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Original Research Article

Degree of Dyslipidemia in Patients of Subclinical and Overt Hypothyroidism

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Abstract
Background: *Hypothyroidism has been established as a common cause of secondary dyslipidemia. There is also a recognized pathogenic relationship of patients with hypothyroidism developing atherosclerotic cardiovascular disease. This possibility of atherosclerotic cardiovascular disease is attributable to dyslipidemia noticed in hypothyroid states. This study was intended to evaluate the level of different parameters of lipid profile in both subclinical and hypothyroid patients.*
Materials and Methods: *104 Hypothyroid patients were divided in two equal groups namely subclinical and overt hypothyroids based on their serum TSH levels. 52 age, sex and weight matched euthyroid controls were used for comparison.*
Result: *Significantly raised serum total cholesterol, LDL-cholesterol and triglycerides were found in hypothyroid patients and dyslipidemia was more profound in overt hypothyroids. Positive correlation of serum TSH with total cholesterol, LDL-cholesterol and triglycerides were seen in overt hypothyroid patients.*
Conclusion: *Deranged lipid profile is more marked in overt hypothyroidism and is characterized by increased total & LDL-cholesterol and triglycerides. Serum TSH level is positively correlated with the degree of dyslipidemia.*

Introduction

Thyroid failure is more common in women and its prevalence rises with age. Hypothyroidism has been established as a common cause of secondary dyslipidemia.[1,2] Long standing hypothyroidism may cause hypercholesterolemia. There may be increase in total cholesterol, LDL cholesterol and triglycerides.

Thyroid hormones activate the synthesis of cholesterol in liver by increasing the gene expression of HMG-CoA reductase, a rate limiting enzyme in the hepatic de novo cholesterol synthesis. This is caused by binding of thyroid hormones to specific thyroid hormone responsive elements (TREs).[3] Thus hypothyroidism may result in a decreased intracellular cholesterol concentration.

Thyroid hormones increase the formation of LDL receptors by inducing the sterol regulatory element binding protein-2(SREBP-2), which

regulates LDL receptor's gene expression.[4] These extrahepatic LDL receptors are responsible for the internalization of LDL particles containing ApoB-100. Hypothyroidism results in decreased activity of LDL receptors resulting in defective receptor mediated catabolism of LDL cholesterol in extrahepatic tissues.[5,6,7]

Thyroid hormones increase cholesteryl ester transfer protein (CETP) activity, which exchanges cholesteryl esters from HDL-2 to VLDL and triglycerides from VLDL to HDL-2.[8] Hypothyroidism causes decreased activity of the CETP which results in elevated levels of HDL cholesterol due to increased HDL-2 particles concentration. Thyroid hormones stimulate both the lipoprotein lipase (LPL) and the hepatic lipase (HL) by regulating their gene expression. Thyroid hormones also promote the synthesis of Apo CII which is an activator of LPL. By the action of LPL, extrahepatic tissue removes triglycerides from all lipoproteins for their utilization and conversion of VLDL to IDL, IDL to LDL and then LDL to small dense LDL (sdLDL).[9,10] A decrease in LPL activity is found in overt hypothyroidism, decreasing the clearance of TG-rich lipoproteins.[11] Therefore, overt hypothyroid patients may also present with elevated TG levels associated with increased levels of VLDL and occasionally fasting chylomicronemia. [12,13]

Hepatic lipase hydrolyzes HDL-2 to smaller and denser HDL-3. Hypothyroid patients may also exhibit elevated levels of HDL-Cholesterol[14] mainly due to increased concentration of HDL-2 particles. Due to a reduction of hepatic lipase activity a decrease in HDL-2 catabolism is observed.[15]

Hypertriglyceridemia is also a result of an imbalance between synthesis and clearance of VLDL in the circulation. Hypertriglyceridemia in hypothyroidism is due to increased synthesis of apolipoprotein B by the liver and a decrease in very low density lipoprotein remnant receptor.[16] Due to low thyroid hormones, hepatic oxidation of free fatty acids and metabolism of glucose are impaired. Therefore free fatty acids and glucose are shunted to the liver for synthesis of VLDL triglycerides. The VLDL fraction in hypothyroid patients contains many small particles. This increase in small VLDL is due to low levels of hepatic lipase

