Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

CORELATION OF DIABETIC RETINOPATHY AND THYROID DYSFUNCION: PREVALENCE AND SEVERITY

Vidya Bhushan kumar[1], Raviranjan Prakash[2], Pragati Raj[3], Bithi Chowdhury[4], Abhishek Anand[5]

[1]Senior Resident, RIO, IGIMS-Patna, Bihar, India.
[2]SMO, Sadar hospital,Babhua, Bihar, India.
[3]Junior Resident, RIO, IGIMS-Patna, Bihar, India.
[4]Consultant and head eye dept. Hindu Rao hospital, Delhi, India.
[5]Assistant Professor, RIO, IGIMS, Patna, Bihar, India.

Abstract

Diabetes Mellitus is the most common endocrine disorder and there are varying reports regarding the prevalence of thyroid dysfunction among diabetics. The most common thyroid abnormality being sub clinical hypothyroidism. Several studies investigating the relationship between thyroid dysfunction especially subclinical hypothyroidism and diabetic retinopathy. This is a cross sectional observational study conducted on 100 type 2 diabetic patients having diabetic retinopathy. Out of the 100 patients 74% of patients had normal thyroid function and 26% had thyroid dysfunction.18% percent had subclinical hypothyroidism, 5% had clinical hypothyroidism,2% had hyperthyroidism and least common was subclinical hyper thyroidism(1%). In the euthyroid patients 67% of eyes had mild, 24% had moderate diabetic retinopathy and 8% had severe diabetic retinopathy. In the patients with abnormal thyroid function mild, moderate, severe diabetic retinopathy was seen in 50%,29% and 23% respectively. There was a trend towards severe grade of retinopathy in the thyroid dysfunction patients though this did not reach statistical significance.

Corresponding Author: Dr.Abhishek Anand, Assistant Professor, RIO, IGIMS, Patna, Bihar, India.Email: eyehospitalpatna@gmail.com

Introduction

Diabetes Mellitus is the most common endocrine disorder in the world and India is considered the world capital of this disease. The World Health Organisation estimated diabetes prevalence was 2.8% in 2000 and 4.4% in 2030. The total no. of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.[1] Thyroid disorders is second only to diabetes mellitus as the most common condition to affect the endocrine system. There are varying reports regarding the prevalence of thyroid dysfunction among diabetics from 2.2 to 17%, most common thyroid abnormality being sub clinical hypothyroidism.[2,3]

Diabetic Retinopathy is characterized by progressive changes in retinal microvasculature leading to retinal hypo perfusion, increased vascular permeability and neovascularisation causing severe and permanent blindness. Thyroid function contributes to normal retinal vascular density. Hypothyroidism plays a permissive role in the development of retinal

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

neovascularization. Adenosine monophosphate activated protein kinase (AMPK) is a central target for modulation of insulin sensitivity and feedback of thyroid hormones associated with appetite and energy expenditure.[4] Autoimmunity has been implicated to be the major cause of thyroid dysfunction associated with diabetes mellitus.[5,6] Several studies investigating the relationship between thyroid dysfunction especially subclinical hypothyroidism and DR, have reported inconsistent results regarding the association of diabetic retinopathy with thyroid dysfunction.

Aims and Objectives

1. To assess the prevalence of thyroid dysfunction in diabetic retinopathy patients
2. To assess the severity of retinopathy in Type 2 Diabetes patients having thyroid dysfunction.

Material and Methods

This is a cross sectional observational study conducted on diabetic patients having diabetic retinopathy. A total of 100 type 2 DM patients attending the Diabetic clinic and O.P.D of the department of Ophthalmology, Hindu Rao Hospital who satisfied the inclusion 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.

Duration of the study was from June 2015 - May 2016.

Inclusion criteria:

1. Type 2 Diabetic patient having diabetic retinopathy.
2. Age above 18 yrs.

Exclusion criteria:

1. Age below 18 yrs.
2. Patients on drugs known to affect thyroid function like Lithium, Oral Contraceptive
3. Pills, Amiodarone
4. Pregnant Patients.
5. Patients in whom fundus cannot be examined.
6. Systolic BP>140 and Diastolic BP>90
7. Nephropathy

Patient evaluation:

Patients were evaluated for status of diabetic control, thyroid profile and retinopathy grade. All patients underwent complete ocular examination including best corrected visual acuity, slit lamp examination, Dilated fundus examination with slit lamp biomicroscopy with 90D, direct ophthalmoscope and indirect ophthalmoscopy, Intraocular pressure measurement.

