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Original Work

Association between different degrees of hypothyroidism and serum lipids

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ABSTRACT: The association between overt hypothyroidism (OH) and altered lipid profile is well known, however the significance of dyslipidemia in subclinical hypothyroidism (SCH) remain controversial. Therefore, this study was conducted to determine any association between lipid profile and different degrees of thyroid dysfunction. Thyroid and lipid profile parameters were analysed in 58 patients with overt (TSH ≥ 10.0 µIU/L and/or abnormally low fT4 and fT3 levels) and 87 patients with subclinical hypothyroidism (TSH 6.0-9.9 µIU/L with normal fT4 and fT3 levels) in this case-control study. These were compared with 100 age- and sex-matched euthyroid controls. It was found that only mean serum level of total cholesterol in patients with SCH was significantly high from that in controls (p=0.045). Other lipid parameters did not show any statistical significance. Whereas patients with OH had statistically significant higher levels of total cholesterol (p<0.001), triglyceride (p<0.05), LDL-C (p<0.001) and VLDL-C (p<0.05). There was also an increase in HDL-C in both SCH and OH group though not significant statistically. In conclusion, lipid profile is not much deranged in SCH whereas OH is a major cause of secondary dyslipidemia which may lead to increased risk of coronary artery disease. Therefore, thyroid hormone replacement would be most beneficial in patients with OH instead of SCH. However, patients with SCH should be monitored for deterioration of thyroid function and dyslipidemia at regular intervals.

KEY WORDS: ***Cholesterol; Dyslipidemia; HDL cholesterol; Hypothyroidism; Subclinical***

INTRODUCTION

Primary hypothyroidism is a graded phenomenon with different levels of severity, showing a wide inter-individual range of clinical and biochemical presentation. Hypothyroidism results from reduced secretion of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland[1]. Biochemically decrease in T4 and T3 concentrations lead to hyper secretion of pituitary TSH and an amplified increase in serum TSH levels. This is a key laboratory finding, particularly in the early detection of thyroid failure.

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Subclinical hypothyroidism (SCH), also called mild hypothyroidism, is a term used for a condition in which there are small elevations in TSH, yet normal circulating levels of thyroid hormones. This condition is more common in the elderly and is found twice as often in women as in men[2,3]. While it is uncommon in younger persons, by the age of 65 years, the overall prevalence of the disorder is about 17% in women and 7% in men[4]. SCH has been detected with increasing frequency in recent years and is causing major controversies concerning management and treatment. SCH is usually detected during biochemical screening for nonspecific symptoms by TSH measurements[5], especially in tertiary care hospitals.

Overt hypothyroidism (OH) is associated with abnormalities of lipid metabolism, which may predispose to the development of atherosclerotic coronary artery disease (CAD)[6,7]. Whether SCH also has any demonstrable effect on serum lipid

concentrations has been controversial[8-15]. Some studies of patients with subclinical hypothyroidism have shown that patients have elevations in their cholesterol levels[16,17]. However, a precise relationship between different degrees of hypothyroidism and CAD has not been confirmed.
This study was, therefore, planned to evaluate the changes in biochemical lipid profile parameters in subclinical and overt hypothyroid subjects, and to correlate these values with thyroid profile (TSH, fT3 and fT4) of the patient.

METHODOLOGY

Study population

The study was conducted on 245 ambulatory subjects of age group 20 to 50 years referred to thyroid clinic in a tertiary care hospital of northern India after being approved by institutional review board. After informed consent, brief clinical history and examination was done to rule out renal disorders, liver disorder, or any other inflammatory condition which would have influenced the parameters under study.
For these analyses, we excluded subjects who were receiving concurrent treatment with drugs that could contribute to hypothyroidism (lithium, amiodarone, or iodine), those receiving antithyroid medication (methimazole or propylthiouracil) for hyperthyroidism and treatment with lipid lowering drugs for dyslipidemia.
After overnight fasting, 6ml venous blood sample was collected. After centrifugation (10 min at 3000 x g), serum was divided into aliquots for lipid profile parameters and thyroid function tests (TSH, fT3 and fT4). Both the aliquots were independently analyzed, such that the person analysing lipid profile was unaware of patient's thyroid function test results and vice versa. Sample for lipid profile was analyzed immediately. Samples for thyroid function tests were stored at -40ºC until batch analysed.

