International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jms.htm
2015 Vol. 5 (1) January-April, pp. 75-85/Shashi and Sharma
Research Article

ALTERATIONS IN LIPID METABOLISM IN PATIENTS OF THYROID HYPERFUNCTION

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ABSTRACT
The thyroid disorders are found to be prevalent in Himalayan and sub - Himalayan regions and the studies focusing on the association between thyroid function markers and lipid metabolism are sparse. The present study was aimed to study the impact of thyroid hyperfunction on lipoprotein metabolism and hepatic lipase activity. Two ninety subjects (255 females, 35 males) aged 25- 55 years with a clinical diagnosis of thyroid hyperfunction were included in the study. The serum TSH, T3, T4, total cholesterol (TC), HDL and triglycerides (TG) levels were measured using standardized assays. The distribution of subclinical and overt hyperthyroidism was 38% and 62.06%, respectively. Levels of HDL and LDL were significantly ($P<0.05$) low and TC, VLDL and TG were not altered in patients with subclinical hyperthyrodism compared with euthyroid subjects. Serum lipids were significantly ($p<0.001$) less in overt hyperthyroid patients compared to euthyroid controls. The activity of hepatic lipase ($P<0.001$) was elevated in overt cases. Pearson's bivariate correlation analysis revealed that there was a positive relationship between serum TSH and TC ($r = 0.68404$), LDL ($r = 0.76232$), VLDL ($r = 0.89975$) and TG ($r = 0.62905$) in hyperthyroid patients. Hepatic lipase activity was not affected by low levels of TSH ($r= -0.29$). It was noteworthy in this study that even a slight alteration in thyroid hormones showed a significant decrease in serum lipids. The lipid metabolism in overt thyroid hyperfunction was found to be influenced by hepatic lipase activity.

***Keywords*:** *Euthyroid, Lipids, Hyperthyroidism, TC, TG, TSH*

INTRODUCTION
Diseases of thyroid gland are amongst the most abundant endocrine disorder in the world second only to diabetes mellitus (Heuck *et al.,* 2000). Thyroid dysfunction is conditions that affect the amount of thyroid hormones being produced. Excess production leads to hyperthyroidism while diminished production leads to hypothyroidism (Ridgway, 1996). Thyroid hormones are important modulator of intermediary metabolism. They affect synthesis, mobilization and degradation of lipids, although degradation is influenced more than synthesis. Altered lipid profile is a well known manifestation of thyroid dyfunction (Pucci *et al.,* 2004).

The main effect of hyperthyroidism seems to be an enhanced elimination of vary low density lipoproteins (VLDL), low- density lipoproteins (LDL), and also high density lipoproteins and patients tends to have low levels of these lipoproteins (Kung *et al.,* 1995). Overt hyperthyroidism is associated with decreased plasma concentration of total and LDL cholesterol (Diekman *et al.,* 2000), but it is uncertain whether subclinical hyperthyroidism is also associated with hypolipidemia. Changes in LDL are mainly attributable to altered clearance of LDL from plasma by change in the number of LDL receptor on liver cell surface (Soutar and Knight, 1990). Hepatic lipase is the enzyme that takes part in the delipidation process of intermediate density lipoprotein (IDL), LDL, and HDL particles by hydrolysis of triglyceride and phospholipids (Demant *et al.,* 1988). It can also act as a ligand, promoting cellular uptake of apolipoprotein apoB- containing remnant lipoproteins (Zambon *et al.,* 2000). The present study assessed the effect of thyroid hyperfunction on lipoprotein metabolism and hepatic lipase activity

MATERIALS AND METHODS
This cross-sectional study has been conducted on 490 subjects (180 overt hyperthyroid and 110 subclinical hyperthyroid patients, and 200 age and sex matched euthyroid controls) with a mean age of 46

years (ranged- 25-60 years) in Himachal Pradesh, India. The patients were randomly selected among people visiting Govt. Rajindra Prasad Medical College and hospital, Kangra. A detailed history with emphasis on symptoms related to impaired thyroid function was recorded. The research protocol was approved by the institutional ethics committee and informed consents were obtained from all the patients.
The patients affected with primary dyslipidemia, diabetes mellitus, cardiac infections, IDD, pregnant females, taking anti-thyroid medications were excluded from the study.
Fasting venous blood samples were collected, centrifuged promptly, and separated sera stored at -20˚C. TSH, T3 and T4 were estimated by enzyme immuno assay using ELISA microplate reader (Alpha Diagnostic). Serum total cholesterol, triglycerides and HDL were measured using standardized procedure given in respective data sheets provided with the assay test kits. The hepatic lipase activity was analyzed by enzymatic colorimetric method on auto-analyzer (Roche Diagnostic. USA). LDL was calculated by Friedwald formula (Friedwald *et al.*, 1972).
Results were presented as Mean ± SD. Comparison was made by ANOVA and post hoc multiple comparison (Tucky's HSD) test by using SPSS (19.0) statistics package. P value less than 0.05 was considered significant. Correlation between parameters was performed by Pearson's correlation matrices analysis.

