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Original Article

Internal Medicine Section

Predictive Significance of High Sensitive C-reactive Protein in Subclinical Hypothyroidism: A Prospective Observational Study

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ABSTRACT

Introduction: Subclinical hypothyroidism (SCH) is more common than overt hypothyroidism. It is associated with increased risk of dyslipidaemia, Coronary Artery Disease (CAD), left ventricular diastolic dysfunction, peripheral vascular diseases and chronic inflammation. Chronic inflammation plays a significant role in clinical manifestations and systemic organs injury in hypothyroidism. High-sensitivity C-reactive Protein (hs-CRP) is a pentameric protein produced by the liver, and its level increases in response to inflammation. There are not much studies to prove that chronic inflammation could be a major risk factor for conversion of subclinical hypothyroidism in to overt hypothyroidism.

Aim: To study the role of chronic inflammation as a risk factor for conversion of SCH in to overt hypothyroidism with lipid abnormalities and cardiac dysfunction, by using inflammatory markers like hs-CRP.

Materials and Methods: This prospective observational study was conducted at KR hospital, Mysuru, Karnataka, India, from August 2019 to September 2020 among 112 subjects of subclinical hypothyroidism attending the Outpatient Department. The data regarding detailed history and clinical examination were collected from all the patients. Investigations such as Thyroid Stimulating Hormone (TSH), Triiodothyronine (T3), Thyroxine (T4) levels hs-CRP level, lipid profile, Electrocardiogram (ECG), Random Blood Sugar (RBS), Renal Function Test (RFT), Complete Blood Count (CBC), 2D-Echocardiography were done on day one and after 6 months. The data analyses was done by using the Chi-square test or Fisher's-exact test. The factors which were significant as per the Chi-square test were selected and subjected to multivariate analysis.

Results: The number of cases of subclinical hypothyroidism (hs-CRP >3 mg/L, mean TSH=9.1±2.1 microIU/mL) at first day were 23 (20.53%). At the end of 6 months those converted to overt hypothyroidism (mean TSH=11.4±2.3 microIU/mL) were 14 (12.5%) patients. The patients with hs-CRP of >3 mg/L, with mean TSH of 11.4±2.3 microIU/mL at the end of 6 months of study, had left ventricular dysfunction in 68 (60.07%) patients. In the same group, the low-density lipoprotein cholesterol >160 mg/dL was found in 60 (53.57%) patients and serum triglycerides level >200 mg/dL was found in 51 (45.53%) patients (p-value <0.05).

Conclusion: Chronic inflammation is one of the major risk factors for conversion of subclinical hypothyroidism in to overt hypothyroidism with associated cardiovascular dysfunction and dyslipidaemia.

Keywords: Cardiovascular system, Chronic inflammation, Dyslipidaemia

INTRODUCTION

Subclinical Hypothyroidism (SCH) is defined by raised Thyroid Stimulating Hormone (TSH) value and normal levels of thyroid hormones- Triiodothyronine (T3), Thyroxine (T4), associated with few or no symptoms and signs of hypothyroidism [1]. It is referred as a state of mild thyroid failure and is essentially a laboratory diagnosis. The prevalence of SCH increases with age and is the most common thyroid abnormality in older subjects [2]. SCH is more common than overt hypothyroidism [1].

The prevalence of overt hypothyroidism is 4%, while prevalence of subclinical hypothyroidism has been reported to range from 6-8% for women (10% over the age of 60 years) and 3% for men [1]. Euthyroidism is diagnosed if the TSH is 0.3-4.5 microIU/mL, T3 is 80 to 220 ng/dL, and T4 is 5 to 12 microgm/dL. SCH is diagnosed if TSH is 4.5 to 10 microIU/mL with normal thyroid hormones. Overt hypothyroidism is diagnosed if TSH is >10 microIU/mL [1,2].

Subclinical hypothyroidism was associated with increased risk of dyslipidaemia, Coronary Artery Disease (CAD), left ventricular diastolic dysfunction and peripheral vascular diseases and chronic inflammation [3]. Chronic inflammation plays a significant role in clinical manifestations and systemic organs injury in hypothyroidism. If the chronic inflammation is untreated, it damages the thyroid gland and may lead to hypothyroidism [4]. Later it may lead to increased morbidity and mortality due to systemic organ dysfunction [5]. The High-sensitivity C-reactive Protein (hs-CRP) is a pentameric protein produced by the liver and its level increases in response to inflammation [6]. An early diagnosis and treatment may prevent the onset of overt hypothyroidism and its associated complications [4]. Hence, this study was under taken to evaluate the role of chronic inflammation as a risk factor for conversion of SCH in to overt hypothyroidism with lipid abnormalities and cardiac dysfunction, by using inflammatory markers like hs-CRP.