Lipid Profile tests

Serum total cholesterol (TC) was analyzed by enzymatic CHOD-PAP method and triglyceride (TG) was estimated by GPO-PAP method using diagnostic kits by Randox Laboratories (Crumlin, United Kingdom) on Synchron CX4 and CX9 autoanalyzer (Beckman Coulter, USA). High-density lipoprotein cholesterol (HDL-C) was determined directly using system pack kits from Beckman Coulter. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula[18].

Thyroid function tests

Serum TSH, fT4 and fT3 were assayed using fully automated chemiluminescent immunoassay Access 2 by Beckman and Coulter (USA). Reference intervals provided by the manufacturer were TSH 0.34-5.6µIU/L, fT3 2.5-3.9pg/mL and serum fT4 0.6-1.12ng/dL. The sensitivities of the TSH, fT3, and fT4 were 0.0025µIU/L, 1 pg/mL, and 0.4ng/dL respectively. The intraassay coefficients of variation for TSH, fT3 and fT4 were 1.7%, 2.7%, and 3.2% respectively.
After conducting thyroid function tests, subjects having euthyroid state (n=100, TSH≤ 6.0µIU/ml, normal fT3 and fT4 levels) were taken as controls. Patients with TSH levels >6.0µIU/ml were considered as hypothyroid (n=145). These patients were further divided into sub-clinical hypothyroid (n=87; TSH- 6.1 to 9.9µIU/ml with normal fT4 and fT3 levels) and overt hypothyroid (n=58 with TSH ≥10µIU/ml and/or abnormally low fT4 and fT3 levels).

Statistical analysis

Statistical analysis was carried out using SPSS for windows 15.0 software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean ± standard error of mean (S.E.M.). One way analysis of variance (ANOVA) and student's t test was applied to the data. The Pearson correlation was used to test whether TSH, fT4 and fT3 was correlated with TC, LDL-C, HDL-C, TG, VLDL-C, TC/HDL-C and LDL/HDL-C. P value <0.05 was considered statistically significant.

RESULT

In our study population, both the hypothyroid and control groups were age and sex-matched. Majority of the patients and the controls were women, since the hospital is popular mainly for its gynecology and obstetrics services. Mean age of the hypothyroid patients was 31.55 ± 2.1 years and that of euthyroid group was 30.76 ± 1.9 years. Hypothyroid group consisted of 80.22% women whereas the euthyroid group had 78% women. Mean serum TSH level in the control group was 2.428 ± 0.11µIU/ml **(table 1)**. The subclinical hypothyroid (7.615 ± 0.1µIU/ml) patients showed significant increase in TSH levels and it was much more significant in overt hypothyroid cases (39.758 ± 4.46µIU/ml) when compared with controls. The levels of fT4 (0.84 ± 0.03ng/dL) and fT3 (3.08 ± 0.07pg/dL) decreased slightly in subclinical hypothyroid patients as compared to the corresponding values in controls (0.94 ± 0.03ng/dL and 3.20± 0.04pg/dL respectively) but this was significant statistically. In overt hypothyroid cases, fT3 and fT4 (2.60 ± 0.07pg/dL and 0.43 ±

0.1532ng/dL respectively) levels showed a highly significant decrease as compared to the control group.