RESULTS AND DISCUSSION

Results

Among the 490 subjects studied, 200 were euthyroid controls. The subclinical and overt hyperthyroidism was found in 37.94% and 62.06% cases, respectively. There was a trend toward a higher prevalence of overt thyroid hyperfunction in the age group 45- 55 and that of subclinical thyroid dysfunction in the age group 35 – 45 (Table 1).
Thyroid hormone status in the study groups:
The thyroid stimulating hormone level was significantly ($p<0.001$) lower in overt and subclinical hyperthyroid patients compared with euthyroid group. T3 and T4 hormones were significantly ($p<0.001$) increased in overt hyperthyroid patients, while in subclinical patients, these were within in their normal reference range (T3- 0.80 to 1.90 ng/ml, T4- 4.8 to 12.0 µg/dl, Table 2).
The total cholesterol level showed a significant ($P< 0.01$) decrease in overt hyperthyroid patients in comparison to euthyroid controls, whereas in subclinical hyperthyroid patients the total cholesterol level was in the lower quartile of reference range (160 – 220 mg/dl). The HDL and LDL levels were significantly ($P< 0.01$) decreased in both subclinical and overt hyperthyroid patients and the values were below normal reference range (HDL- 50 to 80 mg/dl, LDL – 80 – 130 mg/dl). VLDL levels was significantly ($P<0.01$) declined in overt hyperthyroid patients. In subclinical cases the VLDL concentration was within normal range. Hypotriglyceridemia ($P<0.01$) was evident in overt hyperthyroid patients, however the values were in the lower quartile of reference range (TG- <150 mg/dl). One way ANOVA analysis revealed a significant ($P<0.0001$) variation in levels of TC, HDL, LDL, VLDL and TG within all study groups. Comparison of the changes of various lipid parameters in overt cases with the respective changes in other groups (Tucky's HSD test), showed that the decreased TSH levels were accompanied by decreased lipid levels (Table 3).
Pearson's bivariate correlation analysis revealed that there was no significant relationships between TSH, T3, T4 and lipid parameters in subclinical hyperthyroid patients. Positive correlation was observed between serum TSH and TC ($r = 0.68404^*$), TSH and LDL ($r = 0.76232^*$), TSH and VLDL ($r = 0.89975^*$), and TSH and TG ($r = 0.62905^*$) in overt hyperthyroid patients. T3 exhibited significant ($P<0.05$) negative relationship with and HDL ($r = - 0.4426^*$), LDL ($r = -0.7378^*$) and TG ($r = - 0.5454^*$) in overt hyperthyroid patients. A significant ($P<0.05$) negative relationship existed between T4 and HDL ($r = - 04061^*$), and LDL ($r = -7843^*$) (Table 4).
The mean level of hepatic lipase in overt hyperthyroid patients revealed a percentage elevation of 18.53 compared to euthyroid controls. One way ANOVA analysis showed that difference between the study groups was statistically significant ($P<0.0001$). Tucky's HSD multiple comparison revealed that

hyperthyroid patients had a significantly (P<0.0001) higher activity of hepatic lipase in comparison to subclinical cases and euthyroid controls (q = 10.56, 95% CI = 9.21 – 11.91, Table 5).

Discussion

This study found that there was a higher prevalence of subclinical cases in the age group 35 – 45 and overt thyroid hyperfunction in the age group 45- 55. Conversely, Regmi *et al*., (2010) reported overt thyroid dysfunction in the age group <20 and subclinical thyroid dysfunction in age group 40 – 60.

In subclinical hyperthyroid patients, non significant differences in the levels of TC, VLDL and TG were observed in comparison to euthyroids, however, all the lipid parameters were in the lower quartile of normal reference range. Similarly, Heemstra *et al*., (2006) recorded no significant difference between lipid parameters in subclinical hyperthyroid patients and euthyroidism group. In contrast to our results Parle *et al.*, (1992) determined the effect of subclinical hyperthyroidism (n=27) on fasting levels of blood lipids and reported a marked (12.2 %) reduction in serum total cholesterol in subclinical hyperthyroidism (P< 0.01). Erem (2006), demonstrated that total cholesterol levels were significantly higher in patients with subclinical hyperthyroidism than in controls (P<0.05).

The overt hyperthyroid patients exhibited a significant (P<0.01) decrease in level of TC, LDL, VLDL and TG compared to euthyroid controls. The hyperthyroid patients showed significant (P<0.05) positive relationship between TSH concentration and TC, LDL and TG levels. Our results are in accordance with the findings of Giusti *et al*., (2008).

