Thyroid disorders and diabetes
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Abstract
Thyroid disorders and diabetes mellitus are two of the most common endocrine conditions, which occur with greater frequency along with each other. This communication describes current knowledge about these twin diseases. Epidemiology, clinical features, laboratory abnormalities, screening and therapeutic implication of this relationship are discussed. The article underlines the clinical relevance of thyroid disorder in diabetes management.

Keywords: Thyroid disorders, Endocrine conditions,

Introduction
Diabetes mellitus is a multifaceted syndrome, whose clinical presentations extend far beyond the pancreas. Various endocrine and non-endocrine organs are affected in persons with diabetes. Similarly, the impact of thyroid disorders is much more than what would be expected from dysfunction of a "mere 25g" gland. As both diabetes and thyroid dysfunction take on epidemic proportions, the frequency of their occurring as comorbid conditions in the same person is bound to grow.

This article reviews the multiple links between diabetes and thyroid dysfunction, and highlights their clinical relevance (Table-1). Since the advent of genome with association studies (GWAS), fresh insights have been gained into the common susceptibility loci of diabetes and thyroid disease.1

Frequency of Co-Occurrence
Many studies, including community-based, clinic- based, and indoor patient based, have demonstrated the higher prevalence of thyroid dysfunction in both type 1 and type 2 diabetes, across all age groups. Some of this data has been elegantly reviewed by Kadilaya et al in 2010.2 The largest study on type 1 diabetes and thyroid dysfunction reported so far, found a prevalence of 9.5% thyroid dysfunction among 7097 children and adolescents.3 A large clinic based study of 1310 type 1 and type 2 diabetes in adults reported a 13.4% overall prevalence of thyroid dysfunction, including 8.8% in men and 16.8% in women.4 A smaller study from north India reported a prevalence of 17.4% hypothyroidism, and 13.1% subclinical hypothyroidism, in girls with type 1 diabetes, and 4.2% subclinical hypothyroidism in boys with the same condition. In a longitudinal study, up to a third of patients with type 1 diabetes were found to finally develop thyroid dysfunction.5 Up to 25% of women with the condition experienced postpartum thyroid dysfunction.6 The earlier onset of diabetes that is being experienced now, and longer survival of persons living with diabetes, coupled with better screening for thyroid function, may lead to a greater prevalence of thyroid dysfunction in persons with diabetes in the near future. This makes it important for us to study the relationship between these two endocrine conditions.

Thyroid Dysfunction in Type 1 Diabetes
Both type 1 diabetes and autoimmune thyroid disease (AITD) share a common auto immune etiology. A combination of genetic and environmental factors Table-2: Thyroid dysfunction in type 1 diabetes.


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Table-1: Diabetes mellitus and thyroid disorders: multifaceted relationship.

<table>
<thead>
<tr>
<th>Co-Existence</th>
<th>Co-Morbidity</th>
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<tbody>
<tr>
<td>Type 1 diabetes and autoimmune thyroid disease</td>
<td>Obesity/ weight loss</td>
</tr>
<tr>
<td>Type 2 diabetes and thyroid disorders</td>
<td>Dyshlipidaemia</td>
</tr>
<tr>
<td>Common Co-Morbidity</td>
<td>Depression</td>
</tr>
<tr>
<td>Unrecognized/ untreated thyroid dysfunction may precipitate</td>
<td>Impact on Therapy</td>
</tr>
<tr>
<td>Hypoglycaemia and Poor glycaemic control</td>
<td>Reduction in absorption of L-thyroxine by concomitant drug therapy.</td>
</tr>
<tr>
<td>Serum TSH- modulating effect of metformin.</td>
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</tbody>
</table>

Table-2: Thyroid dysfunction in type 1 diabetes.

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Hashimoto's thyroiditis</td>
</tr>
<tr>
<td>Euthyroid</td>
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<tr>
<td>Hypothyroid</td>
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<tr>
<td>Graves' disease</td>
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<tr>
<td>Postpartum thyroiditis</td>
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<tr>
<td>Polyglandular autoimmune syndromes (PAS)</td>
</tr>
<tr>
<td>PAS-1</td>
</tr>
<tr>
<td>PAS-2</td>
</tr>
<tr>
<td>Co-occurrence with coeliac disease, Addison disease</td>
</tr>
</tbody>
</table>
interacts to produce immune dysfunction, in the pancreas, the thyroid, or other susceptible organs. The temporal profile of occurrence of organ-specific autoimmune dysfunction, however, varies from person to person. The thyroid dysfunctions noted in type 1 diabetes are listed in Table-2.

