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Raghu Kadiyala, R Peter, O Okosieme

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Complete List of Authors:	Kadiyala, Raghu; Prince Charles Hospital, Endocrinology and Diabetes Department Peter, R; University Hospital of Wales, Diabetes & Endocrinology Okosieme, O; Prince Charles Hospital, Endocrinology and Diabetes Department
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Thyroid dysfunction in patients with diabetes:

Clinical implications and screening strategies

Kadiyala R, Peter R* and Okosieme OE

Prince Charles Hospital, Cwm Taf Local Health Board

Merthyr Tydfil, Mid Glamorgan, CF47 9DT, UK

*Neath Port Talbot Hospital

Abertawe Bro Morgannwg University Health Board

Baglan Way, Port Talbot, SA12 7BX.

Correspondence to:

Dr Onyebuchi E Okosieme MD MRCP

Endocrinology and Diabetes Department

Prince Charles Hospital, Cwm Taf Local Health Board

Merthyr Tydfil, Mid Glamorgan, CF47 9DT, UK

E-mail: okosiemeoe@cf.ac.uk

Tel: 01685 728353, Fax: 01685 728448

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Abstract

Background: Patients with diabetes mellitus are at increased risk of thyroid disease. The frequency of thyroid dysfunction in diabetic patients is higher than that of the general population and up to a third of patients with type 1 diabetes (T1DM) ultimately develop thyroid dysfunction. Unrecognised thyroid dysfunction may impair metabolic control and add to cardiovascular disease risk in diabetic patients. **Aims:** Our aims were to review the current literature on the association between thyroid dysfunction and diabetes mellitus, to highlight relevant clinical implications, and to examine present thyroid disease screening strategies in routine diabetes care. **Results**: The pleiotropic effects of thyroid hormones on various metabolic processes are now better understood. Uncontrolled hyperthyroidism in diabetic patients may trigger hyperglycaemic emergencies while recurrent hypoglycaemic episodes have been reported in diabetic patients with hypothyroidism. Furthermore, thyroid dysfunction may amplify cardiovascular disease risk in diabetic patients through inter-relationships with dyslipidaemia, insulin resistance and vascular endothelial dysfunction. However, the significance of subclinical degrees of thyroid dysfunction remains to be clarified. While these developments have implications for diabetic patients a consensus is yet to be reached on optimal thyroid screening strategies in diabetes management. **Conclusions**: The increased frequency of thyroid dysfunction in diabetic patients and its likely deleterious effects on cardiovascular and metabolic function calls for a systematic approach to thyroid disease screening in diabetes. Routine annual thyroid testing should be targeted at diabetic patients at risk of thyroid dysfunction such as patients with T1DM, positive thyroid autoantibodies or high-normal TSH concentrations.

Message for the clinic

Clinicians should be aware of the frequent co-existence of thyroid dysfunction and diabetes mellitus. Periodic thyroid screening should be targeted at diabetic patients at risk of thyroid dysfunction i.e. patients with type 1 diabetes, positive thyroid autoantibodies, or TSH concentrations in the upper range of normal. Recognition and prompt correction of thyroid dysfunction will optimise metabolic control and reduce cardiovascular disease risk in patients with diabetes.

Review criteria

We searched Medline for relevant articles using various combinations of the search terms: thyroid dysfunction, diabetes mellitus, prevalence, incidence, progression, glucose metabolism, pathogenesis, genetics, cardiovascular disease and screening. In addition we consulted the websites of the major Endocrine and Diabetes professional organisations for current practice guidelines on thyroid disease screening in patients with diabetes.

1.0 Introduction

Thyroid disorders and diabetes mellitus are the two most common endocrinopathies encountered in practice. Both conditions frequently co-exist and the prevalence of thyroid dysfunction in patients with diabetes is higher than in the general population [1, 2]. Type 1 diabetes (T1DM) and autoimmune thyroid disease (AITD) share common susceptibility genes and frequently occur with other disease models of organ-specific autoimmunity [3]. Unrecognised thyroid dysfunction may impair metabolic control in patients with diabetes [4, 5] and in addition may amplify existing cardiovascular disease risk. The multifaceted relationship between thyroid disease and diabetes mellitus has implications for the clinician. Although recognition and treatment of thyroid dysfunction in diabetic patients will benefit glycaemic control, attenuate cardiovascular risk, and improve general wellbeing, there is no consensus regarding optimal thyroid screening strategies in routine diabetes care. In this review we examine the association between thyroid dysfunction and diabetes mellitus, highlight clinical implications of their inter-dependent relationship, and outline strategies for thyroid disease screening and surveillance in patients with diabetes.