Thyroid hormones stimulate the bile acids synthesis by activating 7-α-hydroxylase which is the rate limiting enzyme in bile acid synthesis. Bile acids/salts are involved in the excretion of cholesterol in the bile. Decreased concentration of bile acids/salts in hypothyroidism causes supersaturation of the bile with cholesterol which may result in gall stones.[17,18]

Aim

Our study was aimed to compare the lipid profile of subclinical and overt hypothyroid patients with each other and with euthyroid controls. An effort was also made to correlate the parameters of lipid profile with T3, T4 and TSH in subclinical and overt hypothyroid patients.

Material and Methods

The present study was conducted in the Department of Biochemistry of Govt. medical college, Nagpur with cooperation from Medicine Department of the institute during period of May 2014 to October 2015. The study was approved by institutional Ethics Committee for research work. It was a Cross sectional comparative study. The study consisted of 3 groups of 52 subjects each between 18-72 years of age as follows:

1. Subclinical hypothyroidism (TSH 3.6-10 µlU/mL)
2. Overt hypothyroidism (TSH >10µlU/mL)
3. Age, sex and weight matched controls (Table1,2,3)

Patients with severe infections, renal diseases, hepatobiliary diseases, diabetes mellitus, heart diseases, past history of hyperlipidemia, myopat-hies, pregnancy, patient taking lipid lowering agents, alcohol users and smokers were excluded from the study. Serum T3, T4 and TSH were measured by quantitative solid phase enzyme linked immunsorbent assay. Total cholesterol was measured by CHOD-POD enzymatic method. HDL-cholesterol was measured by precipitation

method. Triglycerides were measured by glycerol phosphate oxidase peroxidase method. LDL-cholesterol was calculated by Friedewald Equation. Data was analyzed using Analysis of Variance (ANOVA), Bonferroni test, Karl pearsons correlation and Chi square test. $P < 0.05$ was considered to be statistically significant and $P < 0.001$ was taken as statistically highly significant.

Result

Table 1: Age distribution of study subjects

	Controls (n=52)	Subclinical hypothyroids (n=52)	Overt hypothyroids (n=52)	ANOVA F value	*P* value
Age (yrs.) Mean ± SD	37.75 ± 9.85	38.19 ± 9.53	39.84 ± 11.46	0.59	0.55

Table 2: Sex distribution of study subjects

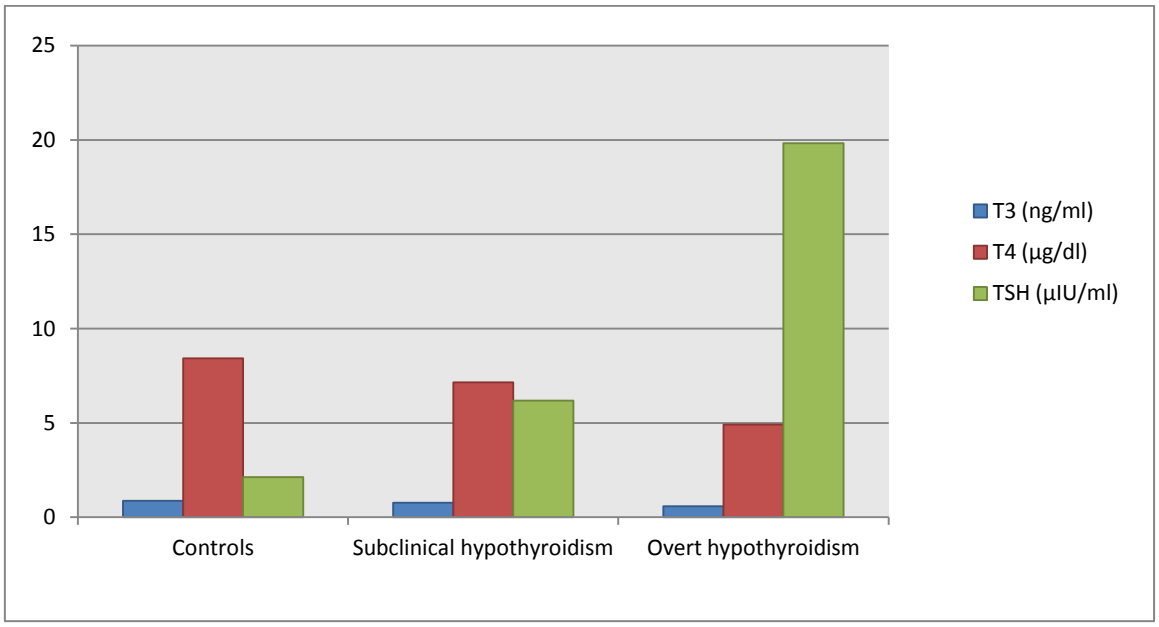
Gender	Controls	Subclinical hypothyroids	Overt hypothyroids	Chi square value	*P* value
Females	42 (80.8%)	43 (82.7%)	44 (84.6%)	0.2687	0.874
Males	10 (19.2%)	9 (17.3%)	8 (15.4%)		
Total	52	52	52		

