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 glycemic 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 socio-economic burden of illness associated with diabetes. Common risk factors for the development of microvascular complications include duration of diabetes, poor glycaemic

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control, elevated blood pressure, and dyslipidaemia.[1,2] Further, the thyroid hormone axis has an important role in development of the retina and contributes to normal retinal vascularity. 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

CASES	CONTROLS
• Age more than 40 years	• Age more than 40 years
• Diabetic patients with diabetic retinopathy	• Diabetic patients without diabetic retinopathy
• Hb A1 c > 6.5% Subclinical hypothyroidism: TSH>4μIU/ml , normal FT3:10-23pmol/L FT4levels2.3-6.3pmol/L	• Hb A1 c > 6.5%

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 ophthalmoscope. 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

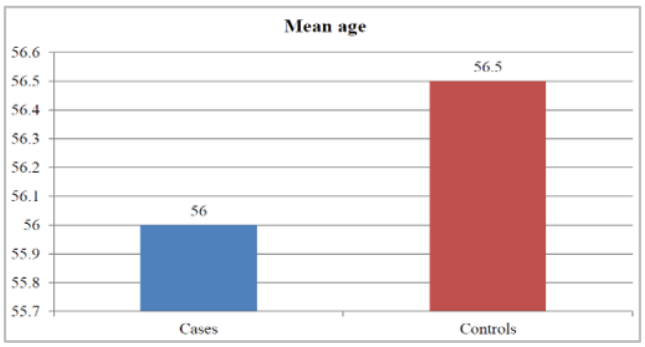

Figure 1. Bar Diagram Showing Age Distribution of Cases and Controls

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% wee males, among controls 47.3% were females and 52.7% wew males. There was no significant difference in gender between two groups.

		Group			
		Cases		Controls	
		Count	SD%	Count	SD%
Gender	Female	70	46.7%	71	47.3%
	Male	80	53.3%	79	52.7%

Table 1. Gender Comparison between Cases and Controls

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

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
FBS	183.13	47.78	185.19	33.40	0.666
PPBS	224.14	52.20	216.52	42.64	0.168
HbA1c	7.38	0.780	7.32	0.743	0.513

Table 2. Glycemic Profile Comparison between Cases and Controls |

In Cases mean FBS was 183.13 ± 47.78 mg/dl, mean PPBS was 224.14 ± 52.20 mg/dl, mean HbA1c was 7.38 ± 0.780. In Controls mean FBS was 185.19 ± 33.40 mg/dl, mean PPBS was 216.52 ± 42.64 mg/dl, mean HbA1c was 7.32 ± 0.743. There was no significant difference in mean FBS, PPBS and HbA1c between two groups.

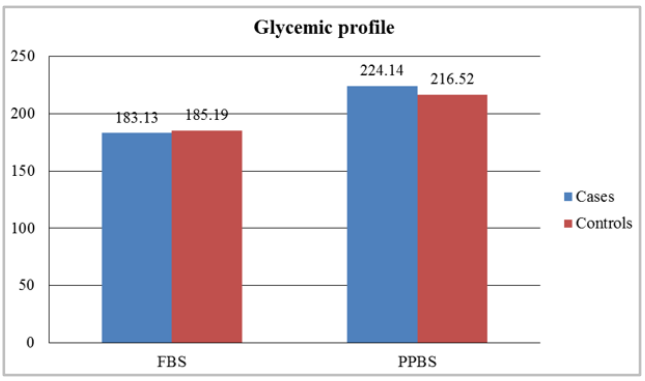

Figure 2. Bar Diagram Showing Glycemic Comparison between Cases and Controls

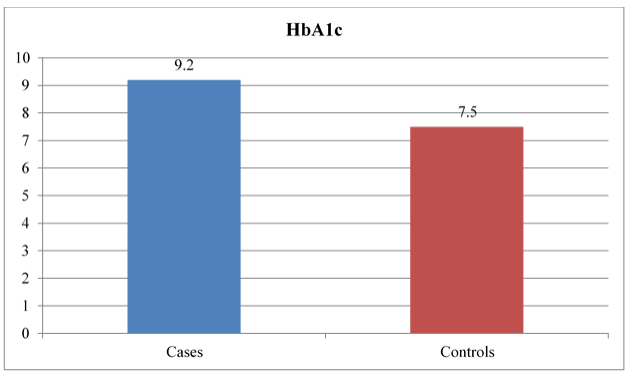

Figure 3. Bar Diagram Showing HbA1c Comparison between Cases and Controls

	Group						P value
	Cases			Controls			
	Mean	Median	SD	Mean	Median	SD	
T3	1.9	1.21	2.3	1.5	1.19	1.8	0.205
T4	8.8	8.36	5.0	7.9	8	3.3	0.287
TSH	35.2	19	36.3	12.0	5.25	22.7	<0.001*

