International Journal of Research in Medical Sciences
Borooah M et al. Int J Res Med Sci. 2017 May;5(5):1818-1822
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20171556

Original Research Article

A study on relationship between severity of diabetic retinopathy and subclinical hypothyroidism

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Received: 04 April 2017
Accepted: 08 April 2017

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is defined as an asymptomatic condition characterized by normal serum levels of free thyroxine and elevated serum concentration of thyrotropin (>4.0µIU/ml). Association between diabetic retinopathy and SCH is unclear. Aim was to study the relationship between severity of diabetic retinopathy and SCH in patients of diabetic retinopathy with type 2 diabetes mellitus.
Methods: 120 patients of diabetic retinopathy with known type 2 diabetes mellitus were taken and categorized them according to severity of diabetic retinopathy as per ETDRS classification. Serum thyrotropin (TSH) and free thyroxine (FT4) concentration were measured in all 120 patients. Patients with normal TSH and FT4 values are euthyroid patients and those with normal FT4 but TSH value >4µIU/ml are considered as having subclinical hypothyroidism. Severity of diabetic retinopathy is compared between the euthyroid and subclinical hypothyroid group.
Results: Out of the 120 patients included in the study, 72 (60%) were male and 48 (40%) were female. 97 patients (80.83%) were Euthyroid and 23 patients (19.17%) had subclinical hypothyroidism. It was observed that prevalence of more severe form of diabetic retinopathy (severe NPDR and PDR) was higher in SCH group as compared to euthyroid group. Severity of diabetic retinopathy was compared with serum TSH level and it was seen that severity of diabetic retinopathy significantly increases with increase in serum TSH value.
Conclusions: Patients with SCH had more severe form of diabetic retinopathy as compared to patients with euthyroidism. Severity of diabetic retinopathy significantly increases with increase in serum TSH value.

Keywords: ETDRS, Free thyroxine, Subclinical hypothyroidism, Thyrotropin

INTRODUCTION

Diabetic retinopathy (DR) is one of the major micro vascular complications of diabetes. If untreated, it may lead to blindness. If diagnosed and treated promptly, blindness is usually preventable.

Diabetes is fast gaining the status of epidemic in India and as of 2000, India (31.7 million) topped the world with the highest number of people with diabetes. With the increasing prevalence of diabetes, burden of blindness due to the disease is also increasing. Assessing the risk factor of DR, particularly modified risk factor, is important for early intervention to reduce the onset and progression of DR. Hence the present observational study was conducted to study the relationship between severity of diabetic retinopathy and subclinical hypothyroidism. Association between diabetic retinopathy with duration of diabetes, poor glycemic control, dyslipidemia and elevated blood pressure are already found in various studies.[1,2] Whereas studies are still going on regarding its relationship with other factors like plasma fibrinogen

level, plasma homocysteine level, thyroid dysfunction including subclinical hypothyroidism etc. Association between diabetic retinopathy and subclinical hypothyroidism is a topic of growing interest and there are only few studies in recent literature.

Subclinical hypothyroidism (SCH) is defined as a condition where thyroid stimulating hormone (TSH) levels is above the upper limit of the reference range in addition to a normal free thyroxine level (FT4).[3]

SCH is a common endocrine disorder and has been reported to range from 4-10% in general population. The frequency of thyroid dysfunction in diabetic patients is higher than that of the general population, the most common dysfunction being SCH. Prevalence of SCH in diabetes varies between 2 and 17%.[4,5] Few reported studies have investigated the association between Subclinical hypothyroidism and microvascular complications in type 2 diabetes.

METHODS

The present study was conducted taking up 120 diabetic retinopathy patients with known type 2 diabetes mellitus. The study was conducted in the Department of Ophthalmology, Assam Medical College and Hospital, Dibrugarh, Assam, India for a duration of 1 year from July 2014 to June 2015. Ethical clearance was taken from institutional ethics committee.

