatocytes[47]. Obesity and IR are considered to be the most important risk factors for development of NAFLD. IR causes lipolysis in visceral adipose tissue that causes accumulation of fat in the liver by increasing the hepatic flow of free fatty acids. Additionally, fibrosis takes place as a result of insulin induced collagen and fibrinogen generation in hepatic stellate cells[20]. Therefore, NAFLD patients with inflammation or fibrosis show increased oxidative stress along with increased hepatocellular apoptosis and ferritin levels[48]. Studies on animals demonstrated the marked role of gut microbiota in NAFLD, though research on humans is still going on. Intestinal bacteria can influence the calories extracted from food by digesting indigestible polysaccharides[49]. The steatosis and NASH generally witnesses the presence of proteobacteria, prevotella or veillonella is usually observed in cirrhosis, while clostridium and lactobacillus overlaps between NAFLD and T2D[50].

Relationship between NAFLD/NASH risk pre and postmenopause

Premenopausal women using OC have shown an OC-induced higher incidence of lobular inflammation, which is an indicator of NAFLD[51]. A higher prevalence of PCOS development (43.7%) was found in women with NAFLD in comparison to women without NAFLD (23.1%)[52]. In fact, women with no prior history of PCOS can develop NAFLD with prevalence similar to premenopausal PCOS women[53]. As discussed earlier, women are more prone to developing NAFLD; especially, older or postmenopausal women in comparison to men, which may be due to hormonal changes that occurs during menopause. Apart from hormonal alterations, the changes in body composition, waist circumference and intra-abdominal fat also contribute to metabolic diseases, particularly T2D and IR, ultimately leading to NAFLD in some cases[9]. In both pre and postmenopausal women risk factors associated with NAFLD are metabolic syndrome and weight gain[11]. One study reported higher prevalence of advanced fibrosis (36.1%) in postmenopausal women compared with premenopausal women (13.5%)[14]. Occurrence of advanced fibrosis was also evident in another study on postmenopausal women with NAFLD (27.6%), compared to premenopausal women (14.4%)[15]. A study on age and BMI-matched women demonstrated significantly higher prevalence of developing F2-F4 fibrosis in postmenopausal women than premenopausal women, particularly, in women with premature menopause (before 40 years)[54]. In premenopausal women, low HDL, obesity and IR are associated with increased risk of NAFLD, while in postmenopausal women, T2D, hypertriglyceridemia, obesity and serum uric acid levels are associated with increased risk of NAFLD[55,56]. Therefore, healthy diet and regular activity is recommended for middle-aged women, who are approaching menopause to minimize chances of NAFLD development.

Assessment of NAFLD/NASH

In general, there is no consensus yet on screening and diagnostic guidelines. Majority of patients with NAFLD are asymptomatic with no alterations in any blood indices. A study have suggested that an increase in serum ferritin level can be used as an indicator of NAFLD as the latter causes systemic inflammation and elevates the iron level[57].

In another study, detection of serum autoantibodies (anti-nuclear antibodies, anti-centromere antibody, anti-histone antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, etc.) by indirect immunofluorescence was found to be associated with advanced liver fibrosis in NAFLD patients[58]. From simple fat accumulation, this disease can progress to the most severe form of steatosis (liver fat fraction > 5-10% by weight) known as NASH, ultimately resulting in hepatic fibrosis, cirrhosis and liver cell failure[3,59]. According to percentage of fat within the hepatocytes, the hepatic steatosis is categorized into three grades: 0 (healthy, < 5%), 1 (mild, 5-33%), 2 (moderate, 34-66%) and 3 (severe, > 66%)[60]. Till now, various parameters have been proposed for NAFLD diagnosis (Table 1) and the diagnosis is made only after excluding secondary causes responsible for fatty liver like Wilson's disease, viral hepatitis, autoimmune hepatitis, hemochromatosis, hepatotoxic medicine or excessive alcohol consumption[61,62]. Despite its disadvantages, invasive liver biopsy is still the definitive diagnostic modality for both NAFLD and NASH, but imaging methods like ultrasound, computed tomography, MRI and Hydrogen 1 (^{1}H) magnetic resonance spectroscopy are also gaining attention nowadays for their noninvasive nature of testing[48,63]. Other newer diagnostic approaches include transient elastography, ultrasound-based acoustic radiation force impulse imaging, real-time shear wave elastography, magnetic resonance elastography, several serological markers and biochemical markers like aminotransferases and PIIINP[48]. NASH activity score is also used that includes steatosis (0-3), lobular inflammation (0-3) and ballooning degeneration (0-2) along with fibrosis score consisting of stages namely delicate (1A), dense peri-sinusoidal fibrosis (1B) and portal fibrosis without peri-sinusoidal fibrosis (1C)[64]. Other non-invasive scoring systems like NFS, FIB-4, APRI, AST/ALT ratio and BARD score are also used[65,66]. The measurements of these scores are done as follows[66]:

- NFS = −1.675 + 0.037 × age (year) + 0.094 × BMI (kg/m²) + 1.13 × impaired fasting glucose/ diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio-0.013 × platelet (x109/L)-0.66 × albumin (g/dL)
- FIB-4 = age (year) × AST (IU/L)/platelet count (x109/L) × √ALT (IU/L)
- APRI = AST (IU/L)/(upper limit of normal)/platelet count (109/L) × 100
- AST/ALT ratio = AST (IU/L)/ALT (IU/L)
- BARD score = Sum of three variables (BMI ≥ 28 = 1 point, AST/ALT ratio ≥ 0.8 = 2 points, diabetes = 1 point)

Table 1: Different diagnostic approaches for assessment of NAFLD/NASH

Invasive method	Imaging method	Biochemical markers	Indices
Liver biopsy	Ultrasound	ALT	NAFLD liver fat score index
	Computed tomography	AST	Fatty liver index
	MRI	PIIINP	Visceral adiposity index
	^{1}H-magnetic resonance spectroscopy	Triglyceride	Fibrosis index
	Transient elastography	Fasting glucose	Fibrosis score:
	US-based acoustic radiation force impulse imaging	Cytokeratin-18	▪ Delicate: 1A
	Real-time shear wave elastography	Type IV collagen	▪ Dense peri-sinusoidal fibrosis: 1B
	Magnetic resonance elastography	Matrix metalloproteinase	▪ Portal fibrosis without peri-sinusoidal fibrosis: 1C
		Hyaluronic acid	NASH activity score:
			▪ Steatosis: 0-3
			▪ Lobular inflammation: 0-3
			▪ Ballooning degeneration:0-2

- The primary intervention of NAFLD management is weight loss by managing lifestyle choices. Calorie restriction and incorporation of physical activity can improve both AST and ALT levels as well as other radiological and histological markers of NAFLD[67]. In PCOS mediated NAFLD patients too, lifestyle change with healthy diet and regular exercise are beneficial[22].
- The AASLD, the EASL-EASD-EASO and KASL have all suggested weight reduction by 3-5% and ≥ 7% for the improvement of hepatic steatosis and fibrosis along with NASH respectively[68].
- TZD reduces both steatosis and hepatocellular damage by reducing plasma lipid levels and modifying fat topography in combination with insulin sensitizing effects by improving glucose tolerance and reducing androgen level[20,59,69]. Side effects of this drug include weight gain, fluid retention, heart failure and fractures[69].

- Other drugs with relatively less side effects like GLP-1 receptor agonists are used to decrease the liver enzymes, IR and lipotoxicity in NASH patients[70,71].
- Use of SGLT2i in NASH/NAFLD patients is proved to be effective as it reduces ALT, body weight, fatty liver index, fibrosis, hepatic steatosis[72].
- Administration of various drugs, such as metformin to lower liver enzymes level and IR, liraglutide (GLP-1 receptor agonists) to lower fat content and visceral adipose tissue, pioglitazone to improve liver histology and vitamin E to ameliorate steatosis, inflammation and ballooning are also used for NAFLD treatment[22,61,62].
- Metformin reduces IR and improves metabolic functions by inhibiting key enzymes for gluconeogenesis, thus decreasing glucose production in liver and by increasing peripheral insulin sensitivity. The ensuing lowered insulin concentration decreases androgen production and increases SHBG concentration[73].
- The daily administration of 1.8 mg of liraglutide, resulted in a 66% reduction in NAFLD along with reduction in body weight (5.6%), fat content (44%) and visceral adipose tissue (18%)[74].
- A randomized controlled trial, showed that vitamin D supplementation decreased ALT in vitamin D deficient PCOS women, though other liver parameters remain unaltered[75].
- DPP4i were found to prevent liver fibrosis and NAFLD in mice model[76].
- Some lipid lowering agents like statins, fibrates and others have been shown to be useful in the treatment of NAFLD/NASH, though, statins may have the potential to cause transaminitis[77].
- UDCA improves NASH by stimulating GLP-1 secretion, by reducing hepatocytes apoptosis, by preventing steatosis and by restoring adiponectin levels[78]. The efficacy of UDCA increases when combined with other drugs like statins, TZD and vitamin E[78,79]. Similar to UDCA, Obeticholic acid is also used in NAFLD management as it improves fibrosis and helps in weight loss[80].
- Pentoxifylline, a methylxanthine derivative elevates cyclic AMP and reduces tumor necrosis factor-α, thus is important in NAFLD treatment[81].
- Bariatric surgery viz., adjustable gastric band, sleeve gastrectomy, gastric bypass, repopulation of gut microbiota and composition of bile acid are involved in weight loss and metabolic improvement in NAFLD patients[82].

Future direction for NASH/NAFLD management

Drugs targeting metabolic pathways, IR, hepatocyte death, inflammatory cell recruitment or activation, the gut-liver axis, matrix expression or matrix turnover etc. are in various stages of clinical development. Many promising drug candidates have failed in early stage clinical trials (for example, elafibranor, emricasan and selonsertib), while the farnesoid X receptor agonist obeticholic acid, the pan-PPAR agonist lanifibranor and the chemokine receptor CCR2/CCR5 inhibitor cenicriviroc, have shown promising results and they could be effective management options for liver fibrosis in the years to come[83]. Combining drug therapy and effective lifestyle changes seem to be the best hope to manage NAFLD-associated fibrosis.

Summary

NAFLD/NASH are associated with T2D and its increasing prevalence along with comorbidities is a matter of concern worldwide. Because of the difference in hormonal levels and body fat distribution, women are more susceptible to developing NAFLD, especially the older age group. In fact, women who have PCOS, tends to develop NAFLD more easily than women without the condition, owing to their unfavourable reproductive hormone profile as well as higher BMI, disordered metabolic function and IR. In addition, GDM with or without further progression to prediabetes or T2D is also associated with NAFLD de-

velopment. Studies on the Indian GDM population have highlighted the alarmingly greater prevalence of NAFLD and associated CVDs at a very young age. Furthermore, NAFLD can also be associated with pathological conditions of other organs, like, muscle, bone, thyroid gland and nervous system and must be treated at an early stage. Numerous lifestyle and pharmaceutical interventions have been suggested for NAFLD management. Although not entirely successful, these modalities could potentially reduce the burden of the disease considerably.

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Section 3

Pre-GDM Care & Management of Diabetes in Pregnancy

Editor: Dr. Usha Sriram

CHAPTER 10 TYPE 1 DIABETES IN WOMEN

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Pathophysiology of T1D in Women

T1D previously known as Juvenile Diabetes or Insulin Dependent DM is a common autoimmune disease that is observed in 15 individuals per 100,000 people in Asia, primarily in adolescent below 18 years of age[1]. Globally, the annual prevalence of T1D is estimated as 98,200 and 128,900 below 15 years and below 20 years of age respectively[2]. In comparison to the males, the adversities of T1D have been more obvious in the female counterpart[3]. Studies indicate that women with T1D have decreased protection against CVD and significantly worse CVD risk profile when compared to women without T1D and men with T1D[4,5]. Additionally, women are also at a greater risk of neuropathy and blindness due to DR[6,7].

The development of T1D autoimmune disease depends on multiple factors including immunologic, genetic and environmental factors. It is mediated by type IV hypersensitivity, driven by T cells leading to organ-specific immune destruction of insulin making β-cells present in the islets of Langerhans within the pancreas[8]. The β-cells are elegant glucose 'thermostats', sensing glucose and releasing insulin to maintain physiological glucose levels within a relatively narrow range[9]. Some researchers believe that the destruction of the β-cells results in activation of cytotoxic T cells against self-antigens of the human system and thus leads to progression of T1D[10]. Once those cells are destroyed, patients with T1D have reduced blood glucose control, which can result in acute conditions like ketoacidosis and severe hypoglycemia as well as secondary complications inclusive of heart disease, blindness and kidney failure[9]. In the newly diagnosed T1D patients, one or more of the islet autoantibodies reactive to insulin, glutamic acid decarboxylase, insulinoma-associated autoantigen 2 and zinc transporter 8 are found[11,12].

Fulminant immune infiltration within individual islets of pancreas have been observed in individuals with T1D, demonstrating an important role for CD4 and CD8 T cells in β-cell destruction[13]. Within the insulitis lesion, the CD8+ T cells are present in highest number along with other cells like macrophages (CD68+), CD4+ T cells, B lymphocytes (CD20+) and plasma cells (CD138+)[14]. Nevertheless, the regulatory T cells i.e., FOXP3+ cells and natural killer cells are rarely found[12]. The genes responsible for T1D are carried on a specific band in the genetic markers i.e., the DQ band of the short arm of the chromosome 6 (locus 6p21.3) and the insulin gene region at chromosome 11 (locus 11p15)[10,15]. Such genes that can identify themselves as constituents of their own system are known as the MHC and control the immune system. In human beings, this system is known as the HLA complex[10,15]. The HLA genes encode for 3 different molecule types namely:

- Class I molecules that are present as transmembrane glycoproteins on the surface of all nucleated cells and are identified as self[10].
- Class II molecules that are present only on cells that actively take part in body defense mechanisms like macrophages, dendritic cells, T cells and epithelial cells of the islets of Langerhans[10]. These are further divided into 3 subclasses, namely: HLA-DQ, HLA-DP and HLA-DR that play a major role in T1D[10,12]. The haplotypes of class II molecules: DRB1*0401-DQB1*0302 and DRB1*0301-DQB1*0201 present greatest susceptibility while DRB1*1501 and DQA1*0102-DQB1*0602 provide disease resistance in individuals with T1D[12].
- Class III molecules that are important in inflammation includes complement components C2, C4, and factor B, TNF-α, lymphotoxin and three heat shock proteins[16,17].

Apart from gene regions of chromosome 6 and 11, other regions like cytotoxic T-lymphocyte antigen-4, protein tyrosine phosphatase non-receptor type 22 and IL-2α chain receptor have shown to be involved in T1D susceptibility[18]. In addition to these, T1D is found to be associated with frequent SNP. SNP typing technology has led to the identification of numerous susceptible loci such as CLEC16A, CI1QTNF6, UBASH3A, CD226, PTPN2, CTSH, SH2B3, ERBB3, PRKCQ, TAGAP, IL-2RA, TNFAIP3, BACH2, IL-7R, IL-2, CCR5, IFIH1, IL-18RAP, RGS1, IL-10, IL-19, IL-20, GLIS3, CD69 and IL-27[19].

Studies are instrumental in suggesting that factors inclusive of diet, vitamin D intake, infections as well as the gut microbiota, could modify gene expression through epigenetic mechanisms, further playing a major role in favoring T1D development[20]. In comparison to men, women may be more vulnerable as they have fewer opportunities of medical supervision, may not have access to regular health care and receive less support to deal with the consequences of diabetes. In low-income countries where there is no health insurance and universal health coverage, women deal with the brunt of economic, political and social discrimination, resulting in their poor health, lack of education and unemployment. Diabetes also brings stigmatization and discrimination, especially for girls and women[7].

The link between T1D and menstrual disturbances, such as delayed menarche, alterations in the menstrual rhythm along with its effect on fertility and fecundity in females has long been established and researchers believe that these may be mediated through hormonal (prolactin, adrenal hormones, estrogens and androgens) alterations in the hypothalamic-pituitary-ovary axis[21]. The putative mechanism may be involvement of dopaminergic tonus along with the consequent alterations in the menstrual cycle and in circulatory levels of GnRH, FSH, LH and feedback mechanism of steroid hormones[21].

PCOS and diabetes

PCOS is one of the most common endocrine disorders with 6-15% prevalence in premenopausal women worldwide and is associated with metabolic manifestations like IR[22]. PCOS is accountable for anovulatory infertility[23] and can be defined by a combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of other specific diagnoses such as hyperprolactinemia and congenital adrenal hyperplasia[24]. Apart from IR, PCOS is also frequently associated with abdominal adiposity, obesity, metabolic disorders, peripheral hyperinsulinemia and CVD[25,26]. T1D raises the risk of hyperandrogenic disorders, including PCOS and hirsutism (presence of terminal hair with male distribution) in women[24,27]. Exposure of the ovary and other glands to hyperinsulinemia due to non-physiological, exogenous insulin administration have been implicated as factors in development of hyperandrogenemia and PCOS morphology in women with T1D[28]. These women are also reported to have elevated levels of serum testosterone and androstenedione along with higher incidence of PCOS, demonstrated by increased ovarian volume and follicle number[29].

Table 1: Characteristics of PCOS in women

T1D + PCOS		PCOS
Elevated AMH/ adrenal androgens	Childhood	Elevated AMH/ adrenal androgens
Not reported	Precocious pubarche	Associated
Normal or Mild delay	Puberty	Normal or early
Late	Onset of hyperandrogenism	Perimenarcheal
Begins during puberty/ adolescence	Onset of weight gain or increase in adipose tissue	Begins during childhood
System circulation	Source of hyperinsulinemia	Pancreas/portal vein
Secondary to glucose toxicity	IR	Primary/obesity related
Muscle, adipose tissue	Tissue that are exposed to higher insulin concentration	Liver
Mild	Degree of hirsutism	More severe
Hyperandrogenism clinical or biochemical	Most prevalent phenotype	Oligomenorrhea + Hyperandrogenism + PCOS
Elevated	Total testosterone/ androstenedione	Elevated
Normal or elevated	Free testosterone	Very elevated
Normal or elevated	SHBG levels	Diminished
Normal	LH levels	Elevated
Normal	AMH levels	Elevated
Unknown	Anovulation	Yes
Yes	PCOS on ultrasonography	Yes

Source: Codner et al., 2012[30]

The characteristics of PCOS in women with and without T1D are given in Table 1[30]. There has been considerable evidence implicating that 24% of women with T1D have PCOS in comparison to the general population[31]. However, another study also reported no significant differences in the phenotypic characteristics of T1D women with PCOS (except higher visceral adiposity index and androstenedione level) when compared with women with PCOS but without diabetes[32].

PCOS also increases the risk of dysglycemia associated with development of GDM and T2D in women[33]. IDF included PCOS as a non-modifiable risk factor of T2D[34]. A study reported 11.2% and 5.2% prevalence of GDM and T2D respectively, in women suffering from PCOS[34]. A meta-analysis showed greater prevalence for both IGT and T2D in women with PCOS that appeared higher with obesity[35]. The development of T2D in women with PCOS is likely because of the IR along with hypertension in some cases[36]. Interestingly, a previous study demonstrated higher risk for developing GDM (51%) and pregnancy induced hypertension (8.9%) in lean women with PCOS than lean women without PCOS[37]. On the contrary, a study on Asian pregnant women with PCOS indicated race and prepregnancy obesity as the strongest predictors of GDM that further progressed to diabetes after undergoing pharmacological treatment[38]. Amongst women with GDM, PCOS has been implicated as an independent risk factor for the development of preeclampsia and significant gestational weight gain[39].

Obesity in adolescent girls and women with T1D

The concerns with respect to body weight seem visibly more prevalent in females with T1D in comparison to the general population. Weight gain in patients with T1D is not that obviously observed during childhood. However, obesity is common in females, who are in their peripuberty stage or are older[40]. A correlation has been observed between T1D and waist-to-hip ratio that is considered as an index of central adiposity and this increase in body weight and BMI has been linked to changes in lipid levels[40]. A study conducted by Thong et al., in 2020 on 15,926 women demonstrated that nearly half of the women with T1D were obese or overweight with a higher median BMI. The obesity was further associated with menstrual irregularity and PCOS development[41]. Another study showed that T1D results in increased levels of CRP in the luteal phase and decreased levels of IGF-1 in both follicular and luteal phases of the menstrual cycle of young adolescents, particularly in overweight T1D patients as the excess weight may elevate the inflammatory state and complications in these women[42].

Complications in women with T1D

Introduction of insulin in 1923 was a major breakthrough as before that woman with T1D used to suffer from severe hypogonadism and low fertility rates. Though these conditions have improved with insulin therapy, but still the primary and secondary amenorrhea along with severe pubertal delay persist in women with diabetes[30]. Women with T1D are reported to have a delayed menarche and higher prevalence to develop menstrual disorders than women without T1D[43]. Other risk factors associated with T1D includes CVD, osteopenia and fractures, with premenopausal women are at a higher risk to develop these complications than male with T1D[30]. A study showed 5.6 times higher mortality rate in females with T1D, compared to the general population[44]. A study (with 3 year follow-up period) on Finnish population involving 978 women with T1D, revealed no effect of the latter on the age of menopause[45]. On the other hand, another study on T1D patients from Pittsburgh showed late menarche (13.5 years) and early menopause (41.6 years), and a consequent 6 years shorter reproductive period, compared to non-diabetic controls[43]. Decreased IGF-1 levels are associated with kidney disease, IR and CVD or death in women with diabetes[26,42,46]. In women with T1D, androgen level is elevated that is further associated with microalbuminuria (marker of incipient nephropathy), a reflection of poor glycemic control, alterations in IGF-1 axis and ovarian function[26]. The development of diabetic nephropathy and DR is related to increased secretion of GH and generation of local paracrine IGF-1[47,48].

T1D and CVD risks in women

T1D is known to be associated with CVD, such as myocardial infarction, heart failure and ischemic stroke[49]. A meta-analysis reported a significant association between T1D and 47% greater risk of heart failure in women, compared to men[50]. In fact, women are on verge to develop CVD and have higher mortality rate than males as found in a study conducted on UK populati-

on[51]. CRP levels, which is a marker of subclinical inflammation was found to be elevated in luteal phase of obese females with T1D[42], indicating one of the mechanisms involved in subclinical CVD in obese women with diabetes[28]. Other factors such as increased androgen levels or waist-to-hip ratio are also found in women with T1D, which are commonly associated with risk of CVD development and IR[29].

Pregnancy complications in women with T1D

A direct relationship between T1D and complications during pregnancy has been noted[52]. A 2-5 fold increase in the risk of adverse pregnancy outcomes including congenital anomalies, stillbirth, preterm delivery, fetal growth retardation and perinatal mortality is observed in women with T1D[53,54]. T1D is also associated with severe hypoglycemia that occurs 3-5 times more frequently in early pregnancy than in the prepregnancy period[55]. A history of severe hypoglycemia in the year preceding pregnancy, poor hypoglycemia awareness, chronic diabetes, reduced HbA1c level in early pregnancy, fluctuating plasma glucose values (≤ 3.9 mmol/l or ≥ 10 mmol/l) and excessive supplementary insulin administration between meals are accountable for severe hypoglycemia in pregnant women[55]. Hyperglycemia exerts its teratogenic effect (drug, chemical or infection responsible for abnormal fetal development) during the first 42 days of pregnancy and the pregnancy is generally confirmed after this time period, increasing the risk of congenital malformations[56]. Despite having a lower HbA1c (≤ 7%) and an overall glycemic control, maternal and perinatal complications still remained high in women with T1D[57]. Macrosomia or birth weight > 4,000 g occurs in some T1D patients that increases risk for birth injury and greater risk of trauma and poor pelvic floor function in the mother[56]. BP even in normotensive normoalbuminuric women and 4 times higher incidence of preeclampsia was noted in women with T1D[58,59].

Diabetic nephropathy is frequent in women with T1D and is probably the most common CKD observed in pregnant women[58]. The two putative mechanisms behind diabetic nephropathy affecting pregnancy are[54]:

- Development of severe maternal hypertension, leading to termination of the pregnancy and thereby preterm delivery.
- Impaired placental development, leading to fetal growth restriction and risk of stillbirth.

Management of T1D

Intensive insulin therapy helps to control glycemic index along with prevents other microvascular and macrovascular diseases as well as mortality. As a part of the therapy, rapid and long-acting insulin analogs, blood glucose meters, newer insulin pumps with integrated sensor-augmented systems and with automatic threshold suspend capabilities, and CGM devices are used[60].

The standard of care for T1D management is stringent glycemic control, which is achieved by[60,61]:

1. Self-monitoring using BGMS.
2. CGM.
3. Flash glucose monitoring systems.
3. Real-time glucose monitoring systems.

BGMS involves the use of glucose meter, i.e., a small electronic device that analyzes glucose levels in capillary whole blood. In this, the patient pricks a finger and places a drop of blood onto a glucose test strip, which is already inserted into the glucose meter. Alternate sites such as the earlobe, heel, forearm and palm can also be used as the blood source[62]. Real-time glucose concentrations in the interstitial fluid are measured using CGM, which correlates with plasma glucose values. In this a sensor is inserted into the subcutaneous tissue. The effectiveness of CGM devices depends on adherence and does not completely eliminate the need for capillary testing[61]. However, CGM is shown to be effective in improving glycemic control when compared with conventional self-monitoring[63]. It allows data to be continuously sent to a receiver device and provide real-time alerts, which can be customized to manage the glycemic index[60].

Insulin is the mainstay of therapy of T1D in individuals

Generally, in T1D patients the starting insulin dose is around 0.4-1 units/kg/day that also depends on the patient's body weight with a higher dose required during puberty[64]. A number of insulin products are available that are indicated to improve glycemic control and can be grouped on the basis of their profile actions (Figure 1). Selection of appropriate insulin product depends on the desired time course of insulin action and its pharmacokinetics (absorption, distribution, metabolism and excretion)[60,61].

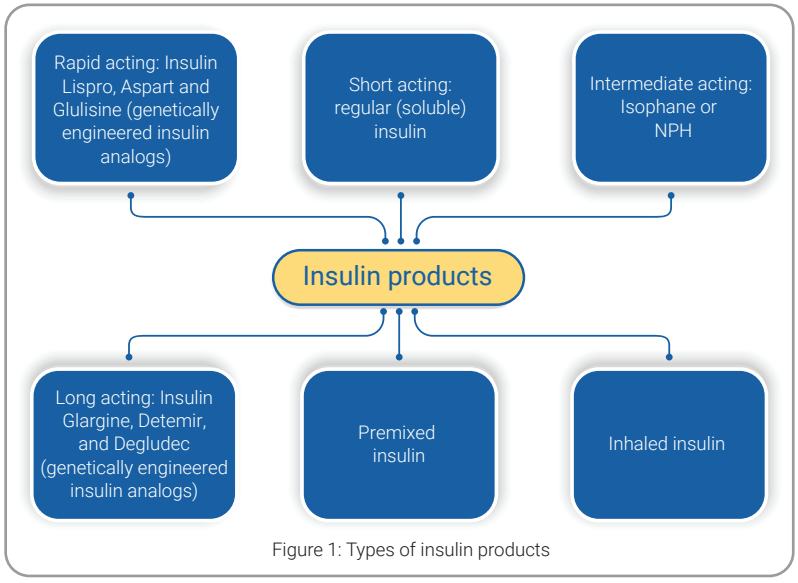

Figure 1: Types of insulin products

T1D patients should participate in continuous diabetes self-management education programmes, which help them to be updated about the roles of nutrition, exercise and insulin therapy in controlling glucose levels. ADA recommends that T1D patients should engage themselves in 150 mins of moderate to vigorous intensity physical activity per week with no more than 2 consecutive days without activity[61,64]. A multidisciplinary framework that can be useful in the management of T1D is provided in Figure 2.

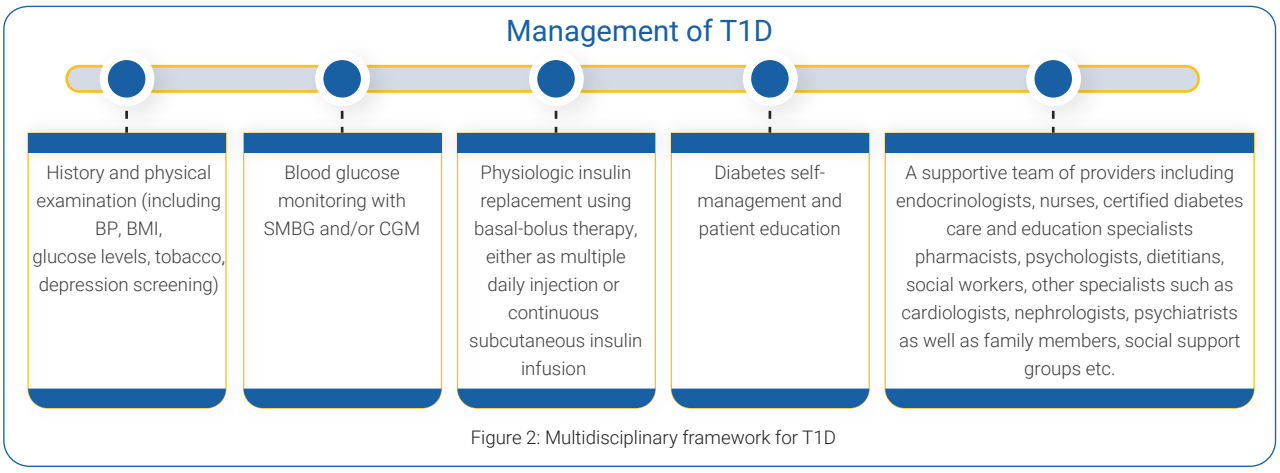

Figure 2: Multidisciplinary framework for T1D

Psychological issues in women with T1D

Individuals living with T1D suffer from psychological issues such as depression, anxiety, eating disorders and cognitive impairment. The most serious mental health comorbidity of diabetes is MDD, generalized anxiety, panic or post traumatic stress[65]. DD is different from MDD, and is also experienced by patients with T1D. It is defined as distress linked specifically to diabetes and its management, and involves emotional burden, physician-related distress, regimen-related distress and interpersonal distress[65].

It leads to serious repercussions like:

- Poor adherence to treatment.

- Poor glycemic control.
- Higher rates of diabetes complications.
- Impaired quality of life that makes the life of patients more difficult.

Women with T1D have a 2.4 times increased risk of developing an eating disorder and a 1.9 times increased risk for developing sub-threshold eating disorders than women without diabetes[65]. Disturbed eating behaviors in women with T1D include binge eating and caloric purging through insulin restriction and have poorer glycemic control, with higher rates of hospitalizations and retinopathy, neuropathy and premature death compared with similarly aged women with T1D but without eating disorders[65].

Transition to motherhood is a major life event, but sometimes accompanied by increased risk of diabetes-related complications and result in adverse pregnancy outcomes[66]. All these changes implicated psychosocial issues in the mother, such as, increased anxiety levels, guilt, DD, a tendency to be disconnected from health professionals, and shift of focus from motherhood to medicalization of pregnancy[66].

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CHAPTER 11 PRE PREGNANCY COUNSELLING

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Introduction

The prevalence of diabetes in pregnancy has been increasing globally, in parallel with the worldwide epidemic of obesity. Not only is the prevalence of T1D and T2D increasing in women of reproductive age, but there is also a dramatic increase in the reported rates of GDM. GDM is defined as glucose intolerance with onset or first recognition during pregnancy, and is a common metabolic complication during pregnancy, generally detected in the 2nd or 3rd trimester that is clearly not overt diabetes. Increasingly, it has been recognized that women who develop GDM during pregnancy usually have chronic β-cell dysfunction and/or IR prior to pregnancy. Therefore, women with GDM are likely to have impaired glucose metabolism before or during early pregnancy, although not as severe as those with overt diabetes before pregnancy[1].

Any degree of dysglycemia is associated with adverse materno-fetal outcomes. In general, specific risks of hyperglycemia in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, hyperbilirubinemia, and neonatal respiratory distress syndrome, among others. In addition, there is an intergeneration transmission risk of NCDs, and there is now sufficient evidence that hyperglycemia in pregnancy may increase the risk of obesity, hypertension and T2D not only in the mother but also in her offspring later in life[2,3].

It therefore becomes pertinent that not only the current pregnancy needs optimized hyperglycemia management if the woman is diagnosed with GDM, but she needs to be counselled on the importance of preconception care and planning for a subsequent pregnancy. Furthermore, preconception care and counselling needs to start in all females with pre-existing diabetes, both T1D and T2D, right from adolescence to make them aware of the importance of tight glycemic control in ensuring a complication-free pregnancy and improving materno-fetal outcomes.

Family planning practices among women with diabetes

All women of childbearing age with diabetes should be informed about the importance of euglycemia and must maintain it before conception and throughout the pregnancy. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, renal anomalies and caudal regression are directly proportional to elevations in A1c during the first 10 weeks of pregnancy[4]. Although observational studies are confounded by the association between elevated periconceptional A1c and other poor self-care behaviour, the quantity and consistency of data are convincing and support the recommendation to optimize glycemia prior to conception, given that organogenesis occurs primarily at 5–8 weeks of gestation, with an A1c < 6.5% (48 mmol/mol) being associated with the lowest risk of congenital anomalies, preeclampsia, and preterm birth[4-8].

There are opportunities to educate all women and adolescents of reproductive age with diabetes about the risks of unplanned pregnancies and about improved maternal and fetal outcomes with pregnancy planning[9].

Effective preconception counselling could avert substantial health and associated cost burden in offspring[10]. Family planning should be discussed, including the benefits of long-acting, reversible contraception, and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant[11-14].

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all girls and women with diabetes of childbearing potential should receive education about (i) the risks of malformations associated with unplanned pregna-

ncies and even mild hyperglycemia and (ii) the use of effective contraception at all times when preventing a pregnancy. Preconception counselling using developmentally appropriate educational tools enables adolescent girls to make well-informed decisions. Young women need to be aware that uncontrolled diabetes affect lives of two generations, one of the mother and other of the offspring.

Preconception counselling resources tailored for adolescents are available at no cost through the ADA[15].

Prepregnancy care for pre-GDM

Women with T1D or T2D diagnosed prior to pregnancy are classified as having pre-GDM. The prevalence of HIP has been estimated at 17% globally and 5.4% in Europe[16,17], differences existing among racial and ethnic groups[18,19]. Only a minority (approximately 15%) of the cases of diabetes during pregnancy represent women with pre-existing diabetes[20]. Because of the rising prevalence of obesity and limited screening for diabetes in young women, there has been, globally, an increase in the diagnosis of previously unknown overt diabetes early in pregnancy[19]; these women should be treated as women with pre-existing diabetes, as they may already have unrecognized complications (e.g., nephropathy and retinopathy).

While rates of unintended pregnancy have decreased in recent years, nearly half of pregnancies are still unplanned[21]. Appropriate prepregnancy planning is one of the most important steps in reducing risk of birth defects in mothers with pre-existing diabetes, because organogenesis occurs very early in pregnancy. The ADA recommends HbA1c of < 6.5% at conception, with a lower goal of < 6% during pregnancy if this can be achieved without significant hypoglycemia[22]. Targets may be relaxed to < 7% if hypoglycemia occurs at lower HbA1c levels[22]. Discussions regarding the risks of congenital anomalies with unplanned pregnancy and the importance of effective contraception should be initiated at the onset of diabetes or puberty, and continued thereafter. LARC such as implantable progestin or IUD, should be recommended as first-line therapy for women who do not desire fertility in the near future, as these are the most effective forms of contraception[14,23]. Patients should alert their clinicians before ceasing contraception, and ideally this step would be preceded by monthly meetings between the patient and care team to optimize glycemic control.

Women should ideally be referred to a maternal-fetal medicine specialist (high-risk obstetrician) prior to conception. These specialists can counsel women on possible maternal and fetal complications, and the need for intensified fetal surveillance during pregnancy.

1. Effective contraception is recommended for all sexually active women of reproductive age with T1D or T2D:

   - COCs should be used only in women with duration of T1D of < 20 years with no micro or macrovascular complications.
   - Progestogen-only contraceptive pills or an intrauterine contraceptive device should be used in the case of long-term DM (> 20 years) or presence of micro or macrovascular complications.

2. Individualized preconception counselling can be used depending on the type, duration of DM, and the personal history of each woman. The counselling should include information about the importance of optimal glycemic control before pregnancy, underlining the complications caused by hyperglycemia in fetal anatomy and the short and long term health of the woman.

3. The current pharmacologic therapy be adjusted to ensure fetal safety:

   - Insulin regimens that are approved for use during pregnancy (lispro, aspart and detemir) should be administered.
   - There is no recommendation on superiority of one insulin regime over the other and the choice of insulin regime needs to be individualized from patient to patient. Women who are well controlled on glargine insulin prior to pregnancy may continue taking it during pregnancy as it has now been found safe in pregnancy. However, an informed consent should be obtained from the pregnant woman to continue on glargine.

- Insulin pump therapy should be started at least 6 months before conception, in women with T1D, similar to women with high glycemic variability or brittle diabetes, where there is a strong need of insulin pump therapy.
- Antidiabetic medication should be discontinued and insulin therapy initiated in women with T2D.
- The statin treatment should be discontinued.
- The antihypertensive therapy should be adjusted, since ACEi and ARB are contraindicated in pregnancy. Methyldopa, labetalol, nifedipine or diltiazem should be used.

5. The glycemic targets should be maintained:
   - HbA1c < 6.5% (measurement by HPLC).
   - Fasting glucose, 80–110 mg/dL.
   - 2 h postprandial glucose ≤ 140 mg/dL.

6. Thyroid function should be evaluated by measuring TSH and anti-thyroperoxidase.

7. A glucagon kit should be prescribed, particularly for pregnant women with T1D.

8. Dietary counselling for weight loss should be offered in overweight and women with obesity before conception and dietary plan to reduce hypoglycemic episodes should be applied.

9. Systematic and appropriate physical activity should be undertaken.

10. Folic acid (5 mg/day) should be prescribed 3 months before the cessation of contraception or initiation of efforts to conceive; the dosage should be reduced to 0.4 mg/day from the 12th week of gestation until the end of the breastfeeding period.

11. Quit smoking.

12. Possible micro and macrovascular complications should be investigated and treated:
    - Retinal function should be assessed by fundoscopy with mydriasis and, in the case of proliferative retinopathy, should be treated before pregnancy. Euglycemia should be restored gradually, as long as time permits, taking into consideration that rapid optimization of blood glucose control may accelerate retinopathy.
    - Serum creatinine and eGFR should be measured and 24 h urine collection for albumin and creatinine should be performed.

Table 1: Management of pre-existing diabetes in prepregnancy

Diagnostic steps for preconception	
Laboratory studies	1. HbA1c 2. Urine ACR or PCR 3. TSH in T1D
Clinical screenings	1. Discuss contraception (ideally LARC) 2. OSA screening in obesity 3. Retinal exam-consider CAD screening if multiple risk factors
Therapeutic steps for preconception	
Nonpharmacologic interventions	1. Weight optimization via lifestyle modifications 2. Referral and follow-up with nutritionist to review diet +/− ICR
Pharmacologic interventions	1. Optimize glucose with HbA1c goal < 6.5% 2. May require initiation of insulin in T2D 3. Stop non-insulin agents including SU, TZD, DPP4i, GLP-1RA, SGLT2i 4. Initiation of daily prenatal vitamin (≥ 400 mcg folic acid, 1,000 mg elemental calcium, 600 IU vitamin D/day) 5. Switch off ACEi/ARB to accepted anti-hypertensive agents 6. Stop statin

Source: Alexopoulos et al., 2019[25]

13. A nephrologist consultation should be considered in case of difficult to control arterial hypertension, serum creatinine > 1.5 mg/dl, and/or albumin ≥ 3 g in a 24 h urine collection.

- A medical history should be obtained and a physical examination should be performed to evaluate possible peripheral or autonomic diabetic neuropathy.

- A cardiovascular assessment should be performed in all women with T2D and women with T1D for > 10 years by resting ECG, stress ECG, or/and heart ultrasound. Women with findings of macroangiopathy should be examined by a cardiologist[24].

Table 1 present the diagnostic and therapeutic interventions followed to manage diabetes during prepregnancy[25].

Prepregnancy obesity and weight loss in women with T2D

Obesity is reaching epidemic proportions, present in one of three women of child bearing age. Obesity, recognized as a disease by WHO, is preventable. According to the WHO, a BMI score greater than 30 is considered to indicate obesity. However, BMI among women in the reproductive age group is used often as an indicator of maternal obesity and its likely effect on pregnancy outcomes. Weight loss target and managing obesity before pregnancy may have widespread short- and long-term benefits for pregnancy outcomes and subsequent health of the woman and her child and reduce the risk to transgenerational transmission of complications from mother to child[26].

Obesity is common in T2D and is increasing now in T1D[27] as well and represents an independent risk factor for congenital malformations; particularly cardiac defects[28,29]. As such, efforts should be made to optimize weight, in addition to glycemic control, prior to conception. In a recent study by Persson et al[29], rate of aortic arch defects, atrial septal defect and patent ductus arteriosus increased incrementally with maternal BMI, and rate of transposition of the great arteries was nearly double (adjusted PRR 1.85, 95% CI, 1.11-3.08) in mothers with BMI above 40 kg/m² vs. those with normal BMI. Furthermore, women who are obese are more likely to have comorbid illnesses that can affect outcomes, such as hyperlipidemia[30,31], hypertension[32], and OSA[33,34]. OSA is particularly notable since it is often under-diagnosed[35], and prevalence of OSA in pregnancy may be as high as 5% in Europe and 20% in the US[34]. OSA has been linked to higher rates of gestational hypertension, preeclampsia, preterm birth, low infant APGAR scores, and greater need for neonatal ICU[33,34]. It is also correlated with worse glycemic profiles and IR[36]. Therefore, clinicians should screen for OSA in overweight or women with obesity planning pregnancy, and prompt treatment with continuous positive airway pressure should be initiated for all confirmed cases[37].

All women with diabetes should be referred to a dietician prior to or early in pregnancy. Referral to a registered dietician is particularly recommended for all women with overweight or obesity, to generate a nutrition plan that accounts for pregestational weight, and targets at least 5–10% loss of body weight prior to conception[38].

To prevent neural tube defects, prospective mothers should take ≥ 400 mcg of folic acid daily for at least 1 month prior to conception[39]. They should also ensure intake of 1,000 mg of elemental calcium and 600 IU of vitamin D daily to support bone health in the neonate[40]; these can be prescribed in the form of a prenatal multivitamin and/or consumed via diet.

BMI

As maternal BMI increases, practical difficulties in providing every aspect of obstetric care also increase, such as more antenatal visits, more intensive maternal and fetal monitoring, increased induction of labour, and increased risk of operative delivery. The cost of hospitalization during pregnancy for a woman with a BMI > 26 kg/m² is 5 times greater than for a woman of normal weight (BMI 18–25 kg/m²). Women should be encouraged to enter pregnancy with a BMI < 30, and ideally in as close to the healthy range as possible[41].

Diet and exercise

These are the cornerstone of weight management in preconception and pregnancy. Dietary modifications for weight loss and optimizing nutritional status, combined with aerobic and strengthening exercises, are the first-line therapy for the management of obesity before conception. However, the use of VLED to achieve substantial weight loss in obese women before pregnancy offers the possibility of reducing the healthcare costs associated with antenatal care while improving maternal and fetal outcomes. Women on VLED programs are advised to use contraception[42].

Bariatric surgery

Various studies show that preconception weight loss, achieved by more non-surgical/surgical interventions, has the potential to improve maternal health and reduce risk of pregnancy complications. Numerous retrospective studies of bariatric surgery before conception have demonstrated a reduction in adverse pregnancy outcomes for the mother[42]. After bariatric surgery, women have been found to have a variety of vitamin and mineral deficiencies in pregnancy including vitamins A, C, D, B1, B6, B12, and K, iron, calcium, selenium, and phosphorous. Where possible, women with a history of bariatric surgery should be referred to a specialist dietician for treatment of any nutritional deficiencies before pregnancy and they should wait at least 12–18 months after treatment to conceive, especially in the case of malabsorptive surgery. Therefore, appropriate contraceptive advice should be given. Due to insufficient safety data, medications and surgery for weight loss are not recommended around the time of conception, though should be considered as part of the management of obesity in women who are planning a pregnancy in the future, especially for those with comorbidities and greater severity obesity[43].

Risk and prevention of congenital anomalies

Maternal diabetes has several adverse effects on embryogenesis and fetal development and causes multiple congenital anomalies, and secondary medical complications collectively referred to as diabetic embryopathy. Mothers with diabetes have 2-3 times more chances of having GDM affected with birth defects than mothers without diabetes. High maternal blood glucose itself is a major teratogenic agent as it alters many normal signalling pathways involved in fetal development and organogenesis, though the exact cellular reason for teratogenicity is not clear.

