ASSOCIATION BETWEEN SUBCLINICAL HYPOTHYROIDISM AND DIABETIC RETINOPATHY IN TYPE 2 DIABETIC PATIENTS
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ABSTRACT

BACKGROUND
Several studies have demonstrated an association between subclinical hypothyroidism and diabetic retinopathy with conflicting results. This study is aimed to find out if any such association exists as it may have therapeutic implications as both conditions are commonly seen.

MATERIALS AND METHODS
This case-control study was done at RLJ hospital, Kolar, Karnataka. A total of 150 cases and 150 controls were screened for thyroid function. SCH patients were defined as having TSH level >4.0 μIU/ml under normal free thyroxine level conditions without taking any thyroid medications.

Euthyroid was defined as normal TSH and free thyroxine levels. Blood samples from diabetic patients satisfying the inclusion and exclusion criteria were taken, after written informed consent was obtained. Subject’s height and weight were measured. Body mass index was calculated as weight divided by height squared. Blood pressure was measured in the sitting position after 10 minutes of rest. Fasting venous blood sample was collected for measurement of glucose, lipid profile and thyroid function. HbA1c was measured using high-performance liquid chromatography instruments.

RESULTS
Mean age of cases was 56 ± 9 years and mean age of controls was 56.5 ± 10.2 years. There was no significant difference in mean age between two groups. (Age matching achieved). Majority of cases and controls were males. There was no significant difference in Gender distribution. (Gender Matching achieved). There was no significant difference in mean FBS, PPBS and HbA1c between two groups.

CONCLUSION
The study concludes that TSH levels were significantly higher in cases than in controls after matching age, gender and glycem control. Subclinical hypothyroidism is more frequently seen in diabetic retinopathy patients and was more common in PDR patients than NPDR patients.

KEYWORDS
Subclinical Hypothyroidism, Non-Proliferative Diabetic Retinopathy, Diabetic Complication.

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BACKGROUND
Diabetes is the most common chronic endocrine disease characterized by hyperglycaemia resulted from impaired insulin secretion and or insulin action.¹ Chronic diabetic hyperglycaemia is associated with long-term organ damage, dysfunction and failure. Complications, such as vision loss, renal failure and cardiovascular diseases, are often outcomes of diabetes.²-⁴ As the population ages and obesity increases, diabetes will increase as well. The global prevalence is predicted to be 11.1% in 2033, affecting 600 million people.

Diabetic retinopathy (DR) is the most common ocular complication of diabetes, and is the leading cause of visual impairment and blindness in working-aged people. It is common in diabetic patients but is asymptomatic until a significant visual impairment occurs. DR results in the socioeconomic burden of illness associated with diabetes. Common risk factors for the development of microvascular complications include duration of diabetes, poor glycaemic...
Further, the thyroid hormone axis has an important role in development of the retina and contributes to normal retinal vasculature. Experimental studies have shown that hypothyroidism is associated with preretinal neovascularisation and that systemic thyroxine supplementation is associated with changes in vessel density and area (Mookadam et al 2004; Mutapcic et al 2005)\(^5\) DR can be classified as non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. Neovascularisation is the principal hallmark of PDR. Neovascularisation frequently leads to vitreous haemorrhage and retinal detachment in diabetic patients. Now PDR is a leading cause of visual loss in adults worldwide.

Subclinical hypothyroidism (SCH) is defined as an asymptomatic state characterize by a normal serum thyroxin level and elevated serum concentration of thyrotropin (thyroid-stimulating hormone (TSH)). Patients with SCH sustain an obvious increase in cardiovascular eventrates.\(^3\)\(^4\) Despite this, there is a distinct lack of relevant research into risk factors associated with microvascular complications in type 2 diabetes with SCH. In fact, only a single study conducted by Chen et al.\(^1\) has attempted to elucidate these issues. Yet this study focused predominantly on the issue of diabetic nephropathy, as defined solely by elevated microalbuminuria, rather than retinopathy. However, in most diabetic patients with elevated microalbuminuria, other chronic kidney diseases should be considered in the absence of diabetic retinopathy. Our investigation examined the relationship between SCH and diabetic retinopathy in type 2 diabetic patient samples.

SCH has been reported to be associated with endothelial dysfunction independent from other well-known atherosclerotic risk factors (Cikim, 2004).

Infants born very prematurely (27 weeks) were more likely to have low thyroxin levels indicating an abnormal function of hypothalamo- pituitary- thyroid axis (Kristen, 2000)\(^6\) Premature infants with low serum thyroxin were at risk of retinopathy of prematurity (Fisher, 1990)\(^7\) In addition hypothyroidism increased retinal vascular permeability in rats (Tilton et al., 1989).\(^8\) Also; it was reported that methimazole- induced hypothyroidism in neonatal rats was associated with preretinal neovascularization (Mookadam et al., 2004).