2.0 Review Methods

We searched Medline for relevant articles published in the English language from 1970 through October 2009. We used the search terms thyroid dysfunction and diabetes mellitus in conjunction with other terms, including prevalence, incidence, progression, glucose metabolism, pathogenesis, genetics, cardiovascular disease and screening. Further queries were performed with the phrases, subclinical hypothyroidism and subclinical hyperthyroidism and additional relevant publications were sourced from references in individual papers. In addition we consulted the websites of the major Endocrine and Diabetes professional organisations for current practice guidelines on thyroid disease screening in patients with diabetes.

3.0 Frequency of thyroid dysfunction in patients with diabetes

Thyroid dysfunction is common in the general population. In a survey in an iodine-replete community in the north east of England (the Whickham survey), the prevalence of thyroid dysfunction was 6.6% in the adult general population [6]. Other large scale studies of thyroid dysfunction in the United States have reported comparable rates in unselected populations [7, 8]. The frequency of thyroid dysfunction rises with age and is higher in females than in males. Studies in various settings have shown that thyroid dysfunction is more common in patients with diabetes than in the background population (table 1) [1, 2, 9-14]. Perros and colleagues observed a prevalence of thyroid dysfunction of 13.4% in 1301 adult diabetes clinic patients with T1DM and type 2 diabetes (T2DM) [1]. A study in a general practice with 223 registered diabetic patients reported a prevalence of thyroid dysfunction of 10.8% [11]. Thyroid dysfunction is more common in patients with T1DM than those with T2DM, and indeed up to a third of patients with T1DM ultimately develop thyroid dysfunction [15]. Postpartum thyroid dysfunction occurs in as much as 25% of women with T1DM [16]. Nevertheless, the frequency of thyroid dysfunction in T2DM still exceeds that of the general population and in some reports equals that of T1DM due to the older age group of patients with T2DM [13, 14].

4.0 Autoimmune thyroid disease and type 1 diabetes

The clinical spectrum of AITD includes Graves' disease (GD), Hashimoto's thyroiditis (HT), and postpartum thyroiditis (PPT). These conditions account for considerable morbidity in affected individuals and are responsible for most thyroid dysfunction in iodine-replete populations [17]. AITD and T1DM often co-exist in the same individual and also occur in combination with other organ-specific autoimmune disorders such as coeliac disease, Addison's disease and autoimmune gastritis [3]. Like T1DM, AITD is a model of organ specific autoimmunity arising from the interplay of genetic and environmental factors [17]. The immune response in AITD is characterised by T-cell infiltration of the thyroid gland and the production of autoreactive antibodies, namely antibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) [17]. These antibodies are prevalent in patients with T1DM [2, 12] as well as in their first degree relatives [18], and their presence may predict subsequent thyroid dysfunction [19].

T1DM and AITD also form part of the polyglandular autoimmune syndromes [20]. The rare type 1 polyglandular autoimmune syndrome (PAS-1) results from mutations in the autoimmune regulator gene (AIRE) and is inherited as an autosomal recessive trait. PAS-1 typically manifests in childhood or early adolescence and is characterised by chronic mucocutaneous candidiasis and multiple autoimmune endocrinopathies including T1DM and AITD. The polyglandular autoimmune syndrome type 2 (PAS-2) occurs more commonly, is inherited as a polygenic trait, and typically presents in adulthood with multiple endocrine dysfunction. In many instances T1DM is the earliest manifestations of these syndromes and the association of T1DM with AITD occurs more frequently than other disease combinations [20].

