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Research Article

Hypothyroidism is associated Dyslipidemia

Evaluation Of Lipid Profile In Thyroid Dysfunction

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Abstract: Thyroid hormones play an important role in the regulation of lipid metabolism. Subclinical hypothyroidism is defined as a slight increase in thyroid-stimulating hormone (TSH) with normal levels of thyroxine (T4). Hypothyroidism could be associated with altered lipid panels. This study aimed at evaluating the association between hypothyroidism and altered lipid profile. Data of 54 patients with subclinical hypothyroidism and 54 healthy individuals were collected from SBMCH laboratory. The participants belong to the age group of 20-50 years. Patients with TSH in the range of 4.2 to 10 mU/L, and T4 in the range 0.8 to 2.8 ng/dL were ruled out as hypothyroid. Control had a normal TSH ranging from 0.5 to 4.2 mU/L. The total serum cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels were examined in both groups and the results were recorded. Participants with hypothyroidism had significantly higher LDL and lower HDL levels than the control group irrespective of age group and gender (P-value <0.001), but no difference in TG and TC levels (P-value <0.05) were observed. The prevalence of dyslipidemia and hypothyroidism was only significant in females (P-value =0.009). There was significant correlation between the prevalence of dyslipidemia and hypothyroidism regardless of gender (P-value =0.04). Hypothyroidism is associated with dyslipidemia, and biochemical screening for dyslipidemia is recommended in all patients with subclinical hypothyroidism.

