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STUDY OF LIPID PROFILE IN SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Background: There is growing evidence that subclinical hypothyroidism is associated with increased risk of atherosclerosis and cardiovascular diseases. The relationship between subclinical hypothyroidism and lipid profile has been widely investigated, but the findings remain controversial. Objectives: This study was done to find out the association between subclinical hypothyroidism and lipid profile. Materials and Methods: Case control study was done taking 30 Subclinical hypothyroidism patients as cases and 30 age and sex matched healthy euthyroid subjects as controls. Results: The results showed a significant increase in total cholesterol, LDL cholesterol, triglycerides ($p< 0.001$) and a significant decrease ($p<0.001$) in HDL cholesterol in subclinical hypothyroidism cases as compared to controls. Conclusion: It can be concluded that Subclinical hypothyroidism cases exhibit an atherogenic serum lipid profile pattern which increases the risk of atherosclerosis and cardiovascular diseases. Therefore the routine assessment of serum lipid profile if done early in subclinical hypothyroidism would be helpful to prevent or reduce the risk of development of atherosclerosis and its associated cardiovascular complications.

KEYWORDS: Subclinical hypothyroidism; Dyslipidemia; Atherosclerosis, Cardiovascular disease.

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INTRODUCTION

The significant effect of thyroid hormones on synthesis, mobilization and metabolism of lipids leads to an alteration in the composition and transport of lipoproteins in thyroid disorders[1]. Subclinical hypothyroidism is a state of high serum thyroid stimulating hormone (TSH) levels with normal serum total/free thyroxine (T_4) and triiodothyronine (T_3) levels, associated with few or no clinical signs and symptoms of hypothyroidism. It is much more common than overt hypothyroidism and is found in 6–8% of women and 3% of men[2]. Recently, subclinical hypothyroidism has been claimed to be a risk factor for coronary artery disease, peripheral vascular disease and various biochemical abnormalities including dyslipidemia and negative influence on haemostatic profile[3]. Also subclinical hypothyroidism may progress to overt hypothyroidism and this progression rate is higher with the concomitant presence of thyroperoxidase antibodies (TPO-Ab) or higher levels of TSH[4]. The relationship between lipid profile and overt hypothyroidism is well established. However, there is a lack of consistent data on whether and to what extent does subclinical hypothyroidism affects lipid profile. Many studies have reported a significant increase in total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels in patients with subclinical hypothyrodism[5,6] but not in all studies[7,8]. Few studies have found a significant elevation of triglycerides (TG) levels in subclinical hypothyrodisim[8, 9], while others refuting any relation between the two[5-7]. Similarly, high density lipoprotein cholesterol (HDL-C) has been reported to be normal[5, 6, 8] or decreased[7, 9] in subclinical hypothyroidism as compared to normal euthyroid controls. Slight change in serum TSH leads to significant development of dyslipidemia, a well established risk factor of cardiovascular disease. To prevent cardiovascular disease in subclinical hypothyroidism patients, it is important to investigate the association between subclinical hypothyroidism and lipid profile. Since the results of previous studies on relationship between lipid profile and subclinical hypothyroidism are inconsistent, the present study is undertaken to study the association between lipid profile and subclinical hypothyroidism.

MATERIALS AND METHODS

The study was conducted for a period of one year in Bapuji Hospital and Chigateri Hospital, Davangere (both these hospitals are attached to teaching institute, J.J.M. Medical College, Davangere). Each participant gave an informed consent and this study was approved by the ethical and research committee.

A) Selection of the study subjects

Based on inclusion and exclusion criteria, a total number of 60 subjects (30 cases and 30 controls) were selected for the present study.

Inclusion criteria

Cases – 30 newly diagnosed cases of subclinical hypothyroidism in the age group of 18–70 years attending the outpatient department of medicine were included in this study. Those patients who were presenting with history of fatigue, weakness, weight gain, coarse, dry hair, dry, rough and pale skin, hair loss, cold intolerance, constipation were suspected to have subclinical hypothyroidism. Blood samples were collected from such suspected cases and it was analyzed for T_3, T_4 and TSH levels. Based on the result of thyroid profile, those patients with elevated serum TSH levels (> 5.45 µIU/ml) with normal serum T_3 (0.5 – 2.0 ng/ml) and normal serum T_4 (4.4-10.8 µg/dl in males; 4.8-11.6 µg/dl in females) levels were diagnosed as subclinical hypothyroidism. Later in these patients, fasting lipid profile was estimated.Controls: 30 age and sex matched healthy euthyroid subjects.

