

Should we be screening for thyroid dysfunction in patients with type 2 diabetes mellitus?

INTRODUCTION

There are increasing data to support a link between type 2 diabetes mellitus (T2DM) and thyroid disease. Screening for thyroid disease in patients with T2DM may therefore warrant consideration, particularly because the biochemical testing involved is straightforward. However, this is not recommended in current guidelines. This article will discuss the link between these conditions and explore the gaps in guidance regarding screening patients with T2DM for thyroid dysfunction.

PREVALENCE OF THYROID DYSFUNCTION IN PATIENTS WITH T2DM

Data from a large European meta-analysis indicate that the prevalence of thyroid dysfunction in the general population, including subclinical disease, is 3.82%, with 3.05% and 0.75% for hypothyroidism and hyperthyroidism, respectively.¹ Several cross-sectional studies have illustrated a significantly higher prevalence of thyroid disorders in patients with T2DM.²⁻⁶ The largest of these studies found that prevalence of thyroid dysfunction in patients with T2DM was 6.9% in males and 10.9% in females.² Similar findings have been reported in a number of smaller studies (details available from authors on request). Consistent with findings in the general population,¹ in patients with T2DM, thyroid dysfunction was more prevalent in females than males and cases of hypothyroidism more frequent than hyperthyroidism. Biochemically subclinical hypothyroidism was generally the most common finding, though one study demonstrated preponderance for overt disease. A number of studies either excluded participants with previously known thyroid disease,^{3,4} or performed a sub-analysis on this group.^{2,5,6} In these circumstances, subclinical hypothyroidism was clearly the predominant finding, suggesting that the majority of undiagnosed thyroid disease would be of this type; this observation was consistent with those made in the general population.¹

A number of studies have examined this association by directly comparing the prevalence of thyroid dysfunction in groups of patients with T2DM with that in non-diabetes groups. Diez and Iglesias studied 1112 patients with T2DM and 911 controls, and found that 18.3% of patients with T2DM had hypothyroidism, compared with 2.9% in

the comparator group ($P \leq 0.001$), with overt hypothyroidism the most common form (9.9%).⁷ Consistent with other studies, when patients with pre-existing thyroid dysfunction were excluded, subclinical hypothyroidism was most prevalent (6.9%, compared with 0.4% for overt hypothyroidism).⁷ Other studies support a higher prevalence of thyroid dysfunction in T2DM (details available from authors on request). However, a small number of studies have failed to show a significant association. Gopinath *et al*⁸ found that, although 7.1% of T2DM patients had thyroid dysfunction, compared with 3.8% in those without diabetes, this was not statistically significant ($P = 0.1$). Similarly, Ishay *et al*⁹ found no difference in subclinical hypothyroidism prevalence between patients with T2DM and controls.

Support for a link is further emphasised by a meta-analysis of subclinical hypothyroidism in T2DM, which showed subclinical hypothyroidism was almost twice as likely [adjusted odds ratio 1.93, CI = 1.66 to 2.24] in the T2DM population compared with the general population.¹⁰ The authors also concluded that patients with both T2DM and subclinical hypothyroidism were more likely to suffer the complications of diabetes and therefore recommended screening patients with T2DM for thyroid disorders.

CONSEQUENCES OF THYROID DISEASE ON TYPE 2 DIABETES MELLITUS

Although the increased prevalence of thyroid dysfunction in T2DM is of importance with regard to thyroid disease itself, there are also potentially significant implications for diabetes management.