Table 3: Weight distribution of study subjects

	Controls (n=52)	Subclinical hypothyroids (n=52)	Overt hypothyroids (n=52)	ANOVA F value	*P* value
Wt. (Kg)	57.96 ± 7.77	58.13 ± 8.41	58.51 ± 8.46	0.062	0.939

Table 4: Comparison of T3, T4 and TSH among controls, subclinical and overt hypothyroids (by using ANOVA test)

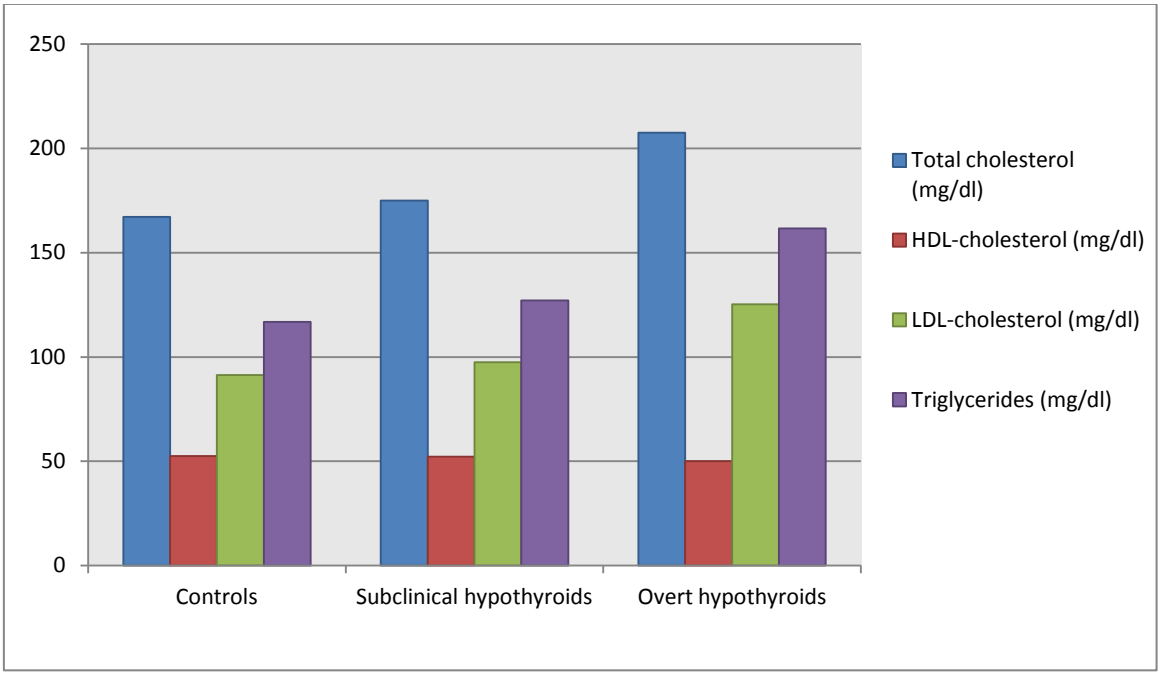
	Controls (n=52)	Subclinical hypothyroids (n=52)	Overt hypothyroids (n=52)	ANOVA F value	*P* value
T3 (ng/ml)	0.87 ± 0.27	0.77 ± 0.30	0.59 ± 0.27	12.8	<0.001
T4 (µg/dl)	8.42 ± 2.38	7.15 ± 2.68	4.91 ± 3.13	21.66	<0.001
TSH (µIU/ml)	2.13 ± 1.13	6.18 ± 1.48	19.83 ± 5.55	390.85	<0.001