Patients were explained the nature of the study and prior written informed consent was taken from every patient before enrolment. After obtaining detailed history, a comprehensive ophthalmological examination was done with special emphasis on the fundus examination. The level of severity of retinopathy was determined by indirect ophthalmoscopy for a pan retinal view, and stereoscopic slit lamp biomicroscopy of the disc and macula using +90D lens. Ancillary tests selectively done were stereo fundus photography, fluorescein angiography and OCT.

Based on ETDRS criteria patients were graded according to their severity of retinopathy into mild NPDR, moderate NPDR, severe NPDR, very severe NPDR, early PDR and high risk (HR) PDR. Out of the two eyes, the eye having more severe form of retinopathy was considered in grading. Patients with severe NPDR and very severe NPDR were considered in one group and those with PDR and HR PDR were considered in one group for data analysis.

Serum free T4 and TSH was obtained in all patients. Free T4 level was estimated by Radioimmunoassay using BRIA COAT-1 RIA KIT for free thyroxin, (two step assay), Isotopes and radiation: Health and prosperity, Board of Radiation and Isotope Technology (BRIT) and TSH level by Immunoradiometric assay using IRMA Kit for human thyroid stimulating hormone, IRMAK-9, Isotopes and Radiation: Health and Prosperity, Board of Radiation and Isotope Technology. The normal reference range considered are- for free T4- (10-20) pg/ml and for TSH- (0.17-4.05)µIU/ml. Patients having TSH value >4.0µIU/ml in presence of normal free T4 value were considered as having subclinical hypothyroidism. Patients having TSH and free T4 value within normal reference range were euthyroid patients. Severity of diabetic retinopathy was compared between the two groups.

Exclusion criteria

- Patients with significant media opacity interfering in diagnosis and classification of DR.
- Patients taking thyroid hormones, after thyroidectomy or radioactive iodine therapy.
- Patients with overt hypothyroidism, overt hyperthyroidism and subclinical hyperthyroidism.
- Pregnant patient.
- Critically ill patients

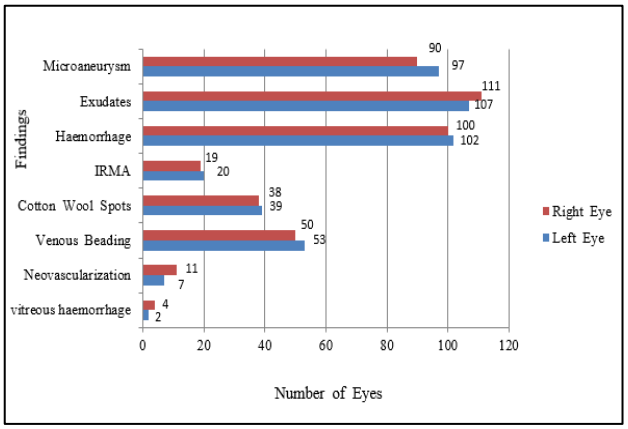
Statistical analysis

Data are represented in terms of number, percentage, mean±SD. 'p' value is calculated using chi square and ANOVA test. 'p' value <0.05 is considered as significant.

RESULTS

In the present study, most of the patients were found to be in the age group of 51-60 years. Out of the 120 patients included in the study, 72 (60%) were male and 48 (40%) were female. It was seen that most of the patients with subclinical hypothyroidism were female with male: female ratio of 1:1.3.

On fundoscopy, various features of DR were observed carefully on both the eyes. Different fundus findings on both the eyes of study subjects are presented on the Figure 1. Table 1 shows distribution of diabetic retinopathy according to different stages.



IRMA- Intraretinal microvascular abnormalities.

Figure 1: Fundus findings of diabetic retinopathy patients.

Table 1: Distribution of severity of diabetic retinopathy.

Retinopathy group	Number (n)	Percentage (%)
Mild NPDR	34	28.33
Moderate NPDR	49	40.83
(Severe+very severe) NPDR	24	20.00
PDR (early+high risk)	13	10.84
Total	120	100.00

Figure 2 shows distribution of SCH among patients of diabetic retinopathy with type 2 DM. 97 patients (80.83%) were Euthyroid and 23 patients (19.17%) had subclinical hypothyroidism. So, the prevalence of SCH among the patients of DR with type 2 DM was found to be 19.17%.

