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Original Research Article

ASSOCIATION AND DETERMINANTS OF CLINICAL AND SUBCLINICAL HYPOTHYROIDISM IN PATIENTS WITH DIABETIC RETINOPATHY: A CLINIC BASED STUDY FROM NORTH INDIA

Bithi Chowdhury [*1], Raviranjan Prakash [2], Sanjay Jain [3], Hemant Sharma [4].

[*1] Senior Specialist, Department of Ophthalmology, Hindu Rao Hospital &NDMC Medical College, Delhi, India.

[2] Specialist medical officer, Department of Ophthalmology, Sadar Hospital, Madhapur, Bihar, India.

[3] Chief Medical Officer, Department of Microbiology, Hindu Rao Hospital & NDMC Medical College, Delhi, India.

[4] Senior specialist, Department of Medicine, Hindu Rao Hospital, &NDMC Medical College, Delhi, India.

ABSTRACT

Introduction: The association of type 2 diabetes mellitus and thyroid dysfunction is well known. Thyroid dysfunction especially subclinical hypothyroidism has been reported to be a risk factor for sight threatening diabetic retinopathy. Therefore, it is of importance to investigate the determinants of clinical and subclinical hypothyroidism in patients with diabetic retinopathy. This study was aimed to investigate the effect of hypothyroidism on diabetic retinopathy and the determinants of hypothyroidism.

Aims: To study the association of hypothyroidism and diabetic retinopathy and its effect on severity of retinopathy in type 2 diabetes and investigate the determinants of hypothyroidism in patients with diabetic retinopathy.

Subjects and methods: A cross sectional study conducted on one hundred patients of type 2 diabetes with diabetic retinopathy. They were evaluated for status of diabetes control, thyroid function, lipid profile and retinopathy grade. Those found to have clinical and subclinical hypothyroidism were analyzed for various clinical and biochemical parameters for possible determinants of thyroid dysfunction.

Results: There were seventy-four euthyroid patients and eighteen with subclinical hypothyroidism and five with clinical hypothyroidism. Patients with subclinical hypothyroidism had severe form of retinopathy (61.11% versus 32.43%). The odds of having a subclinical hypothyroidism in patients with severe form of diabetic retinopathy was found to be significant (OR 3.23; p=.048 CI=1.10-9.88). High HBA1c was an independent determinant of abnormal thyroid function.

Conclusions: About one fourth of type II diabetes patients with retinopathy have thyroid dysfunction. These patients are also likely to have severe form of the retinopathy especially those having subclinical hypothyroidism. Thus, we recommend thyroid function test should be done in all patients with type II diabetes mellitus with retinopathy. Those identified as having subclinical hypothyroidism should be closely followed so as, to detect and prevent vision threatening complications.

KEY WORDS: Diabetic retinopathy, subclinical hypothyroidism, type 2 diabetes, thyroid dysfunction.

Address for correspondence: Dr. Bithi Chowdhury, Department of Ophthalmology, Hindu Rao Hospital&NDMC Medical College, Delhi, India, Phone numbers: 9811362844
E-Mail: bithic@rediffmail.com

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INTRODUCTION

Diabetic retinopathy is one of the most common microvascular complication seen in diabetic population. About 1 in 3 people living with diabetes have some degree of diabetic retinopathy and 1 in 10 will develop a vision threatening form of diabetic retinopathy [1]. Several studies have found a positive association between diabetic retinopathy and subclinical hypothyroidism, but the findings are varied or even contradictory.

Thyroid disorders is second only to diabetes mellitus as the most common condition to affect the endocrine system. In a population-based study done in Cochin, the prevalence of hypothyroidism was 3.9%, and the prevalence of subclinical hypothyroidism was 9.4% [2]. There are varying reports regarding the prevalence of thyroid dysfunction among diabetics the most common thyroid abnormality being sub clinical hypothyroidism [3,4]. The reported prevalence of sub clinical hypothyroidism in diabetes vary between 2.2% to 17% [5,6].

Insulin secretion is directly controlled by thyroid hormones. In hypothyroidism, there is a reduction in glucose-induced insulin secretion by beta cells, and peripheral resistance to glucose uptake [7]. In subclinical hypothyroidism, abnormal expression of glucose transporter type 2 gene (GLUT 2) translocation is thought to be the cause of insulin resistance. Sub clinical hypothyroidism is often complicated with endothelial dysfunction of the capillary and precapillary arterioles including thickening of the capillary basement membrane and increase in C reactive protein leading to small vessel dysfunction [8].

The association of hypothyroidism with diabetic retinopathy remains controversial. While some have found a positive association of subclinical hypothyroidism with nephropathy but not with diabetic retinopathy others have found a higher prevalence and sight threatening diabetic retinopathy with subclinical hypothyroidism [9,10].