Keywords:, Subclinical Hypothyroidism, TSH, dyslipidemia, HDL, LDL, TG

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1. INTRODUCTION

Hypothyroidism is defined as a deficiency in thyroid hormone secretion. [1]Many Indian adults suffer from hypothyroidism. This is a common disorder affecting 2 to 15% of the population. The impact of hypothyroidism is greater in women, mainly between the ages of 18-35, than in men.The probability of developing hypothyroidism increases with age.[2-4]Thyroid hormones are synthesized from the amino acid tyrosine. The hormone biosynthesis begins with the active transport of iodide (I^-) into the thyroid gland via the Na^+ /I^- (sodium-iodide) symporter.[5] Thyroglobulin (Tg), a glycoprotein homodimer is necessary for thyroid hormone synthesis. The synthesis of Tg is stimulated by Thyroid Stimulating Hormone (TSH). Though Tg is released into the follicular lumen, a small amount of Tg is released from the follicular cells and is not transported into the colloid. This Tg is not iodinated. In the lacuna, iodide is oxidized to an iodine radical by the thyroperoxidase (TPO) enzyme. TPO catalyzes the mono- and di-iodination of Tg tyrosines to monoiodotyrosine (MIT) and di-iodotyrosine (DIT) respectively. After iodination to MIT and DIT the enzyme catalyzes the coupling reaction for T_3 and T_4. The biologically important thyroid hormones are thyroxine (T_4) and triiodothyronine (T_3). [1]In hypothyroidism the patients are presented with mental dullness, depression, fatigue, hoarseness of voice, irregular menstruation, cold intolerance, weight gain, dry skin, puffy eyes, bradycardia, myopathy and in most severe cases congestive heart failure or coma may develop.[1,6] Based on TSH and FT_4, hypothyroidism is classified as primary hypothyroidism thyroid gland failure (low FT_4 and increased TSH) and central hypothyroidism (low FT_4 and usually a normal or low TSH concentration). Biochemically, overt hypothyroidism is defined as an elevated serum TSH and free T_4 concentration that is below the population reference range whereas Subclinical hypothyroidism (SCH) is a milder form of hypothyroidism when TSH is elevated, for 6 to 12 weeks or longer, in which the free thyroxine level is normal. Subclinical and overt thyroid dysfunction is differentiated on the basis of the measurements of serum free T_4.[6] Laboratory evidence of hypothyroidism encompasses hyponatremia, a normocytic or macrocytic anemia, elevated creatine kinase due to myopathy, hypercholesterolemia/hypertriglyceridemia caused by decreased lipoprotein-lipase activity and decreased low density lipoprotein (LDL) receptor expression.[7,1] Hyperlipidemia is one of the components of metabolic syndrome. [2,8] Thyroid hormones have an important regulatory effect on glucose and lipid metabolism, and blood pressure control. The changes in the synthesis, metabolism, and mobilization of fat might be the cause of increased total cholesterol and low-density lipoprotein (LDL) in hypothyroidism. [9] Thyroid hormone increases the activity of 3-hydroxy-3-methyl-glutaryl- coenzyme A (HMG-COA) in the liver and, thus, reduce cholesterol. Besides, thyroid hormones increase LDL receptors on fibroblasts, liver, and other tissue, thus increasing the absorption of cholesterol from the intestine. These hormones also affect the excretion of cholesterol from the intestine by bile acids by altering levels of high-density lipoprotein (HDL) cholesterol and hepatic lipase activity. [9] While the relationship between subclinical hypothyroidism and an increased risk of cardiovascular disease caused by atherosclerosis is shown in some studies, it is inconsistent in the other studies. [9,10] Dyslipidemia is a well-known risk factor for heart disease. The risk of coronary heart disease and atherosclerotic vascular disease increases as plasma cholesterol concentrations rise, particularly as the total cholesterol to HDL cholesterol ratio rises. There is also a weak positive correlation between plasma triglyceride concentrations and coronary heart disease. Early detection and management of dyslipidemic cardiovascular diseases can significantly reduce mortality and morbidity. Several studies have shown that lowering total and LDL cholesterol lowers the risk of cardiovascular events. Thyroid hormones has its known effect on cardiovascular pathways affecting systolic and diastolic functions.[11]Patients with underlying subclinical hypothyroidism might be more prone to cardiovascular diseases. Though SCH is a milder form, if untreated Subclinical hypothyroid it might increase the risk of developing heart disease. The study also found that patients with untreated hypothyroidism had 3-fold increased risk of developing cardiovascular complications whereas treated hypothyroid patients had with low and normal TSH had 2.1 and 1.8 fold increased risk respectively. [12] Even though the effects of subclinical hypothyroidism on serum lipids are unclear, it is anticipated that the changes that occur in clinical hypothyroidism, exist in subclinical cases as well, which will be much less severe. This study is done to find out the association of hypothyroidism and lipid profile in our study participants. Earlier detection of abnormal lipid parameters will help in preventing them from cardiovascular complications. The current study aimed at correlating the lipid profile in patients with subclinical hypothyroidism

2. MATERIALS AND METHODS

This case control study was conducted in the Department of Biochemistry, Sree Balaji Medical College and Hospital, Chrompet, Chennai during the period of July 2019 – September 2019. The ground work for the study was started after getting clearance from the research committee and the Institutional human ethical committee (reference number for approval: CSP/19/SEP/80/348). The study included Cases- 54 patients with subclinical hypothyroidism (10mU/L>TSH>4.2 mU/L), normal T4 (10.3 – 34.7 pmol/L) and T3 (3.2 - 6.8pmol/L), controls - age, gender and body mass index (BMI) matched 54 healthy participants with normal levels of thyroid function test. The age range of the cases and controls were 20 to 50 years. The following information was collected: age, gender, height, weight, BMI, general history, family history, medications, and blood pressure. A routine clinical examination was carried out. Before taking the blood sample, the study was explained to the participants and informed consent was obtained from them. After an overnight fast of 10-12 hours, venous blood was drawn from all subjects via venepuncture under aseptic conditions. Serum was separated from that to be analysed for fasting thyroid function test and lipid profile. Estimation of Free T3, free T4 and TSH was done by direct competitive chemiluminescence immunoassay (CLIA) in Siemens ADVIA CENTAUR CP Immunoassay (Siemens Healthcare Diagnostics. Inc). Lipid profile parameters total cholesterol was estimated by CHOD-POD method, triglycerides by GPO-POD method, HDL and LDL by direct method in Mindray BS-390. The serum concentrations of thyroid hormones were measured by Siemens ADVIA CENTAUR CP Immunoassay (Siemens Healthcare Diagnostics. Inc).