Graph 1: Comparison of mean of T3, T4 and TSH among controls, subclinical and overt hypothyroids.

Table 5: Comparison of mean of different parameters of lipid profile in the study groups (ANOVA test)

	Controls (n=52)	Subclinical hypothyroids (n=52)	Overt hypothyroids (n=52)	ANOVA F value	*P* value
Total cholesterol (mg/dl)	167.23 ± 26.74	174.96 ± 27.53	207.53 ± 38.37	24.23	<0.001
HDL-cholesterol (mg/dl)	52.53 ± 6.3	52.13 ± 6.98	50.07 ± 4.9	2.41	0.092
LDL-cholesterol (mg/dl)	91.4 ± 26.16	97.46 ± 26.84	125.25 ± 37.59	18.02	<0.001
Triglycerides (mg/dl)	116.78 ± 26.87	127.09 ± 34.12	161.69 ± 26.99	33	<0.001



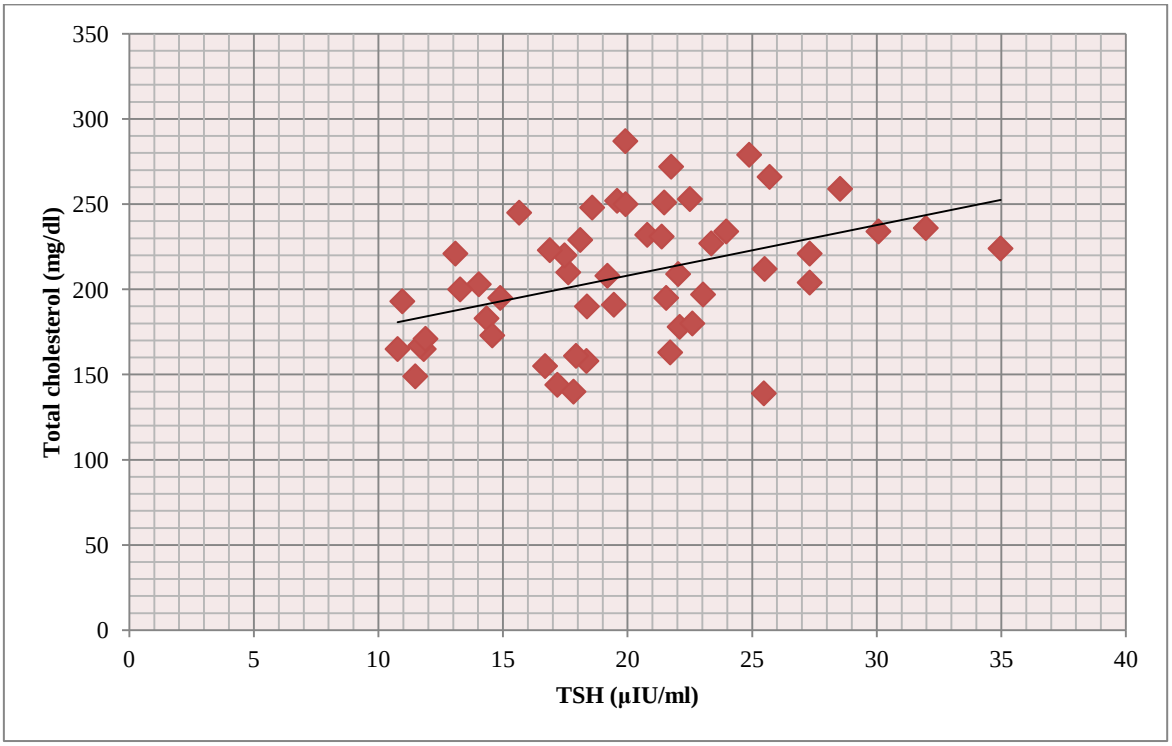
Graph 2: Comparison of mean of different parameters of lipid profile in the study groups

