Original Article

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Subclinical Hypothyroidism: A Modifiable Risk Factor for Retinal Vein Occlusion

Biochemistry Section

AMIT KUMAR GUPTA[1], KAPIL DEB LAHIRI[2]

ABSTRACT

Introduction: It is well established that overt hypothyroidism, itself was a risk factor for atherosclerosis. Retinal Venous Occlusion (RVO) is caused by localised atherosclerosis. Subclinical Hypothyroidism (SCH) also cause arteriosclerosis thereby could be an important causative factor for RVO. But no study on SCH in RVO has taken place in Indian population.

Aim: To find the prevalence of SCH in RVO in Indian Population.

Materials and Methods: Thyroid hormones and Anti-Tissue Peroxidise (TPO) antibody was measured in 479 RVO cases in this two year prospective cross-sectional study in ESIC medical college. Data was entered into Microsoft Excel and presented in tables.

Results: In this study, 312 males (aged 52±7.2 years) and 167 females (aged 47±7.7 years) with RVO were screened for thyroid hormones and anti-TPO antibody. Thyroid disorders were found in 162 patients out of 479 participants in this study (33.8%). Moreover, 52 cases were found to have SCH (10.8%) which is 32.1% of total thyroid disorder among RVO cases. Total of 118 patients had high anti-TPO antibody among 162 RVO cases with thyroid disorders (72.8%) and only 67 had high anti-TPO antibody among 317 euthyroid RVO cases (21.1%).

Conclusion: This study has shown that SCH was a modifiable risk factor of RVO. Therefore, understanding the prevalence of SCH in this population might help in the prevention of RVO by secondary preventive intervention. Moreover, all SCH cases should be referred to ophthalmologist for evaluation of retinal vasculature.

Keywords: Retinal venous occlusion, Subclinical hypothyroidism, Thyroid peroxidase antibody

INTRODUCTION

The Retinal Venous Occlusion (RVO) is the second most common retinal vascular diseases after diabetic retinopathy [1]. It is associated with systemic diseases (diabetes mellitus, hypertension, hyperlipidaemia, hyperhomocysteinemia (HHcys) and circulating antiphospholipid antibodies although the major cause of this disease is localised atherosclerosis [2-4].

The Subclinical Hypothyroidism (SCH) is defined as an elevated serum TSH level associated with normal total or free T4 and T3 values [5]. Thyroid function abnormalities were present in 19.6% in a study on adult south Indian population [6]. SCH with positive anti-TPO antibodies can progress to clinical hypothyroidism [7]. There were studies on association between overt hypothyroidism and atherosclerosis [8]. Although Hayreh SS et al., has described the association of thyroid disorder in RVO but no such study on SCH in RVO have taken place in Indian population [9]. Hence, in this study aimed to find the prevalence of SCH in RVO in an Indian population.

MATERIALS AND METHODS

The present study is a two year prospective cross-sectional study of consecutive, unrelated adult patients, with a diagnosis of RVO, attending the Outpatient Department in ESIC Medical College.

Sample size calculation: Sample size was calculated based on the formula

$$\left\{n=\frac{z^2pq}{d^2}\right\}$$

(z=1.96, d=0.04, p=0.196, q=0.804, n=minimum sample size=378).

The Institutional Ethics Committee approved the study (No-412(DEAN/EC/2014-15/VOL-1) dated on 03/01/2015) and informed consent was obtained from all the study populations, in accordance with the Declaration of Helsinki. Family history, social status, and dietary habits, including other habits such as smoking, alcohol intake, history of systemic diseases, other ocular diseases and drug history was taken from all the study subjects.

Inclusion and exclusion criteria: Consecutive, unrelated adult patients, with a diagnosis of RVO patients attending the Outpatient Department in ESIC Medical College were included. Patients with congestive cardiac failure, liver disorders, renal disorders, pregnancy, malignancy and patients on statins, oral contraceptive pills and other medications that might alter thyroid functions (e.g., amiodarone, lithium or γ-interferon) were excluded from the study. Patients with known thyroid disorder with or without treatment were also excluded from the study. Ophthalmic examination of eyes, including visual acuity, Relative Afferent Pupillary Defect (RAPD), Electroretinogram (ERG), and fundus examination, was used for the clinical diagnosis of RVO. A total of 479 subjects were selected in the study based on the inclusion and exclusion criteria.

Biochemical Estimations

Thyroid hormones and Anti-TPO antibody were measured by Siemens IMMULITE 1000 immunoassay (Electrochemiluminescence method). Normal range for TSH was (0.27-4.2) μIU/mL and for FT4 was (0.93-1.7) ng/dL. Patients with normal TSH and FT4 were considered euthyroid. A high serum TSH level (>4.2 μIU/mL) and a normal free thyroxine (FT4) level were required for the diagnosis of SCH. Patients with high TSH (>10 μIU/mL) and low FT4 levels (<0.93 ng/dL) were classified as being overt hypothyroid. A low serum TSH level (< 0.27 μIU/mL) and a normal free thyroxine (FT4) level were required for the diagnosis of subclinical hyperthyroidism. Patients with very low TSH (<0.1 μIU/mL) and high FT4 levels (>1.7 ng/dL) were classified as being overt hyperthyroid. The upper limit of normal range of anti-TPO antibody is less than 35 IU/mL.