2.1 Inclusion Criteria

CASE GROUP: Patients with Subclinical Hypothyoidism (TSH levels between 4.2 and 10 mU/L, normal FT3 and FT4)

CONTOL GROUP: Healthy euthyroid participants (TSH - 0.5 to 4.2 mU/L; T3 and T4 within normal range) without major illness and medications The subjects were randomly selected from the patients visiting OPD of Sree Balaji Medical College and Hospital.

2.2 *Exclusion Criteria*

Participants with family history of hyperlipidemia, obesity, diabetes, kidney disease, pregnant women, thyroxine treatment, and steroid drug use were excluded from this study. These details were collected from the patients while taking history in OP department.

3. STATISTICAL ANALYSIS

Cases and controls had their means and standard deviations (SD) calculated. Statistical Package for the Social Sciences (SPSS) version 19 software was used to perform the statistical analysis. Pearson's correlation was done for lipid profile and TSH in subclinical hypothyroidism. Statistical analysis was done using SPSS 19 software. The outcome variables namely, FT3, FT4, TSH, total cholesterol, triglyceride, LDL and were compared between the cases and controls using Chi-student *t* test and one-sample *t* test. A two sided p-value less than 0.05 was considered to be statistically significant.

4. RESULTS

In the current study, the age range of all the 54 cases with subclinical hypothyroidism, and the 54 cases as the control group was from 20 to 50 years. Among them, females and males were 50% in both groups. In females, the TC levels of cases were higher than those of the control group in all age groups. There was significant positive correlation between hypothyroidism and decreased level of HDL in females regardless of age groups. There was no significant correlation between hypothyroidism and increased level of LDL, Triglycerides and total cholesterol in all age groups and both genders. Overall, there was significant correlation between hypothyroidism and decreased HDL level (table 4). Regardless of age groups and gender, there were no significant correlations between hypothyroidism and increased levels of LDL, TG and TC (P-value >0.05). The prevalence of dyslipidemia and hypothyroidism was significant in females (P-value <0.005), than males. In general, dyslipidemia is seen in both males and females with hypothyroidism (p-value <0.005), but most commonly in females (Table 1a,b).

Table 1a: Characteristics of lipid profile in the case group

Age Groups (Years)	20-29		30-39		40-50	
Gender	Male (Mean±SD)	Female (Mean±SD)	Male (Mean±SD)	Female (Mean±SD)	Male (Mean±SD)	Female (Mean±SD)
HDL	29.2 ± 3.9	28.2 ± 2.5	29.7 ± 2.9	30 ± 3.9	30.4 ± 4.0	29.8 ± 2.9
LDL	142.8 ± 8.9	143.6 ± 12.7	145.3 ±9.0	151.8 ± 14.5	147.5 ±15	166.0 ± 26.5
TG	161.9 ± 6.5	161.8 ± 10.5	167.1 ± 8.6	167.5 ± 10.5	164.5 ± 6.2	159.3 ± 9.1
TC	222.5 ± 9.8	223.1 ± 11.2	233.4 ±10.9	229.4 ± 13.0	223.6 ± 12.3	217.3 ± 12.9

Table 1b: Characteristics of lipid profile in the control group

Age Groups (Years)	20-29		30-39		40-50	
Gender	Male (Mean±SD)	Female (Mean±SD)	Male (Mean±SD)	Female (Mean±SD)	Male (Mean±SD)	Female (Mean±SD)
HDL	54.8 ± 4.9	49.4 ±4.2	50.7 ± 5.1	55.7 ± 4.8	54.1 ± 3.8	50.8 ± 6.0
LDL	73.2 ± 7.1	77.5 ± 8.7	74.7 ± 12.5	66.30 ± 5.9	73.4 ± 8.5	78.4 ± 9.1
TG	107 ±25.4	103.3 ± 22.0	114.11 ± 20.0	114.33 ± 17.7	106.2 ± 8.6	106.6 ± 10.1
TC	141.6 ± 23.7	151.2 ± 23.7	158.1 ± 28.6	152.6 ± 25.6	158.1 ± 29.0	148.3 ± 28.4

SD- standard deviation.

