Diabetes and thyroid disorders

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Abstract
It has long been recognised that thyroid hormones have marked effects on glucose homeostasis. Glucose intolerance is associated with hyperthyroidism and most recently it was shown that hypothyroidism is characterised by insulin resistance. Although autoimmune thyroid disease is more prevalent in type 1 diabetes as a result of their common origin, in patients with type 2 diabetes the prevalence of hypothyroidism and hyperthyroidism is similar to that of the general population. However, in type 2 diabetic patients, the presence of the highly frequent sub-clinical forms of hyperthyroidism and hypothyroidism should be ruled out since they may be associated with higher cardiovascular risk. While there are no doubts about the therapeutic impact of normalising hypothyroidism and hyperthyroidism, the information available about the benefit of treating subclinical thyroid disease in diabetes remains insufficient.

Key words: diabetes, hyperthyroidism, hypothyroidism, insulin resistance, thyroid.

Introduction
The term ‘thyroid diabetes’ was coined in the early literature to depict the influence of thyroid hormone excess in the deterioration of glucose control, and for nearly a century many publications focused on the relationship between diabetes and thyroid disease. The literature concerning the effects of thyroid hormones on glucose metabolism in normal and diabetic states has been evaluated in detail. This review will therefore address only specific issues of a broad field. It is intended to illustrate some aspects of the prevalence of thyroid disorders in the general population and in diabetic patients, the pathological mechanisms underlying both diseases and the use, or potential use, of pharmacological therapies to treat diabetic and thyroid patients. A brief overview of long-term mortality or morbidity studies in patients with thyroid dysfunction and diabetes will also be presented.

Prevalence of thyroid disorders in the general population and in diabetic patients
Both hyperthyroidism and hypothyroidism are graded phenomena, ranging from very mild cases in which biochemical abnormalities are present without any symptoms or signs of thyroid hormone excess or deficiency, to very severe cases that may end up as a life-threatening thyrotoxicosis crisis or myxoedema coma. Their prevalence varies according to the studied population. The Whickham survey, conducted in the north of England, revealed a prevalence of overt thyrotoxicosis or hypothyroidism of at least 2% in females and 0.2% in males. In the NHANES III study it was shown that 4.6% of the US population had hypothyroidism (0.3% clinical and 4.3% subclinical) and 1.3%
had hyperthyroidism (0.5% clinical and 0.7% subclinical). The incidence of progression from sub-clinical to overt hypothyroidism is 5–15% per year; women with positive thyroid antibodies are especially at risk.

Sub-clinical hypothyroidism, the most prevalent form of thyroid diseases, is more common in females and in the elderly, reaching a prevalence of up to 20% in women over 60 years old. This increased prevalence in the elderly was recently questioned by Surks et al. whose re-analysis of the NHANES data revealed that TSH serum values might be shifted toward higher levels with increasing age. Accordingly, TSH levels up to 7.5 µU/mL would be considered normal in a patient 80 years and older and about 70% of the raised values for this age group would fall within the 97.5 centile of their age-specific range. Sub-clinical hypothyroidism is also more common in older age groups, but its female preponderance is less marked. The incidence of progression to overt thyrotoxicosis is approximately 5% per year; and patients with autonomous thyroid adenoma or nodular goitre are especially at risk.

The main causes of hypothyroidism and hypothyroidism are Hashimoto’s thyroiditis and Graves’ disease respectively, both of an autoimmune nature. Since type 1 diabetes also has autoimmunity as a pathophysiological detonator it is not unusual to find patients with concomitant diabetes and thyroid dysfunction. Some genetic factors might contribute to the co-occurrence of AITD and type 1 diabetes. Moreover the association between type 1 diabetes and AITD is considered one of the variants of the autoimmune polyglandular syndrome. The MHC locus on chromosome 6p21 is one of the susceptibility loci for both diseases. An odds ratio of approximately 2 has been reported for the association of the DR3 haplotype with Graves’ disease, which is even higher, between 3 and 4, in people who have type 1 diabetes. Several other factors that intervene in the immune response might also contribute to AITD and type 1 diabetes susceptibility. PTPN22, which encodes lymphoid tyrosine phosphatase, a negative regulator of T-cell antigen receptor (CD3) signalling and the cytotoxic T-lymphocyte antigen-4 (CTLA4) gene have both been confirmed as major joint susceptibility genes for type 1 diabetes and AITD.