Blood sample was taken for the following test:

1. Thyroid profile:T3,T4,TSH
2. Blood sugar (fasting and post prandial)

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

3. GlycocylatedHb
4. Diabetic nephropathy was ruled out by the relevant investigations.

Assessment of Thyroid Profile: Thyroid profile was estimated from the serum samples of the selected patients by the Elisa technique. The following is the

Normal thyroid profile:

Test	Abbreviation	Typical Ranges
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

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 4.20μIU/ml and FT3, FT4 is less than the normal value.
3. Primary hyperthyroidism -- TSH less than 0.270 μIU/ml and FT3, FT4 is more than the normal values.
4. Subclinical hypothyroidism – TSH more than 4.20 μIU/ml and FT3, FT4 is within the normal range.
5. Subclinical hyperthyroidism – TSH less than 0.270 μIU/ml and FT3, FT4 are within the normal range

ETDRS[7] has classified NPDR into mild, moderate, severe and very severe and PDR into early PDR and high-risk PDR.

Analysis

The data obtained was tabulated and statistically compared by applying appropriate statistical methods using computerized data collection software. Statistical analysis consisted of descriptive statistics. Normally distributed data were compared with the ttest. Categorical data were compared with the chi-square test and the Fisher exact test.

Results

Thyroid status in patients with diabetic retinopathy

Out of the 100 patients 74% of patients had normal thyroid function and 26% had thyroid dysfunction. Amongst the patients having thyroid dysfunction 18(69%) had subclinical hypothyroidism followed by 5(19%) of them having clinical hypothyroidism. 2(8%) patients had hyperthyroidism 1(4%) had subclinical hyperthyroidism. The distribution of patients and their thyroid status is shown in [Table 1].

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

Table 1: Patients according to thyroid dysfunction status

Thyroid status	Frequency	Percent
Euthyroid	74	74%
Hypothyroid	5	5%
Subclinical hypothyroid	18	18%
Hyperthyroid	2	2%
Subclinical hyperthyroid	1	1%

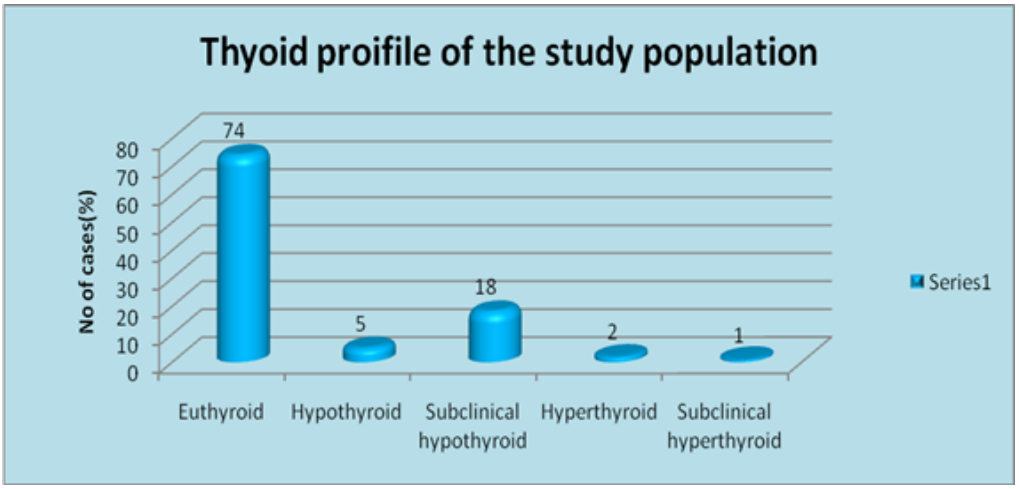

Figure 1: Various types of thyroid dysfunctions in the patients

Profile of Diabetic retinopathy in the patients:

For determination of the grade of retinopathy the worst eye was taken into consideration for each patient. Majority of the eyes (63%) had mild non proliferative retinopathy followed by moderate (25%) and severe (5%) NPDR.Very severe non proliferative retinopathy was seen in 1% eye and proliferative diabetic retinopathy was seen in 6% of cases. [Table 2] Clinically significant macular edema was seen in 30 eyes.