They documented that in differential thyroid carcinoma patients with suppressed thyrotropin, lower HDL-cholesterol levels were recorded. In differential thyroid carcinoma patients, a significant negative correlation was seen between HDL and body mass index. Mahmud *et al.*, (2009) observed that in hyperthyroidism, total and LDL- cholesterol, and TG levels were lower (P<0.05) than those of euthyroid subjects and both the values were lower than reference value. Conversely, Regmi *et al.*, (2010) reported no changes in the concentration of lipid parameters in patients with hyperthyroidism compared to euthyroid controls.

During present investigation, a significant (P<0.0001) increase in hepatic lipase activity in hyperthyroid patients compared to subclinical hyperthyroid patients and euthyroid controls was observed. Toruner *et al.*, (2008) documented that hepatic lipase seem to be dependent on the status of thyroid function, it is low in severe thyroid failure and increased in hyperthyroidism.

Changes in hepatic lipase activity seem to be an important mechanism for the disturbance of cholesterol metabolism in thyroid dysfunction.

Thyroid hormones affects the mechanism of reverse transport of cholesterol by influencing the activity of hepatic lipase and cholesteryl ester transfer protein, and thus modulate the distribution of HDL (Barth *et al.*, 1983). The enhanced hydrolysis of HDL_2, enriched in triglyceride by hepatic lipase and their subsequent conversion in HDL_3 remodels the HDL particles and may lead to decreased HDL levels (Kung *et al.*, 1995).

This study revealed that, HDL and LDL were significantly (P<0.05) low in both subclinical and overt hyperthyroid patients compared to euthyroid subjects. The increased activity of hepatic lipase observed in hyperthyroidism can be one of the factors responsible for the decline of HDL concentration in these patients. Decline in HDL cholesterol could be due to increased activity of cholesteryl transfer protein and hepatic lipase (Kung *et al.*, 1995).

Tan *et al.*, (1998) documented that HDL metabolism was altered in thyroid dysfunction and the effect of thyroid hormone on HDL was mediated mainly via its effect on hepatic lipase activity. Decreased levels of total and LDL cholesterol in the subjects with hyperthyroidism may be due to increased bile excretion of cholesterol and to incresase LDL- receptor gene expression resulting in enhanced LDL- receptor mediated catabolism of LDL- particles. The serum cholesterol levels are decreased mainly because of simultaneous enhancement of the turnover of LDL. This leads to a further decrease of total and LDL cholesterol in hyperthyroidism (Duntas, 2002). Hyperthyroidism exhibited an augmented excretion of

cholesterol by the bile together with unchanged or increased enterohepatic circulation of bile acids (Hsieh and Wang, 2008).

Table 1: Frequency distribution of thyroid dysfunction according to age

Age group (Years)	Ethyroid Control Frequency (%)	Subclinical hyperthyroid Frequency (%)	Overt hyperthyroid Frequency (%)
25-35	60 (30.00)	29 (10.00)	46 (15.96)
35-45	70 (35.00)	43 (14.34)	62 (21.47)
45-55	70 (35.00)	38 (13.20)	72 (25.03)

Table 2: Study group with their thyroid hormone status

Subjects	Number of patients (n)	TSH (mIU/dl)	T3 (ng/ml)	T4 (µg/dl)
Euthyroid	200	2.4 (1.2-3.98)	1.4 ± 0.33	8.60 ± 0.89
Subclinical	110	0.09 (0.02-0.36)[a]	1.63 ± 0.45	8.40 ± 1.40
Overt	180	0.16 (0.01-0.45)	8.45 ± 3.46*	18.71 ± 6.10*

*[a]p>0.05, *p<0.0001 vs. Euthyroid*
Normal range- TSH- 0.4 – 4.20µIU/ml
T3- 0.80 to1.90 ng/ml;
T4- 4.8 to 12.0µg/dl

Table 3: Comparison of mean lipid parameters in euthyroids and hyperthyroid patients

Parameters (mg/dl)	Euthyroid controls (n- 200)	Subclinical hyperthyroid (n- 110)	Overt hyperthyroid (n- 180)	F-Ratio
TC	166.38 ± 15.49	164.34 ± 10.23	150.23 ± 17.53*†	58.43
HDL	63.14 ± 8.33	52.19 ± 12.45*	46.03 ± 7.40*†	170.88
LDL	82.24 ± 18.19	77.24 ± 16.72*	70.43 ± 14.21*†	24.48
VLDL	20.87 ± 4.38	20.43 ± 2.95	18.59 ± 1.73*†	24.22
TG	104.45 ± 22.23	102.60 ± 15.50	92.96 ± 18.65*†	17.74

Values are as Mean ± SD
n= No. of hyperthyroid patients and euthyroid controls
One way ANOVA values are significant, P<0.0001
*Tukey's HSD multiple comparison Test- *P<0.01 vs. Euthyroid, † P<0.01 vs. subclinical hyperthyroid*
Normal reference range-
Total Cholesterol = 130-250 mg/dl
HDL- Female- 35-90 mg/dl
Male- 30-70 mg/dl
Triglcerides = < 150 mg/dl
LDL- 100 - 130 mg/dl

