The Pharmaceutical and Chemical Journal, 2016, 3(1):55-67

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

A Study of an Association between Sub-Clinical Hypothyroidism and Sight Threatening Diabetic Retinopathy in Type-2 Diabetic Patients

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Abstract Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. Diabetic retinopathy caused by complications of diabetes mellitus, which can eventually lead to blindness. It is most common micro vascular complication and also it is a leading cause of blindness in adults between 30-65 years of age worldwide. Sub-clinical hypothyroidism, the most prevalent form of thyroid diseases and it is more common in females and elder ones. The aim of the study is to determine the relationship between Sub-Clinical Hypothyrodism (SCH) and sight threatening diabetic retinopathy in type-2 diabetic patients and find the Correlation of various risk factors of diabetic retinopathy and Sub-Clinical Hypothyrodism. This is concluded from the present study that duration of diabetes, severity of diabetes, hypertension, nephropathy, neuropathy, total cholesterol, triglyceride, HDL have prognostic value in diabetic retinopathy. Males are more prone to Diabetic retinopathy and females patients are more prone to Sub-Clinical Hypothyrodism. Patients who were suffering from diabetes are also having retinopathy along with Sub-Clinical Hypothyrodism in an associated manner.

Keywords Diabetes mellitus, Diabetic retinopathy, Sub-Clinical Hypothyrodism

Introduction

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. Sustained release tablet allowing a twofold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. It is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug [1]. Extended release formulation is an important program for new drug research and development to meet several unmet clinical needs. There are several reasons for attractiveness of these dosage forms viz. provides increase bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug [2-3]. Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. Lack of insulin, whether absolute or relative, affects the metabolism of carbohydrate, protein, fat, water and electrolytes. Long standing metabolic derangement is frequently associated with permanent and irreversible functional and structural changes in the cells of the body, those of vascular system being particularly susceptible. These changes lead in turn to the development of well defined clinical entities, the so called complications of diabetes which most characteristically affect the eye, the kidney, and the nervous system.

Diabetic retinopathy (damage to the retina) is caused by complications of diabetes mellitus, which can eventually lead to blindness. **Diabetic retinopathy** is one of the most common microvascular complications of DM, and the leading cause of blindness in adults between 30 and 65 years of age worldwide.

Common risk factors for the development /worsening of microvascular complications in diabetes include duration of diabetes, type of diabetes (proliferative disease in type 1 and maculopathy in type 2); poor glycemic control, hypertension and dyslipidemia. Clinical classification is as follows:

- Non-proliferative diabetic retinopathy
- Proliferative diabetic retinopathy.

Non-Proliferative Diabetic Retinopathy (NPDR)

The lesions in the retina at this stage are within the retina and include micro-aneurysms, small 'dot and blot' haemorrhages, 'splinter' haemorrhages, intraretinal microvascular abnormalities (IRMA) and 'cotton wool' spots.

The presence of these lesions in various degrees determines whether the NPDR is 'mild', 'moderate', 'severe' and 'very severe'.

1. Mild Non-Proliferative Diabetic Retinopathy

At least one microaneurysm, and also dot, blot or flame-shaped haemorrhages in all four fundus quadrants.

2. Moderate Non-Proliferative Diabetic Retinopathy

Intraretinal microaneurysms and dot and blot haemorrhages of greater severity, in one to three quadrants. Cotton wool spots, venous calibre changes including venous bleeding and intraretinal microvascular abnormalities are present but mild.

3. Severe Non-Proliferative Diabetic Retinopathy

At least one of the following should be present:

a) 'Severe' haemorrhage and microaneurysms in all four quadrants of the fundus,

b) Venous bleeding, which is more marked in at least two quadrants, and

c) Intra retinal microvascular abnormalities, which are more severe in at least one quadrant.

4. Very Severe Non-Proliferative Diabetic Retinopathy

It includes two or more of the criteria for severe non-proliferative diabetic retinopathy, but without any proliferative diabetic retinopathy.