Several common genetic loci have been implicated in the predisposition to both AITD and T1DM. Foremost amongst these are genes on the human leukocytic antigen

(HLA) locus on the major histocompatibility complex (MHC). A high risk of T1DM is associated with the HLA-DR3 and HLA-DR4 alleles [21, 22]. Similar associations with HLA-DR3 have been reported in patients with GD and less consistently in HT and PPT patients [21, 22]. Other immune regulatory genes outside the HLA loci contribute to disease risk in AITD and T1DM and include the protein tyrosine phosphatase-22 (PTPN22) gene and the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) gene [21, 22]. Moreso, the contribution of these genetic loci to disease susceptibility appears to be stronger for individuals with co-existent AITD and T1DM than for patients with single organ disease [21].

5.0 Hyperthyroidism and Diabetes

The occurrence of hyperthyroidism in patients with diabetes is greater than in the general population. Perros et al reported an incidence of 1.0% in diabetic patients [1] compared to an estimated incidence of approximately 0.3% of the general population in the Whickham survey [6]. Graves' disease and toxic nodular disease are the most common causes of hyperthyroidism in the general population while less common causes include thyroiditis and drug-induced hyperthyroidism.

5.1 Metabolic control

Thyroid hormones may influence glucose control through a variety of actions on intermediary metabolism. Some of these effects become clinically relevant in patients with co-existent diabetes and hyperthyroidism. Excess thyroid hormones promote hyperglycaemia by facilitating glucose intestinal absorption, increasing insulin clearance, and enhancing glycogenolysis and gluconeogenesis [23]. Also, hyperthyroidism is associated with increased hepatic glucose output, reduced insulin action and increased lipolysis [23]. Accordingly, diabetic patients with overt hyperthyroidism may experience poor glycaemic control and indeed hyperthyroidism has been known to precipitate diabetic ketoacidosis in patients with diabetes [24]. Furthermore, the hypermetabolic features of hyperthyroidism may cause diagnostic confusion with the typical osmotic state of hyperglycaemia. Consequently, severe diabetes may be missed in patients with thyrotoxicosis, and likewise, life threatening thyroid storm can be masked by hyperglycaemia [25]. An additional consideration is the association of low thyroid hormone levels with acute hyperglycaemic states which may hamper the accurate interpretation of thyroid function tests in patients with uncontrolled diabetes [10, 26].

5.2 Cardiovascular disease risk

In addition to its impact on glycaemic control hyperthyroidism may add to cardiovascular disease risk in patients with diabetes [reviewed in 27]. Prominent cardiovascular features such as tachycardia, arrhythmias, congestive cardiac failure, and systolic hypertension are well recognised manifestations of thyrotoxicosis. Furthermore, an increased cardiovascular mortality has been reported in patients with overt [28] as well as subclinical hyperthyroidism, defined as suppressed TSH in the presence of normal thyroid hormone levels [29, 30]. Atrial fibrillation is reported in as much as 10-15% of patients with overt hyperthyroidism and individuals with subclinical hyperthyroidism are more likely to develop atrial fibrillation than euthyroid persons [31]. Cardiovascular mortality in hyperthyroidism is linked to older age, cardiac arrhythmias, or pre-existing organic heart disease [27].

6.0 Hypothyroidism and Diabetes

Hypothyroidism is the most common form of thyroid dysfunction encountered in patients with diabetes. The prevalence of hypothyroidism was 5.7% in diabetic patients [1] compared to a prevalence of 1.1% in the Whickham survey [6]. Chronic autoimmune thyroiditis accounts for most cases of hypothyroidism in iodine sufficient countries. Other causes include hypothyroidism secondary to radioiodine therapy, surgery, or pituitary disease.

6.1 Metabolic control

In patients with diabetes, hypothyroidism may influence metabolic control through effects on glucose metabolism which are opposite to those seen in hyperthyroidism. These effects include reductions in hepatic glucose output, gluconeogenesis, and peripheral glucose utilization. The net effect of these processes is a predisposition to hypoglycaemia [32]. Frequent hypoglycaemic episodes were documented in children and adolescents with diabetes and subclinical hypothyroidism i.e. elevated TSH and normal thyroid hormones [4]. Moreso, correction of hypothyroidism led to improvement in hypoglycaemic symptoms in these patients [4]. Glycaemic status may in turn influence thyroid function. A low T3 state is observed in patients with severe hyperglycaemia [26]. Celani and colleagues reported a high frequency of thyroid function abnormalities in acute hospital admissions with poorly controlled diabetes [10]. These abnormalities were mostly subclinical and reverted to normal with improvement in blood glucose control in the majority of patients [10]. Co-existent diabetes may affect the efficacy of thyroid hormone treatment in patients with hypothyroidism. A recent study in elderly patients on L-thyroxine treatment showed that the presence of diabetes was independently associated with inadequate thyroid hormone replacement, an association which was not seen with other chronic disorders.