Table 1: Comparison between the TSH, fT4 and fT3 values obtained in hypothyroid and euthyroid subjects

	Euthyroid	SCH	OH
TSH (μIU/ml)	2.428 ± 0.11	7.615 ± 0.11**	39.758 ± 4.46**
fT4 (pg/dl)	0.943 ± 0.03	0.84 ± 0.03*	0.43 ± 0.02**
fT3 (ng/ml)	3.205 ± 0.04	3.08 ± 0.07*	2.60 ± 0.07**

**p value vs controls <0.05; **p value vs controls <0.001*

Mean serum level of TC in patients with SCH (236.724 ± 9.47mg/dl) was significantly high from that of value in controls (179.133 ± 6.69mg/dl) (p=0.045) (**table 2**). All other parameters were not statistically significant as compared to the controls. Patients with OH had statistically significant higher levels of TC (260.04 ± 11.07mg/dl, p<0.001), TG (171.76 ± 1.8mg/dl, p<0.05), LDL-C (151.635 ± 8.44mg/dl, p<0.001) and VLDL-C (34.35 ± 4.06mg/dl, p<0.05) when compared with controls. There was an increase in HDL-C in both SCH and OH group though not significant statistically. LDL-C/HDL-C and TC/HDL-C ratios were also not significant statistically in either group. When subclinical and overt hypothyroid cases were compared, TSH, fT3 and fT4 values showed a statistical significance. The mean levels of atherogenic lipid variables were greater in OH than in SCH, although the differences did not reach statistical significance.

Table 2: Lipid parameters in patients with hypothyroidism vs controls

Parameters	Control	SCH	p value*	OH	p value**
TC	179.133 ± 6.697	236.724 ± 9.472	0.045	260.043 ± 11.073	0.000
LDL-C	113.840 ± 8.467	154.193 ± 17.042	0.212	151.635 ± 8.446	0.001
HDL-C	41.500 ± 3.126	45.296 ± 3.783	0.476	49.059 ± 3.494	0.125
VLDL-C	23.133 ± 2.483	33.296 ± 1.995	0.115	34.35 ± 4.068	0.041
TG	115.667 ± 8.022	166.48 ± 7.481	0.115	171.761 ± 1.800	0.041
TC/HDL-C	4.643 ± 0.404	5.798 ± 0.757	0.278	5.132 ± 0.514	0.281
LDL/HDL	3.035 ± 0.344	3.843 ± 0.669	0.624	3.439 ± 0.38	0.232

**SCH vs control; **OH vs controls*

Correlation coefficients (r) between TSH, fT3 and fT4 levels, and lipid parameters were also calculated to find if any association exists between them. No correlation was found in any of the parameters in SCH except HDL which showed a negative correlation with fT4 (**table 3**). Other parameters did not show any statistically significant correlation.

Table 3: Correlation of lipid profile parameters with thyroid function in subclinical hypothyroid cases

	TSH		ft4		ft3	
	r values	p value	r values	p value	r values	p value
TC	0.033	0.830	-0.004	0.978	-0.007	0.952
LDL-C	-0.278	0.236	-0.089	0.736	0.212	0.278
HDL-C	-0.144	0.544	-0.519	0.005	0.108	0.591
VLDL-C	0.156	0.312	0.057	0.630	-0.151	0.208
TG	0.156	0.312	0.057	0.630	-0.151	0.208
TC/HDL-C	0.359	0.120	0.337	0.086	0.005	0.979
LDL-C/HDL-C	0.158	0.518	0.203	0.321	0.052	0.801

In OH group, TSH showed a positive correlation ($p<0.05$) and fT4 levels showed a negative correlation with TC (**table 4**). There was also negative correlation of serum HDL-C and fT4.Moreover, fT3 also showed significant negative correlation with TC/HDL-C and LDL/HDL-C ratios in OH cases ($p<0.05$).