Table 4: Pearson's correlation coefficients between TSH, T3, T4 and lipid profile

		TC	HDL	LDL	VLDL	TG
Subclinical hyperthyroidism	TSH	0.0120	0.1320	0.0423	0.2360	0.0950
	T3	-0.0230	-0.0710	-0.0823	-0.2841	-0.0789
	T4	-0.1278	-0.0710	-0.0584	-0.1421	-0.2140
Overt hyperthyroidism	TSH	0.68404*	0.3452	0.76232*	0.89975*	0.62905*
	T3	-0.11200	-0.4426	-0.7378*	-0.2190	-0.5454*
	T4	-0.2901	-0.4061	-0.7843*	-0.3701	-0.1230

Correlations is significant at the level of 0.05

Table 5: Hepatic lipase activity in hyperthyroid patients and euthyroids

Study group	n	Hepatic lipase (IU/L)	q	95% confidence interval
Euthyroid	200	56.98 ± 9.95		
Subclinical hyperthyroid	110	57.33± 8.94	0.35	1.98 – 2.68
Overt hyperthyroid	180	67.54 ± 6.97*†	10.56	9.21 - 11.91

n= No. of hyperthyroid patients and euthyroid controls
*Tucky's HSD multiple comparison Test- *P<0.01 vs. Euthyroid, † P<0.01 vs. subclinical hyperthyroid*

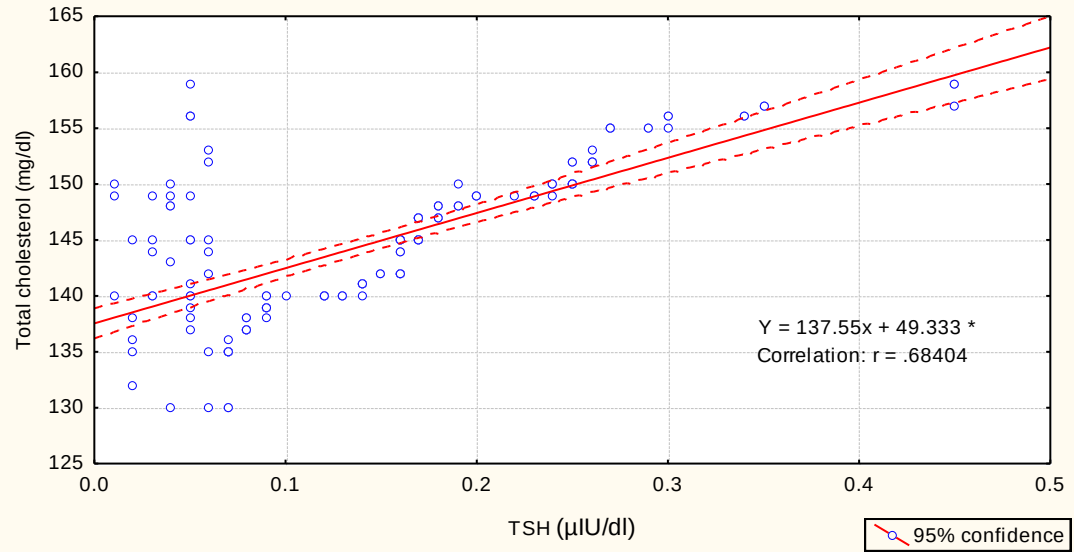

Figure 1: Scatterplot showing correlation between serum TSH and total cholesterol in overt hyperthyroid patients

