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GUIDELINES

RSSDI consensus recommendations for dyslipidemia management in diabetes mellitus

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Abstract

Diabetic dyslipidemia is characterised by low HDL-C and high triglyceride levels. Unlike the Caucasian population, though LDL-C levels are not very high, there is a preponderance of more atherogenic small, dense LDL particles among Indians. Furthermore, apo B levels are elevated. This, unique 'atherogenic dyslipidemia', is frequently encountered in South Asians with diabetes. People with type 2 diabetes are considered to be at high risk for vascular events. Hence, irrespective of other risk factors such as age, male gender, hypertension, family history, smoking, obesity, and polycystic ovary syndrome in women, they must be screened for dyslipidemia.

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Other major ASCVD risk factors include family history of hyperlipidemia, low levels of HDL-C, hypertriglyceridemia, and increased levels of total serum cholesterol level, non-HDL-C, LDL-C, apo B, Lp(a), triglyceride-rich remnants, and small, dense LDL-C. In patients with diabetes, dyslipidemia should be assessed at diagnosis and annually thereafter. In patients with type 1 diabetes, screening for dyslipidemia should be initiated from the age of 12 years. Periodical screening for dyslipidemia is recommended in overweight or obese children with a family history of type 2 diabetes, or those from a predisposed race/ethnicity like Asian, American Indian, etc. Both fasting and non-fasting lipid profiles are important for managing Indian patients with dyslipidemia. For routine screening, a fasting lipid profile is not mandatory; the decision to acquire fasting or non-fasting lipid values must be individually tailored. Apolipoprotein B level is considered an enhanced estimate of an individual's exposure to atherosclerotic lipoproteins, and may be predominantly valuable for assessment of risk in individuals where LDL-C measurement underestimates this burden (those with diabetes mellitus, high triglycerides, obesity, or low LDL-C). The QRISK3 assessment tool algorithm calculates an individual's risk of developing a heart attack or stroke over 10 years, and takes into account ethnicity as a risk factor. Considering the possible genetic influence of Indian ethnicity on CVD, the QRISK3 score exemplifies as the current most accurate CVD screening tool available for the Indian population.

Stratification of ASCVD risk in Indian diabetic patients:

- *High risk:* diabetes with 0–1 other major ASCVD risk factors and no evidence of target organ damage.
- *Very high risk:* diabetes with ≥2 other major ASCVD risk factors or evidence of target organ damage.

High-risk patients necessitate management comparable to that for secondary prevention of CVD. The most important step in defining treatment goals for dyslipidemia in diabetic patients is an extensive assessment of their cardiovascular risk, with LDL-C as the primary target, and non HDL-C, HDL-C, and apo B as secondary targets. A comprehensive strategy is essential in the management of dyslipidemia so as to regulate lipid levels and tackle related metabolic deviations and modifiable risk factors.

Essential considerations to improve lipid profile and glycemic control, and reduce CVD risk:

- Accomplish healthy weight and aerobic activity level,
- Implement an energy-restricted, well-balanced diet,
- No or at most moderate alcohol consumption, and
- Smoking (or any other tobacco use) cessation.

Medical nutrition therapy plays a central part in diabetes management; every individual with diabetes must be actively engaged in self-management, education, and treatment planning with their healthcare team, together with the collective development of an individualised eating plan. Statins are beneficial as a primary or secondary prevention strategy, to reduce the risk of cardiovascular events, in patients with ASCVD or multiple cardiovascular risk factors especially in those with diabetes. Unless contraindicated, first-line cholesterol-lowering therapy includes the use of moderate- to high-intensity statin. Ezetimibe, when combined with statins, provides additive and complementary therapeutic lipid effects, resulting in considerable reductions in LDL-C and significant achievement of target cholesterol levels. It also permits the use of lower dosage of statins without compromising efficacy, reducing the odds of dose-dependent statin adverse effects. Bempedoic acid seems to provide a safe and effective oral therapeutic option for lipid lowering in patients intolerant to statins. PCSK9 inhibitor therapy, in diabetes, induces analogous relative reductions in cardiovascular risk, and is recommended to further reduce LDL-C in patients aged 40–79 years with LDL-C ≥190 mg/dL, with ASCVD risk factors, or other significant additional-high risk markers (including diabetes) and LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL on maximally tolerated statin therapy and/or ezetimibe. Fenofibrate has shown to reduce CVD in diabetic patients with elevated triglycerides and low HDL-C levels. Saroglitazar has well-documented positive effects in the management of diabetic dyslipidemia; not only does it improve lipid parameters (triglycerides, apo B, non-HDL-C), it has a significant impact on glycemic parameters (HbA1c and fasting blood glucose) in dyslipidemic patients. It, hence, appears as a novel therapy for decreasing cardiovascular risk in patients with type 2 diabetes. Omega-3 fatty acids offer additional benefits when administered as an add-on to statins, and could be attributed to the lowering of detrimental chronic inflammatory markers in people with diabetes and high-risk cardiovascular patients. Icosapent ethyl may provide additional risk reduction benefit, beyond a statin, in individuals with ASCVD or diabetes and multiple risk factors and triglyceride ≥150 mg/dL. Considering the evidence in patients with diabetic dyslipidemia combined with the experience and consensus of the experts, we recommend a step-wise approach for the management for diabetic dyslipidemia in the Indian population (Table 7).

Keywords Atherogenic dyslipidemia · Diabetes · Diabetic dyslipidemia · Consensus guideline

Introduction

Dyslipidemia plays a key role in inducing cardiovascular disease (CVD) in persons with type 1 and type 2 diabetes mellitus. The lipid profile in type 1 diabetics with good glycemic control is quite identical to that of the general population. Contrastingly, even with good glycemic control in type 2 diabetes, lipid abnormalities (elevated small dense low-

density lipoprotein cholesterol (LDL), decreased high-density lipoprotein cholesterol (HDL-C), and an increase in triglycerides and non-HDL-C) are frequently noted. Poor glycemic control in type 1 and type 2 diabetes decreases HDL-C levels and increases triglyceride levels with merely meek effects on LDL-C levels [1, 2]. Analogous to global evidence, among Indian patients, the alteration in HDL/LDL ratio in type 2 diabetes is strongly associated with lower HDL and higher LDL levels [3, 4]. In both type 1 as well as type 2 diabetes, an association between atherosclerotic cardiovascular disease (ASCVD) and serum cholesterol and triglyceride levels are commonly encountered. There is an increased risk of coronary heart disease (CHD) at any given level of serum cholesterol in diabetic patients, with an even stronger association with hypertriglyceridemia compared to the general population.

Individuals with type 1 diabetes develop atherosclerosis earlier and with rapid progression, thereby experiencing higher premature mortality as a result of vascular disease, despite higher levels of HDL-C; they seldom exhibit insulin resistance. The exogenous insulin therapy in patients with type 1 diabetes increases the activity of lipoprotein lipase in the skeletal muscle and adipose tissue, which catabolises very low-density lipoprotein cholesterol (VLDL-C), and reduces LDL-C and triglycerides [5]. Dyslipidemia of type 2 diabetes is characterised by low HDL-C and high triglyceride levels. Low HDL-C has been found to be an independent contributor to the development of cardiovascular disease as well as diabetes. There could be a modest surge in LDL-C with poor glycemic control, usually in the small dense LDL sub-fraction, on account of the rise in triglyceride levels [1]. Collectively, these changes could result in accelerated atherosclerosis even before the formal diagnosis of diabetes [6]. In fact, adequate glycemic control in patients with diabetes mellitus has found to aid in a significant decline in triglyceride levels [7]. Hence, optimising glycemic control in patients with diabetes is essential since this will have additional beneficial effects on lipid levels.

Epidemiology

Prevalence of diabetes mellitus

The global prevalence of type 2 diabetes has been growing at an exponential rate [8]. Type 2 diabetes is the most common type of diabetes and accounts for nearly 90% of all diabetes. Almost 463 million adults in 2019 were living with diabetes; by 2045 this number is expected to escalate to 700 million [9]. Latest data from the World Bank demonstrates a global diabetes prevalence of 8.8% in the 20–79 years age group with either type 1 or type 2 diabetes [10]. Recent statistics from the International Diabetes Federation report a prevalence of 8.9% of diabetes in Indian adults [11]. In India, the number of patients with diabetes increased from 26.0 million (95% uncertainty interval [UI], 23.4–28.6) to 65.0 million (95% UI, 58.7–71.1) between 1990 and 2016, with an increase in the prevalence of diabetes in adults aged ≥20 years from 5.5% (95% UI, 4.9–6.1) to 7.7% (95% UI, 6.9–8.4) during the period [12].

Prevalence of dyslipidemia in diabetes mellitus

In 2010, a cross-sectional retrospective analysis of 788 patients with type 2 diabetes in India recorded a prevalence of 85.5% of dyslipidemia among males, and an even higher prevalence of 97.8% among females. Mixed dyslipidemia, defined by high triglycerides, high LDL, and low HDL, was prevalent in 12.1% males and 24.0% females. Combined dyslipidemia was noted in 8.8% males and 9.3% females with high triglycerides and low HDL, 10.2% males and 5.2% females with high triglycerides and high LDL, and 19.4% males and 32.2% females with high LDL and low HDL, whereas isolated single parameter dyslipidemia was detected in 6.4% males and 1.4% females with high triglycerides, 18.2% males and 12.6% females with high LDL, and 10.4% males and 13.1% females with low HDL [13]. The large-scale Indian Council of Medical Research–India Diabetes (ICMR–INDIAB) Study conducted in 16,607 adults revealed increased risks of hypercholesterolemia (OR, 2.47; 95% CI, 1.88–3.24; $p<0.001$), hypertriglyceridemia (OR, 3.41; 95% CI, 2.73–4.26; $p<0.001$), low HDL-C (OR, 1.78; 95% CI, 1.37–2.32; $p<0.001$), and high LDL-C (OR, 2.39; 95% CI, 1.79–3.20; $p<0.001$) in those with dysglycemia [14].

The epidemiological cross-sectional study, SOLID, revealed a prevalence of 48.74% in the control of LDL-C in the Indian diabetic population treated with lipid-lowering drugs [15]. Another recent cross-sectional study by Dayakar et al. reported the incidence of occurrence of hypercholesterolemia to be 58.6% and that of hypertriglyceridemia to be 36.9% in 46 adult patients with type 2 diabetes in a tertiary care centre in Southern India [16].

Bulut et al. found the prevalence of dyslipidemia to be 26.2% in 202 children and adolescents with type 1 diabetes, of which hypercholesterolemia (15.8%) and hyperglyceridemia (12.9%) were the most common. Among those with dyslipidemia, factors such as age, body mass index, glycated hemoglobin (HbA1c), and poor metabolic control were significantly higher. Smoking rate was found to be nearly 14% in those belonging to the pubertal group, with significantly higher dyslipidemia and poor metabolic control ($p<0.05$) [17]. A recent cross-sectional study in underprivileged children and youth in India with poorly controlled type 1 diabetes demonstrated a prevalence of 47.2% of dyslipidemia, with an abnormal lipid profile in 11.9% children below the age of 10 years. High LDL (>2.6 mmol/L; 34.9%) was the most commonly observed lipid abnormality, and was followed by hypercholesterolemia (>5.2 mmol/L; 12.3%), abnormal HDL (<1.1 mmol/L; 12.3%), and hypertriglyceridemia

(>1.5mmol/L in children >10 years and 1.1–1.5 mmol/L in children <10 years; 10.6%) [18].