STATISTICAL ANALYSIS

Data was entered into Microsoft Excel and presented as tables.

RESULTS

In this study, 312 males (aged 52±7.2 years) and 167 females (aged 47±7.7 years) with RVO were screened for thyroid hormones and Anti-TPO antibody. Thyroid disorders were found in 162 patients out of 479 participants in this study (33.8%). Moreover, 52 cases were found to have SCH (10.8%) which is 32.1% of total thyroid disorder among RVO cases [Table/Fig-1]. Total 118 patients had high anti-TPO antibody among 162 RVO cases with thyroid disorders (72.8%) and only 67 had high anti-TPO antibody among 317 euthyroid RVO cases (21.1%) [Table/Fig-2].

	Overt hypothyroid		Sub clinical hypothyroid		Sub clinical hyperthyroid		Overt hyperthyroid		Total thyroid disorders		Euthyroid	
Prevalence	21.3%		10.8%		1.5%		0.2%		33.8%		66.2%	
Number	102		52		7		1		162		317	
Gender	32 M	70 F	22 M	30 F	3 M	4 F	1 M	0 F	58 M	104 F	254 M	63 F

[Table/Fig-1]: The prevalence of thyroid disorders among 479 RVO cases.
M: Male; F: Female

	Overt hypothyroid (n=102)		Sub clinical hypothyroid (n=52)		Sub clinical hyperthyroid (n=7)		Overt hyperthyroid (n=1)		Total thyroid disorders (n=162)		Euthyroid (n=317)	
High Anti-TPO	77		36		4		1		118		67	
Gender	22 M	55 F	14 M	22 F	2 M	2 F	1 M	0 F	39 M	79 F	37 M	30 F

[Table/Fig-2]: High Anti-TPO antibody status among 479 RVO cases.
M: Male; F: Female

DISCUSSION

Arteriolosclerosis is an important causative factor for RVO. Because a retinal arteriole and its corresponding vein share a common adventitial sheath, thickening of the arteriole appears to compress the vein. This causes secondary changes, including venous endothelial cell loss, thrombus formation, and potential occlusion [1]. Hence, it is important to understand the prevalence of associated factors that may lead to development of RVO.

Overt or clinical hypothyroidism is an established risk factor for atherosclerotic cardio-vascular disease because of several reasons of which unfavourable lipid profiles and rising homocysteine levels were of paramount importance [10,11]. The progression to overt hypothyroidism was approximately 2-5% per year. The rate of progression was higher in individuals with anti-TPO antibodies [12]. Hence, it would be very important to identify presence of anti-TPO antibodies in hypothyroid patients.

Screening for SCH remains a controversial area as it has also been associated with arteriosclerosis by increased coagulability, insulin resistance, oxidative stress [13], vascular stiffness and endothelial dysfunction [14]. Patients with SCH had higher coronary calcium scores [15] and enhanced inflammatory activity [16] in carotid plaques compared to euthyroid subjects although no consensus exists on the risk-benefit ratio of levothyroxine therapy in patients with SCH [17]. Hence, it is important to understand the presence of SCH in individuals and also presence of anti-TPO antibodies as well.

Previous study on adult south Indian population showed 19.6% had thyroid disorder and 9.4% had SCH. Positive anti-TPO antibody was found in 46.3% and 9.5% of patients with thyroid dysfunction and euthyroid respectively in that study [6]. One study has shown that a higher prevalence of thyroid disorder ($p<0.0001$) and ($p=0.003$) were seen in patients with central retinal vein occlusion and branch retinal vein occlusion respectively in a population of United States [9]. Although no study on SCH in RVO have taken place in the Indian population, our study was the first to identify high prevalence of thyroid disorder (33.8%) in RVO patients, of them a significant portion had SCH (10.8%) apart from overt or clinical hypothyroidism (21.3%).

Our study also showed that RVO was more prevalent in males over females in euthyroid patients but RVO was more prevalent in females over males in patients with thyroid disorder. High Anti-TPO antibody with thyroid disorder was more prevalent (72.8%) than in euthyroid RVO cases (21.1%). The thyroid follicles may be injured by cytokines thereby exposing the apical enzymes of follicles to TPO antibodies which may then bind to auto antigens and fix the complement leading to hypothyroidism [18].

Limitation(s)

The causal association of SCH with different RVO aetiologies (confounding factors) could not be ascertained hence future study is needed to comment on that.

CONCLUSION(S)

The screening and treatment of SCH still remained a matter of debate. This study has shown that SCH was a modifiable risk factor of RVO. Therefore, understanding the prevalence of SCH in this population might help in the prevention of RVO by secondary preventive intervention. Moreover, all SCH cases should be referred to ophthalmologist for evaluation of retinal vasculature. However, benefit of L-thyroxine substitution in such cases remains to be seen only after randomised clinical trials.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Ophthalmology, IPGME&R and SSKM Hospital, Kolkata, West Bengal, India.
2. Assistant Professor, Department of Biochemistry, IPGME&R and SSKM Hospital, Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Kapil Deb Lahiri,
4/2, Shibchandra Sarbabhauma Lane, Baranagar, Kolkata-700036, West Bengal, India.
E-mail: kapildeb.lahiri@gmail.com

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