Exclusion Criteria

Patients with overt hypothyroidism**,** thyroidectomy cases, history of previous radioactive iodine therapy, consumption of drugs known to cause dyslipidemia, diabetes mellitus, hepatic, renal & cardiovascular diseases were excluded from the study.

B) Collection of blood samples

Under all aseptic precautions, about 5 ml of venous blood was drawn in a sterile plain bulb

from selected subjects after overnight fasting for 12 hours. 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 lipid profile was analyzed by using analytical kits from Erba Diagnostics Mannheim GmbH in semi-autoanaylzer (CHEM-5 Plus V_2, Erba Mannheim). Serum thyroid profile was estimated using thyroid profile Chemiluminescence Immunoassay (CLIA) kit from Acculite-Monobind in LUMAX 4101 CLIA microplate reader.

STATISTICAL ANALYSIS

Descriptive data are presented as mean ± SD. Students't' test was used for comparing different biochemical parameters between cases and controls. The statistical software SPSS 17.0 version was used for analysis of the data. For all the tests, the probability value (p-value) of less than 0.05 was considered statistically significant.

RESULTS

Mean age of cases and controls were comparable. There was a female preponderance, both in patients with subclinical hypothyroidism and controls .The mean serum TSH was higher in subclinical hypothyroidism cases compared to controls and this difference was statistically significant with a p value of < 0.001(Table no. 1). Mean serum TC, LDL-C and TG levels were significantly increased (p value < 0.001 and p < 0.05 respectively) while HDL-C was significantly decreased in subclinical hypothyroidism cases compared to controls (p value of < 0.001) (Table no. 2).

Table 1
Comparison of Thyroid profile between subclinical hypothyroidism cases and controls.

PARAMETER	CASES(Mean ± S.D)	CONTROLS (Mean ± S.D)	p Value
Age (yrs)	38.96 ± 11.43	37.8 ± 13.61	NS
Gender(F/M)	23/7	22/8	NS
T_3 (ng/ml)	1.21 ± 0.24	1.23 ± 0.23	NS
T_4 (µg/dl	7.57 ± 1.88	8.11 ± 1.47	NS
TSH (µIU/ml)	10.70 ± 5.21	2.19 ± 0.88	< 0.001*

Unpaired't' test, p value < 0.001 statistically highly significant
NS: statistically non significant with p value >0.05

Table 2
Comparison of serum lipid profile between subclinical hypothyroidism cases and controls.

Groups		TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
Cases (n=30)	Mean ± SD	203.6 ± 28.99	140.37 ± 32.62	38.1 ± 6.24	135.3 ± 1.36
	Range	152-266	78-223	28-48	76-207
Controls (n=30)	Mean ± SD	164.23 ± 24.34	118.0 ± 36.13	48.33 ± 6.38	94.5 ± 24.25
	Range	115-215	64-184	35-59	37-140
Cases Vs Controls	Mean diff	39.367	22.367	10.233	40.800
	t value*	5.695	2.517	-6.278	5.636
	p value	< 0.001	< 0.05	< 0.001	< 0.001

Unpaired't' test, p < 0.001 statistically highly significant; p<0.05: statistically significant
TC –total cholesterol, TG-triglyceride, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol.