*Mann Whitney U test

Table 3. Thyroid Profile Comparison between Cases and Controls

In cases, median T3 was 8.36, median T4 was 8.36 and median TSH was 19 and in controls, median T3 was 1.19, median T4 was 8 and median TSH was 5.25. There was no significant difference in median TSH values between two groups.

		Group	
		Cases	
		Count	SD%
Eye Changes	Mild NPDR	43	28.7%
	Moderate NPDR	99	66.0%
	Severe NPDR	3	2.0%
	PDR	5	3.3%

Table 4. Eye Changes among Cases

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.

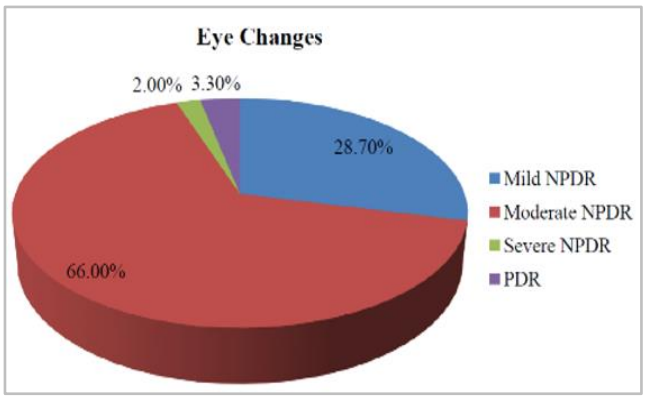

Figure 4. Shows the Eye Changes

		Subclinical Hypothyroidism			
		Present		Absent	
		Count	%	Count	%
Eye Changes	Mild NPDR	11	25.6%	32	74.4%
	Moderate NPDR	21	21.2%	78	78.8%
	Severe NPDR	1	33.3%	2	66.7%
	PDR	3	60.0%	2	40.0%

$\chi 2 = 4.177$, df = 3, p = 0.243

Table 5. Association between Subclinical Hypothyroidism and Eye Changes among Cases

In cases, based on normal T4 and increased TSH, 36 subjects had subclinical hypothyroidism. Out of 43 subjects with mild NPDR, 25.6% had subclinical hypothyroidism. Out of 99 subjects with moderate NPDR, 21.2% had subclinical hypothyroidism, out of 3 subjects with severe NPDR, 33.3% had subclinical hypothyroidism and out of 5 subjects with PDR, 60% had subclinical hypothyroidism. Prevalence of PDR in this study -3.3%. There was no significant association between eye changes and subclinical hypothyroidism.

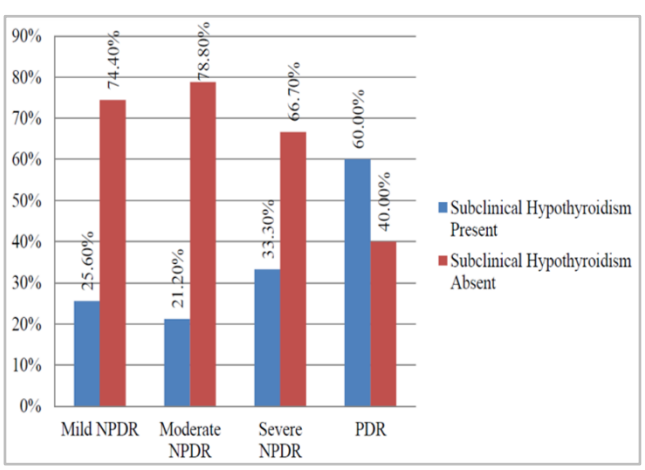

Figure 5. Bar Diagram showing Association between Subclinical Hypothyroidism and Eye Changes Among Cases

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 NDPR 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.[1] 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)[11] 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).[12]

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)[13]

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)[14] 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.

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