

Relationship between autoimmune thyroid dysfunction and diabetes mellitus type 1 in pediatric population

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Abstract

Type 1 diabetes (T1D) and autoimmune thyroid diseases (AITD) frequently occur together within families and in the same individual in most parts of the world. Type 1 diabetes is the most prevalent chronic disease in the population under 18 years of age although there are no reliable data available from many countries. The co-occurrence of T1D and AITD in the same patient is one of the variants of the autoimmune diseases. The two major autoimmune thyroid diseases (ATDs) include Graves' disease (GD) and autoimmune thyroiditis (AT); both of which are characterized by infiltration of the thyroid by T and B cells reactive to thyroid antigens, by the production of thyroid autoantibodies and by abnormal thyroid function (hyperthyroidism in GD and hypothyroidism in AT). While the exact etiology of thyroid autoimmunity is not known, it is believed to develop when a combination of genetic susceptibility and environmental encounters leads to breakdown of tolerance. It is important to recognize thyroid dysfunction at an early stage by maintaining an appropriate index of suspicion. The presence of both thyroid dysfunction and diabetes mellitus is increasing in prevalence and is seen among many patients. Many different studies have been performed globally to ascertain this relationship. Our aim in this article is to access the correlation between thyroid dysfunction and Type 1 diabetes mellitus and to assess the prevalence of T1DM-associated autoimmune diseases in children and adolescents and their impact on the course of T1DM. We also present suggestions concerning screening tests.

Methods: Using internet search, a comprehensive literature review was done and words such as diabetes mellitus, autoimmune thyroid, hypothyroidism, hyperthyroidism, thyroid antibodies, and thyroid problems were searched.

The references of the relevant articles on this subject were also searched for further information.

Results: Analyses of results of various studies from various parts of the world were considered and their prevalence was noted to access the correlation between thyroid dysfunction and diabetes mellitus. Subclinical hypothyroidism is seen as the commonest thyroid problem among female type 1 diabetics.

Conclusion: There is a strong relationship between thyroid dysfunction and Type 1 diabetes mellitus.

Key words: autoimmune Thyroid; Type 1 diabetes; Antibodies; Dysfunction

Introduction

Type 1 diabetes mellitus is an autoimmune disease. It is the most common type of diabetes in children and adolescents. It is also the most common chronic disease in children in the developed countries. The illness is characterized by the body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas. Globally, it is estimated that there are almost 500,000 children aged under 15 years with type 1 diabetes, with large geographical variations in incidence [1]. Children with type 1 diabetes mellitus (T1DM) are more prone to develop other organ-specific autoimmune diseases, among which autoimmune thyroiditis (AIT) is more frequently encountered [2]. Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with type 1 diabetes [3].

At the time of diagnosis 25% of children with type 1 diabetes have thyroid autoantibodies [4]. Females with T1DM are more prone to hypothyroidism than males [5]. Post-pubertal T1DM patients also have a higher incidence of TD when compared to pre-pubertal T1DM children [6]. T1DM is associated with several autoimmune diseases such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, celiac disease (CD), and pernicious anemia, which are more prevalent in this type of diabetes when compared to the healthy population [7].

The autoimmune thyroid disorders and T1DM have similar pathogenesis and inherited through families. Hence, they may have genetic factors [8]. At the time of diagnosis 25% of children with type 1 diabetes have thyroid autoantibodies [9]. Thyroiditis is often clinically silent but it may progress to autoimmune thyroid disease (AITD), recognized as overt or subclinical hypothyroidism or hyperthyroidism [10]. Although serum TSH screening is more sensitive for detecting thyroid abnormalities in children and adolescents with type 1 diabetes [11] the presence of positive serum anti TPO antibodies may be an earlier marker for thyroid disease, as it is specific and sensitive; therefore, patients with positive antibodies should be monitored for serum TSH elevation at yearly intervals. In addition thyroid function tests may be misleading (euthyroid sick syndrome) if performed at the time of diagnosis owing to the effect of previous hyperglycemia, ketosis or ketoacidosis, weight loss, etc. Therefore, if performed at diagnosis and found to be slightly abnormal, thyroid function tests should be repeated soon after a period of metabolic stability and achievement of glycemic targets; also subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia [12]. The American Diabetes Association (ADA) recommended screening TSH after diagnosis of diabetes and then after every one to two years. It also recommended that patients found to have positive anti-TPO antibodies with normal thyroid function tests should be screened more frequently, every six months to a year [13].