Maternal hyperglycemia alters maternal as well as fetal metabolism. Both maternal and fetal hyperglycemia and ketosis have a role in pathogenesis of adverse outcomes. The interplay of environmental factors (maternal diabetes and intrauterine conditions) and genetic predisposition interplay adversely impacts organogenesis[44]. As organogenesis occurs in the 1st trimester, increased maternal metabolic dysregulation, especially in early pregnancy increases the risk of giving birth to a child with congenital malformations.

Even women with good diabetes control with insulin and tight glycemic control show increased malformation and behavioural impairment as compared to the general population without diabetes. The diabetic status of the father does not play a role in causing malformations. However, paternal T1D increases the risk of diabetes in children later in life. Children born from mothers with diabetes may show lower mental and psychomotor scores later in life[45].

Management

Preconceptional surveillance

In high-risk populations can reduce the incidence of fetal malformations. Tight glycemic control and the use of supplementary diets before conception is the best way of prevention and management[46,47]. Reducing and maintaining HbA1c < 6.1% and having a goal of BMI < less than 25 during the preconception period should be advised to all women. Several studies have demonstrated the benefits of folic acid supplementation (5 mg/day) starting even prior to conception reduces the incidence of neural tube defects[48].

Women from high-risk populations with elevated levels of A1c should be strictly advised not to conceive and counselled before conception with the goal to achieve normal glucose homeostasis before pregnancy with A1c on goal. This could potentially prevent structural birth defects because organogenesis starts early in pregnancy, often even prior to women knowing that she is pregnant.

Nutritional interventions

Along with monitoring of blood glucose levels, this should also be the primary therapeutic goal. The DIPSI has recommended plasma glucose measurement in women with GDM, 2 h after ingesting 75 g of glucose load irrespective of meal timings. Change of lifestyle, dietary interventions and daily light exercise is recommended[49]. Exercise can have an overall positive impact on health by reducing both fasting and postprandial hyperglycemia and overcoming IR. Reducing carbohydrate use and maintaining normal blood glucose levels are helpful in the prevention of ketosis and hyperglycemia. Quantity of calorie intake is a challenging part. Many studies recommended that 30 kcal/kg body weight for women of normal BMI, 24 kcal/kg body weight for overweight women, and only 12-15 kcal/kg for obese women should be considered. Diets having a low glycemic index also reduce the chance of macrosomia. Low glycemic and high fibre diets decrease the need for insulin[50].

According to DIPSI, approximately 30-40 kcal of calorie intake/kg bodyweight or an increase of 300 kcal/day above the basal requirement is suggested for pregnant women[51]. The pregnant woman with diabetes can split their breakfast to reduce the plasma glucose as having 4 idlis/chapati/slices of bread in breakfast, can summate to 140 mg glucose after 2 h, but splitting the same portion into 2 (8 am and 10 am) can reduce the plasma glucose by 20-30 mg after 2 h[51]. Multiple human and animal studies have also demonstrated the positive role of vitamin D in insulin sensitivity and insulin secretion.

WBCs are the first line of defense mechanism of body that help in prevention from any kind of infection and the WBCs are made up of proteins[52]. For this reason 1.1 g of protein/kg body weight or approximately 60-70 g of protein along with 175 g of carbohydrate/day and 28 g of fibre/day is recommended for pregnant women[50,52]. In the first, second and third trimester approximately 0.7, 9.6 and 31.2 g of protein/day is recommended for healthy pregnant women by the Nordic Nutrition Recommendations[53]. A balanced diet containing carbohydrate, protein, fat and vitamins is suggested for pregnant women to provide proper nutrition to the fetus and also to prevent COVID-19 and GDM[52,53]. To compensate the daily vitamin and mineral needs, pregnant women can consume amla for vitamin C; whole grains for zinc; orange and yellow vegetables, egg fish, and milk products for vitamin A and selenium; nuts, oils and oilseeds for vitamin E; and ginger, garlic, citrus, spinach, sunflower seeds and red bell peppers to boost the immune system[52].

Inositols

It has been suggested that hyperglycemia has negative effects on inositol regulation and functioning. Dietary supplementation of inositol-rich nutrients such as cereals, maize, legumes and meat has shown some improvement in fetal organogenesis and growth[54]. Administration of inositol isomers (myo inositol or D-chiro-inositol) formulation has been known to be beneficial for GDM[55].

Fish oil

Fish oil is rich in omega-3, which is a source of eicosapentaenoic acid and docosahexaenoic acid that upregulates the peroxisome-proliferator activated receptor-γ gene expression and enhances the adiponectin gene expression[56,57]. Omega-3 supplementation reduces the inflammatory cytokine release by inhibiting the activation of NF-kB[58].

Drug therapy

Some studies have revealed that a mother treated with insulin has fewer chances of anomalies than those without insulin therapy, even after having the same glucose level. The use of oral metformin is considered safe for the treatment of GDM[50]. Administration of antioxidants such as ascorbic acid, Vitamin E and β-carotene are theoretically said to help prevent malformations by counteracting oxidative stress[45].

Surveillance of the fetus during the first trimester can be done with ultrasound, subsequent imaging and fetal echocardiogram, can be done to better delineate anomalies if present. Specific knowledge of the plan for delivery, expected complications, and psychological support for the mother should be considered during follow-up visits.

Psychosocial support

One of extremely important aspect of antenatal care for women with diabetes is psychosocial support[59]. Both DD and more severe psychological/psychiatric problems impact greatly on the care of women with diabetes and specific arrangements should be made for access to appropriate care for these problems. Care providers should have an understanding and supportive attitude[59]. Gilbert et al have recently suggested a positive interaction of psychosocial well-being with diet and physical activity in women with GDM. Also, psychosocial well-being should be integrated with other interventions in clinical practice, as social support and self-efficacy helps with the adoption of a healthy lifestyle following a diagnosis of GDM[60].

Self-management skills for diabetes

The treatment of choice for GDM includes medical and non-medical interventions. Although insulin therapy traditionally has been the first-line treatment, it is not without its challenges. Non-medical interventions are recommended as first-line treatments and involve self-care through lifestyle modifications (typically diet and exercise) and SMBG[61].

Multidisciplinary healthcare teams provide frequent outpatient self-management education, supplemented with self-management support. During the prenatal period, diabetes self-management is multifactorial and includes self-monitoring of blood glucose between 4-7 times/day, administering basal insulin, engaging in accurate carbohydrate counting and administering

bolus insulin according to a specified insulin-to-carbohydrate ratio, and completing routine blood work, including A1c every 3 months. The provision of diabetes self-management education and support interventions during pregnancy provides a promising therapeutic option to lessen the burden of self-management and improve perinatal outcomes.

It is vital to educate patients about the disease, its complications, management strategies, and the importance of adherence. Previous research also suggests that information is crucial for patient adherence to treatment and self-management of the disease[62]. However, the sources of information must be reliable. At all times, HCPs are the greatest source of valid, reliable and comprehensive information on GDM and its management. Although pregnant women try to meet their nutritional needs and are careful about their own health, they disregard the importance of medicine. Studies show that GDM patients often encountered fear and emotional disturbances when informed about the consequences of the disease[62,63]. So, educating them on the importance of medicine and adhering to dietary recommendations improves their medicine intake and makes them more likely to embrace a healthier routine[63,64].

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CHAPTER 12 PREPUBERTY DIABETES CARE

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DM is one of the common diseases in children and adolescents below 18 years of age[1]. The management of DM in this age group can be difficult because of factors such as physical growth, sexual maturity, family dynamics, developmental stages and psychological adjustment during their transition from being dependent to independent[2]. Diabetes in pediatric patients varies from adult patients in terms of epidemiology, pathophysiology, developmental considerations and response to the therapy (Table 1)[3]. There are differences in recommended care for children and adolescents with T1D, T2D and other forms of pediatric diabetes as well.

Table 1: Characteristics of prevalent forms of primary diabetes in children and adolescents

	Age at onset	Onset	Prevalence	Insulin (C-peptide) secretion	Male-famale ratio	Ethnicity	Obesity	Islet autoanti-bodies
T1D	~85%	Childhood and adolescence	Acute severe	Decreased/ absent	1:1	All, Caucasian at highest risk	No	Yes
T2D	~85%	Puberty	Moderate to severe	Variable	1:1.1–1.8	All	> 90%	No
Maturity onset diabetes/Monogenic diabetes	~1-4%	< 25 years	Gradual	Variably decreased	1:1	All	Uncommon	No
Atypical diabetes/ Flatbush diabetes/ Type 1.5 Diabetes/ Ketosis-prone diabetes/Idiopathic T1D	≥ 10% in African-American	Puberty	Acute severe	Variably decreased	Variable	African-American/ Asian	Varies with population	No

Source: Chiang et al., 2018[3]

T1D is the most common form of diabetes in children and adolescents[4], although it may account for a large proportion of cases diagnosed in adult life[5]. The treating physicians must consider the unique aspects of managing children and adolescents with T1D, such as alterations in insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, supervision in the childcare and school environment, susceptibility to hypoglycemia and hyperglycemia in young children, and possible adverse neurocognitive effects of DKA[6,7]. For developing and implementing an optimal management plan, knowledge of family dynamics, developmental stages and physiologic differences related to sexual maturity is vital[8].

Although infrequent, T2D has been seen in pre pubertal children aged < 10 years, and thus it should be part of the diagnosis in children with suggestive symptoms[9]. T1D has been associated traditionally with delayed puberty and recent studies suggest that the onset of puberty in T1D appears similar to that of their peers[10,11]. The secular trend towards a younger age of onset of puberty observed in the general population is also observed in adolescents with T1D, although thelarche (onset of pubertal breast development) still appears to be delayed[12].

As recommended by the ADA, the criteria for the diagnosis of diabetes in pediatric patients are as mentioned in Table 2[3].

Table 2: Criteria for diagnosis of diabetes

CRITERIA 1	CRITERIA 2	CRITERIA 3	CRITERIA 4
Overnight FPG ≥126 mg/dL or 7 mmol/L	2 h plasma glucose ≥ 200 mg/dL or 11.1 mmol/L during an OGTT The test should be performed as described by WHO A glucose load containing ~1.75 g/kg up to a maximum of 75 g anhydrous glucose dissolved in water is recommended	A1c ≥ 6.5% or 48 mmol/mol The test method should be NGSP certified and DCCT assay standardized	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a FPG ≥ 200 mg/dL or 11.1 mmol/L

Source: Chiang et al., 2018[3]

Risk-based screening for prediabetes and/or T2D should be considered in children and adolescents after the commencement of puberty or ≥ 10 years of age, (whichever happens earlier) who are overweight (BMI ≥ 85th percentile) or obese (BMI ≥ 95th percentile) and who have one or more additional risk factors for diabetes. If tests are normal, testing should be repeated at 3 year intervals (minimum) or more regularly if BMI is rising. FPG, 2 h plasma glucose during a 75 g OGTT and A1c can be utilized to test for prediabetes or diabetes in children and adolescents[13-16]. Based on the early occurrence for the onset of puberty or after 10 year of age; risk based screening for prediabetes and/or T2D should be considered especially in case of children and adolescents, who are overweight (BMI ≥ 85th percentile) or obese (BMI ≥ 95th percentile) and who have additional risk factors for diabetes[17].

Once diagnosed with diabetes, a multidisciplinary team comprising of a physician, diabetes care and education expert, registered dietitian and psychologist if available should ideally be involved in the care of the child. In addition to achieving glycemic targets and self-management education[18-20], initial management must include management of other associated comorbidities such as obesity, dyslipidemia, hypertension and microvascular complications.

Self-management education

A multidisciplinary team of physicians trained in pediatric diabetes care and well versed with the challenges of dealing with children and adolescents with T1D and their families should provide care for this population. Diabetes self-management education and support, medical nutrition therapy and psychosocial support should be provided at diagnosis and regularly thereafter in a developmentally appropriate format, which should be built on prior information by individuals skilled in the biological, educational, nutritional, behavioural and emotional requirements of the growing child and family.

Participation of the family is a vital component of optimal diabetes treatment during childhood and adolescence. The pediatric diabetes care team must be proficient in evaluating the educational, behavioural, emotional and psychosocial factors, which impact execution of a treatment plan. The team must work with the individual and family to conquer barriers or redefine goals as suitable. Diabetes self-management learning and support requires regular re-evaluation, especially as the child grows, develops and acquires the need for greater independent self-care skills. It is also vital to provide training to day care workers, school nurses and school personnel who are responsible for the care and management of children with diabetes[21-23].

Management of IR prepuberty

Cross-sectional studies at birth and throughout the prepubertal years have consistently shown higher fasting insulin concentrations in females[24-26]. These have also been observed in longitudinal studies during adolescence[27,28]. The Early Bird longitudinal study has previously reported higher levels of IR in 5 year old girls compared to boys, even after accounting for differences in adiposity and physical activity[29]. Gender differences in IR have been attributed to differences in adiposity, fat distribution, sex hormones and pubertal timing[30,31]. Furthermore, as childhood is a period of growth and development, changes in body composition and insulin sensitivity that occur with puberty may influence the thresholds of components used to define metabolic syndrome.

Children of South Asian ethnicity appear to be more predisposed to develop abnormalities of metabolic syndrome, possibly due to their body fat patterning and genetic influences. A multimodality approach including therapeutic lifestyle changes targeted at the individual, family and community is essential for management. Pharmacotherapy for individual components may be required if initial lifestyle management strategies fail to achieve the goals[32].

Individualized glycemic targets and blood glucose monitoring

Pediatric T1D patients should be treated with intensive insulin regimens, either via multiple daily injections or continuous subcutaneous insulin infusion (Table 3)[33-36]. All pediatric patients should self-monitor glucose levels frequently (6 times/day or more if required by glucometer or CGM) before meals and snacks, at bedtime. They should also monitor it as required for safety in specific conditions such as exercise, driving or the occurrence of symptoms of hypoglycemia. When used appropriately, real-time CGM in conjunction with insulin therapy is a valuable tool to lower and/or maintain A1c levels and/or decrease hypoglycemia. When used suitably, intermittently scanned CGM in conjunction with insulin therapy can be helpful to replace self-monitoring of blood glucose[33-36]. Automated insulin delivery systems may be considered for improving glycemic control. A1c goals must be individualized and re-examined over time. An A1c of < 7% (53 mmol/mol) is suitable for many children. Less strict A1c goals (such as < 7.5% or 58 mmol/mol) may be appropriate for patients who cannot express symptoms of hypoglycemia; have hypoglycemia unawareness; lack access to analog insulin, advanced insulin delivery technology, and/or CGM; cannot test blood glucose regularly; or have non-glycemic factors that raise A1c (e.g., high glycators). Less strict A1c goals (such as < 8% or 64 mmol/mol) may be suitable for patients with a history of severe hypoglycemia, limited life expectancy, or where the harms of treatment outweigh the benefits. Physicians may reasonably propose more strict A1c goals (such as < 6.5% or 48 mmol/mol) for certain individual patients if they can be achieved without significant hypoglycemia, negative impacts on well-being or undue burden of care. Lower targets may also be suitable during the honeymoon phase. CGM metrics calculated from CGM use over the most recent 14 days (or longer for patients with more glycemic variability), including time in ranges (within target, below target and above target) are suggested to be used in combination with A1c whenever possible.

Table 3: Types of insulin preparations and approximate insulin action profiles

Insulin type	Onset of action	Peak of action	Duration of action
Rapid-acting analogs	0.25–0.5 h	1–3 h	3–5 h
Regular insulin	0.5–1 h	2–4 h	5–8 h
Intermediate-acting NPH	2–4 h	4–8 h	12–18 h
Long-acting analogs	2–4 h	none	> 12 h

Source: Rosenbauer et al., 2012[33]; Cameron et al., 2013[34]; Nimri et al., 2006[35] and Doyle et al., 2004[36]

Home self-monitoring of blood glucose regimens should be individualized, taking into consideration the pharmacologic management of the patient. Glycemic status should be examined every 3 months.

Nutrition for girls with diabetes

Adherence to diet is associated with a better glycemic control in pediatric patients with T1D[37]. Individualized medical nutrition therapy is suggested for pediatric T1D patients as a vital component of the overall treatment plan. Monitoring carbohydrate intake is the key for achieving optimal glycemic control, and should be accomplished by either carbohydrate counting or experience-based estimation. Complete nutrition education at diagnosis, with annual updates, by an experienced registered dietitian/nutritionist is suggested to estimate caloric and nutrition intake in relation to weight status and CVD risk factors and to dictate macronutrient choices.

Nutrition for patients with prediabetes and T2D, like for all children, should concentrate on healthy eating patterns that stress consumption of nutrient- dense, high quality foods and reduced consumption of calorie-dense, nutrient-poor foods, particularly sugar added beverages.

Pharmacotherapy

The approach for diabetes treatment in young individuals with overweight/obesity is taking long-term health benefits, stringent targets and adverse effects of drugs into consideration[38]. Patients and his/her family members must be aware about the treatment and lifestyle modification[38]. Pharamacotherapy should be initiated in patients with A1c > 7.5, but can be relaxed for 3 months in patients ready for lifestyle modification (agreed to reduce sugar consumption and increase physical activity). In case of highly motivated patients with A1c < 7.5, the duration to initiate pharmacotherapy may be exceed for 3-6 months[39]. The initial therapy for patients with newly diagnosed T2D is metformin with an initial dose of 500 mg once daily that can be increased slowly to 2,000 mg/day[39]. The management of newly diagnosed T2D in young individuals with overweight/obesity is suggested by ADA (Figure 1)[38].

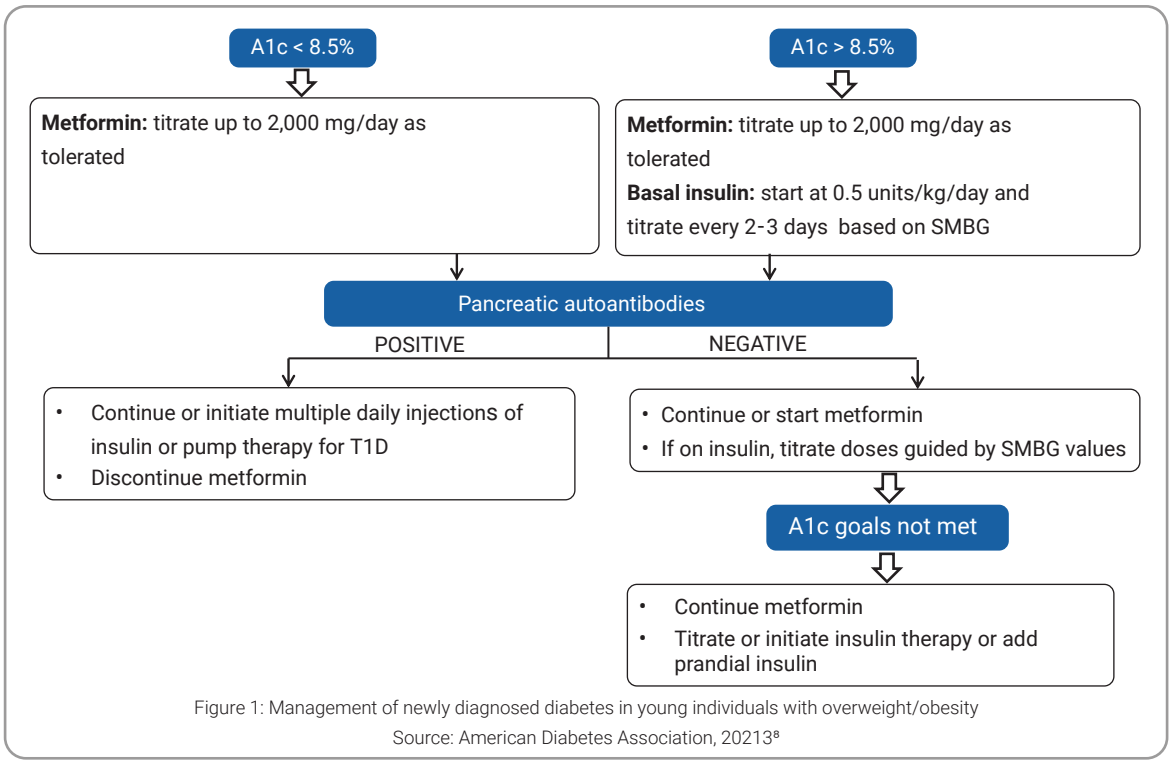

Figure 1: Management of newly diagnosed diabetes in young individuals with overweight/obesity

Source: American Diabetes Association, 20213[8]

Exercise and physical fitness

Exercise positively influences metabolic and psychological health in patients with T1D[40]. It is recommended for all children and adolescents with T1D with a goal of 60 mins of moderate to vigorous intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week[41-44]. Knowledge of common patterns of glycemia during and post exercise is important and may consist of an initial period of brief hyperglycemia followed by hypoglycemia. Families should also be educated regarding prevention and management of hypoglycemia during and post exercise, that includes ensuring patients have a pre exercise glucose level of 90–250 mg/dL (5.0–13.9 mmol/L) and having access to carbohydrates before, during and post activity, individualized according to the type/intensity of the intended physical activity[45]. Patients should be sensitized regarding strategies to avoid hypoglycemia during and post exercise, and overnight following exercise, which may include reducing prandial insulin dosing for the meal/snack before (and, if needed, following) exercise, reducing basal insulin doses, increasing carbohydrate intake, eating bedtime snacks, and/or using CGM. Frequent glucose monitoring before, during, and post exercise, with or without use of CGM, is important to prevent, diagnose and treat hypoglycemia and hyperglycemia with exercise.

All patients with T2D and their families should be given complete diabetes self-management education and support that is specific to patients with T2D and is culturally suitable. Patients with overweight/obesity and T2D and their families should be provided with developmentally and culturally suitable comprehensive lifestyle programs that are incorporated with diabetes management to achieve 7–10% decline in excess weight. Given the requirement of long-term weight management for children and adolescents with T2D, lifestyle intervention should be based on a chronic care model and presented in the framework of diabetes care. Patients with prediabetes and T2D, like all children and adolescents, should be encouraged to take part in at least 60 mins of moderate to vigorous physical activity daily (with muscle and bone strength training at least 3 days/week) and to reduce sedentary behaviour[29].

Psychological aspects in prepuberty in girls with diabetes

At diagnosis and during routine follow-up care, psychosocial issues and family stresses that could impact diabetes management should be analyzed and apt referrals to trained MHPs, preferably skilled in childhood diabetes should be provided. MHPs need to be considered vital members of the pediatric diabetes multidisciplinary team. Family involvement in diabetes management tasks for pediatric patients should be encouraged; it should be recognized that premature transfer of diabetes management to the child can result in diabetes burnout, non-adherence, and worsening of glycemic control[46,47]. Physicians should assess food security, housing stability/homelessness, health literacy, financial barriers and social/community support and utilize that information to make treatment decisions. Physicians should also consider enquiring from patients and their parents about social adjustment (peer relationships) and school performance to assess whether further intervention is required[48]. Patients with diabetes should be assessed for psychosocial and diabetes related distress, generally starting at 7–8 years of age[49]. Adolescents should be offered time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. Screening of patients with T1D for eating disorders should commence between 10-12 years of age[50-51]. The DEPS-R is a dependable, valid and brief screening tool, which can be utilized for identifying disturbed eating behaviour.

Patient-appropriate standardized and validated tools should be used to assess for DD and mental/behavioural health in patients with T2D, with consideration to symptoms of depression and eating disorders, and refer to specialty care when required. When initiating glucose-lowering or other medications for patients with overweight/obesity and T2D, medication-taking behaviour and their effect on weight should be considered. Patients should be evaluated for tobacco, electronic cigarettes and alcohol consumption at diagnosis and regularly thereafter.

Adherence to self-management

Medications for patients with diabetes play an important role in diabetes care and need a high level self-care behaviour and self-management. However, poor adherence to diabetes treatment is common, which causes severe health complications and increased mortality. Barriers to adherence may consist of complex treatment regimens often along with long-term multi-therapies, side effects due to the medication as well as insufficient, incomprehensible or confusing information or instructions provided by the HCP. Multidisciplinary approaches can support adherence success and can enable a more effective management of diabetes care[52].

Summary

Diabetes is one of the common metabolic disorders in childhood and adolescence, including peripubertal girls and necessitates specialized pediatric diabetes treatment and continuous care. This can ensure that the recurrent changes in therapy that are dictated by the patient's development are carried out in concordance with the relevant guidelines. Globally, the importance of the involvement of a multi-professional team is being recognized, which must be reachable to all pediatric patients with diabetes and their families. Evidence suggests that care facilities, which are far away from patient's place of residence leads to poorer metabolic control and to more frequent and longer hospital stays. Hence, measures should be taken to ensure access of patients to pediatric diabetes care facilities.

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CHAPTER 13 GESTATIONAL DIABETES MELLITUS: PATHOPHYSIOLOGY AND DIAGNOSIS

Dr. Shailaja Kale, Dr. Mary John

Metabolic changes during normal pregnancy

Diabetes complicates 6–9% of pregnancies with the vast majority (90%) of cases due to GDM. The physiological changes during pregnancy, such as IR, gestational weight gain and changes in body composition makes diabetes treatment even more challenging[1].

Glucose metabolism during pregnancy

Insulin sensitivity and function of β-cells both increase and decrease with gestational age in women with normal glucose tolerance. Insulin sensitivity can either increase or decrease in early pregnancy (12–14 weeks). After 34–36 weeks of pregnancy, insulin sensitivity decreases by 40–50% in nearly all women. Women with GDM have greater changes in insulin sensitivity due to their prepregnancy subclinically altered glucose metabolism[1].

Changes in insulin response are assumed to reflect changes in insulin sensitivity (Figure 1 & 2). Early pregnancy increases insulin response regardless of insulin sensitivity. An increase in insulin sensitivity in early pregnancy may reduce insulin doses in women with well-controlled T1D. However, insulin requirements gradually grow from 18 to 20 weeks and through the late 3rd trimester insulin requirements may peak, rise or fall. Decreases in insulin requirements may signal poor placental function and increased risk of perinatal morbidity, while increased requirements may be due to late gestational increases in insulin clearance[1].

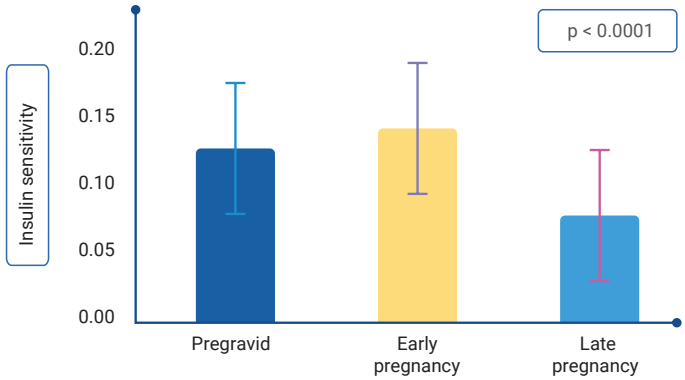

Figure 1: Longitudinal changes in insulin sensitivity. Changes in insulin sensitivity in the pregravid, early pregnancy (12-14 weeks) and late pregnancy (34-36 weeks) period is shown in women with normal glucose tolerance based on hyperinsulinemic-euglycemic clamps. (Mean ± SD; p-values are shown based on ANOVA)

Source: Feghali et al., 2019[1]

An increased risk of GDM is associated with diets that are rich in saturated fats, refined sugars, red and processed meats. Saturated fats directly interfere with insulin signalling, and they can also induce inflammation and endothelial dysfunction—both pathogenic factors in GDM[2].

Strategies to diagnose GDM

GDM, defined as glucose intolerance that develops or is first recognized during pregnancy, is a common antepartum condition that affects approximately 9–25% of pregnancies globally. GDM is characterized by IGT caused by maternal pancreatic β-cell dysfunction, which results in an insufficiency of insulin to maintain glucose homeostasis during pregnancy[3]. An overview of the most commonly used guidelines for screening and diagnosis of GDM is shown in Table 1[4].

In 2019, nearly 20 million pregnancies were complicated by gestational diabetes worldwide. The South East Asian region had the highest prevalence, with 27% of the pregnancies affected by hyperglycemia[5].

GDM diagnosis can be accomplished with either of two strategies:

1. The "one-step" 75 g OGTT derived from the IADPSG criteria (Figure 3), or the diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:
   - **Fasting:** 92 mg/dL (5.1 mmol/L)
   - **1 h:** 180 mg/dL (10.0 mmol/L)
   - **2 h:** 153 mg/dL (8.5 mmol/L)[6]

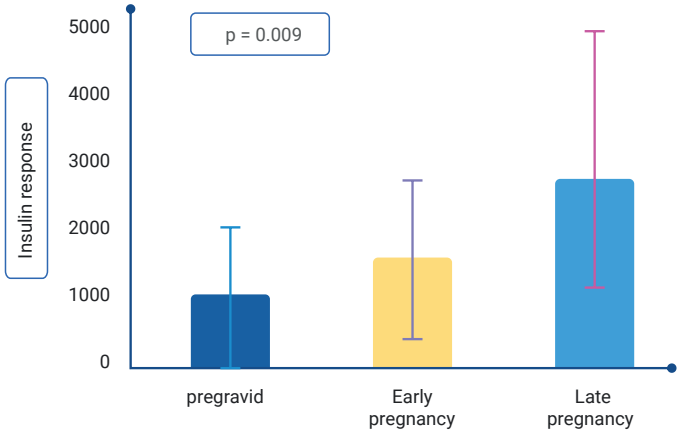

Figure 2: Longitudinal changes in insulin response. Changes in insulin response in the pregravid, early pregnancy (12–14 weeks) and late pregnancy (34–36 weeks) period is shown in women with normal glucose tolerance based on first phase insulin response to an intravenous glucose tolerance test (0–10 min). (Mean ± SD, p values are shown based on ANOVA)

Source: Feghali et al., 2019[1]

2. The older "two-step" approach with a 50 g (non-fasting) screen followed by a 100 g OGTT for those who screen positive, based on the work of Carpenter and Coustan's interpretation of the older O'Sullivan criteria.

   The diagnosis of GDM is made when at least two of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria):

   - **Fasting:** 95 mg/dL (5.3 mmol/L)
   - **1 h:** 180 mg/dL (10 mmol/L)
   - **2 h:** 155 mg/dL (8.6 mmol/L)
   - **3 h:** 140 mg/dL (7.8 mmol/L)[6]

Table 1: Current guidelines for screening and diagnosis of GDM

Guideline, Year	Range	One step	Two step	OGTT criteria	OGTT time	Risk factors list	Screening in early pregnancy
IADPSG, 2010	Global	✓		≥ 5.1 (fasting), ≥ 10.0 (1 h) and/or ≥ 8.5 mmol/L (2 h)	24-28 Weeks	✓	FPG ≥ 5.1 mmol/L in early pregnancy is diagnosed as GDM
WHO, 2013	Global	✓		IADPSG	Any Time		Criteria apply for the diagnosis of GDM at any time during pregnancy
FIGO, 2015	Global	✓		IADPSG	24-28 Weeks/ any other time	✓	Not applicable due to lack of clear evidence
NICE, 2015	UK	✓		≥ 5.6 mmol/L (fasting) or ≥ 7.8 mmol/L (2 h)	24-28 Weeks	✓	75 g 2 h OGTT in women with previous GDM as soon as possible after booking
ACOG, 2018	US		✓	CC/NDDG	24-28 Weeks	✓	Consider testing in all women with BMI > 25 kg/m² (or > 23 kg/m² in Asian Americans) and with ≥ 1 additional risk factors
ADA, 2021	US	✓	✓	IADPSG/CC	24-28 Weeks	✓	OGTT for high-risk women at the first antenatal visit and classified as T1D or T2D

Note: The OGTT threshold value of IADPSG criteria is 5.1–10.0–8.5 mmol/L for a 2 h 75 g OGTT. One or more of these threshold values must be equaled or exceeded for the diagnosis of GDM. The OGTT threshold value of CC criteria is 5.3–10.0–8.6–7.8 mmol/L for a 3 h 100 g OGTT. The OGTT threshold value of NDDG criteria is 5.8– 10.6–9.2–8.0 mmol/L for a 4 h 100 g OGTT. For CC and NDDG criteria, a diagnosis generally requires that two or more thresholds be met or exceeded, although some clinicians choose to use just one elevated value. FIGO: International Federation of Gynecology and Obstetrics, CC: Carpenter and Coustan, NDDG: National Diabetes Data Group

Source: Minschart et al., 2021[4]

Risk factors for GDM

Numerous epidemiological studies have identified a number of risk factors for GDM including advanced maternal age, ethnicity, a previous history of GDM, and a family history of T2D. Data support the importance of periconception and preconception risk factors in the development of GDM:

- Overweight or obesity (BMI ≥ 25 kg/m²)
- Advanced age
- Non-white ancestry
- Family history of T2D
- Previous history of GDM
- Parity (number of pregnancies > 20 weeks)
- Male fetus
- Multiple pregnancy
- Genetic factors
- PCOS
- Cigarette smoking
- Psychosocial factors (depression in pregnancy)
- Unhealthy dietary factors before pregnancy
- Physically inactive lifestyle before and during pregnancy[7]

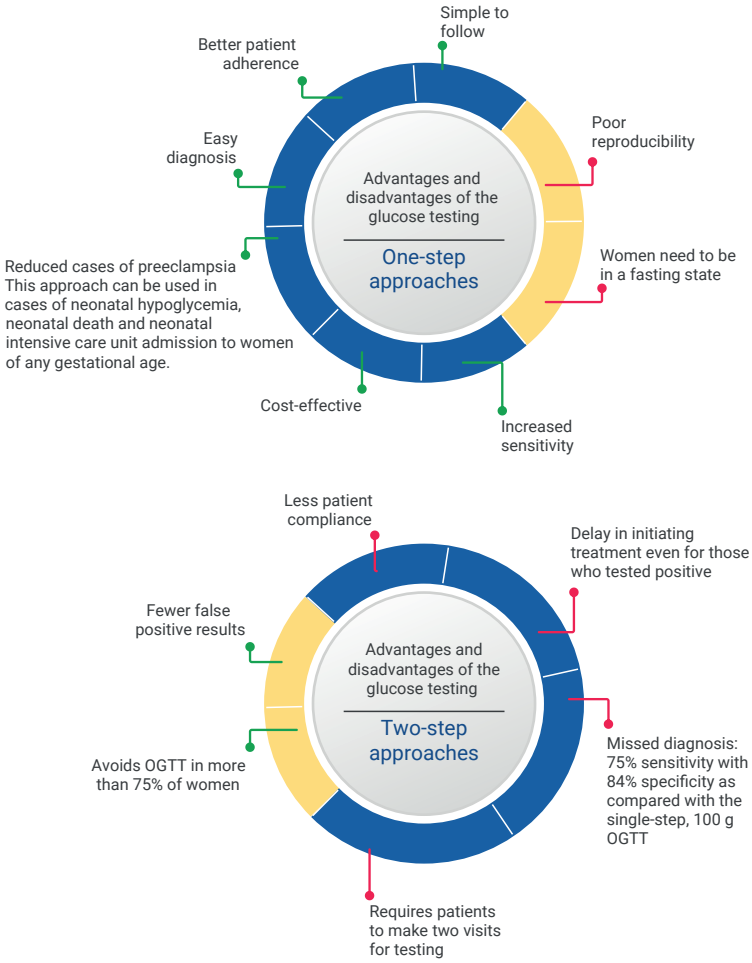

Figure 3: Advantages and disadvantages of the one-step and two-step approaches of glucose testing

Note: NICU: Neonatal intensive care unit

Source: Alejandro et al., 2020[3]

β-cell dysfunction and IR

Hyperinsulinemia and β-cell defects are two metabolic abnormalities in GDM. In many cases, especially in populations prone to diabetes and obesity, these defects predate conception (Figure 4). The metabolic adaptations during pregnancy place additional stress on β-cells[7].

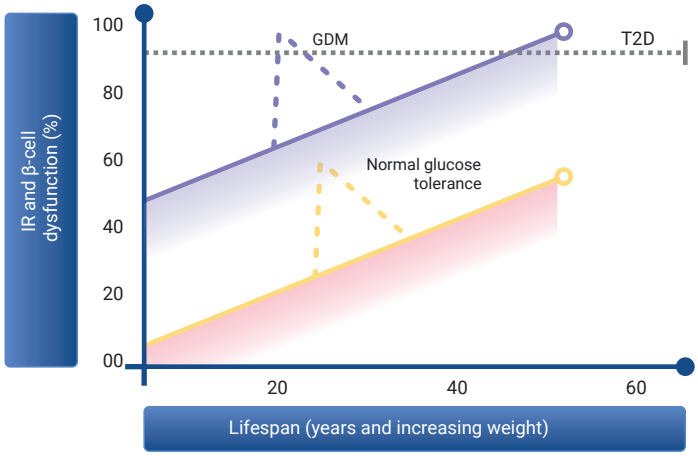

Figure 4: Pregnancy as a metabolic stress test for future metabolic disorders

Source: McIntyre et al., 2019[7]

The increased risk of T2D in women with a history of GDM after pregnancy is related both to pre-existing (often undiagnosed) baseline abnormalities and to further, progressive β-cell dysfunction after the index GDM pregnancy, which are associated with factors such as retention of excessive gestational weight gain and increase in IR[7].

Insulin resistance

There is evidence of decreased peripheral insulin sensitivity in women who are normoglycemic before pregnancy but develops GDM later in pregnancy. The ability of pancreatic β-cells to increase insulin response enables these women to maintain normoglycemia early in pregnancy. By late pregnancy, the insulin response is inadequate due to IR. Pregnancy-induced IR leads to hyperglycemia in many cases[7].

IR is caused by a lack of plasma membrane translocation of glucose transporter 4, the primary transporter responsible for bringing glucose into the cell for energy use. Compared to a normal pregnancy, GDM slows insulin-stimulated glucose uptake by 54%. A decrease in the tyrosine or increase in serine/threonine phosphorylation of the insulin receptor dampens insulin signalling. In addition, GDM has been linked to altered expression and/or phosphorylation of downstream regulators of insulin signalling such as insulin receptor substrate-1, phosphatidylinositol-3-kinase and glucose transporter 4. Many of these molecular changes last postpartum[2].

β-cell dysfunction

β-cells store and secrete insulin in response to glucose load. β-cell dysfunction is thought to be caused by chronically high insulin levels. Defects can occur during pro-insulin synthesis, post-translational modifications, granule storage, sensing of blood glucose concentrations or the complex machinery that supports granule exocytosis. IR exacerbates β-cell dysfunction. Reduced insulin-stimulated glucose uptake contributes to hyperglycemia by overburdening β-cells to produce more insulin. Glucotoxicity is the direct contribution of glucose to β-cell failure. This results in a cycle of hyperglycemia, IR and further β-cell dysfunction[2].

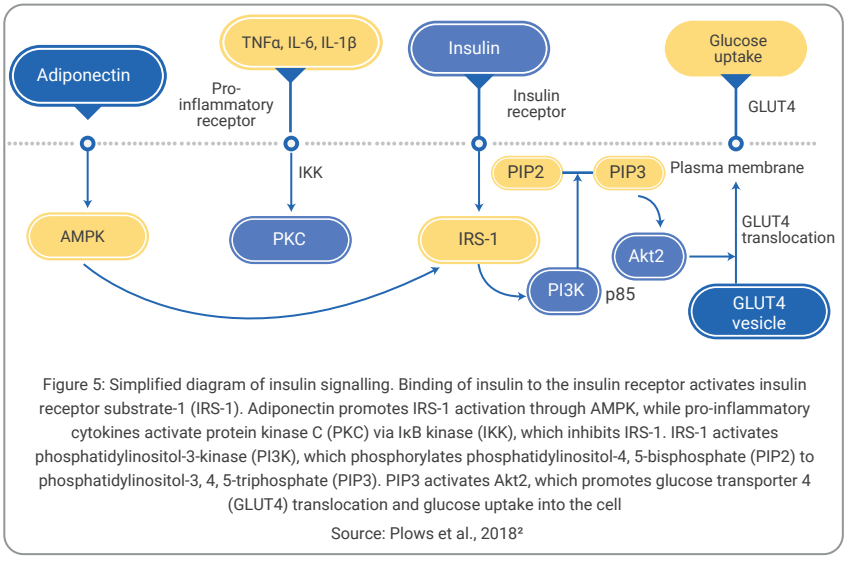

Figure 5: Simplified diagram of insulin signalling. Binding of insulin to the insulin receptor activates insulin receptor substrate-1 (IRS-1). Adiponectin promotes IRS-1 activation through AMPK, while pro-inflammatory cytokines activate protein kinase C (PKC) via IκB kinase (IKK), which inhibits IRS-1. IRS-1 activates phosphatidylinositol-3-kinase (PI3K), which phosphorylates phosphatidylinositol-4, 5-bisphosphate (PIP2) to phosphatidylinositol-3, 4, 5-triphosphate (PIP3). PIP3 activates Akt2, which promotes glucose transporter 4 (GLUT4) translocation and glucose uptake into the cell

Source: Plows et al., 2018[2]

Glucotoxicity may also cause β-cell apoptosis over time. Pancreatic samples from T2D patients can show a reduction of β-cell mass by 40–60%, but less than 24% loss after 5 years of disease has also been reported. Reduced β-cell mass, reduced β-cell number, β-cell dysfunction or a mix of all three contribute to GDM, depending on the individual[2].

Neurohormonal network

Molecular, cellular and epidemiologic findings suggest that neurohormonal, epigenetic and microbiologic mechanisms may influence risk for obesity by interacting with socio-environmental factors. The complex neurohormonal systems controlling weight and adiposity can be categorized as either homeostatic or non-homeostatic. People are predisposed to obesity due to homeostatic and non-homeostatic neural controls of energy, which may be exacerbated by the influence of media, marketing and sleep patterns. Epigenetic gene regulation may influence modifiable early life or maternal exposures on obesity risk. Changes in gut flora caused by infant feeding or diet may affect energy absorption and storage of energy[8].

Neurohormonal dysfunction has been associated with IR diseases like GDM. This network, which controls appetite, active energy expenditure, and BMR, is composed of a complex network of central (e.g., cortical regions that control cognitive, visual and "reward" cues) and peripheral (e.g., satiety and hunger hormones) signals. These affect adiposity and glucose utilization, triggering GDM. The circadian clock regulates this network, which may explain why pathological sleep disorders or shift workers have higher GDM rates. Animal studies show that neural networks controlling body weight are established early in life. For example, rats those are both under and over-fed in early life experience epigenetic alteration of the regulatory set-point of hypothalamic neurons. This emphasizes the hypothesis that GDM predisposition may be set in womb. Adipokines (cell signalling proteins) that are secreted primarily by adipose tissue are important regulators of neurohormonal metabolic control[2].

Adipose tissue, liver and gut microbiome

Adipose tissue

GDM is characterized by maternal peripheral IR to glucose disposal, dysregulation of adipokines, altered lipid metabolism, low-grade inflammation, and elevated circulating free fatty acids. All of these metabolic changes increase the risk of developing T2D[9].

Adipose tissue dysfunction is characterized by excessive lipolysis (adipocyte IR) and inflammation, leading to an increase in adipocyte-derived circulating lipids and cytokines that contribute to defective total body insulin-mediated glucose utilization mainly in skeletal muscle. In general IR, including adipocyte IR, is acquired with obesity but not all obese individuals develop adipocyte and systemic IR[9].

Obesity, T2D and GDM are associated with an increased number of resident adipose tissue macrophages that secrete pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β that have been discovered to both impair insulin signaling and inhibit insulin release from β-cells[2].

Liver

GDM is associated with upregulated hepatic glucose production (gluconeogenesis). Fasting increases gluconeogenesis, which is not adequately suppressed in the fed state. The majority of glucose uptake by the liver (~70%) is not insulin dependent, so this is not entirely due to inaccurate glucose sensing due to IR. Common factors between the insulin signalling pathway (Figure 5) and the pathways controlling gluconeogenesis, such as phosphatidylinositol-3-kinase, might contribute to these effects. Increased protein intake and muscle breakdown may also stimulate the process by providing excess gluconeogenesis substrate. The liver, however, does not seem to be a primary pathogenic driver of T2D or GDM[2].

Gut microbiome

The gut microbiome appears to play a role in metabolic diseases like GDM. The gut microbiome can be influenced by early-life events, such as preterm delivery and breastfeeding, and by events in later life, such as diet composition and antibiotic use. The gut microbiome differs between metabolically healthy and obese people, including during pregnancy[2].

