RESEARCH ARTICLE

ASSOCIATION BETWEEN BODY MASS INDEX, LIPID PEROXIDATION AND CORONARY LIPID RISK FACTORS IN HYPOTHYROID SUBJECTS

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ABSTRACT

Background: Thyroid hormones plays an important role in control of metabolism in human. Hyperlipidaemia particularly hypercholesterolemia, is a well-documented significant health consequence associated with hypo-thyroidism. Oxidative stress is a common factor associated with several clinical conditions including hypothyroidism.

Aims & Objective: To evaluate the association between BMI, Hyperlipidaemia, Lipid Peroxidation and Atherogenic risk in newly diagnosed hypothyroid patients.

Material and Methods: 85 newly diagnosed hypothyroid cases and 41 euthyroid controls were studied for their Thyroid profile [TSH, T_4 and T_3], Lipid profile , Oxidative stress marker, Malondialdehyde {MDA} Lipid risk ratios, [TC/HDL-C and LDL-C / HDL-C ratio] , Atherogenic index [AIP] - log TG/HDL-C and Body Mass Index [BMI].

Results: Hypothyroid patients had hyperlipidaemia, especially hypercholesterolemia [224 ± 43.8 mg/dl], increased LDL-C level [150.4 ± 42.3 mg/dl] when compared to controls [169.5 ± 25.1 and 97 ± 25.5 respectively]. MDA was significantly increased [p< 0.0001] in hypothyroid subjects [6.14± 1.83μ mol/L] versus the controls [2.9 ± 0.86 μmol/L] .BMI had positive correlation with TSH [r =4.421; p<0.0001].

Conclusion: Hypothyroidism leads to hyperlipidaemia enhancing risk for cardiovascular diseases, the connecting link being oxidative stress. It was found that TSH had positive significant correlation with BMI, Lipid profile and oxidative stress in hypothyroid patients when compared to the controls making them more prone for coronary artery diseases.

Key-Words: Hypothyroidism; Body Mass Index (BMI); Thyroid Stimulating Hormone (TSH); Atherogenic Index

Introduction

Thyroid disorders are the most common among all endocrine disorders in India, hypothyroidism being more common than hyperthyroid state and carcinoma of thyroid. Yet a majority of them remain undiagnosed and untreated. It is estimated that out of the 108 million affected with endocrine disorders, about 42 million people have thyroid dysfunction of various categories in the post iodization phase.[1]

BMI in Thyroid Disorders

Increase in thyroxin almost always decreases the body weight, and a decrease in thyroid hormone increases the body weight.[2,3] These effects do not always occur, because thyroid hormone also increases the appetite and this may counterbalance the change in metabolism. So it is clear that overt hypothyroidism is associated with weight gain, while hyperthyroidism is associated with weight loss.[4] Therefore overt thyroid dysfunction clearly influences Body Mass Index (BMI). BMI or Quetelet index has been used by the World Health Organisation (WHO) as the standard for recording statistics of obesity since the early 1980s. It is a statistical measurement which compares a person's weight and height and is calculated by the formula, BMI = Weight (in Kg) / (Height in meter)^2.

The distribution of BMI in Indians with desirable upper limit of body mass is < 23 kg/m^2. Evidences indicate that obesity occurring at an earlier age (20 – 40 years) has a greater influence on cardiovascular diseases than late onset obesity. Hypothyroidism should be considered as one of the causes of obesity. Much of weight gain that occurs in hypothyroidism is due to myxedema.[5]

Dyslipidemia in Hypothyroidism

In general, overt and sub clinical hypothyroidism is associated with hypercholesterolemia mainly due to elevation of LDL- C levels, whereas HDL-C levels are normal or even elevated. Levels of total

and LDL cholesterol tend to increase, as the thyroid function declines. Therefore, hypothyroidism constitutes a significant cause of secondary dyslipidaemia.[6]

Decreased activity of LDL – receptors resulting in decreased receptor mediated catabolism of LDL and IDL is the main cause of hypercholesterolemia observed in hypothyroidism. LDL oxidation is affected by thyroid hormones increasing the level of o- LDL level.[7]

There are various lipid factors such as NHDL, TC/HDL-C and LDL-C / HDL-C ratio to assess the risk for atherosclerosis.

Oxidative Stress in Hypothyroidism

The origin of lipid peroxidation in hypothyroidism is still unclear. Increased oxidative stress and atherosclerosis associated with enhanced cardiovascular risk in hypothyroidism is due to interplay of various factors. It is currently believed that lipid peroxidation is involved in the oxidative modification of LDL ultimately resulting in the formation of atherosclerotic lesions.

