

A Study on Lipid Abnormalities in Hyperthyroidism and their Response to Antithyroid Drugs

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ABSTRACT

Introduction: Alterations in various lipid parameters have been reported in patients with thyroid dysfunction but the evidence is controversial. The magnitude of changes in plasma Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) levels after restoration of the euthyroid state varies from patient to patient and depends on multiple factors including the severity and duration of the thyroid dysfunction and the presence of any pre-treatment primary lipid disorder apart from diet and body weight. In addition, Asians have dyslipidemia at a lower Body Mass Index (BMI) than Western population and the effect of thyroid disorders and response to treatment may also be different.

Aim: To explore the relationships between hyperthyroidism and the lipid profile of patients and the response to antithyroid drugs.

Materials and Methods: A case-control study was conducted over one year, in 57 newly diagnosed patients with hyperthyroidism and 57 control subjects. All patients and controls had thyroid hormone and Thyroid Stimulating Hormone (TSH) levels and fasting lipid profile; the patients had a repeat fasting lipid profile after restoration of euthyroid state with

antithyroid drug. The data was analysed using IBM-Statistical Package for the Social Sciences (SPSS) version 21.0.

Results: The mean age of patients (34.7 ± 10.93 years) and controls (32.3 ± 10.75 years) were comparable ($p=0.239$). Hyperthyroid patients presented with significantly lower serum levels of Total Cholesterol (TC), (125 ± 29.7 mg/dL), LDL, (74.7 ± 19.43 mg/dL), HDL, (37.8 ± 7.87 mg/dL), Triglycerides (TG), (123.2 ± 64.5 mg/dL) and Very Low Density Lipoprotein Cholesterol (VLDL-C), (24.6 ± 12.91 mg/dL) than the control subjects- 174.6 ± 34.68 mg/dL, 109.3 ± 23.4 mg/dL, 41.35 ± 7.56 mg/dL, 157.2 ± 86.21 mg/dL and 31.4 ± 17.28 mg/dL respectively ($p < 0.05$). All the patients were treated with carbimazole; with a mean starting dose of 33.2 ± 6.59 mg/day. Post-treatment, after achieving euthyroidism, the mean levels of TC, LDL, HDL, TG, VLDL of the patients were significantly higher than pre-treatment value ($p < 0.05$). Significant negative correlation was seen between serum thyroxine and LDL ($p < 0.04$) and TSH and HDL ($p < 0.001$), once patients achieved control of thyrotoxicosis.

Conclusion: There was significant decrease in lipid parameters in hyperthyroid state which showed improvement after achieving control of thyrotoxicosis with carbimazole.

Keywords: Carbimazole, Graves' disease, Lipid profile

INTRODUCTION

The thyroid hormones- thyroxine (T4) and triiodothyronine (T3) play a major role in both lipid and protein metabolism, as they affect lipid synthesis, mobilisation, and catabolism [1]. Plasma LDL and HDL levels decrease in hyperthyroidism [2]. Changes in LDL are mainly attributable to altered clearance of LDL from plasma by changes in the number of LDL receptors on liver cell surfaces. In addition, thyroid hormones activate these receptors and the promoter of receptor gene contains a Thyroid hormone Responsive Element (TRE) which up-regulates the gene expression of the LDL receptor by T3 [3]. HDL metabolism is complex and changes in plasma levels are due, in part, to remodeling of HDL particles by hepatic lipase and Cholesterol Ester Transfer Protein (CETP). Activity of CETP increases in hyperthyroidism correlating with plasma HDL. Adipose tissue lipolysis is increased in thyrotoxicosis and the turnover rates of Free Fatty Acids (FFA), glycerol, and glucose are enhanced. The increase in lipolysis in hyperthyroidism might be at least partly dependent upon a catecholamine β -receptor-mediated mechanism. The efficiency of TG clearance from plasma has been reported to be either normal or increased [4]. Serum cholesterol, LDL and TG levels are lowest in hyperthyroid patients than in euthyroid patients and are highest in hypothyroid patients [5].

Whether the low concentration of LDL in hyperthyroidism gives any protection to coronary artery disease is not known. In contrast, hyperthyroidism has been associated with myocardial infarction with normal coronaries and recurrent pulmonary embolism [6,7].