The gut microbiota composition of women with GDM resembles that of non-pregnant women with T2D and associated intermediary metabolic traits. A higher proportion of family prevotellaceae and lower phylum Firmicutes was reported in stool bacteria from women with previous GDM. Firmicutes appear to be involved in GDM pathogenesis independent of diet, but the mechanisms are unknown. Prevotellaceae may contribute to increased gut permeability regulated by tight junction proteins, such as zonulin. Increased 'free' serum zonulin is associated with GDM. Increased gut permeability may promote systemic IR by allowing inflammatory mediators to move from the gut into the circulation[10].

In women with GDM, altered normal gut microbiota composition has been linked to adiposity, low-grade inflammation, IR, and hyperglycemia. The gut microbiota of those with GDM remained persistent in the postpartum period, suggesting its potential as a predictive biomarker of T2D[11].

Oxidative stress and placental transport

Oxidative stress

Pathologic pregnancies, including GDM, are associated with heightened oxidative stress due to overproduction of free radicals, leading to abnormal mitochondrial function, and impaired free radical scavenging mechanisms. Reactive oxygen species interfere with insulin receptor substrate-1 and glucose transporter 4 inhibiting insulin-stimulated glucose uptake. The activation of NADPH oxidase by lipid accumulation in adipocytes has been shown to increase TNF-α, IL-6 and monocyte chemoattractant protein-1 production while decreasing adiponectin. Iron supplementation in already iron-replete women is linked to GDM, possibly due to increased oxidative stress. Homocysteine may also cause GDM via oxidative stress. Exposure of β-cells to even small amounts of homocysteine results in impaired insulin secretion. A recent meta-analysis reported significantly higher homocysteine concentrations among women with GDM. Deficiencies and imbalances of vitamin B that are essential for homocysteine homeostasis are associated with GDM[10].

Placental transport

The placenta contributes to IR during pregnancy via its secretion of hormones and cytokines. The placenta itself is also exposed to hyperglycemia and its consequences during GDM. This can impact transport of glucose, amino acids and lipids across the placenta (Figure 6)[2,13]:

GLUCOSE- Glucose is the primary energy source for the fetus and the placenta. Therefore, insulin is not required for the placental transport of glucose. Instead, glucose transport occurs via glucose transporter 1, by carrier-mediated sodium-independent diffusion. However, the placenta still expresses the insulin receptor, influencing placental glucose metabolism. Because the placenta is sensitive to maternal hyperglycemia, it contributes to increased fetal growth and macrosomia[2].

PROTEIN- Amino acid transport across the placenta influences fetal growth. GDM increases System A and L activity. TNF-α and IL-6 are pro-inflammatory cytokines that can modulate these changes. Altered amino acid transport, thus, may also contribute to GDM[2].

LIPIDS- The rise in obesity-associated GDM has shifted the focus from hyperglycemia to hyperlipidemia. The majority of placental gene expression alterations in GDM occur in lipid pathways (67%), as compared with glucose pathways (9%). Preferential activation of placental lipid genes is also associated with GDM compared with T1D. The HAPO Study found independent effects of maternal obesity and glucose on excessive fetal growth[2].

FATTY ACIDS/CHOLESTEROL- Increased expression of some lipases and fatty acid binding proteins improves maternal-fetal transfer of non-esterified fatty acids and/or cholesterol across microvillous and basal membranes. Inhibition of fatty acid oxidation (β oxidation) by byproducts of glycolysis shifts placental fatty acid metabolism to non-esterified fatty acids esterification and triglyceride accumulation. Placental metabolism changes may help regulate fetal exposure and ultimately determine the impact of abnormal maternal metabolism on fetal growth and development[12].

Molecular biomarker of GDM

Many biomarkers have been investigated in the field of GDM research (Table 2), revealing a greater understanding of the complexities of GDM pathophysiology, as well as serving as potential diagnostic markers[13].

Pathophysiology of fetal phenotype in GDM

Maternal glucose is the main macronutrient that sustains fetal growth (Figure 7)[12]. The prolonged exposure of the fetal pancreas to hyperglycemia in pregnant women with T1D or GDM, accelerates maturation of the stimulus–secretion coupling mechanism in pancreatic β-cells, resulting in early hyperinsulinaemia and fetal hyperglycemia. Some amino acids, such as arginine, also stimulate the fetal pancreas and contribute to hyperinsulinaemia. Free fatty acids are released from maternal lipoproteins by lipolysis, but only a small proportion crosses the placenta and contributes to the fetal free fatty acid pool. This pool primarily consists of free fatty acids synthesized in the fetal liver via de novo lipogenesis using excess maternal glucose as a precursor (Figure 8)[7]. Fetal insulin stimulates triglyceride synthesis and fat storage in white adipocytes in the fetus in a sex-dependent manner, which is reflected by a stronger association of cord blood insulin with neonatal fat deposition in males than in females[7].

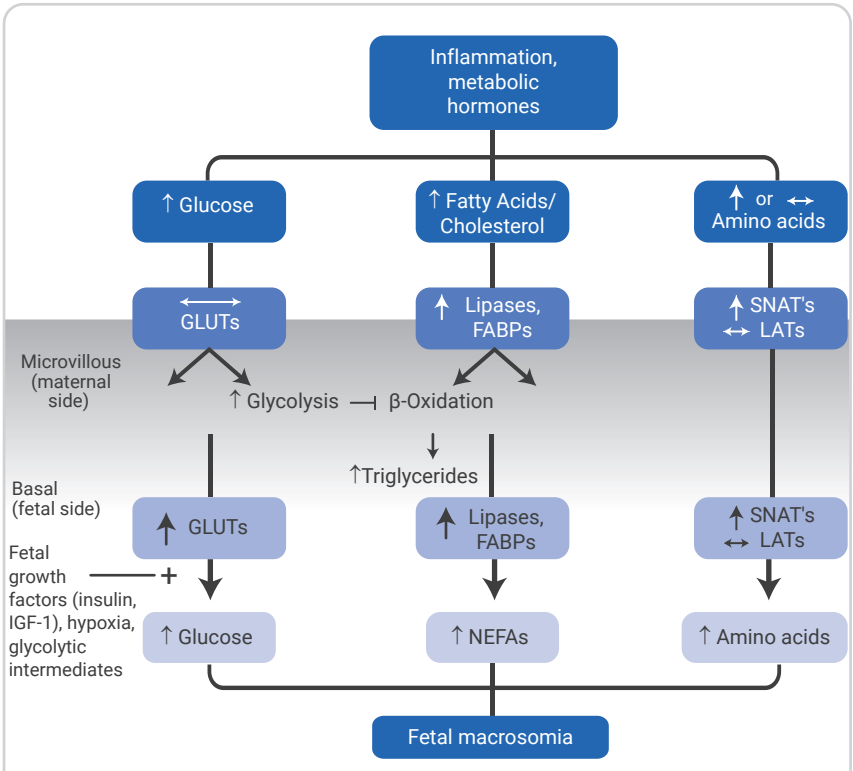

Figure 6: Placental transfer and metabolism of energy substrates in maternal overweight, obesity, and/or DM. Maternal circulating levels of glucose, fatty acids/cholesterol, and amino acids may be altered. FABPs: Fatty acid binding proteins, GLUTs: Facilitated glucose transporters, LATs: System L amino acid transporters, SNATs: System A amino acid transporters

Source: Gallo et al., 2017[13]

Short-term consequences for the mother and the offspring

The short-term complications include preeclampsia, polyhydramnios, operative delivery, shoulder dystocia, birth canal lacerations, fetal overgrowth (also called macrosomia), neonatal hypoglycaemia, jaundice and, in some studies of untreated GDM, perinatal mortality.

The HAPO study documented that maternal hyperglycemia independently and in a graded linear way increases the risk of preeclampsia, preterm delivery, caesarean section, large for gestational age infants, shoulder dystocia, neonatal hypoglycaemia, hyperbilirubinemia and admission to

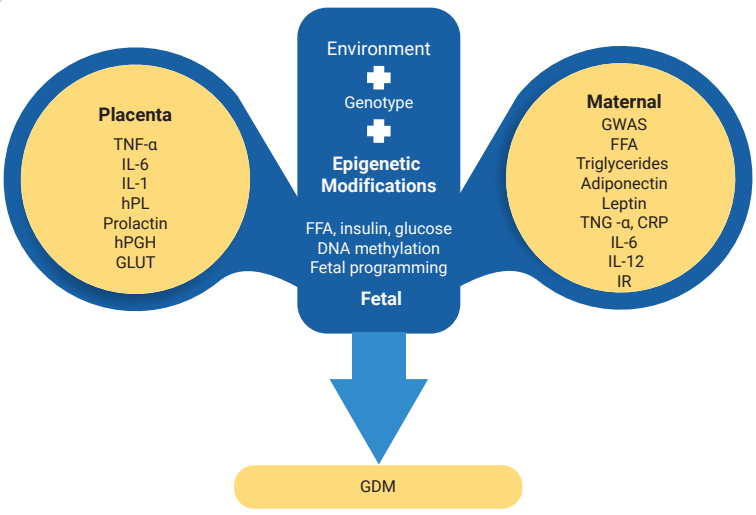

Figure 7: Known pathophysiologic mechanisms in GDM. GWAS: Genome-wide association study, FFA: Free fatty acids, hPL: Human placental lactogen, hPGH: Human placental growth hormone, GLUT: Facilitated glucose transporters

Source: Rodrigo et al., 2018[12]

neonatal special care units. The absolute risk of these complications in women with GDM diagnosed using the IADPSG criteria ranges from 1.8% for shoulder dystocia to 16.6% for neonatal adiposity[7].

Long-term offspring consequences

The risk of hyperglycemia, diabetes, obesity, CVD and structural hypothalamic changes during their subsequent pregnancies in offspring of GDM mothers can be reduced by normalizing maternal blood glucose levels during pregnancy. In a Danish follow-up study of women with GDM, 21% of their offsprings (18–27 years old) had prediabetes or diabetes showing an 8-fold increased risk compared to the general population. Moreover, insulin sensitivity and secretion were reduced, increasing the risk of obesity and metabolic syndrome to 2-fold and 4-fold respectively[7].

Table 2: Biomarkers under investigation in GDM.

Advantages	Biomarker	Disadvantages
In certain sub-populations of GDM women, 1st trimester elevated levels are associated with a risk of GDM prediction at 24-28 weeks	IR	Predictive in all studies, no demonstrated conclusion
GDM association demonstrated in early studies	Insulin sensitivity	Universal comparison is limited by the diversity of calculation methods used
Women who proceed to GDM show an inverse relation of elevated insulin levels in 1st and 2nd trimester	SHBG	Clinical risk factors and multivariate analysis show a loss in significance
Reduction in HDL levels and elevated triglycerides have been observed in women with GDM	Lipids	No demonstrated prediction and diagnosis capacity
TNF-α, CRP, IL-6 are elevated in women with GDM	Inflammatory markers: TNF-α, CRP, IL-6	Lack of prospective data, Non specific
Maternal hyperglycemia alters the response	Placental GLUT	Prospective clinical utility is lacking
Many targets are pointed out: GDM has strong association with common genetic factors found in T2D like CDKAL1 and MTNR1B Gestational glucose level has a positive correlation with DNA methylation	Epigenetic markers	Promised role as a diagnostic tool Identification of more epigenetic sites is required

Note: GLUT: Facilitated glucose transporters
Source: Gallo et al., 2017[13]

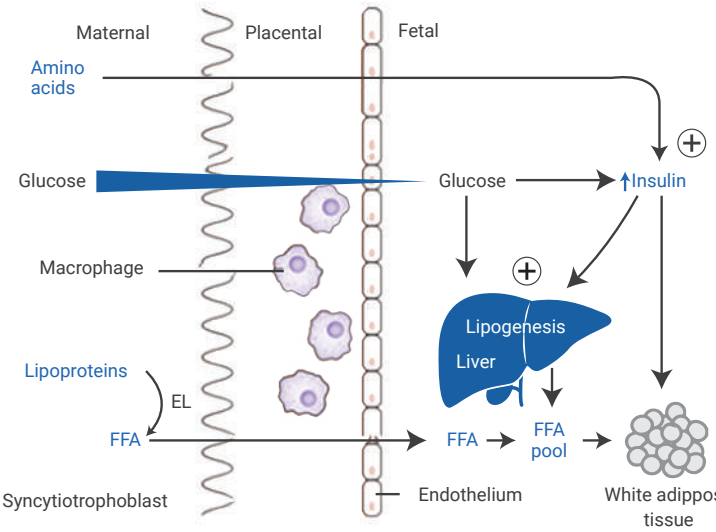

Figure 8: Pathophysiology of fetal phenotype in GDM. Solid lines represent macronutrient flow; dotted lines represent regulating effects of fetal insulin. EL: Endothelial lipase, FFA: Free fatty acids
Source: McIntyre et al., 2019[7]

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CHAPTER 14 GLYCEMIC MONITORING IN PREGNANCY

Dr. Jayashree Gopal, Dr. Anjali Bhatt

The two aspects of glycemic monitoring needs to be considered important during pregnancy. First is the screening for abnormalities in glucose tolerance and second is the monitoring of glycemic control to make sure that proper management is provided to achieve the recommended targets. In most ideal situation, the screening for impairment in glucose tolerance should be done prior to a planned pregnancy but practically we do come across impairments in glucose tolerance first time in a woman's life only during pregnancy.

Screening of GDM

The evidence suggests that most cases of GDM are pre-existing hyperglycemia identified by routine screening in pregnancy. Obesity and diabetes have increased the incidence of pregnant women with undiagnosed T2D. Given the increasing prevalence of undiagnosed T2D in pregnant women, it is reasonable to screen women with risk factors for diabetes during their first prenatal appointment[1].

Recommendations from the ADA, 2021

- Test for undiagnosed prediabetes and diabetes at the first prenatal visit in those with risk factors using standard diagnostic criteria.
- Test for GDM at 24–28 weeks of gestation in pregnant women not previously found to have diabetes.
- Test women with GDM for prediabetes or diabetes at 4–12 weeks postpartum, using the 75 g OGTT and clinically appropriate non-pregnancy diagnostic criteria.
- Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes at least every 3 years.
- Women with a history of GDM found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes[1].

The HAPO study found that even within previously considered normal pregnancy levels, maternal glycemia at 24-48 weeks of gestation increased the risk of adverse maternal, fetal and neonatal outcomes. These results have led to careful reconsideration of the diagnostic criteria for GDM[1].

GDM diagnosis (Table 1)[1] can be accomplished with either of the following two strategies:

- The "one-step" 75 g OGTT derived from the IADPSG criteria, or
- The older "two-step" approach with a 50 g (non-fasting) screen followed by a 100 g OGTT for those who screen positive, based on the work of Carpenter and Coustan's interpretation of the older O'Sullivan criteria[1].

The ACOG and UK-NICE recommend that women who have had GDM in a previous pregnancy should be offered diagnostic testing.

ACOG also recommends early testing in obese women or women with impaired glucose metabolism as early as possible to identify undiagnosed T2D.

ADIPS recommends risk factor assessment in early pregnancy; risk factors are ranked by severity and either one "high" risk factor or two "moderate" risk factors are needed before an OGTT is offered[2].

Table 1: Screening and diagnosis of GDM

One-step strategy	Two-step strategy
Perform a 75 g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.	Step 1: Perform a 50 g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes
The OGTT should be performed in the morning after an overnight fast of at least 8 h.	If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100 g OGTT.
The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded: • Fasting: 92 mg/dL (5.1 mmol/L) • 1 h: 180 mg/dL (10.0 mmol/L) • 2 h: 153 mg/dL (8.5 mmol/L)	Step 2: The 100 g OGTT should be performed when the patient is fasting.
	The diagnosis of GDM is made when at least two of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria): • Fasting: 95 mg/dL (5.3 mmol/L) • 1 h: 180 mg/dL (10.0 mmol/L) • 2 h: 155 mg/dL (8.6 mmol/L) • 3 h: 140 mg/dL (7.8 mmol/L)

Source: American Diabetes Association, 2021[1]

Glucose monitoring in GDM

Fasting and postprandial blood glucose monitoring

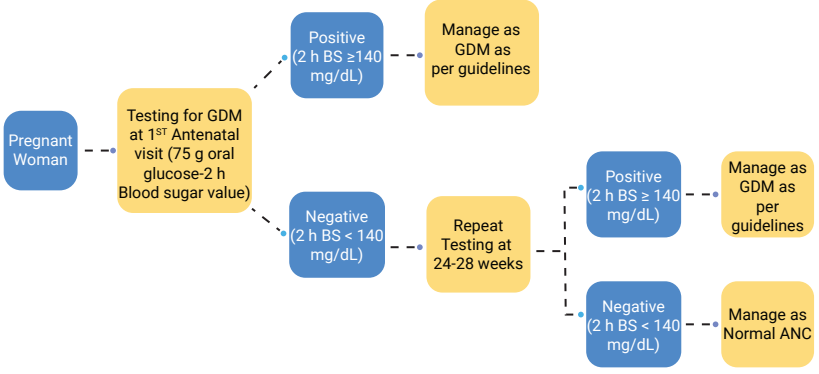

Figure 1: Methodology for diagnosis suggested by The Federation of Obstetric and Gynaecological Societies of India or FOGSI
Note: BS: Blood sugar, ANC: Antenatal care
Source: Gestational Diabetes, Endocrinology Committee FOGSI[2]

Fasting and postprandial blood glucose monitoring is recommended for pregnant women with diabetes. Both 1 h as well as 2 h after major meals are reasonable points to monitor postmeal glucose levels with targets as specified later in the sections below. Insulin pumps or basal-bolus therapy requires preprandial testing to adjust premeal rapid-acting insulin dosage. Postprandial monitoring improves glycemic control and reduces the risk of preeclampsia[3].

Women with T1D may struggle to meet these goals without hypoglycemia, especially those with a history of hypoglycemia or hypoglycemia unawareness. Therefore, based on clinical experience and individualization of care, the ADA recommends less stringent targets for women who cannot attain these criteria[3].

Maternal metabolic surveillance should be directed at detecting hyperglycemia severe enough to increase risks to the fetus. Daily SMBG seems to be preferable than intermittent office monitoring of plasma glucose. Postprandial monitoring is preferable for women on insulin[4].

Pregnant women should self-monitor their blood glucose 6–8 times daily, according to some experts. This includes a fasting measurement in the morning, premeal measurements 3 times daily, 1 h postprandial measurements following breakfast, lunch and dinner as well as 1 final measurement at bedtime. Inconsistencies in the technique or self-reporting of results are potential drawbacks of SMBG[5].

A1c in pregnancy

Increasing A1c levels within the normal range are associated with adverse outcomes in women without diabetes. A1c < 6–6.5% (42–48 mmol/mol) early in gestation is associated with the lowest rates of adverse fetal outcomes in pregnant women with pre-existing diabetes.

A1c < 6% (42 mmol/mol) in the second and third trimester, had the lowest risk of large for gestational age infants, premature birth, and preeclampsia. Therefore, a target of < 6% (42 mmol/mol) is desirable throughout pregnancy, if achieved without hypoglycemia[3].

CGM in pregnancy

CGM measures peak postprandial glucose, mean glucose, nocturnal hyperglycemia episodes, and percent time in range for a 24 h period. CGM and frequent SMBG showed similar outcomes in a meta-analysis: cesarean birth (RR 0.91), large for gestational age newborn (RR 0.67) and neonatal hypoglycemia (RR 0.79). There were no perinatal deaths[6].

CGM in Pregnant Women with T1D Trial showed that CGM, in addition to standard care was associated with a mild improvement in A1c without increasing hypoglycemia, and a reduction in large-for-gestational-age births, length of stay, and neonatal hypoglycemia. An observational study found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes. Given the fluctuations in A1c during pregnancy, CGM-reported mean glucose is preferred over estimated A1c, glucose control indicator, and other calculations. CGM-TIR can be used to assess glycemic control in T1D patients; however it does not provide data to address fasting or postprandial hypoglycemia or hyperglycemia. TIR is not recommended for women with T2D or GDM[3].

The international consensus on TIR endorses pregnancy target ranges, and goals for TIR for patients with T1D using CGM as reported on the ambulatory glucose profile.

- Target range 63–140 mg/dL (3.5–7.8 mmol/L): TIR, goal > 70%.
- Time below range (< 63 mg/dL [3.5 mmol/L]), goal < 4%.
- Time below range (< 54 mg/dL [3.0 mmol/L]), goal < 1%.
- Time above range (> 140 mg/dL [7.8 mmol/L]), goal < 25%[3].

Glycemic targets in pregnancy

Glycemic targets for GDM women according to various guidelines are summarized in Table 2[3,7,8].

Recommendations by the ADA, 2021

- Fasting and postprandial SMBG are recommended in both GDM and pre-existing diabetes in pregnancy to achieve optimal glucose levels.
- Glucose targets are FPG < 95 mg/dL (5.3 mmol/L) and either 1 h PPG <140 mg/dL (7.8 mmol/L) or 2 h PPG < 120 mg/dL (6.7 mmol/L). Some women with pre-existing diabetes should also test blood glucose preprandially.

- Ideally, the A1c target in pregnancy is < 6% (42 mmol/mol) if this can be achieved without significant hypoglycemia, but the target may be relaxed to < 7% (53 mmol/mol) if necessary to prevent hypoglycemia.
- When used in addition to pre- and post-prandial SMBG, CGM can help to achieve A1c targets in diabetes and pregnancy[3].

Due to insulin-independent glucose uptake by the fetus and placenta, and diabetogenic placental hormones, pregnant women with normal glucose metabolism have lower FPG levels than non-pregnant women. In patients with diabetes, combination of insulin and medical nutrition therapy are effective for achieving euglycemia. Pregnancy glycemic targets are stricter than non-pregnant targets, thus women with diabetes must maintain adequate carbohydrate intake to match insulin dosage and avoid hyper- or hypo-glycemia[3].

The ADA and ACOG recommend that FPG values be below 95 mg/dL and PPBG values be below 140 mg/dL at 1 h or 120 mg/dL at 2 h to reduce the risk of macrosomia. Generally, these values are reviewed weekly; however, when there are many abnormal values, more frequent review is common[9].

The Australian Carbohydrate Intolerance Study in Pregnant Females showed a reduction in the primary perinatal composite outcome consisting of neonatal death, shoulder dystocia, bone fracture and nerve palsy, when individuals with GDM were treated to the target of FPG ≤ 5.5 mmol/L, and 2 h PPBG ≤ 7.0mmol/L[10].

Table 2: Glycemic targets for GDM women

CDA 2008	
Fasting	95 mg/dL (< 5.3 mmol/L)
1 h after starting a meal	< 140 mg/dL (< 7 .8 mmol/L)
2 h after starting a meal	< 120 mg/dL (< 6.7 mmol/L)

ADIPS 2014	
Fasting	≤ 90 mg/dL (≤ 5.0mmol/L)
1 h after starting a meal	≤ 133 mg/dL (≤ 7.4 mmol/L)
2 h after starting a meal	≤1 20 mg/dL (≤ 6.7 mmol/L)

NICE 2015	
Fasting	63 and 106 mg/dL (3.5and 5.9 mmol/L)
1 h after starting a meal	< 140 mg/dL (< 7.8 mmol/L)
2 h after starting a meal	-

AICOG 2018	
Fasting	< 95 mg/dL
1 h after starting a meal	< 180 mg/dL
2 h after starting a meal	< 155 mg/dL

ADA 2021	
Fasting	< 95 mg/dL (5.3 mmol/L)
1 h after starting a meal	< 140 mg/dL (7.8 mmol/L)
2 h after starting a meal	< 120 mg/dL (6.7 mmol/L)

Source: American Diabetes Association, 2021[3]; Chiefari et al., 2017[7]; Lende and Rijhsinghani, 2020[8]

A major randomized control trial, conducted by the Maternal-Fetal Medicine Units Network demonstrated that an even tighter glycemic target of FBG < 5.3 mmol/L and 2 h PPBG < 6.7 mmol/L was associated with a significantly decreased risk of large for gestational age, shoulder dystocia, caesarean section, gestational hypertension, and preeclampsia in individuals with GDM. Retrospective cohort studies have found that in GDM, patients treated to a target of FBG ≤ 5.0 mmol/L and 1 h PPBG ≤ 7.0 mmol/L, there was a similar rate of large-for-gestational-age and short-for-gestational-age as those without GDM[10].

Monitoring of weight and nutrition

Obesity is a risk factor for congenital abnormalities, especially cardiac defects. A study found that mothers with BMIs above 40 kg/m^2 had approximately twice the rate of aortic arch defects, atrial septal defects, and patent ductus arteriosus than mo-

thers with normal BMIs. The risk of comorbid disorders such as hyperlipidemia, hypertension and OSA is higher in women with obesity[11]. In ideal situation, weight loss of 5–10% body weight in overweight or women with obesity is recommended prior to conception[11].

During pregnancy, it is important to monitor weight gain as excess weight gain during pregnancy may be associates with poor outcomes. Gestational weight management is important in individuals with GDM. Recommendation of weight gain during pregnancy by the Institute of Medicine guidelines is as mentioned in Table 3[10].

Table 3: Recommended gestational weight gain in pregnancy

Prepregnancy BMI (kg/m^2)	Total weight gain (kg)	Rate of weight gain in second and third trimester (mean [range] kg/week)
Under weight (< 18.5)	12.5-18.0	0.51 (0.44-0.58)
Normal weight (< 18.5-24.9)	11.5-16.0	0.42 (0.35-0.50)
Overweight (25.0-29.9)	7.0-11.5	0.28 (0.23-0.33)
Obese (> 30.0)	5.0-9.0	0.22 (0.17-0.27)

Source: Jiang et al., 2020[10]

MNT for GDM is a personalized nutrition plan involving a dietary assessment to balance sufficient micro and macronutrients for maternal well being and fetal growth, while avoiding excessive carbohydrate and fat intake along with excessive weight gain[10].

The dietary plan should offer enough calories to ensure fetal/neonatal and maternal health to achieve glycemic targets and promote weight gain[3]. Energy requirement increases during second and third trimester. Consumption of calories should be sufficient to promote appropriate pregnancy weight gain. ICMR recommends addition of 350 kcal/day to the adult requirement throughout the second and third trimester for an average weight gain of 10-12 kg. Severe calorie restriction may cause ketonemia, ketonuria and impair the physical and mental development of the offspring[2].

Monitoring for diabetes complications

Women should be screened for complications of diabetes including retinopathy and nephropathy prior to pregnancy. DR can worsen during pregnancy and with brisk improvement in glycemic control. The cause of worsening of retinopathy even with improvement in glycemic control is unknown, though it has been documented in non-pregnant people and is often transient[11].

Pre and postnatal care for women with nephropathy should include a nephrologist and a maternal-fetal medicine specialist. Preeclampsia, preterm delivery, small for gestational age infants, and caesarian section are more common in women with baseline nephropathy[11].

The ADA recommends systolic and diastolic BP of 120–160 mmHg and 80–105 mmHg respectively, for women with chronic hypertension and diabetes to prevent impairment of fetal growth. Canadian guidelines have adopted lower BP thresholds for antihypertensive initiation (start medication if diastolic BP > 90 mmHg and then target < 85 mmHg). Guidelines from the UK recognize end-organ damage as reason to consider lower BP goals, such as diastolic BP < 90 mmHg[11].

A low-dose aspirin 60–150 mg daily (usual dose 81 mg) is recommended between 12 and 28 weeks gestation (ideally before 16 weeks) to reduce the risk of preeclampsia[11].

TSH levels should be monitored for autoimmune thyroid disease in women with T1D, planning for pregnancy[11].

Pre-existing diabetes increases the risk of adverse maternal and neonatal outcomes including preeclampsia, congenital abnormalities, preterm delivery, macrosomia, and stillbirth. Planning and optimizing glycemic control prior to pregnancy can help reduce the risk associated with diabetes[11].

Monitoring for anticipated changes in insulin requirements during pregnancy

Women with pre-existing diabetes are most insulin sensitive during early stages of pregnancy. Close glucose monitoring is therefore essential to avoid hypoglycemia, altered consciousness, seizures and maternal injury, and can further lead to low in-

fant birth weight. Insulin response to glucose and insulin sensitivity change dramatically even during pregnancy (Table 4)[8]. The changes may be different and possibly unpredictable in women who are obese and impaired glucose metabolism during pregnancy. Women with diabetes may become more IR after 16 weeks of pregnancy and insulin requirements may alter weekly, so regular glucose monitoring is necessary[11].

All pregnant women with diabetes are predisposed to diabetic ketoacidosis DKA due to increased IR, accelerated lipolysis and surplus of free fatty acids which can be shunted to ketone bodies. Women should be educated regarding ketone testing and supplied with urine or serum ketone testing supplies. Women (particularly with T1D) should monitor urine ketones, if they vomit, are unable to eat or drink, are otherwise sick, or if their glucose remains > 250 mg/dL after appropriate measures. Women with ketonuria should seek medical attention to reduce maternal and neonatal risk[11].

Table 4: Typical pattern of insulin requirements during pregnancy

Stages of pregnancy	Insulin requirements
0-9 weeks	Increase
9-14 weeks	Decrease
14-16 weeks	Low
16-37 weeks	At least double
37-40 weeks	Can decrease
Immediately postpartum	Can drop to half prepregnancy needs

Source: Alexopoulos et al., 2019[11]

Barriers of glycemic monitoring in pregnancy

Social taboos and cultural habits

Familial and social concerns for a pregnant woman's kid are key barriers for pregnant women in India. Gaps in community information and cultural biases can hinder GDM care. Myths like “exercise harms the baby” and “pregnant mothers must consume food for two” discourage pregnant women from exercising and adhering to a healthy diet[11].

Dietary intake and exercise for optimal glycemic control

Temptation for certain non-nutritional foods during pregnancy, especially carbohydrates, is a major hindrance to adherence. Misconceptions arise from poor engagement with HCPs as some patients are reluctant to ask questions. As a result of these perceived obstacles, many pregnant women remain sedentary. Although studies show that exercise is beneficial to pregnant women, cultural practices make it difficult for GDM patients to adhere to diet, exercise and medication regimens[12].

Lack of awareness on GDM

Most patients are unaware of blood glucose monitoring and treatment adherence. Insufficient knowledge of nutritional issues and disease management causes malnutrition in both mother and fetus. Patient education and self-management are critical to treatment adherence. HCPs are always the best source of valid, reliable and comprehensive information on GDM[12].

Lack of support for optimal glycemic control

Support from partner, family, friends, work colleagues and health professionals are significant for acceptance of diagnosis, treatment adherence and maintenance of optimal glycemic control. This support facilitated self-management and healthy lifestyle behaviors by promoting exercise and the provision of healthy meals in women can assist in achieving optimal glycemic control[13].

Lack of self-monitoring

Despite being aware of GDM, women may not always self-monitor their glycemic control as advised. Women were less likely to do the CBG testing or stopped altogether for a variety of reasons including, fear and anxiety about pricking their finger for CBG testing, playing a musical instrument, feeling that high CBG concentrations would harm their baby, being asked to leave a restaurant when testing, not testing due to busy schedule, and not believing that their recorded CBG results were correct[13].

Financial burden

Adding to the disease burden, the expenses of GDM management prevent pregnant women from seeking prenatal care. Many pregnant women in India lack health insurance. Equipment such as glucometers and related supplies, medications, and diet modifications cause financial burdens. Rural pregnant women have additional financial challenges due to poor income, restricted access to public health care, and travelling issues for hospital visits[10]. A study reported lack of finances to buy insulin, glucose testing strips, snacks, and gym equipment as financial barriers. Shortages of adequate test strips have also been documented to affect diabetes care[14].

Complicated therapeutic regimen

A study reported that complicated therapeutic regimen may be overwhelming to follow due to complexity of storage of insulin, self-injection and SMBG on a daily basis. Intensified insulin regimens for optimal glycemic control, matching prandial insulin needs with carbohydrate intake, premeal blood glucose and anticipated activity can be complicated and overwhelming to a woman with diabetes in pregnancy[14].

Summary

Glycemic monitoring during pregnancy may be a challenging exercise due to fear of medicalization of pregnancy on one hand to lack of clear understanding about the exact targets during pregnancy as each case may be different from the other. Many guidelines and recommendations are available to help in monitoring and directing the management to reach a target. But, in clinical practice, individualization of the targets depending upon the individual risk and benefit ratio is recommended. Fetal monitoring is evolving but yet to be popularized concept which might help to individualize the targets as well as care in high risk women with diabetes during pregnancy.

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CHAPTER 15 MANAGEMENT OF DIABETES AND HYPERTENSION IN PREGNANT WOMEN

Dr. Aakanksha Patharia, Dr. Priyachinnappa

Chapter 14 dealt with GDM. This chapter will cover the management of HDP in women with diabetes or GDM. HDP include gestational hypertension or preeclampsia.

Background

Hypertension affects majority of patients with DM[1]. Even in patients who do not have hypertension, those with DM have a higher BP than those without DM[2]. The twin epidemic of DM and hypertension is prevalent in India[3].

Several shared pathophysiological mechanisms and genetic factors contribute to the coexistence of the two conditions[1]. IR in DM causes hyperinsulinemia and hyperglycemia, which in turn causes vascular remodelling and increased body fluid volume. This increases peripheral artery resistance and thereby the systolic BP[4]. As DM progresses, vascular remodelling contributes to complications like diabetic nephropathy, where afferent arteriolar remodelling leads to increased glomerular pressure. This further contributes to hypertension of renal origin[4].

Thus, patient awareness, risk attenuation, timely diagnosis and management are critical for limiting this twin epidemic.

Definition

Hypertension affects majority of patients with DM[1]. Even in patients who do not have hypertension, those with DM have a higher BP than those without DM[2]. The twin epidemic of DM and hypertension is prevalent in India[3].

Gestational hypertension: BP ≥ 140 systolic or ≥ 90 diastolic, on 2 separate occasions at least 4 h apart, after 20 weeks gestation in a previously normotensive woman and without proteinuria and severe features of preeclampsia (thrombocytopenia, renal insufficiency, elevated liver transaminases, pulmonary edema, cerebral or visual symptoms)[5].

Preeclampsia: BP ≥ 140 systolic or ≥ 90 diastolic, on 2 separate occasions at least 4 h apart, after 20 weeks gestation in a previously normotensive woman or systolic BP ≥ 160 mmHg or diastolic BP ≥ 110 mmHg confirmed within a short interval (mins) and proteinuria or thrombocytopenia, renal insufficiency, elevated liver transaminases, pulmonary edema, cerebral or visual symptoms[5].

Eclampsia: A patient with preeclampsia and seizures without any other cause[5].

Chronic hypertension: Hypertension diagnosed before 20 weeks of gestation (including hypertension diagnosed before pregnancy)[5]

Chronic hypertension superimposed with preeclampsia: Sudden increase in previously well controlled hypertension or new onset proteinuria[5].

Gestational hypertension and diabetes: Common risk factors

GDM and gestational hypertension are major complications of pregnancy, affecting to 16% and 8% of global pregnancies[6]. Glucose intolerance is a significant predictor of hypertension and non-proteinuric hypertension in pregnancy ($p < 0.01$)[7]. The association between pregnancy induced hypertension and level of glucose intolerance during pregnancy appears to be inde-

independent of other known hypertension risks[8]. During early pregnancy, women with prehypertension had increased risk of GDM, but this risk of GDM increased 2-fold in women with hypertension as compared to women with normal BP[9].

Hypertension and DM risk in subsequent pregnancy are greater in women with both HDP/GDM than those with HDP only when compared with women who have neither[10]. Younger women (15-29 years) with HDP/GDM are at 44% higher risk of developing DM than older women (40-44 years)[10].

Apart from genetic link, risk for both GDM and HDP is influenced by environmental and behavioural factors. Hence, to assess the future GDM/gestational hypertension risk, couples should be considered as a unit as they affect each other's environment and behaviour[11]. A study conducted on 63,438 couples over an average of 12.8 years found that compared to couples with neither GDM/gestational hypertension, couples with either GDM/gestational hypertension had 9 times higher DM risk (hazard ratio: 8.9, 95% CI, 6.4, 12.2), whereas couples with both GDM/gestational hypertension had 16 times higher DM risk (hazard ratio: 16.0, 95% CI, 10.9, 23.5)[11]. Corresponding comparison for hypertension risk showed 2 times and 6 times higher risk in couples either GDM/gestational hypertension (hazard ratio 1.8, 95% CI,1.5, 2) vs. those with both GDM/gestational hypertension (hazard ratio 5.8, 95% CI, 4.9, 7)[11].

Preeclampsia and hypertension: Impact of pregnancy outcome

A survey conducted on 3,695 female nurses found that participants who experienced HDP or GDM showed higher rates of delivering lower birth weight or preterm babies or delivering via cesarean section[12].

A retrospective population-based cohort study (n=506,483) found that preterm birth before 37 weeks occurred in 6% of pregnancies, of which 24.5% of mothers had prepregnancy DM or obesity or hypertension[13]. However, provider initiated preterm birth were more common than spontaneous preterm birth. Compared to women who did not have these conditions, aRR for preterm birth before 37 weeks was higher for DM (3.51, 95% CI, 3.26–3.78) and hypertension (3.81, 95% CI, 3.55–4.10)

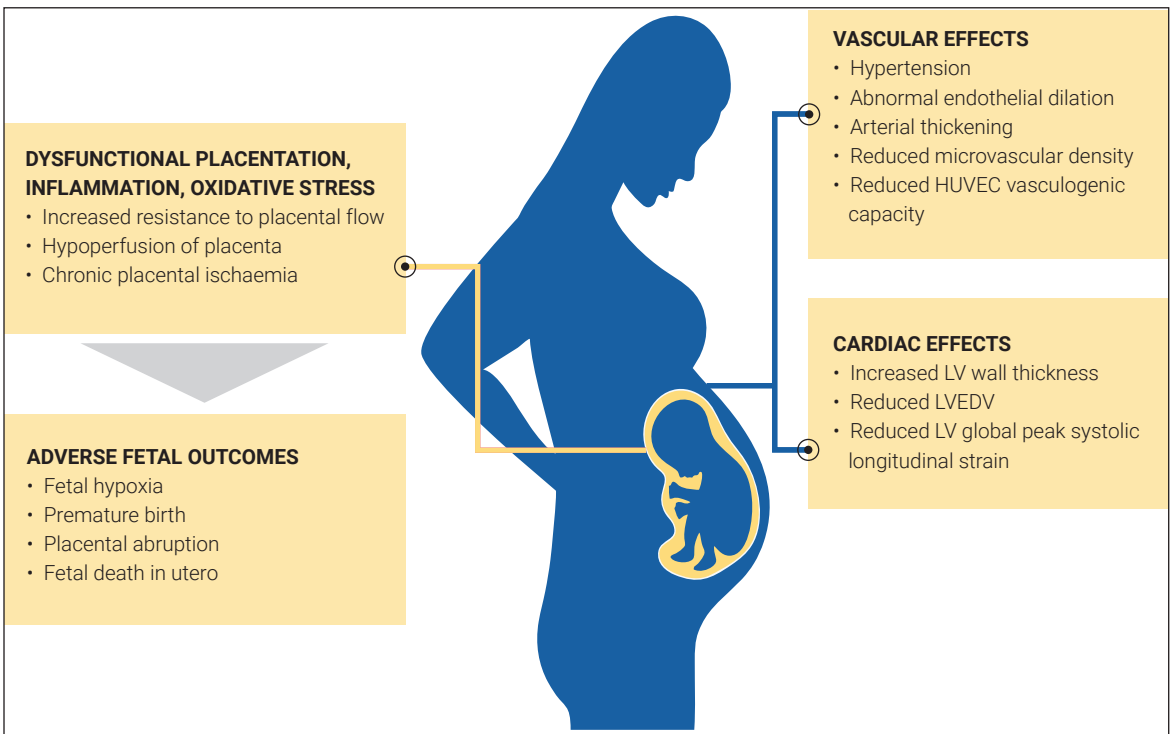

Figure 1: Effects of preeclampsia on the fetus. HUVEC: Human umbilical vein endothelial cells, LV: Left ventricle, LVEDV: Left ventricular end diastolic volume

Source: Fox et al., 2019[14]

(3.81, 95% CI, 3.55–4.10) than for obesity (1.14, 95% CI, 1.10–1.17). Coexisting DM/hypertension was associated with a significantly higher aRR for preterm birth before 37 weeks (6.34, 95% CI, 5.14–7.80) and preterm birth before 34 weeks (aRR 10.33, 95% CI, 6.96–15.33) than DM alone[13].

In this study, prepregnancy hypertension was associated with the highest risk for preterm birth with preeclampsia (aRR 45.42, 95% CI, 39.69–51.99) and preterm birth with small for gestational age (aRR 9.78, 95% CI, 7.81–12.26)[13]. On the other hand, prepregnancy diabetes was associated with increased risk for preterm birth with large for gestational age babies (aRR 28.85, 95% CI, 24.65–33.76)[13].

HDP has a significant adverse cardiovascular impact on the growing fetus[14]. As shown in Figure 1, there are several adverse changes in the placenta and vasculature which result in fetal hypoxia, premature birth, placental abruption and fetal death in utero[14]. These effects persist in offspring after birth.

Cardiovascular risk in GDM

The survey conducted on 3,695 female nurses, also found a strong association between cardiovascular risk factors and HDP and GDM[12]. Conversely, a systematic review and pooled meta-analysis of nine studies (n=5,390,591 women and 101,424 cardiovascular events), found that women with GDM had a 2-fold higher risk of future cardiovascular events as compared to women without GDM (RR 1.98, 95% CI, 1.57-2.50)[15].

Coexisting preeclampsia and GDM is associated with a very high prevalence of coronary microvascular dysfunction, which may correlate with an increased risk for future cardiovascular events[16]. Further, excessive weight gain during pregnancy and GDM are major intra pregnancy risk factors for postpartum chronic hypertension in women with preceding HDP[17]. Other risk factors for developing chronic hypertension included age, prepregnancy BMI, HDP severity, smoking and overt DM[17].

A population based retrospective cohort study (n=64,232 couples) found that having either GDM or gestational hypertension was associated with hypertension (hazard ratio 1.9, 95% CI, 1.8-2), and CVD/mortality (hazard ratio 1.4, 95% CI, 1.2-1.7) as compared to having neither[6]. Participants who had both GDM and gestational hypertension had still higher association with hypertension (hazard ratio 5.7, 95% CI, 4.9-6.7) and CVD/mortality (hazard ratio 2.4, 95% CI,1.6-3.5) than those with neither. Another retrospective cohort study (n=9,118 women with GDM and 37,281 controls) also found a significant risk of hypertension (IRR: 1.85, 95% CI, 1.59 ± 2.16) and ischemic heart disease (IRR: 2.78 95% CI 1.37 ± 5.66) in women who had GDM[18]. Needless to say, both the study found an increased risk of T2D in women who had GDM[6,18]. Interestingly, the study by Daly et al., 2018 did not find an increased risk of cerebrovascular disease in women who had GDM[18].

Endothelial inflammation and early atherosclerosis is likely to be responsible for cardiovascular changes in HDP and GDM, independent of other underlying conditions[19–22]. Increased IR seen in conditions such as GDM, PCOS and obesity, may predispose women to essential hypertension, HDP, hyperinsulinemia, and hyperlipidemia; and high levels of leptin, plasminogen activator inhibitor-1, and TNF-α[23]. These findings may possibly be associated with an increased risk of cardiovascular complications.[24]

Pregnant women who had prepregnancy obesity, chronic hypertension, dyslipidemia, metabolic syndrome or DM are more likely to develop HDP and GDM. This shows that genetic factors and inherent susceptibility to CVD could also result in HDP and GDM[22,25–28]. Subsequent pregnancies add to the stress by causing lipoprotein changes, and increased IR and fluid retention, thereby increasing the risk of gestational hypertension and GDM in genetically susceptible women[22]. History of HDP, high prepregnancy BMI and weight gain of >7 kg from preconception to postdelivery among women with GDM increase the risk of hypertension during 1-5 years postpartum[29].

Diseases prevalence and risks in offspring of hypertensive and mother with diabetes

HDP is associated with higher BP in the offspring, irrespective of other confounders, suggesting that HDP has a strong genetic link[27]. A meta-analysis (n=45,000) showed that children and young adults born to mothers with preeclampsia had a 2.39 mmHg higher systolic, and 1.35 mmHg higher diastolic BP[30]. If this risk persisted into adult life, it would be associated with

12% and 8% increased risk of stroke and mortality from ischemic heart disease respectively[30].

