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RESEARCH ARTICLE

CARDIOVASCULAR RISK IN SUBCLINICAL HYPOTHYROIDISM DUE TO DISLIPIDEMIA

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ABSTRACT

Background and objectives:

Thyroid hormones play an important role in regulating lipid metabolism. Overt hypothyroidism is associated with atherosclerotic lipid profile pattern and coronary heart disease. Whether subclinical hypothyroidism (SCH) is associated with increased lipid profile parameters leading to cardiovascular risk is controversial. Data on the risk of cardiovascular disease are conflicting. This study was done to investigate the changes in the lipid profile parameters in subclinical hypothyroidism indicating the risk of cardiovascular diseases.

Materials and Methods:

60 SCH cases were compared with 30 euthyroid controls. Serums T3, T4, TSH were estimated by ELISA method, Serum Total-Cholesterol, HDL-Cholesterol by enzymatic CHOD-PAP method, Triglycerides by GPO-POD method and LDL-Cholesterol using Friedewald formula.

Results:

Significant increase was found in the mean serum levels of TSH ($P<0.001$), Total cholesterol ($p<0.001$), Triglycerides ($P<0.001$), LDL Cholesterol ($P<0.001$). No significant change was observed in levels of serum T4, HDL-Cholesterol. Percentage of subjects with increased Total Cholesterol , Triglycerides, LDL-C and decreased HDL-C were more in subclinical hypothyroidism as compared to euthyroid controls indicating the dyslipidemia in subclinical hypothyroidism.

Conclusion:

The Study revealed that the dyslipidemic state is seen in subjects with subclinical hypothyroidism leading to increased risk for cardiovascular disease. This indicates the importance of screening the patients for subclinical hypothyroidism and weigh in favor of treating the patients with subclinical hypothyroidism.

Keywords: Subclinical hypothyroidism (SCH), overt hypothyroidism, coronary heart disease, cholesterol.

INTRODUCTION:

Subclinical hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum T3 and T4 concentrations are within the reference ranges [1]. Thus the measurement of serum TSH is the important test for diagnosis of mild thyroid failure when the peripheral thyroid hormone levels are within normal laboratory range [2]. Subclinical hypothyroidism or mild thyroid failure has a prevalence rate of 3% to 8% in the population without known thyroid disease. The prevalence increases with age and is higher in women as compared to men. After the sixth decade of life, the prevalence in men reaches to that of women, with a combined prevalence of 10%[3].

Patients with subclinical hypothyroidism have no definitive signs or symptoms of thyroid dysfunction . The subclinical hypothyroidism is purely based on laboratory diagnosis as patients do not present with clinical signs and symptoms[1]. The clinical importance of subclinical hypothyroidism and the treatment for mild elevation of serum TSH (<10 mIU/L) is controversial aspect[1]. The exact upper limit of normal for the serum TSH level to categorize the patient under subclinical hypothyroidism is the subjects of debate [4]. Patients with Subclinical hypothyroidism have presented with higher levels of some cardiovascular risk factors. Although the results are conflicting, many studies have found that subjects with subclinical hypothyroidism have higher total cholesterol and low density lipoprotein cholesterol levels as compared to euthyroid subjects. Subclinical

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hypothyroidism has been associated with increased risk for atherosclerosis. The data on coronary heart disease (CHD) in subjects with subclinical hypothyroidism are conflicting [5].

Small percentage of patients with subclinical hypothyroidism advance to overt hypothyroidism, Lipid abnormalities are reported to be more common in patients with overt hypothyroidism and are thought to contribute to the disproportionate increase in cardiovascular risk in these persons. Controversy continues over whether elderly individuals should be screened for subclinical hypothyroidism the decision for screening the patients for this disorder is clouded by inconsistent evidence of association of dyslipidemia and other risk factors of cardiovascular disease with SCH and also any benefit from early treatment. A few trials have found that persons with subclinical hypothyroidism who are given L-thyroxine have shown some improvements in their energy level and feelings of well-being [6].

Cardiovascular diseases (CVDs) are the most common cause of mortality. Previous studies have suggested that abnormal levels of thyroid stimulating hormone (TSH) represent a novel cardiac risk factor [7].

There are few population-based studies that have compared lipid levels in patients who have subclinical hypothyroidism with lipid levels in euthyroid persons. So the purpose of this study is to determine whether the known risk factors for the cardiovascular diseases as lipid abnormalities is more significant in patients with subclinical hypothyroidism when compared with those in euthyroid individuals.