This hypercoagulability is likely due to an increase in factor X activity, observed in hyperthyroidism patients [8].

The magnitude of changes in plasma LDL and HDL levels after restoration of the euthyroid state varies from patient to patient and depends on multiple factors including the severity and duration of the thyroid dysfunction and the presence of any pre-treatment primary lipid disorder [9]. Diet, body weight, and smoking habits can also modify absolute LDL levels [10]. In addition, Asians have higher percentage of body fat at the same BMI as compared to Western population and the effect of thyroid disorders and response to treatment may also be different [11]. There is very scarce of data regarding lipid abnormalities in hyperthyroidism from Asia.

So, this study was conducted to evaluate lipid profile in patients with hyperthyroidism before and after restoration of euthyroidism (defined as return of serum T3 and T4 levels into the normal range) and to compare lipid parameters of hyperthyroid patients with age and sex-matched healthy controls.

MATERIALS AND METHODS

This was a case-control observational study conducted by the Department of Endocrinology, SKIMS Srinagar, a tertiary care Institute, Union territory of Jammu and Kashmir, India. This study involved 57 patients with a diagnosis of hyperthyroidism. The study was conducted from January 2018 to December 2018. The study protocol was reviewed and cleared by the Institutional Ethical Committee (IEC) (Ref no. SIMS 1 131/IEC-SKIMS/2018-412), and an

informed consent was obtained from patients/relatives for utilisation of data for research purposes.

The sample size was calculated by Daniel's formula, $n = Z^2 P(1-P) / d^2$ where, n =sample size, Z =Z static for a level of confidence, P =expected prevalence or proportion, and d =precision. Presuming a prevalence of lipid abnormalities of 50% in hyperthyroidism and relative error of 15%, a total of 43 patients needed to be studied, for a 95% confidence level. To account for loss of cases in the follow-up, 20% more cases were included, approximately 50 cases.

Inclusion criteria: Consecutive treatment-naïve adult patients with hyperthyroidism, with evidence of increased uptake on radionuclide scan (technetium-99 or radioactive iodine scan) referred to the out-patient clinic, were studied.

Exclusion criteria: Patients treated with radioactive iodine or surgery, pregnant women, documented thyroiditis, renal, hepatic or pancreatic insufficiency or any other disease like diabetes mellitus, cushing's syndrome (known to affect the lipid profile), patients on medication like statins, steroids or estrogen known to affect the lipid profile.

Equal number of apparently healthy age and sex-matched adults with normal Thyroid Function Test (TFT) and no underlying chronic disease were recruited as controls. Among the controls those with Fasting Blood Glucose (FBG) in the impaired range (100-125 mg/dL) were included whereas those in diabetes range (≥ 126 mg/dL) were excluded. The controls included attendants of accompanying patients and medical staff who agreed to participate in the study. All the participants were nonvegetarian and were taking iodised salt.

Neither patient nor control was on statin therapy. The clinical assessment for patients and controls included detailed history, clinical examination and anthropometric assessment including height, weight, BMI, Waist Circumference (WC), and Waist-to-Hip Ratio (WHR). A baseline fasting blood sample for blood counts, serum chemistry including blood glucose, lipid profile (total cholesterol, LDL, HDL, VLDL, TGs), TFT (total T3, total T4, TSH) was obtained from all the participants. All patients were treated with antithyroid drug-carbimazole. After documentation of control for thyrotoxicosis (serum T3 and T4 in normal range) repeat lipid profile estimation was done in all the patients. Twelve patients (21%) presented between 8-12 weeks with clinical and biochemical evidence of euthyroidism, while 15 (26.3%), 13 (22.8%) and 17 (29.8%) patients reported between 12-16 weeks, 16-20 weeks and >20 weeks, respectively. Pre-treatment data of hyperthyroid patients were compared with those of healthy controls as well as their own post-treatment data using appropriate statistical analysis methods.