Diabetic retinopathy often has no early warning signs. Even macular edema, which may cause vision loss more rapidly, may not have any warning signs for some time. In general, however, a person with macular edema is likely to have blurred vision, making it hard to do things like read or drive. In some cases, the vision will get better or worse during the day [1].

It has long been recognized that thyroid hormones have marked effects on glucose homeostasis. Glucose intolerance is associated with hyperthyroidism and hypothyroidism are characterized by insulin resistance**.** Sub-clinical hypothyroidism, the most prevalent form of thyroid diseases, is more common in females and in the elderly, it is defined as an asymptomatic state characterized by high serum thyrotropin (TSH>4 mU/l) with peripheral thyroid hormone concentrations within the laboratory reference ranges. Such abnormalities in thyroid function tests are very common. Sub-clinical hypothyroidism, also referred to as mild hypothyroidism, is defined as normal serum free T4 levels with slightly high serum TSH concentration [2].

Cristiansen *et al* (1978) found no association between smoking and prevalence of microangiography in juvenile onset insulin dependent diabetes mellitus [3]. There was found absence of a relationship between smoking and microangiopathy [4]. Gordon *et al* (1991) also found that lowering serum lipid concentration, specially serum total cholesterol and LDL cholesterol levels can improve diabetic retinopathy while reducing hard exudates [5].

A relationship of higher triglyceride levels and retinopathy was found in diabetic persons of Maxican origin [6]. Maioli *et al* (1993) also found no difference in total cholesterol, HDL cholesterol or triglycerides between diabetes with and without retinal lesions [7].

The objective of this research article is to determine the relationship between subclinical hypothyroidism (SCH) and sight threatening diabetic retinopathy in type-2 diabetic patients as well as to find out correlation of various risk factors of diabetic retinopathy and hypothyroidism.

Material and Methods

The present study has been done in the diabetic care research center, S.P. Medical College and associated group of PBM Hospital, Bikaner, Rajasthan. Outdoor, indoor patients suffering from type -2 diabetes mellitus and hypothyroidism were included.

Diabetes will be diagnosed according to the American Diabetes Association (ADA) revised criteria:

1. Fasting blood glucose level greater or equal to 126 mg/dl (7.0 mmol/L) on two separate occasions.
2. A random plasma glucose level of 200mg/dl (11.1 mmol/L) or more.

A blood glucose level of 200mg/dl (11.1mmol/L) or more two hours after ingestion of 75 gms glucose.

The selected patients were evaluated for presence of vascular (micro and macro vascular) complications i.e. coronary artery disease, peripheral vascular disease, retinopathy, nephropathy and neuropathy by relevant investigations.

Peripheral vascular disease (PVD) were diagnosed by definitive history of intermittent claudication or if one or more peripheral pulses were absent in both feet. The grading was done using ankle brachial pressure index (ABPI) by Doppler Study [Vascular Doppler Recorder, Versalab Dx]. PVD was diagnosed when ankle brachial index was <0.9.

Coronary artery disease (CAD) were diagnosed by history of angina or myocardial infarction or documented by previous treatment records. Interpretation of ECG was recorded as per Minnesota codes.

Neuropathy was diagnosed by history of numbness, paraesthesias, tingling sensation, burning sensation and confirmed by touch sensation using 10 gm monofilament, vibration sense by biothesiometer (VPT *i.e.* Vibrometer at great toe >25 was considered significant) and diminished/absent ankle reflex. Autonomic neuropathy was diagnosed by history of postural fall of blood pressure history of constipation or diarrhea and variability in ECG during deep breathing.

Retinopathy was done by detailed fundus examination and was classified according to Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study.

Incipient nephropathy was diagnosed by Micral test using semi auto analyser. Incipient nephropathy was presumed to be present if any two readings (out of three) of urinary albumin were ranging from 30 to 300 mg/day (*i.e.* microalbuminuria). Nephropathy was diagnosed by elevated level of serum creatinine and blood urea, or presence of macroalbuminuria.

