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Diabetes mellitus and hypothyroidism: Strange bedfellows or mutual companions?

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Abstract

Clinicians should be cognizant of the close relationship that exists between two of the most common endocrine disorders, primary hypothyroidism and diabetes mellitus. This applies to patients with both type 1 and type 2 diabetes mellitus (T1DM and T2DM respectively). However, the association is greater in T1DM, probably because of the shared autoimmune predisposition. In patients with T2DM, the relationship is somewhat weaker and the explanation less clear-cut. Factors such as dietary iodine deficiency, metformin-induced thyroid stimulating hormone suppression and poor glycemic control may all be implicated. Further translational research is required for greater clarification. Biochemical screening for abnormal thyroid function in individuals who have diabetes is warranted, particularly in females with T1DM, and therapy with L-thyroxine appropriately instituted if hypothyroidism is confirmed.

Key words: Type 1 diabetes; Type 2 diabetes; Primary hypothyroidism; Autoimmune disorders; Thyroid screening; Thyroid treatment

Core tip: Clinicians should be cognisant of the close relationship that exists between two of the commonest endocrine disorders, primary hypothyroidism and diabetes mellitus. This applies to both type 1 and type 2 diabetes. However the association is greater in type 1 diabetes, probably due to shared autoimmune predisposition. In type 2 diabetes, the connection is more complex. Biochemical screening for thyroid dysfunction in patients with diabetes is advised.

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INTRODUCTION

Two of the main clinical disorders encountered in endocrine clinics are diabetes mellitus and primary hypothyroidism. Diabetes can be divided into type 1 diabetes mellitus (T1DM), frequently the result of autoimmune islet-cell destruction, and T2DM, whose pathogenesis embraces both environmental and genetic components[1,2]. Primary hypothyroidism, on the other hand, usually follows autoimmune damage to thyroid tissue by circulating antibodies[3]. The concurrence of these two frequently encountered endocrine conditions in a particular patient has aroused much debate[4]. T1DM and primary hypothyroidism both share an autoimmune predisposition, while T2DM and hypothyroidism could be connected by the concurrence of two frequently occurring endocrine disorders.

The purpose of this review was to evaluate the evidence for an association of both T1DM and T2DM with hypothyroidism. The comparative frequencies of hypo-

Table 1 Prevalence of hypothyroidism in patients with type 1 diabetes *n* (%)

Gender	Number of subjects	Prevalence of hypothyroidism
Female	246	76 (30.9)[b]
Male	258	26 (10.1)
Total	504	102 (20.2)

[b]$P < 0.001$ *vs* males.

thyroidism in T1DM and T2DM were also assessed.

TYPE 1 DIABETES AND HYPOTHYROIDISM

Autoimmune thyroid disease is the commonest autoimmune disorder associated with T1DM[5]. This should not be surprising as T1DM and autoimmune thyroid disease share an autoimmune disposition, and recent studies have shown a shared genetic susceptibility to both conditions[6,7]. Regarding the shared genes involved in this immune predisposition, the *CTLA-4*, *HLA* class 11 and *FOXP3* genes have been implicated. Like T1DM, autoimmune thyroid disease is due to organ-specific autoimmunity. There is infiltration of the thyroid gland with T-lymphocytes and the formation of autoreactive antibodies, particularly against thyroglobulin and thyroid peroxidase (TPOAb). These antibodies are commonly found in patients with T1DM and may be present in up to 25% of patients with T1DM at the time of diagnosis of the diabetes[8]. The presence of thyroid antibodies is predictive of the later development of autoimmune thyroid dysfunction, usually hypothyroidism but also, less commonly, hyperthyroidism[9]. Umpierrez *et al*[10] reported that in patients with type 1 diabetes who had been followed for 18 years, those who were TPOAb-positive were much more likely to become hypothyroid than patients who showed negative antibodies at the outset.

Should hypothyroidism occur, even in a subclinical form, it may be associated with increased risk of hypoglycemia, by reduced hepatic glucose output and especially from impaired gluconeogenesis[11]. There may also be reduced linear growth in children and adolescents[12].

The prevalence of hypothyroidism in patients with T1DM has been estimated to be between 17% and 30%[5]. In our own recently published survey of T1DM at a private diabetes clinic in Johannesburg, South Africa[13], we found a 20.2% prevalence of hypothyroidism in 504 patients with established T1DM. Females showed a significantly higher prevalence than did males (30.9% *vs* 10.1%, $P < 0.001$) (Table 1). Our prevalence rate was slightly higher than that in a study by González *et al*[14], which involved smaller patient numbers. That report again emphasized that the presence of thyroperoxidase autoantibodies at T1DM onset was highly predictive for the development of subsequent thyroid dysfunction. In our survey, we also noted an increased prevalence of other organ specific autoimmune diseases such as Addison's disease, celiac disease and pernicious anemia, but at a much lower frequency.