Prevalence studies show that AITD is higher in type 1 diabetes. Perros et al. reported thyroid dysfunction in up to 31.4% of adult type 1 diabetic females. Moreover, in children with type 1 diabetes, the proportion of positive thyroid antibodies might increase up to 20% and about 3–8% of children and adolescents with type 1 diabetes have been reported to develop autoimmune hypothyroidism. Postpartum thyroiditis, a rather common event, with an incidence of 4–6% as evident from several population-based studies, is threefold higher (up to 25%) in women with type 1 diabetes.

Although thyroid disease, overt or sub-clinical, is reported to be relatively common in type 1 diabetes, a longitudinal Australian study in type 2 diabetic women without known thyroid disease showed that sub-clinical hypothyroidism is a common, but incidental finding. Nevertheless, increased risk for thyroid autoimmunity in adult type 2 diabetic patients with GAD65 autoantibodies has been reported, and these findings have been confirmed in paediatric populations. As regards the metabolic syndrome, as might be expected, the prevalence of sub-clinical hypothyroidism is higher in patients with the condition than in non-metabolic syndrome subjects. These findings can be explained by the concomitance of deranged serum lipid concentrations, obesity, hypertension and insulin resistance, all components present in metabolic syndrome as well as in hypothyroid patients.

In view of the relatively high prevalence of both endocrinopathies, it is important to investigate all diabetic patients for thyroid disorders. However, screening has been recommended only in children and adolescents with type 1 diabetes. 7,16 TSH should be tested several weeks after the diagnosis of type 1 diabetes, when metabolic control has been established. If the TSH level is normal, patients should have a repeat measurement every 1–2 years. Additional thyroid function testing should be obtained whenever thyroid dysfunction is suspected or thyromegaly is detected. With regards to diabetic adults, there is no consensus as to whether screening for thyroid disorders should be mandatory.

Pathological mechanisms common to thyroid disorders and diabetes

Thyroid hormones exert profound effects in the regulation of glucose homeostasis. These effects include modifications of circulating insulin levels and counter-regulatory hormones, intestinal absorption, hepatic production and peripheral tissues (fat and muscle) uptake of glucose (figure 1). It has long been known that thyroid hormones act differentially in liver, skeletal muscle and adipose tissue – the main targets of insulin action. While thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis, they up-regulate the expression of genes such as GLUT-4 and phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin in

![Figure 1. Thyroid hormone (TH) effects on glucose homeostasis](image-url)
facilitating glucose disposal and utilisation in peripheral tissues. The recent identification of another gene regulated by thyroid hormones in cultured human fibroblasts,\textsuperscript{22} the transcription factor HIF-1\textalpha, responsible for elevated expression of glycolytic enzymes and glucose transporters, is an example that the field of thyroid diabetes is still open to new discoveries.

Thyroid disorders have a major impact on glucose control. When thyroid dysfunction ensues the glucose homeostatic balance is broken (figure 2). Insulin resistance, mainly associated with increased hepatic gluconeogenesis, is characteristic of an excess of thyroid hormones and explains why glucose control deteriorates when diabetic patients develop hyperthyroidism. Thyrotoxic patients show an increased glucose turnover with increased glucose absorption through the gastrointestinal tract, postabsorptive hyperglycaemia and elevated hepatic glucose output, along with elevated fasting or postprandial insulin and proinsulin levels, elevated free fatty acid concentrations and elevated peripheral glucose transport and utilisation. In peripheral tissues there is a massive arrival of glucose to the cells that overwhelms the Krebs cycle resulting in an increased metabolism of glucose through the nonoxidative pathway. Lactate produced in great quantities in the cells returns to the liver and participates in the Cori cycle where four ATP molecules are wasted for each glucose molecule that is created.\textsuperscript{23}