Material and Methods: The study is carried out in the Department of Biochemistry, BLDEU'S Shri. B. M. Patil Medical College Hospital and Research Centre, Bijapur (Karnataka) India. We studied 60 subclinical hypothyroid cases aged above 35 years and 30 euthyroid controls from the general population according to the inclusion and exclusion criteria mentioned below. This study was approved by the Institutional Ethics Committee. All the subjects gave an informed consent before undergoing further investigations.

Inclusion criteria: Subclinical hypothyroidism cases having TSH in the range of 4.50 to 14.99 mIU/L, T3 and T4 within normal limits and the euthyroid controls having normal TSH [0.3-4.5 mIU/L.] were included in the study.

Exclusion criteria: Known hypothyroidism cases, thyroidectomy cases, patient with external radiation, previous radioactive iodine therapy, consumption of drugs known to cause SCH, primary or secondary dyslipidemia, patients with other systemic illness, renal and hepatic failure cases, patients on statins were excluded from the study.

Venous blood samples were drawn at 8 a.m. following a 12 hours fast, in a plain bulb from the subjects, with all the aseptic precautions. Blood samples were centrifuged within 30 minutes at 3000 rpm for 5 min. and serum was separated. Serum samples were stored at -20°C until assayed serum T3, T4, TSH were estimated by ELISA method [8-10]. Serum Total-Cholesterol, HDL-Cholesterol by enzymatic CHOD-PAP [11] method, Triglycerides by GPO-POD [12]method and LDL-Cholesterol using Friedewald formula.

RESULTS:

Table 2 shows comparison of parameters among the study groups. Serum mean levels of TSH, T3, Total cholesterol, Triglycerides, LDL-C, HDL-C were significantly higher in SCH patients than in controls and were statistically significant ($p < 0.05$). Serum mean levels of T4 were not statistically significant. Table 3 shows the percentage of cases with elevated TC (>200 mg/dL), LDL (130> mg/dL), TG (150> mg/dL), and decreased HDL (<30 mg/dL) was higher in SCH patients than in controls.

DISCUSSION:

TABLE 1: GENDER DISTRIBUTION OF STUDY GROUP

GENDER	SUBCLINICAL HYPOTHYROIDISM	EUTHYROID CONTROLS
FEMALE	55(91%)	26 (86.6%)
MALE	5 (8.3%)	4 (13.3%)

Table 1 shows the gender distribution of the study group. In Subclinical Hypothyroid cases out of 60 cases 55(91%) were female and 5(8.3%) were male. In Euthyroid controls out of 30 controls 26 (86.6%) were females and 4 (13.3%) were males. This shows that gender distribution is well matched between the two groups and indicates that Subclinical Hypothyroidism is more common in female population.

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TABLE 2: COMPARISON OF PARAMETERS BETWEEN SUBCLINICAL HYPOTHYOIDISM SUBJECTS AND HEALTHY CONTROLS

VARIABLE	SCH Patients (Mean±SD)	Euthyroid controls (Mean±SD)	P value	Statistical significance
Age (yrs)	46.1± 7.2	49.5 ± 5.9	-	-
TSH (µIU/ml)	7.68 ± 2.46	2.64 ± 1.09	P<0.0001	HS
T3 (nmol/ml)	1.36 ± 0.41	1.83 ± 0.97	P<0.0035	HS
T4 (nmol/ml)	85.12 ± 16.72	89.27 ± 22.78	P<0.4060	NS
TC (mg/dL)	245.72 ± 38.36	183.66 ± 39.13	P<0.0001	HS
TG (mg/dL)	165.25 ± 18.74	104.37 ± 31.58	P<0.0001	HS
LDL-C (mg/dL)	185.63 ± 37.94	126.24 ± 36.39	P<0.0001	HS
HDL-C (mg/dL)	27.03 ± 4.07	36.23 ± 6.63	P<0.0001	HS

P value ≤ 0.05 is considered as statistically significant

TSH = Thyroid stimulating hormone; T3 = Tri-iodothyronine; T4 = Tetra-iodothyronine; TC = Total cholesterol; TG = Triglycerides; LDL-C = Low density lipoprotein; HDL-C = High density lipoprotein; NS = Statistically Not significant; HS = Highly significant.