Laboratory evaluation: A 10ml venous blood sample was drawn for measurement of biochemical parameters and TFT in vacutainer. The blood samples were allowed to settle for 15 minutes at room temperature before they were centrifuged at 1100g for 10 minutes and the serum samples were transported in cold boxes to the lab/storage site (SKIMS). Lipid profile estimation was performed by automated chemical analyser whereas TFT was performed using DXI 600, Beckman Coulter Chemiluminescence Immunoassay (CLIA), and random access analyser following manufacturer's protocol. LDL was measured by a direct method. This LDL-Cholesterol test involved two distinct phases; in phase one LDL cholesterol was separated from non-LDL cholesterol, whereas in second phase cholesterol from LDL lipoproteins reacted with cholesterol esterase, cholesterol oxidase and a chromogen to yield a blue colour complex which was measured biochromatically at 540/660 nm. The resulting increase in absorbance is directly proportional to the LDL-C concentration in the sample. VLDL was calculated by Freidewald's formula (i.e., $VLDL = TG/5$) [12].

STATISTICAL ANALYSIS

The data was entered in Microsoft excel and analysed using IBM-SPSS version 21.0 (SPSS Inc, Chicago, IL, USA). The results were

expressed as percentages or mean \pm SD, as specified. Pearson's Chi-square method was used for comparing proportions and percentages whereas student's t-test was used for comparison of continuous variables. A two-tailed p-value was used for calculating statistical significance; a value of <0.05 was taken as significant.

RESULTS

A total of 57 patients were included in the study and 57 controls. The mean age of patients was 34.7 \pm 10.93 years (18 to 65 years), and that of controls was 32.3 \pm 10.75 years ($p=0.239$). There was a female preponderance (70.2%). Smoking history was present in 31 patients. Heat intolerance was the most common presenting complaint ($n=57$; 100%), followed by sweating ($n=55$; 96.4%) and palpitations ($n=55$; 96.4%) in patients with hyperthyroidism.

The mean duration of symptoms was 9.8 \pm 13.9 months. Goiter was present in 56 (98.2%) study patients; grade I goiter in 34 and grade II in 22 patients. All of the patients, except one had Graves' disease. The anthropometry of both cases and controls is summarised in [Table/Fig-1].

Anthropometry	Cases mean \pm SD	Controls mean \pm SD	p-value
Weight (Kg)	57.1 \pm 8.45	61.4 \pm 6.01	<0.001
Height (Metre)	1.60 \pm 0.05	1.62 \pm 0.07	0.06
Waist Circumference (M) [†] cm	83.05 \pm 6.39	86.76 \pm 3.40	0.04
WHR (M) [‡]	0.97 \pm 0.02	0.98 \pm 0.02	0.155
Waist Circumference (F) [‡] cm	81.62 \pm 8.55	83.52 \pm 4.15	0.210
WHR (F) [‡]	0.95 \pm 0.04	0.96 \pm 0.04	0.210
BMI (kg/m ²)	22.1 \pm 2.84	23.2 \pm 1.73	0.007

[Table/Fig-1]: Anthropometric characteristics of study subjects.

[†]M: Male; [‡]F: Female; Student's t-test was used for statistical analysis

[Table/Fig-2] shows the biochemical profile of patients and controls. Patients had significantly lower level of all parameters of lipid profile as compared to controls. Twenty nine (51%) patients had normal FBG, 27 (47.4%) Impaired Fasting Glucose (IFG) and one had DM before treatment [Table/Fig-3]; whereas after restoration of euthyroidism, 39 (68.4%) had normal FBG and 18 (31.6%) had IFG.

Biochemical parameter (Normal range)	Cases mean \pm SD	Controls mean \pm SD	p-value
Blood Glucose (mg/dL) (<100)	104.4 \pm 11.14 mg/dL	88.2 \pm 11.37 mg/dL	<0.001
T4 (μ g/dL) (4-13)	19.68 \pm 4.006	7.761.769	<0.001
T3 (ng/mL) (0.7-2.5)	3.14 \pm 1.307	1.15 \pm 0.303	<0.001
TSH (IU/mL) (0.5-6.5)	0.034 \pm 0.030	3.24 \pm 1.322	<0.001
TC (mg/dL) (5-200)	125.8 \pm 29.7	174.6 \pm 34.68	<0.001
LDL (mg/dL) (100-130)	74.7 \pm 19.43	109.3 \pm 23.44	<0.001
HDL (mg/dL) (30-75)	37.8 \pm 7.87	41.35 \pm 7.56	0.016
TG (mg/dL) (50-200)	123.2 \pm 64.5	157.2 \pm 86.21	0.019
VLDL (mg/dL) (5-30)	24.6 \pm 12.91	31.4 \pm 17.28	0.020

[Table/Fig-2]: Blood glucose, lipid and thyroid parameters in hyperthyroid patients and controls.

