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LIPID PROFILE ABNORMALITIES IN HYPOTHYROIDISM

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ABSTRACT
The present investigation was conducted to study the contributive role of clinical and subclinical hypothyroidism in causing dyslipidemia. A total of 220 clinical hypothyroidism patients, 146 subclinical hypothyroids and 200 euthyroid controls, with a mean age of 39 years (range- 25 – 55 years) were included. The thyropropin, triiodothyronine and thyroxine levels of the patients were assayed by enzyme immunoassay method on ELISA Reader and lipid profile of the patients was estimated by enzymatic colorimetric method. The clinical hypothyroid patients exhibited decline in T3 and T4 concentration (T3 < 0.80 ng/ml, T4 < 4.5 µg/dl) and elevation in TSH level (TSH > 6 mIU/dl) whereas subclinical hypothyroidism patients have high thyrotropin concentration (TSH >6 mIU/dl) with normal thyroxin and triiodothyronine levels. The patients with clinical hypothyroidism exhibited significant increase in concentration of total cholesterol ((p<0.0001), LDL (p<0.0001) and triglycerides (p<0.0001), whereas HDL (p<0.0001) showed a decrease in its concentration in comparison to euthyroid controls. A decline in the the hepatic lipase activity (p<0.0001) was also noted. Subclinical hypothyroid patients revealed significant increase in concentration of total cholesterol (p<0.0001), LDL (p<0.0001) and triglycerides level (p<0.0001). Non significant decrease in HDL was observed in subclinical hypothyroid patients. We have found that hypothyroidism is associated with an atherogenic lipid and lipoprotein profile, characterized by an increase in concentration of total cholesterol, LDL and triglycerides and by decrease in HDL levels.

KEY WORDS: Lipid, Hypothyroidism, Clinical, Subclinical, Euthyroids.

INTRODUCTION

Hypothyroidism is defined as a deficiency of thyroid activity. It results from reduced secretion of total thyroxine (T4) and triiodothyronin (T3). Biochemical decrease in T4 and T3 lead to hyper secretion of pituitary thyroid stimulating hormone (TSH) and an amplified increases in serum TSH levels. Thyroid hormones have significant effects on the synthesis, mobilization and metabolism of lipids. They affect serum cholesterol mainly by altering lipoprotein metabolism (Erem *et al*., 1999). Overt hypothyroidism is associated with significant increases in circulating concentration of total and low density lipoprotein cholesterol (LDL) (O'Brien *et al*., 1993).

Hypercholesterolemia is favored due to the hormone deficit and to the decreased activity of the lipoprotein lipase (Mansourian *et al*., 2008).

A relationship between dyslipidemia and atherosclerosis is well established in overt hypothyroidism. It is uncertain whether subclinical hypothyroidism (increased serum TSH, normal serum, T4 and T3) is also associated with hyperlipidemia. Some case-control studies, have reported increased concentration of serum total cholesterol and LDL-C in subjects with subcliical hypothyroidism compared with euthyroid controls (Caraccio *et al*., 2002). Several large cross-sectional studies found no significant difference in total cholesterol or LDL-C between

subjects with subclinical hypothyroidism and euthyroidism (Vierhapper *et al*., 2000; Kanaya *et al*., 2002; Hueston and Pearson, 2004).

The present study was designed to assess the contributive role of clinical and subclinical hypothyroidism in development of dyslipidemia.

SUBJECTS AND METHODS

Subjects

In this cross-sectional study, 566 subjects (220 clinical and 146 subclinical hypothyroid patients, and 200 euthyroid controls) with a mean age of 39 years (ranged- 20-55 years) were included. A detailed history with emphasis on symptoms related to impaired thyroid function was recorded. Subclinical hypothyroidism was established on the basis of elevated TSH level (≥4.5 µIU/ml) and normal T4 and T3 values, while clinical hypothyroidism was diagnosed as increased TSH level with lowered T3 and T4 levels. The research protocol was approved by the institutional ethics committee and informed consents were obtained from all the patients.

