

# Type 2 diabetes mellitus and thyroid dysfunction: an intertwined duo

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## Introduction

Diabetes and thyroid diseases are two common endocrinopathies seen in the general population. Diabetes is a group of aetiologically different metabolic defects characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both.

The World Health Organisation (WHO) has projected that the global prevalence of diabetes will rise to 300 million (7.8%) by 2030.<sup>1</sup> Factors such as sedentary lifestyle, dietary indiscretions, ethnicity, hypertension and obesity are thought to be major contributions to this epidemic.<sup>2</sup>

Thyroid disorders are also common, with variable prevalence among different populations. Abnormal thyroid hormone levels can also be found in individuals with diabetes. The first reports showing the association between diabetes and thyroid dysfunction were published in 1979.<sup>3,4</sup> Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism and excess and deficit of either one can result in functional derangement of the other. Studies have shown that hypothyroidism (Hashimoto's thyroiditis) or hyperthyroidism (Grave's disease) are associated with diabetes. A meta-analysis reported a prevalence of thyroid dysfunction in patients with diabetes of 11%.<sup>6</sup> In chemically induced diabetic animals, the alterations in the hypothalamo-pituitary-thyroid axis include reduction in hypothalamic and plasma thyrotrophin-releasing hormone (TRH), pituitary and plasma thyroid-stimulating hormone (TSH) as well as diminished tri-iodothyronine (T3) and thyroxine (T4) production.<sup>7,8</sup> Unmanaged pre-diabetes, both type 1 and type 2, may induce a 'low T3 state' characterised by low serum total and free T3 levels, increase in reverse T3 (rT3) but near-normal serum T4 and TSH concentrations.<sup>9</sup> The relation between type 2 diabetes and thyroid dysfunction is an important area of research as it could give further insights into the pathophysiological processes of metabolic syndrome, atherosclerosis, and related cardiovascular disorders.

## Epidemiology

The reported prevalence of thyroid disorders in the

diabetic population varies with the characteristics of the study population. A study was carried out among diabetic patients in Calabar, Nigeria for which 161 diabetic subjects and 105 non-diabetic controls were selected. The authors reported a high incidence (46.5%) of abnormal thyroid hormone levels among diabetic patients; the prevalence of hypothyroidism was higher in women than in men, while the prevalence of hyperthyroidism was higher in males.<sup>10</sup> Similarly, Radaideh et al. in Jordan, reported a prevalence of thyroid dysfunction in type 2 diabetic patients of 12.5%.<sup>11</sup> Bal et al. in India also found a prevalence of thyroid diseases of 40.4% among 184 type 2 diabetic patients, with a positive correlation with age of patient in the thyroid dysfunction group.<sup>12</sup>

Pasupathi et al. investigated the effect of diabetes on thyroid hormone levels and other biochemical variables. In their study, it was found that the levels of TSH were significantly decreased, whereas the levels of T4 and free T4 (FT4) were significantly increased, in diabetic patients compared with control subjects. However, the T3 and FT4 levels did not differ significantly between groups.<sup>13</sup> Islam et al. investigated thyroid hormone levels in 52 uncontrolled diabetic patients and 50 controlled subjects. They reported that patients with type 2 diabetes had significantly lower serum FT4 levels compared with the control and study subjects.<sup>14</sup> Bazrafshan et al. in their study of 210 type 2 diabetic patients assessed the relationship between thyroid dysfunction and diabetes. The observed disorders included goiter (30%), sub-clinical hypothyroidism (13%), clinical hypothyroidism (4%), and clinical hyperthyroidism (0.5%). A significant positive correlation was observed between haemoglobin (HbA1c) concentration and TSH levels among the subjects.<sup>15</sup>

These studies further emphasise that diabetes and thyroid dysfunction are related and have common pathophysiological mechanisms, as will be explained below.

## Pathophysiological correlates of thyroid disease and type 2 diabetes

Insulin resistance is a key pathological feature of type 2 diabetes and also occurs in both hypothyroidism and hyperthyroidism.<sup>16</sup> Insulin resistance and B-cell function are inversely correlated with TSH, which may be explained by the insulin-antagonistic effects of thyroid hormones along with an increase in TSH.<sup>17</sup> The high serum TSH corresponds to lower T<sub>3</sub> and T<sub>4</sub> levels which weakens the insulin antagonistic effects. This observation demonstrates that insulin imbalance is associated

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closely with thyroid dysfunction and is mediated via B-cell dysfunction.<sup>18</sup>