T4: thyroxine; T3: Triiodothyronine; TSH: Thyroid stimulating hormone; TC: Total cholesterol; LDL: Low density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; VLDL: Very low density Lipoprotein; Student's t test was used for statistical analysis

Blood glucose fasting	Cases	Controls	p-value
Normal (60-99 mg/dL)	29 (50.9%)	39 (68.4%)	<0.05
IFG* (100-125 mg/dL)	27 (47.4%)	18 (31.6%)	
Diabetes mellitus (≥ 126 mg/dL)	1 (1.85)	0	

[Table/Fig-3]: Glycaemia in cases and controls based on Fasting Blood Glucose (FBG) levels.

*IFG: Impaired fasting glucose; Chi-square test was used for statistical analysis

All the study patients were put on carbimazole at a mean initial dose of 33.2±6.59 mg/day. Twelve patients (21%) presented between 8-12 weeks with clinical and biochemical evidence of euthyroidism, while 15 (26.3%), 13 (22.8%) and 17 (29.8%) patients reported between 12-16 weeks, 16-20 weeks and >20 weeks respectively.

[Table/Fig-4] shows anthropometry and biochemistry of patients before and after achieving euthyroidism. All the lipid parameters increased significantly, post-treatment. By Pearson's correlation, significant negative correlation was documented between T4 levels and LDL ($p<0.04$) and TSH and HDL ($p<0.001$), once patients achieved control of thyrotoxicosis. Correlation between BMI and all the lipid parameters (TC, LDL, HDL, TG and VLDL) revealed that statistical significance was achieved only between post treatment BMI and TG which was positively correlated ($r=0.310$, $p=0.01$) [Table/Fig-5].

Biochemical parameter	Before treatment mean±SD	After treatment mean±SD	p-value
Weight (kg)	57.10±8.5	60.01±8.4	0.03
BMI (kg/m ²)	22.1±2.84	23.3±2.83	0.026
Blood glucose (mg/dL)	104.4±11.14	92.5±6.71	<0.001
T4 (µg/dL)	19.68±4.006	9.06±2.610	<0.001
T3 (ng/dL)	3.14± 1.307	1.34±0.385	<0.001
TSH (IU/mL)	0.034±0.030	1.391±5.331	0.019
Total cholesterol (mg/dL)	125.8±29.7	170.8±28.64	<0.001
LDL (mg/dL)	74.7±19.43	107.5±19.10	<0.001
HDL (mg/dL)	37.8±7.87	41.8±4.97	<0.001
TG (mg/dL)	125.8±29.7	170.8±28.64	<0.001
VLDL (mg/dL)	24.6±12.91	29.4±8.87	0.004

[Table/Fig-4]: Anthropometry, blood glucose, lipid and thyroid parameters in hyperthyroid patients before and after treatment with carbimazole.

BMI: Body mass index; T4: Thyroxine; T3: Triiodothyronine; TSH: Thyroid stimulating hormone; LDL: Low density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; VLDL: Very low density Lipoprotein; Student's t-test was used for statistical analysis

		TC	HDL	TGs	LDL	VLDL
T3	r-value	-0.193	-0.003	-0.195	-0.207	-0.162
	p-value	0.15	0.984	0.146	0.122	0.228
T4	r-value	-0.241	0.018	-0.082	-0.270	-0.086
	p-value	0.071	0.893	0.546	0.042	0.525
TSH	r-value	0.065	0.443	0.135	0.154	0.14
	p-value	0.63	0.001	0.317	0.252	0.301
BMI	r-value	0.086	0.099	0.310	0.050	0.176
	p-value	0.952	0.463	0.01	0.711	0.190

[Table/Fig-5]: Correlation of thyroid profile with various lipid parameters and BMI after treatment.