Methods

Fasting venous blood semples were collected, centrifuged promptly, and separated sera stored at -20˚C. TSH, T3 and T4 were measured by enzyme immuno assay using ELISA microplate reader (Alpha Diagnostic). Serum total cholesterol was measured using a cholesterol oxidase enzymatic method, triglycerides by a glycerol oxidase enzymatic method and HDL by a cholesterol oxidase enzymatic method in supernatant after precipitation with phosphotungastic acid $MgCl_2$. and hepatic lipase activity were analyzed by using enzymatic colorimetric method on

auto-analyzer (Roche Diagnostic). LDL was calculated by using Friedwald formula (Friedwald *et al*., 1972).

Statistical analysis

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 0.001 was considered significant. Correlation between parameters was performed by correlation matrices analysis.

RESULTS

Table 1 summarize the hormonal profile of the study subjects. Compared with euthyroids, the TSH level was significantly ($p<0.0001$) increased in clinical and subclinical hypothyroids. T3 and T4 concentrations were significantly ($p<0.0001$) decreased in clinical hypothyroid patients, while in subclinical patients these hormones showed non-significant difference.

TABLE 1. Hormonal status of the hypothyroidism patients and euthyroid controls.

Subjects	Number of patients	TSH (mIU/dl)	T3 (ng/ml)	T4 (µg/dl)
Subclinical	146	9.3 ± 2.9**	1.5 ± 0.45	8.4 ± 1.4
Clinical	220	12.6 ± 4.7**	0.1 ± 0.16**	2.8 ± 1.1**
Euthyroid	200	3.4 ± 1.6	1.4 ± 0.33	8.6 ± 0.89

**p<0.0001

The mean serum cholesterol level was increased significantly ($P < 0.001$) in clinical and subclinical hypothyroid patients in comparison to euthyroid controls. Tucky HSD multiple comparison test revealed that the cholesterol level was significantly increased, in subclinical ($q = 40.79$, 95% CI = 36.05 – 45.53, $p<0.0001$) as well as in clinical ($q = 51.07$, 95% CI = 46.42 – 55.32, $p<0.0001$) hypothyroid patients in comparison to the euthyroid controls. The %age elevation was higher in clinical hypothyroid patients (30.79) than in subclinical patients (24.61) (Table 2)

TABLE 2 Total cholesterol level of hypothyroid patients and euthyroid controls.

Subjects	N	Total Cholesterol (mg/dl)	q	95% confidence interval	%age elevation
Subclinical	146	207.34 ± 16.31*	40.79	36.05 – 45.53	24.61
Clinical	220	217.62 ± 21.48*‡	51.07	46.42 – 55.32	30.79
Euthyroid	200	166.38 ± 15.49			

*P<0.0001 vs. Euthyroid, ‡ P<0.0001 vs. subclinical hypothyroid

The mean serum HDL level was decreased significantly ($P < 0.001$) in clinical and subclinical hypothyroid patients in comparison to euthyroid controls. Tucky HSD multiple comparison test revealed that the HDL level was significantly decreased, in subclinical ($q = -21.39$, 95% CI = -23.29 – -19.51, $p<0.0001$) as well as in clinical ($q = -21.53$, 95% CI = -23.23 – -19.84, $p<0.0001$) hypothyroid patients in comparison to the euthyroid controls (Table 3)

TABLE 3. HDL level of hypothyroid patients and euthyroid controls.

Subjects	N	HDL (mg/dl)	q	95% confidence interval	%age elevation
Subclinical	146	40.67 ± 5.8*	-21.39	-23.29 – -19.51	-35.58
Clinical	220	41.67 ± 7.68*‡	-21.53	-23.23 – -19.84	-34.06
Euthyroid	200	63.14 ± 8.33			

*P<0.0001 vs. Euthyroid, ‡ P<0.0001 vs. subclinical hypo

The mean serum LDL level was increased significantly ($P < 0.001$) in clinical and subclinical hypothyroid patients in comparison to euthyroid controls. Tucky HSD multiple comparison test revealed that the LDL level was significantly increased, in subclinical ($q = 52.14$, 95% CI = 47.02 – 57.26, $p<0.0001$) as well as in clinical ($q = 59.82$, 95% CI = 55.22 – 64.41, $p<0.0001$) hypothyroid patients in comparison to the euthyroid controls (Table 4)

TABLE 4. LDL level of hypothyroid patients and euthyroid controls.