Impact of hyperthyroidism on diabetes

It has been observed that hyperthyroidism promotes hyperglycaemia,¹¹ and a number of mechanisms have been put forward to explain this effect. The half-life of insulin is reduced in a thyrotoxic environment; this is thought to be due to an increased degradation of the active hormone and release of inactive precursors.¹² In addition, hyperthyroidism is thought to stimulate glucose production, via a number of proposed mechanisms including

up-regulation of gluconeogenesis, secondary to increased lipolysis and overproduction of lactate, as well as increased hepatic output through increased expression of the GLUT2 glucose transporter.¹² These are compounded by enhanced absorption of glucose in the gastrointestinal tract.¹² Together, these mechanisms contribute to the understanding of why diabetes patients with hyperthyroidism may find their blood glucose levels worsening when their hyperthyroidism is not controlled.¹²

Impact of hypothyroidism on diabetes

Hypothyroidism can also affect diabetes control. Hypoglycaemic episodes can occur due to the decreased production of glucose from the liver,¹² meaning that hypothyroidism may mask the clinical signs and symptoms of diabetes. This also explains why diabetes patients with hypothyroidism may require less insulin than their counterparts without thyroid disease.¹³

The meta-analysis by Han *et al* demonstrated a possible association of subclinical hypothyroidism with the development of diabetic nephropathy (odds ratio [OR] 1.74, confidence interval [CI] = 1.34 to 2.28), diabetic retinopathy (OR 1.42, CI = 1.21 to 1.67), peripheral artery disease (OR 1.85, CI = 1.35 to 2.54), and diabetic peripheral neuropathy (OR 1.87, CI = 1.06 to 3.28). The authors hypothesised that this may be because patients with abnormal thyroid function have reduced cardiac output, which can affect renal function.¹⁰

WHAT DO THE GUIDELINES SAY?

In contrast to guidance for T1DM, there is a lack of clear and consistent recommendations on the screening for thyroid disease in patients with T2DM. The UK National Screening Committee concluded that thyroid disease screening in the general population is unwarranted as there is lack of agreement as to what is considered a normal thyroid hormone level and some patients' thyroid levels will return to normal without treatment.¹⁴ Similarly, the US Preventive Service Taskforce states, 'the current evidence is insufficient to assess the

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balance of benefits and harms of screening for thyroid dysfunction in non-pregnant asymptomatic adults', and does not classify T2DM as a risk factor for thyroid disease.¹⁵

In the 2015 National Institute for Health and Care Excellence (NICE) guidelines *Type 2 Diabetes in Adults: Management*, there is no mention of monitoring thyroid function in T2DM,¹⁶ as is the case for the American Diabetes Association *Standards of Medical Care in Diabetes—2017*.¹⁷ The British Thyroid Association recommends that patients with T2DM should be screened for thyroid disease at diagnosis only.¹⁸ The American Thyroid Association recommends that adults aged ≥35 years should be screened for thyroid disorders every 5 years, regardless of whether they have diabetes or not.¹⁹ The evidence behind this is based on a cost–utility analysis using a computer-based decision model for the US healthcare system, and so may not be generalisable.

CONCLUDING REMARKS

The literature suggests an increased prevalence of thyroid disease in patients with T2DM. In studies where patients with prior known thyroid dysfunction were excluded, subclinical hypothyroidism was the most frequent new diagnosis, whereas in studies that included all patients with T2DM, the prevalence of overt and subclinical disease was similar. The studies examined did not generally consider whether prior thyroid dysfunction was identified incidentally, or due to regular screening, outside guidance, because of the T2DM status. It is therefore difficult to assess the impact of a move to routine screening. Nonetheless, it is reasonable to assume that subclinical hypothyroidism would constitute a substantial proportion of new cases, and the merits of identifying this milder form are subject to ongoing debate. However, there is clear guidance from the British Thyroid Association,¹⁸ supported by a NICE Clinical Knowledge Summary,²⁰ on the actions required on identifying subclinical hypothyroidism. In some cases, treatment will be necessary; in others, determining thyroid peroxidase (TPO) antibody status will inform frequency of monitoring. Something that further feeds into the debate for this population is the suggestion that subclinical hypothyroidism may promote the development of diabetic complications.¹⁰

Anecdotal, we know that a proportion of patients with T2DM are already screened regularly for thyroid disease. Given the evidence presented here and the relatively low cost of a serum TSH measurement, this may be appropriate. However, we are

not aware of work that has evaluated this formally. A future assessment of the extent of this practice, using relevant real-world data, along with an evaluation of cost–benefit, may help inform the case for routine screening and ultimately bring clarity to this area of clinical practice.

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