MATERIALS AND METHODS

This prospective observational study was conducted at KR hospital, Mysuru, Karnataka, India, from August 2019 to September 2020 among 112 subjects of subclinical hypothyroidism attending the Outpatient Department. The data collection was started after obtaining ethical clearance from Institutional Ethics Committee, Mysore Medical College and Research Institute, (IEC No.ECREG:ECR/134/Inst/KA/2013).

Inclusion criteria: Subjects with subclinical hypothyroidism with normal thyroid hormone levels with TSH level between 4.5 to 10 microIU/mL [1].

Exclusion criteria: Patients with familial hyperlipidaemia, coagulation disorders, severe systemic disease, overt hypothyroid

patients, systemic arterial hypertension, diabetes mellitus, renal failure, underlying known cardiac disorder, pregnancy, connective tissue diseases and malignancy were excluded from the study.

Sample size calculation: The sample size was calculated based on the average prevalence rate of SCH (5%) by using the Cochran's formula [7]:

Z^2PQ/e^2

Where Z is z score (1.962),

p is prevalence of subclinical hypothyroidism,

q was (1-p),

e^2 was precision value

The actual sample size by calculation was 76, but it was increased to 112 to have adequate number and to draw significant conclusion.

Procedure

Information was collected as per proforma after obtaining the informed consent from the study subjects. The subjects underwent detailed history, clinical examination, investigations such as Thyroid Stimulating Hormone (TSH), Triiodothyronine (T3), Thyroxine (T4) level, hs-CRP, Electrocardiogram (ECG), Random Blood Sugar (RBS), Renal Function Test (RFT), Complete Blood Count (CBC), 2D-Echocardiography on day one. The study subjects were followed-up for 6 months and the same investigations were repeated.

- TSH of 0.30 to 4.5 microIU/mL was considered normal.
- hs-CRP levels [4]
  - 0.01 to 1 mg/L was considered as low-risk group,
  - 1 to 3 mg/L intermediate-risk group, and
  - >3 mg/L as severe-risk group
- LDL cholesterol >160 mg/dL and Triglycerides >200 mg/dL were taken as abnormal values, as per National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) guidelines for metabolic syndrome [8].

The T3, T4, and TSH was measured by using electro chemiluminescent immunoassay, fasting lipid profile was measured by enzymatic calorimetric method, and hs-CRP was measured by infrared particle immunoassay method [9].

STATISTICAL ANALYSIS

The data analyses was done by using the Statistical Package for Social Sciences (SPSS, Inc, Chicago) for windows software, version 18.0. Descriptive statistics such as mean and Standard Deviation (SD) for continuous variables, frequency, and percentage for categorical variables were determined. Chi-square and Fisher's-exact tests (wherever appropriate) was used to find association between chronic inflammation with SCH and overt hypothyroidism and its complications. The level of significance was set at 0.05. The factors which were significant by Chi-square test were selected and subjected to multivariate analysis.

RESULTS

In this study 84 (75%) patients were in the age group of <60 years. The majority were female 68 (60.7%) patients [Table/Fig-1]. The number of patients with SCH converted to overt hypothyroidism by the end of 6 months of study were 12.5% [Table/Fig-2].

Parameters	n,%	
Age (years)		
<60	84 (75%)	
≥60	28 (25%)	
Gender		
Male	44 (39.3%)	
Female	68 (60.7%)	
Variables	**1st day**	**At end of 6th month**
hs-CRP (mg/L)		
<3	89 (79.46%)	72 (64.28%)
≥3	23 (20.53%)	40 (35.71%)
TSH (microIU/mL)		
4.5-10	112 (100%)	79 (70.53%)
>10	0	33 (29.46%)

[Table/Fig-1]: Distribution of demographic parameters [1].

At 6 months, in patients of SCH, with hs-CRP >3 mg/L had significant Left Ventricular (LV) dysfunction with high LDL cholesterol and triglycerides level (p-value <0.05) [Table/Fig-3].

DISCUSSION

This study was done to know the association between chronic inflammation and conversion of SCH in to overt hypothyroidism with cardiac dysfunction with lipid abnormalities. There were significant changes found at the end of six months of study with respect to conversion of SCH to overt hypothyroidism with cardiac dysfunction and lipid abnormalities.