Subjects	N	LDL (mg/dl)	q	95% confidence	%age elevation

				interval	
Subclinical	146	134.49 ± 17.49	52.14	47.02 – 57.26	63.53
Clinical	220	142.57 ± 22.89*‡	59.82	55.22 – 64.41	73.35
Euthyroid	200	82.24 ± 18.19			

*P<0.0001 vs. Euthyroid, ‡ P<0.0001 vs. subclinical hypo

The mean serum triglycerides level was increased significantly (P < 0.001) in clinical and subclinical hypothyroid patients in comparison to euthyroid controls. Tucky HSD multiple comparison test revealed that the triglycerides level was significantly increased, in subclinical (q = 49.05 , 95% CI = 44.77 – 53.33, p<0.0001) as well as in clinical (q = 64.87, 95% CI = 61.03 – 68.71, p<0.0001) hypothyroid patients in comparison to the euthyroid controls (Table 5)

TABLE 5. Triglycerides level of hypothyroid patients and euthyroid controls.

Subjects	N	Triglycerides (mg/dl)	q	95% confidence interval	%age elevation
Subclinical	146	153.60 ± 11.60*	49.05	44.77 – 53.33	47.05
Clinical	220	142.57 ± 22.89*‡	64.87	61.03 – 68.71	62.26
Euthyroid	200	82.24 ± 18.19			

*P<0.0001 vs. Euthyroid, ‡ P<0.0001 vs. subclinical hypo

In clinical hypothyroid patients a significant positive correlations between TSH and total cholesterol (r =0.79), triglycerides (r =0.59) and LDL (r =0.54) and significant negative correlation between TSH and HDL (r = -0.41) was observed. T3 and T4 showed negative relationship with total cholesterol (r=-0.78, r=-0.93, respectively), triglycerides (r = -0.78, r = -0.78, respectively) and LDL (r = -0.69, r = -0.63), and positive correlation with HDL (r = 0.71, r = 0.58, respectively) in these patients. Subclinical hypothyroid patients showed significant positive correlation between TSH and total cholesterol (r = 0.37), triglycerides (r = 0.61) and LDL (r = 0.38), and negative relationship with HDL (r = - 0.58). Non significant relationship was observed between T3, T4 hormones and lipid parameters in subclinical hypothyroid patients.

TABLE 6. Correlation between thyroid hormones and serum lipid concentrations

	TSH		T3		T4	
	Clinical	Subclinical	Clinical	Subclinical	Clinical	Subclinical
Total Cholesterol	0.79 (p<0.01)	0.37	-0.78 (p<0.01)	-0.02	-0.93 (p<0.001)	-0.05
Triglycerides	0.59 (p<0.05)	0.61 (p<0.05)	-0.78 (p<0.01)	-0.12	-0.78 (p<0.01)	-0.12
HDL	-0.41	-0.58 (p <0.05)	0.71 (p<0.01)	0.17	0.58 (p<0.05)	0.15
LDL	0.54 (p<0.05)	0.38	-0.69 (p<0.05)	-0.02	-0.63 (p<0.05)	-0.04

Tucky HSD multiple comparison test revealed that the activity of hepatic lipase was significantly lowered (q = -36.92, 95% CI = -37.81 - -34.38, p<0.0001), in clinical hypothyroid patients in comparison to the euthyroid controls (Table 7).

TABLE 7. Hepatic lipase activity in hypothyroids and euthyroids.

Subjects	N	Hepatic lipase (IU/L)	q	95% confidence interval	%age elevation
Subclinical	146	56.45 ± 8,65	-0.50	-2.44 – -1.44	-0.93
Clinical	220	20.38 ± 4.64*‡	-36.92	-37.81 – -34.38	-64.23
Euthyroid	200	56.98 ± 9.95			

*P<0.0001 vs. Euthyroid, ‡ P<0.0001 vs. sublinical hypothyroid

A non significant negative relationship existed between hepatic lipase activity and TSH in hypothyroid (r =-0.30, Fig. 1) patients. A significant positive correlation between enzyme activity and triiodothyronin (r = 0.54, Fig. 2), and thyroxine (r = 0.33, Fig 3) was observed in Clinical hypothyroid patients.

