

Is Cardiovascular Risk Associated with Subclinical Hypothyroidism: Role of C Reactive Protein and Interleukin-6

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ABSTRACT

Background: Subclinical hypothyroidism causes development of cardiovascular risk is not very well defined due to contradictory findings over the years. Role of inflammatory markers in Subclinical hypothyroidism is not very well studied in the past. **Objective:** The main objective of this study was to assessment of the role of interleukin-6 and C reactive protein in subclinical hypothyroidism patients having TSH <10μIU/ml. **Material and Method:** Total 90 young adult males from 20-40 years age group were recruited for the study in which 60 males were with recently diagnosed subclinical hypothyroidism and remaining 30 males were healthy controls. Subclinical hypothyroidism was diagnosed by measuring TSH and FT4, which were estimated by enzyme linked immunosorbent assay (ELISA). Total cholesterol, triglycerides, and High Density Lipoprotein-cholesterol were estimated by spectrophotometric method. Friedewald formula was used for the estimation of Low Density Lipoprotein cholesterol. Lipoprotein ratios (total cholesterol/HDL-cholesterol and LDL-Cholesterol/ HDL-cholesterol) were also estimated. C reactive protein and interleukin-6 were also estimated by ELISA. **Results:** Significant results were obtained among the various parameters between the groups. Thyroid stimulating hormone was significantly (<0.001) different between patients and control group. In subclinical hypothyroidism patients total cholesterol, triglycerides and LDL cholesterol were significantly higher (<0.01). HDL cholesterol was significantly (<0.001) lower in the patient group. Lipoprotein ratios were also highly significant (<0.001) between the groups and concentrations were higher in the patient group. C reactive protein and interleukin-6 were highly significant (<0.001) between the groups. **Conclusion:** Subclinical hypothyroidism patients having TSH<10μIU/ml are characterized by the atherogenic lipid profile. Increased concentration of interleukin-6 along with higher concentration of C reactive protein might be the sign of early risk of atherogenic risk progression.

Key words: Lipoprotein ratios, C reactive protein, Interleukin-6, Atherogenesis.

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INTRODUCTION

Subclinical hypothyroidism (SCH) is an asymptomatic disorder, although it may be associated with milder symptoms of overt hypothyroidism e.g., depression, constipation, cold intolerance, fatigue, weight gain, loss of hairs, muscle pain, etc. and diagnosed with mildly elevated thyroid-stimulating hormone (TSH) along with free thyroxine (FT4) within the normal range.¹ Usually, SCH is quite common in women and the elderly population² but recently an Austrian cohort study has concluded that SCH may be an independent risk factor for overall or vascular mortality especially in males below 60 years.³ SCH is associated with cardiovascular disease (CVD), it would be quite unfair to say due to contradictory findings in previous studies.^{4,5} Since inflammatory markers have been emerged as a assessor of cardiovascular risk they may provide better view of the developing risk of cardiovascular disease.⁶ Interleukin-6 (IL-6), an inflammatory cytokine, plays an important role in pathophysiology of cardiovascular disease due to its potential link with obesity, inflammation and coronary heart disease.⁷ IL-6 regulates the production of C-reactive protein (CRP), an acute-phase protein usually synthesised in the liver,⁸ which has been observed a positively association with TSH in SCH patients.⁹ Colocalization of CRP with activated complement by CRP/LDL-cholesterol complex suggests an involvement of CRP in complement activation in atherogenesis.¹⁰ Both IL-6 and CRP are related to the convectional factors for assessment of cardiovascular risk.¹¹ Since the controversial outcome of previous studies have supported that the developmental risk of atherogenesis cannot be neglected in SCH male patients and still a topic of discussion. Therefore the main objective of this study was to an assessment of IL-6 and CRP along with lipid profile in SCH male patients.

MATERIALS

This cross-sectional study was conducted in Department of Biochemistry, Santosh Medical College and Hospital, Ghaziabad. Total 90 persons were included in the study, in which 60 patients were with recently diagnosed subclinical hypothyroidism, termed as cases. They were compared with remaining 30, healthy individuals defined as controls.¹² All the participants have voluntarily participated for being a part of the study, a written consent was obtained from each individual. The fasting blood sample was taken from the entire participants to perform the various tests.

Exclusion criteria

SCH patients were having any previous and family history of thyroid disorder or thyroid medication. Patients having any cardiovascular risk, any inflammatory disease, diabetes, hypertension, smoking, alcoholics, renal disorder and any other acute or chronic illness were excluded from the study. SCH patients, taking lipid lowering drugs, were also excluded. SCH patients having TSH (>10μIU/ml) were not included in the study.

Inclusion criteria: Only recently SCH patients on the basis of range of TSH (6.16-10μIU/ml) along with healthy individuals were recruited for participate in the study. Age group criteria was 20 to 40 year for cases as well as controls group.