Pathogenesis of Autoimmune Diseases

Advances in understanding the molecular and cellular biology of disease have led to greater comprehension of the pathogenesis of these autoimmune disorders.

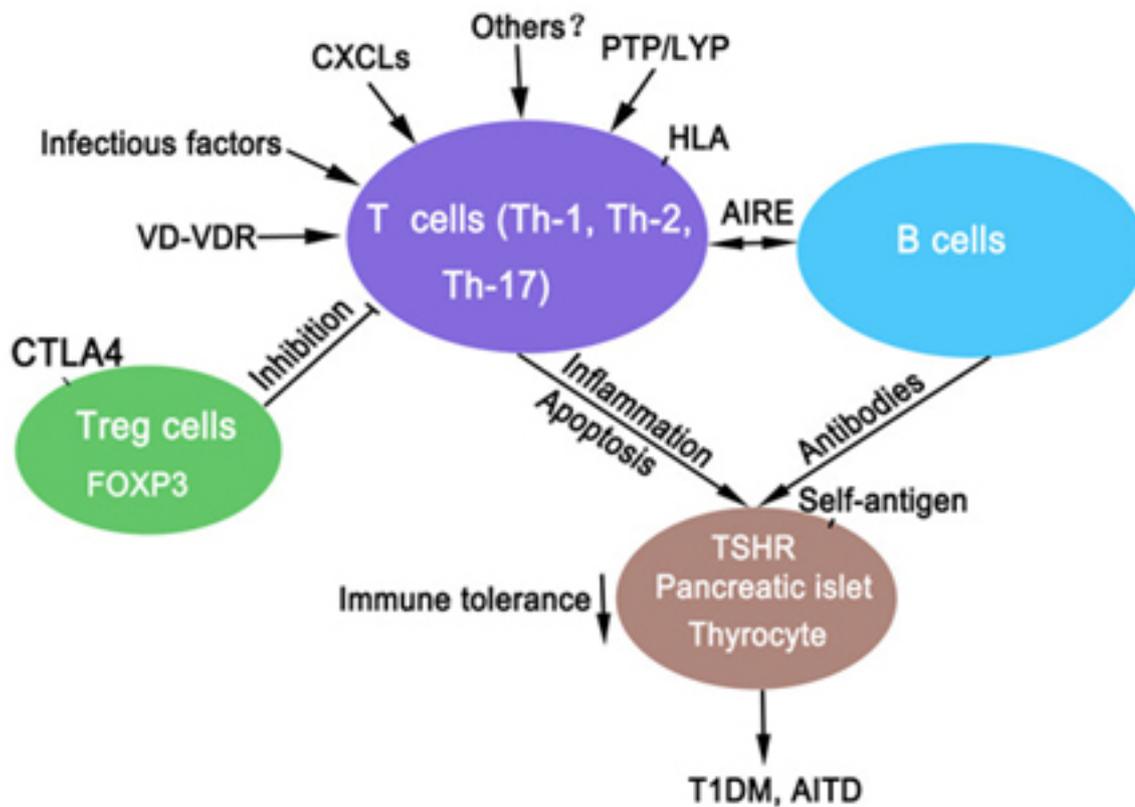
Many studies confirm the association between autoimmune thyroid dysfunction and type 1 diabetes. The results indicate that all subjects with type 1 diabetes should undergo annual screening by serum TSH measurement to detect asymptomatic thyroid dysfunction, particularly those with positive TPO antibodies. Natural autoantibodies provide immediate protection against infection and also prevent inflammation by facilitating the clearance of oxidized lipids, oxidized proteins, and apoptotic cells [14].