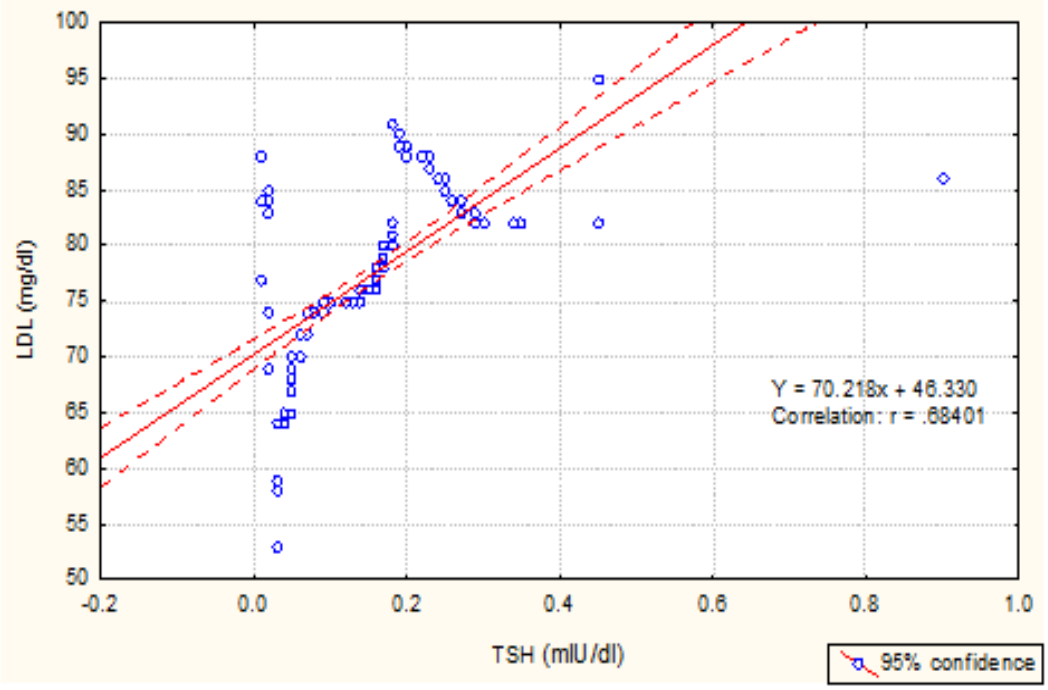

Figure 2: Scatterplot showing correlation between serum TSH and LDL in overt hyperthyroid patients

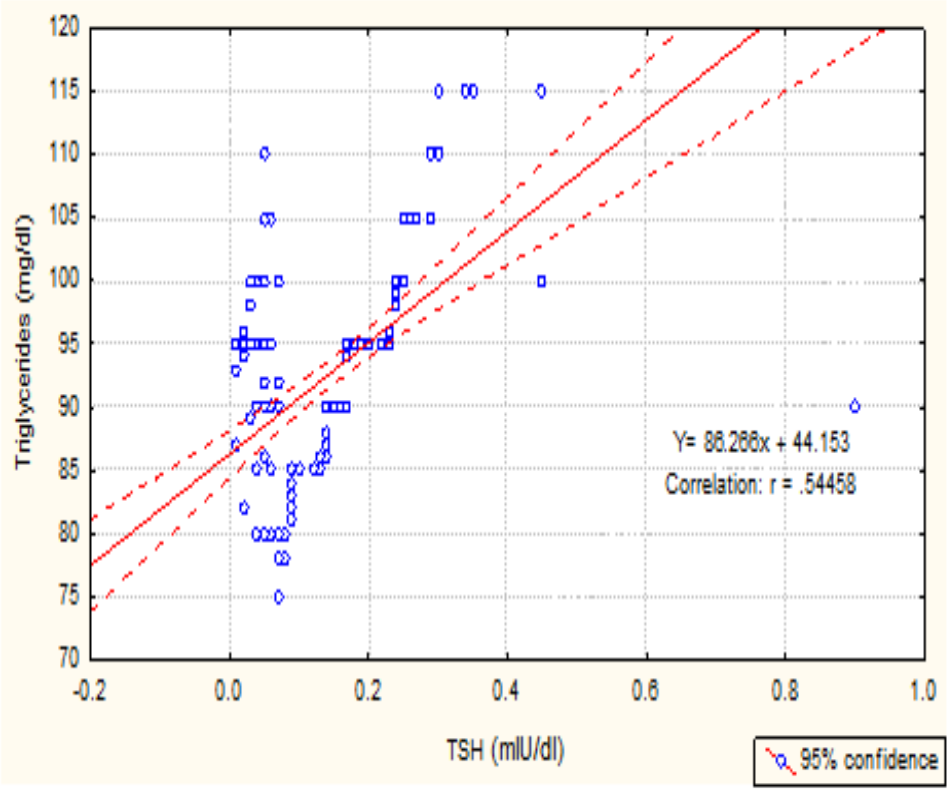

Figure 3: Scatterplot showing correlation between serum TSH and triglyceride in overt hyperthyroid patients

