



RSSDI guidelines on thyroid dysfunction and diabetes

Banshi Saboo¹ · Krishna Seshadri² · Sanjay Agarwal³ · Rakesh Sahay⁴ · Sujoy Ghosh⁵ · Shashank Joshi^{6,7}

Published online: 29 December 2021

© The Author(s), under exclusive licence to Research Society for Study of Diabetes in India 2021

Abstract

Diabetes and thyroid dysfunction coexist. There are several published guidances on screening detection and management of thyroid dysfunction in diabetes. The RSSDI has reviewed the evidence in the publish literature including India and provided a guidance to clinicians based on an expert review of the literature. Methods: A literature review was conducted of all published studies and the evidence was categorised by levels. The evidence was then reviewed by the expert group and a recommendation was provided with a grade. Summary: The relationship of hypothyroidism with T1DM is strong and warrants screening detection and treatment. While T2DM is frequently associated with thyroid dysfunction, the association is less strong. There appears to be a relationship between thyroid dysfunction and diabetes comorbidities. Drugs such as metformin may alter TSH levels. Thiazolidinediones may worsen dysthyroid orbitopathy. Gaps: The relationship between thyroid dysfunction and diabetes requires further study from a translational clinical and epidemiologic perspective leading to better evidence and recommendations.

Keywords Type 1 Diabetes · Type 2 Diabetes · Screening · Hypothyroidism · Thyrotoxicosis · Comorbidities · Thionamides · Insulin · Pregnancy

Abbreviations

AACE American Association of Clinical Endocrinology

ADA American Diabetes Association

AITD Autoimmune thyroid disorder

AITD Association of autoimmune thyroid disease

AMD Italian Association of Clinical Diabetologists

AME Association of Clinical Endocrinologists

AMPK Adenosine monophosphate-activated protein kinase

APS3 Autoimmune polyglandular syndrome type 3 variant

ATA American Thyroid Association

ATD Anti-thyroid drug

BTA British Thyroid Association

CRP C reactive protein

CVD Cardiovascular disease

DM Diabetes mellitus

DKD Diabetic kidney disease

FNAC Fine needle aspiration cytology

FT4 Free T4

GD Graves' disease

GLP-1 Glucagon-like peptide-1

GO Graves' orbitopathy

HbA1c Hemoglobin A1C

HLA Human leukocyte antigen

HT Hashimotos thyroiditis

LT4 Levothyroxine

NICE National Institute for Health and Care Excellence

OHAs Oral hypoglycemic agents

✉ Sanjay Agarwal
agarwalclinic@gmail.com

¹ Diabetes Care & Hormone Clinic Dia-Care, Ahmedabad-15 National President, RSSDI, New Delhi, India

² Clinical and Research Lead Apollo Sugar and Senior Consultant Endocrinology and Diabetes, Apollo Hospitals, Chennai, India

³ RSSDI, Aegle Clinic - Diabetes Care, A-11 Narsimha Housing Society, 194 Boat Club Road, Pune 411001, India

⁴ Department of Endocrinology, OSMANIA Medical College, Hyderabad, India

⁵ Department of Endocrinology, Institute of Post Graduate Medical Education and Research Kolkata, Room 9B, 4th floor. Ronald Ross building, 244 A J C Bose Road, Kolkata 700020, India

⁶ Indian College of Physicians, Mumbai, India

⁷ Joshi Clinic, Lilavati Hospital, Apollo Sugar Clinic & Bhatia Hospital, Mumbai, India

RAI	Radioactive iodine
RCTs	Randomized clinical trials
RSSDI	Research Society for the Study of Diabetes in India
SCH	Sub clinical hypothyroidism
SU	Sulfonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TD	Thyroid disorders
TES	The Endocrine Society
TFT	Thyroid function test
TPO-Ab	Thyroxine peroxidase-antibody
TRAb	TSH receptor autoantibodies
TSH	Thyroid-stimulating hormone

Introduction

Diabetes mellitus (DM) and thyroid disorders (TD) are two common endocrine disorders, which often co-exist in clinical practice [1]. In the South Asian population, 9.83% of individuals with type 2 diabetes mellitus (T2DM) have clinical hypothyroidism, and another 5.9% have subclinical hypothyroidism [2].

In India, the prevalence of hypothyroidism in T2DM patients is approximately 26.8% and that of subclinical hypothyroidism is 22.22% [3]. In a study conducted in Eastern India, the prevalence of subclinical hypothyroidism (SCH) was found to be much higher than overt hypothyroidism [4]. SCH was seen in 23% of the population and overt hypothyroidism was found in 3% [4]. Thyroid autoantibody results were positive in 13.1% patients [4]. In the presence of other comorbidities like hypertension, the risk of hypothyroidism in T2DM patients is elevated to almost 33.5% [3]. In patients with T1DM, the prevalence of thyroid disorders is much

higher than in patients with T2DM [5]. Anti-TPO and anti-thyroglobulin antibodies are positive in 51% and 25% of the patients respectively [5].

In patients with Diabetic complications such as diabetic kidney disease (DKD), the prevalence of hypothyroidism in the Indian population is 34.1%, of which, 29.3% of the cases had SCH [6]. Due to the higher prevalence of SCH in the Indian population, there is a need for regular screening and evaluation.