Autoimmune diseases are typically multi-etiological entities, where genetic and environmental abnormalities along with derailed immunoregulatory processes contribute to the development of disease. In the healthy immune system, various tolerance mechanisms, such as activation induced cell death, anergy, or clonal ignorance, play a protective role to prevent the activation of self-reactive lymphocytes [15]. In autoimmune conditions, self-reactive lymphocytes may not be subjected to the aforementioned tolerance mechanisms raising the possibility of the survival and activation of autoreactive T and B cells upon autoantigen encounter [15,16]. However, there is a fine line between autoimmune processes, which also appear in healthy individuals and manifested autoimmune diseases. In autoimmune diseases, one or several tolerance mechanisms permanently fail due to the constellation of various environmental factors, specific HLA- and non-HLA genes and/or derailed immunoregulatory processes, leading to the persistence of self-reactive T- and B-cell clones and ultimately organ damage [16-17]. Immunoregulatory abnormalities and/or the imbalance of immunoregulatory and inflammatory processes could lead to the progression towards autoimmune diseases. Besides faulty tolerance mechanisms, several other factors, such as imbalance of the pro- and anti-inflammatory cytokines, extracellular vesicles, abnormal autoantigen scavenging machinery, and antigen presentation, can contribute to the development and perpetuation of autoimmune processes and eventually to the progress towards autoimmune diseases.

An extensive study in families with a high frequency of T1DM and AITD revealed that cytotoxic-T-lymphocytes antigen A-4 (CTLA-4) carries a major genetic risk for the joint diagnosis of T1D and AITD [18]. CTLA-4 is expressed on T cells and acts as a costimulatory receptor which downregulates T cells. Any structural changes in CTLA-4 leading to an inhibition of its function may result in T-cell activation as a common cause of an increased frequency of autoimmune disease [18].

Recent findings have determined that HLA, AIRE, PTPN22, FOXP3, CTLA-4, infection, VD deficiency, and CXCLs confer susceptibility to the development and prognosis of AITD and T1DM, to various degrees (Figure 1). Despite

Figure 1: Proposed diagram of the pathogenic mechanisms involved in the development and progression of thyroid autoimmune disease and type 1 diabetes mellitus [19]



accumulated data, a complete understanding of the mechanisms underlying the etiology and pathogenesis of T1DM and AITD is lacking. More studies are needed to further investigate and explore novel therapeutic targets, for example LYP, VD, and CXCLs, in the treatment of various autoimmune diseases, including T1DM and AITD [19].

AIRE, autoimmune regulator; AITD, autoimmune thyroid disease; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; CXCLs, chemokine (C-X-C motif) ligands; FOXP3, forkhead box protein P3; HLA, human leukocyte antigen; PTP/LYP, lymphoid protein tyrosine phosphatase; Th, T helper cell; T1DM; type 1 diabetes mellitus; Treg, regulatory T cells; TSHR, thyroid-stimulating hormone receptor; VD, vitamin D; VDR, vitamin D receptor

The prevalence of thyroid autoimmune disease in Type 1 DM

Diabetes mellitus (DM) is a widely prevalent disease that may affect any individual at any age [20]. The incidence of DM has risen globally from 108 million in 1980 to 422 million in 2014, according to World Health Organization [20]. In the general population, about 6% of people have some forms of thyroid disorders [21]. However, the prevalence of thyroid disorders increases to over 10% or more in people with DM. This is commoner in women as most women with type 1 DM have a 30% chance of developing auto-immune thyroid diseases [21].

Many studies were done to determine the prevalence of thyroid disorders among diabetic patients. Recently, they found an association between autoimmune hypothyroidism and T1DM [22]. A study, on 233 Brazilian children and adolescents suffering from T1DM, found that 23% of them had thyroid disorders, and most of them were females [23]. Another study, on 382 Type 1 diabetic children and adolescents in Poland, found that 14.4% of the participants had an elevation in antibodies against thyroid peroxidase [24].

Sanchez-Lugo reported a total of 78 patients who had Type 1 DM and were confirmed to have thyroid dysfunction. 15% had thyroid auto-immunity while 40% had goiter and more than 75% were females. This was the lowest prevalence of thyroid autoimmunity in diabetic children among the Hispanic group in USA [25].

Rodrigues studied a group of individuals to study the prevalence of thyroid dysfunction and anti-thyroid antibodies in Type 1 DM and their first-degree relatives. They found that the prevalence of autoimmune thyroid diseases (AITD) among diabetic patients was 35.5% which was higher among the first-degree relatives of diabetics than among relative of diabetics without auto immune thyroid disease (AITD) [26]. Similarly, Ghawil et al. defined the prevalence of thyroid autoimmune disease among the patients with type 1 DM in Libya. They found that the major thyroid pathology was subclinical hypothyroidism (2.3%). About 23.4% of their patients had positive thyroid peroxidase (TPO) antibodies, while 7.8% had Tg antibodies. Most of the affected patients were females

and 57% of these patients had type 1 DM for more than 5 years [27].