Adolescent offspring exposed to HDP have adverse cardiac remodelling[31]. Gestational hypertension exposure was associated with a greater left ventricular wall thickness compared to adolescents not exposed, while preeclampsia exposure was associated with a reduced left ventricular end diastolic volume[31]. Preterm young-adult offspring of women with HDP have a further reduction in left ventricular global peak systolic longitudinal strain compared to controls born to normotensive pregnancies[32]. Thus, offsprings of women with GDM and HDP are at increased risk for CVD later in life[33]. Furthermore, they are also at increased risk for metabolic disorders and obesity[33].

Cardiovascular follow up after hypertensive disorder of pregnancy

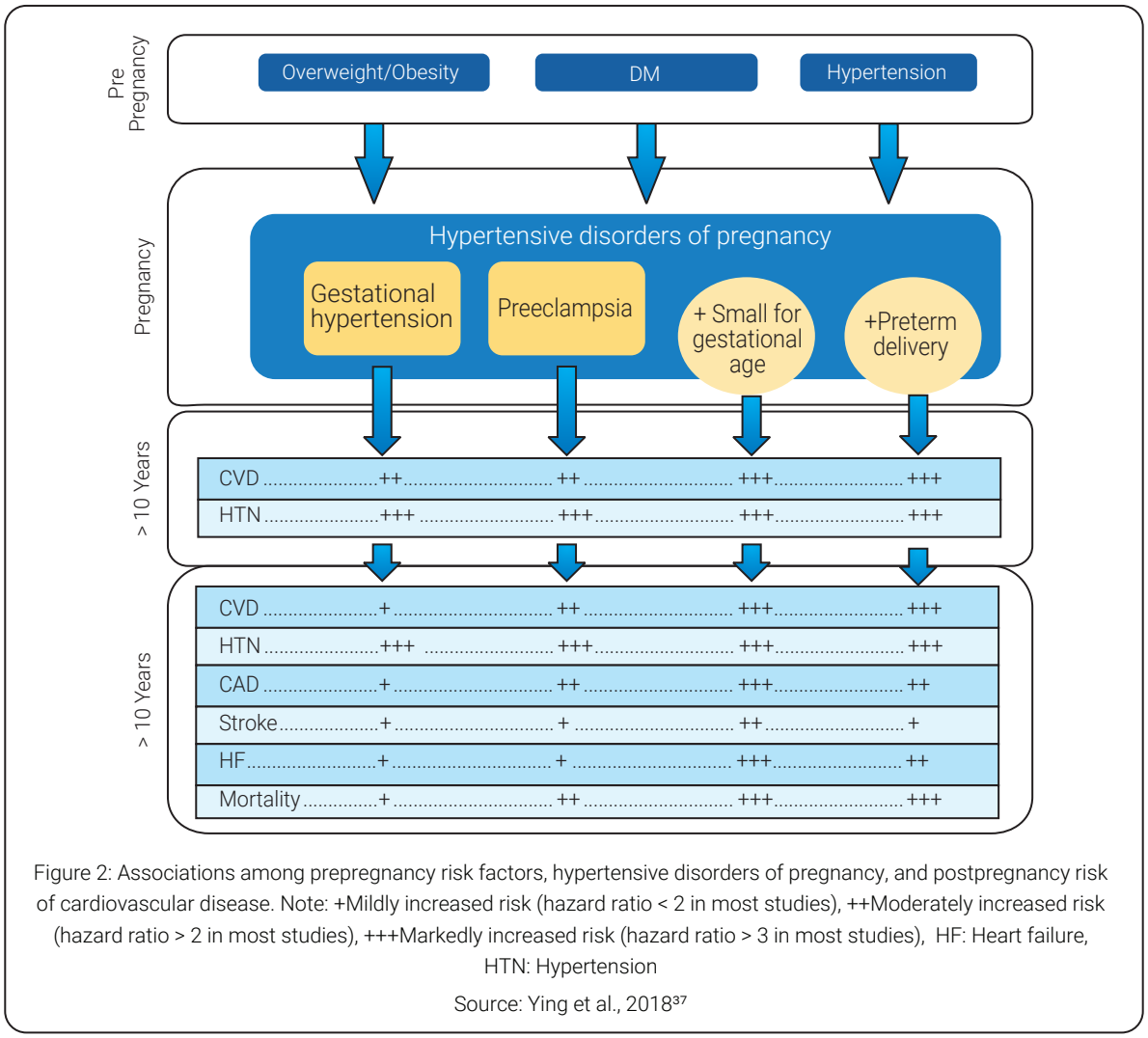

Figure 2: Associations among prepregnancy risk factors, hypertensive disorders of pregnancy, and postpregnancy risk of cardiovascular disease. Note: +Mildly increased risk (hazard ratio < 2 in most studies), ++Moderately increased risk (hazard ratio > 2 in most studies), +++Markedly increased risk (hazard ratio > 3 in most studies), HF: Heart failure, HTN: Hypertension

Source: Ying et al., 2018[37]

Need for follow-up

Cardiovascular follow-up after HDP is necessary because HDP is a well known risk factor for subsequent hypertension/chronic hypertension, T2D, CAD and CVD (like stroke), heart failure and mortality (Figure 2)[17,34–37]. Prepregnancy hypertension increases the risk of preeclampsia, while prepregnancy obesity/overweight and DM increase the risk of HDP. The risk of CVD outcomes further increases if the woman with HDP delivers preterm or has small for gestational age baby[37].

A meta-analysis of 17 cohort/case–control studies (n=approximately 3 million women) showed > 2-fold increase in future T2D risk in women with a history of HDP[35]. In a prospective cohort study(n=6,587), a history of HDP was found to significantly predict the risk of developing T2D midlife (50-60years) (OR 1.96, 95% CI, 1.29–2.98)[36].
Adverse pregnancy outcomes (preterm delivery and low birth weight) and preeclampsia are also known to be associated with future risk of maternal ischemic heart disease related hospital admissions or death[38]. Women who had preterm delivery, low birth weight babies and preeclampsia were at 7 times higher risk of ischemic heart disease related hospital admission and death than women without these complications[38].

Family history of premature CVD, which has a strong correlation with HDP and GDM, is also a well known risk factor for future coronary heart disease[39]. Thus, it is seen that common genetic factors form a likely link between family disease, HDP/GDM, and future ischemic heart disease risk. Also, in genetically susceptible women, the risk of gestational hypertension and GDM is significantly higher in next pregnancy[22].

Therefore, women with these gestational conditions should be screened for family history of premature CVD, and those with a strong family history would need a more rigorous follow-up in future than women with HDP/GDM but no family history of premature CVD.

Evaluation

Once a woman is found to have increased BP in pregnancy the following needs to be evaluated:

- **Clinical evaluation for presence of severe disease:** Look for symptoms of visual disturbances, severe headache or right upper quadrant pain and if present this would indicate hepatic abnormality.
- **Presence of proteinuria:** A urine dipstick for the presence of protein can be performed but this test has false positives and false negatives. Hence, it is better to quantify the protein excretion by measuring a urine protein/creatinine ratio with a value of ≥ 0.26 mg protein/mg creatinine considered elevated. A 24 h urine protein is a more cumbersome test.
- **Other laboratory tests:** Liver function tests, renal function tests and platelet count.
- **Severity assessment:** Severe HDP is the presence of BP ≥ 160 systolic and or ≥ 110 diastolic.
- **Fetal well-being assessment:** Performed by obstetrician.

Preventive strategies

Non-pharmacological

Prenatal exercises could have a role in preventing GDM and HDP. A systematic review and meta-analysis (106 studies; n=273,182) found 'moderate' to 'high'-quality evidence from randomized controlled trials that showed that compared to no exercise, interventions that included only exercise, reduced the odds of GDM (OR: 0.62, 95% CI, 0.52-0.75), gestational hypertension (OR 0.61, 95% CI, 0.43-0.85) and preeclampsia (OR 0.59, 95% CI, 0.37-0.9)[33]. However, the beneficial effect of exercise was not seen when it was clubbed with other co-interventions.

To reduce their risk of GDM, preeclampsia and gestational hypertension by 25%, women would need to include 600 MET min/week of moderate intensity prenatal exercise, such as 140 mins of briskwalking, stationary cycling, water aerobics or resistance training[33]. Accumulated exercise volumes > 600 MET min/week resulted in a greater reduction in the odds of developing GDM, preeclampsia and gestational hypertension. Results from meta-regression analyses showed maximum benefit was attained when exercise was performed at a frequency of 3 days/week for ≤ 25 mins[33].

Other than this, most guidelines recommend that women should be physically active throughout the pregnancy, if not contra-indicated[40,41].

Pharmacological

Metformin is likely to be a good preventive strategy. A systematic review of 15 studies found that metformin use in women with GDM was associated with a significantly reduced risk of pregnancy induced hypertension (RR 0.56, 95% CI, 0.37–0.85) and a non-significant reduction in preeclampsia risk (RR 0.83, 95% CI, 0.60–1.14) vs. insulin use; and a non-significant reduction in any HDP risk vs. glyburide (RR 0.71, 95% CI, 0.41–1.25)[42]. Metformin use in obese women was associated with a non-significant reduction of preeclampsia risk when compared to placebo (RR 0.74, 95% CI, 0.09–6.28)[42]. After conducting Bayesian random effects meta-regression with treatment type as a covariate, the probability of metformin having a beneficial preventive effect vs. any other treatment/placebo was 92.7%, 92.8% and 99.2% for prevention of preeclampsia, pregnancy-induced hypertension and any HDP respectively[42].

Cardiovascular targets and recommendations

Since HDP has significant impact on future maternal CVD risk, it is important to identify the right time to treat HDP and the high risk women who need preventive intervention. There are multiple guidelines on the management of hypertension in pregnancy, but no clear consensus on when to initiate antihypertensive treatment (at what BP threshold) and the target BP to achieve.

It is important to keep the BP under control during pregnancy. Women with GDM and gestational hypertension history, who did not take antihypertensives during index pregnancy had a 3.94 times higher risk (95% CI, 1.94–8.02) of developing T2D, compared with normotensive women in index pregnancy. Compared with women with GDM who were normotensive during interconception examination, women who were hypertensive were 3.38 times (95% CI, 1.66–6.87) more likely to develop diabetes and 2.97 times (95% CI, 1.75–5.05) more likely to develop prediabetes. Each 5 mmHg increase in systolic BP was associated with 1.25 times (95% CI, 1.03–1.51) higher risk for T2D and 1.20 times (95% CI, 1.06–1.35) higher risk for prediabetes. Each 5 mmHg increase in diastolic BP was associated with 1.49 times higher risk (95% CI, 1.18–1.88) for T2D and a 1.42 times higher risk (95% CI, 1.22–1.65) for prediabetes[43].

Antihypertensive medications that are regarded safe in pregnancy, such as methyldopa, β-blockers (labetalol) or calcium antagonists can be used to achieve the desired BP targets[44]. ACEi/ARB/ACE are not used in pregnancy due to increased risk of congenital malformation (first trimester use) and abnormal fetal renal development and renal failure (associated with last trimester use)[44]. Table 1 shows the various BP target, BP threshold and recommendations by various guidelines[37,45-48].

Overview of antihypertensive drugs in pregnancy

All antihypertensive drugs cross the placenta and studies comparing the various commonly used drugs are few[49].

However, the following pharmacological therapies can be started after weighing all pros and cons of the treatment[50].

β blockers

Labetalol is a commonly used drug in this class and has both α and β blocking action. It is preferred to other β blockers and it may preserve the uteroplacental blood flow. Asthma is a contraindication to its use. Its use has been associated with hepatotoxicity, although rare.

Intravenous labetolol are given in doses of 20 mg over 2 mins and repeated in 10 mins intervals until the BP reduces or a cumulative dose of 300 mg is reached.

For stable outpatients the dose is oral labetalol 100 mg twice daily and increased by 100 mg every 2-3 days until a maximum of 2,400 mg is reached.

Table 1: BP thresholds and targets for treatment of HDP and recommended strategies for preventing CVD

	Treatment of HDP		Prevention of future CVD	
Guideline	**BP threshold**	**BP target**	**HDP category targeted**	**Recommendations for HCPs**
American College of Cardiology/ American Heart Association[45]	No recommendation	No recommendation	Preeclampsia, gestational hypertension	**Lifestyle modifications:** » Smoking cessation » Dietary approaches to hypertension -like diet » Regular physical activity » Weight management
ACOG[46]	**Preeclampsia:** Systolic BP ≥ 160 or diastolic BP ≥ 110 mm Hg **Chronic hypertension:** Systolic BP ≥ 160 mm Hg or diastolic BP ≥ 105 mm Hg	Systolic BP 105–160 mm Hg and diastolic BP 80–120 mm Hg	Recurrent preeclampsia	**Lifestyle modifications:** » Smoking cessation » Exercise » Weight management
European Society of Cardiology[47]	**GH, pre-existing hypertension or organ damage:** Systolic BP ≥ 140 or diastolic BP ≥ 90 mm Hg **Otherwise:** Systolic BP ≥ 150 and diastolic BP ≥ 95 mm Hg	No recommendation	Preeclampsia, gestational hypertension	**Lifestyle modifications:** » Lifestyle modifications » BP monitoring » Controlling metabolic factors
NICE[48]	Systolic BP ≥ 150 mm Hg or Diastolic BP ≥ 100 mm Hg	Systolic BP < 150 mm Hg and Diastolic BP 80–100 mm Hg	Preeclampsia, gestational Hypertension	Educate women about the increased CVD risk **If preeclampsia:** Keep BMI between 18.5 and 24.9 before next pregnancy

Source: Ying et al., 2018[37]

Calcium channel blockers

Nifedipine is a commonly used drug. There is sparse data on the use of other calcium channel blockers. The oral dose of the extended release tablet is 30-60 mg a day.

Methyldopa

This is a mild antihypertensive and has been used in pregnant women. The dosage is 250 mg 3 times a day.

Hydralazine

Intravenous hydralazine can be used. However, labetolol is preferred over oral hydralazine. Thiazide diuretics are generally not used in pregnancy.

Drugs that are contraindicated

ACEi, ARB, mineralocorticoid receptor antagonists and nitroprusside are contraindicated in pregnancy.

Non-pharmacological treatment

Diet: A healthy diet without significant salt restriction is recommended[50].

Activity: Activity levels are individualized. In patients with stable hypertension, regular physical activity maybe continued, however, in some women with poorly controlled hypertension bed rest may improve uteroplacental circulation[50].

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CHAPTER 16 POSTNATAL CARE OF MOTHER WITH DIABETES

Dr. Usha Sriram, Dr. Roopal Panchani

GDM related comorbidities and its management in mother and newborn

Maternal diabetic complications

Women with GDM are at higher risk of hypertensive disorders including gestational hypertension, preeclampsia and eclampsia. The HAPO study showed positive correlation between impaired glucose tolerance and risk of preeclampisa. The study observed a 5.9% prevalence of gestational hypertension and 4.8% prevalence of preeclampsia in women with GDM. The HAPO study also showed increased frequency (23.7%) of Cesarean section in women with increased glucose levels[1].

A study reported increased perinatal mortality in T2D (46.1/1,000) as compared to general population (12.5/1,000), T1D (12.5/1,000) and GDM (8.9/1,000). Congenital malformations accounted for only 10% of the perinatal mortality. There was a 7-fold increase in the rate of late fetal death and 2.5 fold increase in the rates of intermediate fetal and late neonatal death[2].

Another study from Birmingham, UK showed a 2.5 fold greater risk of perinatal mortality and 11-fold greater risk of a congenital malformation as compared to background population[3]. Women with prior GDM have a 70% greater risk of CVD than women having normoglycemic pregnancies[4].

Diabetic retinopathy

DR is the leading cause of acquired blindness in young and middle-aged adults in the world. Together the hormonal, hemodynamic, metabolic and immunologic changes increase the risk of progression of DR in pregnancy. The proposed mechanisms of retinopathy involve rapid improvement in glycemic control, altered hemodynamic properties, with the reduction of blood flow in the retina and immuno-inflammatory processes[5].

Diabetic nephropathy

Women with nephropathy have increased perinatal risk due to increased risk of preeclampsia, preterm delivery, small for gestational age infants and caesarian section. Women with mild CKD (estimated GFR of > 60 mL/min/1.73 m^2) are less likely to experience maternal adverse effects during pregnancy. Women with more severe kidney disease or with proteinuria may have decline in kidney function that can be exacerbated by hypertension[6].

Macrovascular complications

There is a 3-4 fold increased risk of myocardial infarction in pregnancy with the greatest risk in the peripartum period. Risk factors for ischaemic heart disease include maternal diabetes, obesity and increasing age. Older women with T2D and those with a previous or suspected cardiac history are at increased risk and should be referred to a cardiologist before pregnancy[7].

Obesity

Maternal obesity is one of the leading causes of maternal and infant mortality and increases the risk of congenital malformations, stillbirth, preeclampsia, GDM, induction of labour, emergency caesarean sections, postpartum haemorrhage and infections[7].

Preeclampsia

Women with poorly controlled diabetes, both gestational and overt, are at 2 times higher risk of developing gestational hypertension and preeclampsia. Pregnant women with T1D are at increased risk of developing preeclampsia. Incidence varies from 11-22% reaching up to 36% in patients with vasculopathy. Odds of developing preeclampsia increases approximately 8-fold from the lowest to highest category of BMI[8].

Preterm delivery

Preterm delivery is usually defined as delivery < 37 weeks gestation. Preeclampsia and hypertensive-associated conditions such as intrauterine growth restriction and placental abruption are thought to influence premature birth in GDM women[4]. Spontaneous preterm delivery is seen in approximately 20% among women with diabetes[8].

Caesarean delivery

The reported risk of caesarean delivery is 52% in T1D, 48% in T2D and 37% in GDM. Macrosomia, prolonged labour, preeclampsia and induction of labour in women on insulin are possible risk factors for caesarean delivery[8].

Neonatal complications

Hyperglycemia in pregnancy is associated with various maternal and fetal complications with increased risk of obstetric and neonatal complications, morbidity and mortality[5].

Fetal and Neonatal Consequences of Maternal Diabetes are shown in (Figure 1)[5].

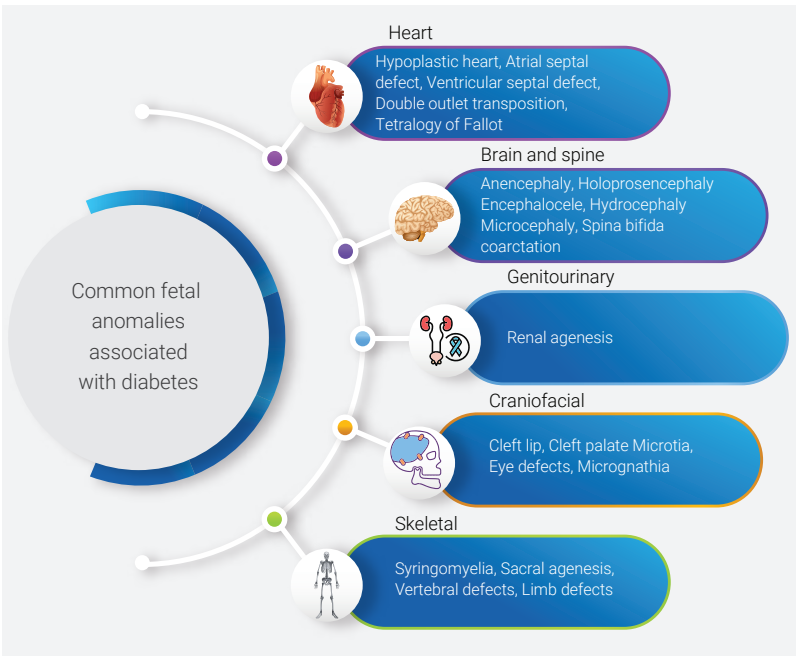

Figure 1: Common fetal anomalies associated with diabetes

Source: Negarto et al., 2012[5]

T2D

Maternal diabetic intrauterine environment is strongly associated with T2D development in offspring. In a study, 30.4% of youth aged 10-22 years with T2D had been exposed to maternal diabetes, compared to 6.3% of healthy youth controls. The risk of developing IGT in offspring of mothers with GDM is 5 times higher than in offspring of mothers without GDM[4].

Lung function

Neonatal hyperinsulinemia can interfere with the production of lecithin resulting in lack or insufficient amount of surfactant leading to inadequate opening of alveoli and consequent respiratory distress syndrome. Signs and symptoms of respiratory distress syndrome include tachypnea, nasal flaring or retractions, radiographic evidence of hyaline membrane disease and/or persistent

oxygen requirement. Babies of mothers with diabetes may develop respiratory distress syndrome even if they are not premature. Pregnancies with good glycemic control have no increased risk of respiratory distress syndrome.

Macrosomia

Macrosomia is an estimated fetal weight > 4500 g that can occur in up to 50% of patients with GDM and in up to 40% of patients with pre-existing diabetes. Babies with macrosomia are at increased risk of shoulder dystocia due to disproportionate accumulation of fat in the shoulders and chest[9]. Maternal IR increases the risk of macrosomia. Macrosomia increases the risk of brachial plexus injury and newborn ICU hospitalizations[4].

Hypoglycemia

Neonatal hypoglycemia is a blood glucose of < 40 mg/dL in the first 12 h of life. Persistent maternal hyperglycemia can cause high blood glucose levels in fetus resulting in increased insulin production and β-cell hyperplasia[9]. Neonatal hypoglycaemia develops in 25-50% of infants of mother with diabetes. Babies with neonatal hypoglycemia may be asymptomatic or may display symptoms such as apnoea, respiratory distress, jitteriness, cyanosis, irritability, poor feeding, hypotonia, lethargy, high-pitched or weak cry and convulsions[10].

Hypocalcemia & hypomagnesemia

Hypocalcemia is defined as ionized calcium levels of < 4 mg/dL or serum calcium level of < 8mg/dL in a term infant and < 7 mg/dL in preterm infant. It occurs in up to 50% of babies born to mothers with diabetes. The severity of hypocalcemia is related to the severity of maternal diabetes and involves decreased function of parathyroid gland. A serum magnesium level of < 1.52 mg/dL indicates hypomagnesemia, severity of which is correlated to severity of maternal diabetes. The signs and symptoms of neonatal hypocalcemia and hypomagnesemia are similar to hypoglycemia and include jitteriness, sweating, tachypnoea, irritability and seizures[10].

Shoulder dystocia

Shoulder dystocia is defined as delivery of the fetal head with impedance of delivery of the fetal shoulders that can result in clavicular fracture and brachial plexus injury. Risk of shoulder dystocia increases with increase in infant weight. When the mother is having diabetes and the birth weight is > 4,500 g, the risk of shoulder dystocia increases to 19–50%[9].

Congenital anomalies

Babies born to women with diabetes are at 2-4 fold greater risk of having a congenital malformation than unaffected infants. Cardiac anomalies, spinal agenesis-caudal regression syndrome, neural tube defects, gastrointestinal and urinary tract anomalies are more frequently seen[10]

Role of nutrition during pregnancy and in postnatal period in T2D

Nutrition and weight management

The ADA Standard of Medical Care in Diabetes, 2021 recommends 15–25 lb weight gain during pregnancy for overweight women and 10–20 lb for women with obesity. There is no adequate data on optimal weight gain vs. weight maintenance in women with a BMI > 35 kg/m^2 [11].

A review of current guidelines for exercise during pregnancy from 8 countries recommended 60-150 mins/week of aerobic exercise in healthy pregnant women with an upper limit of 30 mins/day. Additionally, resistance exercise was recommended by 5 national guidelines (Australia, Canada, Denmark, Norway and UK). Potential benefits of exercise for all pregnant women include improved fitness, less gestational weight gain, reduced risk of GDM and hypertensive disorders of pregnancy[11].

Medical nutrition therapy

Goals for MNT in pregnancy include:

- Adequate nutrient intake.
- Excellent glucose control.
- Adequate but not excessive weight gain.
- Learning appropriate food and exercise behaviours that can contribute to long-term maternal health[12].

Excess weight gain during pregnancy is associated with worse perinatal outcomes, including macrosomia, shoulder dystocia and neonatal hypoglycaemia. Thus, adequate food intake along with a daily minimum of 175 g recommended carbohydrates should be taken to ensure strict glycemic control and minimize the risk of DKA[6].

All women with diabetes should be referred to a dietician prior to or early in pregnancy to generate a nutrition plan that accounts for pregestational weight and targets at least 5–10% weight loss prior to conception[6].

Women should be advised to consume wholesome, balanced diet consistent with ethnic, cultural and financial considerations. Efforts should be made towards making timing of meals and snacks consistent on a daily basis to minimize hypoglycemia and in proper relation to insulin doses to prevent hyperglycemia[12].

The total recommended calorie intake for non–breastfeeding women is about 25 kcal/kg/day and for breastfeeding women is 27-30 kcal/kg/day[13].

RSSDI recommends diet including high carbohydrate (up to 45–65%), predominantly low glycemic index sources, low fat and adequate protein (up to 15%). The diet plan recommends substitution of saturated fats and trans fats with monounsaturated fatty acids in patients with IGT, diabetes and obesity. A low-carbohydrate ketogenic diet is preferred over a low-calorie diet[14].

Postpartum lifestyle change

Women with GDM who have a higher BMI after pregnancy or with weight gain following pregnancy are at particularly high risk for developing T2D in the future. In one study, over 60% of participants did not return to their pre-gravid weight and some participants gained weight between the 6 week and 6 month postpartum visits[15].

The Nurses' Health Study found that obesity, physical inactivity and low-fiber, high-fat diets increased the risk of diabetes in women aged 30-55. Moreover, lifestyle changes have shown to delay or prevent the onset of T2D in high-risk individuals. One study indicated that women were too tired to exercise during pregnancy and postpartum, which explains the low levels of physical activity in women[6].

Postpartum care should include healthy lifestyle counselling. Nurses with GDM who followed or were in the highest quartile of the Mediterranean diet scale had a 40% lower risk of diabetes than those in the worst quartile. Thus, a culturally acceptable, individualized nutrition plan should be developed for each woman, taking lactation into account[16].

According to the Institute of Medicine's Subcommittee on Nutrition During Lactation, nursing women typically lose 0.5-1 kg/month in the first 4-6 months of lactation due to physiologic changes. The Committee also highlighted that some women lose up to 2 kg/month while still producing milk. The Subcommittee advised that daily caloric intake during lactation should not be < 1,800 kcal and preferably not < 1,500 kcal[17].

Furthermore, overweight lactating women can lose 2 kg/month (0.5 kg/week) by reducing their caloric intake by 500 kcal/day and aerobic exercising 4 days/week. A Cochrane systematic review endorses moderate food restrictions (alone or with exercise) for postpartum weight loss. Another study found that exercise, with or without dietary changes, helps mothers lose weight faster than normal care postpartum. A 12 week intervention in lactating women (overweight or obese before pregnancy) resulted in an average weight loss of 8.3 kg shortly after the intervention and 10.2 kg at 1 year follow-up, with improvements in cardiovascular risk factors[17].

Diabetes management during delivery, postpartum and lactation

Most guidelines agree with an elective induction of 38–40 weeks to reduce the risk for stillbirths (Diabetes Canada, 2018; Ministry of health malaysia, 2017; NICE, 2015; Permanente, 2018). A caesarean section around 40 weeks plus 6 days is recommended, but this should be done before that time for those with comorbidities or maternal or fetal complications[18]. ACOG and the society for maternal fetal medicine does not indicate a late preterm or early term birth, i.e., before 39 completed weeks of gestation for women with well-controlled diabetes, whether pregestational or gestational[19].

Management during labour and postpartum

The primary objective of the intrapartum nursing management of GDM is to maintain maternal euglycemia to prevent neonatal hypoglycemia. Close monitoring of women with GDM during labour and delivery should therefore be done at least once an hour or, according to NICE (2015), every 30 mins till delivery. Maternal blood glucose levels must be maintained between 4–7 mM/L. NICE (2015) recommends that, if the capillary plasma glucose is above 7 mM, intravenous dextrose and insulin infusion must be given during labour and delivery[18].

There is no consensus on the timing and mode of delivery in GDM women. Obstetric complications related to fetal overgrowth and late perinatal death can be avoided by inducing labour. To avoid birth trauma, the ACOG recommends elective caesarean delivery if the anticipated fetal weight is over 4.5 kg. Insulin needs to be decreased during labour due to increased physical activity and prolonged fasting. Some women may also need glucose infusion to prevent ketosis. The Endocrine Society recommends maintaining glucose level in the range of 72-126 mg/dL during labour[20].

The Endocrine Society advises monitoring glucose levels for 72 h after birth to rule out hyperglycemia. Even If T2D is diagnosed or not, a 2 h 75 g OGTT is recommended 6-12 weeks after delivery to test for glucose intolerance or T2D[20].

Postpartum glycemic management

The postpartum care should emphasize on the assessment of the future risk of DM and mitigating that risk. Summary of recommendations for management after pregnancy to reduce diabetes[21] is presented in Figure 2 and Table 1.

Breastfeeding is recommended for women with GDM as it has been associated with reduced obesity of offspring. Need for family planning should be highlighted as additional pregnancies can further increase the risk of DM and conception after development of DM can lead to major birth defects, preventable by appropriate preconceptional glycemic control[21].

Effective DM prevention strategies include antepartum, postpartum, delayed postpartum, long-term preventative counselling care, and preconception counselling[13].

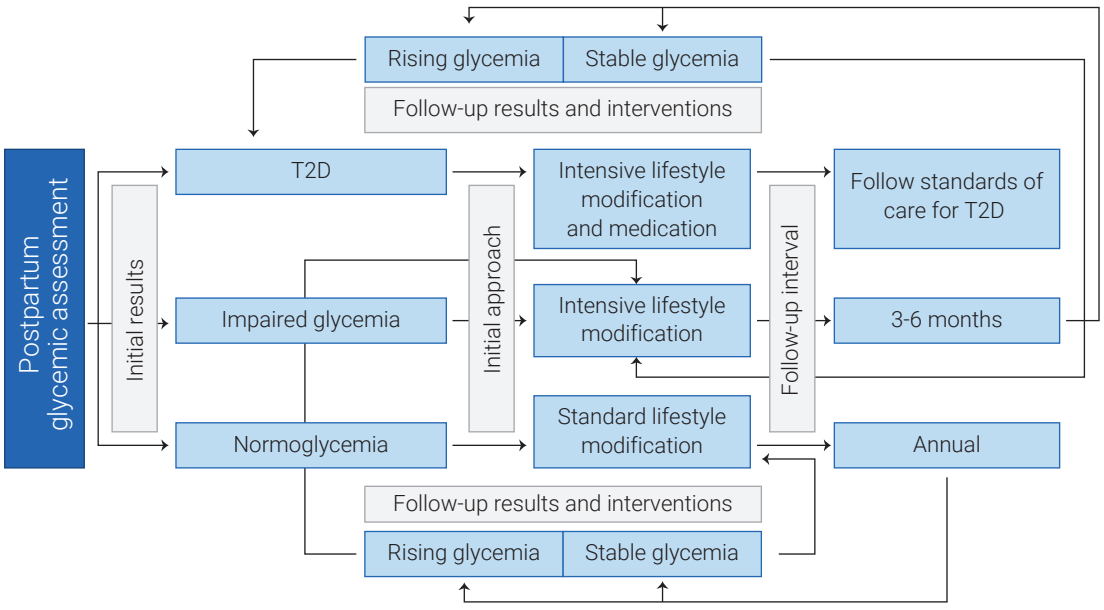

Figure 2: Suggested management of women with prior GDM when risk appears to be for T2D

Source: Buchanan et al., 2012[21]

Breastfeeding in women with GDM

Various guidelines (ACOG, 2018b; IDF, 2009; Blumer et al., 2013; FIGO, 2015; Queensland, 2015; Diabetes Australia/RACGP, 2016; Ministry of Health Malaysia, 2017; Diabetes Canada, 2018) recommend that women with GDM should be encouraged to breastfeed their newborns immediately after delivery to prevent hypoglycemia in the newborn. It is recommended that continuous breastfeeding should be done for at least 3–4 months postpartum or longer to reduce childhood obesity, glucose intolerance and diabetes later in life[18]. Research has indicated that breastfeeding reduces the risk of overweight in children and adolescents by 20–50% depending on duration of breastfeeding and degree of supplementation. A meta-analysis of 17 studies found a strong dose-response association between breastfeeding duration and a 4% reduction in risk of overweight/month of breastfeeding[22].

Table 1: Postpartum care in women with GDM

	Education	Screening
Early postpartum (1-3 days)	• Invigorate the importance of balanced diet, physical activity, weight reduction, suitable contraception usage, harmful effects of smoking. • Breastfeeding should be done for atleast 3 months. • Educate on topics of DM, CVD, metabolic syndrome, family planning and preconception counselling.	• Fingerstick glucose tests (postprandial and fasting)
Late postpartum (6-12 weeks)	• In addition to previous points advise on importance of 1-3 year follow-up, infant care & prevention of childhood obesity.	• Importance of monitoring of BP, BMI and perofrming 75 g 2 h OGTT, lipoprotein and cholesterol levels

Source: Khandelwal et al., 2008[13]

Lactation benefits in women

Breastfeeding benefits both mothers and their children. Women who breastfeed have a lower chance of breast and ovarian cancer, as well as T2D. Findings in Pima Indians suggest that breastfed children of mothers with and without diabetes may have lower rates of T2D. Lactation improves glucose tolerance in women with GDM, however some studies suggests that the effect remain even after weaning[23].

Prospective studies in which maternal weights were measured before or during early pregnancy have found lower postpartum weight retention, more rapid return to pre-gravid weight, or greater weight reduction within 1 year among lactating women. Prolonged breastfeeding (> 6 months) compared with formula feeding was associated with a 2 kg higher maternal weight loss by 1 year postpartum, as well as a reduced waist girth after weaning. Longer breastfeeding duration is linked to lower maternal weight gain 10–15 years later. Lactation may also alter long-term management of body weight as well as regional fat distribution in women[22].

One study suggested that nursing in mothers with GDM is associated with enhanced pancreatic β-cell activity, at least in the short term. In the Atlantic Diabetes in Pregnancy study, the prevalence of persistent hyperglycemia was markedly decreased by 10% in women who breastfed compared with those who bottle-fed their newborn. SWIFT found that breastfeeding was associated with a small but significant reduction in the 2 h glucose concentration (mean reduction 5%) and the 2 h insulin concentration, as well as higher insulin sensitivity indices at 0 and 120 mins. These data show that breastfeeding reduces glucose and insulin levels within 2 h of a glucose test[23].

Mechanisms underlying the possible protective effects of breastfeeding against progression to T2D

Breastfeeding may reduce the risk of T2D progression following a GDM-complicated pregnancy. However, these protective effects of breastfeeding are still poorly understood and most relevant studies in this context have focused on animal models[23] were presented in Figure 3.

Management of new borns of mothers with untreated GDM

Insufficient glycemic management during pregnancy is associated with fetal-neonatal complications. Poor glycemic control during pregnancy is related to spontaneous abortions, growth delays and significant congenital abnormalities[24].

Macrosomia

Maternal hyperglycemia is a risk factor for macrosomia and it is critical to identify it in premature infants. Treatment of GDM significantly reduces the risk of macrosomia[25].

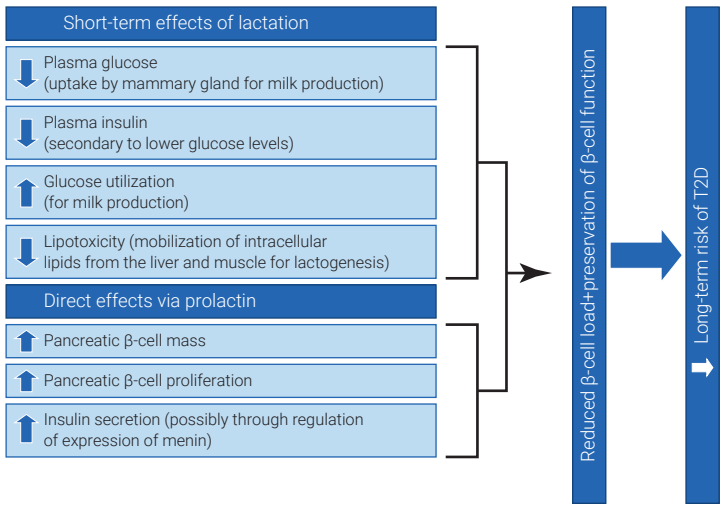

Figure 3: Potential mechanisms involved in the short-term effects of breastfeeding on glucose metabolism and its long-term effect on the development of T2D based on evidence from animal models T2D

Source: Much et al., 2014[23]

Metabolic disorders

Hypoglycemia

Newborns should be fed within 30 mins of delivery and subsequently at regular intervals (every 2-3 h)[26].

In neonates with no clinical indications, therapeutic intervention can begin at 0.36 g/L (2 mmol/L). Early and frequent breast-feeding is still the best way to prevent hypoglycemia in infants. Even in mildly symptomatic newborns with low blood glucose levels, continued nursing or formula supplementation should be tried first, if an acceptable clinical response is established. If the baby is unable to feed, a steady intravenous glucose infusion (3-6 mg/kg/h) should be given to avoid rebound hypoglycemia[25].

Hypocalcemia

Hypocalcemia can be defined by plasma calcium concentration below 2 mmol/L or ionized calcium concentration below 1.1 mmol/L, regardless of gestational age or body weight. Maternal hypomagnesemia and subsequent fetal hypomagnesemia have been linked to transient neonatal hypocalcemia in pregestational insulin dependent women with diabetes. Hypocalcemia appears to be clinically insignificant, especially in GDM, unless other complications are present. Screening for hypocalcemia and hypomagnesemia in healthy babies is not indicated. Therapy includes oral vitamin D supplements, calcium gluconate orally or intravenously (40-60 mg/kg/day) and magnesium treatment based on plasma levels[25].

Respiratory disorders

Respiratory distress in an infant of mother with diabetes provides a diagnostic challenge. The treatment of these disorders is variable and may require similar symptomatic treatment, such as oxygen and ventilator support as needed. Respiratory distress syndrome may require administration of surfactant, asymmetrical septal hypertrophy may require β-blockers, and transient tachypnea of the newborn only time to improve. Those experiencing respiratory symptoms should undergo: (i) a chest X-ray, and (ii) an ECG (to verify for an anatomic heart disease or of asymmetrical septal hypertrophy[24].

Cardiac disorders management

ECG evaluation is essential to distinguish among cardiac anomalies, septal hypertrophy and/or cardiomyopathy in case of signs of congestive heart failure or cardiomyopathy with cardiomegaly, hypotension or significant cardiac murmur. Once diagnosed, the treatment is similar to any other newborn with a similar cardiac condition. Cardiotonic drugs for hypertrophic cardiomyopathy or significant septal hypertrophy requires extreme caution due to risk of a decrease in left ventricular output in certain infants. β-blockers, such as propranolol can help to reduce septal hypertrophy induced outflow obstruction[27].

Indications for transfer of infants (born to mothers with diabetes) to newborn ICU

- Respiratory distress syndrome.
- Perinatal asphyxia with signs of encephalopathy.
- Malformation requiring immediate specialized treatment.
- Signs of heart failure linked to heart defect or hypertrophic cardiomyopathy.
- Symptomatic polyglobulia.
- Severe icterus.
- Premature birth < 34 weeks' gestation or < 36 weeks' gestation[26].

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Section 4

Challenges in Women with Diabetes

Editor: Dr. Chitra Selvan

CHAPTER 17 CONTRACEPTIVE IN WOMEN WITH DIABETES MELLITUS

Dr. Piya Ballani Thakkar, Dr. Rajeshwari Janakiram

Contraception need and challenges in women with diabetes

The prevalence of diabetes is increasing in epidemic proportions worldwide. While T2D is primarily responsible for this upsurge, T1D is also rising. Obesity, lifestyle changes and PCOS are contributing to higher proportions of diabetes in our younger population, which in turn leads to fertility issues. Ovulation, although often delayed, does happen in women with diabetes; those with PCOS have intermittent ovulation and hence unpredictable periods. Contraception is therefore required not just preconception, but also for spacing of pregnancies and to avoid unwanted pregnancies after completion of the family.

Normal fetal development requires optimal diabetes control at the time of conception and during organogenesis in the first 5-7 weeks. Poor glycemic control during pregnancy increases the risk of adverse pregnancy outcomes such as congenital abnormalities, stillbirth and perinatal mortality. DM related neonates are 5 times more likely to be stillborn, 3 times more likely to die in their 1st months and twice as likely to have a major congenital anomaly[1], which increases proportionately with HbA1c.

Hence, pregnancy should be planned to maximise glycemic control. Prepregnancy counselling must include highly qualified advice on reliable and acceptable contraceptive agent and achievement of good metabolic control[2].

According to WHO estimates, only 30–40% of the 182 million pregnancies reported every year in developing countries are intentional and only 40–50% of the 23 million pregnancies occurring in industrialized countries are wanted[3].

Awareness about contraception

Improving maternal health is a challenge for HCPs as only half of the women with DM plan their pregnancies. Poverty, lack of education, unresolved desires to become pregnant, lack of marital support, poor relationships with HCP and a perception of discouraging advice from health professionals are all linked to poor pregnancy planning[4]. In a population-based state-wide sample, 59% of the women failed to fully plan their pregnancies. Another study found that women struggled to follow contraceptive advice and most did not use reliable contraception prior to pregnancy. A US National survey found that women with DM were less likely to use contraception than women without DM. Findings from a study revealed that two-third of women were not able to remember discussing pregnancy or contraception with a HCP. This combined with the fact that younger patients are likely to be unmarried, HCP should bring this up for all girls or women with diabetes irrespective of marital status. Those who had a pregnancy knew nothing about risks of pregnancy and DM. Despite previous miscarriage, fetal anomaly and stillbirth experiences, some women were reluctant to seek preconception care due to past negative experiences, social issues, fertility concerns, or simply practical reasons associated with attending services. It is important to educate women with DM from all social groups about the importance of modern contraceptive methods[1].

A population-based survey of non-pregnant women found that approximately 40% of women with diabetes and up to a 3rd of women with elevated BMIs did not use contraception. Among women who were sexually active and nonsterile, having diabetes was associated with more than a 2-fold greater odds of not using contraception, while class II or III obesity (BMI ≥ 35.0 kg/m^2) was associated with a 1.6 fold greater odds of not using contraception[5].

The perceived side effects of contraceptive methods are a major deterrent for women of all ages. Some non-users who did not

plan to use contraception in the future have cited health concerns and side effects. Another key barrier is lack of awarenes-sand financial access to family planning commodities. Women complain of frequent stock-outs and the associated costs of lost wages, transport and other financial challenges. Studies have shown that, among youth, lower socioeconomic status has been associated with less condom use[6]. Condoms were the most popular method (65%) of contraception. Use of hormonal contraception were less likely to be used by women with diabetes than women without diabetes-T1D (RR 0.83, 95% CI, 0.59-0.93), T2D (RR 0.6, 95% CI, 0.42-0.83). Prescription of combined contraceptive pill is less in diabetes vs. non-diabetes 0.39 (0.24-0.62)[7].

Characterization of women who carry condoms as promiscuous, sexually wayward or untrustworthy is common among young people. While married people can freely ask for contraception, unmarried people are inhibited. At service level, many HCPs indicate that family planning are only for those who are "mothers" and are not suitable for those who have not yet had a child[6].

Hormonal contraception

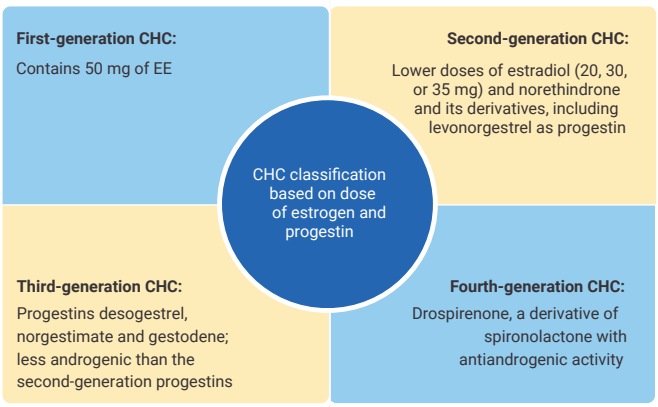
Estrogen and progestin combination pills and other methods

Combination therapies of ethinyl estradiol and progestin prevent pregnancy by blocking the LH surge and by thickening cervical mucus. All combination contraceptives have similar efficacy and continuity data, with a 0.3% failure rate with perfect use in the 1st year and an 8.7% failure rate with typical use in the 1st year. However, only about 68% of patients continue using combination contraceptives a year later[8]. Table 1 reviews different generations of CHCs depending on the type and dose of estrogen and progestin[9]:

CHCs, like, COCs and progestin-only pills are eligible for women with DM (Table 2)[9]. CHCs are available in several routes of administration including pills (monophasic and multiphasic), transdermal patches and vaginal ring. Progester-one-only methods are Implanon, LNG-IUD, progestin-only pills and Depo-Provera. Table 3 reviews different forms and routes for CHC[9].