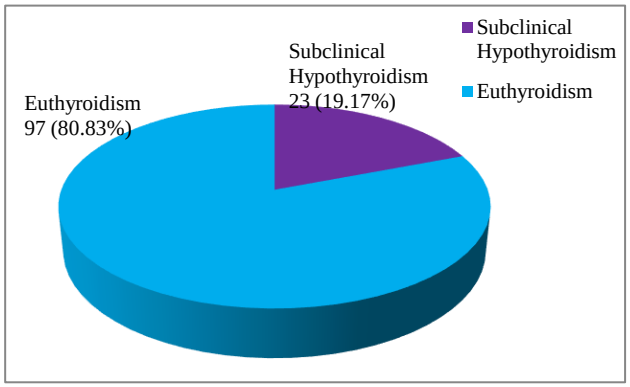
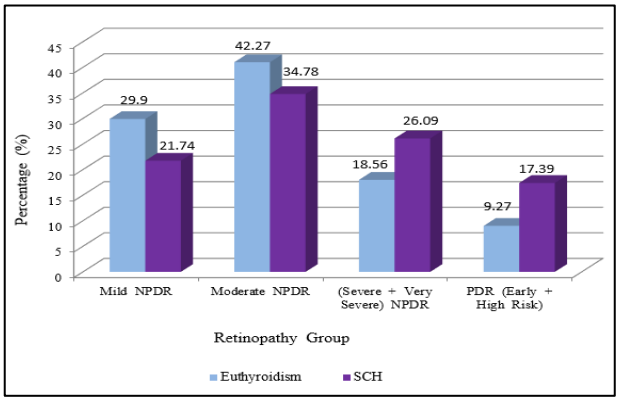


Figure 2: Distribution of SCH in patients of diabetic retinopathy with type 2 DM.

Figure 3 shows comparison of different stages of diabetic retinopathy in SCH and euthyroid patients. We have observed that 29 out of 97 euthyroid patients and 5 out of 23 SCH patients had mild NPDR (29.9% vs 21.74%). 41 out of 97 euthyroid patients and 8 out of 23 SCH patients had moderate NPDR (42.27% vs 34.78%). Severe NPDR was seen in 18 euthyroid and 6 SCH patients (18.56% vs 26.09%). PDR was seen in 9 euthyroid and 4 SCH patients (9.27% vs 17.39%). So, we have seen that prevalence of severe NPDR and PDR was higher in the SCH group as compared to euthyroid group and prevalence of mild and moderate NPDR was higher in the euthyroid group as compared to SCH group. However, this association is found to be statistically not significant (p=0.503296). Here 'p' value is calculated using chi square test.



NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, SCH: Subclinical hypothyroidism.

Figure 3: Comparison of different stages of DR in SCH patients with euthyroid patients.

Table 2 shows serum thyroid stimulating hormone (TSH) levels according to different stages of diabetic retinopathy in type 2 diabetic patients with subclinical hypothyroidism. It was seen that severity of diabetic retinopathy significantly increases with increase in serum TSH value. When statistical analysis was done using ANOVA test, this association was found to be statistically significant (p=0.025554).

Table 2: Serum thyroid stimulating hormone (TSH) levels according to different stages of diabetic retinopathy in type 2 diabetic patients with subclinical hypothyroidism.

Retinopathy group	Number (n)	TSH Range (µIU/ml)		p-value
		Mean±SD	Range	
Mild NPDR	5	5.42±0.94	4.30-6.56	0.0255554 (S)
Moderate NPDR	8	5.45±0.73	4.73-7.00	
(Severe+very severe) NPDR	6	6.68±0.77	6.03-8.00	
PDR (early+high risk)	4	7.08±1.69	4.73-8.40	

NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy.