Previous studies have shown that there is a significant change in thyroid profile with different stressors indicating the relationship between the level of thyroxin and oxidative stress. With this background of studies and various work done on lipid peroxidation in hypothyroidism, we analysed the relationship between BMI, TSH levels and degree of dyslipidaemia with the level of lipid peroxidation and cardiac risk in terms of atherogenic index in primary hypothyroidism.

Materials and Methods

This case control study was conducted in the department of Biochemistry, Vinayaka Missions Medical College, Karaikal. Samples were collected from patients referred from clinical departments of VMMC & H, Karaikal. A total of 85 cases and 41 controls of age group 14-50 years were included in this study. Internal control from the study groups was contributed by the euthyroid subjects from general population.

Inclusion criteria: Newly diagnosed hypothyroid patients in the age group 15 – 45.

Exclusion Criteria: Diabetics, hypertensives, renal and hepatic diseased patients, hypothyroid patients already on treatment, alcoholics, patient on any other medications were excluded from this study.

Clinical history was taken from all the subjects. General examination of these patients including weight, height, heart rate and blood pressure measurement was done and recorded in a structured protocol format.

Collection of Blood Sample: The fasting blood sample of volume 5ml was collected in serum vacutainer and EDTA tubes separately under aseptic condition.

Analysis of Blood Samples: *(a) Thyroid Profile:* Serum TSH, free T_4 (fT_4) and freeT_3 (fT_3) were estimated by Enzyme Immunoassay method using ELISA Kit from Ranbaxy laboratories. *(b) Lipid Profile* estimation was carried out by commercial kits by enzymatic colorimetric end point method like CHOD- POD Kit for total cholesterol, Serum Triglycerides by GPO- PAP Method and HDL-Cholesterol by precipitating reagent method. (c) Serum Glucose, Urea and Creatinine were estimated by standard enzymatic kit methods. (d) Lipid peroxide product, MDA was estimated by Esterbauer and Steinberg method (1989)[8]

Apart from the estimated biochemical parameters, calculated parameters were worked as follows: *(a) Body Mass Index (BMI):* BMI = Weight (in Kg) / (Height in meter)². *(b) LDL AND VLDL-C* using Friedewald's formula[9], VLDL-C = Triglyceride/5; LDL-C = TC – (HDLc+TG/5). *(c) Atherogenic Index*[10] = log (TG/HDLc)

Statistical analysis was done using MS Excel. Chi square value was calculated. P value less than 0.05 was taken as the level of significance. Also Odds Ratio (OR) was determined.

Results

The study subjects were found to be in their early thirties with mean age of 33.1 and 30.2 in cases and controls respectively. The median age group were 34 and 31 in cases and controls, which suggests late adulthood onset of hypothyroidism. The routine biochemical parameters like FBG,

urea, and creatinine were found within normal limits in both control and hypothyroid groups.

As shown in table- 1, the hypothyroid cases were categorised into four groups according to their TSH, fT$_4$ and fT$_3$ level as *subclinical* [SHT] (9/85) a distinct entity with increased TSH and normal T$_3$ and T$_4$, *Group I (mild hypothyroids)* (29/85) with TSH 5- 10 µIU/ml, *Group II (moderate hypothyroids)* with TSH 10- 20 µIU/ml, (26/85) and *Group III (severe hypothyroids)* with TSH > 20 µIU/ml, (21/85) and are compared against the control group (41) with TSH < 5 µIU/ml . The mean TSH in each group is 7.4, 7.33, 14.48 and 36.79 µIU/ml respectively and in controls it is 2.72 µIU/ml. [ref range 0.39 – 5.0 µIU/ml]

Hypercholesterolemia was found in 78.8% of hypothyroids and only 9.8% in controls with OR of 34.43, which was a very significant finding. When compared with the controls by t test, there is significant p value of 0.0001. There was negative correlation between TSH and TC in SHT and group I cases, positive correlation in group II, III, total cases and controls group, with significant r and p value in severely hypothyroid group III and total cases. Hypertriglyceridemia was found in 34% of cases and 2.4% of controls with Odds Ratio of 20.71 and significant t and p value. LDL-C, which is an important atherogenic factor, was increased in the cases, 75.3% of them had higher LDL-C level and in controls it is only 2.4% with OR of 121.9. SHT and group I cases had negative correlation with TSH whereas group II, III, total cases and controls had positive correlation with significant p value in group III and total cases. The increased total lipids is considered to be an important contributory factor for the development of atherosclerosis. The risk ratio TC:HDL-C is increased in 89.4% of hypothyroids with OR of

16.3 (p<0.0001). The other ratio LDL:HDL-C was elevated in 80% of cases with OR of 28.8% (p<0.0001) increasing the cardiac risk in hypothyroid patients. All the study groups had mean BMI above the assign cut off of 23 kg/m^2. We found that the BMI was increasing with TSH level with significant t and p for all the groups against controls.