Table 4: Correlation of lipid profile parameters with thyroid function in overt hypothyroid cases

	TSH		fT4		fT3	
	r values	p value	r values	p value	r values	p value
TC	0.315	0.035	-0.264	0.023	-0.098	0.952
LDL-C	0.127	0.628	-0.282	0.512	-0.237	0.278
HDL-C	-0.010	0.969	-0.447	0.017	0.398	0.114
VLDL-C	0.139	0.362	0.078	0.512	-0.115	0.452
TG	0.139	0.362	0.078	0.146	-0.115	0.452
TC/HDL-C	0.013	0.959	0.343	0.074	-0.541	0.025
LDL-C/HDL-C	0.031	0.906	0.214	0.275	-0.526	0.030

DISCUSSION

The data in our study shows that the mean age of the hypothyroid subjects was 31.55 ± 2.1 years, majority were women, and prevalence of hypothyroidism (overt and subclinical) was high in this group. The hypothyroidism in young adult women could be iodine deficiency- related as at this age, Hashimoto's disease is most unlikely.

In our study, it was found that patients with OH had significantly higher levels of TC, LDL-C, TG and VLDL-C as compared to control group. Moreover, there was positive correlation of TC with TSH level ($p=0.035$) and negative correlation with fT4 ($p=0.023$) in overt hypothyroid group. However, in SCH patients, only TC was slightly high ($p=0.045$) as compared to the controls. The explanation for these observed findings lie in the fact that thyroid hormones regulate the activity of some key enzymes in lipoprotein transport and therefore alter the lipoprotein levels in hypothyroidism. The primary mechanism for hypercholesterolemia in hypothyroidism is accumulation of LDL cholesterol due to a reduction in the number of cell surface receptors for LDL[19], resulting in decreased catabolism of LDL. The promoter of the LDL receptor gene contains a thyroid hormone responsive element (TRE) which allows the triiodothyronine (T3) to upregulate the gene expression of the LDL receptor[20]. Furthermore, decreased thyroid function not only increases the number of LDL particles but also promotes LDL oxidability[21,22]. Hypertriglyceridemia associated with increased levels of VLDL is attributable to the decreased activity of lipoprotein lipase, which results in a decreased clearance of triglyceride-rich lipoproteins[23]. Thus, hypothyroidism is a major cause of secondary dyslipidemia, and may represent an increased risk for coronary heart disease.

It is interesting to note that in the levels of HDL were progressively increased from euthyroid to SCH to OH, though not statistically significant. Further, there was increase in TC/HDL-C and LDL-C/HDL-C ratios in both the hypothyroid groups as compared to the controls which emphasizes the fact that the increased HDL alone does not protect against coronary heart disease[24]. Plasma HDL concentrations have been reported to be elevated in severe hypothyroidism[25-27]. These conflicting results are partly because of the recently reported regulation of cholesterol ester transfer protein (CETP) and hepatic lipase (HL) activity by thyroid hormone[24]. CETP transports cholesteryl esters from HDL2 to VLDL, IDL and remnants, and replaces it with triglycerides[28]. HDL2 is consequently hydrolyzed and converted to HDL3 by HL. The activity of CETP and HL are low in hypothyroidism thereby leading to increased HDL2 levels[29].

An increasing number of patients with SCH are being detected by the widespread use of TSH screening. However, until now, no direct association between SCH and atherosclerosis has been proven[6,30,31] and whether SCH should be treated for the risk of cardiovascular disease is controversial[32]. A few studies[33,34] have suggested

that the majority of patients with SCH did not differ from controls in risk factors for coronary heart disease. In this respect, in our study, patients with SCH had only moderate increase in TC ($p<0.05$), whereas other lipid profile parameters did not differ significantly when compared with control individuals.

CONCLUSION

Our study concludes that overt hypothyroidism is a major cause of secondary dyslipidemia as it is associated with increase in the levels of total cholesterol, LDL-C, VLDL-C and triglycerides which may lead to increased cardiac risk. Our study also shows high prevalence of hypothyroidism in women of reproductive age group which is a cause of serious concern due to its effects during pregnancy and its association with dyslipidemia. Subclinical hypothyroidism has only a moderate increase in total cholesterol. Further, as SCH progresses to OH, there is gradual derangement of lipid profile. Thus, patients with dyslipidemia should be screened for hypothyroidism before being given specific lipid-lowering drug therapy. It seems that thyroid hormone replacement, if used, would be most beneficial in patients with OH instead of SCH.

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