There is insufficient evidence to recommend for or against screening for thyroid disease with thyroid function tests in high-risk patients, including elderly persons, postpartum women, and persons with Down syndrome, but recommendations may be made on other grounds, such as the higher prevalence of disease and the increased likelihood that symptoms of thyroid disease will be overlooked in these patients (Kenneth and Michael, 2005). The preferred test is measurement of thyroid-stimulating hormone (TSH) using a sensitive immunometric or similar assay, because of its superior sensitivity and specificity and measurement of free T4 at the same time (Kadiyala et al., 2010).\(^9\)

Symptoms of subclinical hypothyroidism are particularly insidious and often overshadowed by coexisting health problems, or the symptoms are attributed to aging. Certain static and changing symptoms have been identified as the highest indicators of hypothyroidism. Static symptoms include constipation, hoarse voice, and deep voice. Changing symptoms include increased constipation, hoarser voice, feeling colder, having puffier eyes, and having weaker muscles. In general, symptoms associated with hypothyroidism are high in specificity but low in sensitivity. Therefore, the absence of a symptom does not rule out thyroid disease (Capen et al., 2008)\(^10\)

### MATERIALS AND METHODS

#### Study Population and Methodology

A case-control study was performed at RLJH in Kolar, India over a period of 6months in 2017. Blood samples from diabetic patients satisfying the inclusion and exclusion criteria were taken, after written informed consent was obtained. Patients with thyroid diseases like hypothyroidism, hyperthyroidism, thyroidectomy, malignancy, pregnancy, acute intercurrent illness like sepsis were excluded.

### Inclusion Criteria

<table>
<thead>
<tr>
<th>CASES</th>
<th>CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age more than 40 years</td>
<td>- Age more than 40 years</td>
</tr>
<tr>
<td>- Diabetic patients with diabetic retinopathy</td>
<td>- Diabetic patients without diabetic retinopathy</td>
</tr>
<tr>
<td>- HbA1c &gt; 6.5%</td>
<td>- HbA1c &gt; 6.5%</td>
</tr>
</tbody>
</table>

Subclinical hypothyroidism: TSH<4µIU/ml; normal FT3/10-23pmol/L. FT4level<2.3-6.1pmol/L.

### Exclusion Criteria

- Hypothyroidism
- Hyperthyroidism
- Thyroidectomy
- Pregnancy
- Acute intercurrent illness like sepsis

### Data Collection and Analysis

Subject’s height and weight were measured. Body mass index was calculated as weight divided by height squared. Blood pressure was measured in the sitting position after 10 minutes of rest. Fasting venous blood sample was collected for measurement of glucose, lipid profile and thyroid function. HbA1c was measured using high-performance liquid chromatography instruments.

Thyroid functions were measured using chemiluminescent immunometric assay. The reference range of serum thyrotropin (TSH) was 0.4-4 µIU/ml, the reference range of free thyroxine was 10-23 pmol/L and the reference range of free triiodothyronine was 2.3-6.3 pmol/L. SCH patients were defined as having TSH level >4.0 µIU/ml under normal free thyroxine level conditions without taking any thyroid medications. Euthyroid was defined as normal TSH and free thyroxine levels.

### Diabetic Retinopathy

All the subjects were assessed using opthalmoscope. A trained ophthalmologist performed examination of the...
fundus using ophthalmoscopy in all patients who were given tropicamide eye drops to dilate the pupil. The retinal status was classified into NDR, NPDR and PDR.

**RESULTS**

**Statistical Analysis**

In the study mean age was 56±9 years and mean age of controls was 56.5±10.2 years. There was no significant difference in mean age between two groups.

Among cases 46.7% were females and 53.3% were males, among controls 47.3% were females and 52.7% were males. There was no significant difference in gender between two groups.

**Table 1. Gender Comparison between Cases and Controls**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cases Count</th>
<th>SD%</th>
<th>Controls Count</th>
<th>SD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>70</td>
<td>46.7%</td>
<td>71</td>
<td>47.3%</td>
</tr>
<tr>
<td>Male</td>
<td>80</td>
<td>53.3%</td>
<td>79</td>
<td>52.7%</td>
</tr>
</tbody>
</table>

$X^2 = 0.013$, df=1, $p=0.908$

**Table 2. Glycemic Profile Comparison between Cases and Controls**

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases Mean</th>
<th>SD</th>
<th>Controls Mean</th>
<th>SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS</td>
<td>183.13</td>
<td>47.78</td>
<td>185.19</td>
<td>33.40</td>
<td>0.666</td>
</tr>
<tr>
<td>PPBS</td>
<td>224.14</td>
<td>52.20</td>
<td>216.52</td>
<td>42.64</td>
<td>0.168</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.38</td>
<td>0.780</td>
<td>7.32</td>
<td>0.743</td>
<td>0.513</td>
</tr>
</tbody>
</table>