Effects of Diabetes Mellitus on Thyroid

In euthyroid individuals with diabetes mellitus, the serum T3 levels, basal TSH levels and TSH response to thyrotropin releasing hormone (TRH) may all be strongly influenced by the glycemic status [33]. In diabetic patients, the nocturnal TSH peak is blunted or abolished, and the TSH response to TRH is impaired [34]. Reduced T3 levels have been observed in uncontrolled diabetic patients. Low serum T3 is due to reduced peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) via 5' monodeiodination reaction. However, in a study by Coiro et al involving type 1 diabetes patients with absent residual pancreatic beta cell function, an amelioration in glycemic control did not restore the normal nocturnal TSH peak suggesting a diabetes dependent alteration in the central control of TSH [35]. A study concluded that fasting blood sugar (FBS) and HbA1c levels were increased with increasing of both T3 and T4. Based on this study all the thyroid patients' especially hyperthyroid patients should have regular checkup of their glucose levels [36]. Higher levels of circulating insulin associated with insulin resistance have shown a proliferative effect on thyroid tissue resulting in larger thyroid size with increased formation of nodules [37]. A higher prevalence of type 1 diabetes is observed in patients with Grave's orbitopathy than in the normal population.

Effects of Thyroid Hormones on Glycemic status

There is inter-dependence between insulin and thyroid hormones for normal cellular metabolism so that diabetes mellitus and thyroid diseases can mutually influence the other disease process.

Thyroid hormones affect glucose metabolism via several mechanisms. Variable glucose intolerance is seen in up to 50% of patients with Graves' and frank diabetes occurs in 2-3%, when hyperthyroidism develops in normal individuals. In known diabetic patients, the diabetic control deteriorates [38]. Analysis of C-peptide clearance kinetics using multivariate analysis demonstrated that the mean clearance rate of C-peptide was significantly increased in the hyperthyroid group. Thus, stimulated insulin secretion rates are significantly increased in thyrotoxicosis possibly reflecting an increased sensitivity of the beta-cell to glucose in subjects who are hyperthyroid [39]. During hyperthyroidism, the half-life of insulin is reduced most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive insulin precursors [39-40]. In untreated Graves' disease, increased proinsulin levels in response to a meal were observed in a study by Bech et al [41]. In addition, untreated hyperthyroidism was associated with a reduced C-peptide to proinsulin ratio suggesting an underlying defect in proinsulin processing [42]. Another mechanism explaining the

relationship between hyperthyroidism and hyperglycemia is the increase in glucose gut absorption mediated by the excess thyroid hormones [43-44]. Endogenous production of glucose is also enhanced in hyperthyroidism via several mechanisms. Thyroid hormones produce an increase in the hepatocyte plasma membrane concentrations of GLUT2 which is the main glucose transporter in the liver, and consequently, the increased levels of GLUT-2 contribute to the increased hepatic glucose output and abnormal glucose metabolism [45-46]. It is well known that diabetic patients with hyperthyroidism experience worsening of their glycemic control and thyrotoxicosis has been shown to precipitate diabetic ketoacidosis in subjects with diabetes [47-48]. In diabetic ketoacidosis without an obvious triggering factor, the presence of hyperthyroidism should be investigated [47]. As for hypothyroidism, glucose metabolism is affected as well via several mechanisms. A reduced rate of liver glucose production is observed in hypothyroidism [49]. Recurrent hypoglycemic episodes are the presenting signs for the development of hypothyroidism in patients with type 1 diabetes and replacement with thyroid hormones reduced the fluctuations in blood glucose levels as demonstrated by Leong et al [50]. A recent study involving subjects from a Chinese population found a higher TSH level in patients with metabolic syndrome compared to that in the nonmetabolic syndrome group suggesting that subclinical hypothyroidism may be a risk factor for metabolic syndrome [51]. More recently, Erdogan et al. found an increased frequency of metabolic syndrome in subclinical and overt hypothyroidism compared to healthy controls [52]. Hyperthyroidism results in deterioration of diabetic control while hypothyroidism increases the susceptibility to hypoglycemia in diabetic patients thereby complicating the diabetic management in these individuals.