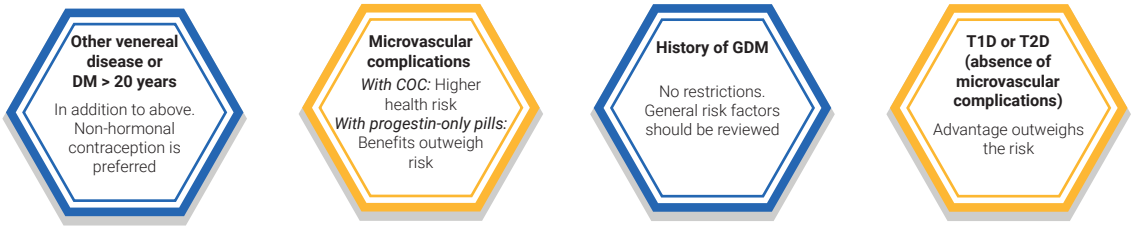
ACOG recommends that the use of COC in women with diabetes should be limited to patients younger than 35 years who do not smoke and are otherwise healthy, with no evidence of hypertension, nephropathy, retinopathy or other vascular disease[9].

Table 1: CHC classification depending upon the dose of estrogen, progestin, and type of progestin



Note: EE: Ethinylestradiol
Source: Arya et al., 2018[9]

Table 2: Medical eligibility criteria for COC and progestin-only pills in women with DM



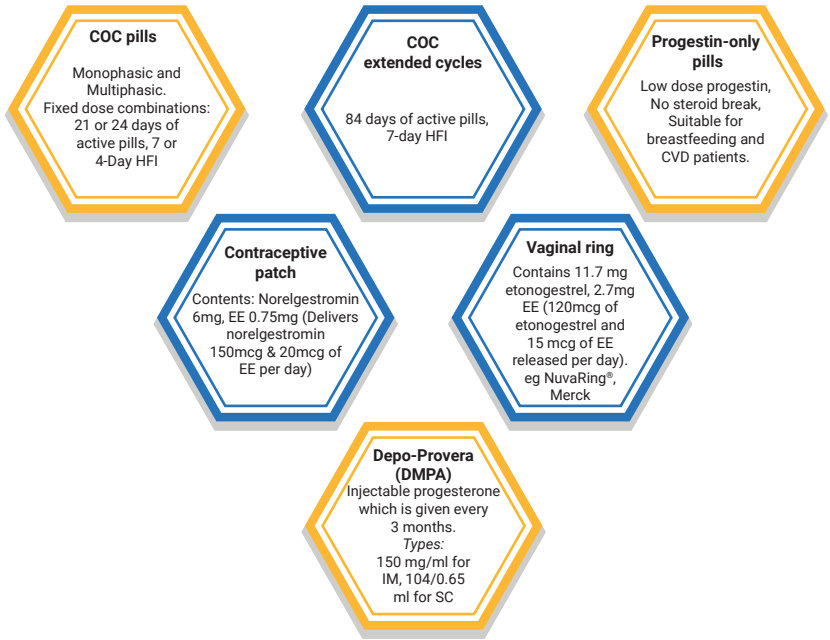
Source: Arya et al., 2018[9]

Oral progestogen only preparations

The oral progestogen-only preparations contain norethisterone, norgestrel, ethynodiol or levonorgestrel. They are considered safe for breastfeeding and older women who are at an increased risk of cardiovascular problems, such as those with hypertension, diabetes, or who smoke. Progestogen-only preparations are less effective than combined preparations and can lead to more menstrual irregularities[7].

Progestin-only pills are categorized as safe for all patients with DM—with or without vascular disease by the CDC. While progestin-only pills are safe, they require consistent daily dosing, and noncompliance results in significantly decreased efficacy[8].

Table 3: Different forms and route of combined hormonal contraception



Note: DMPA: Depot-medroxyprogesterone acetate, HFI: Hormone free interval, EE: Ethinylestradiol, IM: Intramuscular injection, SC: Subcutaneous

Source : Arya et al., 2018[9]

Parenteral progestogen-only preparations

There are several injectable or implantable parenteral progestogen preparations. They work well for women who need long-term contraception but do not want to undergo sterilization. They also cause menstrual irregularities. The local action of progestogen is thought to reduce the risk of pelvic infection associated with insertion of the device. The progestogen may have a minor impact on carbohydrate and lipid metabolism[7].

Contraceptives LARC methods include copper IUD, intrauterine system, progestogen-only injectable contraceptives, progestogen-only subdermal implantsand combined vaginal ring[1]. LNG-IUD has shown to be safe in patients with diabetes and no significant changes in glycemic control or throboembolic events or infections.

Table 4: Contraindications for use of long acting reversible contraceptive methods

Contraindication for hormonal LARC use	Contraindication for IUD use
Unexplained vaginal bleeding	Active sexually transmitted infection
Acute DVT/PE	Anatomic abnormalities of the uterus
SLE with antiphospholipid antibodies	
Severe cirrhosis, liver tumour	
Current breast, ovarian, or endometrial cancer	

Note: DVT: deep vein thrombosis, PE: pulmonary embolism, SLE: systemic lupus erythematous

Source : Arya et al., 2018[9]

Progestogen-only injectable contraceptives, such as medroxyprogesterone acetate and norethindrone enanthate are suitable for women with DM without complications. Women with DM who want to start families as soon as possible before developing DM complications may find injectable methods unsuitable as injectable methods may also cause a delay in returning to fertility[1]. The contraindications for use of long acting reversible contraceptive methods is presented in Table 4[9].

Effect of hormonal contraceptives on glycemic regulation

Studies indicate that the progestin component appears to produce IR in a dose-and potency-dependent manner[10]. Synthetic progestins are structurally similar to testosterone and traditionally believed to produce androgenic side-effects. Metabolic effects include reduced tissue insulin sensitivity and glucose tolerance that may be related to dosage and differing androgenicity of various progestins. Newer generations of progestins limit androgenic side effects, particularly on lipoproteins and insulin sensitivity[11]. In contrast, estrogens have no effect on insulin sensitivity or glucose tolerance and may enhance insulin action in vitro and in vivo, enhances insulin sensitivity of metformin. Estrogens have also shown to improve pancreatic β-cell function in animal models of diabetes[10].

Estrogens improve lipid profiles by lowering LDL and raising HDL and no change in insulin doses, while progestins have the reverse effect. Estrogen increases triglycerides, while progestins have no effect. Combining estrogens with low dose progestins produces a milder, more estrogen-dominant effect on carbohydrate and lipid metabolism, with no effect on glucose tolerance and positive changes in serum lipid[12].

These findings show that when estrogen levels are low (as during breastfeeding), progestational drugs may have a greater impact on IR and glucose tolerance. Conversely, the co-administration of estrogen should mitigate the diabetogenic effects of progestational agents[10].

Table 5 gives an overview of general metabolic effects on glucose tolerance, serum lipids, BP and coagulation factors[12].

These metabolic effects are crucial in presence of comorbidities, particularly hypertension or hyperlipidemia. Serum lipids and BP need to be assessed to select the best formulation with the least possible metabolic effect. Generally, the lowest dose and potency formulations should be chosen[12].

Table 5: Metabolic effects of hormonal contraceptive components

	Oral estrogen	Oral progestin	Progestin intr amuscular and implants
Glucose tolerance	Neutral	↑IR ↑Glucose tolerance	↑IR ↑Glucose tolerance
Serum lipids	↑HDL-Cholesterol ↓LDL-Cholesterol ↑Triglyceride	↓HDL-Cholesterol ↑LDL-Cholesterol	↓Triglyceride Minimal effect on HDL and Cholesterol
Blood pressure	Slight↓	Neutral	Neutral
Coagulation factors	↑Globulins: Dose-dependent↑	Neutral	Neutral

Note: ↑ increase, ↓ decrease

Source: Tsatsoullis et al., 2009[12]

A study showed that the use of low-dose progestin and estrogen combination OCs did not appear to increase the risk of developing diabetes in high risk women. In Nurse's health Study, healthy women on OC pills were not associated with increased risk of diabetes. Studies have shown a nearly 3-fold increase in the incidence of diabetes with the use of a progestin-only OC during breastfeeding compared with the non-hormonal or combination OC groups. This risk rose with increasing duration of uninterrupted OC use(Figure 1)[10].

A 2014 Cochrane Review showed no marked differences in carbohydrate metabolism and HbA1c levels with hormonal contraception in both healthy women and women at greater risk of metabolic disorders[11].

Hormonal contraception and thromboembolism in women with diabetes

The risk of thromboembolism is less with combined pills, higher with progesterone alone preparations. In an analysis of data of 146,080 women with diabetes between 14-44 years, using hormonal contraception, the absolute risk were very minimal in 3,012 thromboembolism events. It was highest with patch (16/1,000 years), 3.4/1,000 years with IUD and 0/1,000 years with subdermal route. Progestin only pills posed higher risk with hazard ratio 12.5 vs. 4.69 women/1,000 years among IUD. Therefore, IUD or subdermal contraception are very effective and of low risk and can be used ideally for spacing pregnancies.

Non-hormonal contraception

Barrier and natural methods of contraception

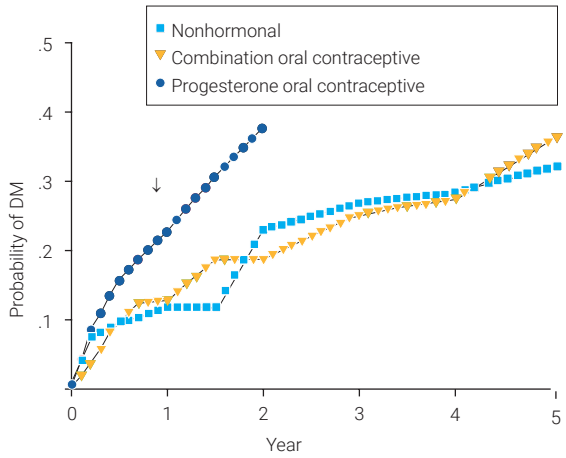


Figure 1: Cumulative incidence rates of T2D as determined by interval-censored survival analysis in 904 Latinas with recent GDM. The incidence of DM is depicted during the first 5 years after delivery for women who never used hormonal contraception, women who continuously used low-dose combinations oral contraceptives, and those who continuously used progestin-only oral contraceptives

Source: Kjos et al.,1998[10]

Barrier methods include diaphragms, cervical caps as well as male and female condoms and usage depends upon personal acceptability and efficacy. Some involve using spermicide such as nonoxynol-9; however, there appear to be no studies contraindicating the use of spermicide from a diabetic perspective. Barrier methods alone may not be reliable enough for women with DM who are seeking to lose weight or lower their HbA1c levels. Male and female condoms are best to prevent sexually transmitted infections but should be used in conjunction with a more effective contraceptive such as hormonal treatments or an IUD[1].

Table 6: Summary of coitus-related and barrier methods

Periodic abstinece	
Remark on use	High motivation
Effectiveness	13.4-47/100 woman-years
Coitus interruptus	
Remark on use	Acceptable method: Withdrawal Requires no device Has no cost or any contraindications
Effectiveness	Sperm present in pre-ejaculate may cause failure.
Diaphragm	
Remark on use	High risk of UTI (postcoital voiding is recommended), Risk decreases with age. Requires motivation by women.
Effectiveness	2.8% for continuous user and 9.8% among those who used it with intercourse
Male condom	
Remark on use	Better sensitivity, High slippage rate, Latex condoms are recommended. First year failure rates are between 3-6% when women was older than 30 compared to 8-10% failure rate in women < 25 years.
Effectiveness	6 month typical-use pregnancy probabilities for polyurethane and latex group are 9-10.8% and 5.4-6.4%, respectively.
Female condom	
Remark on use	Types: Women's condom and reality. Female controlled, effective protecting against sexually transmitted infections.
Effectiveness	Typical use failure rate is 21%
Lactational amenorrhea method	
Remark on use	Depends on frequency, duration and night nursing.Exclusive for breastfeeding and upto 6 months after delivery.
Effectiveness	Failure rate 0.9-1.2% among amenorrheic & breastfeeding women

Source: Arya et al., 2018[9]

Fertility awareness methods may not be effective in women with diabetes. Natural family planning can be 99% effective in healthy women with regular menstrual cycles and concurrent use. These may be options in early postpartum or in conjuction with emergency pill in situations of unexpected sexual encounters. However, women with DM may have more irregular menstrual periods, which might reduce efficacy and increase failure rate[1]. There are no contraindications for the use of coitus-related and barrier methods of contraception in women with diabetes. Table 6 provides a brief summary of the coitus-related and barrier methods[9].

Sterilization

Surgical sterilization is an excellent option for women with diabetes who have completed their family[16] or who do not wish pregnancy. Surgical complications can be reduced by optimizing glycemic control at the time of the procedure[16]. Surgical sterilization options in women include minimally invasive tubal occlusion, laparoscopic tubal ligation (clips, rings, or cautery) and tubal ligation during caesarean section or other laparotomy. Efficacy is excellent for all three sterilization methods, with minimally invasive tubal occlusion having the fastest recovery time, lowest surgical risk and highest efficacy rates. Vasectomy for the male partner is a surgical sterilization option for any couple in a life-long relationship. However, vasectomy does not provide individual contraception for the woman, in case of change of partner[8].

Contraception post gestational period

Postpartum depression affects women and their families. Postpartum care is recommended to assess postpartum recovery, need for contraception, lactation success, risk of postpartum depression and ongoing medical conditions such as GDM. The necessity to change drug regimens to ensure euglycemia further complicates the postpartum period for women with DM[13].

Postpartum, estrogen and progesterone levels drop significantly, removing the inhibitory effect on prolactin action, permitting breast milk production. Suckling by new born further stimulates the release of prolactin, sustaining milk production and interrupting the cyclic release of pulsatile GnRH from the hypothalamus. This in turn interrupts the pulsatile release of LH, blocking FSH mediated stimulation of the ovary and ovulation. Ovulation can return 25 days at the earliest after delivery in non-breastfeeding women. The need for contraception may arise 4 weeks postpartum.

Exclusive breastfeeding, when used as birth control is called LAM and effectively delays ovulation up to 6 months with 98% efficacy. It is advised to start breastfeeding immediately postpartum, for at least 4 h during the day and 6 h at night, to properly use LAM. At 6 months, LAM has a 1.2% cumulative pregnancy rate. Lactating mothers may avoid unnecessary medication and this method is ideal to encourage exclusive breastfeeding along with use of condoms to provide pregnancy protection[12]. Every woman with diabetes and postnatal or post abortion should be educated about contraception and given options and encouraged to use. They should be counselled and be given positive hope for contraception while improving glycemic status prior to planning future pregnancy.

Oral progestins and depot-medroxyprogesterone acetate are preferred and can be started 6 weeks postpartum in breastfeeding women and immediately in non-lactating women[14].

WHO guidelines establish that during the breastfeeding period, the use of progestins alone is recommended although no hormonal contraceptive should be used during the first 6 weeks postpartum (category 3 or 4)[14].

Almost one-half of abortions are repeat abortions and nearly 1 in 5 births to teenagers is a repeat birth. The CDC specifies time frames for postpregnancy contraception. The use of estrogen-containing methods should be delayed for 3-6 weeks postpartum due to the risk of venous thromboembolism. Progestin-only methods can be safely started immediately postpartum[15] is presented in Table 7.

Personal counselling and selection of method

A woman's reproductive desires and contraceptive preferences change throughout her reproductive life, irrespective of whether she has diabetes. Pregnancy plans and contraception preferences must be discussed regularly from the time of diagnosis of diabetes. This will help lower the chance of an abnormal or early birth in women with diabetes. Reliable and proper use of contraception depends upon a woman and her partner. It must suit her/their individual lifestyle and sexual practices. Many women have high success rate with high failure risk methods such as condoms or diaphragms. Some find daily administrations methods, like the pill, ineffective. A simple procedure like an IUD or implant may be preferred by some. Thus, contraceptive history and daily practices must be coordinated[12].

Possible contraceptive failure and suspected early pregnancy are other crucial topics to cover during counselling as unplanned pregnancies still occur despite contraceptive regimens. Women with diabetes often take many medications for hypertension, hyperlipidemia and for renal disease as well. Safety of all the drugs should be evaluated during early pregnancy[12].

Table 7: Postpregnancy risk classifications for selected contraceptive Methods

Category	Combined hormonal pill, patch, or vaginal ring	Progestin-only pill	Depot Medroxy-progesterone acetate (Depo-Provera)	Etonogestrel Implant (Nexplanon)	Levonorgestrel IUD (Mirena)	Copper IUD (Paragard)
Postpartum, non-breastfeeding women						
< 21 days	4	1	1	1	2	2
21 to 29 days						
With other risk factors for VTE	3	1	1	1	2	2
Without other risk factors for VTE	2	1	1	1	2	2
30 to 42 days						
With other risk factors for VTE	3	1	1	1	1	1
Without other risk factors for VTE	2	1	1	1	1	1
> 42 days	1	1	1	1	1	1
Postpartum, breastfeeding women						
< 21 days	4	2	2	2	2	2
21 to 29 days						
With other risk factors for VTE	3	2	2	2	2	2
Without other risk factors for VTE	3	2	2	2	2	2
30 to 42 days						
With other risk factors for VTE	3	1	1	1	1	1
Without other risk factors for VTE	2	1	1	1	1	1
> 42 days	2	1	1	1	2	1
Postabortion, spontaneous or induced	1	1	1	1	1	1

Note: WHO Categories: 1 = no restriction on method use; 2 = method has theoretical or proven risks, but its advantages generally outweigh those risks; 3 = method's theoretical or proven risks usually outweigh its advantages; 4 = unacceptable health risk if method is used. VTE: Venous thromboembolism

Source: Klein et al., 2015[15]

Unprotected coitus, a broken condom, multiple missed OC pills etc., can require prescribing emergency contraception within 72 h. The shorter the time between method failure and emergency contraception, the more effective the pregnancy protection, i.e., 0.5% pregnancy rate within first 12 h to 4.1% pregnancy rate within last 12 h of the 72 h window. In women with diabetes, the progestin only regimen, levonorgestrel (1.5 mg total dose) is recommended and has no contraindications to use. It is recommended that all women requiring contraception should be offered (and prescribed) an emergency contraceptive regimen in advance[12].

The CDC recommends a systematic approach to contraceptive counselling and education to ensure safe, high quality care. Figure 2 includes a summary of the 5 steps clinicians should take when providing contraception to patients[15].

Steps in providing contraceptive services

After detailed review of the diabetic patient's medical history hormonal contraceptive methods can be considered. CHC do not increase the risk of developing diabetes, even in patients with a history of GDM. CHC can be prescribed in women with insulin dependent diabetes unless they have severe microvascular disease such as retinopathy, nephropathy and neuropathy, or the duration of disease is > 20 years. Estrogen-containing contraceptives are contraindicated in women with diabetes and persistent hypertriglyceridemia or uncontrolled hypertension. Women with diabetes should have lipid and BP screening prior to and after the initiation of CHC. Progesterone-only contraceptive methods, including pills, injections, implants and the LNG-IUD, are generally considered safe for women with diabetes. These methods have minimal impact on glucose metabolism, lipids and thrombotic markers[16].

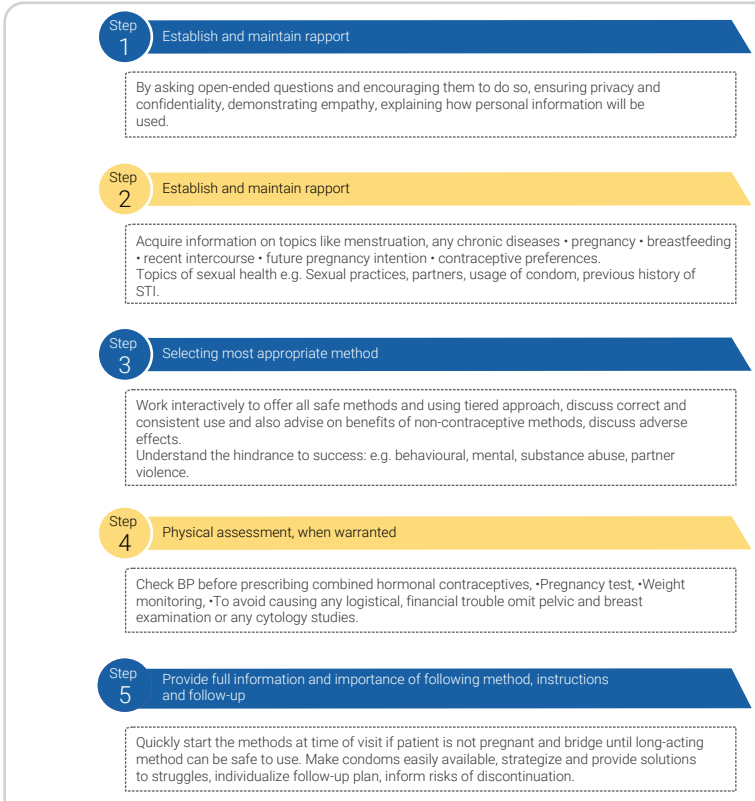


Figure 2: Steps in providing contraceptive services

Source: Klein et al., 2015[15]

Clinicians should discuss all safe contraceptive options with patients, regardless of whether they are adolescents or nulliparous women or when the method is offered on site. Physical examinations mainly consist of weight assessment, BP examination or pelvis examination before implanting an IUD. If the patient is not pregnant, a contraceptive can be started immediately. Hormonal contraceptives supplied and prescribed over a year should be of help. Condoms should be easily accessible. Contraception appointments should involve patient education regarding use, advantages and risks along with an individualized follow-up plan. They should be advised about changing antihypertensives from ARB/ACEi and stopping statins before planning pregnancy. Contraception should be used to prevent unintended pregnancy until menopause, or at least until age 50-55 years[15].

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CHAPTER 18 SEXUAL HEALTH IN WOMEN WITH DIABETES MELLITUS

Dr. Shehla Shaikh, Dr. Dakshata Padhye

Introduction

Globally, DM is one of the most common NCD[1]. It is associated with many long-term systemic complications in both genders and sexual dysfunction is one of them[2]. Due to social taboos on female sexuality, sexual dysfunction in women is often ignored[3]. In the National Health and Social Life Survey conducted on the US population, sexual dysfunction was found to be more common in women (43%) than in men (31%)[4]. In recent years, FSD has received considerable attention. WHO declared female sexuality as not only a part of health quality but also a basic human right[5].

Sexual activity is related to numerous health benefits such as, superior quality of life, quality of social relationships, mental well-being and is a good form of exercise as well[6]. FSD is a heterogeneous group of disorders that can be related to sexual desire, arousal (female genital arousal disorder), orgasm or sexual pain[7] and is often undiagnosed and undertreated[2]. Therefore, information on the real prevalence of FSD is not available and is generally underestimated. In PRESIDE, a population-based cross-sectional study on 31,581 US women showed that 43.1% of were afflicted with sexual problems[8]. The most common dysfunctions reported were hypoactive sexual desire (38.7%), low arousal (26.1%) and problems related to orgasm (20.5%)[8]. A recent systematic review and meta-analysis of 95 observational studies (n=215,740) reported global prevalence of self-reported sexual dysfunction in premenopausal women as 41%[9]. A study from Italy on 595 T2D women showed 53.4% overall prevalence of FSD among these women[10]. 27 out of 120 women with T1D were reported to have depressive symptoms and lower quality of marital relationship[11]. In fact, depression is considered as the major co-existing factor of DM and is likely responsible for greater prevalence for sexual dysfunction in women[12].

Mechanism of interaction between diabetes and sexual health

The pathogenesis of FSD in women with diabetes is complex and multifactorial, and includes psychological and organic factors along with physical effects[13]. Organic factors, including hyperglycemia, neurovascular alterations, hormonal changes and recurrent genital infections can also contribute to the onset of FSD. Hyperglycemia decreases the hydration of vaginal mucous membranes, leading to vaginal infection, characterized by decreased lubrication and dyspareunia (painful intercourse)[13]. In diabetic population, UTI and mucosal candidiasis are more common and often more severe than healthy people[2]. *Candida albicans* is the most frequent cause of VVC. Hyperglycemia increases the risk not only for incident of infection but also for its recurrence[14]. Evidence supports the link between lower urinary tract dysfunction and FSD as urinary incontinence and UTI was noted in women with DM that doubled the risk for decreased libido, vaginal dryness and dyspareunia[2].

Specific problems related to diabetes like wearing of medical devices, scarring and lumps (lipo-hypertrophy) at injection sites can affect body image, ultimately affecting physical intimacy[15]. Moreover, the daily demands of DM that relate to tiredness or inconvenience of diabetes management such as the need to test prior to sexual intercourse to avoid hypoglycemia or the fear of hypoglycemia, may all affect the spontaneity of sex[16].

The sexual response is a neurovascular event in women. In women with diabetes, vascular damage results in decreased vaginal blood flow or vasocongestion, leading to a significantly impaired arousal response[17]. The lack of lubrication is one of the most common sexual problems and it may explain the increased prevalence of dyspareunia, difficulty to achieve orgasm and HSDD, observed in women with DM compared to healthy controls[18]. In addition, diabetic neuropathy may alter the normal

transduction of sexual stimuli, contributing to the pathogenesis of sexual dysfunction[19]. Altered steroid hormone profile plays a major role in the pathogenesis of FSD in women with diabetes as these hormones are responsible for preserving the anatomy and function of female reproductive system involved in sexuality[20]. DM interferes with synthesis of steroid hormones as insulin and IGF regulates the enzyme activity of aromatase and 3ßHSD[21,22]. Furthermore, DM is often associated with other endocrine disorders, such as PCOS or thyroid diseases, which may contribute to the impairment of sexual function in women with diabetes[23].

Regarding the relationship between the type of the therapeutic strategy for DM and sexuality, previous studies have shown a higher prevalence of FSD in women with multiple-dose injection, compared to continuous subcutaneous insulin infusion[24,25]. This difference could be related to lower glycemic variability in patients undergoing the continuous subcutaneous insulin infusion, compared to multiple-dose injection[26]. Recently, Corona and colleagues have investigated the effects of novel anti-hyperglycemic drugs like GLP-1RA and SGLT2i or neutral DPP4i on the sexuality of both women and men and found promising metabolic and positive effects of these agents on genital fungal infections that may impair sexual function in patients with DM[2].

Recurrent vaginal and urinary infections as a symptom of diabetes in women

DM, uncontrolled in particular, is a risk factor for both urinary and reproductive tract infections (involving the vulva, vulvar vestibule and/or vagina). 14% of women with T1D and 23% of women with T2D are diagnosed with UTIs[27]. Infections are prevalent in perimenopausal patients with longer disease duration. In a well-documented trial involving 1,357 female patients with T1D, increased prevalence was observed for acute cystitis, acute vaginitis and acute vulvitis[28]. In a group of 241 women with T1D, the most significant risk factors associated with symptomatic infections included sexual intercourse, use of OCs and microangiopathy[27]. Urinary incontinence, another contributing factor of infection is more prevalent in females with diabetes than in the general population[28]. Asymptomatic bacteriuria is more frequent in T2D patients (17.5%) than healthy controls and it further progressed to symptomatic UTI in 20% of patients during next 6 months[29,30]. Asymptomatic bacteriuria also acted as the primary risk factor for developing a symptomatic infection in a study on 348 women with T2D[29]. It may also lead to decreased renal function[31].

Diabetes constitutes a significant risk factor for UTI in postmenopausal women[32,33]. A total of 256,725 females with T2D showed significantly prevalent UTI (100% and 80%) in the 45-49 and 50-54 years age groups respectively[33]. Acute UTI was also observed in women with diabetes aged 55-75 years[32]. Diabetes along with pharmacotherapy or insulin treatment turned out to increase UTI risk by 2 fold in postmenopausal women[34].

Sexual dysfunction in women with diabetes

Owing to lack of standardization in methods and changes in FSD definitions and classifications, data on prevalence of FSD in women with diabetes is not readily available and is often discordant[24].

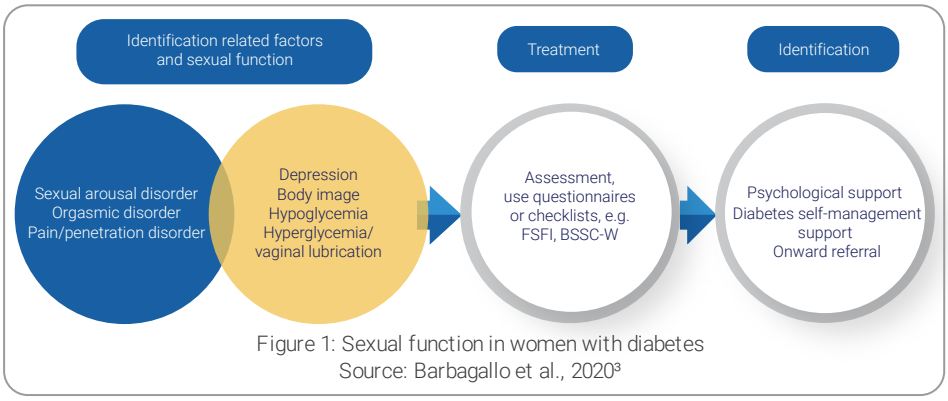

Figure 1: Sexual function in women with diabetes
Source: Barbagallo et al., 2020[3]

The factors affecting sexual function in women with diabetes is presented in Figure 1. A previous study showed a higher prevalence of FSD in women with diabetes vs. healthy ones[35]. Higher prevalence of FSD was reported among pre- and post-menopausal women with T1D and T2D[13,18,25,36–38]. A meta-analysis of 26 observational studies (n=3168) noticed a higher prevalence of sexual dysfunction in women with any type of diabetes and with any duration of the disease. Also, a higher BMI in these pa-

tients was significantly associated with lower scores on FSFI[18]. Another meta-analysis involving 25 studies (n=3,892) sho- wed 68.6% as overall prevalence of FSD in women[39]. Impaired sexual desire, arousal, lubrication, orgasm and satisfaction were found in women with diabetes. In a study involving 270 women with diabetes, Meeking et al described a reduction in sexual desire (64%), loss of vaginal lubrication (70%), difficulty of achieving orgasm (50%), decrease satisfaction (47%), loss of genital sensation (36%) and dyspareunia (43%)[13].

Psychosocial factors affecting sexual health

Epidemiological studies have shown that psychosocial factors are more important than organic factors in the pathogenesis of FSD in women with diabetes[10,37]. Patients with diabetes have an increased risk of developing depressive symptoms, compared to the healthy population[40]. Depression may significantly impair the quality of life as well as sexual function in these patients[41]. In addition, psychopharmacological therapies, such as anti-depressants, anti-psychotics drugs, mood stabilizers and anxiolytic drugs used in such conditions has its own side effects on the sexual functions[42,43]. Moreover, other psychological issues such as altered self-image, feeling of loneliness or isolation and loss of attractiveness are common in women with diabetes[13]. Higher risk of FSD in women with higher BMI is also common and increased BMI can also strongly alter the self-image of a woman, impairing the quality of sexual life as well[24].

Management of sexual dysfunction in women with diabetes

Diagnosis

Recently, the International Society for the Study of Women's Sexual Health has developed a POC that provides practical recommendations to diagnose sexual dysfunction in women[7]. This POC is addressed to clinicians with any level of competence in sexual medicine and not only to specialists in sexual medicine. Most women find it difficult to talk about their sexual life and would like clinicians to bring up the topic to give them the opportunity to speak about sexual health. So, as first step, the POC recommends a patient-centered communication in which the clinician asks about sexual satisfaction or problems. If sexual dysfunction is identified, a four-step model is suggested[7] that includes:

(i) Eliciting the story.
(ii) Naming/reframing attention to the problem.
(iii) Empathic witnessing of the patient's distress and the problem's impact.
(iv) Referral or assessment and treatment.

The aim of this communication is to discover the negative effect of the problems in a woman's life. In fact, distress is a key element for the diagnosis of FSD, as emphasized by the more recent classifications[7].

Self-administered questionnaires can be very useful. The FSFI-19 is one of the most used psychometric diagnostic tests to identify FSD[44]. A reliable short version of this questionnaire, FSFI-6, is well validated for the screening of sexual dysfunction in women. It includes six domains: desire, arousal, lubrication, orgasm, satisfaction and dyspareunia. The score for each question ranges from 0 or 1 to 5. A total score of ≤ 19 allows identifying those women, who need further investigation, including the full version of FSFI-19 and a patient-centered interview[45]. In addition, another version of the FSFI-6, the FSDI-6 has been recently developed[46]. A question on the interest in having a satisfying sex life is added in FSDI-6 to better investigate the level of distress that may arise from the identified sexual problems. Since, women with sexual dysfunctions have a decreased perception of the orgasmic intensity, compared to healthy women, a new quick and easy psychometric tool, the orgasmometer-F, has been validated recently for measuring the orgasmic intensity in women[47]. A physical examination should be performed to identify potential contributing factors including infections, inflammation, atrophy and neoplasms[7].

Inadequate evaluation of FSD is one of the main factors responsible for the lack of association between sexual dysfunction

and cardiovascular health in women[48]. The main marker of sexual arousal is the increase in blood flow in the genital region. Recently, different diagnostic systems have been validated to study the blood flow in female genitalia, including indirect measures of heat dissipation (vaginal thermistors, labial thermistor and heated oxygen electrode), VPP and doppler USG. VPP is one of the most used tools to evaluate genital arousal and the doppler USG is a quick and noninvasive technique that provides a real-time assessment of anatomy and blood flow of female genitalia[48]. Women with T1D showed lower clitoral peak systolic velocity, end-diastolic velocity and higher resistance index, compared to healthy controls. After the administration of 100 mg sildenafil, the mean resistance index in these women was significantly decreased, indicating an improvement of the clitoral blood flow[49]. The clitoral pulsatility index has been correlated with metabolic syndrome and with a subjective decrease in sexual arousal[46].

Treatment

The management of sexual dysfunction in women with diabetes should be performed by a multidisciplinary team, including a diabetologist, a specialist in sexual health and psychotherapist.

Non-pharmacological interventions

Weight loss

No specific guideline is available for the treatment of sexual dysfunction in women with diabetes. The change of lifestyle, including weight loss and more physical activity is the key step for the treatment of FSD in patients with diabetes. Treating sexual dysfunction by reducing weight and perhaps thereby improving perceived body image may be a useful strategy for treatment. Bond and colleagues reported that 60% of obese women with FSD were seeking bariatric surgery and after 6 months of the surgery the FSFI score was significantly increased (24-29.4) and 68% of them have resolved their sexual problems[50]. Women with diabetes and higher adherence to a Mediterranean diet showed a lower prevalence of FSD, compared to women with lower adherence to the same diet[51]. In the Look AHEAD study (16-center, randomized controlled trial evaluating the health effects of intensive lifestyle intervention), T2D women with obesity demonstrated a statistically significant improvement in sexual function based on the FSFI at 1 year follow-up[52].

Psychological interventions

Attempts to implement psychological interventions to improve sexual dysfunction have been made. Such interventions include PLISSIT framework, which have been developed to assist treatment of sexual problems[53,54]. This framework encompasses four stages:

(i) Permission, which relates to the patient giving permission to raise sexual issues.

(ii) Limited information, which relates to giving the patient limited information about sexual side effects of treatment.

(iii) Specific suggestions, which entail suggestions based on comprehensive evaluation of presenting problems.

(iv) Intensive therapy, which refers to including psychological intervention, biomedical and/or sex therapy.

Limited evidence currently exists on the effectiveness of the PLISSIT framework for women with diabetes[53,54]. To make a diabetic woman comfortable to social interactions and interpersonal relationships, it is necessary for their partner to instill confidence and motivation in them. Patient education and patient autonomy should also be provided to the spouse and the in-laws family by the HCPs[55,56]. The experience and understanding of the spouse must be improved to maintain harmonious sexual relation with the diabetic wife. Counselling must be arranged for the partner to make him aware that sex is not important than the person's health and well-being to bestow support to the patient.

Pharmacological interventions

PDE5 inhibitors

PDE5 inhibitor relaxes vascular smooth muscle and increases vasodilatation, and is already considered to be very effective to cure erectile dysfunction and FSD in men[57]. In a randomized double-blind crossover trial, use of 100 mg sildenafil (viagra) in 36 premenopausal women with sexual arousal disorder and T1D for 8 week periods demonstrated statistically significant improvements in arousal, desire, orgasm, improved blood flow to the clitoris and enjoyment of sexual activity[58]. Results from a placebo controlled crossover study, using 5 mg tadalafil in premenopausal women with T1D and sexual genital arousal disorder (characterized by spontaneous genital arousal, triggered by sexual or non-sexual stimuli that are unresolved by orgasm) suggests its effectiveness in improving the arousal and quality of sex life[59].

Hormonal replacement therapy

HRT is approved for post-menopausal women[25], but the use of androgens to treat FSD is still debated. A meta-analysis including 43 studies on 8,480 postmenopausal women showed that testosterone administration was associated with a significant increase in the number of satisfying sexual events and sexual desire[60]. However, oral testosterone was associated with an increase in LDL, whereas non-oral testosterone did not significantly affect the lipid profile[60]. In a 6 month, placebo-controlled, double-blind trial, 272 naturally menopausal women with HSDD, who have received a transdermal testosterone patch (300 µg/day) twice per week, or an identical placebo showed significant improvements in sexual desire, satisfying sexual episodes and a significant decrease in distress[61]. In postmenopausal women with HSDD, with or without estrogen therapy, testosterone exerts a beneficial effect on sexual function at doses within the physiological premenopausal range[62]. However, at present, no androgen therapy has been approved for FSD by the FDA.

Anti-depressant therapy

There is some evidence to suggest that treating depression in diabetes can lead to improved sexual function. Most anti-depressants such as selective serotonin reuptake inhibitors are associated with reduction in sexual functioning[63]. BU is an atypical anti-depressant (a norepinephrine-dopamine reuptake inhibitor) which is commonly used in smoking cessation and to treat MDD, improves sexual dysfunction in women with T2D and MDD[64]. In a secondary analysis assessing sexual function, mood and glycemic control in 90 women with T2D, of which 63.3% were treated with BU for MDD, revealed that 71.1% of patients had insufficient sexual function at baseline. However, mean sexual energy scores improved significantly during treatment with BU. Furthermore, it was established that mean sexual energy scores were improved among participants with hyperglycemia and persistent depression (25.9% and 18.2% respectively)[64]. Therefore, it was concluded that BU treatment for MDD in women with diabetes may significantly improve sexual function, mood and glycemic control. Improvements in sexual functioning were, however, also demonstrated in approximately 20% of women with persistent MDD and hyperglycemia, suggesting that BU treatment may enhance sexual function, regardless of improvements in mood and glycemic control.

Conclusion

Prevalence of sexual dysfunction among women with diabetes is high and can correlate with depression, anxiety and difficulties in living with diabetes including body image issues, cardiovascular risk and hyper or hypoglycemia. Untreated sexual dysfunction can lead to relationship difficulties and breakdown. Sexual dysfunction and its role in well-being should be given parity with male sexual dysfunction in diabetes consultations and targeted or holistic treatments need to be made available in diabetes services.

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CHAPTER 19 PSYCHOSOCIAL ISSUES IN WOMEN WITH DIABETES MELLITUS

Dr. Shruti Chandrasekharan, Dr. Archana Juneja

Introduction

MDD is a risk factor associated with T1D and T2D with a higher risk of development in T2D patients, especially in women[1,2]. The poor glycemic control in DM is mainly responsible for depressive symptoms along with comorbid MDD[3,4]. Prevalence of developing and dying from T2D has been observed to be higher in American Indians, compared to their Non-Hispanic White counterparts, with greater prevalence in older people[5]. Despite a higher prevalence of diabetes, the management of the psychological issues in patients with diabetes in India is still very poor[6].

Impact of psychological factors on patients with diabetes

Depression often compromises quality of life by decreasing physical activity, inducing metabolic disorders and obesity[7]. The mental health disorders such as depression or anxiety are associated with ineffective control of T2D and subsequent high risk of mortality[5]. The stress of life-long medication for DM treatment further worsens the patient's psychological condition, resulting in poor management of diabetes[6]. MDD is associated with tremendous stress that activates or rather over-activates hypothalamic-pituitary-adrenal axis, which, in turn, releases cortisol. The latter has a substantial deleterious impact on body in the form of obesity and IR. Additionally, MDD is related to inflammation or chronically elevated pro-inflammatory substrates like CRP, TNF-α and IL-6[8].

Psychological problems in diabetes patients further lead to depression, anxiety or poor self-care behaviour that influences metabolic outcomes, quality of life, increases healthcare cost and mortality[9]. The physical and mental health is compromised as a part of diabetes and the patient fails to meet their emotional and psychological needs[10]. Patients with T2D are at greater risk of developing comorbid depression than healthy individuals which increases the risk of obesity by modulating self-care, physical activity and over-eating[9]. Symptoms of anxiety and depression are also responsible for poor diabetes control and lead to health complications[11]. Emotional stress in patients with diabetes causes unhealthy lifestyle and may lead to bad eating, physical inactivity and unhealthy habits of smoking and alcohol consumption[12,13]. Mental health conditions like depression, anxiety, eating disorders, cognitive impairment and DD may affect the adherence of the patient to diabetes management[14,15].

Screening for psychological impact in women with diabetes

Patients with diabetes are less likely to be screened for mental disorders, which leads to worsening of such conditions. Integration of regular psychotherapy sessions improves medication compliance, glycemic control and quality of life, improving the depressive disorder in patients with diabetes[16,17]. Use of PHQ-9 is a globally accepted scoring system that measures depressive symptoms in patients with DM [4]. The frequency of any particular sign as assessed is as follows: 0 = not at all, 1 = several days, 2 = more than ½ of the days, 3 = nearly every day with a score of 0-4 for minimal, 5-9 for mild and ≥ 10 for moderate to severe depression[18]. The Beck Depression Inventory has been utilized with considerable success as well. This questionnaire comprises of 21 questions with 4 answers for each and a score of 0-3; 0 indicating the absence of disorder and 3 indicating the most severe disorder. 0 is the minimum and 63 is the maximum score, where 0-13 indicates minimal depression, 14-19 demonstrates mild depression, 20-28 depicts moderate depression and 29-63 presents with severe depression[19]. Patients with severe mental illnesses like schizophrenia, bipolar disorder and MDD who are already at risk of premature death must be screened for T2D as they are more susceptible to developing the latter[20,21]. Furthermore, clinical features of anxiety in patients with diabetes can be assessed using HRSA[22].

Depression in women with diabetes

The most common psychological disorder that occurs in a patient with diabetes is depression. The causes of depression in patients with diabetes ranges from increased medication, obesity, end-organ damage and comorbidities[22]. Around 41% of patients with diabetes are reported to suffer from poor psychological health and increased depression and anxiety disorder[10]. In a study from Pakistan, 40% of the population with diabetes was found to have depression with a higher frequency in women and middle-aged patients[23]. A higher prevalence of depression was found in women with diabetes (46.9%) from Iran in comparison to men with diabetes (36.8%)[19]. A study on the North Indian population showed PHQ-9 score of severe, moderate and mild depression in 4, 10 and 27% of study population with higher prevalence in patients with diabetic microvascular complications, elevated fasting glucose level and hypertension[18]. Increased HbA1c level was reported in patients with higher depressive symptomatology with/without social support[5]. T2D patients showed 24% higher risk of developing depression in one study and associated depression in another study in newly diagnosed T2D patients from the US[24,25]. The prevalence of depression was higher among T2D patients (17.6%), compared to non-diabetic patients (9.8%)[26]. Depression could further lead to obesity in patients with diabetes by influencing self-care, regular activity and over-eating[9]. Diabetic nephropathy, retinopathy and neuropathy were also reported to increase the risk of depression by 4.2, 3.8 and 2.1 times[23].

Anxiety and stress in women with diabetes

Another common psychological disorder in patients with diabetes is anxiety with 14% of patients reported to suffer from a generalized anxiety disorder, 27% with subsyndromal anxiety disorder and 40% (majority women) with elevated anxiety disorder in comparison to non-diabetics[27,28]. The anxiety symptoms in patients with diabetes must be addressed similar to depression symptoms, as it is also a comorbid condition of diabetes[29]. Another study reported a higher HRSA score (21.07 ± 5.44 vs. 6.88 ± 3.43) in T2D patients with depression, compared to the non-depressed group[22]. Besides high level of depression, anxiety symptoms were also found in women with diabetes from 10 hospitals of New Delhi, India[29]. Women in this study showed anxiety symptoms with recently diagnosed diabetes that resulted in altered blood glucose levels, restricted daily function and household burden[29]. The disabilities in daily functioning increased the anxiety level 2 fold and depression by 20%[29]. In veteran women with diabetes, the higher blood glucose level was related to anxiety symptoms responsible for poor diabetes management and health complications[11]. Interestingly, the number of children also predicts anxiety and depression level as the former may influence the mental health of women with diabetes[30].