DISCUSSION

In the present study, we have seen that out of the 120 patients, 23 patients (19.17%) had subclinical hypothyroidism. So, the prevalence of SCH among the patients of diabetic retinopathy with type 2 diabetes mellitus was found to be 19.17%. Present study found the prevalence of SCH in type 2 DM patients similar to other

studies. The prevalence of SCH in general population was estimated to be 4.3-9 %.[6,7] Patients with diabetes mellitus are at an increased risk of thyroid dysfunction, with the reported prevalence of SCH in diabetes varying between 2 and 17%.[8] We have seen that prevalence of more severe form of retinopathy, i.e. severe NPDR and PDR was higher in the SCH group as compared to euthyroid group. Present results are consistent with the following studies:

Kim BY et al found that prevalence of severe diabetic retinopathy was significantly higher in the SCH group compared to the euthyroid group (32.8% vs 19.6%, p=0.036). They mentioned several mechanisms for this involvement like dyslipidemia, insulin resistance etc.[9]

Yang GR et al in a case control study found that the prevalence of Subclinical hypothyroidism in the proliferative diabetic retinopathy group (51/187, 27.3%) was higher than that in the non-proliferative diabetic retinopathy group (32/184, 17.4%). In their study, they had done a logistic regression analysis to identify an independent relationship between SCH and PDR. They gave the conclusion that, PDR was at increased risk in patients with SCH.[10]

Similar observation was found by Yang JK et al in 2010. In their study, they found that the trend for severe retinopathy was significantly higher in the Subclinical hypothyroid group than in the euthyroid group. Subclinical hypothyroidism was associated with greater prevalence of diabetic retinopathy, especially sight-threatening diabetic retinopathy.[11] In a meta-analysis by Wu J et al, obtaining eight observational studies, found that there is a significant association between DR and SCH, and exposure to SCH can increase the DR risk 2.13 times.[12]

In present study, we have also seen that, severity of DR significantly increases with increase in TSH value (p=0.05554).

Khodeir et al in 2012 conducted a study taking newly diagnosed patients of type 2 diabetes mellitus. They found that subclinical hypothyroidism is associated with diabetic retinopathy in type 2 diabetic patients. Their results showed a higher rate of diabetic retinopathy in euthyroid patients who had higher levels of TSH value.[13] In the same way, Guang et al in 2010, reported that patients with higher levels of TSH had a significantly higher rate of PDR than patients with lower levels of TSH.[10]

Yang et al reported an association between retinopathy and subclinical hypothyroidism, especially sight threatening diabetic retinopathy. They also mentioned that, even euthyroid patients with TSH levels between 2 and <4μIU/ml had a higher rate of sight threatening diabetic retinopathy than those between 0.4 and <2.0μIU/ml (p=0.008).[11]

Several mechanisms may be involved in the association of diabetic retinopathy and SCH. Endothelial dysfunction and dyslipidemia seen in SCH are two important factors which may contribute to the pathogenesis of DR. Hyperlipidemia causes endothelial dysfunction by decreasing expression of endothelial nitric oxide synthase and by increasing dimethylarginine levels, which is an endogenous inhibitor of endothelial nitric oxide. Other possible mechanism supported by Kim et al was that Insulin resistance might be a probable factor in the association between SCH and Diabetic retinopathy.[14] They found higher status of insulin resistance in the SCH group than in the euthyroid group.

Other mechanisms which may contribute to the pathogenesis of diabetic retinopathy in patients of SCH are inflammation, raised C-reactive protein (CRP), oxidative stress etc. Oxidative stress has been linked to the histopathological changes of DR, such as retinal basement membrane thickening and capillary cell loss.[15,16]

CONCLUSION

In the present study, the prevalence of SCH among the patients of DR with type 2 DM was found to be 19.17%. Prevalence of severe NPDR and PDR was higher in patients with SCH as compared to euthyroid patients. Severity of DR significantly increases with increase in serum TSH value. Therefore, SCH may be associated with severity of diabetic retinopathy. However, this is a hospital based observational study and further prospective population based studies are required in this field to come to a definite conclusion and to comment on whether thyroid function screening in required in patients of DR.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Borooah M, Phukan S. A study on relationship between severity of diabetic retinopathy and subclinical hypothyroidism. Int J Res Med Sci 2017;5:1818-22.