**Hypothyroidism and Type 2 Diabetes**

Hypothyroidism is the most common form of thyroid dysfunction in the general population as well as those with diabetes. The etiology is similar in both diabetes and non-diabetic cohorts.

Hypothyroidism predisposes to hypoglycaemia, and at the same time, causes insulin resistance. Types of diabetes, per se is associated with abnormal thyroid function in certain clinical settings, including severe hyperglycaemia and nephropathy. Presence of diabetes is also associated with inadequacy of thyroid hormone replacement in elderly hypothyroid patients. Such a link has not been demonstrated for other chronic diseases. Metformin, a commonly used drug for diabetes, has demonstrated TSH-lowering properties.

Diabetes and hypothyroidism also meet each other through various common clinical characteristics. Both are independently associated with overweight/obesity, dyslipidaemia, hypertension, and depression. A combination of both diabetes and hypothyroidism puts the person at higher risk of insulin resistance and cardiovascular disease (Table-3). Uncontrolled hypothyroidism may mask the clinical features of diabetes, which becomes evident only after a euthyroid state is achieved.

Subclinical hypothyroidism has been the focus of interest in the past few years. Researchers aim to identify specific subjects of persons with subclinical hypothyroidism that may benefit from early thyroxine replacement. The presence of diabetes has not been shown to predict faster progression from subclinical to overt hypothyroidism.

**Hyperthyroidism and Type 2 Diabetes**

Hyperthyroidism is more common in persons with type 2 diabetes than in the general population, with the etiological profile remaining the same.

Uncontrolled hyperthyroidism and uncontrolled diabetes share many clinical characteristics, and may be a differential diagnosis for each other in many clinical settings. Severe hyperglycaemia may mask life threatening thyroid storm, especially as T3 levels may transiently be lowered in such patients. Uncontrolled hyperthyroidism may be a cause of poor glycaemic control, and of recurrent diabetic ketoacidosis.

Both hyperthyroidism and diabetes exhibit similar features related to cardiovascular risk, and may lead to increased cardiovascular mortality (Table-4).

**Investigations**

Serum TSH should be assessed in all persons with newly diagnosed type 1 diabetes mellitus, after having achieved glycaemic control. Routine screening of newly diagnosed type 2 diabetes patients is not recommended. Selective screening may be indicated, based upon presence of surrogate markers (dyslipidaemia) or risk stratification markers (antibody positivity).

Regular follow up, at yearly intervals, is indicated for all persons with type 1 diabetes. An individualized approach should be followed for those with type 2 diabetes.

All women with type 2 diabetes should be screened for postpartum thyroiditis at 3 and 6 months after delivery. Patients with poor glycaemic control, frequent episodes of hyperglycaemia, frequent episodes of ketosis, and brittle diabetes, must undergo thyroid function testing. Laboratory values which should prompt a thyroid function test include altered lipid profile elevated liver enzymes, both surrogate markers of tissue hypo-thyroidism. Unexplained atrial fibrillation in a person with diabetes also requires thyroid function assessment.

In persons with acute illness, FT3 and FT4 estimation may be more reliable than T3 and T4 values.
Management
The aim of management for both diabetes and thyroid dysfunction is similar: to achieve, and maintain, euglycaemia and euthyroid status. In patients with subclinical hypo-thyroidism or subclinical hyperthyroidism, with concomitant diabetes, application of clinical acumen may be necessary. A person with recurrent hypoglycaemia, detected to have subclinical hypothyroidism, may benefit from low dose thyroxine replacement. Similarly a hypothyroid patient with high TSH levels in spite of high thyroxine supplementation may respond to metformin treatment. Persons with diabetes, unable to achieve symptomatic or glycaemic control in spite of seemingly adequate therapy should undergo thyroid function testing. Relatively mild degrees of hyperthyroidism, treated with anti thyroid drugs, may help achieve glycaemic control. An inappropriately suppressed FT3 may be due to poor glycaemic control, while an inappropriately suppressed TSH may be due to metformin therapy.

In the absence of large-scale studies, or definitive evidence from available guidelines, an individualized approach will be necessary. Keeping a high index of suspicion for thyroid dysfunction in diabetes, and for diabetes in thyroid disorders, however, is necessary.

Conclusion
Thyroid dysfunction and diabetes are closely associated with each other, through multi-directional pathways. The co-occurrence of these common endocrine conditions impacts clinical presentation and laboratory results, while influencing screening, diagnostic and therapeutic strategies. A high index of suspicion should be kept for thyroid dysfunction in diabetes, especially difficult-to-treat diabetes, and for diabetes in thyroid dysfunction, especially difficult-to-manage cases.

References