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Research Paper

Effect of Hypothyroidism on Proatherogenic Lipid Levels.

Biochemistry

KEYWORDS : Hypothyroidism, Lipoproteins, Atherosclerosis

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ABSTRACT

Overt hypothyroidism is associated with abnormalities of lipid metabolism, which may predispose to the development of atherosclerotic coronary artery disease. Therefore the aim of the study was to assess proatherogenic lipid levels in 30-45 years aged women with newly diagnosed hypothyroidism and compare the same witheuthyroid control. The serum Lipoprotein(a)[Lp(a)],LDL cholesterol[LDL-C] and Oxidized LDL[Ox-LDL] levels were analyzedin two cohorts each of 25 divided into newly diagnosed cases of overt hypothyroidism and euthyroid women between the ages of 30-45 years in KMC Hospital, Mangalore, Karnataka, India. The results analysed using Statistical Package for Social Science version 20.0 arepresented as Mean ± SD and compared by Kruskal –Wallis test and MANN-Whitney U test.Correlation analysis was done by Spearman's correlation coefficient test. The mean levels of Lipoprotein, Direct LDL and Ox-LDL were high in cases of newly diagnosed hypothyroidism.Thyroid Stimulating Hormone levels were very well correlated with Lp(a) and Direct LDL. Dyslipidemia in patients with thyroid disease because of the effects of thyroid hormones in almost all steps of lipid metabolism, consisting of high levels of LDL cholesterol and Lp(a). High proatherogenic lipid levels particularly Lp(a) and LDL suggests risk of atherosclerosis in patients of hypothyroidism.

Introduction

The thyroid gland produces two hormones predominantly, thyroxine (T_4) and triiodothyronine (T_3).[1] Reduced production and action of thyroid hormones is the central feature of the clinical state termed hypothyroidism. Primary hypothyroidism is due to permanent loss or destruction of the thyroid, through processes such as autoimmune destruction or irradiation injury. Central or secondary hypothyroidism, due to insufficient stimulation of a normal gland, is the result of hypothalamic or pituitary disease or defects in the thyroid-stimulating hormone (TSH). Primary hypothyroidism which is the cause in more than 99% of the patients, there is a significant increase in basal serum TSH concentration. As hypothyroidism progresses, the serum TSH increases further, the serum free T_4 falls, and finally at the most severe stage, serum T_3 concentrations may become subnormal. [2]Thyroid hormones effects on lipid metabolism include: (a) enhanced utilization of lipid substrates (b) increase in the synthesis and mobilization of triglycerides stored in adipose tissue; (c) increase in the concentration of non esterified fatty acids (NEFA) and (d) increase of lipoprotein-lipase activity.[3] In hypothyroid patients the most frequent lipid abnormality is hypercholesterolemia mainly due to an increased concentration of low density lipoproteins (LDL).[4] Oxidized LDL is a modification of the LDL that occur when free redicals react with polyunsaturated fatty acids and induce lipid peroxidation. These modified lipid are proatherogenic and proinflammatory.[5] Overt hypothyroidism accompyning hypercholesterolemia, is widely recognized as a risk factor for atherosclerosis and cardiovascular disease. Apart from altered lipid profile patients of hypothyroidism has been associated with the elevated lipoprotein profile particularly a modified LDL that is Lipoprotein(a).[6] Therefore the aim of the study was to analyse the proatherogenic lipid levels[Direct LDL, Oxidised LDL and Lipoprotein(a)] in 30-45 years aged women in newly diagnosed hypothyroidism and compare the same with euthyroid control.

Materials and Methods

Case control study was done in which only women aged between 30-45 years were included on the basis of T_3, T_4 and TSH levels, present complains and history of treatment taken. From the KMC hospital, Ambedkar Circle and KMC hospital Attavar, 25 newly diagnosed hypothyroid women were included in the study with their consent. 25 euthyroid women were chosen from the general population as a control. Newly diagnosed cases of overt hypothyroidism and euthyroid women between the ages of 30-45 years were included in the study.Patients with history of diabetes, hypertension, ischemic heart disease , congestive cardiac failure, chronic renal failure were excluded. Pregnant women with known dylipidemic status and women on oral contraceptive pills and lipid lowering drugs were excluded.