There is increased incidence of oxidative stress hypothyroid cases. i.e., 92.9% against controls with 9.7%, about 10 times increased risk in hypothyroids with Odds Ratio of 121.8. The MDA values were increasing with TSH values; also the percentage of cases with increased MDA level increased from group I to III. All the hypothyroid groups are at high risk range of AI (> 0.21) with p value < 0.001 making them more prone for atherogenesis and in due course to coronary as well as peripheral vascular risk.

Table-2: BMI with Range in Study Groups and Controls

Groups	TSH (µIU/ml) Mean ± SD	BMI (Kg/m^2) Mean ± SD	t – Value	P – Value
Subclinical	7.40 ± 1.45	26.7 ± 4.16	2.848	0.0065
Group I	7.33 ± 1.18	27.2 ± 4.02	4.122	**0.0001**
Group II	14.48 ± 3.3	28 ± 3.8	8.813	**0.0001**
Group III	36.79 ± 12.8	29 ± 5.5	5.557	**0.0001**
Total Cases (85)	16.81 ±13.61	27.9 ±4.41	4.421	**0.0001**
Controls (41)	2.72 ± 1.12	23.91 ± 1.68		
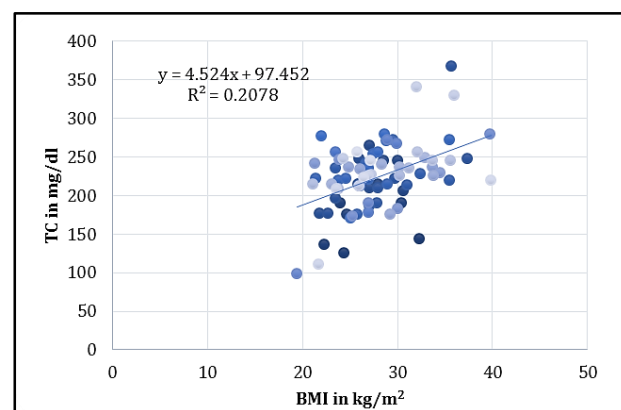
Figure-1: Scatter Diagram of BMI vs. Total Cholesterol in Hypothyroid Subjects

Table-1: Study Parameters in Cases and Controls

Groups	SHT (9)	Group I (29)	Group II (26)	Group III (21)	Total Cases (85)	Controls (41)
TSH (µIU/ml)	7.4 ± 1.4	7.3 ± 1.2	14.4 ± 3.3	36.7± 12.8	**16.8 ± 13.6***	2.7 ±1.1
TC (mg/dl)	206 ± 25.9	209.4 ± 30.6	**224 ± 47.4***	**254 ± 48.6***	**224 ± 43.8***	169.5 ± 25.1
TGL (mg/dl)	125 ± 33.7	122.6 ± 31.8	137.9 ± 37.1	**154.9 ± 37.6***	**136 ± 37***	99.7 ± 24.5
HDL-C (mg/dl)	50.5 ± 7.8	48 ± 5.1	44.9 ± 4.4	44.7 ± 5.7	**46.6 ± 5.6***	53 ± 5.9
LDL-C (mg/dl)	130.2 ± 27	**136.8 ± 29***	**151.4 ± 45.9***	**176.4 ± 47.1***	**150.4 ± 42.3***	97 ± 25.5
TC:HDL-C	4.1 ± 0.6	4.1 ± 0.8	**5 ± 1.1***	**5.8 ± 1.5***	**4.9 ± 1.3***	3.2 ± 0.6
LDL:HDL-C	2.6 ± 0.6	2.6 ± 0.7	**3.4 ± 1.1***	**4.1 ± 1.4***	**3.3 ± 1.1***	1.8 ± 0.5
BMI (kg/m^2)	**26.7 ± 4.1***	**27.2 ± 4.0***	**28 ± 3.8***	**29 ± 5.5***	**27.9 ± 4.4***	23.9 ± 1.6
MDA (µmol/L)	**6.6 ± 2.7***	5.1 ± 1.7	**6.2 ± 1.8***	**7.3 ± 1.3***	**6.1 ± 1.8***	2.9 ± 0.8
AI Risk	0.38 ± 0.12 High	0.40 ± 0.12 High	0.47 ± 0.14 High	0.52 ± 0.15 High	**0.44 ± 0.13***	0.20 ± 0.11 Intermediate