Table 6: Pairwise comparison of the mean difference of parameters of lipid profile among the study groups (by using Bonferroni test)

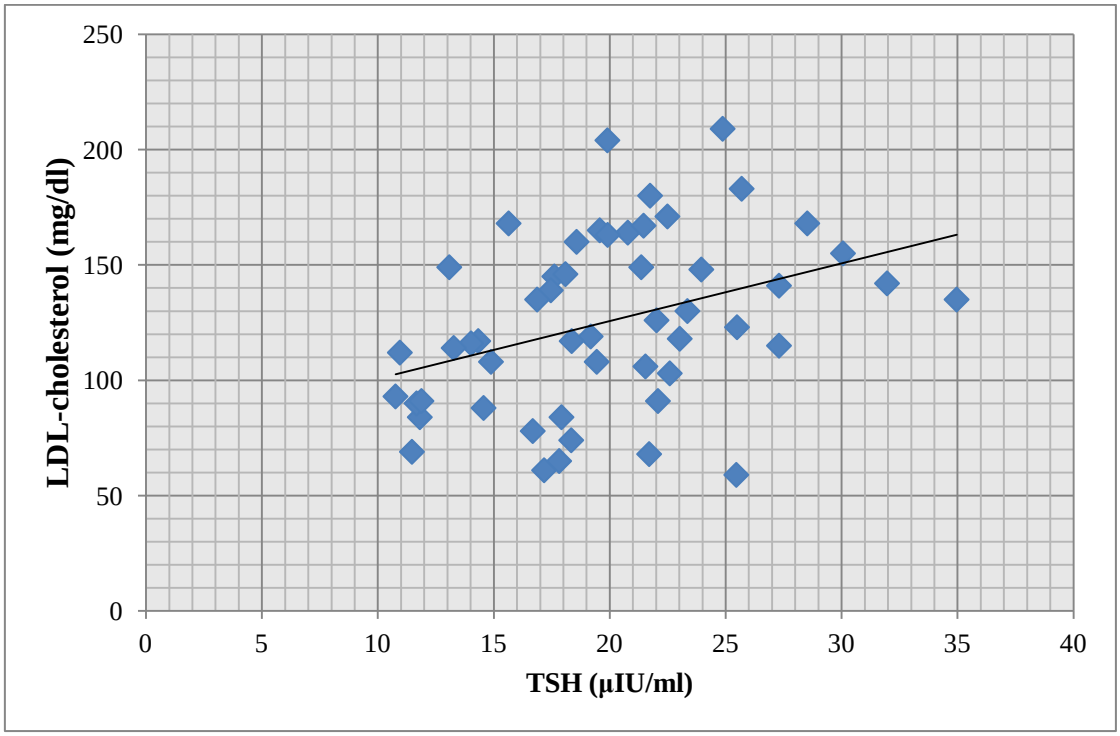
	Compared Groups		Mean difference	*P* value
Total cholesterol (mg/dl)	Controls	Subclinical hypothyroids	-7.73	0.63
		Overt hypothyroids	-40.3	<0.001
	Subclinical hypothyroids	Overt hypothyroids	-32.57	<0.001
HDL-cholesterol (mg/dl)	Controls	Subclinical hypothyroids	0.4	2.21
		Overt hypothyroids	2.46	0.12
	Subclinical hypothyroids	Overt hypothyroids	2.06	0.26
LDL-cholesterol (mg/dl)	Controls	Subclinical hypothyroids	-6.06	0.945
		Overt hypothyroids	-33.85	<0.001
	Subclinical hypothyroids	Overt hypothyroids	-27.79	<0.001
Triglycerides (mg/dl)	Controls	Subclinical hypothyroids	-10.31	0.231
		Overt hypothyroids	-44.91	<0.001
	Subclinical hypothyroids	Overt hypothyroids	-34.6	<0.001