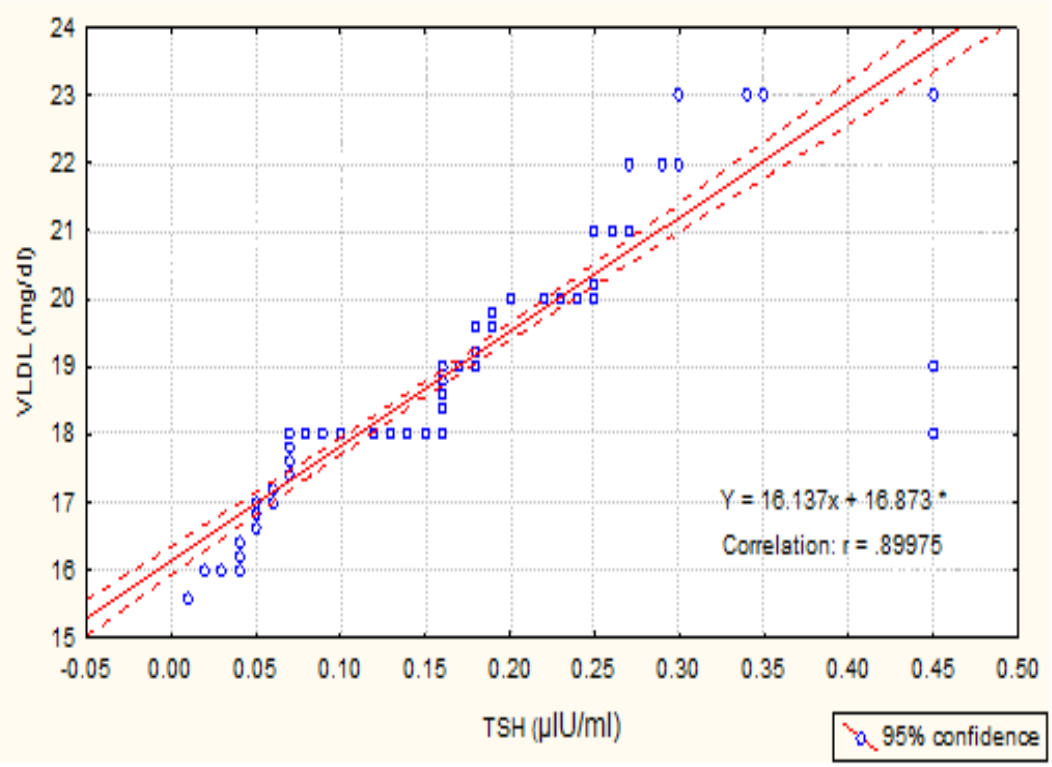

Figure 4: Scatterplot showing correlation between serum TSH and VLDL in overt hyperthyroid patients

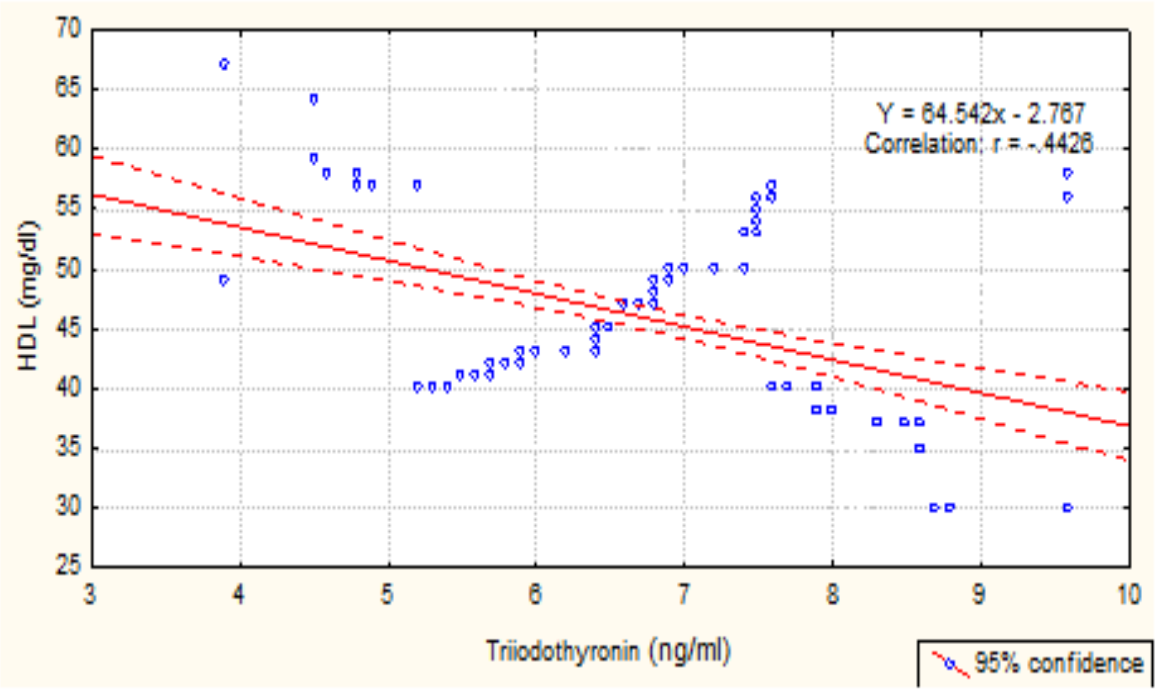

Figure 5: Scatterplot showing correlation between serum T3 and HDL in overt hyperthyroid patients