DISCUSSION

In India, thyroid disorders are the most common endocrine disorders. They are more commonly seen in the middle age[10]. Elevation of TSH levels reflects the sensitivity of the hypothalamic-pituitary axis to a small decrease in the circulating thyroid hormones; as the thyroid hormone falls, the TSH level may rise above the upper limit of normal when the free T_4 level has fallen only slightly and is still within the normal range[11]. A decrease of free T_4 by a factor of 2, leads to an increase in serum TSH by a factor of 100. Therefore, TSH may be recognizably abnormal months or years before there is a diagnostic change in the serum concentrations of T_4 or T_3. Therefore an elevated TSH in an individual patient, thus, means that the circulating thyroid hormone concentrations are insufficient, with a few rare exceptions[12, 13]. Dyslipidemia is a common finding in patients with thyroid disease, explained by the effects of thyroid hormones on almost all steps of lipid metabolism[14]. The association between dyslipidemia and overt hypothyroidism is well established and so is about the beneficial effects of thyroid hormone substitution on serum lipids and on the risk of cardiovascular disease[15]. Recently, many studies have suggested an association between subclinical hypothyroidism and coronary heart disease. However, the relationship between subclinical hypothyroidism and lipid profile remains controversial. The Colorado study, which screened 25,862 subjects found that mean TC and LDL-C progressively increased with increasing serum TSH levels[5]. No relation was found between subclinical hypothyroidism and hyperlipidemia in the Whickham Survey[16]. In the NHANES III, mean cholesterol levels and rates of elevated cholesterol levels were higher in people with subclinical hypothyroidism than in euthyroid controls; there were no differences in LDL-C or HDL-C levels[17]. In the Rotterdam Study, TC was lower in women with subclinical hypothyroidism than in euthyroid women[18]. A study by Tanis et al., found that subclinical hypothyroidism was two to three times more frequent in people with elevated total plasma cholesterol[19]. In the present study, we observed a significant increase in TC and LDL-C in subclinical hypothyroidism cases compared to controls. Our results are in accordance with studies of several researchers[6, 20]. In subclinical hypothyroidism the depletion of the thyroid hormones leads to reduced numbers of LDL receptors on the liver cell surface, resulting in decreased uptake and degradation of LDL-C. Furthermore, decreased thyroid function not only increases the number of LDL particles, but also promotes LDL oxidation, thereby increasing the risk of atherosclerosis[1,21]. In the present study, there is an increase in mean TG levels in subclinical hypothyroidism cases as compared to controls. Although LDL-C is widely accepted as the major atherogenic lipoprotein, TG-rich lipoproteins such as chylomicron remnants and very low-density lipoprotein remnants still play an important role in atherogenesis. These remnants are taken up by macrophages in the arterial walls to produce foam cells and thus may be a risk factor for atherosclerosis. So, there may be some risk involved in cases of subclinical hypothyroidism. In subclinical hypothyroidism, lipoprotein lipase enzyme has been found to be decreased resulting in high levels of TG[1, 15]. Previous reports on HDL-C levels in subclinical hypothyroidism have been inconsistent. This is because of complex HDL-C metabolism. Plasma cholesteryl ester transfer protein concentration decreases with slight reductions in serum thyroxine level in subclinical hypothyroidism patients, which may result in higher HDL-C levels. On the other hand, the activities of hepatic lipase, lecithin cholesterol acyl transferase, and ATP-binding cassette transporter decreases with increase in serum TSH levels resulting in reduction of HDL-C levels[1, 22]. We found that HDL-C is significantly decreased in cases compared to controls and the difference is statistically significant with $p < 0.001$. These results are in accordance with other studies[7, 14] It has been reported that significant reduction in the levels of TC and LDL-C following levothyroxine therapy, decreases the incidence of coronary artery diseases, stroke and peripheral vascular disease in subclinical hypothyroidism. This is further supported by other workers who reported that cardiovascular mortality of 9-31% can be reduced by improving the levels of LDL-C[23, 24].

The sample size of this study was small. The study can be further extended by including large population size and also observing the effect of thyroid hormone replacement therapy on lipid profile in subclinical hypothyroidism cases.

CONCLUSION

Subclinical hypothyroidism is associated with atherogenic serum lipid profile pattern. Such atherogenic lipid profile pattern may increase the risk of atherosclerosis and cardiovascular diseases. Therefore there is a potential association between subclinical hypothyroidism and atherosclerosis. So assessment and monitoring of serum lipid profile is of utmost importance to reduce or prevent the risk of development of atherosclerosis and cardiovascular diseases in subclinical hypothyroidism patients.

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