The effect of subclinical hypothyroidism on cardiovascular system has been studied extensively and has been found to be an important risk factor for cardiovascular disease [11]. Moreover, the same factors are likely to play an important role in the pathogenesis of retinopathy in diabetic patients. Also, the determinants of hypothyroidism in diabetic retinopathy would help in identify the patient who are at increased risk of developing sight threatening complications. In this study we examined the association and determinants of diabetic retinopathy with hypothyroidism (clinical and subclinical) and explored the severity of retinopathy in these patients.

SUBJECTS AND METHODS

This was a cross sectional study conducted on patients having diabetic retinopathy. A total of 100 type 2 DM patients attending the out-patients department of the department of Ophthalmology, of a tertiary care hospital who satisfied the inclusion and criteria were included in the study. Before start of the study, signed and informed consent was taken from the patient for participating in the study. The approval of the hospital ethical committee was taken and the procedures followed were in accordance with the Helsinki Declaration.

Inclusion and exclusion criteria: Patients of Type 2 diabetes above 18 years having diabetic retinopathy were included in the study. Patients on drugs known to affect thyroid function like Lithium, oral contraceptive pills, amiodarone etc, pregnant patients, patients in whom fundus cannot be examined, blood pressure above 140/90 and nephropathy patients were excluded from the study.

Patient Evaluation: Patients were evaluated for status of diabetes control, thyroid profile and retinopathy grade. All patients underwent complete general physical examination, ocular examination including best corrected visual acuity, slit lamp examination, dilated fundus examination with 90D, direct and indirect ophthalmoscopy, intraocular pressure measurement. The eyes were dilated with tropicamide (0.5%) and phenylephrine (8%) combination. Staging of diabetic retinopathy was done on the basis of ETDRS classification [12]. The worst affected eye was included for statistical calculation in the study.

Blood sample was taken for T3,T4,TSH, blood sugar (fasting and post prandial), glycocylated Hb, LDL, HDL , total cholesterol, triglycerides, and serum creatinine. Urine albumin was also

done. Thyroid profile was estimated from the serum samples of the selected patients and analyzed on a Cobas e411 (Roche Diagnostic, Hitachi, Germany). Normal thyroid profile values considered were Serum thyroxine (Free) FT4 (0.93-1.7 ng/dl); Serum Triiodothyronine(Free) FT3 (2.0-4.4 pg/dl); Serum thyroid stimulating hormone TSH (0.270-4.20uIU/ml). Thyroid dysfunction was catagorised into five groups.

The following guidelines for detection of thyroid dysfunction were considered:

1. Normal – FT3, FT4 and TSH within the normal range.

2. Primary hypothyroidism – TSH more than 4.20ìIU/ml and FT3, FT4 is less than the normal value.

3. Primary hyperthyroidism — TSH less than 0.270 ìIU/ml and FT3, FT4 is more than the normal values.

4. Subclinical hypothyroidism – TSH more than 4.20 ìIU/ml and FT3, FT4 is within the normal range.

5. Subclinical hyperthyroidism – TSH less than 0.270 ìIU/ml and FT3, FT4 are within the normal range.

Analysis: Statistical analysis consisted of descriptive statistics. The average of various parameters studied was expressed as mean ± standard deviation. Normally distributed data were compared with student t-test. Categorical data were compared with the chi-square test and the Fisher exact test. Odds ratio was used to study the association between retinopathy and thyroid function.

RESULTS

There were seventy four patients who were euthyroid and eighteen patients with subclinical hypothyroidism and five with clinical hypothyroidism. Two patients with clinical hyperthyroidism and one with subclinical hyperthyroidism were excluded from the study. The patient characteristics, diabetes status, and retinopathy and thyroid function status is shown in table 1.

The patients characteristic and biochemical parameters of euthyoriod patients were compared to clinical and subclinical hypothyroid patients. Number of females were significantly more among the patients with thyroid dysfunction 76.9 % v 23.1% (P = 0.041).There was no statistical difference in the duration of diabetes between those with and without thyroid dysfunction.

Table 1: Demography and baseline variables.