Evidence of Shared genetic susceptibility to T1D and AITD

Epidemiological data support a shared genetic susceptibility to autoimmune thyroid disease (AITD) and type 1 diabetes (T1D). Both diseases frequently occur within the same family and in the same individual. Several studies across different populations have shown, using serology for thyroid and islet cell antibodies, that there is a frequent co-occurrence of T1D and AITD within the same individuals. In most of these studies, researchers analyzed the occurrence of two thyroid-specific antibodies [anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg)] in T1D patients as an indicator of thyroid autoimmunity. [Please note that in this review the abbreviation TAb refers to the presence of anti-TPO antibodies, anti-Tg antibodies, or both; it does not include TSH receptor antibodies.] The frequency of TAb in T1D patients varied among studies from 8% to as high as 44% [54-55]. However, even the lowest frequency reported is still significantly higher than the prevalence of TAb in age-matched controls .

In family studies, prevalence rates of Hashimoto's thyroiditis (HT) and/or thyroid antibodies in relatives of T1D was as high as 48%, compared with a general

Table 1: DIABETES MELLITUS – THYROID DISEASE INTERACTION [53]

CLINICAL CONDITION	EFFECT ON GLYCEMIA	EFFECT ON THYROID FUNCTION
Diabetes Mellitus-In euthyroid Individuals		Serum T3 ↑ rT3 ↓ TSH response to TRH ↓ impaired nocturnal TSH peak
Diabetes Mellitus in hyperthyroidism individuals	Poor glyceemic control	↑ Incidence of dysthyroid optic neuropathy
Hyperthyroidism in diabetic individuals	Deterioration of diabetic control	
Hypothyroidism in diabetic individuals	Predisposition to recurrent hypoglycemia Exacerbation of symptoms.	
Hyperthyroidism in euglycemic individuals	Glucose intolerance-in 50% cases overt diabetes in 2-3%	

general population prevalence of only 3–10%. Moreover, T1D and AITD frequently occur within the same individual [56].

One study examined the reverse phenomenon, namely the frequency of ICA among AITD patients. This study showed that 2.3% of AITD children had islet antibodies ICA, compared with 0% of control children [57]. In the same study, 30% of T1D children had TAb compared with 4.3% of controls [57]. In a nationwide study of multiplex families from Japan, a country with low incidence of T1D, it was found that the frequency of T1D among siblings of diabetic probands was 1.3–3.8% compared with a very low frequency in the general population of 0.014% [58]. The increased frequency of TAb in children with T1D has been consistent across different populations. In Germany and Austria, 10 to 21.6% of T1D patients tested positive for one or both TAb, compared with 0 to 3.7% of the general population [59–60]. Interestingly, in one study [60], a follow-up on 16 patients with T1D showed that in an average of 3.5 years after first detection of TAb, eight (50%) patients had developed thyroid disorders, and in another study [58] 16% of T1D patients having thyroid autoimmunity, as determined by elevated TAb levels, had elevated TSH levels indicating clinical AITD. Similarly, a study done in northern Europe on 105 individuals showed that 16.2% of T1D patients were TAb positive [61]. In addition, a study by Burek et al. [62] examined the frequency of AITD in African-American, compared with Caucasian children with T1D in the United States. They showed that AITD was more prevalent in Caucasian children with T1D than in African-Americans; however, the prevalence of TAb in both Caucasians (50%) and African-Americans (16%) was higher than in the general population [62]. Finally, in Brazil, a study done on 383 T1D patients showed that 64 (16.7%) tested positive for TAb, with positive subjects being predominantly females [63]. In addition to gender, age seems to play an important role in the onset of AITD in T1D patients. In a study by Holl et al. 495 T1D patients were screened for TAb at multiple time points; the screening demonstrated that the prevalence of TAb in T1D patients increased dramatically with age, from 3.7% (at ages <5 years) to 25.3% (at ages 15–20) [59].