Lipid profile was done by semi autoanalyzer. Estimated values of Total Cholesterol>240 mg/dl, Serum Triglycerides >160 mg/dl, HDL <40 mg/dl, LDL >130 mg/dl and VLDL >40 mg/dl were considered as abnormal.

A total 100 subjects comprising hospital based patients with type-2 diabetes (aged >20 years) were investigated. Diagnosed normal T3, T4 and TSH level (i.e. <3 euthyroid, 3-5 subclinical, and >5 frank hypothyroidism) by using Automated Chem Well, Chemistry analyser. Both groups were compared with euthyroid patients which was taken as standard. 50 type-2 diabetic SCH patients were selected randomly form 100 subjects and conducted further investigation on them.

Retinal photography graders were examined independently using Non medriatic auto fundus camera-AFC-230/210 at 45º, by following quality assurance protocols. The severity of diabetic retinopathy was graded based on the international clinical diabetic retinopathy scale. After checking diabetic retinopathy in given subjects' eyes (50 patients) with very severe NPDR to mild NPDR, the criteria were followed as given in International Clinical Diabetic Retinopathy (DR) Disease Severity Scale.

Table1: International Clinical Diabetic Retinopathy Disease Severity Scale

Proposed Disease Severity Level	Findings Observation upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild nonproliferative diabetic retinopathy	Microaneurysms only
Moderate non proliferative diabetic retinopathy	More than just microaneurysms but less than severe NPDR
Severe non proliferative diabetic retinopathy	Any of the following: More than 20 intraretinal haemorrhages in each of four quadrants Definite venous bleeding in two or more quadrants Prominent IRMA in one or more quadrants And no signs of proliferative retinopathy
Proliferative diabetic retinopathy	One or both of the following: Neovascularization Vitreous/ preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy.

Table 2: International Clinical Diabetic Macular Edema Disease Severity Scale

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole.
Diabetic macular edema apparently present	Some apparent retinal thickening or hard exudates in posterior pole
If diabetic macular edema is present, it can be categorized as follows:	
Proposed Disease Severity Level	**Findings Observable upon Dilated Ophthalmoscopy***
Diabetic macular edema present.	Mild diabetic macular edema: Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula
Moderate diabetic macular edema: Retinal thickening or hard exudates approaching the center of the macula but not involving the center	
Severe diabetic macular edema: Retinal thickening or hard exudates involving the center of the macula.	

* Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening; this requires a three-dimensional assessment that is best performed by dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography [8].

Selection of Patients

Inclusion criteria:

1) Diagnosed diabetic patients.
2) Patients >20 years in age.
3) TSH Level:
   a) <3, Euthyroid
   b) 3-5, Subclinical Hypothyroidism
   c) >5, Frank Hypothyroidism

4) Diabetic Retinopathy:
   a) Mild NPDR
   b) Moderate NPDR
   c) Severe NPDR
   d) PDR
   e) High Risk PDR
   f) Maculopathy

Exclusion criteria

Patients suffering from diseases like sickle cell anemia, leukaemia, hyperviscosity syndromes, hypertension, CRF or any other condition which could cause retinopathy as well as the patients not willing to cooperate will be excluded from the study. Frank patients of hypothyroidism will be excluded from the study.

Results

Table 1: Age distribution of cases of diabetic retinopathy

S. No	Age group (in yrs)	Number of cases	Percentage (%)
1	20-30	0	0
2	31-40	3	6
3	41-50	12	24
4	51-60	14	28
5	61-70	20	40
6	>70	1	2
7	Total	50	100
	Mean =55.72 years		

Maximum number of patients were in the age group of 51-70 years (68%).

