Dyslipidaemic Changes in Women with Subclinical Hypothyroidism

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ABSTRACT

Background: In overt hypothyroidism, many lipid abnormalities have been documented. This study was intended to demonstrate the levels of lipid in women with subclinical hypothyroidism (SH).

Material and Methods: This was a case control study which was done at referral Centre in Chennai. Women with subclinical hypothyroidism and euthyroid women attending our master health checkup clinic were enrolled in this study. Their lipid profile, fasting blood sugar, T3, T4 and TSH levels were measured. In subclinical hypothyroidism, various parameters were compared.

Results: Thirty euthyroid and 30 age matched subclinical hypothyroid women were enrolled in this study. There were significant dyslipidaemic changes is SH women as compared to euthyroid controls. Serum total cholesterol and triglyceride levels were significantly higher as compared to those in controls. LDL levels were higher is SH women, but did not reach statistical significance and lower levels of HDL were noticed in SH subjects as compared to those in euthyroid women. A positive association was also reported between serum TSH and lipid parameters in our study group.

Conclusion: SH, the earliest form of thyroid failure, has negative metabolic effects on the affected subjects. SH could be one of the causes of secondary hyperlipidaemia and should be viewed as an independent risk factor for atherosclerosis, along with obesity, hypertension, diabetes, etc.

Key words: Dyslipidaemia, Subclinical hypothyroidism, Lipid profile

INTRODUCTION

Subclinical hypothyroidism (SH), defined as the clinical status of mildly elevated serum TSH levels (up to 10 μU/L) with normal levels of FT4 and FT3, is a far more common and asymptomatic disorder than overt hypothyroidism. It is diagnosed in 1% to 10% of the adult population. It shows a higher prevalence among women and older subjects [1]. Subclinical hypothyroidism, characterised by modifications in cardiovascular and neuromuscular functions and lipid metabolism, may be the first phase or beginning of a progressive disease state [2].

Overt and subclinical hypothyroidism have adverse effects on the serum lipid profile, that may predispose to the development of atherosclerotic disease. Patients with SH tend to have higher levels of serum total and LDL cholesterol. Small changes in thyroid function tests within the reference range may influence the severity of atherosclerosis [2].

Most of the studies on SH have shown slightly elevated levels of total cholesterol, with all the other lipids being within the normal range. In this study, we have compared the lipid profile of SH subjects with age and sex matched euthyroid subjects and also correlated serum TSH with the lipid levels. Assessment and management of decline in thyroid deficiency may provide a comprehensive management of dyslipidaemia.

MATERIAL AND METHODS

This case control study was performed from October 2008 to January 2009 at a referral centre in Chennai. Thirty women with subclinical hypothyroidism, defined by normal free thyroxine and elevated serum TSH and thirty healthy age matched euthyroid women among women voluntarily attending our master health checkup clinic, were enrolled in this study after taking their written informed consents. Euthyroid subjects were defined as those having normal serum free T4 and TSH levels. The diagnosis of subclinical hypothyroidism was based on serum thyroxine (0.8–1.8 ng/dl) and serum TSH between (4–10 μU/L). Euthyroid subjects had serum T4 with 0.8–1.8 levels and serum TSH levels of 0.35–4.0 μU/L. A detailed questionnaire was used to assess the past history of any disease, alcohol consumption, smoking and occupational history. Anthropometric measures were recorded. Blood pressure was measured using a standard mercury sphygmomanometer. Fasting blood glucose (FBS) was measured to rule out diabetic mellitus. Only subjects with FBS (range) were included in the study. None of the subjects had symptoms of overt hypothyroidism and had they never received levothyroxine (LT4) replacement therapy. None of the cases had a previous history of radiiodine treatment, surgery of thyroid, external radiation and/or drug therapy which could cause SH. Persons with severe obesity and history of alcohol abuse, smokers, patients receiving drugs such as oestrogens, diuretics and beta-blockers, patients with familial or secondary dyslipidaemia, diabetic mellitus and renal, hepatic or other systemic diseases, were excluded from the study. Other exclusion criteria included thyroid hormone medication for up to 3 months before enrollment, lipid-lowering agents within 6 months before enrollment. Handling and storing of blood samples were done as per criteria furnished by National Committee for Clinical Laboratory Standards (NCCLS).