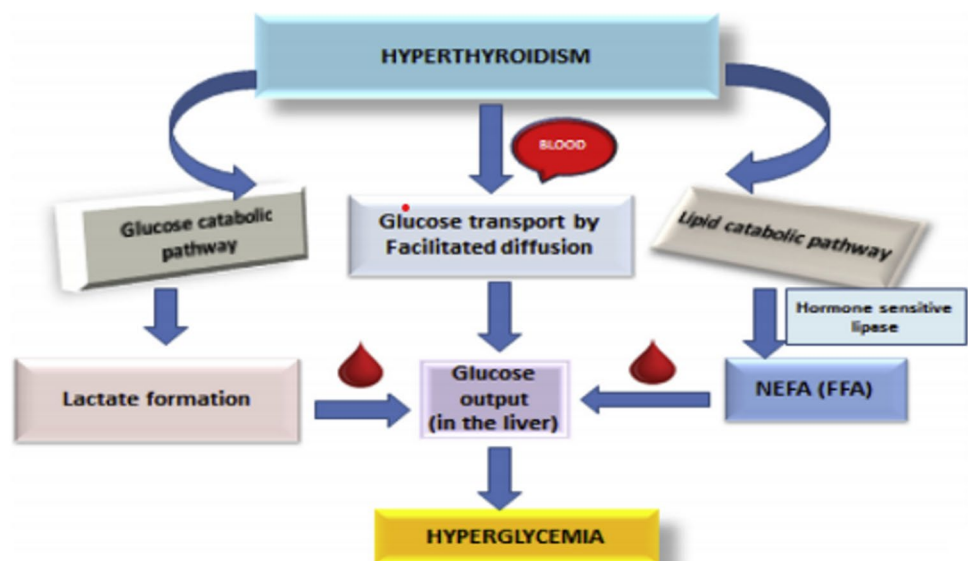
The correlation between TD and DM can be attributed to the overlapping functions of the thyroid and insulin hormones as well as the common autoimmune pathways between T1DM and hyperthyroidism (Fig. 1). This relationship is denominated as auto-immune polyglandular syndrome type 3 variant (APS3) where human leukocyte antigen (HLA) is the genetic determinant [7, 8].

The thyroid hormone is a regulator of the metabolic and energy expenditure processes, which is directly involved in the regulation of insulin secretion as well as the maintenance of glucose homeostasis. In patients with T2DM or insulin resistance, there is a surge in the levels of circulating insulin, which has a proliferative effect on the thyroid tissue [4, 9]. As a result, the size of the thyroid gland may increase and the risk of formation of nodules is elevated [4, 9].

The co-existence of TD and DM results in several complications, which become difficult to manage in clinical practice, especially in the absence of clear screening and treatment recommendations. Acute critical situations such as diabetes ketoacidosis, thyroid storm, and myxedema coma are reported in these cases, which necessitate emergency management following an early multi-disciplinary approach [11–13].

This guidance document will provide recommendations for the co-management, screening, and treatment of TD and DM in co-existence. It will be based on gathered clinical evidence stating levels of recommendations. Along with this, it

Fig. 1 The Relationship between hyperthyroidism and diabetes mellitus [10]



will combine evidence from recommendations gleaned from existing guidelines.

Methodology

RSSDI guidelines for screening and management of TD and DM were formed based on consensus-based recommendations of expert panelists including senior endocrinologists and diabetologists. These recommendations were supported by literature evidence and clinical overview obtained from existing Indian and international guidelines. Literature evidence included data and recommendations from Indian, international, and South Asian journals, which were gathered based on extensive literature research, primarily conducted in PubMed and Cochrane libraries. Published RCTs, systematic reviews, meta-analysis papers, cross-sectional studies, cohort studies, and expert opinion papers were considered for inclusion after thorough quality assessment. Standard guidelines that were referred in the paper included American Diabetes Association (ADA), American Thyroid Association (ATA), American College of Endocrinology (ACE), British Thyroid Association (BTA), and Indian

guidelines such as the Indian Thyroid Society (ITS) among many others. Based on the strength of evidence, grades were awarded to each recommendation (Tables 1 and 2).

The first draft of recommendations was prepared and circulated among RSSDI panelists to gather suggestions for improvements. All authors provided written recommendations for improvements in each section following the rigorous review of the document based on their expertise in the field. Following this, the draft was revised to address the identified gaps and was sent out to the authors for further review and feedback. Since all the expert authors approved the recommendations made in the second draft, it was finalized and sent out for publication.

Discussion

Summary of evidence

Thyroid screening recommendations for patients with type 1 diabetes mellitus

- A randomized observational study of 1310 patients suggested annual thyroid functional test (TFT) and thyroid-

Table.1 Levels of recommendation based on the type of literature evidence

Level	Type of evidence
I	Systematic review (with homogeneity) of RCTs OR RCTs with a large sample size depicting significant results
II	Systematic review (with homogeneity) of cohort studies OR Small-scale RCTs with unclear results OR consistent recommendations from multiple consensus guidelines (more than 2 national / international guidelines) OR randomized observational studies
III	Individual Cohort studies or clinical studies without randomization OR “Outcomes” research OR cross-sectional studies OR evidence gathered from existing consensus guidelines
IV	Systematic review (with homogeneity) of case-control studies OR Individual Case-control studies OR guidelines with improper evidence / lack of consensus OR retrospective analysis of patient data
V	Case series OR independent case study observations OR Expert opinion without explicit critical appraisal based on standard principles or narrative reviews or literature reviews without systematic analysis

Table.2 Grades of recommendation for guiding practice implications for the physicians

Grade	Descriptor	Quantifying evidence	Implications for practice
A	Strong recommendation	Level I evidence with consistent findings from multiple studies of levels II, III, or IV	Clinicians should follow grade A recommendations unless a clear and compelling rationale for an alternative approach is defined
B	Recommendation	Levels II, III, or IV evidence with consistent findings but lack of level I evidence	Clinicians should follow grade B recommendation while remaining alert to newly published evidence and sensitive to patient preferences
C	Option	Levels II, III, or IV evidence with inconsistent findings	While considering grade C evidence for individual practice, clinicians should be flexible in their decision-making approach, patient preferences and peer opinions should have a substantial influencing role
D	Option	Level V evidence: little or no systematic empirical evidence	For a grade D evidence, the physician must consider all options in their decision making and be alert to new published evidence that clarifies the benefit versus harm of the selected approach; patient preference should have a substantial influencing role

stimulating hormone (TSH) screening of all patients with T1DM [14]. It was observed that many patients who were diagnosed to be positive for TD during the study period were asymptomatic at the time of their presentation/screening; thus, indicating the need for regular annual screening [14].