Recent data from the National Family Health Survey (NFHS-4)/Demographic Health Survey 2015–2016 (a cross-sectional survey of all 29 states and 7 union territories of India) estimated the prevalence of undiagnosed diabetes in India for 750,924 persons aged 15–50 years. They identified 42% of their population with diabetes were 'undiagnosed', with poor detection rates. About 45% of undiagnosed diabetes individuals had access to healthcare. The researchers have recommended combining access to healthcare with routine and rapid low-cost, opportunistic screening of individuals for high glucose levels [19]. The high prevalence of undiagnosed diabetes increases the risk of macro- and microvascular complications of diabetes on account of the poor glycemic control.

There is very little evidence pertaining to the epidemiology of undiagnosed dyslipidemia even in the general population, let alone in patients with diabetes mellitus. A population-based, epidemiological cross-sectional study (part of the Kerman coronary artery disease risk study [KERCADRS]) assessed 5899 (aged 15–75 years) residents of the largest city in southeast of Iran. They reported the prevalence of undiagnosed dyslipidemia as 16.8%, while that of diagnosed dyslipidemia as 13.2%. The overall prevalence of undiagnosed dyslipidemia was found to be higher and significantly influenced by advanced age, obesity, anxiety, and family history of dyslipidemia [20]. On the other hand, lipid profiles (LDL-C) and lipid ratios (LDL-C/HDL-C and TC/HDL-C ratio) have been shown to be potential markers that can perhaps be used to predict glycemic control in patients with type 2 diabetes [21].

Dyslipidemic states

Primary dyslipidemias can take place independent of type 2 diabetes or metabolic syndrome, on account of single or multiple gene mutations resulting in abnormal serum lipid levels [22]. *Hypertriglyceridemia* is generally defined as fasting serum triglyceride levels of ≥150 mg/dL (1.7 mmol/L), despite the 'optimal' <100 mg/dL fasting triglyceride concentration that confers minimal risk of incident as well as recurrent ASCVD [23]. Even though the prevalence of *hypercholesterolemia* does not rise in diabetes mellitus, mortality from coronary heart disease (CHD) intensifies exponentially as a function of serum cholesterol; lowering of cholesterol levels with statins in diabetic patients' moderates the relative cardiovascular risk [24].

Mixed dyslipidemia is a state with increased levels of LDL cholesterol and triglycerides and reduced HDL cholesterol levels; this state is often encountered in individuals with diabetes and metabolic syndrome [25]. *Dysbetalipoproteinemia*, an unusual familial dyslipidemia, is characterised by nearly similarly raised triglyceride and serum cholesterol levels as a result of accrued remnant lipoproteins in apolipoprotein E2/E2 homozygotes. This condition has been associated with a higher risk for premature CVD. Diagnosis of this dyslipidemic state should be considered either in those with mixed dyslipidemia with a relatively low concentration of apolipoprotein B (apo B) compared to the total cholesterol concentration or in cases of substantial disparity between calculated LDL and direct LDL cholesterol concentrations [26].

Familial hypercholesterolemia (FH), a genetic disorder of lipoprotein metabolism, is a dyslipidemic state with an eminent surge in plasma total-cholesterol levels with detrimental cardiovascular consequences that embark in childhood. It epitomises the phenotypic manifestation of abnormal lipoprotein metabolism triggered by an assortment of genetic abnormalities [27]. *Familial combined hyperlipidemia* (FCH), a common metabolic disorder, is characterised by an upsurge in cholesterolemia and/or triglyceridemia in at least two members of the same family, intra-individual and intra-familial variability of the lipid phenotype, combined with an elevated risk of premature CHD [28]. Untreated FCH has been linked with early-onset CVD; LDL-C levels directly correlate with CVD across a number of populations [22]. *Familial dysbetalipoproteinemia* (also known as type III hyperlipoproteinemia or remnant removal disease), another genetic lipid disorder, is characterised by hyperlipidemia, mutations in the apolipoprotein E gene, and an increased CVD risk [29].

Familial chylomicronemia syndrome (FCS), lysosomal acid lipase deficiency, familial hypoalphalipoproteinemia, β-sitosterolemia, and lipodystrophy are few other uncommon genetic dyslipidemic syndromes [30]. Clinicians could refer such patients to specialists for further investigations (e.g. genetic testing) and appropriate management.

Secondary causes of lipid disorders

It is imperative to identify secondary causes of dyslipidemia before initiating or intensifying treatment. Treating the underlying condition might improve the dyslipidemia, plummeting the need for therapy. Recognising the co-morbidity could amend consequent treatment decisions. In fact, certain dyslipidemias may appear to be refractory to treatment in the presence of an unrecognised secondary cause.

The most common causes of dyslipidemia include diabetes mellitus, excessive alcohol intake, hypothyroidism, liver disease, renal disorders, obesity, ageing, postprandial lipemia, metabolic syndrome, pregnancy, smoking, dysproteinemia, acute stress, and drugs (oestrogen medications, human immunodeficiency virus (HIV) therapy, antipsychotic medications, steroids, immunosuppressive agents, etc.) [31, 32]. Addressal of poor glycemic control, obesity, diets high in refined carbohydrates, alcohol excess, lack of exercise, and smoking as secondary causes of dyslipidemia are advocated [33].

Once diagnosed, secondary causes of dyslipidemia should be excluded in order to rule out individuals that could possibly be treated or cured with approaches other than triglyceride- or cholesterol-lowering therapies. Initially, a complete medical, family, and nutrition history must be recorded, followed by a physical examination to ascertain additional risk factors. Common laboratory tests useful in excluding a secondary cause of dyslipidemia comprise of urinalysis, glucose, TSH, plasma creatinine, protein electrophoresis, alkaline phosphatase, and transaminases. Moreover, all prescriptions, dietary supplements, and over-the-counter medications should be noted. Monitoring of lipid levels must be continued after diagnosing the secondary cause of dyslipidemia, since certain conditions increase the risk of ASCVD, thereby warranting more aggressive lipid-lowering therapy [30].

Atherogenic diabetic dyslipidemia

Hyperglycemia, adipocytokines, and insulin deficiency or resistance could contribute to the modifications in lipid metabolism in patients with diabetes [6]. The pattern of dyslipidemia is not the same in Indians. Contrary to that seen in Caucasians, though LDL-C levels are not very high, the preponderance of more atherogenic small, dense LDL particles is greater among Indians. Furthermore, HDL-C levels are low while levels of triglycerides and apo B are elevated. This pattern, known as 'atherogenic dyslipidemia', is frequently encountered in South Asians with diabetes. The pattern and prevalence of concomitant cardiovascular risk factors moderating the impact of dyslipidemia on cardiovascular risk (e.g. truncal obesity, diabetes and metabolic syndrome) also vary in Indians [5, 24, 34]. In a recent cross-sectional study in naïve Indian diabetic patients, the prevalence of atherogenic diabetic dyslipidemia was 34%, 73% of whom had high HbA1c levels (>8%). The authors also observed a staggering 89.2% patients newly diagnosed with diabetes demonstrating a high prevalence of dyslipidemia [35]. Molar concentrations of lipoprotein a [Lp(a)] have been found to be dose-dependently associated with CAD risk, peripheral artery disease, aortic valve stenosis, heart failure, and lifespan [36].

Role of HDL rise in diabetes mellitus

The cardiovascular protective role of HDLs is generally attributed to their role in reverse cholesterol transport, endothelium-dependent vasorelaxant effects, and anti-inflammatory, antithrombotic, and anti-oxidative abilities. These are, however, compromised in diabetic states, on account of glycation of the HDL protein, oxidative alteration, and the conversion of the HDL proteome into a pro-inflammatory protein. The capability of HDL to subdue inflammatory signals is known to considerably decrease in such patients [37, 38]. Since HDL function is disconcerted in patients with diabetes, HDL-C levels, in isolation, may perhaps not reveal the risk of CVD in diabetes accurately [1].

High-density lipoprotein concentration, composition, and metabolism as well as functionality vary substantially in patients with diabetes compared to the general population. People with type 1 diabetes with nephropathy and type 2 diabetes have low HDL-C. In these states, the activity of cholesteryl ester transfer protein (CETP) increases while that of serum paraoxonase-1 (PON-1) is decreased. This impairment in the functionality of HDL is due to glycation of HDL protein constituents [39].

Though evidence demonstrates normal or even higher plasma concentrations of HDL-C in type 1 diabetes than type 2, there is an increased incidence of CVD in type 1. This enigma could be elucidated by alterations in the abnormal cholesteryl ester/triglycerides ratio, lower phospholipid content, decline in the capacity to stimulate cholesterol efflux from macrophages, compromised anti-inflammatory and anti-oxidant activities, and other probable atherogenic properties disturbing HDL functional properties in patients with type 1 diabetes [40]. In type 2 diabetes, HDL is enhanced in triglycerides, and hence responsible for the higher catabolism of HDL particles. Besides, HDL particles are glycated in this state and an upfront correlation between glycation of apo A-I and plasma glucose level has been noted. Glycation of apo A-I has been shown to bring about a reduction in the solidity of the lipid–apoprotein interaction in addition to that of the apoprotein self-association, expediting dissociation of the former complex and distressing the organisational cohesion of HDL particles. Such structural amendments reduce the binding of HDL to its receptor [37].

Subsequent to the comprehension that higher HDL levels might not always render improved HDL function, newer treatment approaches emphasise not only on enriching HDL levels, but also on augmenting its function, and consist of inhibition of HDL modification (like vitamin E), HDL substitution (like apo-AI mimetics), and rise of HDL (like CETP inhibitors). HDL mimetic agents, for e.g. reconstituted HDL, apo-AI, apo-AI Milano, and apo-AI mimetic peptides signify an innovative therapeutic objective enhancing HDL functionality by not just improving reverse cholesterol transport, but also their antithrombotic, anti-oxidative, and anti-inflammatory properties [39, 41]. The Strong Heart study (n=3,216) noted a 1.32-fold higher hazard ratio (95% CI, 1.06–1.64) for CHD among diabetic adults with high triglycerides and low HDL-C, than those with normal triglycerides and normal HDL levels [42].

Lipoprotein (a) and apolipoprotein B

Lipoprotein (a), bearing a structure similar to plasminogen, attaches to the plasminogen receptor, resulting in amplified thrombosis. Data illustrates Lp(a) measurement to offer clinically significant enhanced risk reclassification in specific situations, and must be in cases with an estimated 10-year risk of ASCVD, or those with high-to-moderate risk [43, 44]. The recent ESC guidelines endorse a one-off measurement of Lp(a) to stratify patients with considerably high inherited Lp(a) levels posing a substantial lifetime risk of ASCVD, those with a family history of premature CVD. Moreover, it can help in defining treatment strategies in individuals whose projected risk is on the verge of risk categories [45].

A recent case–control study of 1,43,087 Icelanders (n=17,715 with CAD; 8,734 with T2D) validated an increased risk of type 2 diabetes with low concentrations of Lp(a). The researchers also revealed a projected reduction in CAD risk without an increase in the risk of type 2 diabetes with a pharmacologic decline in Lp(a) concentration [36]. Another study assessing the relationship between Lp(a) and type 2 diabetes in 2,040 patients with and without CAD, found an independent association between elevated Lp(a) levels with the presence and severity of CAD [46].