Bleed was collected after 12 hours fasting, in the morning between 8–9 am. Blood samples were collected by observing universal precaution for venipuncture. EDTA – treated containers were used for sample collection. Samples were centrifuged at 3000g for 5 minutes. Serum was separated and stored at –7°C until it was assayed. SIEMENS kit was used for lipid profile and thyroid profile analyses.

Data were presented as the mean ± SD. Statistical analysis was performed by an IBM computer with the use of Statistical Package of Social Sciences (SPSS), ver. 16.0. Student’s t-test in the case of non-parametric distribution was used to identify variables showing
differences between SH groups and controls. Pearson’s correlation analysis was carried out between lipids and TSH levels. The level of significance was set at p < 0.05. The study protocol was approved by the ethics committee of our institute.

RESULTS
Thirty women of SH group and thirty healthy age matched euthyroid women were enrolled for the study. [Table/Fig-1] shows the descriptive data and the thyroid profile of the SH women and controls. The BMI of the SH group was similar to that of the euthyroid group.

Fasting blood glucose was within the normal range in both the groups; thereby, diabetics were excluded from this study. Blood pressure was measured in both the groups and it showed normal BP; hence, hypertensive patients were excluded from this study.

On studying the thyroid profile, in the SH group, basal TSH levels were found to be elevated as compared to those in euthyroid subjects. This was statistically significant (p<0.001). The free thyroxine levels were within the normal range in both SH and euthyroid subjects. [Table/Fig-2] shows the lipid profile of SH women and controls. Patients with SH showed significantly higher serum total cholesterol and triglyceride levels as compared to the controls (p < 0.001). LDL levels was not significantly raised in the SH women as compared to those in euthyroid subjects. HDL levels were lower in SH subjects as compared to those in controls (p<0.001). Cholesterol/HDL ratio was higher in the SH group as compared to that in euthyroid subjects (p =0.003).

Correlation between lipid parameters and serum TSH in SH women [Table/Fig-3] showed a strong positive association between serum cholesterol, triglyceride and LDL levels (p<0.001). There was a negative correlation between TSH and HDL (p<0.05) [Table/Fig-4, 5 and 6].

DISCUSSION
Subclinical hypothyroidism, the earliest form of hypothyroidism, is defined by increased concentration of TSH in the presence of normal thyroid concentrations. This disorder is the mildest form of a spectrum of thyroid failures and it commonly occurs in the natural history of autoimmune thyroiditis. Thyroid antibodies are often the sole finding of autoimmune thyroiditis associated with subclinical...
hypothesis. Whether tissues other than the anterior pituitary recognise that thyroid hormones levels are suboptimal, although highly possible, remains difficult to prove. SH cases make up a small proportion of patients with hyperlipidaemia. On the other hand, an unfavourable lipid profile is possible explanation for the reported association between coronary heart disease and SH [3].

An important concept which arises from this discussion is that in an individual with thyroid hormones within the population-based reference range, the peripheral thyroid status is defined by the serum TSH level. Thus, a serum TSH value outside the laboratory reference range in patients with SH strongly suggests that thyroid hormone levels are not sufficient to maintain euthyroidism. This supports the view that SH is a mild form of tissue hypothyroidism. A high-thyroid autoantibody titre and/or serum TSH level of > 6 mU/L indicates ongoing thyroid gland disease, and is a powerful biochemical predictor of progression to overt thyroid gland failure [4].

This state of latent thyroid failure, which should be more properly defined as mild hypothyroidism, may persist for years or may evolve to myxoedema. In the Whickham survey, the annual risk of developing overt hypothyroidism was 4% in women with both raised serum TSH and positive thyroid antibodies, 3% if only TSH was raised, and 2% if only thyroid antibody were positive [5].

It is worth emphasising that the hormonal thyroid secretion should be normal or mildly reduced, but still in the normal range. As a consequence, most metabolic pathways and organ systems influenced by thyroid hormones should be unaffected. In spite of these assumptions, mild complaints consistent with thyroid hormone deficiency and dyslipidaemia have been reported in patients with subclinical hypothyroidism [6].