- Expert opinion and literature reviews highlight the need for screening for TD in T1DM patients for their glycemic control as well as early TD control.
- A retrospective analysis of 200 patients indicates that TSH screening must be performed more frequently in T1DM patients with SCH [15].
- Based on practice variance and survey results obtained from 374 endocrinologists, biennial screening of TSH levels was recommended instead of annual screening keeping in mind cost reduction and efficient practice management [16].
- A cohort study of 58 patients suggested that annual TSH screening must be conducted in all patients with T1DM including men and women below the age of 50 years; although women above this age group are potentially at much higher risk compared to the general population, and have formed the primary focus for screening [17].
- In a cross-sectional study conducted in Eastern India ($n = 50$), it was found that 24% of participants with T1DM had TPO antibodies, but, were asymptomatic for TD [18]. Undiagnosed TD highlighted the need for regular TSH screening as well as TPO antibody evaluation at the time of diagnosis of T1DM [18].

Grade B recommendation

- Annual TSH screening along with TPOAb testing at the time of diagnosis of T1DM is recommended in all patients regardless of their age, clinical presentation, and gender.
 - In patients with SCH, more frequent TSH screening can be performed keeping in mind the economic considerations of the patient.
-

Thyroid screening recommendations for patients with type 2 diabetes mellitus

- A cross-sectional study of 364 patients with T2DM suggested that patients with “high-risk” condition must be screened for TD [2]. This includes patients with frequent hospital visits and poor glycemic control. Community-based TSH screening is not recommended in T2DM patients [2].
- Retrospective analysis of 339 patients with T2DM in the UK suggested targeted screening for patients with poor glycemic control [19].
- A cross-sectional study of 8258 participants identified elderly women with uncontrolled T2DM as high-risk patients and recommended annual TSH screening for them [20].

- TSH screening has also been recommended for patients with an autoimmune thyroid disorder (AITD) and Graves’ orbitopathy (GO) based on expert opinions gathered from individual cases [7].
- Some retrospective analysis and meta-analytical reviews have suggested the need for routine annual screening for TD in patients with T2DM for the diagnosis of SCH and overt hypothyroidism [21, 22].

Grade B recommendation

- There is insufficient evidence to support annual TSH screening in patients with T2DM.
 - Targeted screening for high-risk patients is thereby recommended including elderly women, patients with uncontrolled DM, patients with frequent hospital visits, those with existing comorbid conditions, and patients with prediagnosed AITD or GO.
-

Screening recommendations for thyroid cancer in patients with diabetes mellitus

- A meta-analysis of 16 cohort studies indicated that DM patients, especially women are at increased risk of thyroid cancer.
- According to the findings of a case-control prospective study of 772 patients, the risk of thyroid cancer was similar among patients with T2DM and prediabetes and suggested the need for screening for all patients with a positive family history [23].
- A strong link between DM and thyroid cancer has not yet been established; palpation of the thyroid gland in patients with is recommended with further workup that conforms to established practice.

Grade B recommendation

- Thyroid gland palpation is recommended in patients with DM with a positive family history of thyroid cancer regardless of their glycemic presentation.
-

Thyroid screening recommendations in children with type 1 diabetes mellitus

- A randomized controlled trial of 611 children and adolescents with T1D suggested that TPOAb and TGAb tests are best for the primary diagnosis of TD [24].
- A survey analysis of 374 respondents, suggested that TPOAb is the most suitable screening test for children and adolescents with T1DM, especially newly diagnosed cases [16].

- A cross-sectional study of 2858 subjects annual TSH screening was suggested for children and adolescents with T1DM [20].
- In a cross-sectional study with 100 children and adolescent patients with T1DM and 284 controls, both regular TSH screening and anti-TPO antibody analysis were useful for assessing thyroid dysfunction in the pediatric population [25].
- Children with frequent hypoglycemic episodes may be considered for TD evaluations [26].
- Since the thyroid disease may be asymptomatic all pediatric patients with T1DM must be screened for TD [25].

Grade A recommendation

- Children and adolescent patients with T1DM must be screened for TPOAb and TGAb at the time of diagnosis of T1DM.
- Thereafter, annual TSH evaluations must be performed.

Grade B recommendation

- Asymptomatic children and adolescents with T1DM need to be screened annually to rule out the risk of SCH.
 - For those with frequent hypoglycemic episodes, more frequent TSH assessment is recommended.
-

Treatment recommendations

Treatment with metformin in patients with thyroid disorders

- Metformin may reduce TSH levels, thyroid volume, and nodule size in patients with TD and DM, and can be safely recommended [21].
- In a retrospective analysis treatment with metformin was associated with a decrease in TSH levels in diabetic patients. This appears through the activation of adenosine monophosphate-activated protein kinase (AMPK) [27]. This study recommended a reduction in the dose of levothyroxine in patients on Metformin [27].
- In a pilot study of 11 patients, treatment with metformin was associated with reduction in TSH levels without impacting the levels of FT4 [28]. Re-evaluation of thyroid function every 6–12 months in patients on metformin was suggested [28].