Demography	
Variables	Mean ± SD
Age (Years)	58.61± 9.39
Male:female	58:42:00
Duration of diabetes (years)	8.2±3.8
Diabetic status	
Fasting blood sugar (mg/dl)	162.4±42.11
Post prandial blood sugar (mg/dl)	218.9±50.67
HbA1C (%)	9.39±1.92
Retinopathy grade	
Grade	**No. of Patients**
mild NPDR	40
mild NPDR with CSME	23
moderate NPDR	19
moderate NPDR with CSME	6
severe NPDR	4
severe NPDR with CSME	1
very severe NPDR	1
early PDR	5
high risk PDR	1
Thyroid function status	
Euthyroid	74
Hypothyroid	5
Subclinical hypothyroid	18
Hyperthyroid	2
Subclinical hyperthyroid	1

Majority of the patients had mild diabetic retinopathy in both the groups followed by moderate and severe retinopathy. Clinically significant macular edema (CSME) was seen in 21 eyes (28.4%) in euthyroid patients and in 9 eyes (34.6%) with thyroid dysfunction.

For comparing the severity of retinopathy between groups, all eyes with grades above mild non proliferative diabetic retinopathy (NPDR) i.e., moderate NPDR and proliferative retinopathy (PDR) were considered to have a severe form of the disease. Hypothyroidism was associated with severe form of retinopathy (table 2). Almost (61.11% versus 32.43%) double the eyes with subclinical hypothyroidism had moderate to severe grade of retinopathy. This difference was

Table 2: Association of severity of retinopathy and hypothyroidism (clinical and subclinical).

Retinopathy	Normal Thyroid function [n=74]	hypothyroidism [n=23]	Odds ratio	95% CI	2 tailed p
Mild	50(67.57%)	11(47.83%)	2.27	0.88 -5.89	**0.049**
Moderate to severe	24(32.43%)	12(52.17%)			
Total	74(100%)	23(100%)			

Table 3: Association of severity of retinopathy and subclinical hypothyroidism.

Retinopathy	Normal Thyroid function [n=74]	Subclinical hypothyroidism [n=18]	Odds ratio	95% CI	2 tailed p
Mild	50(67.57%)	7(38.89%)	3.23	1.10-9.88	**0.048**
Moderate to severe	24(32.43%)	11(61.11%)			
Total	74(100%)	18(100%)			

Table 4: Determinants of thyroid dysfunction in patients with diabetic retinopathy by univariate analysis.

	Without thyroid dysfunction (n=74)	With thyroid dysfunction(n=26)	p value
Age (mean years±SD)	58.645±9.29	59.348±9.786	0.751
Duration of Diabetes Mellitus (mean years±SD)	7.972±3.640	8.957±4.538	0.29
Fasting blood sugar(mg/dl±SD)	156.541±38.824	179.609±49.778	**0.022**
Post prandial blood sugar (mg/dl±SD)	212.230 ± 49.297	240.478 ± 53.096	**0.021**
HBA1c (%±SD)	9.027±1.478	10.391±2.676	**0.002**
HDL (mg/dl±SD)	43.297±7.213	40.174±7.578	0.076
LDL (mg/dl±SD)	90.337±17.281	103.696±20.557	**0.0026**
Total Cholesterol (mg/dl±SD)	182.149 ± 23.562	200.870±24.046	**0.0013**
TG (mg/dl±SD)	141.311±32.411	152.522±35.495	0.16
	OR: 0.5253 (CI: 0.2083 -1.3077)		

Table 5: Determinants of hypothyroidism in patients with diabetic retinopathy by multivariate analysis.

Variable	Coefficient	Std Error	F-test	P-Value
Fasting blood sugar	-0.001	0.002	0.269	0.72
Post prandial blood sugar	0.001	0.002	0.619	0.433
HBA1c	0.062	0.025	6.137	**0.015**
LDL	0.006	0.005	1.651	0.202
Total Cholesterol	0	0.004	0.003	0.955
CONSTANT	0.01	0.376	0.001	0.978

found to be statistically significant. There was significant association of severe form of diabetic retinopathy with subclinical hypothyroidism. (OR 3.23; p=.048 CI=1.10-9.88) (table 3).

We analyzed various clinical and biochemical parameters for possible determinants of abnormal thyroid function status in diabetic retinopathy patients. The parameters considered were age, sex, duration of diabetes, fasting and post prandial blood sugar levels, HbA1C values and lipid profile (LDL, HDL, total cholesterol, triglycerides).

On univariate analysis, diabetic retinopathy patients with abnormal thyroid function had higher fasting blood sugar (p=0.022) higher post prandial blood sugar (p=0.021),higher HbA1C values(p=0.002) (signifying worse diabetic control over last 3 months) higher LDL (p=.0.003) and higher total cholesterol levels (p=.0.001) which were statistically significant when

compared to diabetic retinopathy patients with normal thyroid function(table 4).

However on multivariate analysis only higher HBA1c values remained statistically significant independent determinant of abnormal thyroid function in patients with diabetic retinopathy (table 5).