TYPE 2 DIABETES AND HYPOTHYROIDISM

In T2DM, the association with hypothyroidism is more complex. It is unlikely to be a coincidence of two common endocrine disorders, since the prevalence of hypothyroidism is higher than in the general population. This has been demonstrated in a number of epidemiological studies including our own[15-18], with the prevalence of hypothyroidism varying between 11% and over 30% across different ethnic groups, as opposed to 4% reported in the general population[3-19]. The presence of undiagnosed hypothyroidism may increase cardiovascular risk by aggravating dyslipidemia, insulin resistance, obesity and vascular endothelial dysfunction[20,21]. Factors that could be implicated in this association are rather ill defined and may be complex. Insufficient iodine intake in the diet is one possibility, since a recent study highlighted reduced iodine consumption in 3 major American weight reducing programmes[22]. A report documenting a TSH-lowering effect of metformin in T2DM[23] may also be relevant, although the relationship between metformin and hypothyroidism is likely to be a complex one. Our study suggested that metformin usage might actually be protective against hypothyroidism in patients with T2DM or perhaps that suppressed thyroid-stimulating hormone caused by metformin may lead to physicians missing the diagnosis when thyroid-stimulating hormone measurement is the only screening method employed[16]. Additionally, poorly-controlled diabetes may induce alterations in thyroid function tests similar to that occurring in systemic illnesses i.e. lower levels of all thyroid hormone measurements[24]. Finally the possibility of alterations in the gut microflora being detected in both T2DM and thyroid dysfunction warrants attention. Further studies are clearly required to clarify the causal relationships between these two major endocrine disorders.

COMPARATIVE FREQUENCIES OF HYPOTHYROIDISM IN TYPE 1 AND TYPE 2 DIABETES

From our own large database of patients with diabetes in Johannesburg, we were able to establish that the overall frequency of diagnosed hypothyroidism in T1DM was almost double that seen in T2DM (Table 2). This applied to both female and male subjects. The closer association of hypothyroidism with T1DM probably reflects their well-established autoimmune predisposition and confirms the clinical observation that patients with one organ-specific autoimmune condition are at risk of developing other autoimmune diseases[25].

Table 2 Comparative prevalence of hypothyroidism in patients with type 1 and type 2 diabetes *n* (%)

Diabetic subgroup	Number of subjects	Prevalence of hypothyroidism
Type 1	504	102 (20.2%)[b]
Type 2	918	108 (11.8%)

[b]$P < 0.001$ *vs* type 2 diabetes.

RECOMMENDATIONS FOR THYROID SCREENING AND THERAPY

Hypothyroidism can be clinically silent or aspects of poor diabetes metabolic control may mask its clinical features. In view of the extremely high prevalence of hypothyroidism in those with T1DM, screening for thyroid disease should be done in a systematic fashion. Regular screening will unmask a substantial number of individuals with asymptomatic thyroid dysfunction. Current guidelines advise screening type 1 diabetic subjects at the time of diagnosis or initial contact[26,27].

Thereafter, it is recommended that the TSH is measured annually or two-yearly, but more frequently in antibody-positive patients or individuals who develop a goiter[28]. In the event of pregnancy, this becomes a necessity to prevent damage to fetal mental development secondary to undiagnosed maternal hypothyroidism[29].

For patients with T2DM, the recommendations for biochemical screening are less obvious and depend on factors such as sex, ethnic origin and age. Advice regarding routine testing is either vague[27] or firmly against routine yearly screening of type 2 diabetic patients[28]. Gopinath *et al*[30] reported no difference in the 5-year incidence of thyroid dysfunction in elderly patients with and without diabetes and another study by Chubb *et al*[31] also reported no development of frank hypothyroidism in female type 2 diabetes who manifested subclinical disease. This is in contrast to the data presented in this review, which highlights the increased prevalence of hypothyroidism in patients with T2DM. Selective periodic testing of patients with T2DM is probably warranted. Thyroid antibodies and serum thyroid stimulating hormone (TSH) levels are a useful means of identifying patients with diabetes who are at the greatest risk of thyroid dysfunction. Serum TSH concentrations in the upper range of normal appear to predict the development of future hypothyroidism. In one study involving subjects with both T1DM and T2DM, a TSH concentration above 1.53 mU/L predicted later hypothyroidism[32]. Therefore those with TSH concentrations in the upper normal range probably warrant more frequent, perhaps annual, re-testing. Regarding therapy in patients with diabetes, L-thyroxine should be instituted after confirmed biochemical diagnosis. Since patients with T2DM frequently have underlying ischemic heart disease, therapy in these patients should be started at low dosage (*e.g.*, 25 μg daily). This should be gradually increased over time, using the serum TSH level as a marker of adequate replacement. A serum TSH between 0.5 and 2.0 mU/L is generally considered the optimal target range to aim at[33].

CONCLUSION

Diabetes and hypothyroidism are indeed mutual companions based on the clinical studies that we have reviewed. This applies both to patients with T1DM and T2DM, although patients with T1DM are most predisposed. However, in both subtypes of diabetes, females are more vulnerable to develop hypothyroidism. Clinicians should be alerted to the close relationship that exists between these two common endocrine disorders and the importance of biochemical screening for hypothyroidism as indicated above. Appropriate thyroid replacement therapy can be introduced at an early opportunity, when required.

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