Table 2 shows comparison of parameters among the study groups. Serum mean levels of TSH (7.68 ± 2.46), T3 (1.36 ± 0.41), Total cholesterol (245.72 ± 38.36), Triglycerides (165.25 ± 18.74), LDL-C (185.63 ± 37.94), HDL-C (27.03 ± 4.07), were significantly higher in SCH patients than in controls (2.64 ± 1.09 , 1.83 ± 0.97, 183.66 ± 39.13, 104.37 ± 31.58, 126.24 ± 36.39, 36.23 ± 6.63, respectively) and were statistically significant ($p < 0.05$). Serum mean levels of T4 (85.12 ± 16.72) was not significantly different from the values in controls (89.27 ± 22.78).

TABLE – 3: RISK FACTORS FOR CARDIOVASCULAR DISEASE IN SCH PATIENTS

Variable	SCH Patients (%)	Euthyroid controls (%)
TC (> 200 mg/dL)	83.3	30
TG (> 150 mg/dL)	73.3	10
LDL (> 130 mg/dL)	95	33.3
HDL (< 30 mg/dL)	63.3	13.3

Table 3 shows the percentage of cases with higher lipid profile parameters in the study group . The percentage of subjects having elevated TC (>200 mg/dL), LDL (130> mg/dL), TG (150> mg/dL), and decreased HDL (<30 mg/dL) was higher in SCH patients than in controls.