In summary, the increased prevalence of TAb among children with T1D is a consistent phenomenon across geographically and ethnically distinct populations, albeit the frequency of positive TAb in T1D patients varies in different populations. The frequency of TAb in T1D increases with age and is more common in females than in males. Taken together, these epidemiological observations support a strong genetic association between T1D and AITD.

Occurrence of Type 1 Diabetes in Graves' Disease Patients Who are Positive for Antiglutamic Acid Decarboxylase Antibodies

Glutamic acid decarboxylase antibodies (GADAs) are one of the markers of islet cell autoimmunity and are sometimes present before the onset of type 1 diabetes (T1D). GADA can be present in Graves' patients without diabetes; however, the outcome of GADA-positive Graves' patients is not fully understood, and the predictive value of GADA for the development of T1D in Graves patients remains to be clarified. Type 1 diabetes (T1D) and Graves' disease, both endocrine organ-specific autoimmune diseases, frequently coexist and in combination are classified as autoimmune polyglandular syndrome type III [64]. There are common genetic backgrounds for both diseases [65] such as the CTLA-4 gene [66] and PTPN-22 gene [67]. Antibodies to islet antigens are present before the onset of type 1 diabetes [68]. On the other hand, many individuals positive for antibodies to islet antigens do not develop T1D. In Finland, where the incidence of T1D is very high, it was reported that T1D developed only in 26% of GAD positive young subjects from the general population over 25 years [69]. In the same study, only 0.26% of GADA-negative subjects developed T1D. Previous studies have revealed that positivity for more than 2 kinds of islet-associated antibodies, especially the combination of GADA and Protein tyrosine phosphatase IA-2 antibodies, has predictive value [70]. Graves' patients with long duration and high titers of GADA are at high risk for developing T1D. To clarify what factors are involved in the

susceptibility to T1D in Graves' disease, greater numbers of patients need to be followed up intensively over a long period of time.

Clinical Aspects

Autoimmune thyroiditis AT is usually suspected in the presence of goiter, even in the absence of signs and symptoms of thyroid dysfunction. It may also be diagnosed incidentally during medical checkups, screening evaluation of children with growth defects, or follow-up of children with associated diseases, mainly Down syndrome, Turner syndrome, type 1 diabetes, and celiac disease (71,72).

In all patients with associated diseases, AT is usually detected in its initial phase when thyroid function is preserved, with normal or only slightly elevated TSH levels. At this stage, signs and symptoms of thyroid disease are usually absent, but because worsening of thyroid function is a possibility, early recognition of thyroid dysfunction is necessary to prevent the negative effects of hypothyroidism on growth and metabolic function. The enlarged thyroid gland usually is diffuse and nontender; sometimes the gland may be firm [73].

Nearly one third of all newly detected Type 1 diabetes mellitus patients have co-existent thyroid autoimmunity (TAI) and a high prevalence of thyroid dysfunction which is predominantly hypothyroidism (clinical or subclinical) whilst a few have hyperthyroidism. The high prevalence of thyroid dysfunction emphasizes the importance of routine screening for TAI in all newly detected Type 1 diabetes mellitus patients followed by annual TSH assay in case TAI is positive (76-77).

Screening for thyroid dysfunction in patients with DM

The close interactions between thyroid status and metabolic control discussed above argue for close monitoring of thyroid function particularly in patients with T1DM. Currently, a number of guidelines suggests not only baseline testing for thyroid dysfunction in newly diagnosed DM: the British Thyroid Association supports, in addition, Ab-TPO testing at baseline and TSH monitoring at yearly intervals. There are large variations in the different guidelines, ranging from ignoring thyroid function tests to yearly testing. All these recommendations apply only for T1DM, whereas in T2DM thyroid testing is only recommended if an autoimmune disease is suspected. Many laboratories routinely measure FT4 and TSH as first line tests for thyroid function although measurement of TSH-alone is adequate for screening purposes in a stable outpatient setting [78]. Most guidelines advocate measuring TSH and thyroid antibodies at diagnosis of diabetes, and then testing only TSH at subsequent visits [79,80]. TSH is the most sensitive means of detecting thyroid dysfunction and sensitive third-generation assays are readily available in most modern laboratories. A normal TSH concentration has a high negative predictive value for excluding thyroid

disease, and changes in TSH concentrations usually precede changes in free thyroid hormone levels in the development of thyroid failure [78]. However, measurement of TSH alone may be inappropriate in specific clinical situations such as in cases of suspected pituitary disease or in monitoring patients with known thyroid disease. TSH alone will also be inadequate where thyroid disease is suspected in patients with acute presentations such as diabetic ketoacidosis, hyperosmolar states and recurrent hypoglycemic episodes. Estimation of FT4 as well as TSH will be necessary in these instances and these may need to be repeated after the acute illness has subsided to distinguish true thyroid dysfunction from non-thyroidal illness.