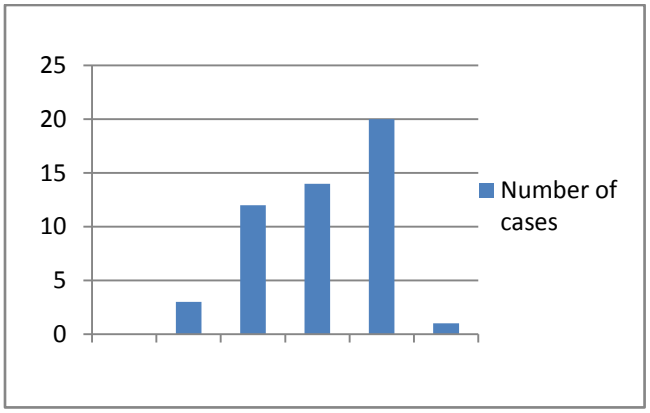

Figure 1: Age distribution of cases of diabetic retinopathy

Table 2: Distribution of cases according to sex of diabetic retinopathy

S. No.	Sex	Number of cases	Percentage (%)
1	Male	34	68
2	Female	16	32
3	Total	50	100

Male were preponderant than females.

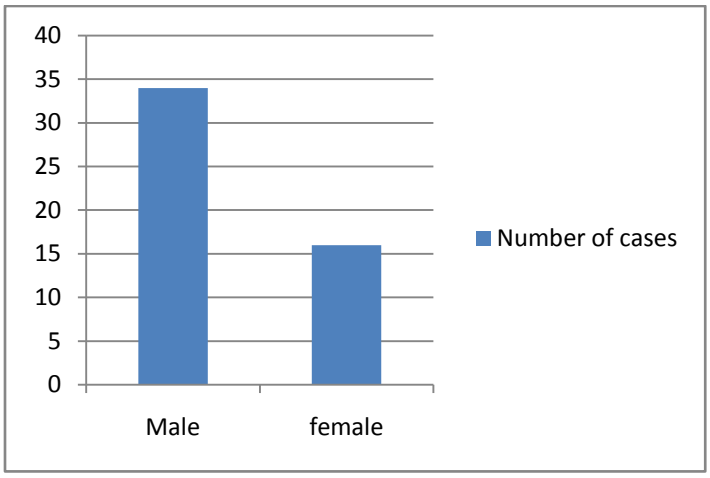

Figure 2: Distribution of cases according to sex of diabetic retinopathy

Table 3: Treatment control of diabetic patients studied

S. No.	Treatment	Number of cases out of 50 Patients	Percentage (%)
1	Only diet	0	0
2	Only Oral	24	48
3	Only insulin	9	18
4	Oral + Insulin	17	34

Maximum patients were in oral drugs and insulin control.

Table 4: Distribution of patients according to smoking habit of diabetic retinopathy

S. No.	Smoking habit	Number of cases	Percentage (%)
1	Smoker	16	32
2	Non smoker	34	68
3	Total	50	100

There is substantial amount of patients with smoking habits.

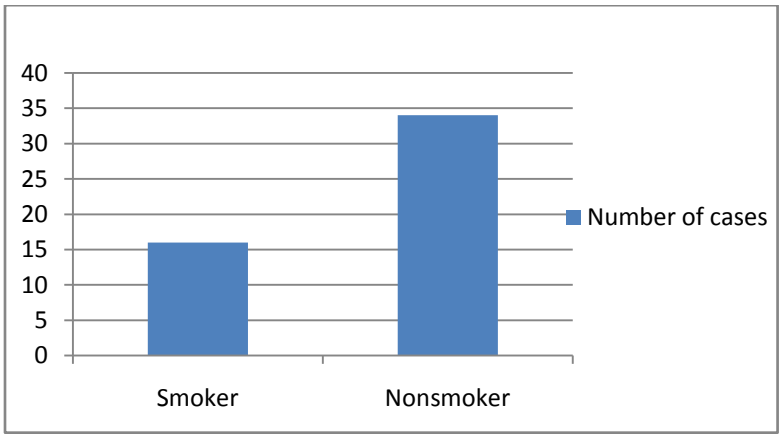

Figure 3: Distribution of patients according to smoking habit of diabetic retinopathy

Table 5: Distribution of cases according to severity of retinopathy

S. No.	Severity of retinopathy	Number of eyes	Percentage (%)
A.	**Non proliferative**		
1	Early	1	1
2	Mild	2	2
3	Moderate	18	18
4	Severe	24	24
5	Very severe	35	35
B.	**Proliferative**		
6	PDR without HRC	14	14
7	PDR with HRC	6	6

Severe and very severe diabetic retinopathy was seen in 64% of patients.