Although glucose uptake in peripheral tissues has been described as either normal or increased,\textsuperscript{24,25} reduced insulin-stimulated peripheral glucose utilisation has also been demonstrated in hyperthyroidism.\textsuperscript{26} The notion that insulin stimulation of glucose uptake in thyrotoxic tissues may be impaired can be interpreted in the context of lower glucose extraction from serum in proportion to increased blood flow.\textsuperscript{27} As regards insulin secretion, thyroxinosis has been associated with either normal, decreased or increased beta-cell function.\textsuperscript{2,28} However, it has been suggested that proinsulin in excess may account for the hyperinsulinemia observed with higher release of insulin both after absorption and at baseline, when compared with the euthyroid situation or with control subjects.\textsuperscript{2} Moreover, recent studies have shown that thyroid hormones increase beta-cell apoptosis and that this could be one major element responsible for deterioration of glucose tolerance in thyrotoxicosis.\textsuperscript{2,29}

In hypothyroidism, glucose homeostasis is also affected although its clinical impact is less obvious (figure 3). Decreased glucose disposal (as compared with euthyroid subjects) has been proved in hypothyroid patients by different methods including clamp studies,\textsuperscript{30,31} the arteriovenous difference technique in the anterior abdominal subcutaneous adipose tissue and forearm muscles after the consumption of a mixed meal,\textsuperscript{32} the insulin tolerance test\textsuperscript{33} and following intravenous\textsuperscript{34} or oral\textsuperscript{35} administration of glucose. Nonetheless, hypothyroidism results in unimpaired\textsuperscript{36} or decreased\textsuperscript{37,38} liver glucose output thereby compensating for insulin resistance present in peripheral tissues and accounting for the diminished insulin requirement for glycaemic control in hypothyroid diabetic patients. As regards to beta-cell function, normal or reduced basal plasma insulin levels have been described in hypothyroidism. These findings are quite consistent with the idea of attenuated endogenous glucose production in the hypothyroid state.\textsuperscript{2} On the other hand, increased glucose-stimulated insulin secretion has been recently described in humans and interpreted as a response to elevated whole-body insulin resistance increasing demand on beta cells.\textsuperscript{31}

Although most of these observations apply to overt hypothyroidism, insulin resistance has been also reported in subclinical hypothyroidism,\textsuperscript{35} adding one more possible mechanism to the association of sub-clinical hypothyroidism and cardiovascular risk. Furthermore, it has been shown, both in euthyroid non-diabetic\textsuperscript{39} and diabetic adults,\textsuperscript{40} that small variations in TSH at different levels of insulin sensitivity might exert a marked effect on lipid levels. The interaction between insulin resistance and lower thyroid function might be a key determinant for a more atherogenic lipid profile in these populations (figure 4).

Even though thyroid status, as assessed by plasma hormone levels, is a key indicator of glucose homeostasis, T3 intracellular pathways are also relevant. The hormonal message is modulated at a local level by a series of control steps, including
the intracellular concentration of T3 via deiodinases, and the relative concentration of T3 receptor isoforms, co-activators, and co-repressors. These systems ultimately result in tissue-specific thyroid hormone action, which is relatively independent of the circulating thyroid hormone levels. Polymorphism Thr92Ala, which confers a lower activity to type 2 deiodinase, has been associated with insulin resistance in some populations and is a good example of hidden regulatory mechanisms.

**Intervention strategies for thyroid disorders**

Among the intervention strategies for hyperthyroidism, conventional treatment modalities include antithyroid drugs, radioiodine or surgery. Hypothyroidism is conventionally treated with replacement doses of levothyroxine. As regards sub-clinical forms of both conditions, due to the paucity of conclusive data derived from clinical trials, evidence-based recommendations are cautious and sometimes not conclusive when TSH levels are slightly deranged. Individualisation of therapy is most probably the answer in these patients. The presence of several cardiovascular risk factors in diabetic patients with sub-clinical thyroid impairment should be taken into consideration for therapeutic purposes.

Some special situations must be considered with regards to the pharmacological aspects of the drugs commonly used to treat diabetic and thyroid patients. It has been reported that certain sulphonylureas can inhibit the synthesis of thyroid hormone. They include older generation drugs such as carbutamide, tolbutamide, methahexamide, and possibly chlorpropamide. Moreover, metformin has been shown to reduce thyrotropin levels in diabetic patients with primary hypothyroidism on thyroxine replacement therapy. Thiazolidinediones, on the other hand, have been reported to induce thyroid-associated orbitopathy. Another situation in which to apply caution is with the use of statins in diabetes. Myopathy can be much more common in statin-treated diabetic patients with undiagnosed hypothyroidism.