Eating disorders in women with diabetes

Emotional stress in DM is associated with unhealthy lifestyle that includes inadequate quality and quantity of food, low physical activity, smoking and drinking habits[12,13]. Eating disorder or diabulimia occurs in patients with T1D, characterized by insulin restriction and weight loss[31]. Women with diabetes, especially T1D depict a 2 fold increased risk of developing an eating disorder and a 1.9 fold increased risk of developing sub-threshold eating disorders compared to non-diabetic women. This disorder includes binge eating and caloric purging through insulin restriction, resulting in poor glycemic control with higher rates of hospitalizations and retinopathy, neuropathy and premature death compared to age-matched T1D women without eating disorders[32]. T1D patients are always under nutrition and medication pressure, resulting in disturbed eating behaviours and eating disorder[33,34]. In patients with diabetes night eating syndrome along with poor glycemic control, obesity, depression and diabetes complications were reported in a previous study[35]. Around 20% of females with diabetes were observed to suffer from eating disorders[33]. Other aspects involved in diabetes management like BMI, body weight, psychological factors and the impact of diabetes on self-image and family interaction also elevate the risk of eating disorders[34]. In addition, some traumatic events like abuse and family breakdown is accountable for eating disorders[36,37]. Clinical practice guidelines for eating disorders suggest cognitive behavioural therapy and family based therapy[34].

As described earlier, patients with diabetes experience many profound emotions that result in greater risk developing of depression, anxiety, eating disorders, all-cause dementia, psychological IR, cognitive impairment and DD[14,38]. These negative emotions (Figure 1)[39] may adversely influence the adherence behaviour of the patients to diabetes care and therapies. MDD is a burdensome disease of global importance affecting the quality of life of patients with diabetes. Apart from depression, DD or diabetes-related distress has emerged in patients with diabetes, defined as an emotional state where people experience feelings such as stress, guilt, or denial that arise from living with diabetes and the burden of self-management[40]. DD is different from MDD, as MDD is diagnosed based on specific symptoms. However, though DD symptoms are similar to those of depression; they are not severe enough to meet the diagnostic criteria for MDD[39] (Figure 1).

Figure 1: Symptoms of diabetes distress
Source: Ibrahim et al., 2019[39]

DD can be assessed using two statistically sound scales namely the PAID scale and the DDS. A multinational, interdisciplinary and multi-stakeholder study was conducted in 2013 that involved 8596 individuals with diabetes across 17 countries and demonstrated that DD (assessed using PAID-5 scale) was prevalent in 44.6% of the participants[41]. A similar prevalence of 52% and 42.1%, evaluated by DDS, was reported by Onyenekwe et al., 2020 and Fisher et al., 2016 respectively[38,42]. Factors such as younger age, female gender, insulin use, difficulty to adhere to dietary recommendations, greater HbA1c, depression, treatment of depression and lower own health rating are associated with greater odds of interpersonal distress on adjusted analysis[43] Literature reveals that elevated DD is significantly related to disease management, glycemic control and quality of life[44]. There is a significant relationship between distress and diabetes management, with high distress associated with higher HbA1c and a more substantial percentage of missed insulin boluses[45]. Therefore, there is a need to identify and address pain in diabetes management programs. Self-management behavioural programs such as CASM, CASM plus DD-specific problem solving, or a computer-administered minimal supportive intervention have reported successful and significant reductions in DD[46].

Psychosocial care for patient with diabetes

Patients with diabetes can achieve reasonable glycemic control and improve their psychosocial responses by opting healthy habits and life style choices and self-management of the disease[47]. Previous studies showed that more robust social support is associated with lower mortality and T2D management[48-51]. Lower HbA1c levels was observed in T2D patients, when their family members cooked food for them, suggesting family as the most useful unit as part of diabetic care strategy[52]. Some psychosocial interventions are opted to improve the diabetic care, glycemic control and quality of life. Such interventions are cognitive behavioural therapy, problem-solving therapy, coping skills training and family behaviour therapy[9]. However, compared to men, women with diabetes tends to cope more poorly from DD, depression and anxiety and therefore, are required to show a more positive attitude towards the disease during self-management[47].

Role of diabetologist and mental health professionals psychosocial care for patient with diabetes

Effective management of depression by psychiatric treatment improves diabetes as found in a randomized controlled trial showing desired glycemic target achievement in patients with psychiatric care[53]. It is reported that medical care settings do not routinely do trauma diagnosis and as it is related to T2D management, it is necessary for primary care settings to routinely screen trauma and engagement of community leaders, providers and patients[5,54]. MDD is infrequently diagnosed in DM patients, as a previous study on population-based DM sample reported proper diagnosis of MDD in 31% of patients (majority of women) and only 6.7% of them received ≥ 4 sessions of psychotherapy[55]. Physician-led psychiatric services including medication management, encouragement of medication compliance, psychotherapy and multidisciplinary care approach improve DM, MDD, quality of life and patient outcome[55,56]. Prevention of Suicide in Primary Care Elderly: Collaborative Trial showed reduced mortality in DM patients over 5 years after psychiatric management[57]. MDD in DM patients can be managed by regular follow-up in an integrated psychiatric and diabetes service[4,58]. Regular follow-up visits to psychiatrists are recommended for patients with diabetes to promote antidepressant medication compliance and optimization as well as reduce their depressive symptoms[55]. Table 1 presents the role of diabetologist and MHP in diabetes management[9,59].

Table 1: Different role of health care professionals in management of diabetes

Role of diabetologist	Role of MHP
Ask and screen for general/mild, intermediate or complex/ severe level difficulties in patients with diabetes. Offer advice or counselling to handle these difficulties with the help of MHP.	Annual screening of all patients with diabetes for depressive symptoms with age-appropriate depression screening measures.
Make DM patients aware about hypoglycemia, which can co-occur with fear of hypoglycemia and must be treated using blood glucose awareness training or any similar kind of intervention.	Further evaluation will be necessary for individuals who have a positive screening.
Re-evaluation of the treatment regimen for DM patients, who have developed symptoms of eating disorder.	Offer support to diabetologist and the patient to address any kind of difficulties.
	Use of cognitive behavioural therapy, interpersonal therapy or other evidence-based treatment approaches in collaboration with diabetologist.

Source: Karla et al., 2018[9] and Young-Hyman et al., 2016[59]

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CHAPTER 20 POSTMENOPAUSAL CARE IN DIABETES MELLITUS

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Diabetes is common in postmenopausal women. In addition to the physiological ageing, ovarian ageing explains the higher risk of diabetes in postmenopausal women. Management of diabetes may be challenging in postmenopausal women as the hormonal milieu influences the choice and outcomes of therapy.

Postmenopausal changes in women

Women experience several physiological changes after menopause that are illustrated in (Figure 1)[1]. These changes are largely attributable to primary ovarian failure and the associated decline or cessation of estrogen and progesterone production and the rise in levels of FSH and LH.

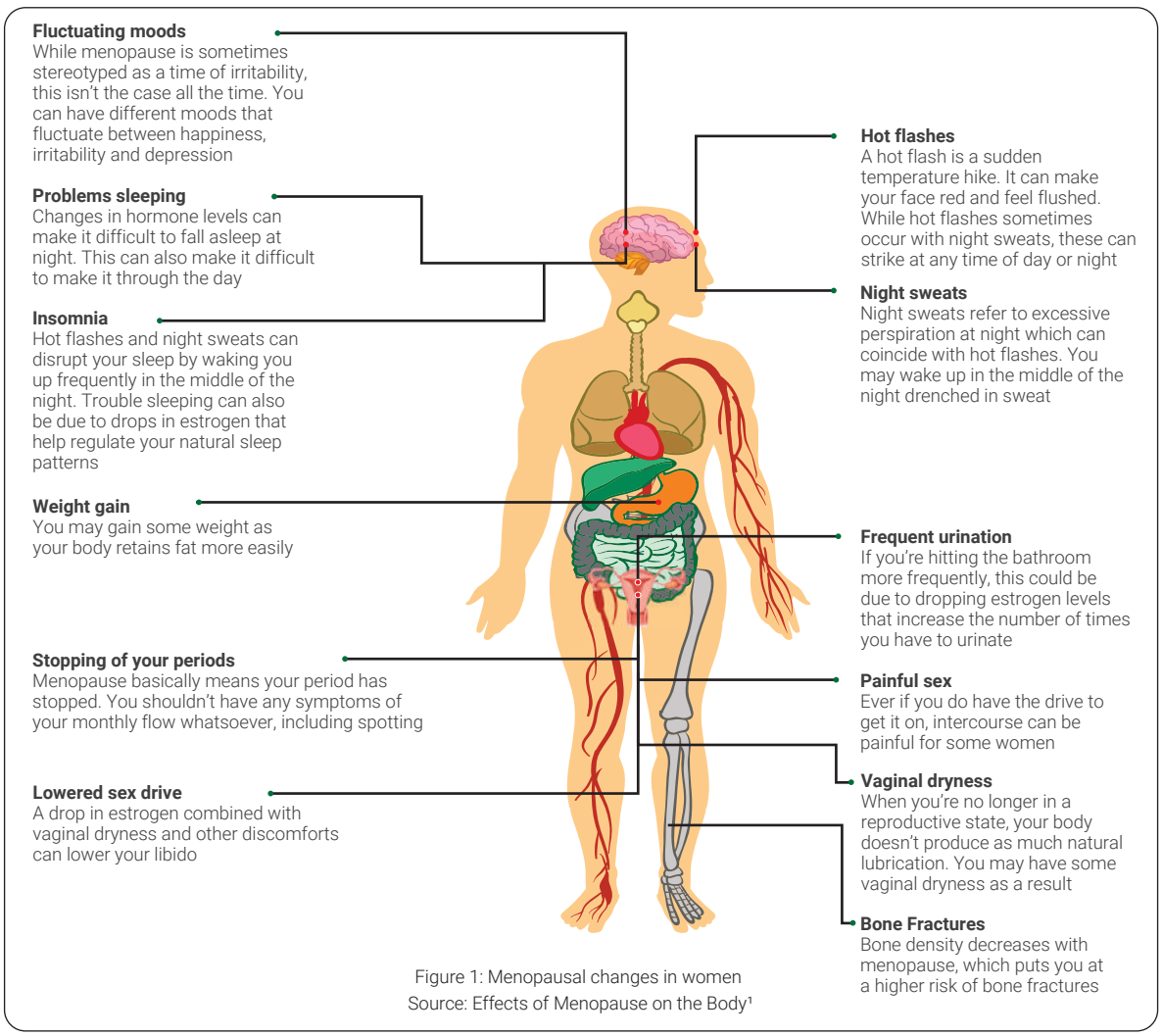

Figure 1: Menopausal changes in women
Source: Effects of Menopause on the Body[1]

Central obesity is a common feature of postmenopausal women and is associated with adverse metabolic consequences like hypertension, CVD and dyslipidemia. Weight gain in middle life is also associated with an increased risk for cancer, arthritis, mood disorders and sexual dysfunction. Changes in lipid metabolism and central adiposity lead to excess fatty acids, adipocytokines, proinflammatory cytokines and reactive oxygen species, which cause lipid peroxidation. These factors together increase the risk for the development of IR and dysglycemia.

Key symptoms and signs in menopausal women include vasomotor symptoms including hot flushes and headaches, urogenital and vaginal atrophy leading to urge incontinence, pruritis and dry vagina, sexual decline and dysfunction, cognitive decline and psychiatric symptoms like confusion, depression and mood swings along with CVD, cancer (increased risk of cervical and breast cancer) and osteoporosis[2]. Osteoporosis may lead to musculo-skeletal symptoms like backache, low impact fractures – both vertebral and non-vertebral, reduced range of mobility and decrease in height. The fluctuating levels of estrogen may influence the levels and function of neurotransmitters and lead to symptoms like difficulty in concentration, dysphoric mood, disturbed sleep and cognitive difficulties. The change in sexual function after menopause is multifactorial. It may be due to physiological changes in the urogenital system along with the psychological and social changes associated with menopause.

Risk of diabetes in postmenopausal women

Hormonal changes associated with menopause may increase the risk of diabetes in postmenopausal women. Menopause is associated with metabolic changes such as increase in adipose tissue, central redistribution of adipose tissue, decrease in energy expenditure and impaired insulin sensitivity. Postmenopausal state is associated with dysglycemia independent of the normal physiological changes of ageing[3]. Decrease in estrogen concentration along with the reduced estrogen receptor activity can cause IR in peripheral tissues[4]. Age of onset of natural menopause influences the development of diabetes in postmenopausal women with an earlier age of menopause being associated with a higher risk for diabetes[5].

In a review of data in the Toranomon Hospital Health Management Center Study 17, the age-adjusted OR for diabetes were 1.40 (95% CI, 1.03-1.89) and 1.59 (95% CI, 1.07-2.37) in women (n=4570) after natural and secondary menopause respectively, compared to premenopausal women (n=6308)[3]. The SWAN suggested that lower estrogen concentrations resulted in a 47% higher risk of diabetes during the menopausal transition in 1407 women aged 42-52 years, who experienced natural menopause[6].

The time, type and severity of menopause impact the risk for diabetes in women. There is definite evidence for an increased risk of diabetes with an earlier (< 45 years of age) onset of menopause. Surgical menopause confers a higher risk for metabolic disturbances and diabetes when compared to the physiological menopause. The risk is particularly higher in women who undergo hysterectomy and bilateral salpingo-oophorectomy. Women with diabetes can have more severe vasomotor symptoms around or during the onset of menopause. Thus, there is a need for targeted screening for diabetes in women who experience an earlier onset of menopause. Diabetes may predispose women to an earlier age at menopause though there is no definitive evidence for this. In women who undergo hysterectomy, preservation of ovaries may help to reduce the risk for diabetes[7].

Long term effect of HRT

Diabetes is not a limitation for the initiation of HRT in postmenopausal women. HRT does not adversely impact the development of diabetes in postmenopausal women. This can be explained by the beneficial effect of HRT on metabolic parameters including reduced abdominal fat deposition and increased lipid oxidation. Long term use of HRT is also associated with an increase in energy expenditure[8]. There is evidence for the role of estrogens in augmenting insulin secretion in the pancreatic β- cells and improving insulin sensitivity through effect on estrogen receptors in the liver, adipose tissue and muscles[9]. Estrogens improve the hyperandrogenic state in postmenopausal women and can improve glucose homeostasis and lipid profiles[10,11].

HRT reduces IR and FPG in postmenopausal women with diabetes. In a meta-analysis of 107 randomized controlled trials of at least 8 week duration, HRT had beneficial effects on components of metabolic syndrome in postmenopausal women with and without diabetes. In women with diabetes, HRT reduced FPG (-11.5%, CI, -18.0 to -5.1%) and homeostasis model assessment – IR (-35.8%, CI, -51.7 to -19.8%)[12]. This antidiabetic effect of HRT may not be sustained after discontinuation of HRT[13]. The use of HRT in postmenopausal women without diabetes, appears to reduce the risk of self-reported diabetes[7].

In the Women's Health Initiative Hormone Therapy Trials in 27,347 postmenopausal women (50–79 years), women who received HRT had significantly lower rates of treated diabetes when compared to women who received placebo. Conjugated equine estrogens (0.625 mg/day) alone (Hazard ratio: 0.86, 95% CI, 0.76–0.98) and in combination with medroxyprogesterone acetate (Hazard ratio: 0.81, 95% CI, 0.70–0.94) reduced the risk for diabetes in postmenopausal women[13]. Large observational studies like the Nurses' Health Study and the postmenopausal estrogen/progestin interventions study suggest reduced risk for diabetes in postmenopausal women who receive HRT[14,15]. Hormone replacement may improve glycemic control in postmenopausal women with pre-existing diabetes.

Further, the use of HRT in cancer management provides insights for the possible effect on glucose metabolism. HRT for breast cancer with aromatase inhibitors and tamoxifen does not increase the risk of diabetes for 2 years after initiation in postmenopausal women[16].

Cognitive health in postmenopausal period

Cognitive state needs attention in postmenopausal women. Areas of the brain controlling memory and cognition have various isoforms of estrogen receptors which are differentially expressed in various pathways. The decline in estrogen levels impacts the balance of neurotransmitter systems by shift in the type of estrogen receptors and modifications in the estrogen-regulated transcription. Falling levels of estrogen can increase oxidative stress and augment neurodegeneration. Postmenopausal women experience cognitive decline which may be subtle or may manifest as profound loss of memory. These can be influenced by various factors including stress, mood changes, physical health and presence of comorbidities.

Longitudinal data for cognitive decline in women transitioning to menopause are available from two key studies, the Kinmen Women-Health Investigation study and the SWAN study[17,18]. These studies have suggested a cognitive decline in women after menopause. This decline can be augmented by diabetes and other comorbidities in menopausal women. The cognitive decline, though not linear, can impact the quality of life of women after menopause. Decrease in attention, working memory, verbal learning and fine motor functions can be evident at various time periods after menopause.

Postmenopausal women with diabetes experience neuropsychiatric symptoms like anxiety and depression. They may also complain about disturbed sleep. Mood swings are a common feature of menopause and can be precipitated by the occurrence of diabetes. Women may attribute cognitive decline to hot flushes which are a cardinal symptoms of menopause. However, there is no substantial evidence for the relation between cognitive decline and self-reported hot flushes[19,20].

In some women, the decline in cognition during menopause may be transient and subtle. Adequate control of diabetes and other comorbidities in postmenopausal women can delay or arrest the decline in cognition.

Special consideration for management of diabetes in postmenopausal women

Postmenopausal women should be screened for diabetes, in particular when there are risk factors like adiposity and other comorbidities. Diabetes should be managed with a multipronged approach in postmenopausal women[21]. Lifestyle interventions are the cornerstone for the management of diabetes. It is important to introduce an optimal diet and adequate physical activity to women who are transitioning to menopause. Weight gain, a common feature of perimenopausal women, should be addressed with active interventions for a gradual and sustainable loss of weight.

Cessation of smoking and alcohol improve the control of diabetes in postmenopausal women. Discontinuation of smoking and alcohol helps to improve the symptoms of menopause, reduce the metabolic complications and reduce the risk of osteoporosis and cancer in postmenopausal women.

Management of diabetes should be intensified in postmenopausal women who have a first-degree family history of diabetes as they are at an increased risk for IR and hyperinsulinemia[22]. Postmenopausal women should undergo annual screening for retinopathy, neuropathy and other possible complications of diabetes.

Dietary interventions

Diet in postmenopausal women should be focused around increasing the intake of fruits, vegetables, whole grains, legumes, nuts and seeds. Dairy being a rich source of calcium makes an important dietary component. The intake of red and processed meat, sugar and sodium should be limited. These dietary patterns are associated with reduction in risk of CVD in postmenopausal women who have diabetes[23].

Dietary supplements

Vitamin D deficiency has a higher prevalence in postmenopausal women and can impact the development of diabetes as well as other conditions such as osteoporosis. Screening for vitamin D should be incorporated in the management of diabetes in postmenopausal women[24]. Postmenopausal women should take daily calcium (1000 mg) for bone health. Supplements for other vitamins and micronutrients may be used, if needed.

Physical activity

Exercise is an integral part of the management of diabetes in postmenopausal women. Exercises may include walking and a composite of endurance, strength and balance exercises. Deep breathing, yoga and stretching can help to beat the stress of menopause and effectively manage the symptoms of menopause. Exercise has several benefits including the maintenance of muscle mass, improved bone health, enhancement of mood, amelioration of neuropsychiatric problems and good control of diabetes.

Oral hypoglycemic agents

Postmenopausal women who fail to achieve target glycemic control with diet and exercise will require pharmacotherapy for the management of diabetes. Hypoglycemic agents have varying metabolic and cardiovascular effects and should be chosen according to the dysglycemia and presence of comorbidities. The first line of treatment is usually metformin especially in women who are obese. Treatment with metformin can be initiated as early as the diagnosis of diabetes in postmenopausal women concurrent with lifestyle interventions. If HbA1c continues to remain high at ≥ 7%, second line therapy can be initiated with DPP4i and GLP-1RA as these agents do not adversely impact bone health in postmenopausal women. TZD and SGLT2i should be avoided in postmenopausal women with osteoporosis and increased risk of fractures[25,26].

Insulin

Women who fail to achieve euglycemia with oral agents are candidates for treatment with insulin. However, insulin should be used in caution in postmenopausal women to avoid hypoglycemia. In addition, there may be an increased risk of fractures with insulin therapy. This may be due to the inadequate control of diabetes per se or due to the increased risk of falls with episodes of hypoglycemia.

Control of blood glucose

Stringent control of dysglycemia is a key to bone health in postmenopausal women. Diabetes is an independent risk factor for increased risk of fractures[27]. Postmenopausal women with diabetes have an increased risk of fractures, in particular hip fracture[28]. Risk assessment for fractures should be done periodically in postmenopausal women with diabetes. The trabecular bone score is a good tool for identification of fragility fractures in these women[29]. Adequate control of diabetes also helps to prevent comorbidities such as hypertension, CVD and renal dysfunction in postmenopausal women[30].

Management of cognitive health

The management of diabetes in postmenopausal women should include counselling for change in lifestyle, behavioural and psychological support. Postmenopausal women with diabetes should receive psychosocial support to keep good mental state. HRT in postmenopausal women does not have a marked influence on episodic memory or other cognitive skills[31]. There is no conclusive evidence for the initiation of HRT to prevent or improve cognitive skills or the onset of Alzheimer's disease in postmenopausal women[32]. Initiation of HRT prior to onset of menopause has a beneficial effect on cognitive performance whereas initiation after onset of menopause has a detrimental effect[18].

Hormone replacement therapy

When appropriate, HRT can be initiated to manage symptoms of menopause. However, it is ideal to initiate HRT in postmenopausal women with diabetes after a cardiovascular risk assessment. With a goal to maximize benefits and minimize risks, treatment should be individualized according to the duration of menopause, presence of comorbidities and patient preferences. Recent postmenopausal women with diabetes have a lower risk for CVD and are good candidates for oral estrogen.

In postmenopausal women with diabetes, HRT has a beneficial effect on metabolic parameters including reduction of central adiposity, increase in lipid oxidation and enhancement of energy expenditure. HRT improves glycemic control, IR and parameters of metabolic syndrome. HRT also reduces the risk of diabetes in women who do not have diabetes during the transition to menopause[7,25].

An ideal candidate for HRT

HRT should be avoided in postmenopausal women > 60 years in age or those who have been in menopause for > 10 years. In these women, HRT may increase the risk of thrombotic episodes[33]. HRT should be considered as a treatment option in postmenopausal women who experience severe vasomotor symptoms and are < 10 years into menopause, are < 60 years in age and are at a low risk of venous thromboembolism, CVD and breast cancer[7].

Oral vs. transdermal HRT

Both oral and transdermal estrogen therapy can improve glycemic control and insulin sensitivity. However, oral therapy is more beneficial when compared to equivalent doses of transdermal therapy[7]. Transdermal estrogen may be preferred for obese postmenopausal women with diabetes who have a moderate risk for CVD.

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CHAPTER 21 BONE HEALTH IN WOMEN WITH DIABETES

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Effect of diabetes on bone health

Globally, there are currently an estimated 463 million adults with DM aged 20-79 years. This number is expected to increase to 578 million by 2030 and to 700 million by 2045[1]. DM influences the functioning of many tissues in the human body, including the bones and joints. Long-term exposure to a hyperglycemic environment causes changes in bone metabolism and impaired bone micro-architecture. These abnormalities are often independent of BMD. Two meta-analysis including 7,832,213 subjects found a higher incidence of fractures in individuals with T1D and T2D than in the general population[2]. While T1D is associated with modest reductions in BMD (Hip Z-scores of −0.37 ± 0.16), patients with T2D have higher BMD (Hip Z-scores of 0.27 ± 0.16)[3]. Indirectly, many factors associated with hyperglycemia affect the bone micro-architecture.

Fracture risk in diabetes

Women with diabetes have a significantly increased risk of hip, pelvis, upper leg, foot and vertebral fractures[2]. The Nurses' Health Study followed 109,983 women aged 34-59 years for over 20 years and found that the risk of hip fracture in women with T1D was 6 times higher than in those without diabetes[4]. The Health Improvement Network study in the UK evaluated the incidence of fractures in men and women with T1D aged 0-89 years, across a median of 4.7 years of follow-up. They found an increased risk of incident fracture of any type in both sexes and across all age groups compared to those without diabetes. When stratified by age, women with T1D aged 40–49 years had the highest risk for fracture at any site; it was 82% higher than that in women without diabetes after multivariate adjustment. Young women with T1D, in the 30–39 years age group had a 316% increase in the risk of hip fracture than in those without diabetes[5].

In the Women's Health Initiative observational cohort, 93,676 healthy postmenopausal women were followed for 7 years. Women with T2D at baseline had a 20% increased risk of fracture after adjusting for multiple covariates, including the frequency of falls[6]. A large registry-based cohort study from Taiwan with 500,868 patients with diabetes found that men and women with diabetes had a 28% and 72% increased risk of hip fracture compared to controls without diabetes. Thus, the risk in women seems to be much higher. The Study of osteoporotic fractures followed 9,654 women aged > 65 years for an average of 9.4 years. Women diagnosed with diabetes after the age of 40 years had a 30% higher risk of non-vertebral fracture and an 82% increased risk of hip fracture compared to those without diabetes[5]. Some studies specifically evaluated vertebral fractures. A cross-sectional study from Japan in subjects aged > 50 years found that women with T2D had 82% increased risk of prevalent vertebral fractures[7]. Ironically, though obesity is a contributing factor for the development of T2D, it might protect against fragility fractures by increasing the BMD[5]. However, it is also associated with a greater risk of falls and impact forces during falls[8].

According to different cohort, the absolute rate of hip fractures (per 1,000 patients) ranged from 3-4.1 in men (compared with 3-3.5 in non-diabetic controls) and 9.1-13.4 in women (compared with 7.8-11.1 in non-diabetic controls). In elderly individuals with and without DM, the absolute risk of non-vertebral fractures was 15.7 in men and 51 in women, compared with 16.5 and 42.5 respectively[9]. An in vivo longitudinal cohort study found that tibial cartilage volume loss and incidence of bone marrow lesions were positively associated with higher levels of fasting serum glucose levels in women but not in men[10]. The factors associated with increased fracture risk in patients with diabetes are summarized in Figure 1.

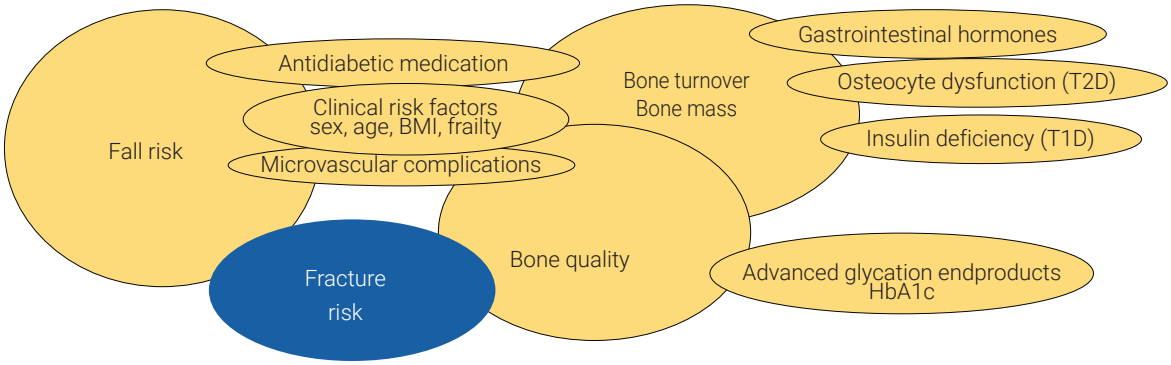

Figure 1: Summary of different factors that contribute to the increased fracture risk in patients with diabetes
Source: Hygum et al.,2019[5]

Pathogenesis of osteoporotic changes associated with DM

Extracellular bone matrix is composed of two materials: (i) the inorganic mineral component, comprising mainly hydroxyapatite, provides stiffness, which is the quality measured by a conventional BMD scan; (ii) the organic component, composed predominantly of interconnecting collagen fibers, provides tensile strength and counteracts shear stresses. These properties are regulated by cellular activity, bone tissue turnover rate and collagen cross-link formation[2]. In turn, the cellular activities are influenced by many environmental factors, including circulating hormones, oxidative stress and level of glycation[11].

An important environmental factor is insulin, which is an anabolic hormone critical for the regulation of metabolism in key organs and tissues[8]. Both osteoblasts and osteoclasts express the insulin receptor. Insulin stimulates osteoclast formation and promotes proliferation, differentiation and survival of osteoblasts. In T1D, absolute insulinopenia decreases bone formation due to an inhibitory effect on osteoblasts and their progenitor cells in the early stages of the disease. However, in T2D, the inhibitory effect caused by insulinopenia would be expected in the advanced stages of the disease. Additionally, hyperglycemia itself has a direct and indirect effect on the function and differentiation of osteoblasts; it leads to a shift of mesenchymal stem-cell differentiation from osteoblastogenesis to adipogenesis. It also affects the metabolism and maturation of osteoblasts by altering gene expression leading to a negative impact on the quality of the bone mineral[2].

Hyperglycemia also increases the level of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8, and IL-10 while simultaneously increasing the RANKL expression, which mediates osteoblast death and osteoclastogenesis[12]. Oxidative stress and hyperglycemia also lead to the accelerated formation of AGEs that cross-link with collagen fibers in both trabecular and cortical bone, increasing the brittleness. Further, they affect the development and function of bone cells by decreasing bone resorption through inhibition of osteoclastic differentiation, thereby affecting the structural integrity of the collagen matrix. Moreover, accumulation of AGEs on collagen leads to reduced cross-linking of collagen and glycosuria, causing hypercalciuria and decreased total body calcium[12,13]. AGEs also disrupt osteoblastic function by upregulating the cell surface receptor for AGE on osteoblasts. These effects of AGEs on bone cells further accelerate bone fragility[14-16].

Sarcopenia, is reported to be associated with osteoporosis, fracture risk and fall risk even in postmenopausal women without diabetes. A cohort study from Korea reported that 15.7% of patients with T2D suffered from sarcopenia compared with 6.9% in subjects without DM. Another cross-sectional study on young patients aged 40-60 years showed lower muscle mass and decreased muscle function in patients with T2D, compared with controls[5].

Many studies have suggested that bone turnover is reduced in patients with diabetes. Serum concentrations of osteocalcin, a marker of bone formation produced by osteoblasts, were found to be lower in patients with T2D. Similarly, the concentration of CTX, a marker of bone resorption, was found to be lower in patients with T2D[9]. Microarchitectural abnormalities of the bone predispose patients with diabetes to fragility fractures and also prolong the healing time of fractures by 87%, thus increasing morbidity[2].

Longer duration of diabetes increases the risk of fracture[4,8,9]. In the Nurses' Health study, significantly greater fracture risk was seen with an increased duration of diabetes; the risk increased by 200% with diabetes duration over 12 years[5]. Anti-diabetic drugs can also modulate fracture risk. TZD increase the risk of fractures in women with T2D, independent of age and duration of exposure[5]. Glitazones are known to have detrimental effects on bone health[2]. These medications should therefore be avoided in postmenopausal women[9]. The effect of other anti-diabetic agents on bone health is debatable as the studies have reported contradicting results (Table 1).

Table 1: Summary of the effect on anti-diabetic therapies on bone health

Antidiabetic intervention	Effect on bone	Implications
Metformin	AMPK activation favours bone integrity Neutral or slightly beneficial effect on fracture risk	No special consideration
SU	Neutral effect on bone resorption markers May induce hypoglycemia and falls	Use with caution or prefer a different agent in patients with known osteoporosis or high risk of fracture
TZD	Activation of PPAR-γ in mesenchymal precursor cells may reduce their differentiation to osteoblasts Use is associated with slightly increased fracture risk among women	Measure BMD and fracture risk in patients who are candidates for therapy with TZD
DPP4i	No known effect on bone physiology Associated with slightly reduced fracture risk	No special consideration
GLP-1 agonists	Short-term studies show preservation of bone mass No association with fracture risk	No special consideration
SGLT2i	Initial signal of increased fracture risk with canagliflozin, later dispelled in meta-analysis No signal of fracture risk with other agents	Advise the patient to take enough fluid to prevent orthostatis and falls
Insulin	Observational association between insulin use and fracture risk	Take measures to prevent hypoglycemic events In patients with long disease duration, guarantee proper treatment of retinopathy/ neuropathy
Bariatric surgery	Increased risk of fractures, especially for malabsorptive procedures	Measure BMD Provide adequate replacement of calcium, vitamin D, and dietary protein

Source :Romero-Diaz et al.,2021[6]

Postmenopausal bone health

Change in the hormonal levels at menopause is associated with an increase in total body fat, particularly, abdominal fat. Women during the mid-life are at a significant risk of T2D due to the high prevalence of excess adiposity and IR. Weight redistribution with an increase in the total body fat might predispose a woman to T2D[17]. A retrospective study showed that weight increases around pregnancy and menopause correlated significantly with higher risk for T2D and/or hypertension[18]. In a prospective, population-based study, 3,639 postmenopausal women were followed for a median duration of 9.2 years. After adjustment for confounders, hazard ratios for T2D were 3.7, 2.4 and 1.6 for women with premature (< 40 years), early (40-45 years) and normal menopause (> 45 years) respectively, relative to those with late menopause[19]. In another study, it was found that for each 1 year delay in menopausal age, the incidence of T2D was reduced by 2%[20]. Three studies reported that the ave-

rage age of menopause among women with diabetes was much earlier than the age at menopause in non-diabetic women[17]. However, in the European Prospective Investigation into Cancer and Nutrition study among 2,58,898 women, no association between T2D and age at menopause was found. Nevertheless, the study reported that women with T2D before the age of 20 years had an earlier menopause compared to non-diabetic women, whereas women with T2D at age 50 years and older had a later menopause[21].

In women without T2D, use of menopausal hormone therapy appears to reduce the risk of T2D. In a meta-analysis of 107 randomized trials comparing menopausal hormone therapy to placebo or no treatment in women without T2D, menopausal hormone therapy was associated with a reduction in fasting glucose and fasting insulin leading to a 13% decrease in IR. This was associated with an estimated decrease of 30% in the incidence of new-onset T2D[22]. However, The Endocrine Society guidelines for the treatment of symptoms of menopause recommend using systemic HRT with caution in women with T2D. In women with T2D, the current and future risk of CVD or existing complications of T2D need to carefully evaluated prior to initiation of HRT. Surgical menopause leads to a greater risk of T2D, especially concomitant hysterectomy and bilateral salpingo-oophorectomy, compared with hysterectomy alone or no hysterectomy. The preservation of ovaries if feasible mitigates the risk of T2D to a certain extent and must be considered before planning surgery[17].

Bone health in GDM

Bone health of women with a history of GDM has received little attention though the prevalence of GDM is increasing worldwide[23]. GDM, defined as IGT during pregnancy, is a major risk factor for future T2D. Women with GDM have up to 7 times higher risk for T2D during the next 5-10 years compared to those without T2D[24]. However, few studies have examined the bone health of women with a history of GDM; most studies focus on the fetal outcomes of maternal GDM. Maternal age and family history of diabetes are known risk factors for GDM[25]. Two studies reported that the maternal serum levels of vitamin D were significantly lower in pregnant women with GDM compared than those without GDM[25,26]. However, another study among 200 women with a history of GDM or obesity followed up for 6 years, reported no adverse bone characteristics in women with GDM than those without a history of GDM. Rather, fat %, physical activity and diet were associated with bone health in women with a history of GDM or obesity, of which fat showed the strongest correlation[27]. Another cohort study among 480 women, of whom 96 had GDM, reported a greater decline in BMD from early pregnancy to the 3rd trimester in women with GDM than in those without GDM. However, the author reported that this was more likely due to factors like BMI than due to GDM alone[28]. Nevertheless, since vitamin D metabolism is known to be affected by glucose homeostasis, the effect of GDM on maternal health could be critical. Moreover, maternal status of vitamin D has a direct effect on fetal growth. It might be important to screen all women with GDM for serum calcium, vitamin D, parathyroid hormone and alkaline phosphatase. Vitamin D supplementation should ideally be initiated in all women with GDM.

Diagnosis of osteoporosis

Though screening patients with diabetes for osteoporosis is critical, the diagnostic criteria for osteoporosis in diabetes are challenging. Current methods such as BMD T-score and FRAX underestimate fracture risk in patients with T1D and T2D. DEXA is relatively inexpensive with less radiation exposure. However, DEXA assesses BMD but not bone quality[5]. FRAX is a computer-based algorithm that computes the 10 year probability of major osteoporotic fracture (hip, clinical spine, forearm and humerus fracture) and hip fracture in the presence of competing mortality. However, T2D is not a direct input variable to FRAX. Hence, there are concerns about its performance[29]. It has been estimated that the fracture risk in diabetes calculated with FRAX is equivalent to adding 10 years of age or reducing the BMD T-score by 0.5 SD. four options have been suggested to enhance the performance of FRAX in patients with DM (using rheumatoid arthritis as a proxy for the effects of DM, trabecular bone score adjustment, reducing the femoral neck T-score input by 0.5 SD and increasing the age input by 10 years). This is based on the observation in several studies that trabecular bone score is lower in those with T2D than in the general population[30]. Another tool is QCT, which assesses both trabecular and cortical bone. QCT can be performed using conventional whole body CT scanners for the spine or with a smaller CT device for the radius, ulna, tibia and fibula. However, standard QCT can

not distinguish the morphological parameters of the trabecular bone. Therefore, a more advanced method, HR-pQCT has been used that creates an in vivo 3D characterization of bone, preferably in the peripheral skeleton (distal radius and tibia) and has a higher resolution along with thinner slice images. Hence, it can evaluate the microarchitectural, geometrical and mechanical features of cortical and trabecular bone[5].

Treatment of osteoporosis

International guidelines recommend the same therapeutic approach for bone health regardless of diabetes status[6]. Modifiable risk factors, including factors that affect fall risk and glycemic control, should be addressed to reduce fracture risk. Physical activity is the first line intervention to decrease pain and functional limitations. Moreover, physical activity controls obesity, thus decreasing the risk of falls and relieving joint pains by reducing the weight on the joints.

Drugs associated with increased fracture risk, such as insulin and TZD, should be avoided when possible. It is also recognized that individuals with diabetes have lower vitamin D levels compared with non-diabetic controls. Vitamin D supplementation was shown to increase bone formation and reduce bone resorption in postmenopausal women with T2D.

Little is known about osteoporosis therapies in young patients with T1D. Caution is important in women during reproductive age, as bisphosphonates are stored and released from bones for a long time and might affect fetal skeletal ossification. Elderly, postmenopausal women with T2D, obesity and osteoporosis treated with long-term bisphosphonates showed no difference in spine BMD, but a significantly greater decline in BMD in the hip, femoral neck and forearm were observed than in non-diabetic controls. In postmenopausal women, raloxifene might decrease bone resorption and improve bone quality by reducing AGEs[8]. In a sub-analysis of the FREEDOM study and its 7 year extension, the rate of vertebral fractures was significantly lower with denosumab compared with placebo. In contrast, the rate of non-vertebral fractures was higher in the denosumab group. Therefore, denosumab seems to be effective against vertebral fractures[3].

Currently, there are no guidelines about how and at which stage of the disease, anti-osteoporotic medication should be initiated in patients with DM. There is no robust evidence about the anti-fracture efficacy of anti-osteoporotic drugs in these patients. The ongoing development of new osteoporosis drugs, such as sclerostin antibodies that specifically improve osteocyte functions, cortical bone microstructure and bone stiffness might provide new opportunities to improve bone strength in patients with diabetes[9].

Vitamin D and calcium

An influential factor in the development of osteoporosis is calcium and vitamin D deficiency[31]. Vitamin D is essential for optimal musculo-skeletal health because it promotes calcium absorption, mineralization of osteoid tissue formation in bone, and maintenance of muscle function. Low vitamin D status causes secondary hyperparathyroidism, bone loss and muscle weakness and lower blood concentrations of 25(OH)D are associated with higher risk of falls and fractures[32]. Hypovitaminosis D is common and associated with a risk of osteomalacia. In older adults, rates of vitamin D deficiency range from 10–66%, depending on the threshold of circulating 25(OH)D[33]. However, the role of taking vitamin D and calcium supplements is less clear and there is no consensus between the recommendations by various international societies. The USPSTF has recently published recommendations on vitamin D and calcium supplements for preventing bone fractures in adults[34]. According to these recommendations, there is currently inadequate evidence about the possible benefit of vitamin D and calcium supplements in preventing osteoporosis in adults with no known osteoporosis or vitamin D deficiency, no history of osteoporotic bone fractures, and no increased risk of falls and who live in the community (not in a nursing home or other institutional care setting). The recommendations also state that evidence shows that taking lower doses of vitamin D and calcium (< 400 IU of vitamin D and < 1,000 mg of calcium daily) does not prevent fractures in postmenopausal women. Further, there is insufficient evidence for taking > 400 IU of vitamin D and > 1,000 mg of calcium daily for preventing fractures in postmenopausal women. It is suggested that exercise can prevent falls in community-dwelling older adults at increased risk for falls. Hence, the USPSTF recommends screening for osteoporosis in women 65 years or older and in younger women at increased risk.

However, the WHO recommends adequate daily intake of calcium and vitamin D as a part of overall health[35]. The National Osteoporosis Foundation recommends 800-1,000 IU of vitamin D daily for adults above 50 years[36]. The Endocrine Society recommends that adults 65 years or older consume 800 IU of vitamin D daily for the prevention of falls and fractures[37]. The American Geriatric Society recommends that adults 65 years or older take daily vitamin D supplementation of at least 1,000 IU as well as calcium to reduce the risk for fractures and falls[38].

Conclusion

There is conclusive evidence about the adverse effects of diabetes on bone and joints in women, and the risk increases with the duration of diabetes. Glycemic control, regular screening, lifestyle modification and selection of the appropriate anti-diabetic agents is the key to minimize the risk of osteoporosis and osteoarthritis along with supplementary therapies specific to both conditions, though there is a lack of robust data about their effectiveness.

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Section 5

Emerging Concepts in Women with Diabetes

Editor: Dr. Benny Negalur

CHAPTER 22 INFECTION CARE IN WOMEN WITH DIABETES MELLITUS

Dr. Isha Bansal, Dr. Charusheela Chaudhary

Introduction

DM is a metabolic disease in which the blood glucose level increases (hyperglycemia) as a result of insulin inadequacy (T1D) or ineffective use of insulin (T2D)[1]. The estimated prevalence of diabetes was recorded as 2.8% (171 million) in 2000 and proposed to be as 4.4% (366 million) in 2030 worldwide for all age groups with higher incidents in women than men[2]. According to a study published in 2015, India is ranked second globally with 65 million of patients with diabetes and > 80 million of prediabetic patients[3]. Besides physical and dietary complications, DM is also responsible for economic burden, development of various infections and other systemic pathophysiology, morbidity and mortality.

Diabetes and infections

DM compromises immunological responses thus increases vulnerability to develop infections, particularly Rhinocerebral mucormycosis due to hyperglycemic condition in these patients[4,5]. Another pathogen is *Candida* species that causes VVC in women with diabetes[6]. Epidemiology of this infection, irrespective of associated reason, showed a prevalence of 57.3% in Nigeria, 48% in Tunisia, 42.7% in Australia, 42.2% in Turkey, 12.1% in Greece, 19.5% in Italy and 17.7-20.4% in India[7]. Immunocompromised women with diabetes are susceptible to develop RVVC (i.e., ≥ 4 episodes/year), characterized by vaginal inflammation and sole presence of *Candida* species[7,8]. *Candida* species *(C. albicans, C. glabrata, C. tropicalis, C. parapsilosis and C. krusei)* is the most opportunistic pathogen that colonizes asymptomatically in the mouth, nails, scalp, skin and on the mucosal surface of the genital, urinary, respiratory and gastrointestinal tracts and develops infection depending on host's vulnerability. The VVC development occurs in women with DM mainly by NCAC species as they are resistant to antifungal therapy, though, 56% *C. albicans* colonization was noticed in T1D patients while 54% *C. glabrata* found in T2D patients in one study[9]. Women with diabetes showed a prevalence of VCC (32-67.5%) with higher *Candida* colonization in vagina, compared to 11-23% prevalence in women without diabetes[10-13]. The symptoms of VVC include itching, irritation, burning, erythema, dyspareunia and sexual dysfunction (particularly in T2D patients)[14,15].