Table 2: Patients according to grades of retinopathy

Retinopathy grade	Number of eyes	Percentage
Mild NPDR	63	63%
Moderate NPDR	25	25%
Severe NPDR	5	5%
Very Severe NPDR	1	1%
PDR (early)	5	5%
PDR(high risk)	1	1%
Total	100	100%

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

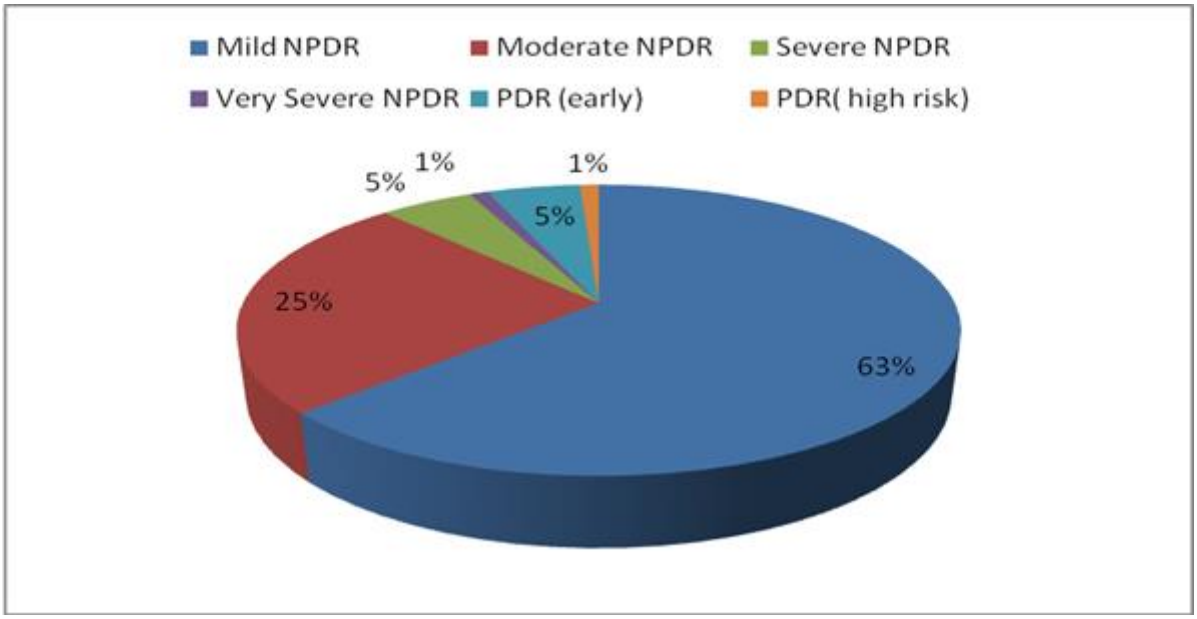

Figure 2:Various grades of retinopathy in the patients

The distribution of various grades of retinopathy amongst those with and without thyroid dysfunction is shown in [Table 3]. Majority of the eyes had mild diabetic retinopathy in both the groups followed by moderate and severe retinopathy. CSME was seen in 21 eyes (28.4%) in euthyroid patients and in 9 eyes (34.6%) with thyroid dysfunction.

Table 3:Various retinopathy grades and thyroid status

	EUTHYROID(N=74)		**ThyroidDysfunction(N=26)**		**Total (N=100)**	**P Value LS**
Retinopathy grade	**No**	**%**	**No**	**%**		
mild NPDR	35	47.30	5	19.23	40	0.023S
mild NPDR WITH CSME	15	20.27	8	30.77	23	0.41NS
moderate NPDR	13	17.57	6	23.08	19	0.74NS
moderate NPDR WITH CSME	5	6.76	1	3.85	6	0.95NS
severe NPDR	2	2.70	2	7.69	4	0.59NS
severe NPDR WITH CSME	1	1.35	0	0.00	1	0.58NS
very severe NPDR		0.00	1	3.85	1	0.58NS
early PDR	3	4.05	2	7.69	5	0.83NS
high risk PDR	0	0.00	1	3.85	1	0.58NS
Total	74	100.00	26	100.00	100	