[33]. A further interaction may result from the use of the anti-diabetic agent, metformin, which has been shown to suppress TSH concentrations in diabetic patients on thyroxine treatment [34].

6.2 Cardiovascular disease risk

Diabetes is associated with significant cardiovascular risk [35]. Hypothyroidism may add to this risk through independent associations with atherosclerotic heart disease [reviewed in 36]. In early case control studies, postmortem atherosclerosis was found to be more common in patients with hypothyroidism than in euthyroid control subjects [37]. In the 20-year follow up of the Whickham study, no relationship was demonstrable between baseline thyroid dysfunction and subsequent coronary heart disease although this cohort included patients who received treatment with levothyroxine [38]. In contrast a population-based cross sectional study of 1149 older female participants, the Rotterdam study, showed an association between subclinical hypothyroidism and myocardial infarction [39]. In addition hypothyroidism may magnify cardiovascular disease risk through multiple interactions with cardiovascular disease indices such as dyslipidaemia and hypertension, features which overlap with the typical phenotype of insulin resistance.

Dyslipidaemia is a well-recognised association of hypothyroidism and typically consists of raised levels of total cholesterol, apolipoprotein B, low density lipoprotein (LDL) cholesterol, and reduced levels of high density lipoprotein (HDL) cholesterol [40]. Such lipid abnormalities are partly reversible with thyroxine treatment in patients with co-existent diabetes [41]. Several studies have reported inter-dependent associations between thyroid status, dyslipidaemia, and insulin resistance. In euthyroid persons low normal thyroid hormone levels were associated with hyperlipidaemia and insulin resistance [42]. Furthermore, Bakker and colleagues demonstrated a positive correlation between thyrotropin (TSH) and LDL cholesterol in euthyroid individuals, an association which was apparent in insulin resistant subjects but was absent in insulin sensitive subjects [43]. Similar interactions have been demonstrated in diabetic patients [44] and taken together these studies suggest a modifying influence of insulin sensitivity on the effects of hypothyroidism on lipid metabolism.

A relationship between hypothyroidism and obesity has mostly been inferred from studies in historical cohorts [45-46]. More contemporary data suggest an association between body mass index and low-normal thyroid hormones or high-normal TSH concentrations [47]. However, these findings were not confirmed by others [48]. The effects of thyroid hormones on blood pressure are also well documented. Diastolic hypertension is seen in hypothyroidism due to increases in systemic vascular resistance [36]. Also, increased central arterial stiffness which is reversible with thyroxine therapy has been described in overtly hypothyroid patients [49]. Furthermore, hypothyroidism is associated with endothelial dysfunction as determined by increased arterial intima media thickness or impairment in flow-mediated endothelial dependent vasodilatation [50]. A study in healthy euthyroid men showed positive correlations between TSH, endothelial dysfunction and insulin resistance [51] lending further support to the three-way relationship between thyroid status, insulin resistance and cardiovascular disease risk.

7.0 Subclinical hypothyroidism and diabetes

Subclinical hypothyroidism is defined as an elevated TSH concentration in the presence of normal thyroid hormones [52]. This biochemical diagnosis accounts for a substantial proportion of thyroid dysfunction encountered in patients with diabetes. A prevalence rate of 5.0% was reported by Perros and colleagues in the hospital outpatient diabetes setting [1] while Chubb *et al* reported a prevalence of 8.6% in community-based female diabetic-patients [14]. A study in an adolescent population of patients with diabetes detected a prevalence of 6% [4]. With the advent of sensitive assays for TSH measurements subclinical hypothyroidism will increasingly be diagnosed in healthy individuals with no overt features of thyroid disease. Despite a considerable amount of research the significance of these subclinical states remain unsettled. The implications of subclinical hypothyroidism in the patient with diabetes will depend on its likelihood of progression to overt disease, its impact on diabetes metabolic control, as well as the potential for therapeutic benefits with LT-4.