Table 6: Distribution of cases according to associated illness in diabetic retinopathy

S. No.	Associated Illness	Number of cases	Percentage (%)
1	HT	9	18
2	Nephropathy	3	6
3	HT + Nephropathy	4	8
4	Neuropathy	25	50
5	HT + Neuropathy	5	10
6	Not associated with any illness	4	8

8% of patients had no associated illness while 92% of patients had associated illness. Neuropathy was maximum (48%).

Table 7: Distribution of cases according to lipid profile

Lipid profile	Characteristics	No. of patients	Percentage (%)
Cholesterol (mg %)	<200	35	73
	200-239	6	13
	>239	7	15
HDL Cholesterol (mg/dl)	<40	6	12
	41-60	38	76
	>60	6	12
Triglyceride (mg/dl)	<120	10	20
	121-160	32	64
	161-200	6	12
	>200	2	4
VLDL Cholesterol (mg/dl)	<30	4	9
	31-40	20	43
	>40	23	49

VLDL was above 40 mg/dl in 49%, triglyceride was 121-160 mg in 64% patients, Cholesterol above 200mg/dl was observed in 76% of cases, HDL in range of 41-60 mg/dl had 84% of patients.

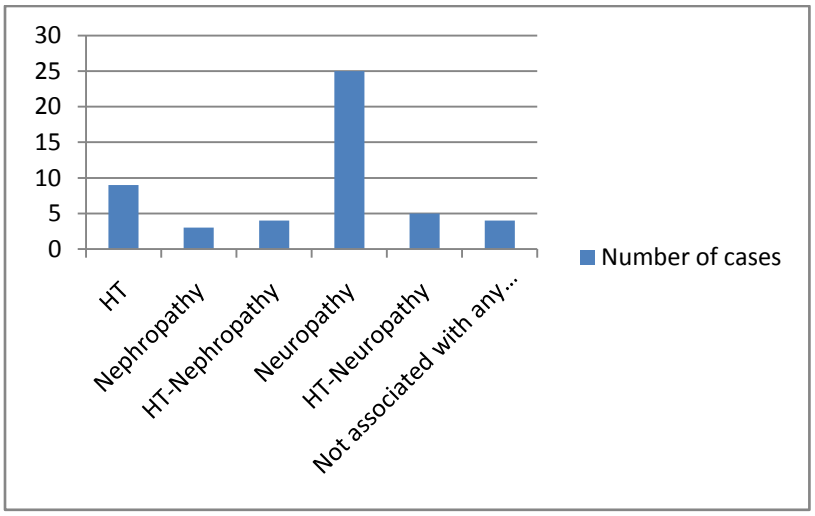

Figure 4: Distribution of cases according to associated illness in diabetic retinopathy

Table 8: Distribution of cases according to Diabetic Retinopathy and Duration of type 2 Diabetes

S. No.	Duration of Diabetes (Years)	Number of Cases (Numbers)	Percentage (%)
1	0-5	4	8
2	6-10	10	10
3	11-15	20	23
4	16-20	10	15
5	> 20	6	11
	Total	50	100

Maximum number of cases of Diabetic Retinopethy along with Type 2 Diabetes duration is 15 – 20 years (66 %)