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

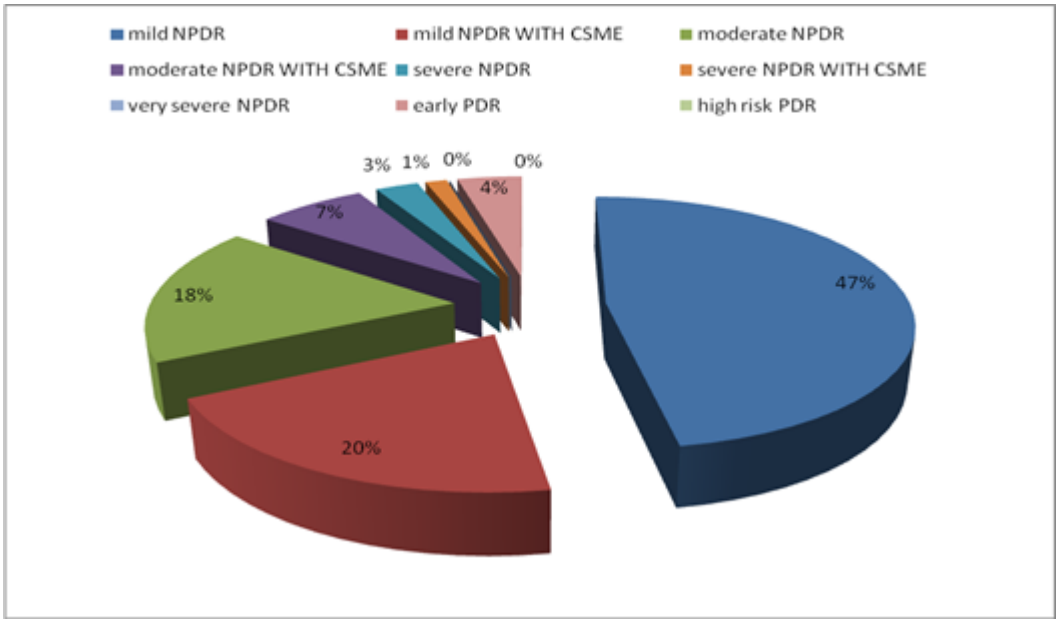

Figure 3: The different retinopathy grades in euthyroid patients

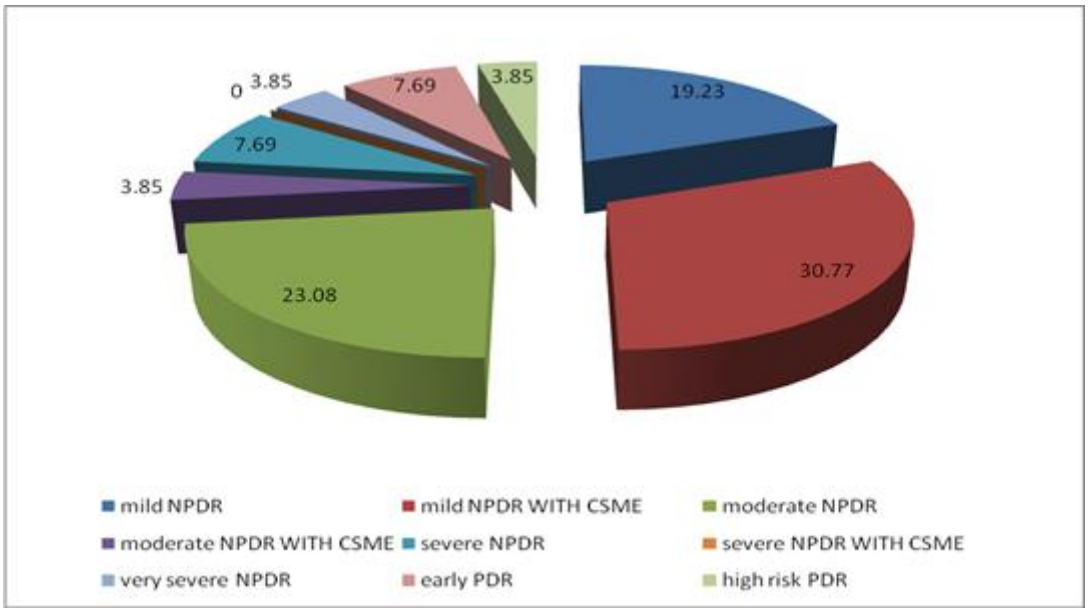

Figure 4: Different retinopathy grades in patients with abnormal thyroid function.