**Table 3. Thyroid Profile Comparison between Cases and Controls**

<table>
<thead>
<tr>
<th>T3</th>
<th>Cases Mean</th>
<th>Median</th>
<th>SD</th>
<th>Controls Mean</th>
<th>Median</th>
<th>SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
<td>1.21</td>
<td>2.3</td>
<td>1.5</td>
<td>1.19</td>
<td>1.8</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>8.8</td>
<td>8.36</td>
<td>5.0</td>
<td>7.9</td>
<td>8</td>
<td>3.3</td>
<td>0.287</td>
<td></td>
</tr>
<tr>
<td>25.2</td>
<td>19</td>
<td>36.3</td>
<td>12.0</td>
<td>5.25</td>
<td>22.7</td>
<td>-0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Eye Changes among Cases**

<table>
<thead>
<tr>
<th>Eye Changes</th>
<th>Cases Count</th>
<th>SD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild NPDR</td>
<td>43</td>
<td>28.7%</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>99</td>
<td>66.0%</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>3</td>
<td>2.4%</td>
</tr>
<tr>
<td>PDR</td>
<td>5</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Among cases 28.7% had Mild Non-proliferative diabetic retinopathy, 66% had moderate Non-proliferative diabetic retinopathy, 2% had severe Non-proliferative diabetic retinopathy and 3.3% had proliferative diabetic retinopathy.
Table 5. Association between Subclinical Hypothyroidism and Eye Changes among Cases

<table>
<thead>
<tr>
<th>Eye Changes</th>
<th>Subclinical Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>11</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>23</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>1</td>
</tr>
<tr>
<td>PDR</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 5. Bar Diagram showing Association between Subclinical Hypothyroidism and Eye Changes Among Cases

DISCUSSION

- Mean age of cases was 56 ± 9 years and mean age of controls was 56.5 ± 10.2 years. There was no significant difference in mean age between two groups. (Age matching achieved).
- Majority of cases and controls were males. There was no significant difference in Gender distribution. (Gender Matching achieved).
- There was no significant difference in mean FBS, PPBS and HbA1c between two groups.
- There was no significant difference in median T3 and T4 between two groups, there was significant difference in median TSH values between two groups.
- Moderate NPDR was the most common eye change noticed among cases.
- Prevalence of PDR in this study is 3.3%.
- The incidence of subclinical hypothyroidism is 24% (36 out of 150 cases had subclinical hypothyroidism).

Thyroid function contributes to normal retinal vascular density. Further, hypothyroidism can play a permissive role in development of retinal revascularisation. Hence screening plays an important role.

Endothelial dysfunction in SCH could be due to inflammation. Acute and chronic inflammation is strongly related to endothelial dysfunction (Hingorani et al., 2000). Furthermore higher levels of IL-6, TNF-alpha and high-sensitive C-reactive protein (hs-CRP) in patients with SCH were reported (Türemen et al., 2011). All of these inflammatory markers were correlated with endothelium-dependent vascular response which was lower in the patients of SCH. These findings show that there is low grade chronic inflammation in patients with SCH due to autoimmune thyroiditis and this inflammation may be one of the contributing factors that lead to endothelial dysfunction in patients with SCH (Türemen et al., 2011).

Also, it was reported that the systolic and diastolic blood pressure and HOMA-IR values were higher in type 2 diabetic patients with SCH than in type 2 diabetic euthyroid patients (Kim et al., 2011).

In type 2 diabetes, there is a complex interaction between impaired insulin sensitivity, vascular endothelial dysfunction, and hypertension, which seems to play an important role in the development of functional disturbances in the microcirculation. Impaired insulin sensitivity is associated with a modification of arterial resistance and increased peripheral microvascular resistance, which contributes to the excessive prevalence of hypertension in type 2 diabetes. In these patients, an increased peripheral microvascular resistance occurs with even minor degrees of impaired glucose tolerance, which coexists with disturbed capillary pressure autoregulation, leading to the development of irreversible structural changes in the microvasculature (Jaap et al., 1994). Actually this complex interaction can be augmented in the presence of SCH.

CONCLUSION

- The study concludes that TSH levels were significantly higher in cases than in controls after matching age, gender and glycemic control.
- Subclinical hypothyroidism is more frequently seen in diabetic retinopathy patients.
- Subclinical hypothyroidism was more common in PDR patients than NPDR patients.
REFERENCES