Thyroid autoimmunity is especially common in T1DM and up to a third of patients with T1DM eventually develop thyroid dysfunction [81]. In these patients' thyroid dysfunction may be asymptomatic or its clinical features may be masked by features of poor diabetes metabolic control. Thus, a systematic approach to thyroid disease screening seems justified in T1DM. Routine screening will identify a significant proportion of patients with thyroid disease and is unlikely to incur excessive costs given that patients with T1DM represent a lesser fraction of all diabetic patients. However, there are differences with respect to subsequent surveillance strategies. While some practice guidelines do not specify the exact interval of periodic testing [82,83] others recommend annual or two-yearly testing [79-80], with more frequent tests suggested for antibody-positive patients [80] or patients with goitre [80] or other autoimmune diseases.

Conclusion

- 1- There is higher prevalence of thyroid autoimmunity in type 1 diabetes mellitus.
- 2- Most of the patients develop subclinical form of disease.
- 3-Gender, age, and duration of diabetes have a significant association with autoimmune thyroid disease
- 4-Hypothyroidism is much more common than hyperthyroidism in autoimmune thyroid disease associated with type 1 diabetes.
- 5- All patients with diabetes should be screened for thyroid function or whether patients with subclinical thyroid disease should be treated merits reconsideration.

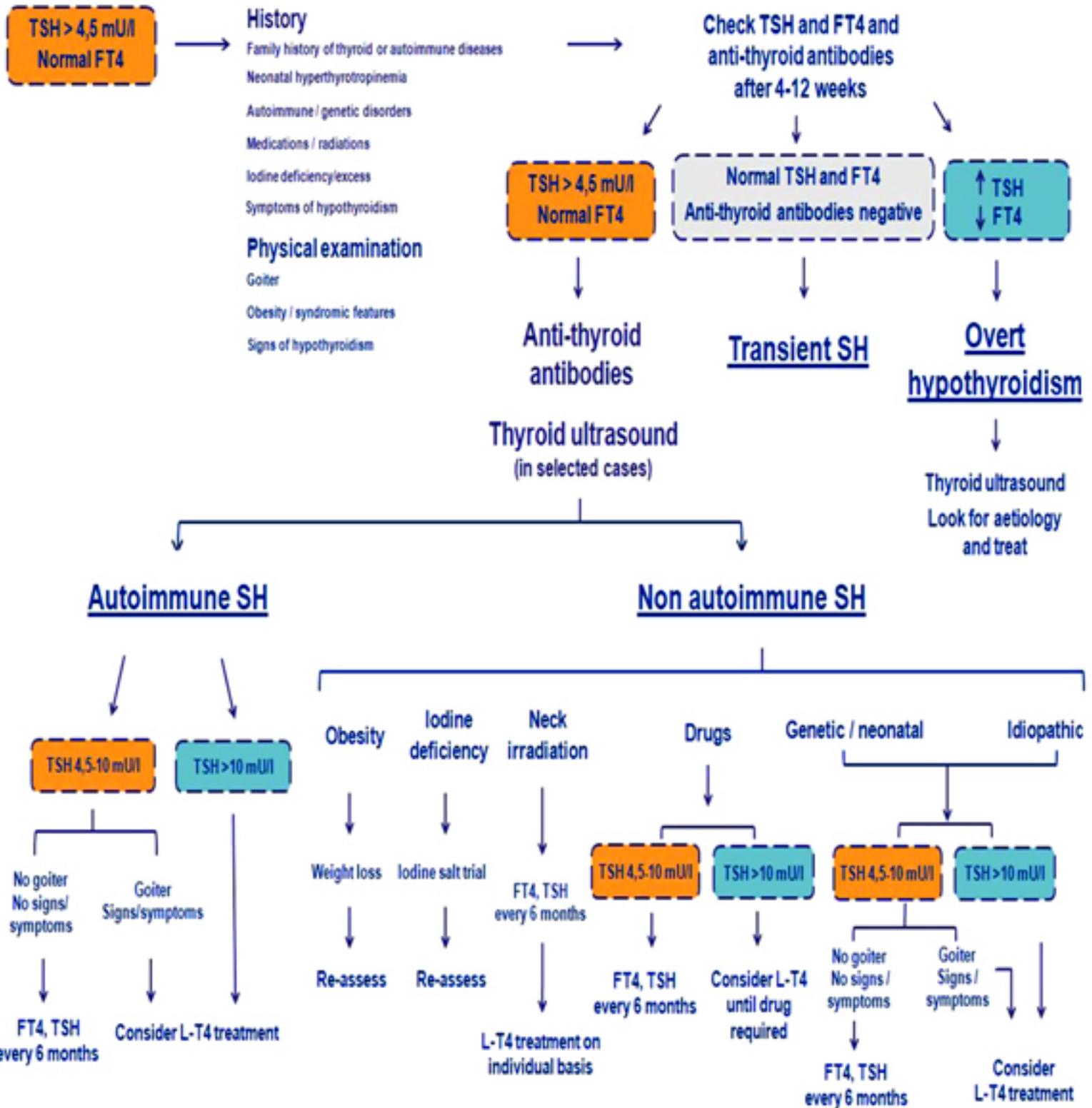
Abbreviations

- T1D Type 1 diabetes
 AT autoimmune thyroiditis
 AITD autoimmune thyroid diseases
 GD Graves' disease
 CD celiac disease
 TSH thyroid stimulating hormone
 TRH thyrotropin releasing hormone
 ICA islet cell antibodies
 GADA: Glutamic acid decarboxylase antibodies)
 TPO thyroid peroxidase
 Tg thyroglobulin
 SH subclinical hypothyroidism

Table 2 Manifestations of Hypothyroidism and Hyperthyroidism (74-75)

Condition	Symptoms	Signs	
