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Elevated high sensitivity c-reactive protein in patients with subclinical hypothyroidism: A case control study

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ABSTRACT

Background: Inflammation in subclinical Hypothyroidism (SCH) imposes a significant cardiovascular risk. The aim of the present study was to assess the elevated levels of high sensitivity C-reactive protein (hs-CRP) in SCH patients.
Materials and Methods: In this study, 50 cases of SCH and 50 cases of euthyroid were selected. The complete history of the subjects were taken and demographic , biochemical parameters like age, BMI, thyroid profiles, lipid profiles and hsCRP were estimated.
Results: The mean TSH levels were significantly ($p<0.05$) elevated in SCH cases as that of the controls (8.56± 1.76 vs 2.28± 0.65 μU/ml). Further, hs-CRP level was significantly ($p<0.05$) higher in SCH cases as that of the controls (2.93 ±0.87 vs 1.16 ±0.45 mg/l). Meanwhile, lipid profiles were also elevated in SCH cases as that of the controls. Coefficient correlation analysis showed significant association between TSH and hs-CRP.
Conclusion: Thus, increased level of hs-CRP in SCH highlights the inflammatory status and thus associated with the development of cardiovascular diseases in SCH.

1. Introduction

Clinically, subclinical hypothyroidism (SCH), is defined as an elevated level of serum thyroid-stimulating hormone (TSH) with a parallel normal serum free thyroxine levels (FT_4) and triiodothyronine (FT_3).[1] Global prevalence of SCH is reported to be around 3% to 12%.[2] In India, the estimated prevalence of SCH is 9.4%.[3] Mounting studies have shown a significant association between SCH and metabolic disorders, hypertension and cardiovascular disorders.[4,5] A recent meta-analysis displayed significant association between SCH and coronary heart disease with an increased risk of cardiovascular mortality in patients with TSH level above 10 ml U/L.[6] Wide array of inflammatory markers has been identified as independent risk factors for CVD. High-sensitivity C-reactive protein (hsCRP), is touted to be a reliable predictor of CVD as compared to the lipid profile markers. Array of observational studies displayed a strong association between hs-CRP and morbidity and mortality associated with coronary heart disease,[7,8] and also increased the prediction of cardiovascular risk by adding hs-CRP to the Framingham risk score.[9] Various clinical studies elicited marked association between hs-CRP and index of subclinical atherosclerosis, like coronary artery calcification and intima-media thickness.[10] The CRP is an acute phase

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reactant, produced in the liver. The mechanism of CRP induced inflammatory condition is due to the upregulated expression adhesion molecules in vascular endothelial cells triggered by CRP.[11] Conflicting scenario exists in the role of hsCRP for analysing the CVD risk in SCH. Wide range of studies showed the elevated hsCRP level in SCH.[12–15] In this backdrop, the present study was undertaken to evaluate the incidence of elevated levels of hsCRP in individuals with SCH and also to delineate the risk of developing coronary vascular events.

2. Materials and Methods

This was a cross-sectional case control study conducted in Veer Surendra Sai Institute of Medical Science and Research, Burla, Odisha. The study group included patients attending the department of pathology.

50 Patients with subclinical hypothyroidism (SCH) based on thyroid status (increased level of TSH, FT3 and FT4) were designated as cases based on the exclusion criteria. Further, 50 patients who were euthyroid based on serum TSH, FT3 and FT4 levels were designated as controls based on the exclusion criteria.

Patients encountered with diabetes, hypertension, renal and liver disorders, coronary heart disease, undergoing thyroxine replacement therapy, affected with systemic infections were excluded from the study. Further, patients on NSAIDS, antibiotics, HRT and statins (which can increase hsCRP were also excluded from the study).

Further the from the selected SCH cases the complete history was collected thorough general and systemic examination was done as per proforma. Under strict aseptic techniques, blood samples were collected after overnight fast, and analysed for the following required parameters. The above mentioned procedure was repeated for controls.

The collected blood samples were centrifuged at 10,000 rpm for 10 minutes and the serum was collected in vials and stored at −80°C until the analysis. Samples were analysed for thyroid hormones, hsCRP, and haematological parameters, Fasting Blood Sugar, Renal Function Tests, Liver Function Tests and Lipid Profiles.