Table 7: Correlation of different parameters of lipid profile with T3, T4 and TSH in the study groups

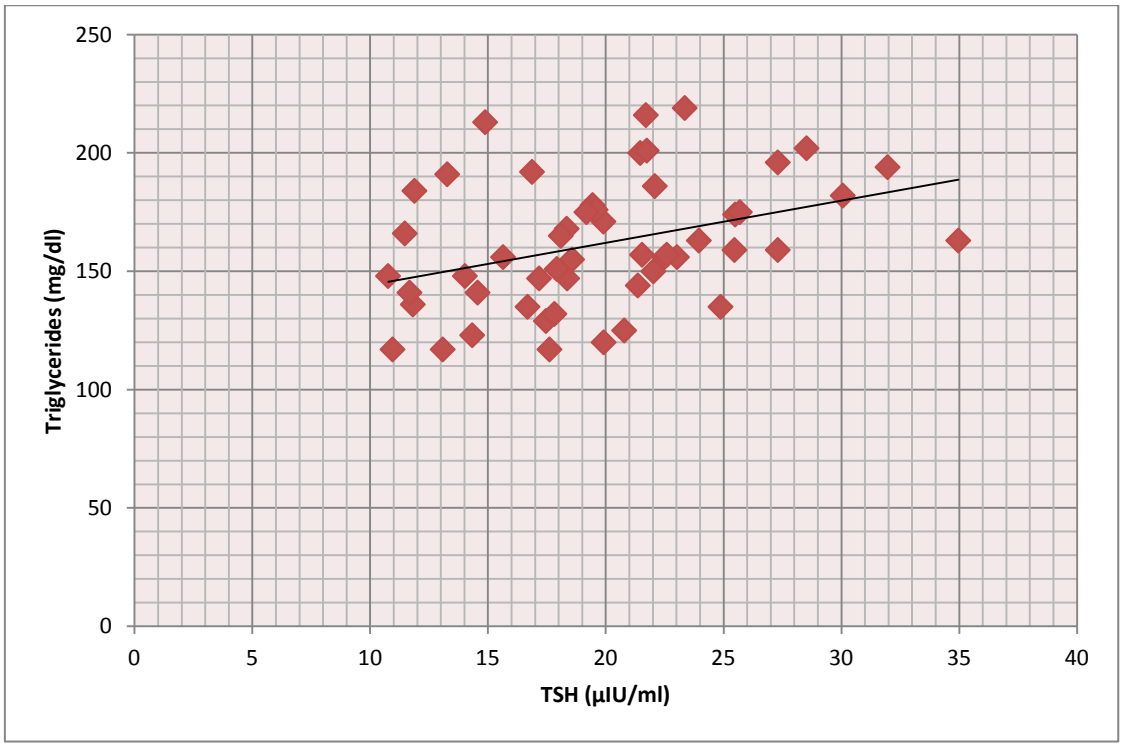
	Groups	T3		T4		TSH	
		r value	*P* value	r value	*P* value	r value	*P* value
Total cholesterol	Controls	-0.0609	0.668	0.1915	0.173	-0.0325	0.819
	Subclinical hypothyroids	-0.2681	0.054	0.0065	0.956	0.1428	0.312
	Overt hypothyroids	-0.1816	0.197	-0.0886	0.532	0.4296	0.001
HDL-cholesterol	Controls	-0.1178	0.405	-0.2656	0.057	0.0901	0.525
	Subclinical hypothyroids	0.1089	0.442	-0.1825	0.195	-0.1729	0.22
	Overt hypothyroids	0.109	0.441	0.1879	0.182	0.1076	0.447
LDL-cholesterol	Controls	-0.0517	0.715	0.2213	0.114	-0.0607	0.669
	Subclinical hypothyroids	-0.2624	0.06	0.1111	0.432	0.1511	0.284
	Overt hypothyroids	-0.1717	0.223	-0.1042	0.462	0.3699	0.006
Triglycerides	Controls	0.0773	0.585	-0.1147	0.418	0.0228	0.872
	Subclinical hypothyroids	-0.1643	0.244	-0.229	0.102	0.1502	0.287
	Overt hypothyroids	-0.1891	0.179	-0.0747	0.598	0.3675	0.007