For comparing the severity of retinopathy between those having and not having thyroid dysfunction mild, moderate and severe retinopathy was considered. Mild and moderate retinopathy were ETDRS mild and moderate NPDR while eyes with ETDRS grade severe NPDR and above/worse were considered to have severe retinopathy. Accordingly. it was seen that 23% of eyes with thyroid dysfunction had severe retinopathy while only 8.1% had severe retinopathy in the euthyroid group.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

Table 4: Distribution of patients as per severity of retinopathy versus thyroid dysfunction

Retinopathy	Normal Thyroid function [n(%)]	Abnormal thyroid function [n(%)]	Total [n(%)]
Mild	50 (67.6%)	13(50.0%)	63(63%)
Moderate	18(24.3%)	7(29.26%)	25(25%)
Severe	6(8.1%)	6(23.1%)	12(12%)
Total	74(100%)	26(100%)	100(100%)

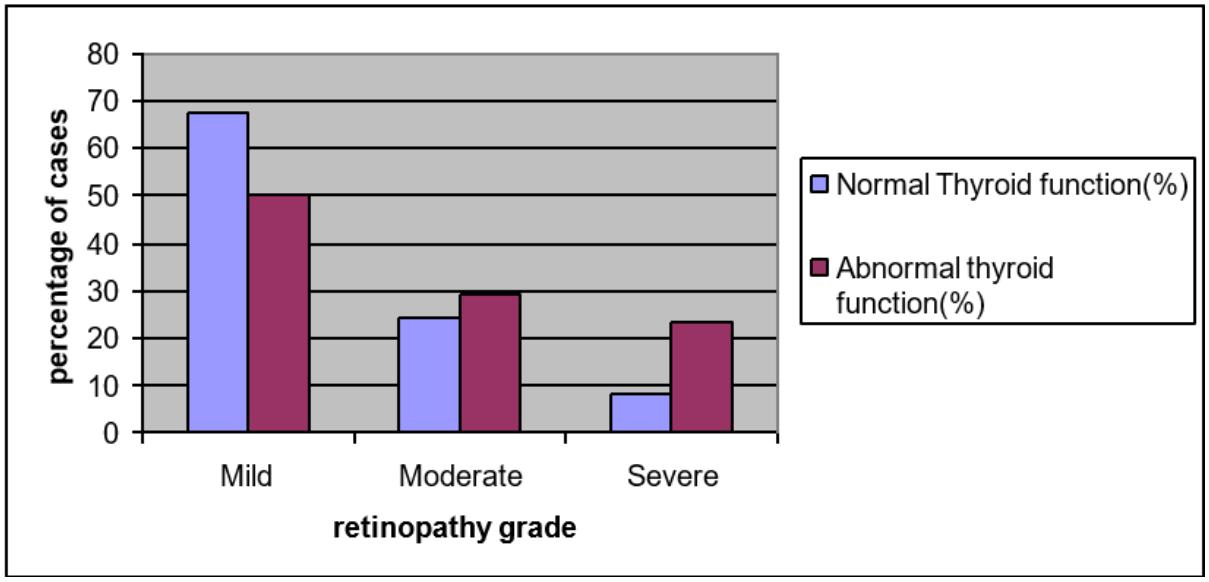

Figure 5: Distribution severity of retinopathy in patients with and without thyroid dysfunction.

Association between severity of retinopathy and thyroid dysfunction.

We analyzed the association of severity of retinopathy and thyroid dysfunction (Table 5). We compared severity of retinopathy between those having mild retinopathy and those having moderate to severe. Among the patients with normal thyroid functions 67.6% of eyes had mild retinopathy and 32.5% had moderate to severe retinopathy. In contrast, patients with abnormal thyroid functions, 50% had mild and 50% had moderate to severe retinopathy. Thus, higher proportion of patients with moderate to severe retinopathy had thyroid dysfunction (32.53% versus 50%).