The reference range for the above mentioned parameters were as follows, Thyroid profile: TSH: 0.34–4.25 mIU/l, Free T4: 0.7–1.24 ng/dl and Free T3: 2.4–4.2 pg/ml; Fasting Plasma Glucose: 75-100 mg/dl; Lipid Profiles: Total Cholesterol: Less than 200 mg/dl; Triglycerides: 30-200 mg/dl; HDL Cholesterol: 40-60 mg/dl.

High Sensitivity C-Reactive Protein (based on the risk for atherosclerosis): Low Risk: Less than 1 mg/l; Intermediate Risk: 1-2.9 mg/l; High Risk: More than or equal to 3 mg/l.

2.1. Data analysis

The data were expressed as Mean ± SD. Statistical analysis was done using unpaired students-t-test. A p value <0.05 was considered as statistically significant. The correlation between the parameters was carried out using Pearson's correlation.

3. Results

In the present study, among the SCH cases most of them were between the age group of 21-30 years (34%), followed by 31-40 years (5.5%), 41-50 years (28%). Thus majority of the cases constitute between 21-50 years. In the control subjects maximum numbers were in the age between 31-40 years (36%).

Further the mean age among the SCH cases and control was found to be 39.44±5.5 and 39.76± 6.5 and it was statistically non-significant (p>0.05).

In the present study, the female preponderance was higher constituting around 90% in both the SCH cases and controls.

In the present the mean height of SCH cases and control was found to be 1.59 m ± 0.07 and 1.64± 0.09 respectively (p> 0.05) and it was not significant. The mean weight was found to be (62.76± 7.65 vs 65.87 ± 8.32; p> 0.05) among the SCH cases and controls. Further, the BMI was found to be (26.76 ± 3.76 vs 27.87±3.56 p> 0.05; Non-significant) among the SCH cases and controls.

The biochemical profiles of SCH cases and controls were displayed in Table 1. In the present study TSH levels were significantly (p<0.05) elevated in SCH cases as that of the control (8.56± 1.76 vs 2.28± 0.65 μU/ml). However, no significant differences (p>0.05) were seen in the levels of free T4 and T3 between the SCH cases and controls.

In addition to the TSH levels, significantly higher levels of the hsCRP were observed in SCH cases when compared with controls (2.93 ±0.87 vs 1.16 ±0.45 mg/L; p < 0.05) respectively.

Furthermore, the lipid profiles total cholesterol and triglycerides were significantly (p < 0.05) higher in SCH cases as that of the controls (176.65± 41.25 vs 135.87 ±51.24 mg/dl; 154.72 ±49.25 vs 125.65 ±24.8 mg/dl) respectively. Meanwhile, HDL cholesterol was significantly (p < 0.05) lower in SCH cases as that of the control (35.76± 7.2 vs 46.96 ±8.52 mg/dl).

As per American Diabetes Association (ADA)/Centers for Disease Control and Prevention (CDC) and National Academy of Clinical Biochemistry (NACB) experts the risk stratification of CVD for hsCRP is <1, 1 to 3, >3 mg/L for low, moderate, and high risk respectively.

In this study, most of the SCH cases (50%) were at moderate risk of developing CVD with hsCRP level between 1-3mg/dl. Meanwhile 14% of the SCH cases were at high risk of developing CVD with hsCRP level between > 3 mg/dl.

The coefficient correlation analysis of hs-CRP with age, BMI, thyroid profiles and lipid profiles were shown in Table 2. In the present study, coefficient correlation analysis

Table 1: Biochemical parameters of controls and SCH cases in the present study

Parameters	Control (N=50) (mean±S.D)	SCH cases (N=50) (mean±S.D)	p -value
TSH (μU/ml)	2.28± 0.65	8.56± 1.76	<0.05*
Free T4 (ng/dl)	1.24±0.87	1.14±0.45	0.07^{NS}
Free T3 (pg/dl)	3.25± 0.76	3.12±0.84	0.06^{NS}
hs-CRP (mg/ml)	1.16 ±0.45	2.93 ±0.87	<0.05*
Total Cholesterol (mg/dl)	135.87 ±51.24	176.65± 41.25	<0.05*
HDL Cholesterol (mg/dl)	46.96 ±8.52	35.76± 7.2	<0.05*
Triglycerides (mg/dl)	125.65 ±24.8	154.72 ±49.25	<0.05*