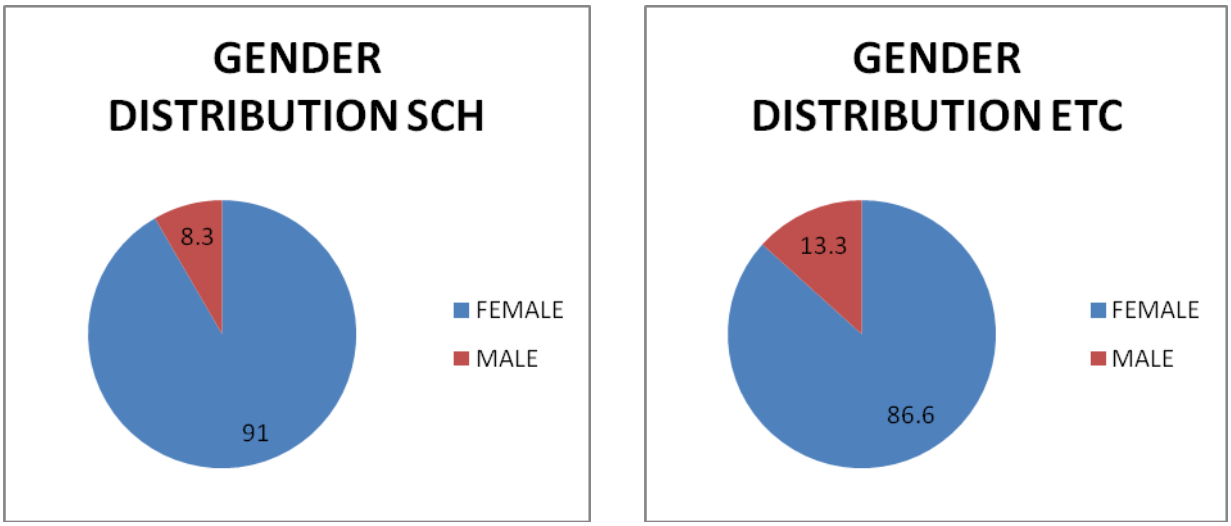

FIGURE 1: SHOWS GENDER DISTRIBUTION OF STUDY GROUP

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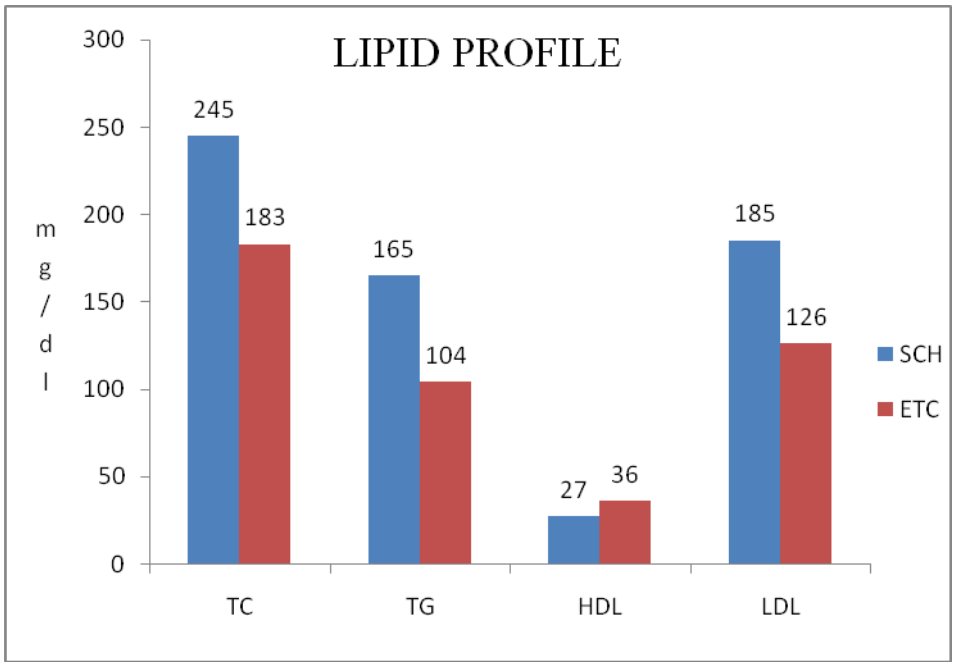

FIG2: SHOWS MEAN LIPID PROFILE IN STUDY GROUP

FIG 2 shows mean lipid profile in study group. Subclinical Hypothyroid cases show significantly higher levels of Total Cholesterol ($p < 0.0001$), Triglycerides ($p < 0.0001$) , High density lipoprotein cholesterol levels ($p < 0.0001$), and Low density lipoprotein cholesterol levels ($p < 0.0001$) .

Subclinical Hypothyroidism (SCH) is more common than overt hypothyroidism. Although it is generally accepted that overt hypothyroidism causes secondary hyperlipidemia and promotes atherosclerosis [13], the studies examining the relationships between hyperlipidemia, atherosclerosis, and SCH have yielded less convincing results. In recent times subclinical hypothyroidism is being diagnosed more frequently as compared to overt hypothyroidism[12].Overt hypothyroidism is associated with abnormalities of lipid metabolism, which may predispose to the development of atherosclerotic coronary artery disease (CAD) [14].

Subclinical hypothyroidism has been associated with increased risk for atherosclerosis. data on coronary heart disease (CHD) in subjects with subclinical hypothyroidism are conflicting[5]. The possible effects of subtle alterations of thyroid function as in SCH on lipid profile and atherogenesis remain unclear[14]. There is growing evidence, that SCH is an indicator of increased risk for atherosclerosis and myocardial infarction in elderly women[15].we observed that subclinical hypothyroidism is more common in females as compared to males (table 1 , fig 1)

Our study demonstrated that the mean levels of Total Cholesterol, Triglycerides, LDL-C, were higher where as mean values for HDL-C was lower in subclinical hypothyroid cases as compared to euthyroid controls (table 2, fig2). Zoe Efstathiadou et al[15] studied lipid profile in subclinical hypothyroidism and concluded that serum total cholesterol and LDL-C were significantly increased in SCH as compared to controls. Our study also showed the similar results.Study done by Nadia Caraccio[16] showed the similar results as our study indicating increased levels of Total cholesterol and LDL-C in subclinical hypothyroidism .Total cholesterol and HDL-C were elevated in several reports, but were not different from those in the controls in most studies[17, 18]. Lower serum HDL-C levels were reported in few studies and were not different from the euthyroid controls in most other studies[17, 19]

We observed the percentage of cases with higher lipid profile parameters in the study group as compared to controls. The percentage of subjects having elevated TC (>200 mg/dL), LDL (130> mg/dL), TG (150> mg/dL), and decreased HDL (<30 mg/dL) was higher in SCH patients than in controls. Our study is in accordance with study done by Rafael Luboshitzky et al[20] , who demonstrated that the percentage of subjects with increased total cholesterol ,triglycerides , LDL-C were more in SCH as compared euthyroid controls.

CONCLUSION:

In our study we found that the percentages of patients with atherogenic lipid profiles were higher in subclinical hypothyroid cases than in euthyroid controls. Thus there is increasing evidence that Subclinical hypothyroidism is associated with dyslipidemia which can be a potential risk

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factor for the development of CVD in the near future. The effectiveness of L-T4 replacement therapy in both reducing levels of Total Cholesterol, Triglycerides, LDL cholesterol levels and improving the condition of SCH patients is still controversial. further studies are required in this aspect involving large population group to obtain the convincing results.

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