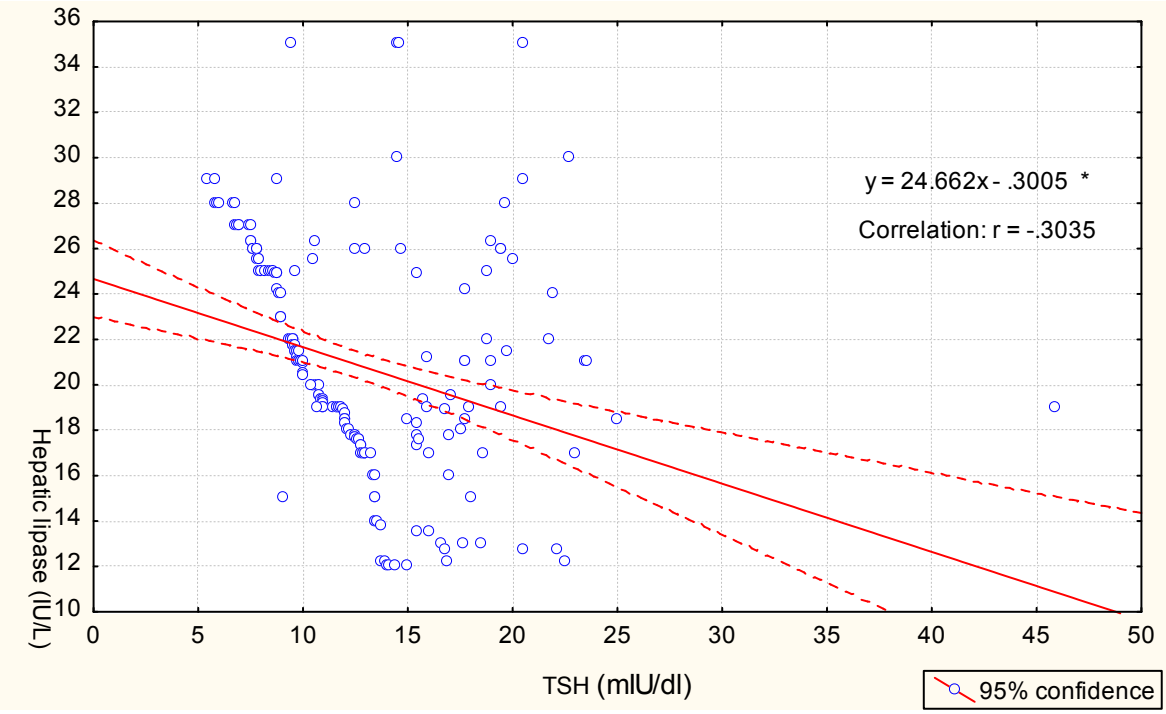

FIGURE 1. Scatterplot showing correlation between serum TSH and hepatic lipase activity in hypothyroid patients.