DISCUSSION

Diabetic retinopathy is the major cause of blindness among the working age group. Well known risk factors of diabetic retinopathy are duration of diabetes, poor glycemic control , elevated blood pressure and dyslipidemia [13,14]. In recent years thyroid dysfunction has been associated with increased risk and severity of diabetic retinopathy [15]. In the present study, 23% of the diabetes patients with diabetic retinopathy had hypothyroidism with subclinical hypothyroidism being the commonest. Subclinical hypothyroidism was associated with increased severity of retinopathy.

We found a higher prevalence of sub clinical hypothyroidism in our patient probably because all the patients had diabetic retinopathy while in other studies retinopathy was not a mandatory inclusion criterion. Also geographic location, elderly study population may have played a role.

Mild retinopathy was the commonest type of retinopathy seen in our study. There was a trend toward increasing severity of retinopathy in patients with hypothyroidism. Subclinical hypothyroidism was seen in 18 patients. Sixty one percent (11eyes) of the patients with subclinical hypothyroidism had moderate to severe retinopathy in contrast to 31% in the normal thyroid function patients. This difference was statistically significant (OR-3.23, P = 0.048, CI=1.10-9.88) indicating that severe form of diabetic retinopathy is associated with subclinical hypothyroidism. This is similar to some studies who observed that the diabetics with thyroid dysfunction had more severe form of retinopathy than those who had normal thyroid function [9,10,15].

The American Diabetes Association [10] performed a cross-sectional study, the underlying hypothesis of which was that there would be a link between poor thyroid function and diabetic retinopathy, because patients with subclinical hypothyroidism have an increase in cardiovascular events, as is often the case with diabetic patients. The results of the study showed a trend towards higher rates of sight threatening diabetic retinopathy in a group of subclinical hypothyroid patients when compared with the euthyroid group.

A study conducted to evaluate the relation between proliferative diabetic retinopathy and subclinical hypothyroid in type II diabetes concluded that the patients with proliferative diabetic retinopathy had higher prevalence of subclinical hypothyroid than those patients without retinopathy. They concluded that type II diabetes patients with retinopathy were at increased risk of subclinical hypothyroidism [16]. A meta analysis of all published epidemiological studies investigating the association between subclinical hypothyroidism and diabetic retinopathy demonstrated that subclinical hypothyroidism was associated diabetic retinopathy and exposure to subclinical hypothyroidism can increase the diabetic retinopathy 2.13 times [17].

The relationship between thyroid disorders and diabetes mellitus is characterized by a complex interdependent interaction [18]. Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism and excess and deficit of any can result in functional derangement of the other. Thyroid disorders, including both hypo and hyper have been associated with insulin resistance due to various mechanisms [10]. In our study diabetic retinopathy patients with subclinical hypothyoriodism had higher fasting blood sugar, higher post prandial blood sugar, higher HbA1C values(signifying worse diabetic control over last 3 months) higher LDL and higher total cholesterol levels which were statistically significant when compared to those with normal thyroid function. Altered thyroid hormones have been described in patients with diabetes especially those with poor glycemic control [19]. This is highlighted in our study where the single independent determinant of thyroid dysfunction in retinopathy patient was found to be HbA1C.

We found in our study significantly higher LDL and higher total cholesterol levels in patients with DR with thyroid dysfunction. The correla-

-tion between diabetic retinopathy and dyslipidemia has been reported [19], and atherogenic disturbances in lipid metabolism have been observed in patients with subclinical hypothyroidism [20,21]. Thus, dyslipidemia in subclinical hypothyroidism may be one of the reasons for the association between diabetic retinopathy and subclinical hypothyroidism. The interaction between thyroid function and insulin sensitivity is an important contributor to diabetic dyslipidemia. It remains to be seen whether treatment of subclinical hypothyroidism has any beneficial effect on retinopathy as an improvement of metabolic control has been reported after treatment of subclinical hypothyroidism.

Our study has several limitations. First, this was a cross-sectional analysis and could not determine causal relationships. Prospective controlled studies are needed to confirm the association between thyroid dysfunction especially subclinical hypothyroidism and diabetic retinopathy in type 2 diabetes. Second, ours is a hospital based study and the results may not be generalizable to all Indian patients of type 2 diabetes with retinopathy. However, the majority of our subjects were typical type 2 diabetic retinopathy patients commonly encountered in outpatient clinics. Third, thyroid function was evaluated at a single time point. It has been reported that some patients with subclinical hypothyroidism develop overt thyroid failure, while others may revert to euthyroid status during the follow up period. Follow-up thyroid function tests are needed to confirm the association between the clinical course of subclinical hypothyroidism and diabetic retinopathy.

However we do feel that despite these limitations our results and conclusions are valid. This should also be viewed in the context that such a study has not been published from India so far, to the best our knowledge.

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