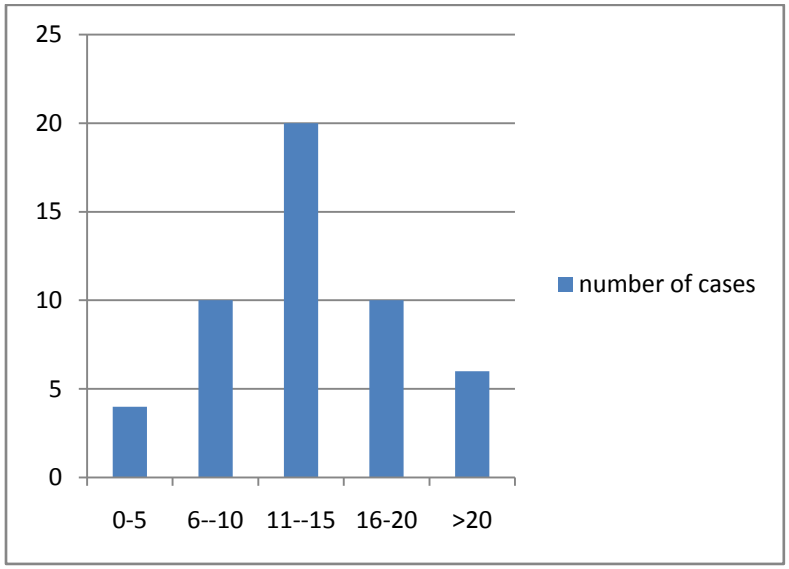

Figure 5: Distribution of cases according to Diabetic Retinopathy and Duration of type 2 Diabetes

Table 9: Age distribution of cases of Sub-clinical Hypothyroidism

S. No	Age group (in yrs)	Number of cases	Percentage (%)
1	20-30	0	-
2	31-40	10	20
3	41-50	18	36
4	51-60	14	28
5	61-70	6	12
6	>70	2	4
7	Total	50	100
	Mean =44.8 years		

Maximum number of patients was in the age group of 31-60 years (84%).

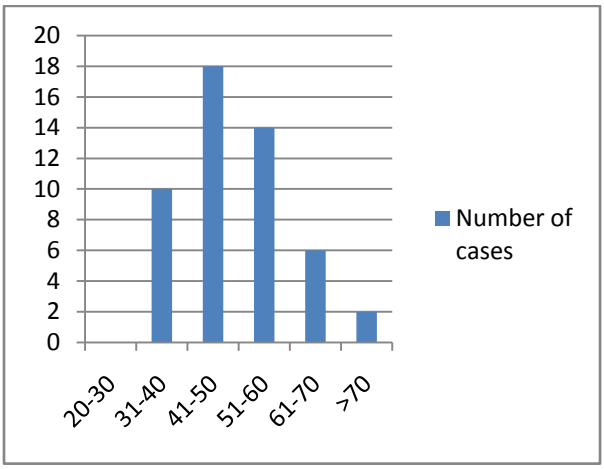

Figure 6: Age distribution of cases of Sub-clinical Hypothyroidism

Table 10: Distribution of cases according to sex of Sub-clinical Hypothyroidism

S. No.	Sex	Number of cases	Percentage (%)
1	Male	19	38
2	Female	31	62
3	Total	50	100

Females are more prone then Males.

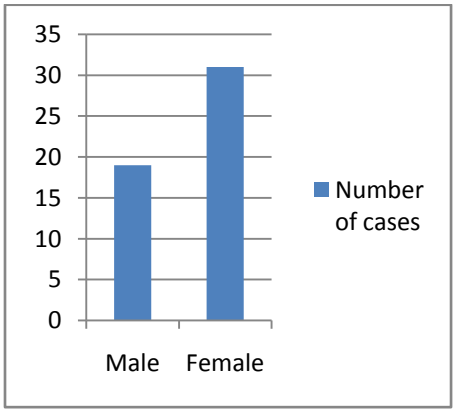

Figure 7: Distribution of cases according to sex of Sub-clinical Hypothyroidism

Table 11: Distribution of cases according to associated illness in Sub-clinical Hypothyroidism

S. No.	Associated Illness	Number of cases	Percentage (%)
1	HT	3	6
2	Nephropathy	4	8
3	HT + Nephropathy	3	6
4	Neuropathy	27	54
5	HT + Neuropathy	9	18
6	Not associated with any illness	4	8
	Total	50	100

8 % of patients had no associated illness while 92% of patients had associated illness. Neuropathy was maximum (54%).