Treatment with other oral hypoglycemic agents in patients with thyroid disorders

- Sulfonylureas (SU) may reduce iodine uptake, and may elevate thyroid hormone levels [29].
- Thiazolidinediones should to be avoided in patients with clinically active Graves' orbitopathy [7]. If treatment

with pioglitazone is necessitated, regular screening of TSH levels is warranted [7].

- Treatment with glucagon-like peptide-1 (GLP-1) receptor drugs must be avoided in patients with a family history of thyroid cancer. There is a possible risk of C cell hyperplasia and increase in medullary thyroid cancer [30].

Treatment with insulin in patients with thyroid disorders

- Insulin requirements of patients may be reduced or increased based on their TD; hence, their dose must be adjusted accordingly [31].

Levothyroxine dosage considerations in patients with diabetes mellitus

- In a cross sectional study in women from the treatment group as opposed to controls, it was observed that treatment with LT4 improved insulin resistance and endothelial dysfunction. It also reduced atherosclerotic risk markers.
- In a large multi-center RCT involving 611 children and adolescents, it was observed that L-T4 treatment reduced the thyroid volume in pediatric patients with AIT and T1D, but had no effect on thyroid function and serum autoantibody levels [32]. However, it helped in the prevention of goiter and had positive treatment outcomes [32].
- In a retrospective analysis of 100 patients with SCH, it was found that LT4 administration normalized the TSH levels lowering the levels of fasting and postprandial glucose levels thereby reducing fasting hyperinsulinemia, CRP and total lipids [25].
- In a retrospective, non-randomized study of 257 patients with diabetic nephropathy, it was found that Levothyroxine therapy at a starting dose of 50 µg/day for patients aged < 60 years and 25 µg/day for older patients helped in reducing the risk of CVD [33].

Treatment with anti-thyroid medications in patients with diabetes mellitus

- Treatment with anti-thyroid drugs (ATDs) or radioactive iodine (RAI) do [34]. Do not have different impacts on glycemic control and may be used based on clinical indication and patient preference.
- In patients with Graves' disease thionamid therapy will help control glycemia in addition to control of the hyperthyroid state [29].

Grade A recommendation

- Levothyroxine at a suitable starting dosage is recommended for adult and pediatric patients with hypothyroidism and DM for thyroid hormone modulation as well as improvement in insulin resistance and management of cardiovascular risk factors.
- 1.6 µg / kg per day is a suitable dosage for euthyroid children with HT.
- Metformin can be safely prescribed in patients with DM and TD; however, regular monitoring of thyroid function is recommended in patients on who are thyroxine and metformin.
- Other OHAs such as SUs, GLP-1 receptor drugs, and pioglitazone must be selected in caution because of their respective risks of hyperthyroidism, medullary thyroid cancer and complications of GO.

Grade B Recommendation

- In patients on a Metformin + Levothyroxine regimen, the dose of Levothyroxine may need to be reduced.
- Early insulin dosage is recommended for elderly patients along with necessary dose reduction.
- Clinical indication and patient preference can indicate treatment choice of ATD vs radioiodine ablation.

Summary of Indian evidence**Thyroid screening recommendations for patients with type 1 diabetes mellitus**

- For Indian population, it has been recommended that annual TSH screening must be performed in all patients with T1DM at the time of their diagnosis including euthyroid subjects [16, 21].
- A comparative cross-sectional study of 30 participants with T1DM suggested that regular TSH screening must be conducted in patients with T1DM for an early diagnosis of SCH [34].
- A cross-sectional study of 66 Indian women suggested TSH levels between 3.1 and 6.2 mIU/L carried the same risk of adverse fetomaternal outcomes as TSH levels < 3 mIU/L [35]. Trimester-specific TSH range in pregnant Indian women was not found to be statistically different from non-pregnant women in a cross-sectional study of 300 women [36].

Thyroid screening recommendations for patients with type 2 diabetes mellitus

- A cross-sectional study of 234 Indian patients recommended TSH screening in T2DM patients with uncontrolled blood glucose levels [4].
- A cross-sectional observational study of 100 patients supported screening for TD in T2DM [17]. Patients with existing neuropathy and nephropathy appeared are at higher risk of TD [21].

- In a cross-sectional study of 1508 patients, conducted across multiple clinical centers in India, the authors emphasized need for regular TSH screening in patients with T2DM and hypertension [37].
- A retrospective analysis of 1152 patients in Thiruvananthapuram reflect a high prevalence of clinical and sub-clinical hypothyroidism in T2DM patients indicating the need for regular TSH screening [38].

Screening for diabetes mellitus in patients with thyroid disorders

- In an observational cross-sectional study of patients with TD and DM, regular screening for diabetic neuropathy and nephropathy was recommended because of their high risk in the Indian population [4].

Grade B recommendations

- Annual TSH screening must be performed in Indian patients with T1DM, especially in pregnant women in whom normal TSH cut-offs must be considered.
- For patients with T2DM, annual TSH screening is recommended in euthyroid patients with detectable TPO antibodies or TSH levels above 2.5 mU/L.
- Patients with TD and DM must regularly be screened for nephropathy and neuropathy.
- High-risk patients including patients with hypertension, neuropathy, nephropathy, and uncontrolled blood glucose levels maybe screened annually.
- Individual case presentations of the patient must be considered to decide the frequency of TSH screening since the burden of hypothyroidism is much higher in the Indian population.

Treatment recommendations**Treatment with insulin in patients with thyroid disorders**

Levels of insulin resistance along with the physiological, and biochemical profile of the patient as well as the impact on treatment on the thyroid status of the patient must be considered before insulin administration [10].