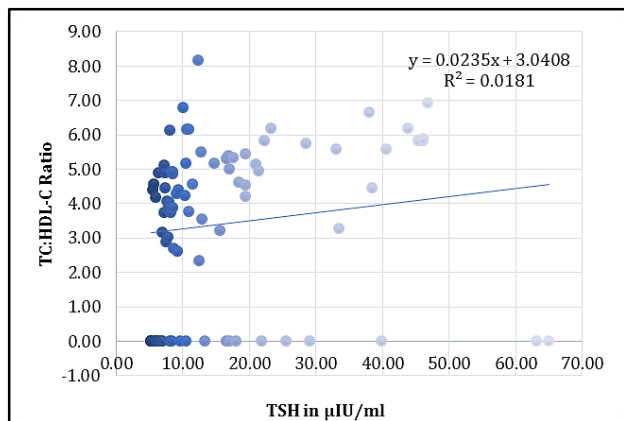SHT: Subclinical hypothyroids; AI: Atherogenic Index; * p value: < 0.001

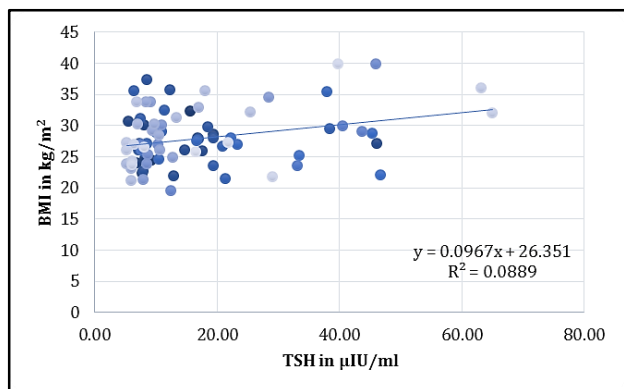**Figure-2: Serum TSH vs. TC: HDL-C Ratio in Total Cases**

On the chart: $y = 0.0235x + 3.0408$, $R^2 = 0.0181$. Y-axis: TC:HDL-C Ratio. X-axis: TSH in µIU/ml.

Figure-3: Serum TSH vs. TC: HDL-C Ratio in Total Cases

On the chart: $y = 0.0967x + 26.351$, $R^2 = 0.0889$. Y-axis: BMI in kg/m². X-axis: TSH in µIU/ml.

Discussion

The relationship between thyroid hormones and lipids has long been studied, having been first described more than 70 years ago. Lipid abnormalities associated with hypothyroidism are at least partially responsible for increased in coronary heart disease. Hypothyroidism not only increases the LDL concentration but also promotes its oxidation. Reason is that T_4 has three specific binding sites on apolipoprotein (apo) B and inhibits LDL oxidation in vitro.

Lipid profile is often used for diagnosing, predicting and treating lipid-related disorders including atherosclerosis. Generally, hyper-lipidaemias are associated risk factors for ischaemic heart disease. Many studies have already proven the accumulated risks of lipids (total cholesterol and triglycerides) and their associated blood transporting lipoproteins (HDL-C, LDL-C, VLDL-C) with the occurrence of atherosclerosis and coronary artery disease. The strong association between the risk of coronary artery diseases (CAD), high levels of LDL-C and low levels of HDL-C has been well established. However the enormous contributions of

triglycerides (TG) to cardiovascular risk have been underestimated. Atherogenic index of plasma (AIP) calculated as log (TG/HDL-C) has been used as a significant predictor of atherosclerosis.[11] It's an early cardiovascular marker and easily available useful measure of response to treatment. Atherogenic index reflects the balance between atherogenic and protective lipoproteins.

The risk categorisation of Atherogenic index is as follows; < 0.11 low risk; 0.11 – 0.21 intermediate risk; > 0.21 high risk.[12] In this study, we have found that all the hypothyroid groups have atherogenic index above 0.21 i.e. high risk level of atherogenic index increasing the chance of coronary artery disease. Since most of the study subjects belong to the middle age population, secondary preventary measures have to be insisted at the earliest to manage the complication including CAD.

Oxidative stress is known for its association with dyslipidaemia. Further increase in BMI and atherogenic index accumulates the risk of CAD. The free radical accumulation in hypothyroidism can be due to atherogenic hyperlipidaemia providing substrate for increased lipid peroxidation, decreased clearance of oxidants due to hypometabolic state and poor defence mechanism against free radicals by antioxidants. Since OS parameters are not routinely estimated in clinical laboratories, biochemical demonstration of increased TSH should be considered as enough indication of increased OS.

Conclusion

To conclude, early detection of hypothyroidism, regular monitoring of lipid profile and body weight control together will help in managing a case of hypothyroidism. Hormonal replacement alone will not be sufficient in treating hypothyroid patients rather keeping a watch on lipid levels, oxidative stress and biochemical markers for cardiac diseases will serve to detect early coronary risks for hypothyroid patients. Oxidative stress parameters estimation should be made a routine investigation for all hypothyroid subjects.

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