Our study showed significant dyslipidaemic changes is SH women as compared to those in euthyroid controls. Serum total cholesterol and triglyceride levels were significantly higher as compared to those in controls. LDL levels were higher is SH women, but did not reach statistical significance. Thyroid hormones affect lipoprotein metabolism through their effects on cholesterol ester transfer protein, hepatic lipase, lipoprotein lipase, and HMG CoA reductase. Both fatty acids and LDL oxidation promote hypothyroidism.

In hypothyroid patients, the most frequent lipid abnormality is hypercholesterolaemia, mainly due to an increased concentration of low density lipoproteins (LDL), resulting from decreased activity of LDL-receptors and, consequently reduced catabolism of LDL. Decreased thyroid function not only increases the number of LDL particles, but also promotes their oxidability, making them even more atherogenic. Plasma triglycerides are increased because of an enhanced esterification of fatty acids at hepatic level. Hypertriglyceridaemia associated with increased levels of VLDL and occasionally, fasting chylomicronaemia, are attributable to the decreased activity of LPL, which results in a decreased clearance of triglyceride-rich lipoproteins in hypothyroid patients.

We found lower levels of HDL in SH subjects as compared to those in euthyroid women. A study was done in rats 1989, to know the cause of decrease in HDL in case of hypothyroidism and it was noted that plasma clearance rate of HDL was reduced in case of both subclinical and overt hypothyroidism [7]. Liver is an important site for HDL-cholesterol catabolism. Hypothyroid cells displayed a lower HDL binding capacity and a higher binding affinity as compared to control cells; these results suggest that thyroid hormone affects the expression of HDL binding site in liver cells, which may contribute to the reduced HDL clearance in hypothyroidism.

Our study also reported a positive association between serum TSH and lipid parameters in our study group. Log linear relation between free thyroxine (fT4) and thyroid stimulating hormone (TSH) makes TSH the first choice for diagnosis of thyroid dysfunction. Subclinical excess or deficiency of thyroid hormones can be diagnosed only by serum levels of TSH [8]. The pituitary gland is sensitive to minor changes in serum thyroid hormones, [9] and when thyroid function is deranged, the association between serum TSH and thyroid hormone is log linear [10, 11].

We also did a follow up study, where the patients were reviewed after 6 months. Out of 30 subclinical hypothyroid women, only 17 participated in the follow up review checkup. Lipid profile, TSH, T3, T4 and other parameters were measured in these 17 subclinical hypothyroid women. Out of the 17 women, only 2 women developed an overt hypothyroidism after 6 months. None of the patients developed cardiovascular disorders. A long follow up study may help in finding the risk and development of cardiac and other disorders. This can be taken as a future goal to work further.

Half-lives of T4 and T3 are approximately 7 days and 1 day, respectively. Serum TSH, which has a half-life of 1 hour, would return to normal if thyroid hormone levels were normal. Conversely, serum TSH remains stably elevated, which means that circulating thyroid hormone levels are not sufficient to restore and maintain the physiologic pituitary secretion rate. Therefore, elevated serum TSH levels in patients with SH do not serve to maintain tissue euthyroidism, but strongly suggest that, although apparently normal, serum thyroid hormones are insufficient. This supports the view that SH is a mild tissue hypothyroidism [12]. Thyroid hormone deficiency, therefore, represents a well-known cause of hyperlipidaemia, both in overt and subclinical hypothyroid patients [13,14].

**CONCLUSION**

SH, the earliest form of thyroid failure, has negative metabolic effects on the affected subjects. In our study, we found significant dyslipidaemic changes in SH women as compared to those in euthyroid subjects. We found higher total cholesterol, LDL, serum triglyceride and lower HDL values in SH subjects than in euthyroid women. This study highlights the significant positive correlation between serum TSH and lipid profile, indicating that increase in serum
TSH was one of the earliest markers of tissue hypothyroidism, even though T3 and T4 were within normal limits. Therefore, SH could be one of the causes of secondary hyperlipidaemia and should be viewed as an independent risk factor for atherosclerosis, along with obesity, hypertension, diabetes, etc. An atherogenic lipid profile is the important forerunner of cardiovascular and cerebrovascular diseases, the major killers in today’s modern world. There has been extensive interest in using thyroid hormones for treating a variety of indications, including dyslipidaemia associated with SH, obesity and familial hypercholesterolaemia.

REFERENCES
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