Graph 3: Correlation of total cholesterol with TSH in overt hypothyroidism



Graph 4: Correlation of LDL-cholesterol with TSH in overt hypothyroidism



Graph 5: Correlation of triglycerides with TSH in overt hypothyroidism

Discussion

There was a statistically significant increase in total cholesterol, LDL-cholesterol and triglycerides in overt hypothyroids as compared to both controls and subclinical hypothyroids (Table 6). These findings are in accordance with those reported by Hueston et al[19], Sheikh et al[20], Efstathiadou et al[21], Costantini et al[22], and Adrees et al[23]. Rizos et al[18] and Maugeri et al[24] observed a great impact of thyroid dysfunction on serum concentrations of lipids. For patients with overt hypothyroidism, substitution therapy is beneficial improving lipid profile. But, whether subclinical hypothyroidism should be treated or not is a

matter of debate. There is a well established correlation between thyroid hormones and lipid metabolism. Many studies prove the presence of an inverse relationship between serum thyroxin levels and cholesterol. Studies also show the effect of thyroid hormones on the catabolism of VLDL, explaining the increase in VLDL and LDL fractions in untreated hypothyroidism. The data regarding an exact correlation between thyroid hormones and triglyceride is more controversial.

Prieur et al[25] observed an elevated level of triglycerides in hypothyroidism which is due to the reduced activity of lipoprotein lipase and hepatic triglyceride lipase, thus decreasing the VLDL-triglycerides clearance. However, increase in total cholesterol, LDL-cholesterol and triglycerides in subclinical hypothyroids as compared to controls were not found statistically significant (Table 6). This finding is in accordance with the result of study done by Hueston et al.[19]

There was no statistically significant change in HDL cholesterol in subclinical hypothyroids and in overt hypothyroids as compared to controls (Table 6). This finding is in accordance with study of Costantini et al[22]. According to a study conducted by Abrams et al[26] hypertriglyceridemia is known to decrease HDL cholesterol levels which was verified in this study.

These findings are in accordance with those reported by Prakash et al[27] which shows that the effect of hypothyrodism in the lipid metabolism is more marked in patients with higher serum TSH levels. There was a statistically significant positive correlation between TSH and total cholesterol, LDL cholesterol and triglycerides among overt hypothyroids (Table 7); which is in accordance with the results of study done by Prakash et al[27], which says that the effect of hypothyroidism in the lipid metabolism is more marked in patients with higher serum TSH levels.

Conclusion

The study concludes that dyslipidemia is more marked in overt hypothyroidism characterized by increased total & LDL-cholesterol and triglycerides. Serum TSH was found positive correlated with total cholesterol, LDL-cholesterol and triglycerides. Thus TSH level can be used as a marker for the future judgment of degree of dyslipidemia in overt hypothyroid patients.