Hypothyroidism	<ul style="list-style-type: none"> • Cold intolerance • Increased sleep • Decreased energy • Muscle weakness, cramps • Menometrorrhagia • Delayed or pseudo-precocious puberty • Galactorrhea • Headache 	<ul style="list-style-type: none"> • Decreased growth velocity • Delayed osseous maturation • Goiter • Weight gain (usually due to myxedema) • Constipation • Bradycardia 	<ul style="list-style-type: none"> • Ataxia • Nerve entrapment • Laboratory changes (hyponatremia, macrocytic anemia, hypercholesterolemia, elevated creatine phosphokinase)
Hyperthyroidism	<ul style="list-style-type: none"> • Hyperactivity, irritability, altered mood, insomnia, anxiety, poor concentration • Heat intolerance, increased sweating • Palpitations • Fatigue, weakness • Dyspnea • Weight loss with increased appetite (weight gain in 10% of patients) • Pruritus • Increased stool frequency • Thirst and polyuria • Oligomenorrhea or amenorrhea 	<ul style="list-style-type: none"> • Sinus tachycardia, atrial fibrillation (rare in children), supraventricular tachycardia • Fine tremor, hyperkinesia, hyperreflexia • Warm, moist skin • Palmar erythema, onycholysis • Hair loss or thinning • Osteoporosis • Muscle weakness and wasting • High-output heart failure • Chorea • Periodic (hypokalemic) paralysis (primarily in Asian men) • Psychosis (rare) 	<p>Signs specific for Graves disease:</p> <ul style="list-style-type: none"> • Thyroid acropachy (rare in children) • Diffuse goiter • Localized dermopathy (rare in children) • Lymphoid hyperplasia • Ophthalmopathy <ul style="list-style-type: none"> ◦ Eye discomfort ◦ Retrobulbar pressure or pain ◦ Eyelid lag or retraction ◦ Periorbital edema, chemosis, scleral or conjunctival injection ◦ Exophthalmos (proptosis) ◦ Extraocular muscle dysfunction ◦ Exposure keratitis ◦ Optic neuropathy

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Algorithm: clinical approach of subclinical hypothyroidism in children (84)

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