7.1 Metabolic control

Only few studies have specifically addressed the influence of subclinical hypothyroidism on glycaemic control. One study in children with diabetes showed that the onset of AITD defined a sub-group of diabetic patients with more severe metabolic disease [5]. In a cross-sectional study in patients with T1DM it was suggested that recurrent hypoglycaemic episodes, inability to lose weight, and mild dyslipidaemia were pointers to underlying hypothyroidism, both overt and subclinical [53]. A retrospective case control study by Mohn *et al* compared metabolic control and frequency of hypoglycaemia before and after diagnosis of hypothyroidism in children and adolescents with T1DM [4]. Subclinical hypothyroidism was associated with an increased frequency of hypoglycaemic episodes which were abolished with LT-4 treatment [4].

7.2 Progression to overt hypothyroidism

In the Whickham study the rate of progression from subclinical hypothyroidism to overt hypothyroidism was 2.6% per year in antibody-negative patients and 4.3% in antibody-positive patients with higher TSH concentrations [54]. It does not appear that the rate of progression to overt hypothyroidism is much higher for patients with diabetes. Gray and colleagues recorded a progression rate of 5% per annum in diabetic patients with positive thyroid microsomal antibodies [55]. However, in the community-based Fremantle study none of the female patients with T2DM and subclinical hypothyroidism progressed to overt hypothyroidism over a 5-year period thus questioning the significance of subclinical hypothyroidism in patients with type 2 diabetes [14].

7.3 Cardiovascular disease risk

While there is compelling evidence to support an association between overt hypothyroidism and atherosclerotic heart disease, this relationship remains less certain for subclinical hypothyroidism. In the Rotterdam study subclinical hypothyroidism was associated with myocardial infarction [39] an association which was unproven in the follow-up of the Whickham study [38]. Several cardiovascular abnormalities have been documented in patients with subclinical hypothyroidism including diastolic dysfunction, hypertension, increased arterial stiffness, and endothelial dysfunction [36, 52]. Studies on lipid profiles have given highly variable results ranging from increased [7] to even lower cholesterol levels [39] in patients with subclinical hypothyroidism compared to euthyroid controls. Furthermore, evidence from various small-sized randomised control trials has given conflicting results on the benefits of LT-4 treatment on lipid parameters in subclinical hypothyroidism [56]. A meta-analysis of 13 studies comprising 247 patients concluded that LT-4 treatment was associated with improvements in some lipid parameters including total cholesterol, LDL cholesterol and apoB levels [56].

To summarise, the existing evidence is inconclusive regarding the benefits of LT-4 treatment on cardiovascular indicators in patients with subclinical hypothyroidism. However, the evidence from a small number of case series in children with diabetes suggest that co-existent hypothyroidism, both overt and subclinical, may define a subset of patients with more severe disease [4, 5, 53] and that LT-4 treatment may be beneficial in reducing the frequency of hypoglycaemic episodes in these patients [4]. Moreso, progression to overt disease is to be expected in a proportion of patients which will add to cardiovascular disease risk. Thus, it seems reasonable, in our opinion to consider treatment of subclinical hypothyroidism in patients with diabetes. Adequately powered randomised controlled trials are however required to determine the impact of such therapy on metabolic and cardiovascular parameters.

8.0 Screening strategies for thyroid dysfunction in diabetic patients

There is little consensus on thyroid disease screening strategies in routine diabetes care. The main discrepancies relate to the choice of thyroid function tests, the intervals between testing, whether routine screening is indicated in all diabetic patients, and whether a specific screening policy is at all necessary in diabetic patients. These uncertainties are reflected in the guidelines published by the major endocrine and diabetes societies on thyroid disease screening (table 2) [57-64]. The recommendations from some guidelines are vague and sometimes contradictory. For example, not all guidelines explicitly mention thyroid testing in patients with diabetes [59, 62], clearly distinguish type 1 from type 2 diabetes [57], or include specific reference to thyroid disease screening in patients with T2DM [58, 59, 64]. In the absence of definitive guidance local policies and practices are likely to remain discrepant as previously observed [65].