METHODS

Body mass index (BMI) was calculated by dividing weight of an individual in kg with square of the height of that individual in metre. TSH and FT4 were estimated by Enzyme Linked Immunosorbent Assay (ELISA) for evaluation of subclinical hypothyroidism. ELISA kits were used from Avantor Performance Materials, India.¹³ Total Cholesterol (TC), triglycerides (TG), and high density lipoprotein (HDL) cholesterol were estimated by

CHOD-POD method, GPO-PAP method and CHOD-POD/Phosphotungstate method respectively. Erba Chem, Germany kits were used for the estimation of lipid parameters. Low density lipoprotein (LDL) cholesterol was estimated by Friedwald formula. TC/HDL-C ratio and LDL-C/HDL-C ratio were estimated by dividing of TC and LDL-C to that HDL-C level.¹⁴ C reactive protein (CRP) was also estimated by ELISA, using reagent from ebioscience, USA.¹⁵ Interleukin-6 was estimated by ELISA using kits from Raybiotech.¹⁶ All these procedures were followed after getting the ethical approval from the institutional ethical committee.

Statistical Analysis

All the baseline parameters (Age, TSH, FT4, T3, BMI, TC, TG, HDL-C, LDL-C, CRP, IL-6, TC/HDL and LDL/HDL) were expressed in Mean \pm Standard deviation (SD). An unpaired student's *t* test was performed to differentiate the various parameters between cases and control groups. A Pearson correlation coefficient was performed between TSH and other variables (IL-6, CRP and BMI) in SCH group. A *p* value <0.05 was considered statistically significant. Statistical software, SPSS (statistical package of social sciences) version 23.0 (Chicago II, USA) for windows was used for statistical analysis.

RESULTS

In this study, the Mean age for the case group as well as control was 35.63 ± 3.64 and 36.46 ± 4.28 respectively. There was a highly significant difference (<0.001) was observed in TSH between the cases and control groups. FT4 and T3 was not statistically significant (>0.05) between the groups. BMI was significantly different (<0.001) between the groups and higher in SCH group compared to control group. In the case of lipid profile, significant difference was observed among the various parameters. Total cholesterol and LDL cholesterol was significantly higher (<0.01) in SCH patients. The level of HDL cholesterol was significantly (<0.01) lower in the SCH patient group. SCH patients having TG >350 mg/dl were excluded from the study and TG level was higher in SCH group and the resulted difference was significant (<0.01). TC/HDL and LDL/HDL ratios were higher in the patient group and the result was highly significant (<0.001) between the groups. (Table 1) Elevated concentration of CRP in SCH patients was highly significant (<0.001) between the groups. Mean concentration of IL-6 was significantly (<0.001) higher in SCH patients compared to control group. (Table 2) There was a positive

association of IL-6, CRP and BMI with TSH in SCH group and this association was significant (<0.05). (Table 3)

DISCUSSION

SCH is an asymptomatic disorder and may lead to overt hypothyroidism with the progression of the disease.¹⁷ Controversial aspects still lie regarding the routine screening of SCH while giving the treatment. The range of TSH in SCH patients is also a challenging concern. Weiss IA *et al* concluded that the treatment of SCH having TSH <10 is controversial but consideration is required in some patients.¹⁸ Significant differences in this cross-sectional study, between SCH male patients and control group, supported the hypothesis that SCH patients are associated with metabolic syndrome components in males.¹⁹ Madathil A *et al* observed that fatigue and another impaired functional status was associated with SCH males.²⁰ There was increased BMI in SCH males compared to control group. BMI was positively associated with TSH in patients with SCH supported by Gupta *et al* study.²¹ Interestingly, Kvetny J, *et al* reported that SCH might be a risk factor for developing cardiovascular disease in younger males by observing the increased level of triglycerides in SCH patients.²² This study shows the significant difference in lipid parameters between cases and controls group. Elevated serum concentrations of TC, TG and LDL-cholesterol in SCH patients were supported by MJ Cheserek *et al* study who reported that subclinical hypothyroidism was associated with metabolic syndrome components in males, not in females²³ while the higher concentration of HDL-cholesterol in the control group is supported by Erdum YT *et al.*²⁴ Clinical and epidemiological studies have found that for the effectiveness of lowering the lipid concentration the ratio between LDL-cholesterol to HDL-cholesterol is an excellent marker. It was concluded that this LDL-cholesterol/HDL-cholesterol ratio describe the two-way route of cholesterol entering and exiting the arterial intima.²⁵ TC/HDL-cholesterol ratio, specific and sensitive index of cardiovascular risk,²⁶ was found to be significantly higher in SCH patients matched with Efsthadiadou Z *et al* study.²⁷ Similarly, LDL-cholesterol/HDL-cholesterol ratio, an atherogenic index²⁸ was significantly higher in SCH patients. This significant difference in this ratio would describe the actual balance between two fractions to predict the risk of cardiovascular disease. Mahto M *et al* study stated that the elevated LDL-cholesterol/HDL-cholesterol ratio can highlight the cardiac risk and have the potential to become a part of the screening process of SCH patients along with CRP to detect the cardiovascular abnormality.²⁹

Table 1: Representation of various parameters between SCH and control group.