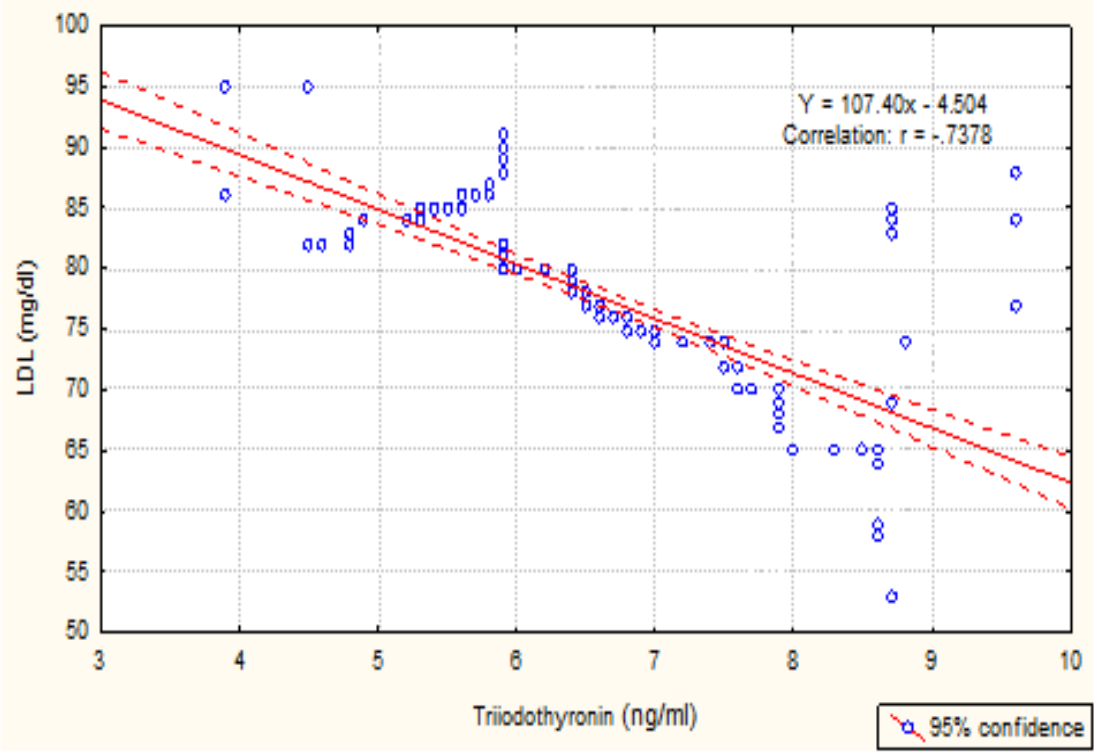

Figure 6: Scatterplot showing correlation between serum T3 and LDL in overt hyperthyroid patients

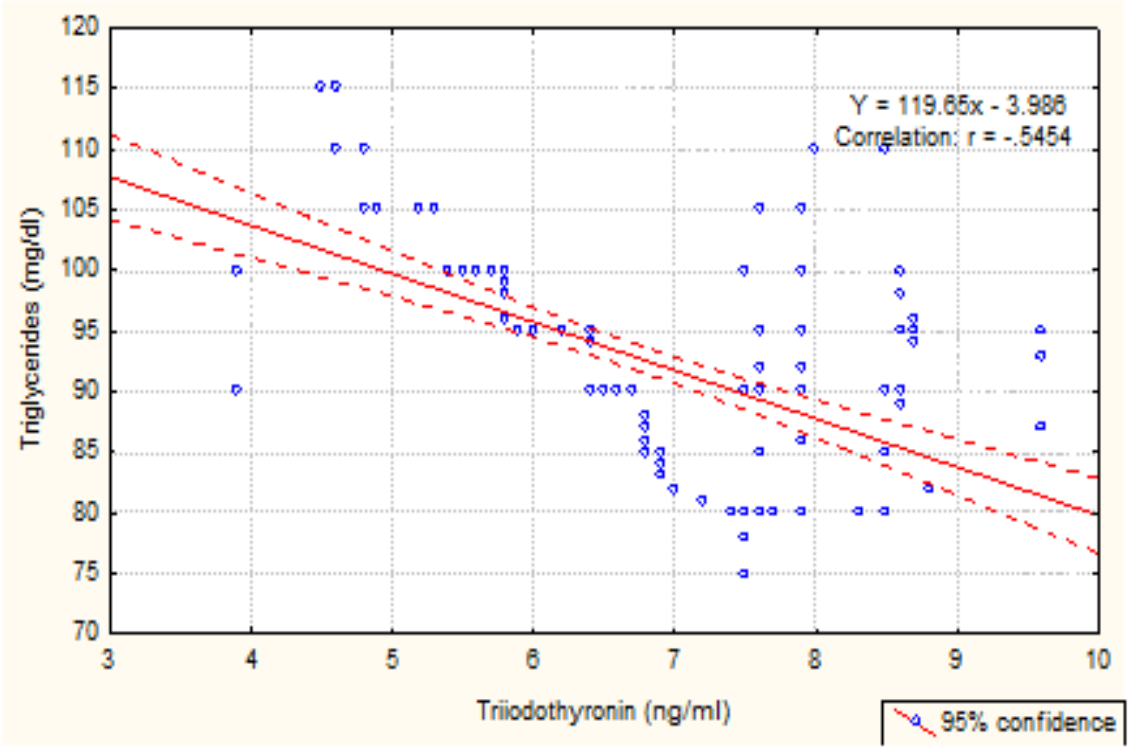

Figure 7: Scatterplot showing correlation between serum T3 and TG in overt hyperthyroid patients