However, this difference was not significant (OR 2.07; 95% CI 0.82 -5.23; p=0.17)

Table 5: Association of severity of retinopathy and thyroid dysfunction

Retinopathy	Normal Thyroid function [n(%)]	Abnormal thyroid function	Total	Odds Ratio	95% CI
Mild	50(67.57%)	13(50.00%)	63(63%)	2.07	0.8217 -5.2311
Moderate to Severe	24(32.43%)	13(50.00%)	37(37%)		2 tailed P value p=0.17
Total	74(100%)	26(100%)	100(100%)		

Association between severity of retinopathy and subclinical hypothyroidism

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

We analysed the association of severity of retinopathy and subclinical hypothyroidism (Table 6). 61.1% of eyes had moderate to severe retinopathy while 31.1% eyes had mild retinopathy % of eyes. Thus, almost double the eyes with subclinical hypothyroidism had moderate to severe grade of retinopathy. This difference was found to be statistically significant. The increased odds (OR 3.23) of higher grade of retinopathy patients having subclinical hypothyroidism was statistically significant (p=.04 CI=1.10-9.88).

Table 6: Association of Severity of retinopathy and subclinical hypothyroidism

Retinopathy	**Normal Thyroid function [n=74]**	**Subclinical hypothyroidism [N=18]**	**Total [N=92]**	**Odds ratio**	**95% CI**
Mild	50(67.57%)	7(38.89%)	57(61.95%)	3.23	1.10-9.88
Moderate to severe	24(32.43%)	11(61.11%)	35(38.05%)		2 tailed P = 0.048
Total	74(100%)	18(100%)	92(100.00%)		

Discussion

Previous studies have reported the prevalence of thyroid dysfunction among diabetes patients to be between 2.2 to 17%.[2,3] We found a higher prevalence probably because all the patients had diabetic retinopathy while in other studies retinopathy was not a mandatory inclusion criterion. Also geographic location and study population may have a role. However, few studies have observed very high prevalence of thyroid dysfunction in diabetes i.e 31% and 46.5% respectively.[8,9] Several Indian studies have also detected a higher prevalence of thyroid dysfunction in type II diabetic patients.[8,10-13]

Subclinical hypothyroidism was the most common thyroid disorder encountered in our study. Eighteen percent of the patients had subclinical hypothyroidism. Several studies have also indicated subclinical hypothyroidism as the most common disorder in patients with type 2 diabetes.[15] The prevalence of subclinical hypothyroidism in patients with type 2 diabetes varies in the literature. Some studies stated that subclinical hypothyroidism was found in 10-17% of patients suffering from diabetes mellitus,[12,15-17] while others gave a prevalence of 5-7%.[6] The latter is comparable with the prevalence quoted in the general population.

Clinical hypothyroidism was found in 5% of patients, hyperthyroidism was found in 2% of patients and least common was subclinical hyperthyroidism (1%) in our study. The reported frequency of hyperthyroidism and hypothyroidism in patients with diabetes has varied from 3.2 % to 4.6 % and 0.7 % to 4.0 % respectively. However, some Indian studies have reported a higher prevalence of hypothyroidism and hyperthyroidism as 16% to 28% and 13%-17% respectively.[10,12,13,18] In a recent study in India among the 32% of diabetic patients with abnormal thyroid hormone levels, 22% of them had hypothyroidism (8% clinical hypothyroidism and 14% subclinical hypothyroidism) and 10% had hyperthyroidism (4% clinical hyperthyroidism and 6% subclinical hyperthyroidism).[19]

Mild retinopathy was the commonest type of retinopathy seen in the study group. In patients with normal thyroid function the proportion of severe retinopathy was less as compared to

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

those having abnormal thyroid function 9.5% versus 19.2%. Thus, there was a trend toward increasing severity of retinopathy in patients with abnormal thyroid function. 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.[20]

Subclinical hypothyroidism was seen in 18 patients. Sixty one percent (11eyes) of the patients with SCH 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. A higher frequency of retinopathy and nephropathy was observed in diabetic patients with subclinical hypothyroidism, and more severe retinopathy was noted in some studies.[21-23]

The American Diabetes Association performed a cross-sectional study,[24] 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.

Conclusion

We conclude that 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.

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ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

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