8.1 Choice of tests

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 [66]. Most guidelines advocate measuring TSH and thyroid antibodies at diagnosis of diabetes, and then testing only TSH at subsequent visits [61, 63-64]. 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 [66]. 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 hypoglycaemic 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.

8.2 Screening in type 1 diabetes

Thyroid autoimmunity is especially common in T1DM and up to a third of patients with T1DM eventually develop thyroid dysfunction [15]. 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. Existing guidelines recommend screening all patients with T1DM at baseline i.e. at the point of diagnosis or initial contact (table 2). However, there are differences with respect to subsequent surveillance strategies. While some practice guidelines do not specify the exact interval of periodic testing [57, 58] others recommend annual [61] or two-yearly testing [63, 64], with more frequent tests suggested for antibody-positive patients [64] or patients with goitre [58, 64] or other autoimmune diseases [58] (table 2).

8.3 Screening in type 2 diabetes

The case for annual screening in patients with T2DM is less clear-cut. A number of guidelines are either not specific regarding routine monitoring [58, 64] or explicitly recommend against routine annual screening in patients with T2DM [61] (table 2). In one report the 5-year incidence of thyroid dysfunction in older patients with T2DM was not significantly higher when compared to subjects without diabetes [67]. The findings by Chubb *et al* of 0% progression rate to overt hypothyroidism in women with T2DM and subclinical hypothyroidism casts further doubts on the value of routine annual screening in T2DM [14]. Moreso, it is debatable whether a routine annual screening strategy in patients with T2DM who constitute the bulk of diabetic patients will be cost effective [65]. Although relatively inexpensive at the unit level, the total annual cost of thyroid function testing in the United Kingdom was estimated at over £30 million [68]. Some of this expenditure will be attributable to routine periodic surveillance in patients with diabetes and other groups at high risk of thyroid dysfunction. The rising prevalence of T2DM coupled with the increasing availability of sensitive thyroid hormone assays will see a growing number of diabetic patients diagnosed with subclinical thyroid dysfunction in years to come. Whether such individuals with minor degrees of thyroid dysfunction will merit treatment remains unresolved but such biochemical diagnoses will nonetheless generate additional work-loads, laboratory costs, and patient anxiety.

In patients with T2DM it may suffice to undertake selective periodic screening using established laboratory predictors of thyroid dysfunction as risk stratification tools. Thyroid antibodies and serum TSH have proven useful in identifying diabetic patients at the greatest risk of thyroid dysfunction. Studies have shown that serum TSH concentrations in the upper range of normal predict the development of hypothyroidism. In the Whickham survey, a TSH concentration above 2.0 mU/L was associated with an increased risk of future hypothyroidism in the general population [54]. In a longitudinal study in hospital clinic patients with T1DM and T2DM, a TSH concentration > 1.53 mU/L predicted subsequent hypothyroidism [69]. Furthermore, the authors of this study showed that restricting thyroid testing to only patients with a TSH > 1.53 mU/L was cost effective [69]. A recent study in a general population (n=1184) demonstrated that a TSH concentration > 2.5 mU/L predicted the long-term risk of hypothyroidism [70]. TPOAbs also predict thyroid dysfunction in patients with diabetes [15, 19]. Umpierrez *et al* prospectively followed-up patients with T1DM over a period of 18 years and showed that TPOAb-positive patients were 18 times more likely to develop hypothyroidism than antibody-negative patients [15].

8.4 Recommended screening algorithm

With the above considerations in mind therefore a pragmatic approach would be to measure TPOAb and TSH in all diabetic patients at baseline, and then restrict subsequent annual testing to only those patients with T1DM, positive antibodies, or TSH concentration in the upper range of normal. Measurement of FT4 may be included in the baseline assessment in some cases to provide a preliminary picture of the thyroid-pituitary relationship. If this is normal then a strategy of TSH alone, with cascade to FT4 if necessary will suffice for subsequent annual testing. A simplified algorithm is suggested in figure 1. Although this approach will fail to identify type 2 diabetic patients with hyperthyroidism the frequency of hyperthyroidism in T2DM is not as significant as to warrant a separate screening approach. This algorithm will nonetheless ensure that those diabetic patients at greatest risk of thyroid dysfunction such as patients with T1DM, antibody-positive status or TSH in the upper reference range are monitored routinely. We have suggested a TSH concentration > 2.0 mU/L as a threshold for subsequent routine testing based on the findings of the Whickham survey which demonstrated a higher risk of hypothyroidism in patients with baseline TSH above this concentration [54]. Others have reported similar but slightly differing TSH cut-offs and further studies will be required to clarify the optimal TSH thresholds for predicting thyroid dysfunction [69, 70].