Singla et al. designed a case–control study to examine (i) Lp(a) levels in 60 age- and sex-matched patients with type 2 diabetes and (ii) their association with LDL:HDL ratio and glycemic control. When compared to the control group, the diabetic group had significantly higher levels of Lp(a) and LDL:HDL ratio. However, there was no association with LDL:HDL ratio or the degree of glycemic control. The authors concluded that elevated levels of Lp(a) do not reflect the glycemic status and are non-dependent of the rise in LDL:HDL ratio [47]. Other researchers have suggested low Lp(a) levels in type 2 diabetes to be beneficial and at the same time unhealthy, and linked to undesirable cardiometabolic phenotype, inferior glycemic control, lesser β-cell function, and amplified microvascular damage in spite of being related to evident reduction in CAD [48].

Furthermore, plasma levels of certain apolipoproteins are altered in type 2 diabetes with CVD or other complications. A number of apolipoprotein polymorphisms have been linked with lipid metabolism and/or diabetes susceptibility [49]. Apo B recognises high-risk dyslipidemic phenotypes in patients with type 2 diabetes, which are not identified by standard lipid profile. Adding apo B to standard lipid profile may perhaps assist in appropriate introduction of lipid-lowering therapy in undetected high-risk patients, thereby plummeting mortality and morbidity due to future cardiovascular complications [50]. Apo B measurement could also aid in assessing cardiovascular risk in those diabetic people with hypertriglyceridemia or CHD, who have already accomplished LDL-C and non-HDL-C targets [51].

The current ESC recommendations advocate Apo B as an enhanced estimate of a person's exposure to atherosclerotic lipoproteins, and may be predominantly valuable for assessment of risk in cases where LDL-C measurement underestimates this burden, for instance people with high triglycerides, diabetes mellitus, obesity, or very low LDL-C [45].

Need for screening for dyslipidemia in diabetes

Who should be tested?

People with type 2 diabetes are considered to be at high risk for vascular events. As a result, regardless of other risk factors on history (age, gender, hypertension, family history, smoking) or physical examination (hypertension, obesity, polycystic ovary syndrome in women), they ought to be screened for dyslipidemia. In patients with type 1 diabetes, screening for dyslipidemia should be initiated from the age of 12 years. In cases of known family history of hypercholesterolemia, early CVD or if the family history is unknown, screening should begin at the age of 2 years. If results are within normal limits, screening should be repeated every 5 years, until adulthood, and annually thereafter [5].

The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines for management of dyslipidemia and prevention of cardiovascular disease recommend annual screening for all adult individuals with T1DM or T2DM for dyslipidemia. In the absence of ASCVD risk factors, middle-aged individuals should be screened for dyslipidemia at least once every 1 to 2 years. Annual screening for dyslipidemia is recommended for older adults with 0 to 1 ASCVD risk factor [52]. The recent RSSDI advocates simultaneous screening and treatment for modifiable risk factors for CVD like dyslipidemia, hypertension, alcohol consumption, and smoking, in patients with prediabetes. In patients with diabetes, dyslipidemia should be assessed at diagnosis and annually thereafter. Periodical screening for dyslipidemia is recommended in overweight or obese children with a family history of type 2 diabetes, or those from a predisposed race/ethnicity like Asian, American Indian, etc. [53].

What should be tested?

Basic physical examination must include patient's height and weight, waist circumference, blood pressure, and peripheral and carotid pulses. Laboratory evaluations should include fasting lipid profile (total cholesterol, HDL-C, triglycerides, LDL-C, and calculated non-HDL-C), comprehensive medical

panel (including uric acid), HbA1c, and thyroid-stimulating hormone. Non-fasting lipid levels are effective in initial screening; non-HDL-C is a reasonable screening test. Non-HDL-C should routinely be calculated in diabetic patients owing to the higher prevalence of elevated triglycerides and small-dense LDL. Assessment of apo B or LDL particles, Lp(a), and high-sensitivity C-reactive protein should also be considered, when deemed necessary. Diagnostic procedures could include resting electrocardiogram, treadmill, chemical, and/or nuclear stress tests, if required [5, 7, 30, 54].

Dyslipidemia testing

Fasting vs non-fasting

In postprandial hyperlipidemia, also known as postprandial hypertriglyceridemia, there is an increase in triglyceride-rich chylomicron remnants and hypertriglyceridemia is protracted. This condition, which induces atherogenesis in the postprandial period, is a vital residual risk factor particularly in patients with diabetes mellitus and metabolic syndrome [55–57]. Guidelines advocate the gold standard, viz. fasting levels of lipids for atherogenic risk assessment, on account of the sensitivity of triglyceride levels to the postprandial state, predominantly in patients with insulin resistance [58]. Fasting triglycerides are said to be more apt for calculating LDL-C, as a number of dietary factors influence triglycerides and hence escalate after a meal, unlike apo B and non-HDL-C levels [59].

The requisite for fasting pressurises patients' as well as laboratory facilities that necessitate accommodation of such patients in the wee hours [58]. Fasting for 8 h or more customarily occurs a few hours prior to breakfast, disparate to the non-fasting state that prevails over 24 h, and in doing so, captures improvised levels of atherogenic lipoproteins. In the latter state, plasma comprises of atherogenic lipoproteins of hepatic descent in the fasting state as well as those of originating from the intestines [60]. Non-fasting lipid assessment is rational in numerous clinical settings as LDL-C can be precisely assessed using modern techniques and that prediction of ASCVD risk is analogous with fasting or non-fasting lipid values. Permitting the alternative for non-fasting lipid assessment may reduce a barrier to lipid testing and enable appropriate ASCVD risk assessment with the eventual prospective effect of plummeting the ubiquitous burden of ASCVD [61].

With the elimination of the requirement to return another day for a fasting lipid profile, non-fasting lipid assessment has the potential to reduce overall costs, decreasing missed work time thereby enhancing patient satisfaction and compliance with lipid testing [59, 60, 62]. Patients with diabetes on anti-hyperglycemic agents (particularly long-acting basal insulin or sulphonylureas) are at a higher risk of developing hypoglycemia in the fasting state [63]. When using non-fasting lipid profiles to decide commencement of a statin or titration of its dose in people with borderline LDL cholesterol, there is a need to consider the lower LDL cholesterol observed mainly 0–4 h after a meal, owing to liberal fluid intake and haemodilution, predominantly in patients with diabetes [56].

Non-fasting LDL-C is by and large valid but for elevated triglyceride levels; the prandial state does not affect non-HDL-C or apo B measurements even when triglyceride levels are not in the normal range [64, 65]. Nonetheless, certain high-risk patients or those with severe hypertriglyceridemias being treated to low LDL-C levels might need fasting lipid panels for an exact diagnosis and to regulate therapeutic monitoring. Since patients with well-controlled LDL-C but discordantly high apo B continue to face a greater risk of ASCVD, a non-fasting lipid profile could reveal a more precise average lipid exposure [61]. The advantages of fasting and non-fasting lipid testing are summarised in Table 1.

A fasting lipid profile should be acquired when non-fasting triglyceride levels are >440 mg/dL (>5 mmol/L) [62]. In individuals with non-fasting non-HDL-C level of ≥220 mg/dL, a familial cause of hyperlipidemia ought to be suspected and assessed further. Among those with features suggestive of familial hyperlipidemia or a family history of premature ASCVD, screening and follow-up must be performed with fasting lipid panels. Though follow-up fasting triglyceride in cases of non-fasting

Table 1 Advantages of fasting and non-fasting lipid testing

Fasting	Non-fasting
• Gold standard for atherogenic risk assessment	• Detects plasma lipid levels of both atherogenic lipoproteins of hepatic descent and those originating from the intestines
• Highly sensitive to detect triglyceride levels especially in patients with insulin resistance	• Preferred in patients with diabetes due to the increased risk of hypoglycaemia with fasting
• Preferable in certain high-risk patients or those with severe hypertriglyceridemias for exact diagnosis and therapeutic monitoring	• Low-density lipoprotein cholesterol can be precisely assessed using modern techniques
• Preferable when non-fasting triglyceride is >440 mg/dL	• Reduces patient barrier to testing
• To be considered after 2–4 weeks when non-fasting triglyceride is ≥200 mg/dL	• Increases patient convenience and compliance
	• Decreases strain on laboratory facilities

Table 2 Suggested cut-off points of serum lipid levels in fasting and non-fasting states

Lipid parameter	Fasting (mg/dL)	Non-fasting (mg/dL)
Total cholesterol	≥190	≥190
Triglycerides	≥150	≥175
HDL-C	≤40	≤40
Non-HDL-C	≥145	≥150
LDL-C	≥115	≥115
Remnant cholesterol	≥30	≥35
Lipoprotein (a)	≥50	≥50
Apolipoprotein B	≥100	≥100

Abbreviations: *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol

triglyceride level 175 mg/dL is not obligatory, patients must be advised for healthy lifestyle changes, while in those with non-fasting triglyceride level ≥200 mg/dL, it is helpful to follow up with a fasting lipid panel after 2–4 weeks [66, 67]. Table 2 enlists the suggested cut-off points of serum lipid levels in fasting and non-fasting states adapted from [62, 68].

Recent studies over the last couple of decades have reported similar prognostic values of non-fasting LDL-C to fasting LDL-C [69–72]. Lipids must be checked every 3 months or more frequently, as deemed necessary, in patients at moderate-to-extreme risk [30]. An increase in the use of non-fasting lipid testing could result in better patient awareness, detection, surveillance, and dyslipidemia control at a population level leading to a substantial decline in the ASCVD burden [61]. The decision to acquiring fasting or non-fasting lipid values must be tailored on an individual basis. On the whole, there is enough evidence in favour of the use of non-fasting testing for dyslipidemia in clinical practice to evaluate and manage the risk of ASCVD.

Non-HDL should be calculated in every subject (LAI)

- Non-HDL-C, which is equal to total cholesterol minus HDL-C, includes all circulating atherogenic lipoproteins and is therefore a more accurate predictor of ASCVD risk, particularly in patients who have elevated triglycerides (e.g. diabetics, obese persons, those with metabolic syndrome) and those already on statin therapy.
- The LAI recommends non-HDL-C as a co-primary target, as important as LDL-C, for lipid-lowering therapy.
- Monitoring of non-HDL-C will provide a simple, practical tool for treatment decisions relating to lipid-lowering therapy since it does not require a fasting blood sample and takes care of both LDL-C and triglyceride targets.
- In all individuals, the non-HDL-C level should be kept within 30 mg/dL of LDL-C levels.

Assessment of cardiovascular risk

Cardiovascular risk scores are considered valuable tools in diabetes management, predominantly when the score is established in an identical population. Scores that categorise risk well are suitable for detecting people at highest risk, where therapy can be directed. On the contrary, the method of predicting risk precisely to offer prognostic information is aided better by risk scores that compute absolute risk accurately [73].