References

1. Tsimihodimos V, Bairaktari E, Tzallas C, Miltiadus G, Liberopoulos E, Elisaf M. Incidence of thyroid function abnormal-lities in patients attending an outpatient lipid clinic. Thyroid 1999; 9:365-8.
2. Stone NJ. Secondary causes of hyperlipidemia. Med Clin North Am 1994; 78:117-41.
3. Bakker O, Hudig F, Meijssen S, Wiersinga WM. Effects of T3 and amiodarone on promoter of human LDL receptor gene. Biochem Biophys Res Commun 1998; 249:517-21.
4. Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through SREBP-2. J Biol Chem 2003; 278:34114-8.
5. Walton KW, Scott PJ, Dykes PW, Davies JW. The significance of alterations in serum lipids in thyroid dysfunction. Clin Sci 1965; 29:217-38.
6. Thompson GR, Soutar AK, Spengel FA, Jadhav A, Gavigan SJ, Myant NB. Defects of receptor mediated LDL catabolism in hypercholesterolemia and hypothyroidism. Proc Natl Acad Sci USA 1981; 78:2591-5.
7. Abrams JJ, Grundy SM. Cholesterol metabolism in hypothyroidism and hyperthyroidism in man. J Lipid Res 1981; 22:323-38.
8. Lagrost L. Regulation of CETP activity: review of in vitro and in vivo studies. Biochim Biophys Acta 1994; 1215:209-36.
9. Kuusi T, Saarinen P, Nikkila EA. Evidence for the role of hepatic endothelial lipase in the metabolism of plasma HDL-2. Atherosclerosis 1980; 36:589-93.

10. Santamarina FS, Navarro GH, Freeman L, Wagner E, Nong Z. Hepatic lipase, lipoprotein metabolism and atherogenesis. Arterioscler Thromb Vasc Biol 2004; 24:1750-4.
11. Nikkila EA, Kekki M. Plasma triglyceride metabolism in thyroid disease. J Clin Invest 1972; 51:2103-14.
12. Al-Tonsi A, Abdel AG, Saad M. Secondary dyslipidemia and deranged serum phosphate conc. in thyroid disorders. Exp Mol Pathol 2004; 76:182-7.
13. Teixeira PF, Reuters VS, Ferreira MM. Lipid profile in hypothyroidism and effects of LT4 in mild thyroid failure. Trans Res 2008; 151:224-31.
14. Pearce EN, Wilson PW, Yang Q, Vasan RS, Braverman LE. Thyroid function and lipid subparticle sizes in patients with short term hypothyroidism and a population based cohort. J Clin Endocrinol Metab 2008; 93:888-94.
15. Lam KS, Chan MK, Yeung RT. HDL-cholesterol, hepatic lipase and LPL activities in thyroid dysfunction - effect of treatment. QJ Med 1986; 59:513-21.
16. Lee WY, Suh JY, Rhee EJ, Park JS, Sung KC. Plasma CRP, apoA1, apoB and Lp(a) levels according to thyroid function. Arch Med Res 2004; 35:540-5.
17. Liberopoulos EN, Elisaf MS. Dyslipidemia in patients with thyroid disorders. Hormones 2002; 1(4):218-23.
18. Rizos CV, Elisaf MS and Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. The Open Cardiovascular Medicine Journal 2011; 5:76-84.
19. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. Am Fam Med 2004; 2:351-5.
20. Sheikh BA, Soomro AA, Soomro MA, Pirzado ZA. Lipid profile in primary hypothyroidism. Medical channel 2009; 15(4):15-8.
21. Efstathiadou Z, Bitsis S, Milionis HJ. Lipid profile in SH: is L-thyroxine substitution beneficial? Eur J Endocrinol 2001; 145:705-10.
22. Costantini F, Pierdomenico SD, Cesare DD. Effect of thyroid function on LDL oxidation. Arterioscler Thromb Vasc Biol 1998; 18:732-7.
23. Adrees M, Gibney J, Saeity N, Boran G. Effects of 18 months of L-T4 replacement in women with SH. J Clin Endocrinol 2009; 71:298-303.
24. Maugeri D, Santangelo A, Barbagallo P, Bonanno MR, Malaguarnera M, Rizza I, Speciale S. Thyroid hormones and lipid metabolism in a group of patients over seventy. Eur Rev Med Pharm Sci 1999; 3:211-6.
25. Prieur X, Huby T, Coste H. Thyroid Hormone Regulates the Hypotriglyceri-demic Gene APOA5. J Biol Chem 2005; 280(30):27533-43.
26. Abrams JJ, Grundy SM, Ginsberg H. Metabolism of plasma triglycerides in hypo and hyperthyroidism. J Lipid Res1981; 22:307-22.
27. Prakash A, Lal AK. Serum lipids in hypothyroidism: our experience. Indian J Clin Biochem 2006; 21(2):153-5.