BMI: Body mass index; T4: Thyroxine; T3: Triiodothyronine; TSH: Thyroid stimulating hormone; LDL: Low density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; VLDL: Very low density Lipoprotein; r-value: Pearson correlation

DISCUSSION

Thyroid hormones regulate a wide array of metabolic activities. Diseases of thyroid gland are among the most abundant endocrine disorders in the world second only to Diabetes Mellitus (DM) [13]. The mean body weight in the study patients was significantly lower than controls similar to that reported by Dutta P et al., [14]. BMI was significantly lower as compared to the control group. Similar results have been observed in previous studies [15,16]. Mean FBG levels in the patients was significant higher than controls. Total 47.4% had IFG whereas only 31.6% controls had Impaired Fasting Glucose (IFG). High occurrence of IFG in controls can be explained by the fact, that the prevalence of abnormal glucose tolerance in present study population has been documented to be in 14.23% [17]. Increased incidence of glucose intolerance in hyperthyroid patients is also reported by other studies [15,18]. However, Oral Glucose Tolerance Test (OGTT) in present study patients was not

performed. Insulin resistance has correlation with thyroid function. TSH was positively associated with fasting and post-prandial insulin concentration and negatively with insulin sensitivity [19].

Present study revealed that there was significant decrease in various components of lipid profile i.e., TC, HDL, LDL, VLDL and TG levels when compared with the age and sex-matched controls. Jabuk SKA et al., also reported statistically significant decrease in all the components of lipid profile (TC, LDL, HDL, VLDL) in hyperthyroid patients compared to control group ($p<0.05$) [20]. An Indian study also observed significant decrease in TG, HDL, LDL, VLDL and TC in patients with hyperthyroidism compared with control group [21]. However, some studies showed that there is no significant change in lipid parameters in hyperthyroidism while some other studies revealed decrease in individual components like TG or LDL only without any significant change in other parameters [22-24]. The serum cholesterol lowering effect of thyroid hormones has been attributed to an enhanced degradation of cholesterol to bile acids associated with relatively less stimulated cholesterol synthesis [25].

Control of thyrotoxicosis has been associated with improvement in lipid profile in a number of studies [11,19]. Kung AWC et al., observed that there was significant increase in TC, LDL and apo B after achieving euthyroidism; TG showed small but significant increase whereas HDL remained persistently on lower side [9]. Diekman MJ et al., reported increase in all lipid parameters post-treatment [16]. The study revealed significant increase in TG compared to another study which observed mixed results (unchanged, decreased or increased) and thus may require further studies in future to confirm [4].

A positive correlation was established between BMI and serum TG levels post-treatment in the study, suggesting increase in TG levels post-treatment were also contributed to by increasing BMI along with decreasing thyroid hormones. Post-treatment, negative correlation was documented between T4 levels and LDL ($p<0.04$) and between TSH and HDL ($p<0.001$). Kung AW et al., reported that serum apo(a), TC, LDL-C, and apo B were negatively correlated with serum T4, free thyroxine index, and T3 and positively correlated with thyrotropin during the transitional period from hyperthyroidism to euthyroidism [9]. The clinical effect of low lipid levels in hyperthyroidism is not known, whether it gives any protection to vascular disease like coronary artery disease, as no study has so far been done in this field. In contrast, hyperthyroidism is known to be associated with thyrocardiac disease. In addition there are multiple case reports showing association of hyperthyroidism with myocardial infarction (some with normal coronaries) as well as recurrent pulmonary embolism [6-8].

Limitation(s)

Limitations of the study include lack of detailed dietary history, short duration of study, exclusion of Apo A and Apo B from lipid parameters and lack of uniformity in the follow-up sampling. Future studies in this regard should have inclusion of non-invasive methods to access the effect of dyslipidemia on vascular atherosclerosis (like carotid intimal medial thickness) in hyperthyroid patients and monitor any change in this component after increase in the lipid parameters at time of euthyroidism, on long term follow-up.

CONCLUSION(S)

The study revealed a significant decrease in all the lipid parameters in hyperthyroid state which showed increase after achieving control of thyrotoxicosis with carbimazole. In addition there was a significant decrease in FBG levels after restoration of euthyroidism. So, the exact value of baseline lipid parameters in patients with thyrotoxicosis should only be considered once patient is euthyroid.

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