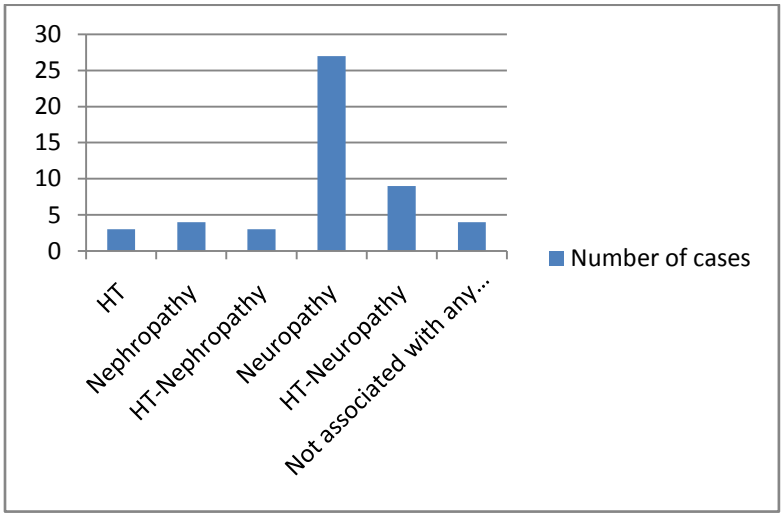

Figure 8: Distribution of cases according to associated illness in Sub-clinical Hypothyroidism

Table 12: Distribution of patients according to smoking habit of Sub-clinical Hypothyroidism

S. No.	Smoking habit	Number of cases	Percentage (%)
1	Smoker	15	30
2	Non smoker	35	70
3	Total	50	100

Non smokers were more prone to Sub-clinical Hypothyroidism.

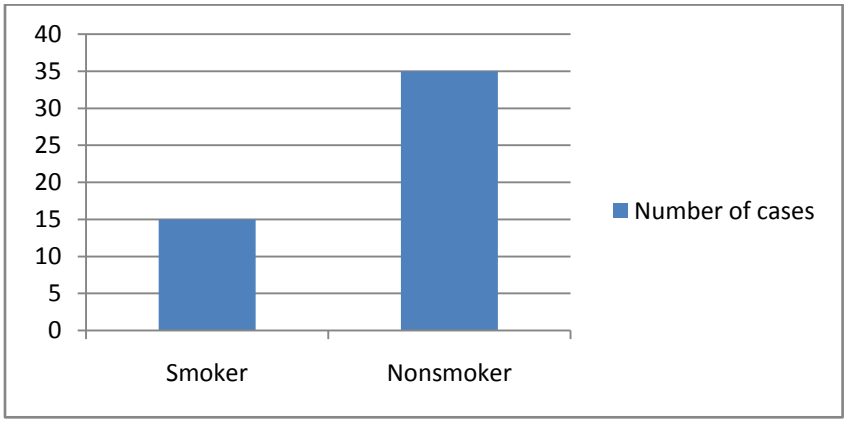

Figure 9: Distribution of patients according to smoking habit of Sub-clinical Hypothyroidism

Table 13: Distribution of cases according to severity of Hypothyroidism

S. No.	Severity of Hypothyroidism	TSH Level	Number of Cases	Percentage (%)
1	Euthyroid	< 3	4	8
2	Sub-clinical Hypothyroidism	3 – 5	43	86
3	Frank Hypothyroidism	> 5	3	6
	Mean TSH level = 3.76		50	100

Maximum number of cases are Sub-clinical Hypothyroidism i.e. 86%

Mean TSH Level observed is 3.76

Table 14: Distribution of cases according to Sub-clinical Hypothyroidism and Duration of Type 2 Diabetes

S. No.	Duration of Diabetes (Years)	Number of Cases	Percentage (%)
1	0- 5	0	-
2	5 – 10	2	4
3	10 -15	8	16
4	15 – 20	28	56
5	> 20	12	24
	Total	50	100

Maximum number of cases of Sub-clinical Hypothyroidism along with Type 2 Diabetes duration: 15-20 yrs (56%).