The liver muscles and fat tissues also play major roles in the inter-relationship between thyroid dysfunction and type 2 diabetes. In hyperthyroidism, endogenous glucose production is increased and this causes a reduction in insulin sensitivity in the liver<sup>19</sup> due to glycogenesis and glycogenolysis. This effect is proposed to be mediated by glucose transporter 2 (GLUT 2) transporters in the liver which ultimately leads to elevation in plasma free fatty acids.<sup>19,20</sup>

In the skeletal muscle, there is a significant increase in the utilisation of glucose in the hyperthyroid state.<sup>21</sup> Hyperthyroidism has also been reported to be associated with enhanced insulin sensitivity.<sup>22</sup> Increased peripheral insulin resistance is mediated by expression of adipokines (interleukin-6 (IL-6) and tumour necrosis factor (TNF)- $\alpha$ ).<sup>23</sup> Insulin resistance has also been demonstrated in hypothyroidism in vitro and in pre-clinical studies.<sup>24–27</sup> Subclinical hypothyroidism has also been reported to be associated with insulin.<sup>27</sup>

The majority of the hormones secreted by the thyroid gland are largely bound to thyroid binding globulin (TBG). A smaller amount circulates in the plasma as FT<sub>4</sub> and FT<sub>3</sub>. Suzuki et al in their study attributed the abnormal thyroid hormone levels found in diabetic patients to the presence of thyroid hormone binding inhibitor (THBI), an inhibitor of the extra thyroidal conversion enzyme (5-deiodinase) of T<sub>4</sub> to T<sub>3</sub>, and dysfunction of the hypothalamo-pituitary-thyroid axis.<sup>28</sup> These features were observed to be aggravated by stress and poorly controlled diabetes.

## Anti-diabetic therapy and thyroid dysfunction

The use of oral hypoglycaemic medications in the treatment of patients with type 2 diabetes also has varying effects on thyroid hormone homeostasis. Cappelli et al. in their study evaluated thyroid hormone profiles by studying the interaction between metformin and circulating thyroid function parameters in patients who were started on metformin. A pilot study of diabetic hypothyroid patients revealed a baseline reduction of TSH level after 6 months. Similarly, a large cohort study carried out on diabetic patients showed a significant fall in TSH level in euthyroid patients on L-T<sub>4</sub> substitution and subclinical hypothyroid patients who did not receive L-T<sub>4</sub> treatment, except in euthyroid patients after 1 year on metformin. This study concluded that the TSH-lowering effect of metformin is only seen in untreated hypothyroid patients and with L-T<sub>4</sub> replacement therapy irrespective of thyroid function test.<sup>30,31</sup>

Insulin also has effects on thyroid hormones. It is known that insulin, an anabolic hormone, enhances the levels of FT<sub>4</sub> while it suppresses the level of T<sub>3</sub> by inhibiting the hepatic conversion of T<sub>4</sub> to T<sub>3</sub>.<sup>32</sup> On the other hand, other hypoglycaemic agents, such as phenylthiourea, are known to suppress the levels of FT<sub>4</sub> and T<sub>4</sub>, while causing raised levels of TSH.<sup>33,34</sup>

## Detection of thyroid dysfunction in type 2 diabetes

Studies done have unequivocally stated that testing for thyroid dysfunction in type 2 diabetes patients is necessary and should be carried out annually.<sup>35</sup> The American Thyroid Association guidelines for type 2 diabetes patients require frequent testing for thyroid dysfunction.<sup>35</sup> They recommend testing at 35 years of age, and every 5 years thereafter in adults. High-risk persons may require more frequent tests. Diabetes is mentioned as a high-risk factor, but no distinction is made between type 1 and type 2 diabetes.<sup>35</sup> The American Association of Clinical Endocrinologists, Thyroid Disease Clinical Practice Guidelines (2002) recommend thyroid palpation and measurement of TSH levels in diagnosis, especially if goiter or other auto-immune disease presents in association with type 2 diabetes.<sup>36</sup> The British Thyroid Association and the Association of Clinical Biochemistry Guidelines recommend assessment of baseline thyroid function tests, TSH and antibodies for diabetic patients in pregnancy and post-partum.<sup>37</sup> For the African region, any of the above could be modified and adopted as protocols for regular screening for thyroid abnormalities in all diabetic patients, which will allow early treatment of sub-clinical thyroid dysfunction. A sensitive serum TSH assay is the screening test of choice.

## Conclusion

There is growing evidence of an association between thyroid dysfunction and diabetes. Uncontrolled hyperthyroidism in diabetes 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 though inter-relationships with dyslipidaemia, insulin resistance, and vascular endothelial dysfunction. It is therefore important to diagnose thyroid dysfunction in diabetic patients and this practice should be inculcated in clinical settings. This would encourage further understanding of the relationship between thyroid function and diabetes, thereby reducing morbidity and mortality from these conditions.

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