Thyroid hormone analogues are still under development. Some special situations must be considered with regards to the pharmacological aspects of the drugs commonly used to treat diabetic and thyroid patients. It has been reported that certain sulphonylureas can inhibit the synthesis of thyroid hormone. They include older generation drugs such as carbutamide, tolbutamide, methahexamide, and possibly chlorpropamide. Moreover, metformin has been shown to reduce thyrotropin levels in diabetic patients with primary hypothyroidism on thyroxine replacement therapy.

**Diabetes plus thyroid disorders: long-term mortality or morbidity**

As previously mentioned, sub-clinical hypothyroidism and hyperthyroidism have both been linked to increased cardiovascular risk. Only a few studies have explored the effects of sub-clinical thyroid dysfunction in the diabetic population. One of these studies was performed in 588 Taiwanese type 2 diabetic patients with sub-clinical hypothyroidism compared with euthyroid patients. In the cross-sectional analysis, sub-clinical hypothyroidism was associated with a higher frequency of nephropathy (after adjustment for, among other factors, age, sex and HbA1c). After 4 years, sub-clinical hypothyroidism was associated with a higher rate of incident cardiovascular events in patients with type 2 diabetes, although this became non-significant after additional adjustment for urinary albumin:creatinine ratio. In line with these findings are the results of another cross-sectional study of 1,170 type 2 diabetic patients. Patients with sub-clinical hypothyroidism had a higher prevalence of retinopathy, especially the sight-threatening form, when compared with their type 2 diabetic euthyroid counterparts.

Mortality has been explored in 382 women with type 2 diabetes belonging to the Fremantle Disease Study, which has a follow-up of 9 years. Only a borderline significance for the effect of serum TSH status on all-cause and cardiac mortality was observed in the lowest serum TSH category. This study was included in a meta-analysis by Haentjens et al. which reported that compared with euthyroid control subjects, sub-clinical hyperthyroidism yielded a significant 1.49-fold increase in relative likelihood of death from all causes. In the general calculation, global mortality was not increased in sub-clinical hypothyroidism. However, after the analysis was stratified by studies with patients with co-morbidities (atomic bomb survivors, type 2 diabetes, cardiac, stroke, or hip-fracture patients) all-cause mortality was significantly higher than in the euthyroid population. On the other hand a retrospective analysis of a diabetes database of 6,540 patients showed a lower mortality rate in patients with elevated TSH levels at baseline (mean age of patients was 73 years) versus an age-matched euthyroid group. These results support the previous notion that the higher mortality risk in a sub-clinical hypothyroid patient is mainly observed in patients below 65 years of age.

**Conclusions**

The impact of thyroid alterations on glucose metabolism has been known for a long time. Thyrotoxic patients usually lose their glucose control when thyroid decompensation is not promptly solved. Most recently, new pathways of thyroid hormone action at the tissue level have been unveiled and may be of relevance to the understanding of insulin resistance present both in the hypothyroid and hyperthyroid state.

While thyroid disorders are more prevalent in people with type 1 diabetes, due to common autoimmune origin, a similar prevalence of thyroid disease has been reported in type 2 diabetes. On the other hand, a much higher frequency of sub-clinical hypothyroidism has been reported in metabolic syndrome patients.
Key messages

- In diabetes mellitus, the development of thyrotoxicosis is associated with deranged metabolic control, increased insulin requirements and ketoacidosis
- Insulin resistance is evident in overt and subclinical hypothyroidism
- Prevalence ofAITD
  - is higher in type 1 diabetes
  - is similar in the general population and type 2 diabetes
- In type 2 diabetes
  - AITD increases cardiovascular risk
  - concomitant subclinical hypothyroidism increases risk of nephropathy and retinopathy

These findings are not surprising since several metabolic syndrome traits are associated with hypothyroidism.

The co-existence of both diabetes and thyroid disorders has been associated with increased long-term morbidity and mortality. Although the benefits of treating overt thyroid disease are clear, the management of sub-clinical hypothyroidism or hyperthyroidism is not yet solved and conclusive intervention studies are required. It has been suggested that the decision to treat should be taken on an individual approach. In this case, insulin-resistant, dyslipidaemic or diabetic patients, who are at higher risk of cardiovascular disease, might be special cases for whom treatment of sub-clinical thyroid disease has to be seriously considered.

References

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