Recommendation of other guidelines and societies**Thyroid screening recommendations for patients with type 1 diabetes mellitus**

- International guidelines including AACE, ATA, and TES recommend screening for anti-TPO antibodies at the time of diagnosis of T1DM. If anti-TPO antibodies are present, annual TSH screening must be performed [39].

- BTA Guidelines recommend TSH screening along with antibody analysis at baseline followed by annual TSH screening, which has been supported by other guidelines and literature reviews [26].
- ADA recommends annual TSH screening in patients with T1DM who have negative TPO Abs evaluation. For those with positive TPO antibodies, more frequent screening (at 6 months) is recommended, especially in patients with goiter and/or unexplained glycemic variation. In addition to TSH and anti-TPO analysis, thyroglobulin screening and serological examination are also recommended by the ADA [7, 29].
- ADA guidelines recommend performing repeat TSH screening in patients with T1DM at 1 year after achieving glycemic control. For patients with AITD, A1C levels must be evaluated regularly [29].
- The Indian Thyroid Society describes type 1 diabetes as a risk factor for hypothyroidism in pregnancy. Untreated hypothyroidism has also been identified as a risk factor for diabetes in pregnancy and thus screening for both T1DM and TD is recommended in pregnant Indian women [29, 36].
- ADA recommends thyroid gland palpation in patients with T2DM at the time of diagnosis. For those with dyslipidemia and those above 50 years of age, TSH screening is also recommended [7].
- Italian Association of Clinical Endocrinologists suggests regular TSH screening in T2DM patients above the age of 65 years, especially those with macrovascular complications. Ultrasound screening is not recommended [29].

Grade B recommendation

- In patients with T1DM, anti-TPO test at the time of diagnosis along with annual TSH screening is recommended henceforth.
 - For patients with T2DM, TSH screening at the time of diagnosis is recommended, followed at every 5 years in individuals above the age of 35 years.
 - Annual screening can be recommended in high-risk cases including patients with macrovascular complications, SCH, positive TPOAb, and dyslipidemia.
-

Thyroid screening recommendations for pregnant women with type 1/type 2 diabetes mellitus

Thyroid screening recommendations for type 2 diabetes mellitus

- The UK National Screening Committee does not recommend screening for TD in the general population since there are no established normal levels of thyroid hormones [40].
- The US Guidelines also state that there is insufficient evidence to assess the balance of benefits and harms of screening for thyroid dysfunction in non-pregnant asymptomatic adults with T1DM. While T1DM was identified to be a risk factor for TD, T2DM was not found to have a significant association [41].
- The National Institute for Health and Care Excellence (NICE) guidelines for T2DM and the American Diabetes Association (ADA) Standards of Medical Care in Diabetes do not provide any guidance for the routine monitoring of thyroid function in T2DM [42].
- The British Thyroid Association has recommended screening at the diagnosis of T2DM along with regular screening in patients with SCH [26].
- The American Thyroid Association recommends screening for thyroid disorders every 5 years in adults aged ≥ 35 years regardless of their diabetes status. This recommendation is supported by a cost-utility analysis based on a decision model for the US healthcare system [43].
- ATA and TES recommend thyroid screening every 5 years for individuals above the age of 35 years. For patients with T2DM, TSH screening must be performed at the diagnosis of DM, and 5 years henceforth [39].
- Italian Guidelines, AME, and AMD recommend TSH and TPOAb screening in women with T1DM who are for planning pregnancy [29]. If this stage has already passed and the woman is pregnant, TSH and TPOAb screening is recommended at the earliest stage. In the case of positive TPOAbs and normal serum TSH during pregnancy, TSH levels must be evaluated at 3, 6, and 12 months postpartum [29].
- BTA Guidelines recommend TSH and TPOAb screening in patients with T1DM at the beginning of pregnancy followed by postpartum evaluations at 3, 6, and 12 months. For patients with T2DM, the frequency of this screening remains unclear [35].
- AACE recommends that TSH levels must be evaluated in all women of the childbearing age group with either T1DM or T2DM [39]. If this has not been achieved, screening during the first trimester is strongly recommended [39].
- ATA and AACE guidelines recommend TSH and anti-TPO antibody screening at the beginning of pregnancy for women with GDM/prediabetes and T2DM in addition to screening patients with T1DM [7]. Women with risk factors such as central obesity are also recommended to be screened at the beginning of pregnancy regardless of their diabetic status of control [7].
- ATA guidelines recommend that in women with T1DM, reflex anti-TPO evaluation needs to be conducted if TSH levels are between the range of 2.5 to 10 mU/L [21].

Thyroid screening recommendations for children and adolescents with type 1 diabetes mellitus

- ISPAD Guidelines recommend that screening for TD must be initiated at 10 years of age or at the beginning of puberty and must be performed at every 2 years. In children with additional risk factors such as obesity or a family history of TD, more frequent screening may be needed [7].
- Italian Guidelines, AME and AMD recommend TSH, TPOAb, and TgAb analysis at the time of diagnosis of T1DM in children. TSH and TgAb must be recommended in TPOA-negative children as well [29]. Annual TSH evaluation is recommended in TPOAb-positive children, and biennial evaluation is suited for negative cases [29].

Treatment recommendations for diabetes mellitus and thyroid disorders in co-existence

- AME and AMD indicated that treatment with metformin reduces the incidence of thyroid cancer and thus recommended its use in patients with DM and TD [29].
- European and American Thyroid Associations recommend treating both overt and subclinical hyperthyroidism including grade 1 subclinical hyperthyroidism in patients with diabetes if TSH levels are persistently low [29].