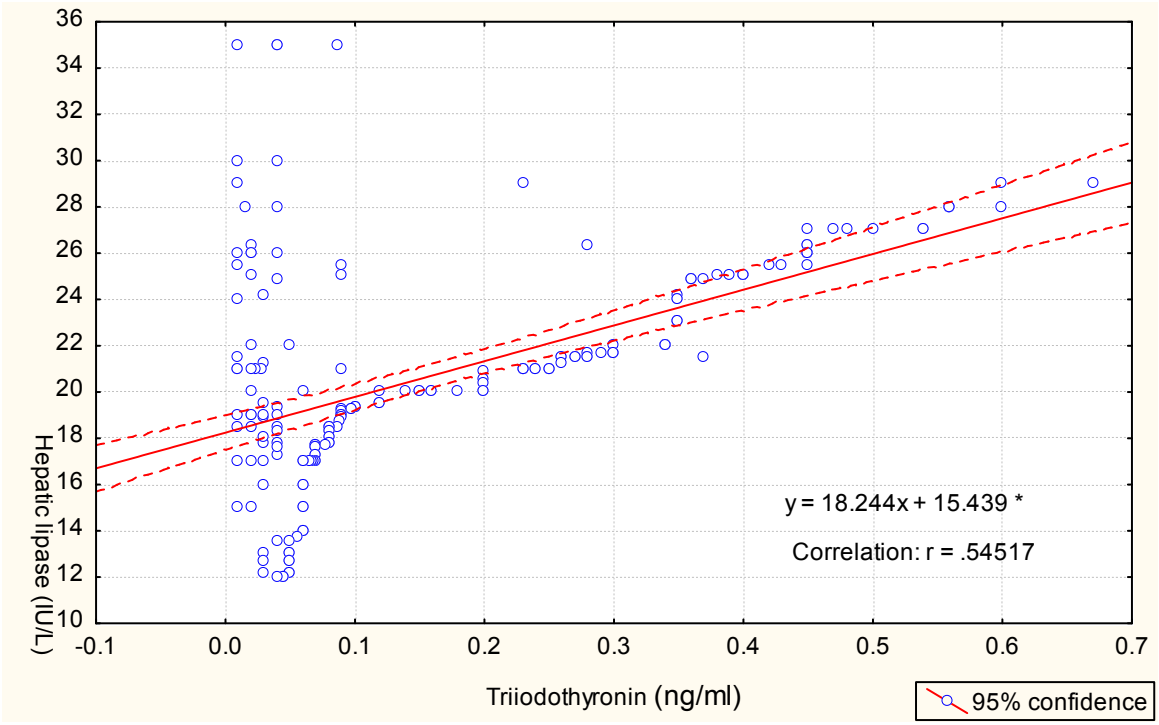

FIGURE 2. Scatterplot showing correlation between serum triiodothyronin and hepatic lipase activity in hypothyroid patients.

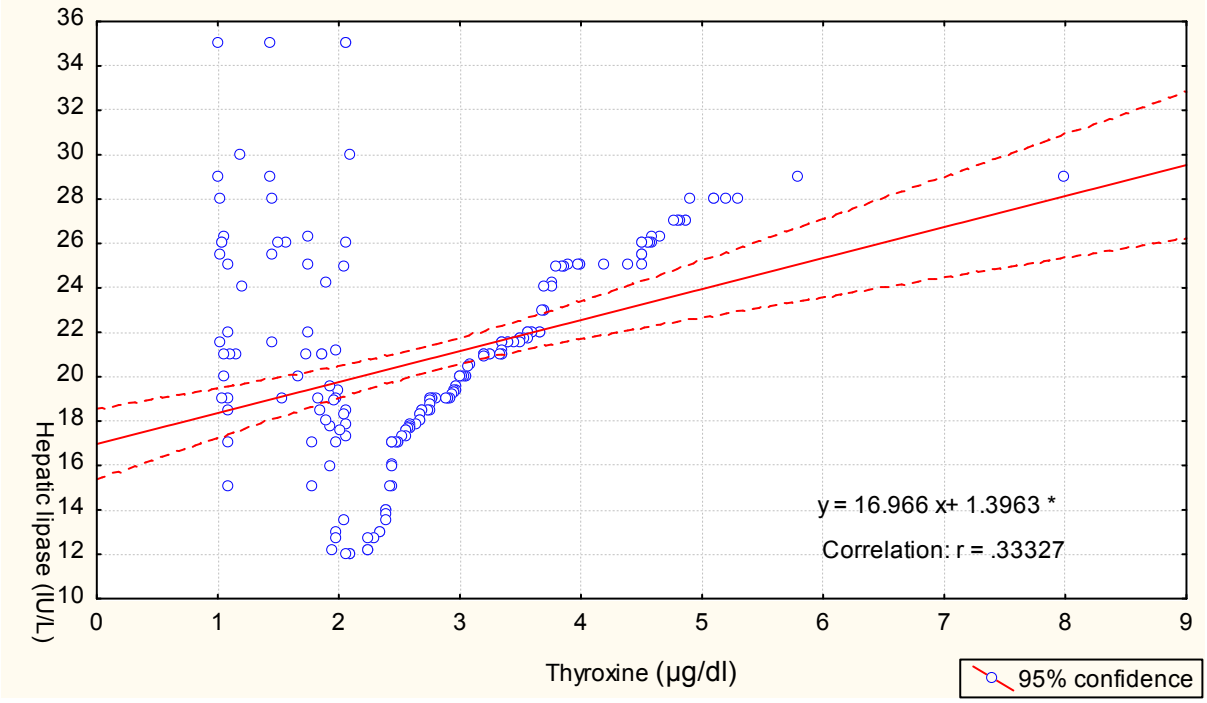

FIGURE 3. Scatterplot showing correlation between serum thyroxine and hepatic lipase activity in hypothyroid patients.