Pathophysiology of infection in diabetes

Patients with diabetes are believed to be immunocompromised due to dysfunction of T-cells, neutrophils and humoral immunity, therefore, are at higher risk of developing infection[4,5]. The infection also takes place due to a hyperglycemic condition that increases the virulence of some pathogens by decreasing IL production, chemotaxis, phagocytic activity and leukocyte immobilization that is responsible for glycosuria, gastrointestinal and urinary dysmotility, hypoglycemia as well as ketoacidosis[1]. Although, previously it was thought that *Candida* species cause infection only in weak or immunocompromised individuals, but studies have indicated active *Candida* infections in comparatively healthy individuals as well. The yeast accommodates in the host using virulence factors that includes: adhesion, biofilm formation, extracellular hydrolytic enzyme production, hyphal formation and phenotypic switching[7]. The microbial biofilm of *Candida* species is presented in Figure 1[16].

In adhesion, the pathogens adhere to the vaginal epithelial cells for initial colonization and to establish infection[17]. Over 65% of all infections in humans are related to microbial biofilms that provides communities to microorganism by attaching to a surface using self-produced extracellular matrix[18] (Figure 1). *Candida* species secretes several hydrolytic enzymes responsible for adhesion, tissue penetration, invasion and destruction of host tissues[19]. Another important virulence factor is alternation from unicellular yeast cells to filamentous phase (hyphae and pseudohyphae)[17] that are considered to have a a role in tissue

invasion. The *C. albicans* can switch from white phase round-ovoid cells to opaque-phase elongated or bean-shaped cells, which are responsible for hyphae formation, drug resistance and adhesion[7].

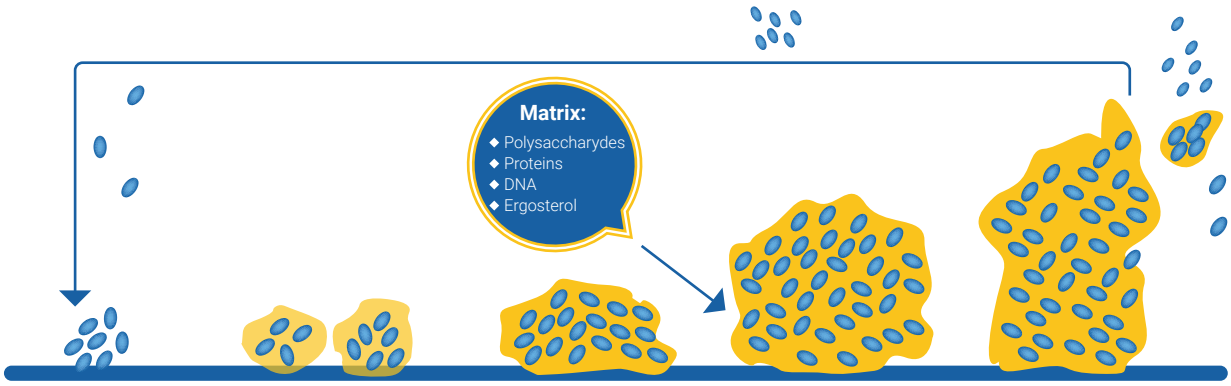

Figure 1: Microbial biofilm of Candida species
Source: Rodrigues et al., 2019[16]

Major infections associated with DM and care

DM is associated with development of respiratory, gastrointestinal, urinary tract and skin infections[20]. *Streptococcus pneumoniae* and influenza virus are responsible for respiratory infection in patients with diabetes with 6 times more incidents of hospitalization in comparison to patients without diabetes[21,22]. Vaccines to reduce respiratory infections are suggested for patients with chronic diseases to further minimize the hospitalization cause or death[22]. In addition, patient with diabetes are at higher risk to get infected by tuberculosis, especially multi-resistant tuberculosis[23]. Antibiotic treatment of tuberculosis with rifampicin further complicates metabolism and glycemic control[24]. Inadequate glycemic control, duration of diabetes, impaired leukocyte function and RVVC increases the risk for UTI in patients with DM[20]. Fungal infections particularly caused by *Candida* species are profoundly common in DM patients, already discussed earlier. *E. coli, Enterobacter, Proteus, Klebsiella* and *Candida* pathogen is responsible for emphysematous cystitis in people with diabetes, especially in women characterized by a condition in which pathogen produced CO_2 is trapped in the bladder cavity and infiltrate the bladder wall in turn cause infection[20,25]. Hyperglycemic condition in DM leads to gastrointestinal and liver infections caused by *Helicobater pylori, C. albicans, Salmonella enteritidis* and *campylobacter, enterovirus*, HBV or HCV[20]. Proper immunization strategies are necessary to prevent these comorbid infections in patients with diabetes.

Susceptibility to infections in women with diabetes

Resistant and recurrent infections are the common complications in patients with DM, with higher prevalence of infection during reproductive age (18-44 years)[9]. Hyperglycemic condition provides glucose to *Candida* to feast on, hence patients with diabetes are unable to clear pathogens and it is found that women with T1D are more prone to develop infection compared to T2D[1]. The defense mechanism of vagina consists of vaginal microflora, i.e., colonization of microorganisms like *Lactobacillus acidophilus, Atopobium vaginae, C. albicans*, which maintains healthy vaginal ecosystem for the reproductive functions[1,26]. Among these, *C. albicans* can be detected in 28% of vaginal cultures of women with vaginitis that increases vaginal pH from

4-7 and thereby induces transition from yeast to hyphal[27,28]. As most of the females with DM are susceptible to develop VVC, the physicians start antifungal therapy even without infection progression[1]. Women with T1D and T2D were reported to develop fungal or bacterial vaginitis (71%) and Candida vaginitis (12.5%)[6]. The NCAC species mediated VVC in women occurs due to transient or incorrect use of anti-Candida or antifungal agents and/or prolonged treatment of antifungal compounds for RVVC[1]. Moreover, the development of VVC depends on lifestyle factors[9], rather than sexual activity as it occurs in single women as well. In fact, in the study of Malazy and group, 92.5% vaginitis patients were housewives[6] presumably with minimal physical activity.

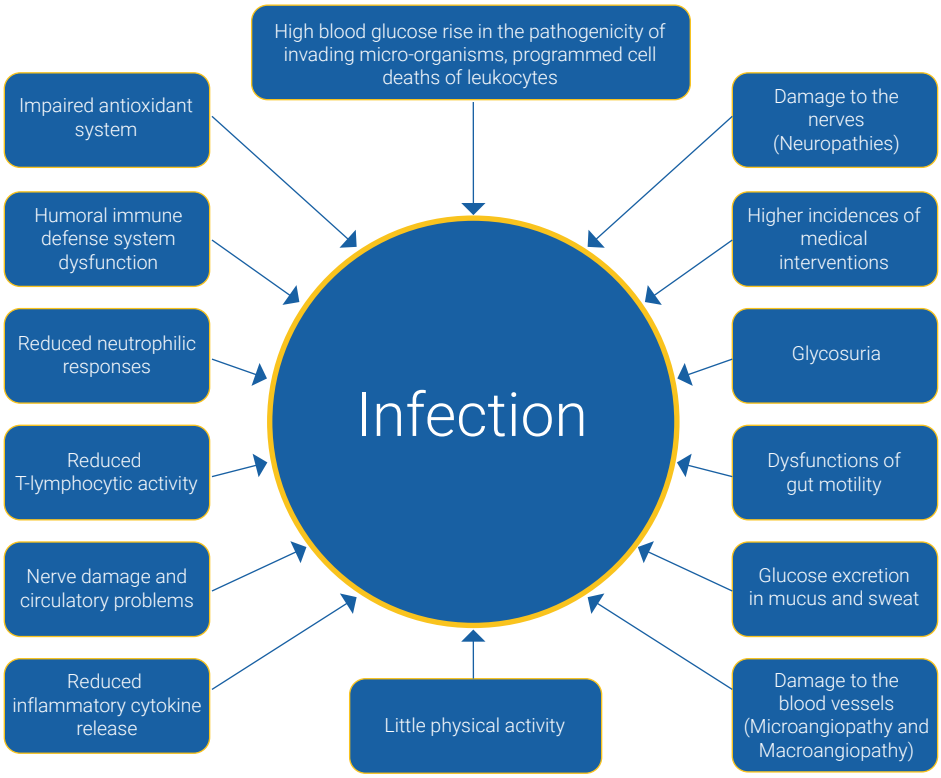

Figure 2: Factors responsible for infection in patients with diabetes

Figure 2 represents the factors associated with diabetes mediated infections. Other factors are discussed below:

- Lifestyle choices along with little physical activity are responsible for infections in women with DM[6,9].
- The vaginal epithelial cells in women with diabetes bind to *C. albicans* with greater adherence than patients without diabetes, either due to increased circulatory glucose level or due to expression of glucose-inducible surface protein that helps to promote adhesion of *C. albicans* to the vaginal epithelial cells in these patients[7].
- Use of glucocorticoids as a treatment of other pathological conditions ultimately results in hyperglycemia, caused by break down of amino acids and IR that further contributes to VVC[29].
- The neutrophils in females with diabetes are also less effective due to hyperglycemic environment to kill the *Candida* pathogens, compared to females without diabetes[7].

Metabolic complications arising from infectious disease in women with diabetes

DM or associated infections also causes metabolic complications in women. The virulence of some pathogens is altered by glycosuria, gastrointestinal and urinary dysmotility, hypoglycemia and ketoacidosis in DM patients[1]. DKA is the common complication associated with diabetes with an occurrence rate of 0.5-3%[30]. Furthermore, viral infection in DM is also related to ketoacidosis as in COVID-19 patients, hyperglycemic episodes were observed[31,32]. Treatment with specific drugs as an alternative to insulin in GDM patients with COVID-19 causes dehydration and increased risk of lactic acidosis[30]. The pathophysiology and preventive strategy for DKA management is presented in Figure 3[33,34].

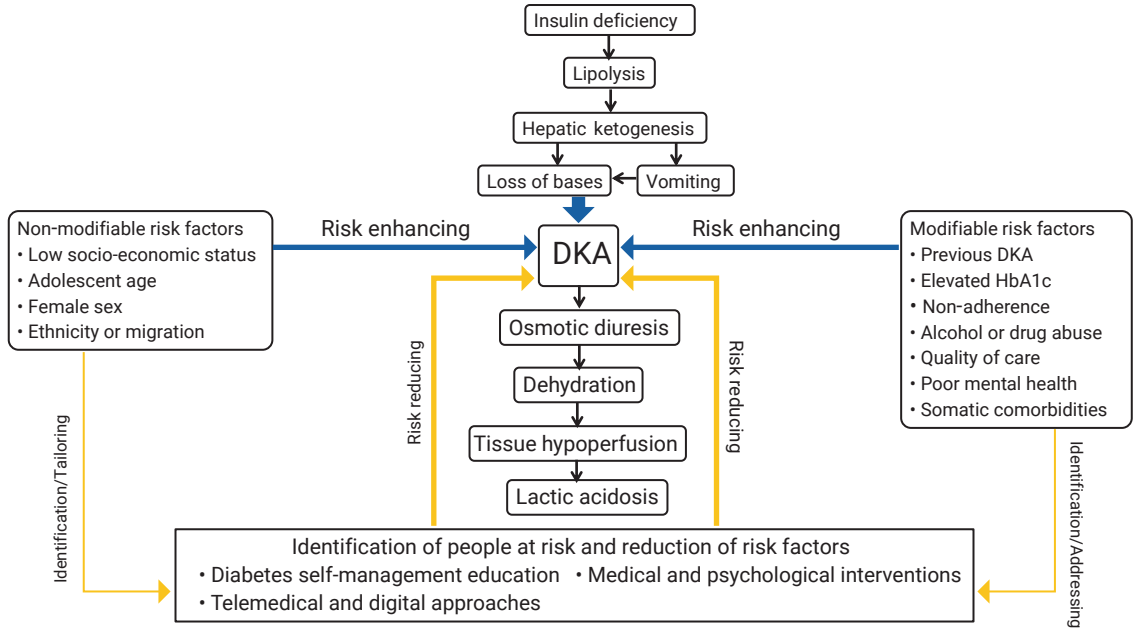

Figure 3: Pathophysiology and preventive strategies for management of DKA
Source: Rosenbloom et al., 2010[33]; Ehrmann et al., 2020[34]

Pneumococcal and influenza vaccinations

DM is an independent risk factor for respiratory tract infection development[3]. As discussed earlier, these patients tend to have compromised immune system, hence, use of influenza and pneumococcal vaccine is necessary. Patients having diabetes with other complications like cardiac and renal disease are at higher risk of further developing influenza and pneumococcal disease and may increase hospitalization and treatment cost[35]. According to ACIP, influenza vaccine is recommended for patients having diabetes with 6 months of age or older and in patients above 64 years specific systematic intervention strategies with regular medical follow-up or hospitalization are suggested[36]. Moreover, depending on patient's age, intramuscular dosage and type of influenza vaccine (split or whole virus) varies[36]. People with diabetes are also prone to develop pneumococcal infection and the risk increases with advanced age, CVD, pulmonary and renal disease[35]. In India, PCV7 and PCV13 (for ≥ 6 weeks aged patients) and PPV (for ≥ 2 years aged patients) are used with PCV13 is slowly replacing PCV7[3].

Immunization strategies

Immunization reduces the cost of human suffering as well as health care expenditures in patients with diabetes. Immunization against influenza and pneumococcal disease is important to prevent life-threatening bacteremic disease[35]. Special care must be taken before immunization, as some individuals do have anaphylactic hypersensitivity to chicken, eggs or additional components of the vaccine[35]. Yearly vaccination is recommended, but not within the same season[37]. However, the recommendation of ACIP is two doses of influenza vaccine, administered at least 1 month apart in patients below 9 years[36]. In addition, immunization for HCPs as well as for patient's family members is also suggested as these infections are contagious[35,36]. Influenza vaccine contains non-infectious viruses that causes common side effects like mild soreness at the vaccination site[35]. Pneumococcal vaccination is proved to be effective in reducing pneumococcus in people with diabetes aged ≥ 2 years, including patients with chronic illness, anatomic asplenia, living in an environment with greater risk for disease or immunocompromised patients[38]. Similar to influenza immunization a likely strategy is also opted for pneumococcal vaccines[35]. Revaccination for one time is recommended for patients older than 64 years if they are immunized more than 5 years ago or for patients with diabetes including chronic renal disease and nephrotic syndrome or patients with organ transplantation[38].

COVID-19 and diabetes in women

Lockdown due to COVID-19 pandemic directly or indirectly affected all lives. Natural immunological and physiological changes in pregnant women as well as those who have other health concerns like diabetes are vulnerable for COVID-19 or any other infection (influenza, varicella, SARS and MERS). COVID-19 in both pregnant and non-pregnant individuals was associated with DM as reported by the previous studies[39,40]. Women with T1D though were benefitted by the extra time during lockdown to monitor their self-management of diabetes, but those who had to work despite the lockdown struggled to prioritize their diabetes self-management[41]. It is necessary to measure OGTT for GDM in pregnant women as without prior testing women showed higher risk of GDM mediated still birth and during the pandemic it was difficult to measure routine OGTT due to several factors like limitation of public transports, higher risk for pregnant women to catch COVID-19 and laboratory social distancing[41,42]. Therefore, pragmatic screening strategy including routine antenatal care blood testing at weeks 12 and 28 during gestation was implemented. In fact, the use of antenatal steroids for fetal lung maturation was stopped after week 34 to minimize the risk for the mother during this pandemic[42]. Remote working was also taken into account with home monitoring of BP, virtual training for self-assessment of blood glucose and CGM, and supply of insulin pump and automated insulin delivery systems by the diabetes health care teams for DM management[41]. Greater risk of COVID-19 infection in patients with DM is explained by COVID-19 mediated dysregulation of the ACE-2 receptor or the DPP4 enzyme, which are crucial factors involved in glucose metabolism[43]. In DM patients with mild or asymptomatic COVID-19 infection, invidualized management is suggested, depending on patient's current glycemic control, self-monitoring capacity to measure blood sugar and ability to return for worsening symptoms[30].

Pharmacological interventions

Millions of women are affected by VVC each year and suffer from mental distress, pain, discomfort, anxiety, poor work and sexual performance as well as economic cost. Additionally, when left untreated, it can elevate susceptibility to develop HIV infection, following pelvic inflammatory disease and abscess, menstrual disorders, ectopic pregnancy, miscarriage and infertility, hence requires timely treatment[7]. Topical antimycotic agents like creams, lotions and vaginal suppositories are used to treat VVC in uncomplicated cases with a cure rate of 75-80% in case of polyenes (eg., nystatin) and 85-90% in case of oral azoles[7]. Fluconazole and itraconazole, two azole agents were found to have good curable rates along with advantage of oral administration[7,44]. Poor outcomes with fluconazole or boric acidic vaginal suppositories have been reported in case of *C. glabrata* infection[1]. Boric acid is a weak acid that disrupts the fungal cell wall and can be considered as a therapeutic option for treating *C. albicans* and *C. glabrata* infections in women with diabetes, while fluconazole is used to treat *C. albicans* only[45]. Another antifungal that is used to treat cutaneous and mucosal infections is sertaconazole nitrate with a remarkable efficacy when tested against a broad spectrum of organisms in comparison to other azoles and terbinafine[1]. In GDM patients, metformin or glyburide is used as a supplement to insulin, though the latter is not approved by US-FDA for pregnancy. But when COVID-19 infection occurs, this treatment leads to acute illness, dehydration and lactic acidosis, and ultimately insulin supplementation is used in hospitalized patients to meet the glycemic target[30,46].

Preventive measures

- Maintenance of blood glucose level below 200 mg/dL, reduces both bacterial and fungal infections in females with diabetes[10].
- OGTT must be performed in women with GDM to avoid diabetes-associated pregnancy complications[41,42].
- Continuous glucose monitoring is considered to be beneficial in glycemic control of non-pregnant and pregnant women with diabetes[41].
- Limited use of antenatal corticosteroids or use of antenatal surveillance should be opted as they cause acute hyperglycemia in mother's body and elevates the requirement for higher doses of insulin[30].

- Guidelines to manage hyperglycemia or hypoglycemia in pregnant women with or without COVID-19 infection must be standardized and followed[30].
- Immunization against influenza and pneumococcal disease is necessary in patients with diabetes to further prevent the associated complications [35].

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CHAPTER 23 RECENT ADVANCES IN MALIGNANCY IN WOMEN WITH DIABETES MELLITUS

Dr. Belinda George, Dr. Minal Mohit

Association of diabetes and malignancy

T2D is associated with increased risks for several cancers, including colon, postmenopausal breast cancer, pancreatic, liver, endometrial and bladder cancers and non-Hodgkins lymphoma. Increased cancer mortality associated with diabetes reflects both increased cancer incidence and decreased survival among people with diabetes who develop cancer[1].

The RR ranges from 2-2.5 for liver, pancreatic and endometrial cancers, and 1.2-1.5 for breast, colon and bladder cancers associated with DM[2].

There is convincing evidence of a role for hyperglycemia in cancer, from oncogenesis to mortality. Consumption of foods with a high glycemic index is associated with increased cancer risk. Breast cancer risk is greater among women in the highest quartile of blood glucose compared to women in the lowest (RR 1.63)[3].

The Vasterbotten intervention project demonstrated increased cancer risk in women with higher post load and fasting glucose. Significant risks of pancreatic cancer, malignant melanoma, endometrial, and urinary tract cancers was observed. Higher HbA1c levels were associated with 28% higher risks of almost all cancers. In a 20 year cohort study, glucose tolerance was associated with an increased all site cancer incidence. Additionally, the risk of premalignant lesions is also higher in hyperglycemic patients[3].

Possible biologic links between diabetes and cancer risk

Insulin resistance

Diabetes-related increase in cancer risk and progression is likely to be mediated by the insulin/IGF axis. Insulin and IGF-1 receptors are overexpressed in cancer cells. Hyperglycemia can indirectly affect cancer development by binding with insulin receptors and/or by increasing levels of circulating IGF-1[2].

Hyperglycemia

The possible mechanisms of hyperglycemia increasing cancer risk include “indirect effect” and “direct effect” (Figure 1). The “indirect effect” takes place at other organs and influence tumour cells by producing circulating growth factors (insulin/IGF-1) and inflammatory cytokines. The “direct effect” is exerted directly upon tumour cells by increasing proliferation, inducing mutations, augmenting invasion and migration and rewiring cancer-related signalling pathways[2].

Chronic inflammation

Chronic inflammation associated with diabetes is characterized by increased levels of IL-6, TNF-α, CRP and other markers of chronic inflammation, enhancing cancer risk[2].

Hyperglycemia also affects the normal cellular system majorly by DNA (genetic), RNA (transcription) and protein (translation), which may contribute to dysregulated growth[3].

Endometrial and breast cancer in women with diabetes

Endometrial cancer is the fourth most common cancer in women in developed countries. Studies suggests obesity is a major modifiable risk factor shared by T2D and endometrial cancer. Excessive adipose tissue reduces progesterone and SHBG. Decreased SHBG leads to increased bioavailable testosterone and estrogen, increasing endometrial carcinogenesis[4].

A prospective study reported a significantly increased age-adjusted risk of death (1.72). T2D was linked to an increased risk of all-cause and endometrial cancer mortality, especially in women with BMI < 25 kg/m². T2D is also linked to poor post-endometrial cancer survival, regardless of tumour stage or grade[4].

In vitro studies have shown that triggering insulin, IGF-1 and ovarian steroid hormone signalling pathways increased proliferation of endometrial cancer cell lines. Endometrial cancer may also be connected to chronic inflammation typical of T2D (Figure 2)[4].

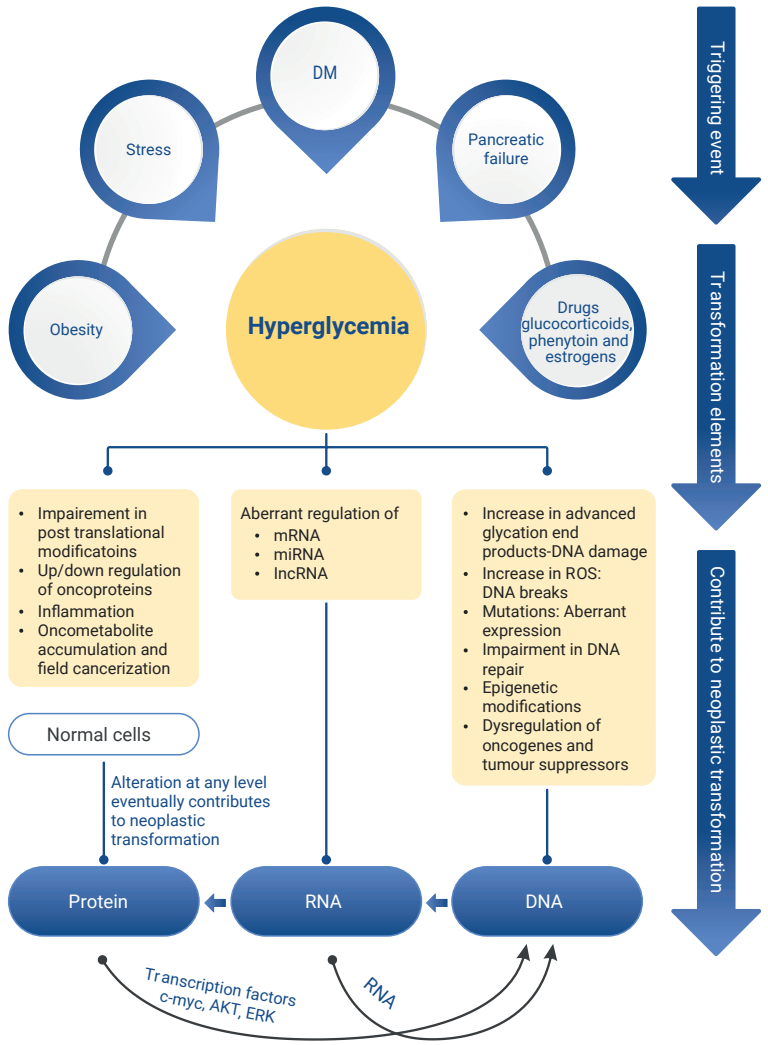

Figure 1: Hyperglycemia associated risk factors for cancer. ROS: Reactive oxygen species, mRNA: Messenger RNA, lncRNA: Long non-coding RNA, c-myc: Cellular myc, AKT: Ak strain transforming, ERK: Extracellular signal-regulated kinase

Source: Ramteke et al., 2019[3]

Diabetes and breast cancer

Breast cancer, the most common malignancy among women, is the second leading cause of cancer deaths. Meta-analysis reports have shown that diabetes is associated with a 20–28% increased risk of breast cancer and poor overall survival and disease-free survival. Postmenopausal women aged 50 years or older with diabetes have shown a 20–27% greater risk of breast cancer. Breast cancer patients with diabetes had a 50% greater risk of death from any cause. Diabetes is found in 16% of breast cancer patients, indicating a 10–20% increased risk of breast cancer in women with diabetes[5].

A meta-analysis showed a 23% greater risk of breast cancer and a 38% increased risk of cancer-specific mortality in T2D patients. A 10 year follow-up revealed a positive association between T2D and breast cancer incidence and mortality[6].

Three main metabolic changes in diabetes include, dyslipidemia/hyperlipidemia, hyperinsulinemia and hyperglycemia, create a low grade chronic inflammatory condition. These metabolic changes subsequently lead to dysregulation of cell signalling pathways (Wnt/β-catenin , Notch, NF-kB, phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin, Mitogen-activated protein kinases), glucotoxicity related oxidative stress, endoplasmic reticulum stress and failure of unfolded protein response, aberrant autophagy, cellular and DNA damage and inhibition of apoptosis in breast cells to initiate or promote cancer in breast cells (Figure 3)[5].

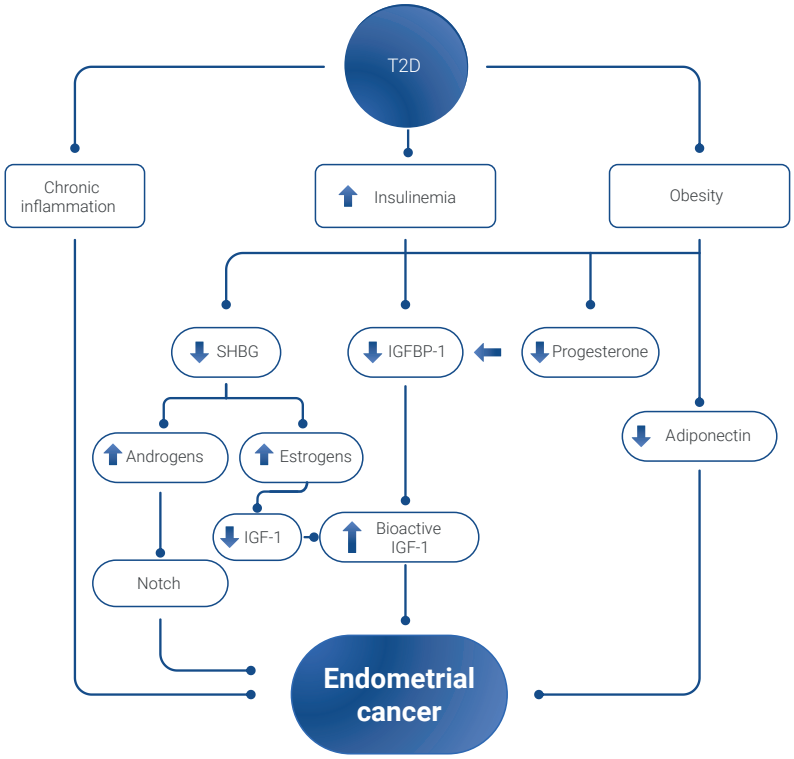

Figure 2: Molecular mechanisms linking T2D and endometrial cancer. IGFBP-1: IGF binding protein 1

Source: Anastasi et al., 2018[4]

Stomach, gastric, pancreatic and colorectal cancer and DM in women

Diabetes and gastric cancer

Four meta-analyses published between 2011 and 2013 indicated a correlation between diabetes and gastric cancer, which may be stronger in females and Asians. Shared risk factors such as, hyperglycemia, *H. pylori* infection, high salt intake, medications and comorbidities are possible pathways. Obesity, IR, hyperinsulinemia and smoking also increase the risk of gastric cancer. Diabetes raises the risk due to higher infection rate, lower eradication rate and higher reinfection rates of *H. pylori*. High salt intake can act synergistically with *H. pylori* infection in the induction of gastric cancer[7] (Figure 4).

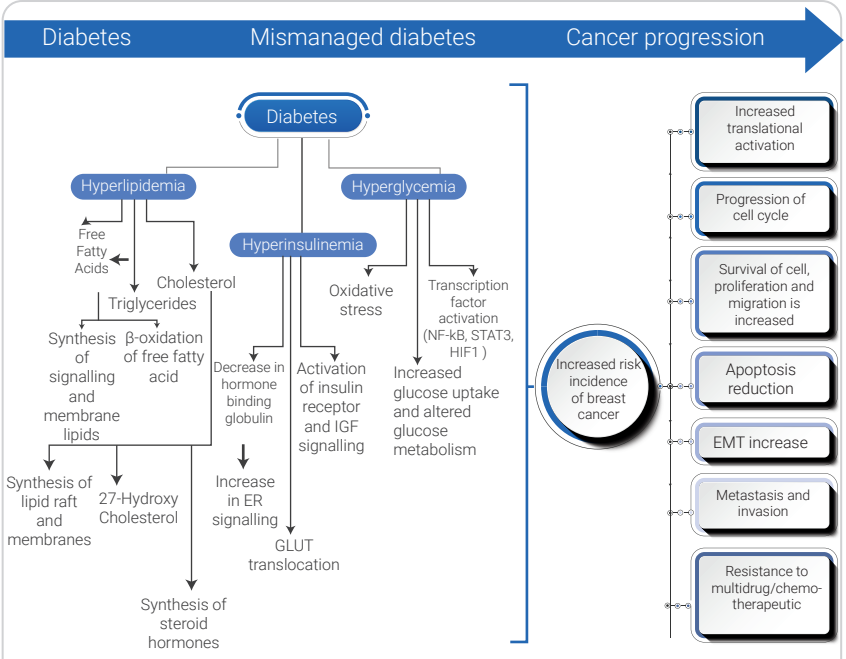

Figure 3: Diabetes and breast cancer progression. ER: Endoplasmic reticulum, STAT3: Signal transducer and activator of transcription 3, HIF: Hypoxia-inducible factor, GLUT: Glucose transporter, EMT: Epithelial-mesenchymal transition

Source: Samuel et al., 2018[5]

The more prominent DM-gastric cancer association in females than in males, in contrast with the male preponderance of gastric cancer in the general population, may be attributable to the decreased SHBG under increased IGF-1 and hyperinsulinemia, leading to increased bioavailability of estrogen in both sexes and increased levels of bioavailable testosterone in women but not in men[8].

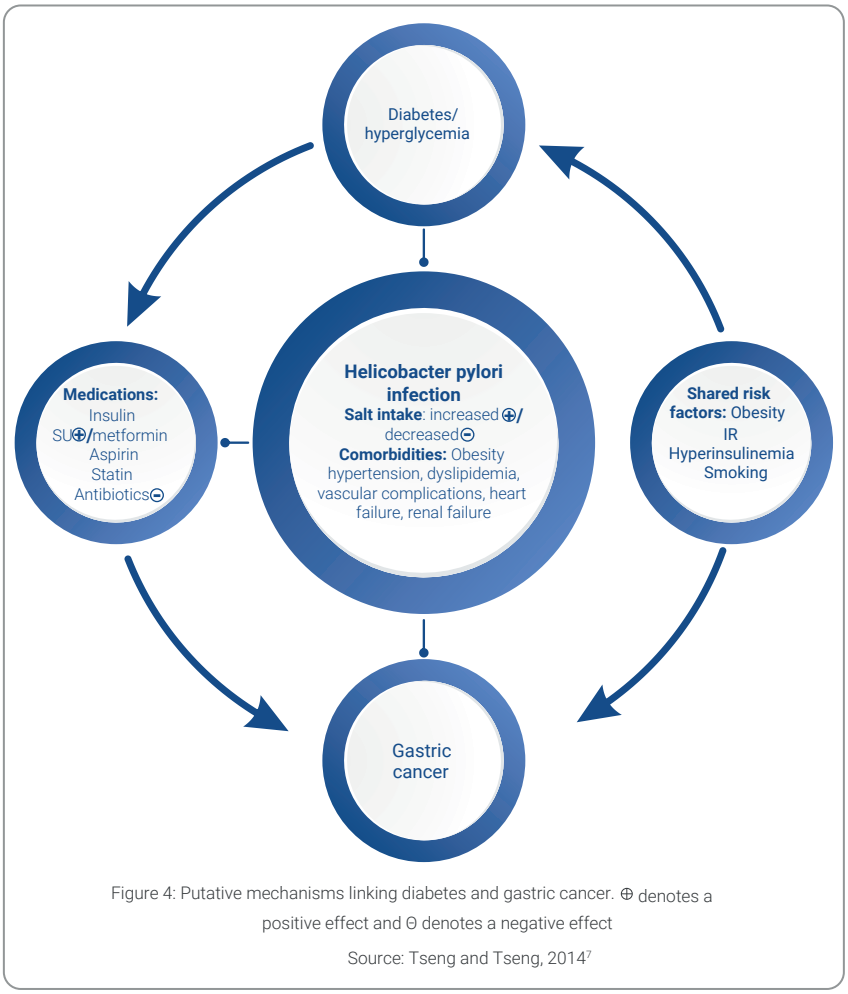

Figure 4: Putative mechanisms linking diabetes and gastric cancer. ⊕ denotes a positive effect and Θ denotes a negative effect

Source: Tseng and Tseng, 2014[7]

Diabetes and colorectal cancer

Colorectal cancer is the second leading cause of cancer deaths, accounting for 0.896 million deaths per year. Colorectal cancer mortality across all ages increased by 27.8% between 2007 and 2017. Patients with DM have a 30% greater chance of developing colorectal cancer. A study of 953,382 DM patients found that women with T1D had a greater risk of colorectal cancer than males. A 12 year prospective study of 75,219 participants in the Norwegian Cancer Registry found that women with DM had a 55% increased risk of colorectal cancer than women without DM. Men showed no significant differences. Cancer incidence was increased in women with FPG levels above 8 mmol (RR 1.98). The Netherlands Cohort Study on Diet and Cancer reported an 80% higher risk of proximal colon cancer in women with DM[9].

One study indicated DM in women was associated with an increased risk of colorectal cancer, and the risk increased by 22% and 17% for women and men respectively[10].

Potential molecular mechanisms of the association between DM and colorectal

The pathogenesis of DM in the development of colorectal cancer is associated with low Vitamin D level, obesity, sedentary lifestyle and a high fat diet[11].The link between DM and colorectal cancer may be due to T2D and cancer risk factors and hyperinsulinemia, hyperglycemia or DM treatment[12]. The DM microenvironment, such as AGEs, hyperlipidemia, local inflammation/oxidative stress, extracellular matrix alterations and altered microbiota or ischemia due to vasculopathy may recruit secondary mediators of injury that may favour the development of both cancer and other complications of DM such as diabetic kidney disease (Figure 5).

Hyperglycemia and AGEs induce oxidative stress and inflammation, which can damage cellular components and contribute to malignant cell transformation. High glucose induced oxidative stress plays a pivotal role in the development of diabetes complications by activating different pathways, such as the transcription factor NF-kB. The Warburg effect refers to the high glucose uptake and metabolism of glucose through glycolysis rather than aerobic phosphorylation in tumour cells despite the presence of oxygen. Upregulation of insulin-independent glucose transporters such as glucose transporter-1 favours glucose uptake by cancer cells[12].

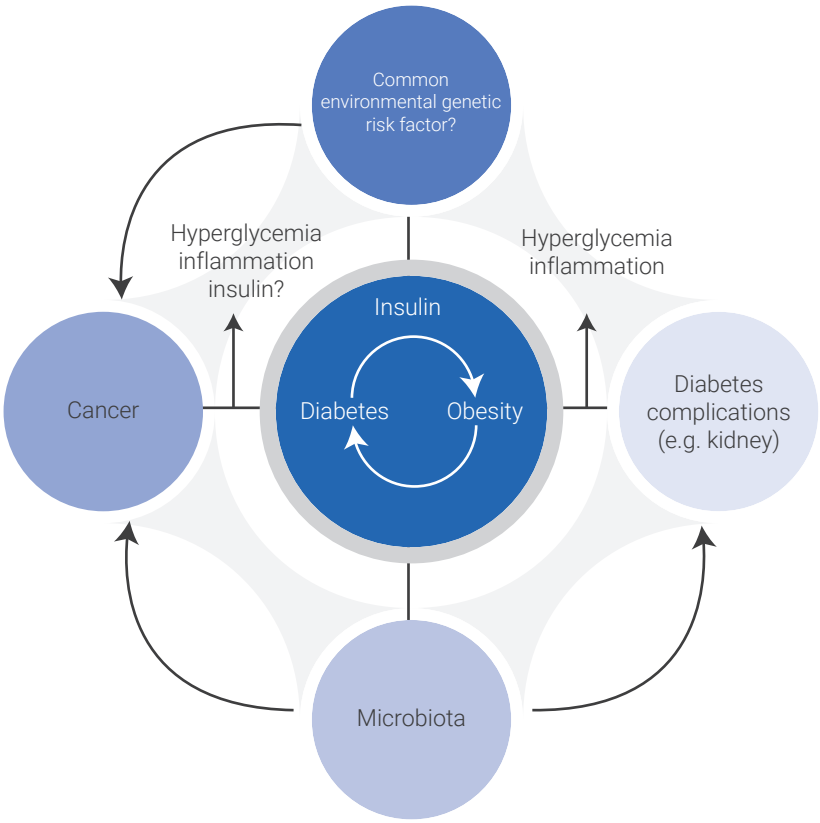

Figure 5: Hypotheses potentially explaining the association between diabetes and colorectal cancer
Source: Gonzalez et al., 2017[12]

In the absence of Wnt signalling, adenomatous polyposis coli-bound glycogen synthase kinase 3β, phosphorylates β-catenin, targeting it for ubiquitination and proteasomal degradation. In the absence of nuclear β-catenin, Groucho binds to transcription factors of the T-cell factor/lymphoid enhancer factor family, repressing transcription. This family includes TCF7L2 which has been associated to DM, DM complications and colon cancer by genome-wide association study or GWAS studies (Figure 6). Colon cancer is characterized by loss of function mutations of adenomatous polyposis coli and in DM Wnt signalling is activated. Klotho and vitamin D prevent Wnt signalling and are protective against tumours and against DM complications[12].

Diabetes and pancreatic cancer

Pancreatic cancer is now the third leading cause of cancer-related deaths with an estimated new cases of 55,440 and deaths of 44,330 in 2018. The lifetime risk of developing pancreatic cancer in any one person is 1.6% and it is expected to surpass colon cancer in mortality by year 2030. Generic symptoms, lack of effective screening strategies and resistance to chemo and radiotherapies increase the mortality rate. Pancreatic cancer is frequently diagnosed at an advanced stage, when the cancer has metastasized to distant organs like the liver, lung, lymph node and peritoneal cavity[13].

A meta-analysis of 22 cohort studies indicated DM patients had a 52% increased incidence of pancreatic cancer than those without DM[9].

Pancreatic cancer can be initiated and accelerated by several factors. Hyperglycemia, with or without IR, accelerate the development of pancreatic cancer by providing glucose as a fuel to cancer cells. Inflammation, oxidative stress and certain immune cells can initiate the development of pancreatic cancer (Figure 7). Angiogenesis can enhance the development of pancreatic cancer[14].

Adipokines, inflammatory mediators and altered microbiota are all involved in pancreatic cancer development and metastasis via distinct molecular processes[13].

Oral cancer and DM in women

According to a 2015 systematic review, oral cancer and precancerous lesions are more common in patients with T2D, with an overall 15% (and 85% for case studies only) excessive risk than in people without diabetes (Table 1). Those with periodontitis and diabetes exhibited a 2.5 fold increased risk of oral squamous cell carcinoma than those with only periodontitis. A 2018 systematic review found that women have a 13% higher risk than men. A large study in India identified a substantial link between diabetes and premalignant oral lesions in women but not in men. After correcting for relevant confounders, women with diabetes had twice the risk of oral leukoplakia and 3 times the risk of erythroplakia[15].

The increased prevalence of premalignant lesions such as leukoplakia has been linked to diabetes[16].

Tumours most typically affect the gums and labial mucosa in people with diabetes. Unlike the general population, where males are more prone to oral cancer than females, among those with diabetes, tumours are more frequent in females. It has been suggested that women may have poorer metabolic control, requiring more insulin and causing more DNA oxidative damage[16].

A cross-sectional study found that those with T2D or T1D had more oral cancer than people without T2D. A Brazilian cross-sectional study found an increased prevalence of potentially

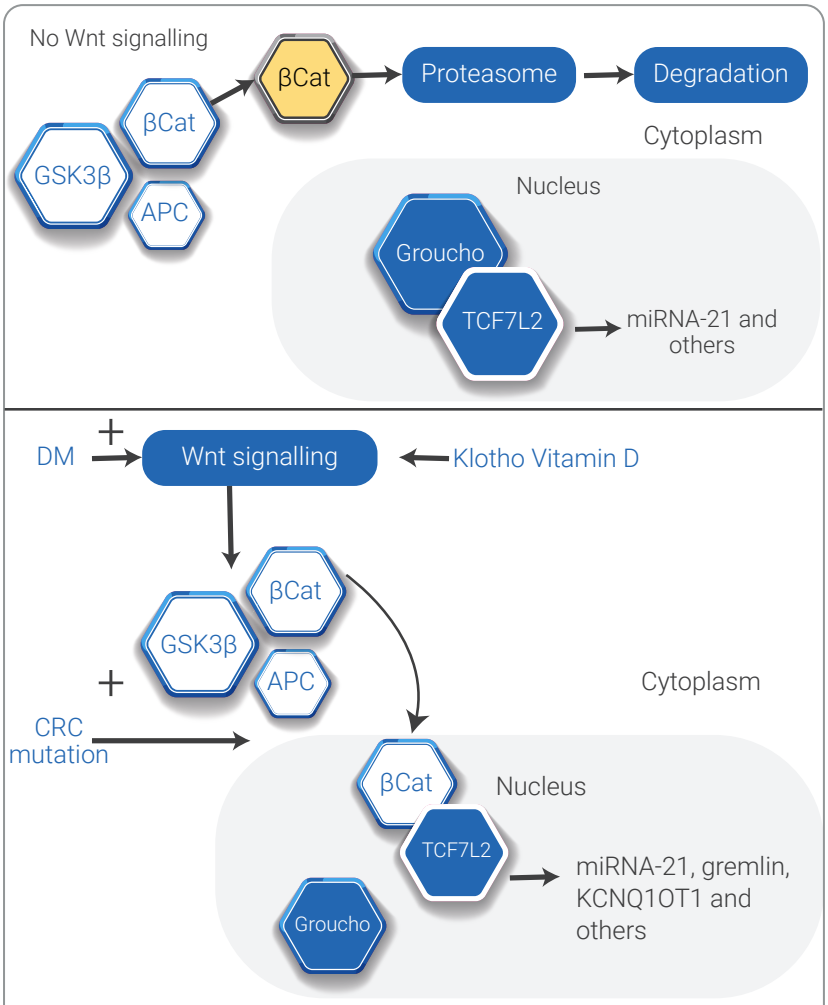

Figure 6: Key molecular pathways potentially linking diabetes and colorectal cancer
Source: Gonzalez et al., 2017[12]

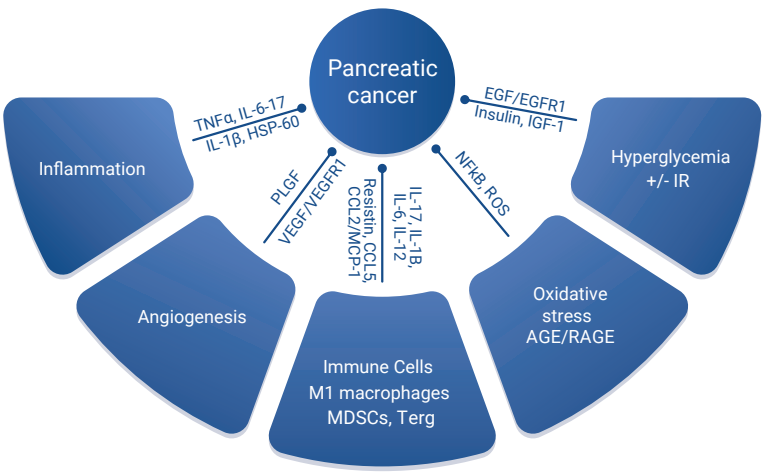

Figure 7: Pathogenesis of pancreatic cancer. HSP: Heat shock proteins, CCL: C–C motif chemokine ligand, MCP-1: Monocyte chemoattractant protein-1, EGF/EGFR1: Epidermal growth factor/epidermal growth factor receptor, ROS: Reactive oxygen species, PLGF: Placental growth factor, MDSCs: Myeloid-derived suppressor cells, RAGE: Receptor for advanced glycation end product
Source: Quoc et al., 2020[14]

malignant mucosal lesions (actinic cheilitis, lichen planus, leukoplakia and nicotinic stomatitis) in T2D patients. Another study found DM to be an independent predictor for oral leukoplakia[17].