Even though a prudent objective in the clinical management of dyslipidemia is achieving normal lipid levels, there is a need to set more aggressive goals for individuals at higher risk. There are a multitude of risk scores that assess cardiovascular risk considering diabetes as a risk factor (Table 3). Despite some variability in calibration in various subgroups, together with gender, race, and diabetes, most studies have found no statistically significant difference in the overall

Table 3 Total CVD risk assessment systems that considered diabetes as a risk factor

System	Risk assessed
Framingham models	10-year risk of CHD events [74]
ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network)	10-year risk of first CVD event [75]
QRISK3	10-year risk of CVD event [76]
Prospective Cardiovascular Munster Study (PROCAM)	Two separate scores calculate 10-year risk of major coronary events and cerebral ischemic events [77]
Reynolds Risk Score	10-year risk of incident myocardial infarction, stroke, coronary revascularisation, or CV death [78]
CUORE	10-year risk of first CVD event [79]
Pooled Cohort equations	10-year risk of CVD event [80]
Globorisk	10-year risk of CVD mortality [81]

Abbreviations: *CHD*, coronary heart disease; *CVD*, cardiovascular disease

Table 4 Coronary calcium scoring recommendations by the National Lipid Association [87]

Age groups	Additional considerations	Recommendations
30–39 years	Long-standing diabetes mellitus (type 1 diabetes, >20 years; type 2 diabetes, >10 years) and risk factors or microangiopathy	CAC scoring may be reasonable to aid in ASCVD risk stratification and statin treatment shared decision making.
40–75 years	LDL-C level: 70–189 mg/dL	Moderate or high intensity statin is indicated, regardless of CAC score
	When decision to initiate statin therapy has been made	Choose a high intensity statin when CAC score >100
>75 years	When decision to employ a statin for primary prevention is uncertain	CAC scoring is reasonable to aid in statin treatment shared decision making

Abbreviations: *ASCVD*, atherosclerotic cardiovascular disease; *CAC*, coronary calcium scoring; *LDL-C*, low-density lipoprotein cholesterol

prediction of CVD risk in those with or without diabetes, authenticating the use of risk calculators in people with diabetes. On the other hand, diabetes itself confers an amplified risk for ASCVD. It should hence be acknowledged that these risk calculators do not account for either the duration of diabetes or the presence of diabetes complications.

Different categorisations of the Framingham risk score are reported to have a potent relationship with the various components of metabolic syndrome [82]. However, since the Framingham Heart Study did not include patients with diabetes, the question regarding the applicability of the score to gauge CVD risk in patients with diabetes arises. Stephens and colleagues retrospectively analysed data of 1176 patients with diabetes attending the diabetes clinic at University College London Hospitals NHS Trust from 1990 to 2001 to observe the efficacy of the Joint British Societies Risk Chart (JBSRC), the CardioRisk Manager (CRM) calculator, the PROCAM calculation and the UKPDS risk engine (specific to diabetes) for risk prediction in patients with diabetes. The researchers concluded that, though these methods have reasonable discrimination, they tend to underestimate future CHD and CVD events [83].

Patients with ASCVD, type 1 or type 2 diabetes, steep levels of individual risk factors, or those with chronic kidney disease are generally considered at very-high or high total cardiovascular risk. Risk estimation models are not essential for such people; all risk factors warrant active management. In fact, risk scores developed for the general population are not endorsed for cardiovascular risk assessment in this subgroup [45]. The United Kingdom Prospective Diabetes Study (UKPDS) risk engine offers estimates of CHD risk for the primary prevention of CHD in patients with type 2 diabetes. This diabetes-specific model integrates glycemia, systolic blood pressure, and lipid levels as risk factors, over and above age, sex, ethnic group, smoking status, and time since diagnosis of diabetes [84].

The QRISK2 assessment tool has now been updated to the QRISK3 assessment tool. The new algorithm calculates an individual's risk of developing a heart attack or stroke over 10 years, and takes into account ethnicity as a risk factor, in addition to age, sex, body mass index, smoking status, type of diabetes, lipid levels, hypertension, family history of CVD, CKD, among others. Considering the possible genetic influence of Indian ethnicity on CVD, the QRISK3 score exemplifies as the current most accurate CVD screening tool available for the Indian population [85, 86].

Coronary artery calcium (CAC) scoring is an extensively available, cost-effective, rapid, safe test that better identifies those at risk for ASCVD and assists superior reclassification of the risk, particularly when used in combination with global risk scoring systems [87]. A plethora of studies have recognised measurement of CAC to enhance the prediction

Table 5 ASCVD risk categories and treatment goals for dyslipidemia in patients with diabetes

	High risk	Very-high-risk	Extreme risk
Definition	Diabetes with no other risk factors	Diabetes with ≥1 major risk factor(s) for ASCVD	Diabetes with established clinical ASCVD
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
Apolipoprotein B (mg/dL)	<90	<80	<70
Triglycerides (mg/dL)	<150	<150	<150

Abbreviations: *ASCVD*, atherosclerotic cardiovascular disease; *DM*, diabetes mellitus; *LDL-C*, low-density lipoprotein cholesterol; *non-HDL-C*, high-density lipoprotein cholesterol

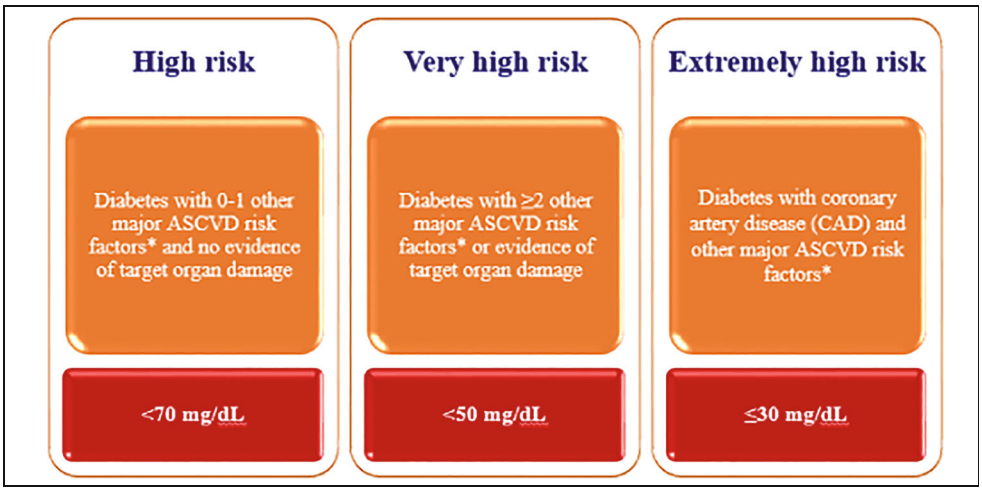

Fig. 1 Treatment goals for LDL-C for patients with diabetes across categories of total cardiovascular disease risk [7]. *Major ASCVD risk factors include age ≥45 years in males and ≥55 years in females, family history of premature ASCVD, current cigarette smoking or tobacco use, high blood pressure, or low HDL-C. *Abbreviations*: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol

of cardiovascular events in asymptomatic patients with type 2 diabetes. In fact, it has been established as an independent predictor of future ASCVD events in patients with diabetes and is consistently superior to the Framingham Risk Score as well as the UKPDS risk engine [88–90]. Conversely, the DIAD study revealed no clinical advantage to routine screening of asymptomatic patients with type 2 diabetes [91].

The recent recommendations from the National Lipid Association on coronary calcium scoring for patients with diabetes are summarised in Table 4.

ASCVD risk category and treatment goals

The AACE has defined five risk categories considering the number and severity of major ASCVD risk factors, viz. diabetes mellitus, family history of hyperlipidemia, fasting/postprandial hypertriglyceridemia, increased levels of total serum cholesterol level, non-HDL-C, LDL-C, apo B, Lp(a), triglyceride-rich remnants, and small, dense LDL-C, and low levels of HDL-C, including others (Table 5) [30].

The European Society of Cardiology (ESC) recommends more intensive reduction of LDL-C across the cardiovascular risk categories. In addition, they advocate LDL-C goal of <1.0 mmol/L (<40 mg/dL) for patients with ASCVD experiencing a consequent vascular event within 2 years while on maximally tolerated statin therapy. For secondary prevention, in patients at very-high risk, a ≥50% reduction LDL-C and LDL-C goal of <1.4 mmol/L (<55 mg/dL) may be considered [45].

In patients with diabetes, cardiovascular risk categories applicable to Indians include (a) high risk, i.e. patients with long-standing diabetes mellitus, especially with other cardiovascular risk factors or with target organ damage, and (b) moderately high risk, i.e. patients with recent onset diabetes mellitus with no other major cardiovascular risk factor and no evidence of target organ damage [5]. The recent Expert Consensus Statement on dyslipidemia by the Lipid Association of India stratifies Indian patients with diabetes as either 'high risk', 'very-high risk', or 'extremely high risk' (Fig. 1) [7].

High-risk patients necessitate management comparable to that for secondary prevention of CVD [92]. The most important step in defining treatment goals for diabetes patients is an extensive assessment of their cardiovascular risk, with LDL-C as the primary target, and non-HDL-C, HDL-C, and apo B as secondary targets [5, 93]. The AACE endorses non-HDL-C goal as an even better indicator of ASCVD risk compared to LDL-C [30]. The ESC recommends apo B analysis for risk assessment, predominantly in those with diabetes mellitus, high triglycerides, obesity or metabolic syndrome, or very low levels of LDL-C. If available, apo B can be used as the primary measurement for screening, diagnosis, and management, and preferred over non-HDL-C in this population [45]. Since all atherogenic particles contain an apo B_{100} molecule, it might deliver precise estimation of atherogenicity. Besides, apo B measurement helps in evaluating the success of lipid-lowering therapy, as it may continue to remain above the target even after achieving the LDL-C goal [30].

In children with type 1 diabetes, a dispute concerning the goals for lipid levels exists. Where the AACE and American Academy of Pediatrics suggest softer LDL-C targets (normal <110 mg/dL, high >130 mg/dL, borderline 110–130 mg/dL), the International Society for Pediatric and Adolescent Diabetes recommends LDL-C target of <100 mg/dL [5].

Management of diabetic dyslipidemia

Goals of therapy

A comprehensive strategy is essential in the management of dyslipidemia so as to regulate lipid levels and tackle related metabolic deviations and modifiable risk factors. Lifestyle

modifications such as smoking cessation, physical activity, medical nutrition therapy, sleep evaluation, and mental health conditions play a crucial part in dyslipidemia management [30]. The basis of such management should encompass an individual's principal phenotype and comprise of treatment regimens demonstrated to reduce cardiovascular events. Despite the need to individualise the choice to initiate drug therapy, regardless of basal plasma cholesterol levels, statin therapy must be considered in high-risk patients with diabetes. Owing to the intricacy of diabetic dyslipidemia, there usually is a need for multiple agents to accomplish therapeutic goals [24].

Non-pharmacological therapy

Lifestyle management continues to form the basis of all lipid-reduction therapies [30]. Healthy behavior interventions are a vital element of diabetes management and CVD prevention strategies. Essential considerations to improve overall lipid profile and glycemic control, and reduce CVD risk include accomplishing a healthy weight and aerobic activity level, implementing an energy-restricted, well-balanced diet, moderating alcohol consumption and smoking cessation [5, 94–98].

Changes in lifestyle behavior, such as weight loss, regular physical activity, and medical nutrition therapy, may assist in decreasing ASCVD risk factors. In order to enhance lipid profile and decrease the risk of developing ASCVD in patients with diabetes, the ADA recommends lifestyle modifications aiming towards weight loss (as and when indicated), increased physical activity, and adapting to a Mediterranean style or Dietary Approaches to Stop Hypertension (DASH) eating pattern, with reduced intake of saturated- and trans-fat, and increased intake of dietary n-3 fatty acids, viscous fibre, and plant stanols/sterols [99]. Modifications in lifestyle can reduce triglyceride levels by up to 50% [7].