DISCUSSION

Hypothyroidism is characterized by a decrease in both synthesis and catabolism of lipoproteins. In most patients with myxedema, the relative greater decrease in catabolism and the resulting preponderance of synthesis results in high cholesterol concentrations. The present study documented that serum total cholesterol, triglycerides and LDL were significantly increased, while activity of hepatic lipase and concentration of HDL was decreased in subjects with Clinical hypothyroidism in comparison to euthyroid controls. The presence of hypercholesterolemia and hypertriglyceridemia in clinical hypothyroidism is well established (Erem, 2006) and is reconfirmed by the results of our investigation, comparable data with regard to subclinical hypothyroidism remain contradictory, since normal (Boger *et al*., 1993, Vierhapper *et al*., 2000) as well as increased (Caraccio *et al*., 2002; Walsh *et al*., 2005) levels has been reported. Total cholesterol and LDL levels are increased in patients with clinical hypothyroidism (Pearce *et al*., 2008). This is due to the decreased LDL-receptors' activity, resulting in decreased catabolism of LDL and IDL (Abbas *et al*., 2008). Moreover, a decrease in LPL activity is found in clinical hypothyroidism, decreasing the clearance of triglyceride-rich lipoproteins (Nikkila *et al*., 1972). Therefore, clinical hypothyroid patients may also present with elevated triglycerides levels associated with increased levels of VLDL and occasionally fasting chylomicronemia (Lee *et al*., 2004; Teixeira *et al*., 2008).

Hypothyroid patients may also exhibit elevated levels of HDL (Pearce *et al*., 2008) mainly due to increased concentration of HDL2 particles. Indeed, due to a reduction of HL activity a decrease in HDL2 catabolism is observed (Lam *et al*. 1986; Packard *et al*. 1993). Moreover, decreased activity of the CETP results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL levels (de Bruin *et al.,* 1993). Hypothyroid patients have increased lipoprotein (a) [Lp(a)] levels, which are associated with increased CVD risk (Tzotzas *et al.,* 2000). 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.

Serum total cholesterol and LDL were found to be significantly elevated in subclinical hypothyroid patients in comparison to euthyroid controls during present study, while HDL showed a non significant decline in its concentration.There is some controversy regarding the presence or the severity of subclinical hypothyroidism - induced dyslipidemia. There have been studies indicating no significant difference in lipid profile between SH patients and controls (Vierhapper *et al*., 2000; Heemstra *et al*., 2006; Brenta *et al*., 2007). Data from the NHANES III revealed increased levels of TC in SH patients (n=215) vs controls (n=8013). However, when adjusted for age, race, sex and the use of lipid-lowering drugs no difference was observed between SH and controls regarding lipid profile (Hueston & Pearson, 2004)

Some studies have shown that subclinical hypothyroidism dyslipidemia may also be accompanied by increased triglycerides (Milionis *et al*., 2005; Toruner *et al*., 2008) and decreased HDL levels (Erdem *et al*., 2008). Subclinical hypothyroidism is associated with biochemical abnormalities including elevated low density lipoprotein cholesterol (Diekman *et al.,* 1995) and impaired level of triglycerides (Waterhouse *et al.,* 2007). Moreover, subjects with high TSH levels also exhibit elevated total cholesterol and LDL

levels (Iqbal *et al*., 2006). Efstathiadou *et al*. (2001) evaluated serum lipid parameters of SH patients (n=66) and age and sex- matched euthyroid controls (n=75). Patients with subclinical hypothyroidism had significantly higher levels of total cholesterol, LDL and ApoB, whereas levels of triglycerides, HDL and ApoAI did not differ significantly compared with euthyroid controls.

We have found that hypothyroidism is associated with an atherogenic lipid and lipoprotein profile, characterized by an increase in concentration of total cholesterol, LDL and triglycerides and by decrease in HDL levels. In patients of subclinical hypothyroidism lipid abnormalities exhibited great individual variability. There might be a potential link between subclinical hypothyroidism and atherosclerosis.

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