Parameters	SCH (60) Mean \pm SD	Controls (30) Mean \pm SD	Mean Difference (CI 95%)	p value
Age	35.63 \pm 3.64	36.46 \pm 4.28	(-2.66-0.99)	0.33
TSH(μ IU/ml)	8.11 \pm 0.80	2.75 \pm 0.78	(5.00-5.71)	<0.001
FT4(ng/dl)	1.12 \pm 0.23	1.12 \pm 0.19	(-0.09-0.08)	0.93
T3(ng/ml)	0.99 \pm 0.18	0.98 \pm 0.20	(-0.08-0.09)	0.89
BMI(kg/m ²)	26.33 \pm 1.86	23.30 \pm 1.78	(2.21-3.84)	<0.001
TC(mg/dl)	198.85 \pm 21.24	185.66 \pm 11.85	(5.97-19.85)	0.001
TG(mg/dl)	119.10 \pm 27.41	107.96 \pm 21.10	(0.70-21.56)	0.037
HDL-C(mg/dl)	43.02 \pm 2.43	47.63 \pm 3.85	(-6.16-3.05)	<0.001
LDL-C(mg/dl)	129.63 \pm 19.15	116.00 \pm 12.34	(6.97-20.29)	<0.001
TC/HDL	4.62 \pm 0.55	3.93 \pm 0.39	(0.44-0.89)	<0.001
LDL/HDL	3.02 \pm 0.49	2.45 \pm 0.33	(0.39-0.75)	<0.001

#by using student t test. All the variables are explained in Mean \pm SD. p value <0.05 is statistically significant.

Table 2: Representation of inflammatory markers between SCH and control group.

Parameters	SCH (60) Mean±SD	Control (30) Mean±SD	Mean Difference (CI 95%)	p value
CRP(ng/ml)	4.23±1.07	2.44±0.70	(1.40-2.16)	<0.001
IL-6(pg/ml)	7.78±1.25	4.00±0.64	(3.38-4.18)	<0.001

#by using student *t* test. All the variables are explained in Mean±SD. *p* value<0.05 is statistically significant.

Table 3: An association between TSH and other variables in SCH group.

Variables	r (CI 95%)	P value
IL-6	0.494 (0.266-0.723)	<0.001
CRP	0.296 (0.045-0.547)	0.022
BMI	0.307 (0.057-0.557)	0.017

#by using pearson correlation. r- pearson coefficient, CI- confidence Interval. *p* value<0.05 is statistically significant.

Kc R *et al* concluded that CVD risk was higher in SCH males by observing significantly higher concentrations of LDL-cholesterol and CRP in support to this SCH male patients based study.³⁰ There was significant higher concentration of CRP in SCH patients compared to control group. Increased concentration of CRP in SCH patients in this study compared to controls group supported the hypothesis to the presence of cardiovascular risk in SCH patients.³¹ Ibrahim *et al* also suggested that cellular hypothyroidism induces an energy lack leading to a chronic intracellular inflammatory process, affecting the endothelial cells causing the development of atherosclerosis.³² In addition, Sharma *et al*³³ reported that potential benefits of treatment of SCH decrease the risk of death from cardiovascular disease by observing the higher concentration of CRP in SCH patients. Christ-Crain *et al*³⁴ concluded that CRP values increase with progressive thyroid failure and may be count as an additional risk factor for development of coronary heart disease. IL-6 might be associated with severity of hypothyroidism³⁵ since in this study increased concentration of IL-6 was observed in SCH patients compared to control group. Adipocytes are important source to produce IL-6,³⁶ additionally receptors of TSH can also be expressed in adipocytes.³⁷ *in vitro* study suggested that TSH stimulates release of IL-6 from adipocytes by cAMP-PKA pathway,³⁸ which might be the reason for increased concentration of IL-6 in SCH patients. Tureman *et al* also supported this study by observing higher concentration of IL-6 in SCH patients when compared with controls.³⁹

CONCLUSION

In conclusion, the outcome of this study specifies that SCH patients (males) show the presence of abnormal lipid profile suggesting the progression of cardiovascular risk. Elevated concentration of CRP in SCH patients might indicate the presence of low grade inflammation along with increased IL-6. The determination of significant IL-6 may also be helpful in the prediction of cardiovascular risk in SCH patient as the disease progresses since it may contribute to the progression of myocardial damage. Lipoprotein ratios are easily calculated and without any additional costs which may play a significant role in assessing developing risk of CVD. The observed data concluded that the SCH patients having TSH<10μIU/ml, should be treated with caution and cardiovascular abnormalities may be developed if left untreated. To establish this fact more studies should be conducted with other establishing tools and large study population.

CONFLICT OF INTEREST

There is no conflicts of interest in this study by any authors

ABBREVIATIONS USED

TSH: thyroid stimulating hormone; **TC:** Total Cholesterol; **TG:** Triglycerides; **HDL-C:** High density lipoprotein Cholesterol; **LDL-C:** Low density lipoprotein cholesterol; **CRP:** C-reactive protein; **IL-6:** Interleukin-6; **BMI:** Body mass index; **CVD:** Cardiovascular disease; **ELISA:** Enzyme linked Immunosorbent Assay.

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