From the tables (1a & 1b), LDL, triglycerides and total cholesterol levels were higher in the case group than in the control group, in both males and females, HDL levels were higher in the control group than in the cases group.

Table 2: Comparison of lipid profile between cases and controls

LIPID PROFILE	CASES (Mean ± SD)	CONTROL (Mean ± SD)	p-Value*
HDL	29.6 ± 3.5	52.6 ± 5.4	0.0001
LDL	149.5 ± 17.7	73.9 ± 9.8	0.0001
TRIGLYCERIDE	163.7 ± 9.3	108.6 ± 19.0	0.0001
TOTAL CHOLESTEROL	224.9 ± 13.0	151.6 ± 27.5	0.0001

Cases have low HDL levels and increased LDL, triglycerides and total cholesterol levels with significant p-value <0.05

Table 3 Comparison of thyroid function tests between cases and controls

THYROID FUNCTION TEST	CASES (Mean ± SD)	CONTROL (Mean ± SD)	p-Value*
TSH	6.8 ± 1.6	1.8 ± 0.8	0.0001
FT3	4.5 ± 0.4	4.4 ± 0.4	0.447
FT4	13.0 ± 2.6	13.2 ± 3.1	0.76

TSH is elevated in Case group when compared with Controls whereas the T3 and T4 levels were within normal range in both the groups.

Table 4: Pearsons Correlation between TSH and lipid profile in Hypothyroid patients

TSH	Lipid Profile	r-value	p-value
	Total cholesterol	-0.07	0.61
	LDL	-0.15	0.27
	HDL	0.07	0.61
	TG	-0.05	0.71

5. DISCUSSION

Hypothyroidism is a common endocrine disorder worldwide.[5] Thyroid hormones are key regulators of human metabolism. It has a great impact on glucose and lipid metabolism. Interactions between thyroid hormone receptors (THRs) and liver X receptors (LXRs) have been reported on lipid metabolism. Both receptors belong to the nuclear receptor family. [8] Hyperlipidemia is one of the components which are associated with metabolic syndrome. Reviews state that T_3 acts on thyroid hormone receptor β1 (THRβ1) isoform and increases reverse cholesterol transport and hepatic lipase activities. This leads to the reduction of TC and TG levels.[8] The role of THRβ1 selective agonists, besides enhancing lipid profiles, also accelerates energy expenditure reducing the risk of cardiovascular events. [8] Subclinical Hypothyroidism is the clinical status of elevated serum TSH levels with normal levels of serum T3 and T4, and is a more common disorder. Patients with subclinical hypothyroidism have no symptoms. Hypothyroidism is associated with significant increase in circulating concentrations of LDL, which can lead to coronary artery disease. [13] In some studies, there is a linear increase in TC, LDL, and TG, and a linear decrease in HDL levels with increased TSH, but within normal range. [6] Lipid levels in people with subclinical hypothyroidism have been studied in observational studies, but the results have been mixed. In our study the LDL levels were found to be higher in cases than the control group. Vierhapper et al. found no significant differences in serum total cholesterol, LDL cholesterol, HDL cholesterol, or triglyceride levels between subclinically hypothyroid patients and the euthyroid control group, despite the fact that total cholesterol and LDL cholesterol were clearly elevated in overtly hypothyroid patients. [14] Kanaya et al. found that total cholesterol was considerably higher in subclinical hypothyroidism in a population-based study with black and white subjects. [15] Similar findings was observed by the most comprehensive cross-sectional survey conducted by Canaris et al. Subclinical Hypothyroidism has been linked to an increase in cardiovascular events. [16] Two studies recently found a link between subclinical hypothyroidism and increased carotid artery intima-media thickness, which could be a sign of early atherosclerosis. [17,18] These findings are intriguing, but they have yet to be replicated. The relationship between lipid disorders, and hypothyroidism and thyroid hormone levels were also evaluated in patients in different studies, and different results were achieved. [11,19] In comparison to previous studies, the current study found a significant correlation ($p<0.005$) between elevated LDL and hypothyroidism, particularly in females in the case group. In the case group, there is also significant correlation with lower HDL and hypothyroidism among females. There was no significant correlation between lower HDL and Higher LDL in males. Though the levels of HDL and LDL were lower and higher respectively when compared to the control group. In our study, the HDL levels were lower in cases than the control group. TC levels in patients in the age group of 30-40 years were significantly higher than the control group. Another study found significant correlation between hypothyroidism, and decreased HDL level and increased TC, LDL level irrespective of the age groups and gender,[20-22] but no significant correlation between hypothyroidism, and increased levels of TG and TC was observed in this study. A rise in cardiovascular events has also been linked to sub clinical hypothyroidism according to two recent studies, subclinical hypothyroidism has been linked to increased carotid artery intima-media thickness, which may be a sign of early atherosclerosis.[17,18] Subclinical Hypothyroidism can have an impact on a variety of tissues. Subclinical hypothyroidism impairs flow-mediated endothelium-dependent vasodilation. This flaw is thought to be an early warning sign of atherosclerosis. The vascular endothelium is important in the regulation of vasomotor tone, which is mediated by a variety of substances, primarily endothelin and nitric oxide (NO). Hypercholesterolemia can cause oxidative stress, decreased NO bioactivity, and unopposed paradoxical vasoconstriction of epicardial conductance vessels. [23,24] The results might be associated with the increased risk of coronary artery disease in patients with hypothyroidism, because higher levels of LDL and lower levels of HDL might worsen the existing atherosclerosis. These factors could increase the risk of cardiovascular accidents in patients with hypothyroidism, and the thyroid replacement therapy could have beneficial effects on CVD risk in such patients. Several studies showed increased levels of TC, LDL and decreased HDL in patients with hypothyroidism when compared with the control group. [19-21] This study showed significant correlation between the females with subclinical hypothyroidism and healthy controls.