Changes in periodontal tissues, oral mucosa, salivary gland function and oral neural function are affected by diabetes. Hormone changes during pregnancy also impact periodontal health in women with diabetes. These oral manifestations, their mechanisms, and their interrelationships are shown in the Figure 8.

Kidney cancer and DM in women

A large prospective study of women found that T2D increased the incidence of renal cell carcinoma. The risk was dose dependent and increased with the number of comorbid metabolic conditions. Obese women with diabetes had nearly twice the risk of renal cell cancer as non-obese women with diabetes[19].

Several underlying mechanisms could explain the diabetes-renal cell cancer relationship. Obesity and IR are common outcomes of western diet and inactivity, leading to metabolic syndrome and T2D[19]. The potential pathomechanisms (Figure 9) leading to the development of kidney cancer in patients with DM, chronic hyperglycemia, renal hypertrophy, Akt/mTOR trail hyperactivation and hyperinsulinemia[20].

Numerous studies link diabetes to non-hereditary kidney cancer development and progression. Both disorders are more common in elderly and in women. Kidney cancer in patients with diabetes is usually of the clear cell subtype with a small tumour size (1–5 cm). The prognosis is worse than for patients suffering from kidney cancer alone due to a higher rate of recurrence and a greater number of distant metastases, contributing to lower survival rates, both overall survival and cancer specific survival [20].

Table 1: Epidemiologic studies that suggest an increased prevalence of oral premalignant lesions in diabetic patients

Authors	Inferences and conclusions
Dikshit and others	Women with diabetes are at increased risk of developing leukoplakia and erythroplakia
Ujpal and others	Among people with diabetes, the prevalence of benign tumours (14.5%) and precancerous lesions (8%) was higher than in the control group (6.4% and 3.2% respectively)
Albrecht and others	The prevalence of oral leukoplakia was higher among patients with diabetes (6.2%) compared with control group (2.2%)
Dietrich and others	Those with a positive history of diabetes had more than 2 fold increase in risk of oral leukoplakia

Source: Auluck A, 2007[16]

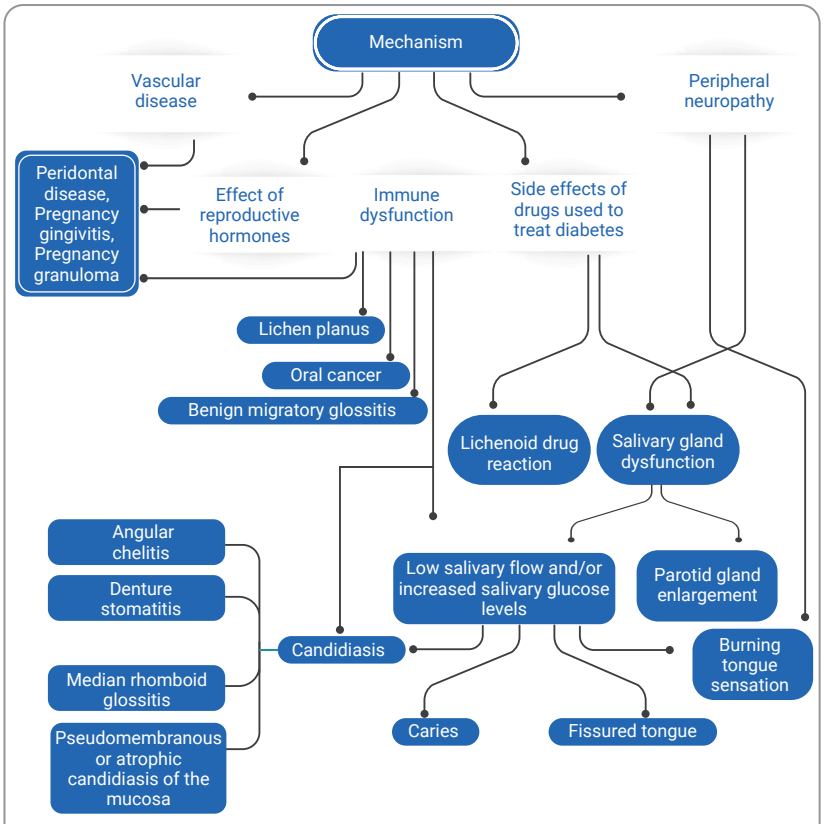

Figure 8: Oral manifestations of diabetes and their mechanisms and interrelationships
Source: Gandara and Morton., 2011[18]

A meta-analysis of 18 studies linked diabetes to kidney cancer (RR 1.40). There was a substantial positive connection among women (RR 1.47) and men (RR 1.28)[21].

A study of over 100,000 females found that diabetes increases the incidence of renal cell carcinoma in women but not in men. The study found that women with T2D had a 1.5 fold increased incidence of renal cell carcinoma compared to women without T2D. The study also found no link between T2D and renal cell carcinoma in men[22].

Leukemia and DM in women

A review of over 19 million people found that people with diabetes had an increased risk of leukemia, lymphoma and some solid tumours. compared to healthy individuals. The women-to-men ratios also showed significantly higher risks for females with diabetes for leukemia (RR 1.15). The women-to-men ratio found that women with diabetes had a 6% increased risk of all-site cancer, compared to men. Women with diabetes had a 27% higher risk of all-site cancer, compared to women without diabetes. There were several hematologic malignancies for which diabetics had an increased risk, as shown in the Table 2[23]:

A meta-analysis of 11 observational studies found a 22% increased risk of leukemia in T2D patients compared to euglycemics. T2D increased the risk of leukemia by 33% in another meta-analysis. However, this significantly positive association was not witnessed in T1D[24].

The epidemiological link between diabetes and blood cancers suggests

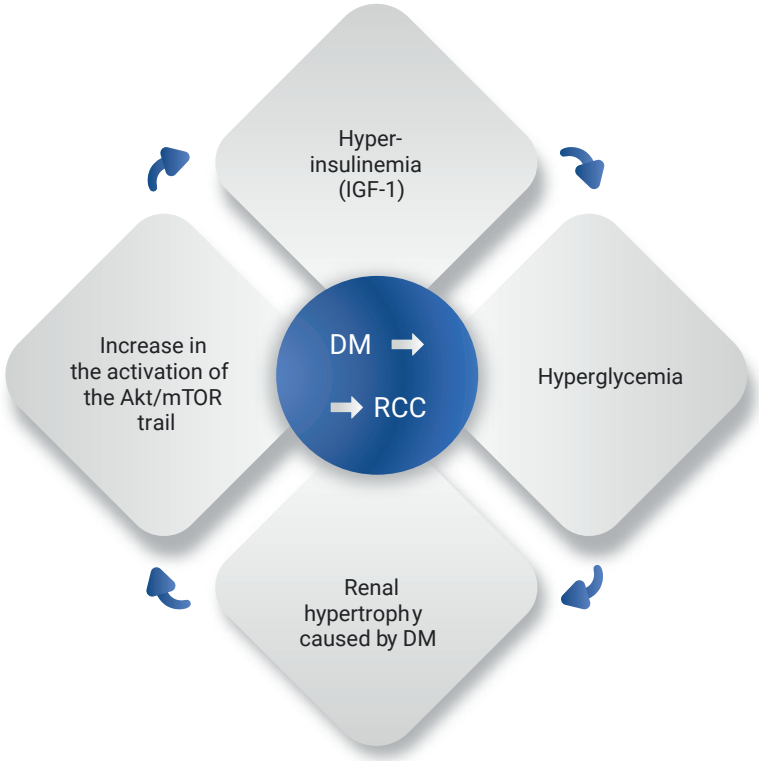

Figure 9: Potential pathways which, when activated by diabetes, can contribute to the development of renal cell carcinoma. RCC: Renal cell carcinoma, mTOR: Mammalian target of rapamycin
Source: Labochka et al., 2016[20]

Table 2: RR of different cancers amongst women and men

	Lymphatic and hematopoietic tissue	Leukemia	Myeloid leukemia
RR for women (99% CI)	1.24 (1.05, 1.46)*	1.53 (1.00, 2.33)	0.83 (0.39, 1.76)
RR for men (99% CI)	1.21 (0.98, 1.48)	1.22 (0.80, 1.85)	1.12 (0.77, 1.62)

	Lymphoma	Non-Hodgkin lymphoma	Hodgkin lymphoma	Multiple myeloma
RR for women (99% CI)	2.31 (0.57, 9.30)	1.16 (1.02, 1.32)*	1.20 (0.61, 2.38)	1.19 (0.97, 1.47)
RR for men (99% CI)	1.80 (0.68, 4.75)	1.20 (1.08, 1.34)*	1.36 (1.05, 1.77)*	1.12 (0.90, 1.41)

	Acute myeloid leukemia	Chronic myeloid leukemia	Lymphoid leukemia
RR for women (99% CI)	1.33 (1.12, 1.57)*	1.67 (1.27, 2.20)*	1.74 (0.31, 9.79)
RR for men (99% CI)	1.14 (0.56, 2.33)	1.62 (1.32, 1.98)*	1.20 (0.86, 1.68)

Note: *denotes statistical significance with a $p < 0.01$
Source: Diabetics have higher risk of hematologic, other cancers[23]

that diabetes causes immunosuppression, chronic inflammation and lymphocyte dysfunction, contributing to hematological malignancies. Hyperinsulinemia, IGF overproduction and IGF-1 receptor over expression are also hypothesized causes for increased risk of cancer in diabetes[25].

Antihyperglycemic drug and risk of cancer

Metformin and breast cancer

The 'indirect' anti-cancer/antitumour actions of metformin are via suppression of mitogenic and pro-angiogenic signalling systems that are otherwise activated by insulin and IGF1. Metformin has 'direct' anti-cancer/antitumour effects via AMPK by suppressing mammalian target of rapamycin-C1 and/or acetyl-CoA carboxylase and/or cellular-Myc and/or NF-kB pathways or activation of the double-stranded RNA specific endoribonuclease and/or the p53 pathways which in turn through several intracellular mediators, activation of anti-oncogenic genes, and downregulation of pro-oncogenic genes eventually accounts for the metformin treatment related antiproliferative, anti-migratory, pro-apoptotic and tumour-suppressive effects of metformin in cancers. The 'AMPK-independent' anti-cancer or antitumour effects of metformin reportedly require the activation of regulated DNA damage-1 and/or the inhibition of Rag GTPases and signal transducer and activator of transcription 3 dependent mechanisms[26] (Figure 10).

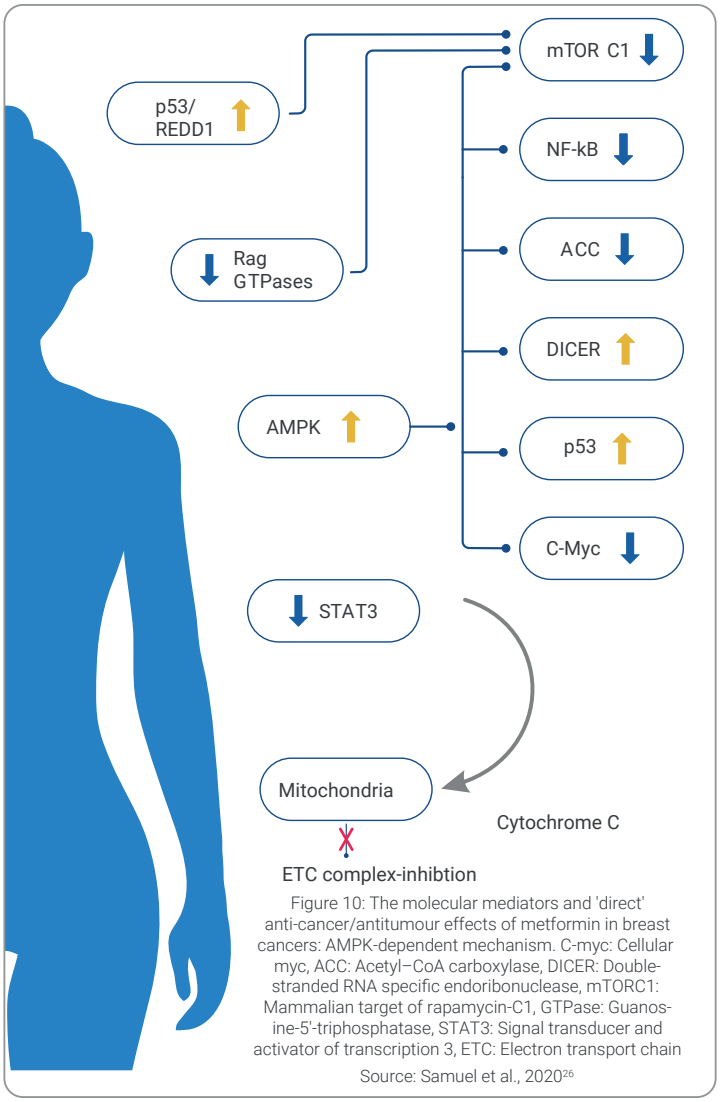

Figure 10: The molecular mediators and 'direct' anti-cancer/antitumour effects of metformin in breast cancers: AMPK-dependent mechanism. C-myc: Cellular myc, ACC: Acetyl–CoA carboxylase, DICER: Double-stranded RNA specific endoribonuclease, mTORC1: Mammalian target of rapamycin-C1, GTPase: Guanosine-5'-triphosphatase, STAT3: Signal transducer and activator of transcription 3, ETC: Electron transport chain

Source: Samuel et al., 2020[26]

A retrospective study found that cancer patients with diabetes getting metformin during neoadjuvant chemotherapy had a greater pathological complete response rate than cancer patients with diabetes not receiving metformin (24% vs. 8%)[27].

Metformin has shown to improve the worse prognosis that is associated with diabetes and insulin treatment in patients with human epidermal growth factor receptor 2+ and hormone receptor positive breast cancer. Metformin use has been linked to improved survival and reduced all-cause mortality in patients with diabetes with breast cancer[28].

Several studies assessed the influence of metformin on metabolic status in cancer patients with and without diabetes. Metformin lowered fasting insulin by 22% and improved various metabolic markers in women without diabetes with early stage breast cancer. A randomized trial of breast cancer patients found that metformin reduced testosterone, insulin and numerous markers of IR. In another study, women without diabetes with breast cancer receiving metformin therapy showed

lowered number of Ki67+ cancer cells while increased expression of mammalian target of rapamycin and AMPK pathway molecules[29].

Metformin for cancer prevention and therapy

Metformin causes inhibition of oxidative phosphorylation, activation of AMPK and the sensitization of cancer cells to chemotherapy. The activation of AMPK, whether via liver kinase B1 or decreased ATP/AMP ratio may antagonize cancer cachexia and promote the generation of memory CD8 T lymphocytes to combat malignant cells[30] (Figure 11).

Colorectal aberrant crypt foci (a surrogate marker for colorectal cancer) were reduced by 40% in patients without diabetes who took metformin in short doses (250 mg/day). A study in 2,529 females with breast cancer showed that the metformin group had higher complete response rates in patients with and without diabetes patients. Numerous epidemiologic studies have shown that T2D individuals taking metformin had a lower risk of cancer than those taking other antidiabetic medicines. This was also confirmed by numerous meta-analyses showing 30-50% reduced cancer incidence with metformin.

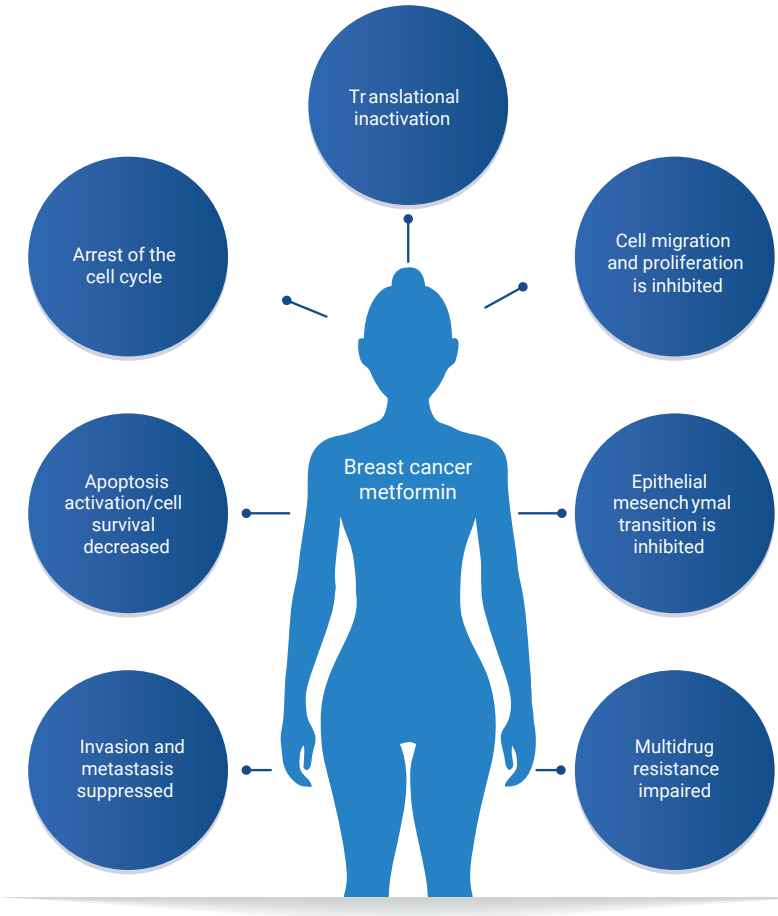

Figure 11: The molecular mediators and 'direct' anti-cancer/antitumour effects of metformin in breast cancers: AMPK independent mechanism

Source: Samuel et al., 2020[26]

Another study found that metformin treatment significantly reduced the incidence of colorectal cancer. One study noted that the use of metformin in patients with diabetes was associated with significantly lower risks of both cancer incidence and mortality[31].

A meta-analysis of 5 observational studies found that metformin reduces cancer risk by 31% compared to alternative diabetic therapies. Promising trends were noted on overall cancer mortality and on specific cancer sites, particularly pancreatic cancer and hepatocellular carcinoma, and to a lesser extent, colon and breast cancers[32].

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CHAPTER 24 SOCIO-ECONOMIC ASPECT AND PUBLIC HEALTH NEED OF WOMEN WITH DIABETES

Dr. Benny Negalur, Dr. Mary D'cruz

Introduction

Healthcare expenditure is an important aspect of public health. WHO has identified the following goals for health system: good health, responsiveness to the expectations of the population and fair financial contribution.

The needs of women with diabetes are different, as they struggle with multifarious needs of accessing medical care, affording the medicines, adjusting to dietary needs and when pregnant, facing the challenges of taking insulin regularly. Women in both rural and urban areas find healthcare expensive.

Diabetes increases the risk of death from CVD, kidney disease and cancer by 1.3–3 times. Diabetes affected 463 million people in 2019. In the last 25 years, diabetes prevalence has doubled in men and increased by 60% in women globally[1].

Diabetes is a major public health issue that affects both individuals and society. Diabetes in pregnancy is a serious condition that can affect both the mother and her unborn child. Moreover, diabetes affects women disproportionately. Women account for over half of the people with diabetes. CVD, the most frequent diabetic consequence, affects women more than men. DCCT and the UK Prospective Diabetes Study found that most T1D and T2D complications are preventable. However, slow application of this knowledge coupled with gender related issues, may serve as barriers for appropriate care of women with diabetes[2].

Diabetes care in adolescent and children

Approximately 3 quarters of newly diagnosed T1D cases are under the age of 18 years. Diabetes management must be integrated with the complex physical and emotional growth demands of children, adolescents and their families[3].

The SEARCH for Diabetes in Youth Study found that prevalence of diabetes was 0.26% in people aged < 20 years. The ADA and the American Academy of Pediatrics advised testing for T2D every 2 years for overweight or obese children aged 10 years and older in the presence of other risk factors[4].

Issues related to youth

Teenage girls with diabetes appear to fare worse than their male counterparts and have greater mortality and morbidity. Obesity, lack of physical activity and smoking among young women increase diabetes and its complications. Adolescents with diabetes face unique problems due to their transition from childhood to adulthood. Support from family, peers and others in the community can help control the disease. The public health community need to balance the opposing aspects of teenage diabetes demands of autonomy and support[2].

Public health interventions

- Diabetes care for children of this age group should be provided by a team that can deal with these special medical, educational, nutritional and behavioural issues[3].

- The public health and medical communities must collaborate to identify modifiable societal and individual level characteristics that can be leveraged to design successful diabetes preventive and control strategies for this age group[2].
- Policy changes that empower adolescent girls with diabetes to manage their disease, provide diabetes education, support smoking cessation and ensure access to counselling and family planning services could help prevent or delay significant complications and lower the disease burden in this population. Guidelines for assessing eating disorders in adolescent girls with diabetes would help identify disease processes and improve early detection and treatment. All adolescents struggle with body image and weight management, however manipulating insulin for weight loss has major effects. Weight loss programs need to be structured that focus on improving self-esteem and body image[2].
- Most experts agree that clinicians should prescribe and support lifestyle (diet and exercise) change for the whole family, not just the patient, as a prerequisite for all overweight and obesity treatments for children and adolescents for primary prevention of the disease. Public health interventions delivered in child care, preschools, schools, communities, medical settings, etc. should continue to focus on improving energy balance in youth[4].
- Policy makers from local community, medicine, public health and education sector must work together to improve self-management behaviours. Policies are needed to provide reimbursement for insulin administration devices that are appropriate for adolescents[2].
- Adherence is a key challenge in this age group. Any medical regimen is only as good as the family's or individual's capacity to follow it. Throughout childhood and adolescence, family engagement in diabetes care is critical for optimal management of diabetes. HCPs must evaluate the behavioural, emotional and psychosocial factors that interfere with implementation and then collaborate with the individual and family to address difficulties and/or alter goals as needed[3].

Maternal and child healthcare

Epidemiological evidence supports the presence of intergenerational transmission of diabetes and associated risk factors (Figure 1). In the Pima Indian population, the risk of diabetes was highest in the offspring of mothers with diabetes at conception (45%), followed by those whose mothers had diabetes after pregnancy (8.6%) and those whose mothers did not have diabetes (1.4%). Data from The HAPO follow-up studies found that untreated GDM increased the incidence of obesity and diabetes in children aged 7 years, regardless of the mother's BMI, with increased adiposity at 10-14 years of age. The SEARCH study estimated that maternal diabetes or maternal obesity caused 47.2% of youth-onset T2D. High birth weight, low birth weight and childhood obesity can result in diabetes diagnosis at an early age. Premature puberty and pregnancy in daughters of mothers with GDM may contribute to intergenerational diabetes transmission[1].

Integrating maternal and child health care, including prenatal education, postnatal examination, and advice on individual maternal diabetes risks can be the starting step for improved maternal and child health and highlight the need for early public health intervention[1].

Prevention of maternal and childhood malnutrition

Before and during pregnancy, adequate nutrition is important to prevent the risk of in utero malnutrition and its consequences. Good diet and physical activity in childhood are essential for a healthy adulthood of the child[5].

Maintenance of optimal prepregnancy bodyweight: the key programme required

The diagnosis of GDM at 24–28 weeks is important for therapeutic care of women and their children throughout and after pregnancy, as well as for primary prevention of diabetes in mothers. To avoid any possible long-term in utero effects, prevention of subclinical maternal hyperglycemia from conception should be explored[5].

Regular physical activity during pregnancy is a crucial method available to prevent maternal hyperglycemia right from the early pregnancy and are the urgent priority to control diabetes epidemic[5].

Strategic directions are needed for comprehensive action on GDM with a focus on health development in all policies:

(i) Community wide primary prevention programme.

(ii) Accessible services for the prevention of diabetes and GDM in individuals at increased risk.

(iii) Accessible services for the optimal early detection and management of GDM.

(iv) Integrated care for GDM.

(v) Qualified and motivated workforce.

(vi) Enhanced surveillance system and research.

(vii) Evaluation and knowledge exchange[6].

The multidisciplinary coordination of services must be flexible, person-centered, and must include prevention and self-management. Public health approach to improve pregnancy outcomes among women with diabetes should include:

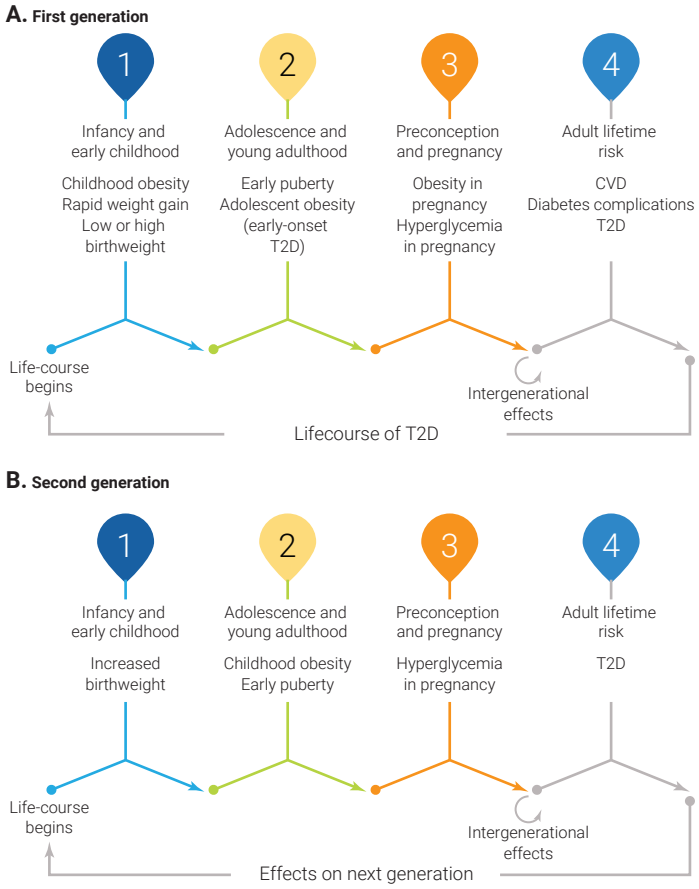

Figure 1: The role of different risk factors at various life-course stages in the development of T2D

Source: Chan et al., 2020[1]

- Development and implementation of guidelines for screening and diagnosis of GDM using feasible, cost effective and pragmatic point of care tests such as the single step diagnostic procedure.
- Identification of women with established diabetes who may become pregnant.
- Ensuring appropriate care for women with diagnosed diabetes with appropriate treatment, education and nutrition counselling, on-site or through referral[6].

Strategic approach for GDM diagnosis and management

The diagnosis and management of GDM should be integrated into all phases of care (Table 1).The main goals are to raise community awareness, early diagnosis, management and establishing linkages with NCDs programme in accordance with the National Guidelines for Diagnosis and Management of GDM[7].

Postpartum follow-up and continuing care of women with diabetes and GDM

Interventions along with effective referral and follow-up mechanisms across the healthcare system are required to improve operational efficiency, reduce costs and ensure early treatment and follow-up. Large nationally representative studies and surveillance systems are required to quantify and monitor trends of GDM, their risks and associated morbidity and mortality to enable effective and timely policies along with public health response[6].

Increasing provider awareness through professional education

To satisfy the growing demand for diabetes and GDM care, all levels of healthcare must incorporate elements of prevention, surveillance, screening and management (primary, secondary and tertiary). The improvement of the public health care system will help provide more equitable service delivery, reducing disease burden and avertable mortality[6].

Coordination of NCD initiatives and integration into other national programmes

Major NCDs have shared risks and offer multiple opportunities for prevention and control. Low birth weight and early childhood malnutrition raise the risk of CVD and diabetes in adulthood. Thus, existing maternal and child health programs must be used to promote maternal and child nutrition to prevent transgenerational transmission of NCD risk. Prenatal and postnatal clinics should educate on healthy eating habits and the dangers of obesity[6].

All opportunities and channels of communication should be used to promote GDM services across the continuum of care. Design and broadcast radio and television commercials promoting the GDM programme can be used to increase awareness. Posters, wall hangings, wall paintings and billboards outlining the GDM initiative and its link to NCD can also be displayed[7].

Table 1: Strategic approach for GDM diagnosis and management

Pregnant woman

Antepartum Care

Demand generation – Community awareness, sensitization for GDM and client mobilization

Diagnosis – First GDM testing OGTT at first antenatal care contact and if < 140 mg/dL, then second testing OGTT at 24-28 weeks of pregnancy

Management – If OGTT result is ≥ 140 mg/dL then start MNT and exercise on the same day. Start medical management if postprandial blood sugar result ≥ 120 mg/dL in subsequent follow-up visit

Follow-up – PPBS monthly till delivery. USG at 18-20, 28-30 & 34-36 weeks of pregnancy

Referral – As per the reasons cited in guideline

Intrapartum Care

GDM positive with controlled PPBS

- ◊ On MNT – Normal institutional delivery
- ◊ On medical management–
  - • Monitoring dose of insulin should not be given on the day of delivery.
  - • 2 hourly monitoring of blood sugar from start of labor till delivery.
  - • Insulin (IV) regular in normal saline (if required)
- ◊ GDM positive with uncontrolled PPBS if 2 h PPBS is ≥ 120 mg/dL, she should be referred to capability to provide comprehensive obstetric care

Immediate postpartum and Early neonatal

New-born care

- ◊ Early breastfeeding to prevent hypoglycemia.
- ◊ Initiate newborn blood sugar monitoring within 1st h of birth and then repeated every 4 hourly till 4 normal readings (> 45 mg/dL)

Maternal Care

- ◊ Counselling for 6 weeks postprandial follow-up
- ◊ Healthy timing spacing of pregnancy to potentially reduce risk of GDM in next pregnancy

Postpartum follow-up care

Follow-up at 6 weeks after delivery through OGTT and link with NCD programme

- ◊ Annual screening for DM at NCD clinic if OGTT < 140 mg/dL
- ◊ Refer to medical management if OGTT ≥ 140 mg/dL

Continuum of Care

Linked to NCD for follow-up

Note: PPBS: Postprandial blood sugar

Source: Diagnosis & Management of Gestational Diabetes Mellitus[7]

Table 2: Creating awareness among the beneficiaries for GDM programme

Immediate postpartum and new born care
A) Maternal care Counselling for postpartum family planning, counsel women for 6 weeks' postpartum follow-up test, detailed examination of woman before discharge
B) New born care Initiate early breastfeeding, blood sugar monitoring of new born of GDM positive woman within first hour of birth and repeated 4 hourly up-to 4 normal readings (> 45 mg/dL), Management of new born hypoglycemia

Source: Diagnosis & Management of Gestational Diabetes Mellitus[7]

Immediate postpartum and newborn care

Essential maternal and neonatal care is required to avoid postpartum complications (Table 2). New borns should be monitored for hypoglycemia and mothers should be counselled for warning signs, need of optimal timing and spacing of pregnancies to avoid GDM associated risk in next pregnancy[7].

Perimenopausal and postmenopausal care

Women undergoing menopause experience significant endogenous hormone shifts that affect their health, quality of life and social roles beyond reproduction. Menopause is a universal milestone for women, thus managing menopausal symptoms can help reduce diabetes risk[8].

The four major goals of health-promoting behaviours among women with diabetes are:

(i) To improve metabolic control of diabetes itself.

(ii) To reduce the frequency and severity of microvascular complications (retinopathy, nephropathy and neuropathy).

(iii) To reduce the frequency and severity of macrovascular complications (including coronary heart disease, stroke and peripheral vascular disease).

(iv) To improve quality of life[9].

Public health implications for research

Real world research is critical to improve public health. Research can bridge information gaps, motivate public health programmes, and inform policy change. It can also identify disease risk factors and protective factors, resulting in longer life, better health-related quality of life and fewer functional limits. Social determinants of health, family support, government policies, socio-demographic characteristics and other factors can be studied to build effective multilevel health promotion initiatives. Applied research is critical in determining the public health implications of issues like income insecurity and social isolation among elderly with diabetes[10].

Policy development

It is critical to expand the participation of perimenopausal and menopausal women with diabetes in clinical studies of diabetes, coronary heart disease and other diabetes related complications. Cultural factors must be considered while developing diabetes policies for women. Community awareness of diabetes risk must be raised. Policies should be developed that ensure access to quality diabetes care for all women with diabetes regardless of ability to pay or insurance status. Policies should be developed to ensure that women with T2D have access to nutrition assistance, diabetes education and appropriate pharmacologic therapy[9].

Health care services

Expansion of the delivery of in-home health care should be done by combining health professionals and lay people to provide services. Assistance should be provided to older adults with diabetes with formal systematic examinations of their physical, emotional and social functioning to identify and, if feasible, remove any impediments to proper self-care. Adequately trained HCPs are needed to satisfy the needs of the ageing population. The shortage of geriatricians, endocrinologists and diabetes educators affects older adults with diabetes. An Institute of Medicine report suggests training informal caregivers to assist with health care[10].

Diabetes education

All women with diabetes should have access to professional diabetes education that teaches diabetes self-care skills. Focus groups or community initiatives to educate women should be supported and evaluated. Women with diabetes should be able to join support groups to promote self and peer education as well as resource sharing[9]. Diabetes education should be expanded to include caregivers for older adults with diabetes[10].

Lifestyle modification

HCPs should ensure that all women with diabetes receive dietary advice. Socio-cultural factors may impact diet and physical activity. There should be more opportunities for women at work, churches, schools, community centers to learn about the benefits of physical activity. Availability of safe exercise spaces, convenient exercise facilities and child care should be ensured. All health care practitioners must be trained in smoking cessation approaches[9].

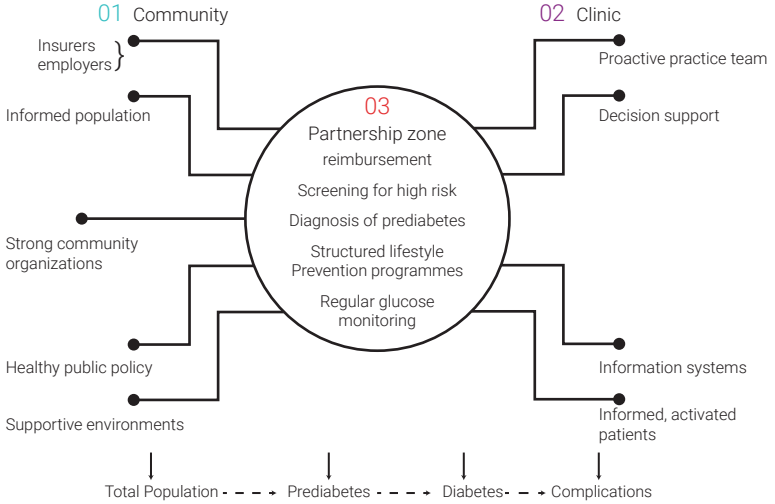

Figure 2: Prevention of T2D: the community-clinic partnership model, provided by Centers for Disease Control and Prevention, Division of Diabetes Translation

Source: Green et al., 2012[4]

Need for multi-stake holders

Effective management is critical to minimize diabetes morbidity and mortality. The enormous public health burden of diabetes necessitates population level action. Existing treatments are costly, have limited efficacy and are less likely to be beneficial for people who have difficulty accessing medical care or following self-care regimens. Most factors of caloric intake, weight management and physical activity are likely to be more responsive to public health measures. Therefore, primary prevention (Figure 2) in primary care requires public health or community interventions along with support of the medical care system[4].

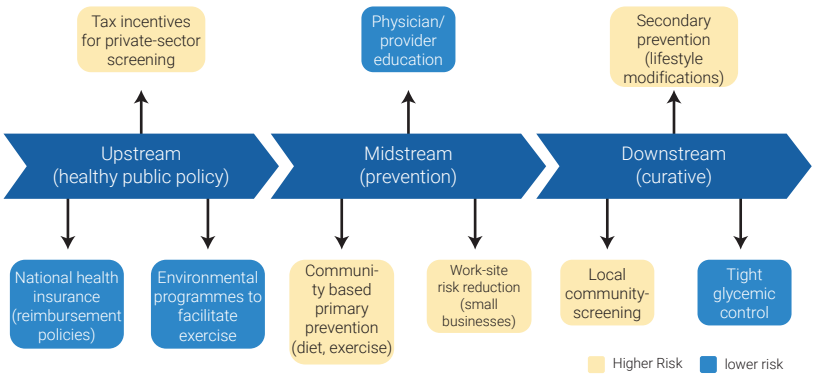

Figure 3: Some possible points of intervention for a new public-health approach to diabetes given the distribution of risk

Source: McKinlay and Marcea, 2000[11]

A new public-health approach to diabetes

All three levels of diabetes prevention (Figure 3): upstream public policy; midstream primary and secondary prevention; and downstream tertiary treatments, must be addressed simultaneously for a balanced public health approach. Downstream efforts consume most resources but cover fewer than 5% of people with diabetes. Midstream prevention is used to reduce the

risk of diabetes in high-risk individuals and groups. Upstream are healthy public policy efforts that target entire populations. These need adequate tax and reimbursement methods for health promotion[11].

An integrated society–population–community strategy to reduce burden of diabetes and other NCDs

A multidimensional solution is required to have short, mid, and long-term impacts on diabetes. When diabetes develops, care fragmentation and lack of patient engagement might deteriorate risk factor control, leading to increased morbidity. Constructive feedback and occasional monitoring are required to improve the practice environment, team structure and workflow. Establishing community-based diabetes teams or centers and strong primary health-care system will enable trained diabetes teams to identify individuals at high risk for lifestyle interventions, including the use of metformin and other medications, to prevent T2D and CVD. This personalized approach needs to be supported by policies that reduce pollution, ensure food security, increase access to healthy foods, promote healthy eating (e.g. nutritional labelling and school meals), promote physical activity (e.g. walking paths and sports) and discourage harmful substances (e.g. tobacco, alcohol). Inter-sectoral policies to improve the ecosystem, protect the environment and minimize social disparities are needed to lessen the long-term cost of diabetes and other NCDs. The provision of education from preschool to secondary school level will improve health awareness and disease prevention[1]. The individual, community and society level strategy to prevent T2D is presented in Figure 4.

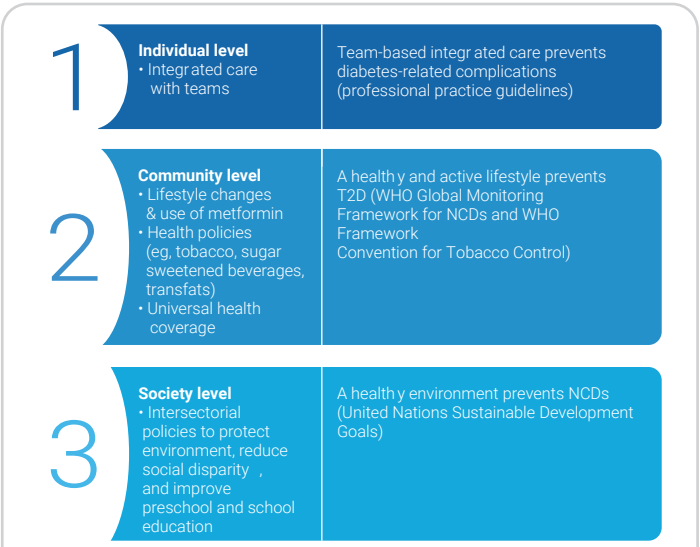

Figure 4: A conceptual framework for a multicomponent society-community individual strategy to integrate primary and secondary prevention of T2D

Source: Chan et al., 2020[1]

Policymakers and planners must design frameworks that align the environment, care settings, providers, processes, supporting systems and payers to translate these efficacy data to real world practice[1].

Awareness and teaching programs in women with diabetes

Education is important in preventing diabetes and its complications. Diabetes education is currently non-existent in rural India. Urban population also lack adequate health and nutrition education. A study of school children indicated inadequate awareness of lifestyle risk factors for NCD. T2D is more prevalent in people with lower education. A study in Chennai found that 25% of people were completely unaware about diabetes. Only 60% recognized diabetes was on the rise in India, and only 22% were aware that it could be prevented. Women are particularly ignorant about diabetes, its prevention and about the ways to improve health[12].

Diabetes education must be integrated into all diabetes care, whether it be specialist, primary care, or through referral to speciality treatment. Strategies for patient education and behaviour modification should be encouraged. Generic home-based educational materials may work in many educated homogeneous groups, but not in poor, illiterate or ethnically diverse populations where dietary advice may need to be customized or language barriers exist[13].

Building awareness

A study on diabetes awareness revealed that most people (90%) had heard of diabetes, but weren't aware of its management or prevention. People with diabetes or with a family history of diabetes were more likely to be educated of the disease, either by their doctor or the media. Even people with diabetes had limited awareness of healthy eating habits and causes of diabetes. This reflects a paucity of diabetes education even among those with diabetes[14].

The major goal is increasing knowledge of the risks and consequences of diabetes in women, including GDM. Future mothers, general public, health professionals and policymakers need to be made more aware of the issue, as well as the importance of women's health in general and during pregnancy in particular[6].

Education to the patient and training of educators

Structured education is an integral part of diabetes care. Lifestyle management encompasses diabetes self-management support, nutrition therapy, physical activity, smoking cessation counselling, and psychosocial care. Nurses and other health-care professionals require adequate training to bridge the gap between medical professionals and patients[5].

Providing patient education for enabling self-care and management

It is well recognized that increased patient awareness of any health issue helps prevent and reduce complications and increase treatment compliance. Providing community health professionals, midwives, women self-help organizations, patients and communities with adequate information on GDM and diabetes prevention can help alleviate shortage of resources and providers and lead to improved health outcomes; reduced unnecessary hospital visits and admissions/hospitalizations, less frequent follow-up visits lower cost to the health system[6].

Programmes to control diabetes epidemic

Awareness campaigns are needed to educate the public on the recommended bodyweight and daily nutrient intake (with adequate proportion of mono and polyunsaturated and saturated fatty acids) while avoiding transfatty acids. Multisectoral population based initiatives for healthy diet, physical activity and exercise are required, including trade and agriculture policies and the workplace, school and other setting based interventions[5].

It is recommended that transport and traffic strategies prioritize pedestrians, cyclists and public transit users. Campaigns and support systems for developing diverse physical activity and exercise programs like regular walking, games and sports, marathon running, aerobic dance and others at the community, school and workplace levels are also required[5].

Using information technology

Integration of services and cost effective investments in information technology is required to identify and track high-risk individuals to enlighten, empower and encourage women to adopt healthy living throughout life. Local community health workers should be empowered to support and follow high-risk persons to safeguard their future good health and prevent or significantly delay the onset of hypertension or T2D. Enrolling, monitoring and tracking pregnant women and their children using technology is appropriate to begin this health system reform[5]. Sophisticated populations may benefit from computer based self-management at home or work. Efforts in audio and video education also need evaluation[13].

Only a few tertiary care centers offer patient education. Studies found that frequent exposure to healthy lifestyle education is required to achieve treatment adherence in people with diabetes. Raising awareness about the causes, treatment and complications of diabetes is essential. Several countries with high diabetes burdens, like India, lack a structured national diabetes awareness campaign[14].

Conclusion

- Sex differences in healthcare expenditure among adults with diabetes:
  - Women with diabetes have statistically higher healthcare expenditure compared to men. Women have higher incremental out of pocket expenses for prescription medications, office based visits and other services, compared to men with diabetes.
  - Evidence suggests that when women have higher healthcare expenses, they often neglect their own care and basic material securities because of medication cost[15,16].
  - Women were more likely to reduce their use of prescribed medicine and spend less on basic needs when met with the difficult choice of paying for prescription.
- In addition to prescriptions, office based visits with providers and procedures are necessary for routine follow up and clinical assessments like HbA1c, lipid measurements, BP etc.
- Finally the literature evaluating sex differences in healthcare expenditure among adults with diabetes is limited.
- Further research is needed to understand the drivers of these differences and to identify potential causes associated with higher costs in women in diabetes[17].

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