9.0 Conclusion

Patients with diabetes are at an increased risk of thyroid dysfunction. Recent decades have seen a growing understanding of the pleiotropic effects of thyroid hormones on various vascular and metabolic processes. Furthermore, insights are being developed into the complex interactions, at the phenotypic and molecular levels, between thyroid dysfunction, insulin resistance, and cardiovascular risk. Thus, our understanding has shifted from the simplistic concept of thyroid dysfunction as a benign disorder of hormone secretion to a more complete appreciation of its multiple deleterious effects on cardiovascular and metabolic function. Unrecognised thyroid dysfunction will amplify cardiovascular risk in diabetic patients although the significance of mild degrees of thyroid dysfunction is yet to be clarified. The increased frequency of thyroid dysfunction in diabetes calls for a systematic approach to thyroid testing. Yet screening practices vary widely and pragmatic guidelines are lacking. At present, a selective annual screening strategy may allow monitoring to be streamlined to those diabetic patients at the greatest risk of thyroid dysfunction such as those with T1DM, baseline positive antibodies or TSH concentrations in the upper half of the normal reference range.

Table 1: Studies of prevalence of thyroid dysfunction in patients with diabetes

Table 2: Recommendations from major endocrine and diabetes practice guidelines on thyroid screening in patients with diabetes

Figure 1: Suggested simplified screening and monitoring algorithm for thyroid dysfunction patients with diabetes

Legend

Table 1:

*median

** SD

+ These were patients with poor glycaemic control; thyroid dysfunction mostly improved with correction of hyperglycaemia.

NA = not applicable

Figure 1:

* FT4 should be measured if TSH is abnormal.

Table 2:

*Only associations with available guidelines on thyroid disease screening or diabetes management were included. Guidelines were unavailable for the following associations: Asia Oceania Thyroid Association, European Thyroid Association, Australia diabetes Association, and European Association for the study of Diabetes.

Author contribution

All authors contributed to the drafting and critical revision of the manuscript and approved the final draft of the article.

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Table 1: Prevalence of thyroid dysfunction in patients with diabetes mellitus

Study [Reference]	Sample size	Female (%)	Age (yrs)		Study setting	Type of diabetes	Thyroid dysfunction %		
			Mean	Range			Total	Males	Females
Gray et al, 1980 [9]	605	51	Not stated	21-84	Hospital clinic	T1DM	12	6.1	17
Celani et al, 1994 [10]	290	55	61	40-93	Hospitalised patients[+]	T2DM	31.4	19.8	40.9
Perros et al, 1995 [1]	1310	58	54	13-95	Hospital clinic	T1DM, T2DM	13.4	8.8	16.8
Smithson et al, 1998 [11]	223	43	65	17-93	Community practice	T1DM, T2DM	10.8	2.6	9.5
Hansen et al, 1999 [12]	105	51	13*	2-18	Community study	T1DM	4.8	1.8	8
Kordonouri et al, 2002 [2]	7097	51	12	0.3-20	Multi-centre study	T1DM	9.5	9.3	10.1
Radaideh et al, 2004 [13]	908	53	50	26-85	Hospital clinic	T2DM	12.5	6.5	17.5
Chubb et al, 2005 [14]	382	100	64	12.5**	Community study	T2DM	10.4	NA	10.4

*median
** SD
+ These were patients with poor glycaemic control; thyroid dysfunction mostly improved with correction of hyperglycaemia.
NA = not applicable

Table 2: Recommendations from major endocrine and diabetes practice guidelines on thyroid screening in patients with diabetes