Grade B recommendation

- In women with T1DM, TPOAb screening is recommended during the planning of pregnancy. If this is missed, the test must be performed at the earliest within the first trimester.
 - After parturition, TPOAb screen must be repeated at 3, 6, and 12 months, followed by regular annual TSH screening as preferred in T1DM patients.
 - In women with T2DM, central obesity/a history of prediabetes as well, TPOAb is recommended at the beginning of pregnancy.
 - In children and adolescents, annual TSH screening is recommended in patients with positive TPOAb at the time of diagnosis of T1DM. If TPOAb test is negative, biennial evaluation will be suitable.
-

Final recommendation of RSSDI

Recommendations for screening for thyroid disorders in patients with type 1 diabetes

- RSSDI recommends screening for anti-TPO antibodies as well as TSH levels at the time of diagnosis of T1DM in all patients including euthyroid patients, young patients and males. In those with positive anti-TPO, annual TSH screening is recommended. In patients with negative TPOAb test, TSH screening can be performed once in 2 years.

- In high-risk patients (uncontrolled DM, high glycemic variability, or symptoms of goiter) with positive anti-TPO evaluation, more frequent TSH screening may be necessary based on their individual risks.

Screening for thyroid disorders in patients with type 2 diabetes

- Routine screening for TD is not necessary for patients with T2DM, but it may be considered depending on their clinical profile.
- For patients above the age of 35 years without any additional risks, TSH screening is recommended every 5 years.
- Patients with TSH > 2.5 mU/L or positive anti-TPO test must be considered for annual screening.
- For patients with uncontrolled diabetes mellitus, presence of comorbid conditions like hypertension, dyslipidemia, poor glycemic control, existing complications like neuropathy, and nephropathy or macrovascular complications and those frequently visiting the hospital settings for poorly managed T2DM, annual TSH screening is recommended.
- In patients above the age of 65 years, especially women, annual TSH screening is recommended, especially in the presence of macrovascular complications/comorbidities.
- In those above the age of 50 years, annual screening may be needed if there is a history of dyslipidemia.

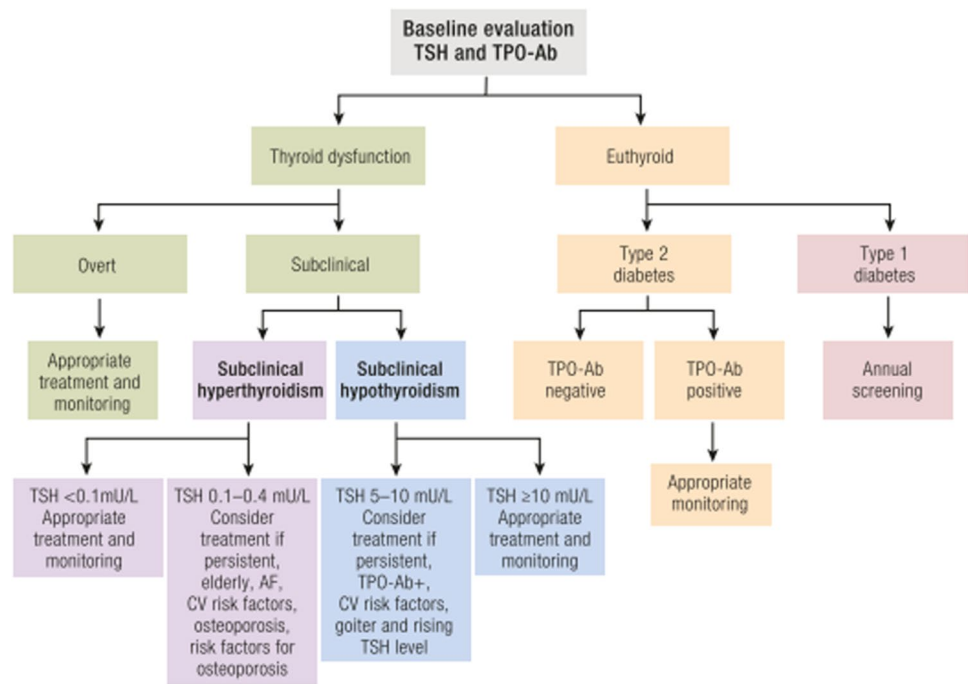
RSSDI recommendations for screening pregnant women and children with diabetes mellitus

- Pregnant women must be screened for TPOAb before pregnancy or at least during the first trimester. TSH screening is also recommended along with TPOAb at the time of planning of pregnancy in women with T1DM.
- Women with positive TPOAb must be screened at 3 and 6 months at (12) months postpartum.
- In patients with T2DM, prediabetes, GDM, and risk factors such as obesity may also be screened for TD during the first trimester of pregnancy regardless of their levels of diabetes control or a euthyroid profile.
- TPOAb evaluation as well as TSH screening is recommended in children and adolescents at the time of diagnosis of T1DM.
- In children with positive TPO antibodies, annual TSH screening is recommended whereas in children with negative TPOAb, TSH evaluation can be performed every 2 years.

RSSDI recommendations for screening thyroid cancer

- Palpation of the thyroid gland must be performed at the time of diagnosis of diabetes mellitus in patients with a family history of cancer.

Fig. 2 Summary of screening, diagnosis and treatment recommendations for co-existing TD and DM [7]



RSSDI treatment recommendations for patients with thyroid disorder

- Metformin can be safely prescribed in patients with DM and TD for regulating blood glucose levels when prescribed at standard dosages.
- The daily dose of insulin must be calculated based on individual profile of the patient. Insulin dose reduction may be needed in some patients (Fig. 2).