*p-value<0.05 significant; SD: Standard deviation

Table 2: Coefficient correlation analysis for the effect of age BMI, thyroid profiles and lipid profiles onhsCRP in SCH

Variables	F-Value	p-value
Age	0.94	0.67^{NS}
BMI	0.67	0.77^{NS}
TSH	55.46	<0.05*
Free T3	1.12	0.54^{NS}
FreeT4	1.34	0.48^{NS}
Total Cholesterol	0.72	0.76^{NS}
Triglycerides	1.43	0.45^{NS}
HDL Cholesterol	0.82	0.82^{NS}

*p<0.05 significant; NS-Non Significant

displayed significant and positive association between hs-CRP and TSH (p< 0.005; F-value: 55.46). However, the other variables like age, BMI, free T3 and T4, lipid profiles had not shown any significant correlation with hs-CRP (p>0.05)

Furthermore, Pearson coefficient analysis revealed the significant (p<0.05) association between TSH and hs-CRP with a Pearson coefficient of 1 for TSH and 0.876 for hs-CRP respectively.

4. Discussion

Subclinical hypothyroidism (SCH) is clinical condition in which the thyroid functions have been altered. SCH is of high clinical important since it has a high prevalence which inturn may overture to cause hypothyroidism and associated CVD risks. Mounting studies indicate that High-sensitivity C-reactive protein (hs-CRP) is a reliable marker of primary proinflammatory conditions and effective CVD.[16,17] In the present study, there exists an elevated level of hs-CRP in SCH as that of normal subjects (euthyroid). The results of our study is in corroboration with other studies done by Similar results were observed in the studies done by Gupta et al.[18] and Vaya et al[19] in their study concluded that the hs-CRP is significantly elevated in SCH patients along with the other inflammatory markers like Interleukin-6 and ESR. Thus in our study, SCH cases has no earlier history of systemic inflammation and the elevation in hs-CRP is not due to prevailing inflammatory condition other than SCH.[20]

It has been noted that TSH level >10 μU/ml has been significantly associated with higher cardiovascular risk. In our study, out of 50 SCH cases, 40 patients has the TSH value >10 μU/ml. Further added, in our study as per ADA, CDC and NACB criteria 14% of SCH cases were at high risk for the progression of CVD. Our results are in line with the study done by Vyakaranam et al.[21] where 23.3% of SCH cases were at high risk for CVD development.

Mounting studies displayed contrasting results regarding the SCH and this association is still under obscure.[22,23] In this study, elevated levels of total cholesterol, triglycerides were observed in SCH cases as that of the control. Our observation is in consistent with the previous studies were SCH subjects displayed higher cholesterol and triglycerides level SCH patients in this study were also observed by various studies.[24,25] Further, decreased HDL cholesterol level was observed in SCH cases in the present study, which is in line with the previous reports.[26]

In our study, coefficient correlation and Pearson coefficient analysis had confirmed a significant positive association between TSH and hsCRP in SCH. However, in our study other variables like age, BMI and lipid profiles were not significantly correlated with hs-CRP. Previous research done by Yu et al.[14] showed confirmed significant positive correlation between hs-CRP and TSH after adjusting for potential confounder.

5. Conclusion

On the basis of data evaluated in this study, it has been revealed that the SCH patients are associated with increased TSH, hs-CRP levels and dyslipidemia. Further, coefficient correlation showed significant association between TSH and hs-CRP. Thus the elevated hsCRP levels in SCH showcases the CVS risk and useful for the potential early diagnosis and treatment. Further, large cohort studies are highly warranted to elucidate the hs-CRP involvement in SCH. Apart from hs-CRP it is highly vital to find out role of various inflammatory mediators status in SCH.

6. Acknowledgment

None.

7. Conflict of Interest

None.

8. Funding of Sources

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