Physical activity

Physical inactivity has been linked with glucose intolerance, hypertension, waist circumference, and obesity, as well as dyslipidemia. Explicit improvements in lipid levels with regular exercise embrace higher HDL-C, decreased VLDL-C and triglycerides, and decline in high-sensitivity C-reactive protein (hsCRP), and even increase the LDL-C particle size thereby making it less permeable. Constant reinforcement for regular physical activity is recommended in non-adherent individuals. In order to improve adherence, healthcare personnel could adapt diverse approaches like personalised advice, instructor-led exercise classes, and ascertaining barriers to adherence, in addition to routine consultation and follow-up [30]. A meta-analysis of randomised controlled trials (RCT) demonstrated progressive resistance training to reduce total cholesterol, total cholesterol to HDL-C ratio, non-HDL-C, LDL-C, and triglycerides in adults [96].

Yoga

Yoga, a lifestyle intervention that uses an integrated approach, aims at reducing raised lipid levels in diabetic patients [100]. Gordon et al. suggested the beneficial role of yoga in the management of dyslipidemia in 35 patients with end-stage renal disease. They noted a significant decrease in total cholesterol after 4 months (−4.58%; p=.0001), triglycerides (−6.26%; p=0.0001), LDL-C (−11.32%; p=0.0001), and total cholesterol/HDL-C ratio (−12.26%; p=0.047) [101]. A recent stratified translational research (NMB-2017 India) trial assessed the efficacy of a validated yoga protocol on dyslipidemia in patients (n=17,012) with diabetes. After 3 months of intervention, 60% patients attained normal total cholesterol (<200 mg/dL), 73.7% patients achieved normal LDL, normal triglyceride levels were accomplished by 63% patients, and 43.7% returned to normal HDL (>45 mg/dL). The authors concluded the implementation of yoga to significantly mitigate the hyperlipidemic states in patients with diabetes [102].

Sleep and optimism

Cappuccio et al. conducted a systematic review and meta-analysis of 15 prospective studies (n=4,74,684; follow-up=6.9–25 years) to examine the relationship between duration of sleep and morbidity and mortality from CHD, stroke, and total CVD. They found both short (relative risk [RR], 1.48; 95% CI, 1.22–1.80; p<0.0001) and long (RR, 1.38; 1.15–1.66; p=0.0005) durations of sleep to be predictors of cardiovascular outcomes [103]. Allowing for optimism in terms of lipids could propose novel approaches for prevention and intervention to improve cardiovascular health. The Midlife in the United States (MIDUS) study investigated the relationship of optimism with total cholesterol, HDL-C, LDL-C, and triglycerides. The authors' reported an association between greater optimism with greater HDL-C and lower triglycerides, and no significant association with LDL-C or total cholesterol [104].

Medical nutrition therapy

Medical nutrition therapy (MNT) plays a central part in diabetes management; every individual with diabetes must be actively engaged in self-management, education, and treatment planning with their healthcare team, together with the collective development of an individualised eating plan [105]. Nutrition intervention must be tailored to each patient's age, type of diabetes, pharmacological regime, lipid levels, and medical issues [99]. Vital elements of MNT include assessment, nutrition diagnosis, interventions like education and counselling, and monitoring with ongoing follow-up so as

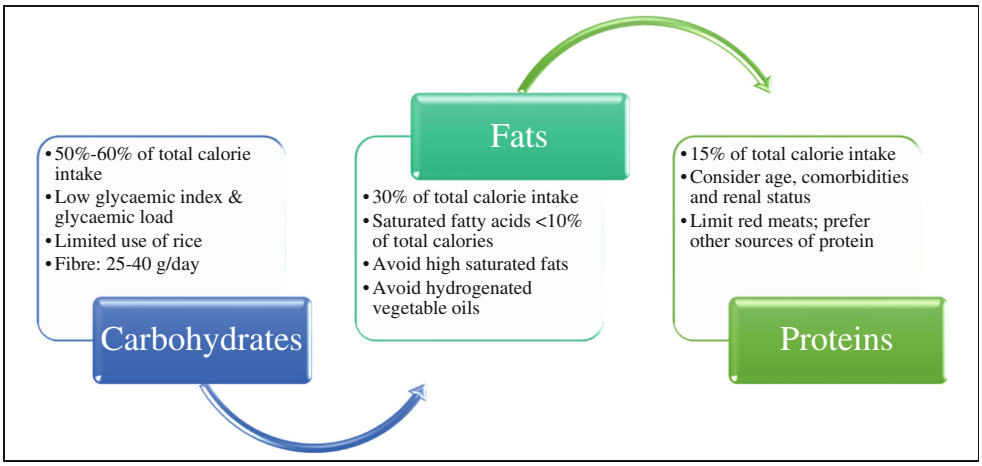

Fig. 2 Recommendation for medical nutrition therapy in patients with type 2 diabetes

support durable lifestyle alterations, estimate outcomes, and amend interventions, whenever necessary [105].

Global clinical practice guidelines for type 2 diabetes from the ADA, IDF, and AACE highlight the significance of incorporating MNT in type 2 diabetes management as a first-line therapy [30, 99]. The goals of MNT are to endorse and support healthful eating patterns, accentuating an assortment of nutrient-dense foods in appropriate portion sizes, in order to improve overall health and:

- Accomplish and sustain body weight goals,
- Achieve personalised lipid, glycemic, and blood pressure targets, and
- Defer or avert diabetic complications.

A tailored MNT programme, delivered by a registered dietician nutritionist, is obligatory to achieve therapeutic targets in type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus. In overweight or obese patients with prediabetes and diabetes, lifestyle adaptation to attain and retain a minimum weight loss of 5% is recommended. As there is no distinct ideal nutritional distribution of calories for people with diabetes, meal plans must be personalised bearing the total calorie and metabolic targets in mind [99]. There is a need for healthcare professionals in India to consider cultural, regional, economic, and agricultural aspects while customising meal plans, since these aspects have a remarkable influence on the reception of MNT by Indian patients [53].

An eating plan emphasising elements of a Mediterranean-style eating pattern rich in monounsaturated and polyunsaturated fats may be considered to improve glucose metabolism and lower cardiovascular disease risk [99]. Keeping in mind clinically relevant observations in the Indian population, the Research Society for the Study of Diabetes in India/Endocrine Society of India (RSSDI-ESI) endorse the implementation of dietician-guided MNT as a fundamental constituent of diabetes management (Fig. 2). They advocate a diet rich in fruits, leafy vegetables, nuts, fibres, whole grains, unsaturated fats, pulses, legumes, unprocessed vegetables, and low fat dairy. Salt consumption must be restricted to <5 g/day and artificial sweeteners <2–3 g/day [53]. Dietary fructose, if consumed >10% of total energy intake, regardless of its low glycemic index, results in hypertriglyceridemia. For that reason, there is a need for a vigilant nutritional evaluation concentrating on fructose intake for individuals with hypertriglyceridemia [5].

The Diabetes in India Nutrition Guidelines Study was a 12-month prospective cluster RCT that compared the outcomes of patients with type 2 diabetes who received dieticians' usual care (n=154) to those who received Evidence-Based Nutrition Practice Guidelines care (n=85). When treated with Evidence-Based Nutrition Practice Guidelines, patients were significantly more likely to achieve LDL-C (mean change from baseline, −11 ± 20 mg/dL), HDL-C (+1.6 ± 4.9), and triglyceride (−74 ± 224) targets over a period of 1 year [106]. A multisite study verifying the efficacy of registered dietician nutritionist interventions in the management of glycemic control and diabetic dyslipidemia reviewed 392 patients with type 2 diabetes completing diabetes self-management education (DSME) and MNT at four regional centres in Alabama from 2013 to 2014. Following DSME and MNT, 62% of patients reached a glycemic target of HbA1c≤7%, compared to 32% patients at baseline (p<0.001). Moreover, there were substantial reductions from baseline to 1-year follow-up in triglyceride levels (162±74 mg/dL [4.19±1.91 mmol/L] vs 109±36 mg/dL [2.82 ±0.92 mmol/L]; p<0.001) and triglyceride-to-HDL ratio (4.07 ±2.41 vs 2.48±1.26; p<0.001), with significant improvement in HDL (45±13 mg/dL [1.16±0.34 mmol/L] vs 48±11 mg/dL [1.24±0.28 mmol/L]; p=0.05) [107].

Pharmacological management

Pharmacological management is recommended when interventions to improve dietary changes and metabolic control are not successful in achieving the recommended lipid targets

[5]. Existing evidence for curtailing the atherogenic impact of lipid aberrations in diabetes is to emphasise on attaining very low plasma LDL-C concentrations, characteristically with statin-based therapy [64]. Second-line LDL-C-lowering therapies should be considered in individuals who do not achieve the recommended lipid targets regardless of maximally tolerated statin therapy or in those with statin intolerance [108]. The latest ADA guidelines recommend intensification of lifestyle therapy and optimisation of glycemic control for diabetic patients with increased triglyceride (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women) levels [99]. Meta-analyses of various lipid-lowering therapies revealed ~20% per 1 mmol/L reduction in LDL-C in the incidence of major vascular events, irrespective of the baseline LDL-C level. Though people with type 2 diabetes were estimated to have a relative risk reduction comparable to non-diabetic patients, being at higher absolute risk, the absolute benefit was predicted to be greater [109, 110].

LDL-C-lowering therapy

Statins Statin therapy is indicated not only in patients with genetic causes of dyslipidemia (e.g. familial hypercholesterolemia) but also in primary and secondary prevention of ASCVD. Moreover, usage of statin therapy in high-risk individuals like those with diabetes duration of more than 40 years and high-risk primary prevention is generally accepted to offer benefit. Nonetheless, there is evidence in patient cohorts where treatment with statin has not been proven to be effective (in cases of haemodialysis or heart failure) or not studied (e.g. malignancy, end of life) [111]. The latest AACE guidelines recommend the use of a moderate- to high-intensity statin as first-line cholesterol-lowering therapy, unless contraindicated. Nonetheless, even with aggressive statin monotherapy, substantial residual risk continues to exist in primary prevention patients with multiple cardiovascular risk factors [30]. Major statin trials that particularly included people with diabetes have shown substantial benefits of statin therapy on CVD events [109].

The ESC suggests delaying statin therapy in asymptomatic patients with diabetes, until the age of 30 years. However, in the presence of ambient levels of LDL-C, microalbuminuria, and end-organ damage, statin therapy could be considered using a personalised approach [45]. On the other hand, the AHA recommends a judicious introduction of statin therapy in adults in the 20–39 years age group with diabetes mellitus, with albuminuria (≥30 mcg of albumin/mg creatinine), long duration of diabetes (≥20 years of type 1 diabetes; ≥10 years of type 2 diabetes), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, neuropathy, retinopathy, or ankle-brachial index (<0.9). In adults between 40 and 75 years of age with diabetes, moderate-intensity statin therapy is indicated, irrespective of the estimated 10-year ASCVD risk. In diabetic patients aged 40 to 75 years with LDL-C ≥70 mg/dL (≥1.8 mmol/L), moderate-intensity statin therapy should be initiated without calculating 10-year ASCVD risk. In this group, but with LDL-C levels between 70 and 189 mg/dL (1.7–4.8 mmol/L), it is rational to evaluate the 10-year risk of a first ASCVD event. A high-intensity statin is considered reasonable in people with diabetes at higher risk, specifically those with manifold risk factors or those in the 50–75 years age group, in order to decrease LDL-C levels by 50% or more [54]. The ESC 2019 Guidelines have recognised the fact that though the relative risk reduction of CV events with statin therapy is same in diabetics as in non-diabetics, but as the risk of events is higher in diabetics, the absolute benefit is more in diabetic population and the number needed to treat is lower [45].