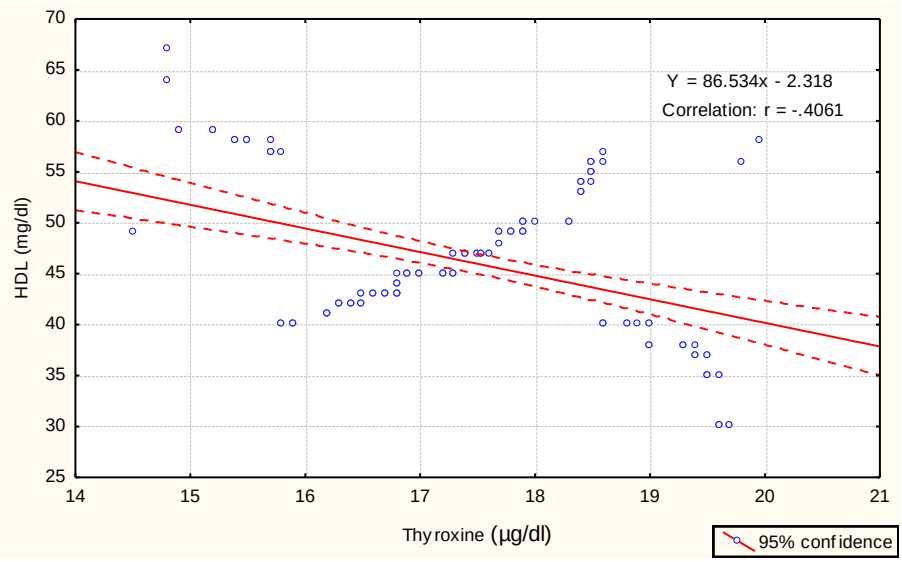

Figure 8: Scatterplot showing correlation between serum T4 and HDL in overt hyperthyroid patients

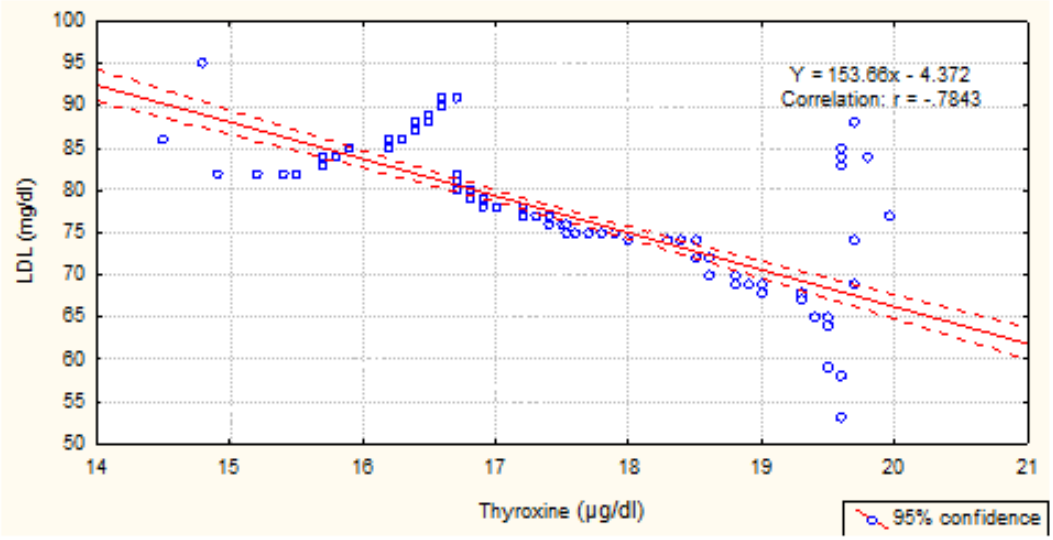

Figure 9: Scatterplot showing correlation between serum T4 and LDL in overt hyperthyroid patients

The lipid metabolism in overt thyroid hyperfunction was found to be influenced by hepatic lipase activity. Increase in hepatic lipase activity may be attributable to the clearance of HDL and TG rich lipoproteins. However, there was no significant relationship of thyroid hormones and hypolipidemia among patients with subclinical hyperthyroidism and euthyroid group.

Conclusion

It was noteworthy in this study that even a slight alteration in thyroid hormones showed a significant decrease in serum lipids. The lipid metabolism in overt thyroid hyperfunction was found to be influenced by hepatic lipase activity.

ACKNOWLEDGEMENT

We thank the University Grant Commission, Govt. of India for providing financial assistance.

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