Guidelines*	Type 1 diabetes	Type 2 diabetes	Comments
American Thyroid Association guidelines for detection of thyroid dysfunction, 2000 [57]	Patients with diabetes may require more frequent testing	Patients with diabetes may require more frequent testing.	Recommends TSH from 35 yrs, and every 5 yrs thereafter in all adults; high risk persons may require more frequent tests. Diabetes mentioned as high risk but does not distinguish between T1DM or T2DM
American Association of Clinical Endocrinologists, Thyroid disease clinical Practice guidelines, 2002 [58]	Thyroid palpation and TSH at diagnosis and at regular intervals, especially if goitre or other autoimmune disease present.	Thyroid palpation and TSH at diagnosis and at regular intervals, especially if goitre or other autoimmune disease present.	No specific recommendation for T2DM
U.S. Preventive Services Task Force recommendation statement, 2004 [59]	No specific mention	No specific mention	Insufficient evidence to recommend for or against routine screening in adults
International diabetes federation global guidelines for type 2 diabetes, 2005 [60]	Not applicable	Not mentioned	Assessment of thyroid function recommended in pregnant patients with diabetes
British Thyroid Association and Association of Clinical Biochemistry Guidelines, 2006 [61]	TSH and antibodies at baseline, and then TSH every year	TFT at baseline but routine annual TFT not recommended	TSH and antibodies recommended in diabetic patients in pregnancy and postpartum
American Association of Clinical Endocrinologists diabetes guidelines, 2007 [62]	Not specifically mentioned	Not specifically mentioned	Assessment of thyroid function in pregnant patients with diabetes recommended
International society for paediatric and Adolescent Diabetes guidelines, 2009 [63]	TSH and antibody at diagnosis, then 2-yearly; more frequently if goitre, antibodies or symptoms	Not applicable	Guideline focused on paediatric and adolescent diabetes
American Diabetes Association. Standards of medical care in diabetes, 2009 [64]	TSH and antibody at diagnosis, then annual or 2-yearly TSH	Not specifically mentioned	Thyroid palpation in all diabetic patients; TSH in adults > 50 yrs, or patients with dyslipidaemia

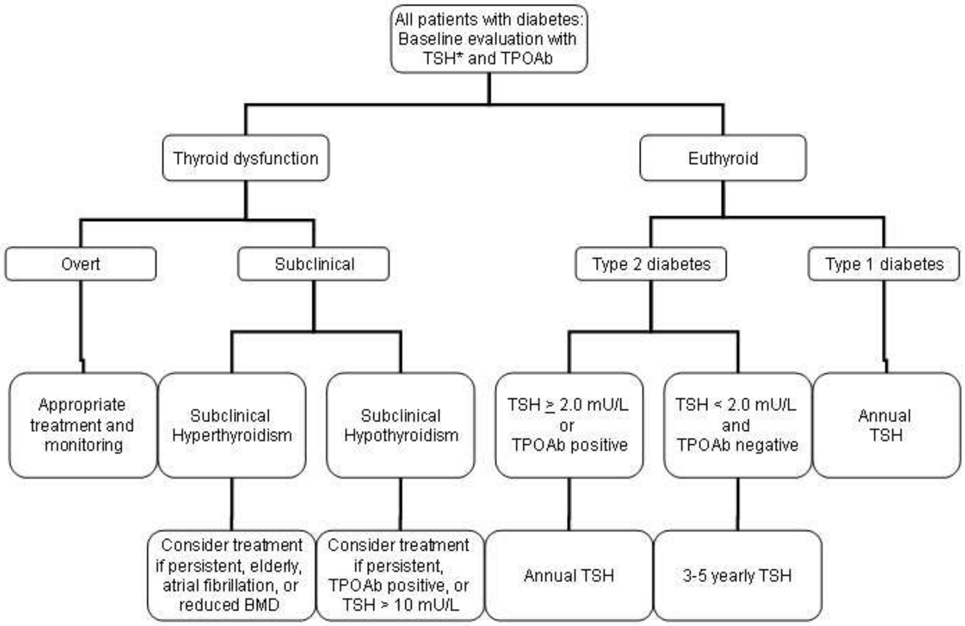

Figure 1: Simplified screening and monitoring algorithm for thyroid dysfunction patients with diabetes
* FT4 should be measured if TSH is abnormal.
254x190mm (72 x 72 DPI)