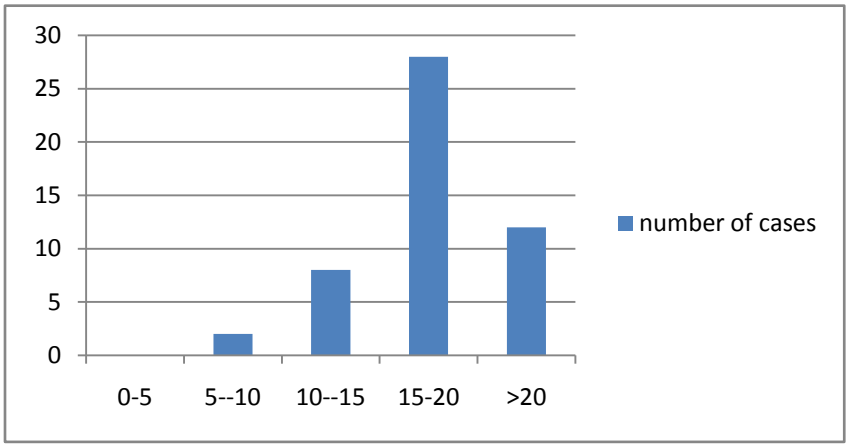

Figure 10: Distribution of cases according to Sub-clinical Hypothyroidism and Duration of Type 2 Diabetes

Table 15: Distribution of cases of Sub-clinical Hypothyroidism according to lipid profile

Lipid profile	Characteristics (mg/dl)	No. of patients (Numbers)	Percentage (%)
Cholesterol	<200	35	70
(mg %)	200-239	8	16
	>239	7	14
HDL Cholesterol	<40	6	12
(mg/dl)	41-60	38	76
	>60	6	12
Triglyceride (mg/dl)	<120	2	4
	121-160	35	70
	161-200	6	12
	>200	7	14
VLDL Cholesterol	<30	5	10
(mg/dl)	31-40	22	44
	>40	23	46

VLDL was maximum (46%) above >40 mg/dl,
Triglyceride was 121-160 mg/dl had the maximum patients 70%
HDL Cholesterol 41-60 mg/dl had 76% of patients
Cholesterol <200mg/dl was maximum in 70% of cases.

Discussion

Weber et al (1986) age had an independent influence on the development of retinopathy. However they could not separate age from puberty and mean blood pressure, both of which are strongly related to age. This limited the specificity of their finding [9]. Agradh *et al* (1994) conducted a cross sectional study of 396 type-1 diabetic patients. They found an incidence of retinopathy to be 47.2% [10]. Olsen *et al* (1998) found the prevalence of retinopathy in 339 young Danish patients with type-2 diabetic to be 60% [11]. In the present study both eyes of 50 patients suffering from diabetes with retinopathy were studied. One eye (2%) had mild, 7 eyes (14%) moderate, 15 eyes (30%) had severe, and 17 eyes (34%) had very severe. 40 eyes (80%) had non proliferative nature of diabetic retinopathy and 7 eyes (14%) had proliferative without HRD and 3 eyes (6%) had proliferative with HRC.

Conclusion

The study revealed a significant association and relationship between subclinical hypothyroidism (SCH) and sight threatening diabetic retinopathy in type-2 diabetic patients. The examined values are (t calc = 0.071) < (t tab= 2.228) and (P = 0.944) > 0.10, so that it can be concluded that patients of Type-2 Diabetes are more prone to both subclinical hypothyroidism and retinopathy. The examination and criteria used to detect retinopathy are relavant in patients with subclinical hypothyroidism. Diabetes Mellitus offers many benefits as a model for study of subclinical hypothyroidism and retinopathy in that it can be used to identify the contributing role of neuropathy, nephropathy, endocrine, BMR, lipid profile, height, weight etc factors in the initiation and propagation of retinopathy and sub-clinical hypothyroidism in those patients having type-2 diabetes. Unrecognized thyroid dysfunction may impair metabolic control and add to cardiovascular, and other chronic complication risk in diabetic patients [12].

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