6. CONCLUSION

Hyperlipidemia and hypothyroidism are both common in the

general population, they may co-exist.[25] Subclinical hypothyroidism is estimated to affect between 1.4 and 11.2 percent of patients with dyslipidemias. [26] A finding of one metanalysis showed subclinical hypothyroidism is two to three times more likely in patients with high total cholesterol levels than in people with normal fasting serum lipids. [27] According to studies, biochemical screening for thyroid dysfunction is recommended for all patients with dyslipidemia; and underlying hypothyroidism should be treated in such patients. All individuals with hypercholesterolemia should be evaluated for thyroid dysfunction, which could be a sign of early atherosclerosis. Studies should be undertaken to determine whether treatment of patients with SH might influence cardiac mortality. The products of LDL oxidation are believed to play a role in atherosclerosis. Even though randomised clinical trials are required for conclusive proof of casuality, this present study shows the importance of thorough monitoring of substitution therapy in hypothyroid individuals to prevent cardiovascular complications Hence, studies should be done to determine the role of oxidatively modified lipoproteins and their oxysterol-enriched subfraction in the initiation and/or progression of atherosclerosis in overt and subclinical hypothyroidism.

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8. ETHICAL STANDARDS

The study involved human participants following the ethical standards of the tertiary health care institution where the study was conducted

9. AUTHORS CONTRIBUTION STATEMENT

Dr.B.Shanthi and Dr. Sumathi contributed to the study conception, design, Ms. Mahalakshmi contributed in the statistical analysis of the findings, Mr.E.Vasudevan contributed in data collection and and Ms.V.P.Nivedhini drafting of the manuscript.

10. LIMITATIONS

Further studies with larger sample sizes are needed to find the effects of hypothyroidism on cardiovascular diseases, such as coronary artery disease and hypertension. It is recommended to conduct a prospective study with a larger sample size to solve the differences that might occur due to cultural ethnicity, physical activity, races. Further the effect of treating patients with levothyroxine has not been elucidated in the study.

11. CONFLICT OF INTEREST

Conflict of interest declared None

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