The recent ADA recommendations are in concurrence with those of AHA. For primary prevention, moderate-intensity statin therapy with lifestyle therapy is advocated in patients with diabetes without ASCVD aged 40–75 years. In those with diabetes with additional ASCVD risk factors in the 20–39 years age group, it may be judicious to start statins with lifestyle therapy. In diabetics at higher risk, particularly those aged 50–70 years with multiple ASCVD risk factors, using high-intensity statin therapy is considered reasonable. In those with diabetes and 10-year ASCVD risk of ≥20%, adding ezetimibe to maximally tolerated statin therapy to reduce LDL-C by >50% may be reasonable. For secondary prevention, the ADA recommends high-intensity statin therapy in addition to lifestyle therapy for patients of all ages with diabetes and ASCVD. For those with diabetes and ASCVD considered very high risk using specific criteria, adding additional LDL-lowering therapy could be considered if LDL-C level is ≥70 mg/dL on maximally tolerated statin dose; ezetimibe may be preferred due to lower cost. In diabetes adults above >75 years of age already on statins, continuing statin treatment may be reasonable. The statin dosing intensities recommended for use in clinical practice for patients with diabetes are high-intensity statin regimens (that achieve nearly ≥50%

Table 6 Recommended high-intensity and moderate-intensity once-daily statin therapy

Intensity of statin therapy	Drug	Dose (mg)
High-intensity	Atorvastatin	40–80
	Rosuvastatin	20–40
Moderate-intensity	Atorvastatin	10–20
	Rosuvastatin	5–10
	Simvastatin	20–40
	Pravastatin	40–80
	Lovastatin	40
	Fluvastatin extended-release	80
	Pitavastatin	1–4

reduction in LDL-C) and moderate-intensity statin therapy (that achieves 30–49% reductions in LDL-C) (Table 6) [99].

Intensification of statin therapy is recommended before initiating a combination therapy. Statin therapy may be considered in both type 1 and type 2 diabetic patients aged >30 years of age with LDL-C level >2.5 mmol/L and/or established end-organ damage, with the exclusion of pregnancy [45]. By and large, low-dose statin therapy is not prescribed for patients with diabetes except in cases where it is the only dose of tolerable statin [112]. Naeem and colleagues reviewed cardiovascular outcome trials with statins in people with diabetes and suggested a substantial benefit in plummeting cardiovascular events as part of primary prevention, whereas for secondary prevention, intensive lipid-lowering therapies with high-dose statins were found to be superior than standard lipid-lowering regimens in further decreasing cardiovascular events; however, higher doses might not be tolerated owing to a surge in adverse events [113].

The prospective, randomised, placebo-controlled Collaborative Atorvastatin Diabetes Study (CARDS) noted reductions in major cardiovascular events (37%), acute coronary heart disease–related events (36%), coronary revascularisations (31%), and stroke (48%) in patients with diabetes [114]. In the individual patient data-meta-analysis of statin therapy in At risk Groups: Effects of Rosuvastatin, atorvastatin, and simvastatin (VOYAGER) database with 27.5% patients with diabetes, rosuvastatin was more efficacious than atorvastatin and simvastatin, in lowering LDL-C and reaching a target level of <70 mg/dL for LDL-C. Furthermore, it was more effective in raising HDL-C than atorvastatin [115]. Pitavastatin is a potent moderate- to high-intensity β-Hydroxy β-methylglutaryl-CoA (HMG-CoA; statin) with LDL-C-lowering effects analogous to atorvastatin or rosuvastatin. Pitavastatin also offers a sustained increase of HDL-C levels, a vital element of diabetic dyslipidemia. Moreover, the pleiotropic effects of pitavastatin, which moderate the metabolic changes linked to adiposity and enhance glucose metabolism, separate it from other statins. This may perhaps not escalate the risk of new-onset diabetes. Therefore, pitavastatin could be preferred in the management of dyslipidemia in patients with diabetes or those at risk of developing diabetes [116–118].

Besides rising HDL-C levels, pitavastatin appears to enhance HDL function and reduce the development of atherosclerotic plaques by transforming HDL-related inflammation and oxidation, frequently encountered in patients with metabolic syndrome and type 2 diabetes. Furthermore, pitavastatin has been identified with distinctive pharmacological features that render wide-ranging activities on apo-A- and apo-B-containing lipoproteins, when compared to other statins. Numerous studies confirmed pitavastatin (1–4 mg) to be well-tolerated, with considerable improvements in LDL-C and triglyceride levels to a degree similar or greater than those of atorvastatin, simvastatin, or pravastatin, regardless of patients' diabetic status. While most statins display varying effects on HDL-C levels, patients treated with pitavastatin show clinically significant rises in HDL-C, which are usually sustained and even increased in the long run [119–122].

A prospective, comparative, randomised, controlled, double-blind, clinical trial by Patil et al. investigated the efficacy and safety of pitavastatin against atorvastatin in 100 dyslipidemic patients with hypertension, diabetes and/or CAD. By the end of 8 weeks, there were significant improvements in HDL-C (+11.00% vs +5.35%; $p<0.001$) and LDL-C/HDL-C ratio (−48.68% vs. −44.71%) with pitavastatin than atorvastatin [123]. The recent Scope for Atherosclerotic Cardiovascular Disease Risk Reduction study conducted in South India found a significant proportion of patients with high ASCVD risk who could benefit from statin therapy did not receive it [124].

Statin intolerance Though statins are generally safe and well-tolerated, for people at an intensified risk of ASCVD, the advantages prevail over the odds of adverse effects. Yet, a considerable proportion of statin-treated patients may encounter statin intolerance; this intolerance to statins or the inability to reach LDL-C targets could restrict the use of intensive statin therapy in such individuals [45].

Statin intolerance is the occurrence of (1) adverse symptoms perceived by the patient to be unacceptable, and/or (2) laboratory abnormalities suggesting undue risk, which are attributed to statin therapy and lead to its discontinuation [125]. The most common symptoms of the statin-induced myopathy include muscular pain, weakness, cramps, or stiffness, and may be caused by advanced age >75 years, female gender, abdominal obesity and metabolic syndrome, frailty, smaller body size, Asian ethnicity, alcohol consumption, vitamin D deficiency, excessive physical activity, uncontrolled hypothyroidism, chronic kidney disease, liver disease, family history of statin intolerance and personal history of intolerance to other statins and lipid-lowering therapies, metabolic muscle disorders, and treatments that elevate circulating levels of statins and/or their active metabolites (e.g., erythromycin, fluconazole) [125–127]. In such scenarios, smaller statin doses and/or less potent statins with lower incidence of myopathy (e.g., pitavastatin, extended-release fluvastatin), with vigilant dose up-titration should be considered [45].

In high-risk patients who are intolerant to statins, an amalgamation of lifestyle measures and non-statin drugs must be prescribed to attain LDL-C levels as close as possible to the established goal [126]. The diverse statin-based approaches suggested to manage muscle symptoms include moving to another statin, down-titrating the dose (de-challenge) or reducing the frequency (intermittent dosages), or re-challenging with the same statin. In order to achieve LDL-C goals with minimal or no muscle complaints, if well-tolerated the doses can be slowly up-titrated. Twice-weekly or alternate-day

dosing can be preferred in those who are unable to tolerate daily-dose statins. In cases where statins are not at all tolerated, other lipid-lowering agents as monotherapy or added to the maximum tolerated statin dose are suggested [127].

Ezetimibe Ezetimibe is an inhibitor of intestinal cholesterol absorption. On combination with statins, this drug provides additive and complementary therapeutic lipid effects, resulting in considerable reductions in LDL-C and significant achievement of target cholesterol levels [128]. Adding ezetimibe to statin therapy permits the use of lower dosage of statins without compromising efficacy, reducing the odds of dose-dependent statin adverse effects. Furthermore, ezetimibe seems to have a neutral effect on glucose metabolism; rather a beneficial effect on glycemic control when used for >3 months [93, 128, 129]. Most guidelines advocate the addition of ezetimibe when targets are not achieved with the maximum tolerated dose of statin [45]. The AHA suggests adding ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by ≥50% in people with diabetes and 10-year ASCVD risk of ≥20% [54].

A pre-specified subgroup analysis demonstrated a greater decrease in LDL-C levels with a combination of simvastatin–ezetimibe in patients with type 2 diabetes than those without diabetes (−16.6 vs. −14.3 mg/dL; p=0.003). Therapy with the combination showed significant relative risk reductions in myocardial infarction (−24%) and ischemic stroke (−39%) in the diabetic sub-population [130]. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the subset of patients with diabetes (27%; n=4933) had a higher rate of major vascular events than those without diabetes (46% vs. 31% 7-year Kaplan–Meier rate vs. placebo). Ezetimibe seemed specifically efficacious in diabetes, with a 15% (95% CI, 6–22%) relative risk reduction and 5.5% absolute risk reduction [131].

The Recognized Effect of Statin and Ezetimibe therapy for Achieving the LDL-C goal (RESEARCH) study was a randomised, multicentre, open-label, prospective study that assessed the 52-week long-term effect of ezetimibe as an add-on therapy in 109 type 2 diabetic patients with hypercholesterolemia, not attaining LDL-C target value despite first-line dose statin (10 mg atorvastatin or 1 mg pitavastatin) therapy. Ezetimibe exhibited a robust advantage in lowering LDL-C and achieving goal LDL-C values than with doubling the dosage of statin. What is more is that sd-LDL displayed noticeable steady decrease when ezetimibe was added to the statin [132]. In a recent multicentre, open-label, parallel-group study by Lee et al., 134 patients with type 2 diabetes were randomised to receive either a combination of rosuvastatin 5 mg/ezetimibe 10 mg once daily or rosuvastatin 10 mg once daily monotherapy for a period of 8 weeks. Compared to rosuvastatin monotherapy, ezetimibe as an add-on led to significant reductions in the apo B/A1 ratio (−46.14 ± 1.58% vs. −41.30 ± 1.58%; p=0.03). Besides, the proportion of patients achieving >50% reduction in LDL-C in the comprehensive lipid target significantly varied (76.5% and 73.5%, rosuvastatin/ezetimibe group; 47.1% and 45.6%, rosuvastatin group; p<0.001) among the groups [133].

Evidence suggests combination therapy of ezetimibe–statin may be a convenient strategy in people with diabetes at a residual risk of major adverse cardiovascular outcomes. In a meta-analysis and meta-regression of seven trials with 28,191 patients (7,298 with diabetes; 25.9%), ezetimibe was linked to a superior decline of MACE risk (pooled relative risk, 0.84 vs. 0.93; $P_{\text{heterogeneity}}$=0.012) in those with diabetes than in those without diabetes, particularly when added to statins (β=0.87, p=0.038) [134].