Gaps and directions for future research

A major gap identified during the preparation of the guidance document was the lack of RCTs with clinically significant results that provide clear recommendations for screening of thyroid disorders in Indian patients with diabetes mellitus, especially T2DM. Although evidence from clinical trials have been included in this paper, it was observed that no large-scale multi-centre RCTs have so far been conducted. Further, the negative impact of lack of screening have not been clearly identified. Thus, future research must be planned in the form of multi-centre RCT with a large sample size where the symptom profile of patients who were screened annually for TSH levels is compared with patients who were not scheduled for screening to state the strength of this recommendation. This research must involve patients with both T1DM and T2DM so that clear recommendations can be formed for the latter population, which is missing in most consensus guidelines.

Acknowledgment

Extended Panel of Experts: Rajeev Chawla, Vasanth Kumar, Vijay Viswanathan, Anuj Maheshwari, Brij Makkar, Vijay Panikar, Sunil Gupta, Anand Moses, JK Sharma, L. Sreenivasa Murthy, Pratap Jethwani, Sanjay Reddy, Bikash Bhattacharjee, Shalini Jaggi, Sudhir Bhandari, Sanjay Kalra, R.V. Jayakumar, A. Unnikrishnan, Sarita Bajaj, Manoj Chadha, Ganapathi B. Mallya, Mithun Bhartia, Prakash Keswani, Anil Bhansali, A.H Zargar, Usha Sriram, Rajesh Rajput

References

1. Chaker L, Ligthart S, Korevaar TI, Hofman A, Franco OH, Peeters RP, Dehghan A. Thyroid function and risk of type 2 diabetes: a population-based prospective cohort study. *BMC Med.* 2016;14(1):1–8.
2. Subekti I, Pramono LA, Dewiasty E, Harbuwono DS. Thyroid dysfunction in type 2 diabetes mellitus patients. *Acta Med Indonesiana.* 2018;49(4):314.
3. Kumar S, Singhal V, Gupta H, Kumar KR, Dara N, Ali I. A study of prevalence of thyroid disorders in patients with type 2 diabetes mellitus. *Open Access J Endocrinol.* 2019. <https://doi.org/10.23880/oaje-16000142>.
4. Pramanik S, Ghosh S, Mukhopadhyay P, Bhattacharjee R, Mukherjee B, Mondal SA, Ghosh I, Bari R, Chowdhury S. Thyroid status in patients with type 2 diabetes attending a tertiary care hospital in Eastern India. *Indian J Endocrinol Metab.* 2018;22(1):112.
5. Basu M, Pandit K, Banerjee M, Mondal SA, Mukhopadhyay P, Ghosh S. Profile of auto-antibodies (Disease related and other) in children with type 1 diabetes. *Indian J Endocrinol Metab.* 2020;24(3):256.
6. Bajaj S, Purwar N, Gupta A, Gupta P, Srivastava A. Prevalence of hypothyroidism in diabetic kidney disease and effect of thyroid hormone replacement on estimate glomerular filtration rate. *Indian J Endocrinol Metab.* 2016;20(6):795.

7. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocr Rev*. 2019;40(3):789–824.
8. Ardestani SK, Keshteli AH, Khalili N, Hashemipour M, Barekattain R. Thyroid disorders in children and adolescents with type 1 diabetes mellitus in isfahan, iran. *Iran J Pediatr*. 2011;21(4):502.
9. Ogbonna S, Ezeani I. Risk factors of thyroid dysfunction in patients with type 2 diabetes mellitus. *Front Endocrinol*. 2019;10:440.
10. Jayanthi R, Srinivasan AR. Biochemical isthmus [nexus] between type 2 diabetes mellitus and thyroid status—an update. *Diabetes Metab Syndr Clin Res Rev*. 2019;13(2):1173–7.
11. Kim JJ, Kim EY. Myxedema coma precipitated by diabetic ketoacidosis after total thyroidectomy: a case report. *J Med Case Rep*. 2019;13(1):50.
12. Ikeoka T, Otsuka H, Fujita N, Masuda Y, Maeda S, Horie I, Ando T, Abiru N, Kawakami A. Thyroid storm precipitated by diabetic ketoacidosis and influenza a: a case report and literature review. *Intern Med*. 2017;56(2):181–5.
13. Al-Rubaye HF. Thyroid dysfunction in patients with uncontrolled type 2 diabetes mellitus. *Mustansiriyah Med J*. 2019;18(1):16–9.
14. Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. *Diab Med*. 1995;12(7):622–7.
15. Elmenshawi I, Alotaibi S, Alazmi A, Alazmi A, Alruwaili F, Alazmi N, Alazmi Z. Prevalence of thyroid dysfunction in diabetic patients. *J Diab Metab Disord Control*. 2017;4:55–6.
16. Wolfram PM, Narala B, Wyatt DT. Practice variance in thyroid screening of youth with type 1 diabetes mellitus. *Hormone Res Paediatr*. 2018;90(4):266–9.
17. Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A, Kitabchi AE. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. *Diab Care*. 2003;26(4):1181–5.
18. Sanyal D, Majumder A, Chaudhuri SR, Chatterjee S. Thyroid profile and autoantibodies in Type 1 diabetes subjects: A perspective from Eastern India. *Indian J Endocrinol Metab*. 2017;21(1):45.
19. Palit T, Heald AH, Fryer AA, Duff CJ. Screening for thyroid disease in patients with type 2 diabetes mellitus: An evaluation of current practice. *Ann Clin Biochem*. 2020;57(3):242–5.
20. Cho JH, Kim HJ, Lee JH, Park IR, Moon JS, Yoon JS, Lee IK, Won KC, Lee HW. Poor glycemic control is associated with the risk of subclinical hypothyroidism in patients with type 2 diabetes mellitus. *Korean J Internal Med*. 2016;31(4):703.
21. Kalra S, Aggarwal S, Khandelwal D. Thyroid dysfunction and type 2 diabetes mellitus: screening strategies and implications for management. *Diab Ther*. 2019;1:1.
22. Han C, He X, Xia X, Li Y, Shi X, Shan Z, Teng W. Subclinical hypothyroidism and type 2 diabetes: a systematic review and meta-analysis. *PLoS One*. 2015;10(8):e0135233.
23. Grimmichova T, Haluzik M, Vondra K, Matucha P, Hill M. Relations of prediabetes and type 2 diabetes to the thyroid cancer. *Endocr Connect*. 2020;1:1.
24. Karges B, Mucic R, Knerr I, Ertelt W, Wiesel T, Hub R, Neu A, Klinghammer A, Aufschild J, Rapp A, Schirbel A. Levothyroxine in euthyroid autoimmune thyroiditis and type 1 diabetes: a randomized, controlled trial. *J Clin Endocrinol Metab*. 2007;92(5):1647–52.
25. Bilic-Komarica E, Beciragic A, Junuzovic D. Effects of treatment with L-thyroxin on glucose regulation in patients with subclinical hypothyroidism. *Med Arch*. 2012;66(6):364.
26. Kadiyala R, Peter R, Okosieme OE. Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. *Int J Clin Pract*. 2010;64(8):1130–9.
27. Meng X, Xu S, Chen G, Derwahl M, Liu C. Metformin and thyroid disease. *J Endocrinol*. 2017;233(1):R43–51.
28. Cappelli C, Rotondi M, Pirola I, Agosti B, Gandossi E, Valentini U, De Martino E, Cimino A, Chiovato L, Agabiti-Rosei E, Castellano M. TSH-lowering effect of metformin in type 2 diabetic patients: differences between euthyroid, untreated hypothyroid, and euthyroid on L-T4 therapy patients. *Diab Care*. 2009;32(9):1589–90.
29. Guastamacchia E, Triggiani V, Aglialoro A, Aiello A, Ianni L, Maccario M, et al. Italian Association of Clinical Endocrinologists (AME) & Italian Association of Clinical Diabetologists (AMD) position statement: diabetes mellitus and thyroid disorders: recommendations for clinical practice. *Endocrine*. 2015;49:339–52.
30. Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. *Diab Care*. 2010;33(2):428–33.
31. Mitrou P, Raptis SA, Dimitriadis G. Insulin action in hyperthyroidism: a focus on muscle and adipose tissue. *Endocr Rev*. 2010;31(5):663–79.
32. Dörr HG, Bettendorf M, Binder G, Karges B, Kneppo C, Schmidt H, Voss E, Wabitsch M, Dötsch J. Levothyroxine treatment of euthyroid children with autoimmune hashimoto thyroiditis: results of a multicenter, randomized, controlled trial. *Hormone Res Paediatr*. 2015;84(4):266–74.
33. Seo C, Kim S, Lee M, Cha MU, Kim H, Park S, Yun HR, Jhee JH, Kee YK, Han SH, Yoo TH. Thyroid hormone replacement reduces the risk of cardiovascular diseases in diabetic nephropathy patients with subclinical hypothyroidism. *Endocr Pract*. 2018;24(3):265–72.
34. Vyakaranam S, Vanaparthy S, Nori S, Palarapu S, Bhongir AV. Study of insulin resistance in subclinical hypothyroidism. *Int J Health Sci Res*. 2014;4(9):147.
35. Joshi D, Dewan R, Bharti R, Thariani K, Sablok A, Sharma M, Biswas K, Batra A. Feto-maternal outcome using new screening criteria of serum TSH for diagnosing hypothyroidism in pregnancy. *J Clin Diagn Res: JCDR*. 2015 9(4):QC01
36. Pramanik S, Mukhopadhyay P, Bhattacharjee K, Bhattacharjee R, Mukherjee B, Mondal SA, Bandhopadhyay S, Biswas S, Chowdhury S, Ghosh S. Trimester-specific reference intervals for thyroid function parameters in Indian pregnant women during final phase of transition to iodine sufficiency. *Indian J Endocrinol Metab*. 2020;24(2):160.
37. Talwalkar P, Deshmukh V, Bhole M. Prevalence of hypothyroidism in patients with type 2 diabetes mellitus and hypertension in India: a cross-sectional observational study. *Diab Metab Syndr Obes Targets Ther*. 2019;12:369.
38. Nair A, Jayakumari C, Jabbar PK, Jayakumar RV, Raizada N, Gopi A, George GS, Seena TP. Prevalence and associations of hypothyroidism in Indian patients with type 2 diabetes mellitus. *J Thyroid Res*. 2018;9:2018.
39. Johnson JL. Diabetes control in thyroid disease. *Diab Spectrum*. 2006;19(3):148–53.
40. UK National Screening Committee The UK NSC recommendation on thyroid disease screening in adults. <https://legacyscreening.phe.org.uk/thyroid> (accessed 11 Sep 2020)
41. LeFevre ML. Screening for thyroid dysfunction: US Preventive Services Task Force recommendation statement. *Ann Internal Med*. 2015;162(9):641–50.
42. McGuire H, Longson D, Adler A, Farmer A, Lewin I. Management of type 2 diabetes in adults: summary of updated NICE guidance. *Bmj*. 2016;353:i1575.
43. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, Smith SA, Daniels GH. American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Internal Med*. 2000;160(11):1573–5.