As per the study by Anwer MS et al., the prevalence of conversion of SCH to overt hypothyroidism was 14%, and patients with SCH have 2.8 times more risk of conversion to overt hypothyroidism as compared to healthy volunteers. The female gender and initial level

hs-CRP (mg/L)	Patients with SCH (n,%)	TSH at Day 1 (Mean±SD) (microIU/mL)	p-value	Patients converted to overt hypothyroidism (n,%)	TSH at end of 6 month (Mean±SD) (microIU/mL)	p-value
Low risk group	48 (42.85%)	6.5±1.4	0.06	6 (5.35%)	10.4±1.8	0.3
Inter mediate risk group	41 (36.60%)	6.8±1.9	<0.05	13 (11.60%)	11.5±1.78	0.06
High risk group	23 (20.53%)	9.1±2.1	<0.001	14 (12.5%)	11.4±2.3	**<0.05**

[Table/Fig-2]: Association between hs-CRP level with mean TSH value and outcome of SCH.
ANOVA was used to assess significance of data between hs-CRP, SCH and TSH from day 1 and at the end of 6th month
Chi-square test was used to assess significance of TSH value at day 1 and at the end of 6th month of study

Level of hs-CRP (mg/L)	Number of LV dysfunction (n,%)		LDL Levels			Triglyceride levels			p-value
			LDL (mg/dL)	(n,%)		Triglyceride (mg/dL)	(n,%)		
	Day 1	End of 6th month		Day 1	End of 6th month		Day 1	End of 6th month	
Low risk group (0.01-1 mg/L)	3 (2.67%)	30 (26.78%)	<130	6 (5.35%)	28 (25.0%)	<150	10 (8.92%)	22 (19.64%)	0.06
Intermediate risk group (1-3 mg/L)	7 (6.25%)	14 (12.5%)	130-160	10 (8.92%)	24 (21.42%)	150-200	13 (11.60%)	39 (34.82%)	0.06
High risk group (>3 mg/L)	12 (10.71%)	68 (60.07%)	>160	16 (14.28%)	60 (53.57%)	>200	21 (18.75%)	51 (45.53%)	**<0.05**

[Table/Fig-3]: Association between hs-CRP and LV dysfunction with Lipid variation in SCH.
The statistical tests used were Chi-square test with multivariate analysis

of high serum TSH (4.5 to 10 microIU/mL) were the most important predictors of conversion of SCH in to overt hypothyroidism [10].

As per Amouzegar A et al., the Thyroid Peroxidase Antibodies (TPOAb) positive cases had a high-risk of converting in to overt hypothyroidism after 3 years with a relative risk of 4.14, 95% confidence interval 2.57-6.67 [11]. Overt hypothyroidism was associated with reduced myocardial contractility, heart rate, and stroke volume [12]. In the present study, 14 (12.5%) patients had hs-CRP level >3 mg/L in subjects who converted from SCH in to overt hypothyroidism. The chronic inflammation with increased hs-CRP was found with progressive thyroid failure and was considered as a risk factor for the development of coronary artery disease [6,13]. The SCH patients were associated with high level of cardiac risk factors. Early treatment of SCH may prevent further progression to overt hypothyroidism, correct dyslipidaemia and decrease the risk of death from cardiovascular disease [14]. Diastolic dysfunction was common in SCH, therefore early diagnosis and treatment may prevent cardiovascular complications [15].

SCH has been shown to be associated with increased risk of CAD, peripheral vascular disease and dyslipidaemia [4,16]. SCH needs no intervention, if the serum TSH value is <10 microIU/L, and unless it is associated with comorbidities like cardiac dysfunction, dyslipidemia, and significant elevation of antiTPO antibodies [14,16]. The present study attempted to find the association between chronic inflammation (hs-CRP), and conversion of SCH in to overt hypothyroidism [17].

In this study, among patients with hs-CRP level >3 mg/L patients, 68 (60.07%) had LV dysfunction, 60 (53.57%) had LDL cholesterol >160 mg/dL, and 51 (45.53%) had triglycerides >200 mg/dL at the end of 6 months. As per the study by Tuzcu A et al., the SCH patients were found to have elevated hs-CRP levels, high total cholesterol, high LDL cholesterol, and triglyceride levels [5]. An elevated TSH level correlates with dyslipidaemia and adversely affects the cardiovascular function [18].

A cross-sectional study on the lipid abnormalities in SCH demonstrated a significant elevation of total cholesterol, LDL-cholesterol, apolipoprotein B and Lp(a) in SCH compared with euthyroidism [19]. The treatment of SCH with thyroxine would have a favourable effect on the lipid profile by decreasing the total cholesterol and LDL-C [20,21]. A study in Naples, Italy, on 26 SCH subjects found a high incidence of LV dysfunction [22]. Age more than 60 years and high hs-CRP level are the strong independent predictors of cardiovascular abnormalities in SCH, and also for the conversion to overt hypothyroidism [22,23].

Limitation(s)

The outcomes need to be further studied for a longer duration of follow-up.

CONCLUSION(S)

This study found that chronic inflammation plays a big role in converting SCH to overt hypothyroidism. It was also associated with significant elevation in lipid levels, cardiovascular abnormalities in undetected and untreated subjects. So, a close follow-up is needed in all patients with SCH to prevent cardiac morbidity and mortality.

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