Bempedoic acid Bempedoic acid is a small molecule ATP-citrate lyase inhibitor being developed as a once-daily, first-in-class, oral drug in the management of hypercholesterolemia [135, 136]. This prodrug is activated by a liver enzyme (not present in skeletal muscle) and inhibits ATP-citrate lyase, which is an enzyme upstream of β-hydroxy β-methylglutaryl-coenzyme A reductase, in the cholesterol biosynthesis pathway. This molecule seems to provide a safe and effective oral therapeutic option for lipid lowering in patients intolerant to statins.

The phase 3, double-blind, placebo-controlled Cholesterol Lowering via bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) Serenity study randomised 345 patients with hypercholesterolemia and a history of intolerance to ≥2 statins to bempedoic acid (180 mg; n=234) or placebo (n=111) once daily over 24 weeks. By week 12, treatment with bempedoic acid significantly lowered LDL-C (placebo-corrected difference, −21.4%; 95% CI, −25.1% to −17.7%; p<0.001), non-HDL-C (−17.9%), total cholesterol (−14.8%), apo B (−15.0%), and hsCRP (−24.3%; p<0.001 for all comparisons) [137].

A pooled analysis of four phase 3 clinical trials assessed the effect of bempedoic acid on glycemic control and new-onset diabetes in patients with hypercholesterolemia receiving stable lipid-lowering therapy. Compared to placebo, the use of bempedoic acid led to significantly lower HbA1c levels at week 12 in those with diabetes at baseline (mean placebo-corrected change: −0.19%; nominal p<0.0001) [138]. A recent systematic review and meta-analysis of 11 trials compared the use of bempedoic acid with either placebo or no treatment for primary prevention of cardiovascular events in 4,391 statin-intolerant patients with

hypercholesterolemia. Treatment with bempedoic acid was associated with a decrease in composite cardiovascular outcome (RR, 0.75; 95% CI, 0.56–0.99; I^2=0%) as well as LDL-C (mean difference, −22.91; 95% CI, −27.35 to −18.47; I^2=99%). The novel drug was also associated with decline in rates of new-onset or worsening diabetes (RR, 0.65; 95% CI, 0.44–0.96; I^2=23%) [110]. In addition to similar reductions in lipid profiles, another recent systematic review and meta-analysis recorded a strong association of bempedoic acid treatment with a decreased risk of new onset or worsening diabetes (OR, 0.59; 95% CI, 0.39–0.90; p=0.01) [136].

Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors Human monoclonal antibodies, which target PCSK9, have demonstrated a reduction in LDL-C levels by 55–72% in diverse high-risk patient groups [139]. Treatment with PCSK9 inhibitors in diabetes induces analogous relative reductions in cardiovascular risk. This class of drugs does not raise blood glucose levels, unlike that seen with statins. A systematic review suggested aggressive use of treatment with PCSK9 inhibitors in patients with diabetes with a target of accomplishing and sustaining goal LDL-C levels even lower than that proposed for non-diabetic patients [140]. Aggressive lowering of LDL-C with human PCSK9 monoclonal antibodies has been established with a very favourable safety profile. Based on evidence from diverse clinical trials, LDL lowering with PCSK9 inhibitors is endorsed for high-risk patients with LDL-C levels ≥70 mg/dL on maximally tolerated oral therapies comprising of statins and/or ezetimibe [139].

As per the recent 2021 Canadian Cardiovascular Society Guidelines, patients with clinically evident ASCVD and diabetes mellitus derive the largest secondary prevention benefit from intensification of statin therapy along with a PCSK9 inhibitor [141]. The National Lipid Association Expert Panel recommend considering PCSK9 inhibitor therapy to further reduce LDL-C in patients aged 40–79 years with LDL-C ≥190 mg/dL, no uncontrolled ASCVD risk factors, or other significant additional-high risk markers (including diabetes) and on-treatment LDL-C ≥100 mg/dL or non–HDL-C ≥130 mg/dL on maximally tolerated statin therapy and/or ezetimibe [142]. These drugs are generally well-tolerated and offer substantial LDL-C lowering in patients with diabetes mellitus and hyperlipidemia when added to the maximally tolerated statin therapy, without affecting glycemic control or increasing the risk of developing diabetes mellitus in pre-existing diabetes mellitus; in fact, they can prevent or reduce further cardiovascular events [143, 144].

Alirocumab as well as evolocumab have demonstrated effective lowering of LDL-C in high cardiovascular risk patients, including those with diabetes mellitus. In the Further cardiovascular OUtcomes Research with PCSK9 inhibition in 27,564 subjects with Elevated Risk (FOURIER) trial, inhibition of PCSK9 with evolocumab in the presence of statin therapy reduced LDL-C levels to a median of 30 mg/dL (0.78 mmol/L) in addition to a fall in the risk of cardiovascular events [145]. A prespecified analysis of the FOURIER trial investigated the efficacy and safety of evolocumab by diabetes status and the effect of evolocumab on glycemia and risk of developing diabetes. The data affirmed the efficacy and safety of evolocumab in patients with atherosclerotic disease with and without diabetes. Neither did evolocumab intensify the risk of new-onset diabetes, nor did it aggravate glycemia [146].

The ODYSSEY DM-DYSLIPIDEMIA trial demonstrated the superiority of alirocumab to usual care in lowering non-HDL-C (−32.5% difference; 97.5% CI, −38.1 to −27.0; p<0.0001) in patients with type 2 diabetes and mixed dyslipidemia on maximally tolerated statin. Besides, alirocumab also significantly reduced LDL-C (−43.0%), apo B (−32.3%), total cholesterol (−24.6%), and LDL particle number (−37.8%) [147]. A systematic review and meta-analysis reported no association of PCSK9 inhibitors with risk of incident diabetes (RR, 1.00; 95% CI, 0.93–1.07; p=0.96; I^2=0%; RD, 0.001; 95% CI, −0.004 to 0.006; p=0.75; I^2=11%; $P_{interaction}$=0.02) [148].

Triglyceride-lowering therapy

In patients with ASCVD or diabetes and multiple risk factors and triglyceride levels of ≥150 mg/dL, icosapent ethyl (IPE) may provide additional risk reduction benefit beyond a statin. If triglyceride level is ≥500 mg/dL, prior to considering a fibrate or other non-statin drug, a statin with or without ezetimibe must be preferred. The primary objective in such cases is to decrease the risk of acute pancreatitis by lowering triglyceride level. Treatment should be initiated with a non-statin drug (e.g., fenofibrate) and later add statin to achieve LDL-C and non-HDL-C targets. Among non-statin drugs, omega-3 fatty acids, especially IPE (4 g/day) is preferred, since it has found to reduce adverse cardiovascular events in those with ASCVD or diabetes and multiple risk factors. In people with very high levels of triglycerides, fibrates must be initiated with simultaneous identification and control of secondary causes [7].

Fibrates The hallmark of diabetic dyslipidemia is increased triglycerides and low HDL-C levels. The exact benefits of fibrates on these parameters are still controversial. Although a meta-analysis in >11,000 diabetic patients showed that fibrates significantly decreased the risk of non-fatal myocardial infarction by 21%, there was no effect on the risk of overall or cardiovascular mortality [149]. The effects on fibrates in people with type 2 diabetes without elevated levels

of triglycerides were demonstrated to be much lesser on increasing HDL-C (5%) and lowering triglycerides (20%) in longer duration studies [150, 151]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed a significant change in lipoprotein levels with fenofibrate in patients with diabetes. Furthermore, there were improvements in glycemic parameters especially in women. It was also effective in reducing total CVD event risk in women with type 2 diabetes, especially those with dyslipidemia [152]. Fenofibrate therapy, in a statin-free cohort with type 2 diabetes (n=171) of the FIELD study, demonstrated long-term benefits on VLDL-C and HDL-C. There was a noticeable decrease in large VLDL particles associated with smaller HDL particles [150].

In the follow-up of Action to Control Cardiovascular Disease in Diabetes (ACCORD) lipid study conducted in >4500 patients, fenofibrate therapy was shown to reduce CVD in diabetic patients with elevated triglycerides and low HDL-C levels (HR, 0.73; 95% CI, 0.56–0.95) [151]. The Diabetes Atherosclerosis Intervention Study (DAIS), conducted in 204 patients with type 2 diabetes, found significant reduction in triglyceride levels with fenofibrate, remnant-like particle cholesterol (RLP-C) and activity of lipoprotein-associated phospholipase A2, along with an increase in the HDL-C levels [153].

Saroglitazar Saroglitazar has well-documented positive effects in the management of diabetic dyslipidemia due to its dual mode of action, viz. agonistic activity on PPAR-α and PPAR- . It not only improves lipid parameters (triglycerides, apo B, non-HDL-C), but also has a significant impact on glycemic parameters (HbA1c and fasting blood glucose) in dyslipidemic patients. It is devoid of conventional side effects of fibrates and pioglitazone. On account of its unique insulin sensitising action, the potential of hypoglycemic effect is low; however, it could occur when combined with other agents like sulphonylureas or insulin [154]. The improvements in lipid parameters with saroglitazar are especially valuable in dyslipidemia patterns commonly seen in Indians. Improvement in insulin sensitivity delivers glycemic control. The innovative chemical entity is a 'first in class' drug to be approved anywhere in the world demonstrating higher efficacy in decreasing triglycerides and non-HDL-C, with a twofold action on both dyslipidemia and hyperglycemia [155].

Long-term real-world evidence of up to 58 weeks, in more than 5000 Indian patients with diabetic dyslipidemia, suggested that saroglitazar improved both lipid and glycemic parameters without major adverse effects [156]. Another randomised, double-blind, placebo-controlled trial in 30 treatment-naive type 2 diabetes patients with serum triglyceride >150 mg/dL found saroglitazar to effectively reduce hypertriglyceridemia and improve insulin sensitivity along with β-cell function by reducing gluco-lipotoxicity, probably directly through PPAR-γ agonism. The latest PRESS XII (Phase III) study, with a primary endpoint of HbA1c reduction, involving >1000 patients with type 2 diabetes found a significant decrease in triglycerides, LDL-C, VLDL-C, total cholesterol, and non-HDL-C, associated with an important increase in HDL-C (<0.016). When added to metformin therapy, saroglitazar resulted in improved glucose control and lipid levels over 56 weeks. It thus appears as a novel therapy for decreasing the cardiovascular risk in patients with type 2 diabetes [157].

Omega-3 fatty acids Due to a considerably diverse mode of action, compared to other lipid-lowering drugs, omega-3 fatty acids offer additional benefits when administered as an add-on to statins. Furthermore, it lacks clinically significant drug interactions with statins and, unlike fibrates and niacin, does not deleteriously affect liver function [158]. Icosapent ethyl, which is available as a prescription form of eicosapentaenoic acid (EPA) ethyl ester, is indicated as an adjunct to diet to reduce triglyceride levels in patients with severe (≥500 mg/dL) hypertriglyceridemia [159]. The recent 2021 Canadian Cardiovascular Society Guidelines strongly recommend the use of IPE to reduce cardiovascular event risk in patients with ASCVD, or those with diabetes and ≥1 CVD risk factors, with an elevated fasting triglyceride of 1.5–5.6 mmol/L in spite of treatment with maximally tolerated statin therapy [141].

The Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) was among the most significant clinical trials in recent history as it evaluated the potential benefits of EPA on cardiovascular outcomes in patients with hypertriglyceridemia. Nearly 8000 patients, already receiving a statin and LDL-C levels of 1.0–2.6 mmol/L (41–100 mg/dL) with cardiovascular risk factors like persistent hypertriglyceridemia (1.7–5.6 mmol/L; 150–499 mg/dL), and either established ASCVD or diabetes mellitus were analysed. Administration of EPA, although at a higher dose (2 g b.i.d.), was associated with ~25% relative risk reduction (p<0.001) in MACE compared to placebo (mineral oil) [160, 161]. ANCHOR, a 12-week phase 3 RCT, examined the effects of IPE 2 g/day or 4 g/day in >700 patients (73%, diabetes mellitus) with hypertriglyceridemia (200–500 mg/dL; although with normalised LDL-C, 40-100 mg/dL) on statin therapy. Significantly favourable effects on lipid parameters were noted with 4 g IPE, with no deterioration of glucose parameters in patients with diabetic dyslipidemia; the positive effects were enhanced in patients with poorly controlled diabetes [159].

A meta-analysis established that omega-3 fatty acids were associated with a significant decrease in apo AII (−8.0 mg/dL; 95% CI, −12.71 to −3.29, p=0.0009), triglycerides (−44.88 mg/dL; 95% CI, −82.6, −7.16, p<0.0001), and HDL (−2.27 mg/dL; 95% CI, −3.72 to −0.83; p=0.002) in the diabetic population compared to their control counterparts. These beneficial effects of omega-3 fatty acids could be attributed to the lowering of detrimental chronic inflammatory markers in people with diabetes and high-risk cardiovascular patients [162].

Special populations

Type 1 diabetes

Statins are recommended as first-line drug therapy in patients with type 1 diabetes with dyslipidemia as they are at high or very-high total CVD risk. If goals are not achieved with the maximum tolerated statin doses, adding ezetimibe is recommended. For patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, combining a PCSK9 inhibitor is recommended for secondary prevention. For very high-risk patients (with ASCVD or another major risk factor) not achieving their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended [45].

Pediatrics

In a metabolically unhealthy child with type 2 diabetes and obesity, a number of cardiovascular risk factors aggregate and intensify the risk of morbidity and mortality later in life [163]. The International Society for Pediatric and Adolescent Diabetes (ISPAD) and ADA advocate lipid screening either once glycemic control is achieved or after 3 months of starting therapy and yearly thereafter. Initial therapy should include optimising glucose control and MNT to avoid trans fats, and restricting calorie intake from fat to 25–30%, ~10% from monounsaturated fats, saturated fat to <7%, and cholesterol to <200 mg/day.

Recommended lipid goals include LDL-C <100 mg/dL, HDL-C >35 mg/dL, and triglycerides <150 mg/dL. A statin may be considered after the age of 10 years, in cases where despite lifestyle changes and MNT, LDL-C is >160 mg/dL (4.1 mmol/L), or LDL-C is >130 mg/dL (3.4 mmol/L) along with ≥1 CVD risk factors. Fibrates are commended when fasting triglycerides are >400 mg/dL or non-fasting triglycerides are >1000 mg/dL. Considering their demonstrated safety and efficacy in adolescents, fibrates are the preferred drug of choice for hypertriglyceridemia in this population. Despite the presence of aberrant levels of atherogenic triglyceride-rich lipoproteins, apo B, and non-HDL-C in pediatric type 2 diabetes, these are not measured for risk assessment or management [164, 165].

Pregnancy

Irregular maternal lipids during pregnancy are linked to adverse pregnancy outcomes for both the mother and the infant; maternal lipids in pregnancies are complicated by diabetes [166]. Regardless of the well-known clinical outcomes and advantages of a number of lipid-lowering therapies on atherogenic lipid profiles, there is a dearth of evidence in pregnancy. As a matter of fact, pregnant women are usually not included in clinical trials. Consequent to this, there are inadequate recommendations on the treatment of significant dyslipidemia in pregnant women, let alone in those with diabetes.

Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy, or during the breastfeeding period. Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or not using adequate contraception. However, for severe FH patients, bile acid sequestrants (which are not absorbed) and/or LDL apheresis may be considered [45]. Monitoring is commended at every trimester or within 6 weeks of treatment initiation, and close follow-up of the mother is strongly advised [167].

Elderly

The latest ESC guidelines recommend statin therapy in the elderly considering the predictable risk level and baseline LDL-C, keeping in mind the patients' health condition and risk of drug interactions. In people aged >75 years, if at high-risk or above, statin treatment may be considered for primary prevention. In cases of substantial renal impairment and/or potential for drug interactions, statin therapy should be initiated at a low dose and later up-titrated to attain LDL-C goals [45]. The AHA guidelines advocate continuation of statin therapy in those aged >75 years with diabetes mellitus and already on statin therapy [54].

The effects of statin therapy are independent of age, and are governed by the baseline ASCVD risk and absolute reduction in LDL-C. A meta-analysis of randomised trials of statin therapy noted a proportional reduction of 25% (RR, 0.75; 95% CI, 0.73–0.78) in the risk of coronary revascularisation procedures with statin therapy or a more intensive statin regimen/1.0 mmol/L lower LDL-C, which did not significantly vary across age groups (p_{trend}=0.6) [168]. Another meta-analysis by the CTT trial investigators revealed an explicit reduction in the risk of major vascular events with statin as well as non-statin LDL-C-lowering therapy among patients aged

75 years and older as that in younger patients. In addition to decreasing morbidity and mortality, there were no offsetting safety concerns with lipid-lowering therapies in this population [169].

Where there is substantial evidence supporting the use of statins for secondary prevention in the elderly population, that for statins as primary prevention is less convincing. Even with scarce data on older people with diabetes, there appears to be no substantial difference depending on their diabetes status [170].

Hepatic conditions

The concurrence of type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), also characterised by atherogenic dyslipidemia, exacerbates metabolic profile, thereby intensifying cardiovascular risk. The underlying disturbances of which include activation of hepatic de novo lipogenesis, hepatic overproduction of large triglyceride-rich very LDL and deferred clearance of triglyceride-rich lipoproteins; amplified secretion of these lipids into circulation results in diabetic dyslipidemia. Subsequently, all these factors, pooled with hyperglycemia, intensify CVD risk [171].

Hepatocellular damage is frequently used to assess the activity of plasma alanine aminotransferase (ALT). Mild ALT elevation is noted in 0.5–2% patients on statin therapy and is more common with high doses or potent statins. Such mild increase in ALT is not linked to changes in liver function or true hepatotoxicity. Since progression to liver failure is exceptional, guidelines no longer recommend routine ALT monitoring during statin treatment [45, 172]. Such trivial rise in ALT levels in asymptomatic statin users is clinically irrelevant. Statin therapy does not aggravate liver disease in those with mild ALT elevation on account of steatosis or NAFLD [173, 174]. Treatment with statins resulting in clinically apparent liver injury is very unusual and probably a class effect of statins [175]. Regardless of original observations of raised liver enzymes in clinical studies, the US FDA concluded that statins, as a class, do not negatively impact the liver; liver monitoring is hence not required. Nonetheless, statins are contraindicated in patients with active liver disease [176].

All guidelines acknowledge that lifestyle modifications play a vital role in the management of NAFLD but any medicines prescribed explicitly for NAFLD should be considered an off-label treatment [177]. In EVIDENCE IV—a phase II, randomised, USA-based study—saroglitazar 4 mg compared to placebo showed significant mean ALT reduction (−44.3 vs 4.1 %), HOMA IR (−5.1 vs −2.5), triglycerides (−70.3 vs −3.4), total cholesterol (−24.2 vs −4.4), and mean liver fat content (−4.2% vs −0.3%) (p<0.05 for all) [178]. A recently published, real-world study from India found saroglitazar to significantly improve transaminases and glycemic control as well as lipid parameters in NAFLD patients with diabetic dyslipidemia [179]. Saroglitazar could hence be considered a potential therapeutic option achieving the unmet need in the management of NAFLD.

Renal impairment

Statin therapy has not been associated with clinically substantial decline in renal function. Dose adjustment, keeping in mind the eGFR, may be judicious in those with severe kidney dysfunction on intensive statin regimes [175]. Additional analyses of the Japanese long-term prospective post-marketing surveillance LIVALO Effectiveness and Safety (LIVES) Study demonstrated an improvement in HbA1c levels in individuals with type 2 diabetes post long-term pitavastatin therapy and a significant upturn in eGRF in patients with chronic kidney disease [180]. A recent meta-analysis found both atorvastatin and rosuvastatin to improve GFR, whereas when compared to rosuvastatin, atorvastatin was more effective in reducing proteinuria [181].

With diabetes being a major cause of chronic renal failure worldwide, renal transplant has emerged as a dominant therapeutic option in the high-risk diabetic population with end-organ damage. The post-transplant period is complicated by pre-existing risk factors in these patients, which include severe insulin resistance, higher triglyceride levels, lower HDL-c, abnormalities in fibrinolysis and coagulation and endothelial dysfunction, thereby increasing cardiovascular mortality [182]. Moreover, the use of inhibitors of the mammalian target of rapamycin (m-TOR) immunosuppressants like sirolimus and everolimus further deteriorates hyperlipidemia [183].

The new drug inclisiran is an inhibitor of the mRNA transduction of the PCSK9 gene. It could be considered in clinical practice for the overall management of patients with dyslipidemia on account of its sustained action and evident ability to lower LDL-C [184, 185]. Results from the ORION-1 RCT pointed towards the possibility of PCSK9-targeted small interfering RNA (siRNA)–driven strategies as a novel therapeutic option for managing dyslipidemia both in the presence and absence of diabetes [186]. Inclisiran has been found to be safe in patients with mild, moderate, or severe renal impairment without the need for adjustments in dose or dosing regimen in patients with established ASCVD and in those at high risk for subsequent major adverse

cardiovascular events [185]. As the common cause of renal transplant is diabetic kidney disease, inclisiran could be included in the future for the management of dyslipidemia in diabetic patients with solid organ transplant (liver, kidney, etc.)

Taking into account the evidence available in patients with diabetic dyslipidemia and the experience and consensus of the experts, we recommend a step-wise approach for the management for diabetic dyslipidemia in the Indian population (Table 7).

Table 7 Step-wise management strategy for Indian patients with diabetic dyslipidemia

Step-wise management strategy for Indian patients with diabetic dyslipidemia		
Stratify risk for ASCVD	**Age** <40 years ≥40 years	**ASCVD risk** Moderate risk High risk
	ASCVD risk score	Use the QRISK3 tool
Set lipid goals as per ASCVD risk	**LDL-C** goals for patients at: Moderate risk High risk Very high risk	**Target goal** Baseline to 30% Baseline to <50% Baseline to >50% OR Equivalent to HDL-C
	Triglycerides	<150 mg/dL
Initiate and escalate lipid lowering drugs based on established goals	**LDL-C** *Statins* Moderate-intensity High-intensity *Ezetemibe* *PCSK9 inhibitors*	**Management** Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pitavastatin 2-4 mg Atorvastatin 40-80 mg Rosuvastatin 20-40 mg When goal not met with high-intensity statins In patients with established ASCVD
	Triglycerides Statins Fibrates* Saroglitazar* Omega 3-fatty acids*	At moderate- or high-intensity per CVD risk *Can be initiated when triglyceride is >200mg/dL

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; *PCSK9,* Proprotein convertase subtilisin-kexin type 9.

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Declarations

Competing interests The authors declare no competing interests.

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