Biochemical measurements: Serum was obtained from the blood, collected in a sterile vacutainer from each subject. The serum sample were taken for estimation of direct LDL-cholesterol, Oxidized LDL and Lipoprotein(a) at the Department of Biochemistry, Center for Basic Sciences, KMC Bejai**.**

Methods: The serum Lipoprotein(a), Direct LDL and Ox-LDL levels were analyzed by ECLIA, Enzymatic colorimetric assay and TBARS[7] methods respectively. The results analysed using Statistical Package for Social Science version 20.0 are presented as Mean ± SD and compared by Kruskal –Wallis test and MANN-Whitney U test. Correlation analysis was done by Spearman's correlation coefficient test. P-value <0.05 was considered as a significant.

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Results:

Variables	Euthyroid (group 1) N= 25	Newly diagnosed (group 2) N= 25	P value
Lipoprotein(a) (mg/dl)	21.36±8.82	37.14±14.92	<0.001
Direct LDL(mg/dl)	95 ± 10.93	136.76 ± 30.16	<0.001
Oxidized LDL(µmol/L)	7.99 ± 1.55	13.7 ± 3.68	<0.001
Age(years)	38.08 ± 6.06	37.88 ± 5.82	0.252
TSH(µIU/ml)	2.40 ± 0.85	11.96 ±13.18	<0.001
T_3(ng/ml)	1.46 ± 0.52	1.19 ± 0.32	0.01
T_4(µg/dl)	8.53 ± 2.0	7.28 ± 2.07	0.07

The study included 75 women aged between 30-45 years, divided into three groups on the basis of T_3 ,T_4,TSH levels, present complains and history of treatment taken.

Table 1.Comparison of variables among the groups.
The mean age and serum T_4 were similar without any significant difference among the groups. But a significant difference in mean TSH and T_3 values were noted. The difference was also significant for LDL-C, Ox-LDL and Lp(a).

Parameters	Group-I	Group-II	Mean Difference Z	p-value
Lipoprotein(a)	Euthyroid	Newly Diagnosed	-4.357	<0.001
Direct LDL	Euthyroid	Newly Diagnosed	-4.941	<0.001
Oxidised-LDL	Euthyroid	Newly Diagnosed	-5.229	<0.001

Table-2 Comparison of Lp(a), Direct LDL and Ox-LDL within the groups.
Z= MANN-Whitney U Test
The mean level of Lp(a), LDL-C and Ox-LDL were high in cases of newly diagnosed hypothyroidism in comparison to euthyroid group. (Fig.1-3)

Table-3 Correlation analysis between proatherogenic lipids with each other and with TSH among all the groups by Spearman's correlation coefficient test.

Category			LDL	Ox-LDL	TSH
Euthyroid	Lp(a)	r	-.281	.201	.222
		p	.174	.335	.285
	LDL	r		-.212	-.197
		p		.308	.346
	Ox-LDL	r			.189
		p			.365
Newly diagnosed	Lp(a)	r	.718**	.170	.739**
		p	**<0.001**	.416	**<0.001**
	LDL	r		.301	.725**
		p		.144	**<0.001**
	Ox-LDL	r			.295
		p			.152

There was a significant linear correlation was found between TSH and Lp(a) [r=0.739] , TSH and LDL-C [r=0.725] and also between Lp(a) and LDL-C[0.718] in newly diagnosed hypothyroid group. However Ox-LDL levels were not correlating with TSH levels in the same group. In other groups correlation analysis was not significant statistically.

Fig.1 Comparison of mean values of Lp(a) among the groups.

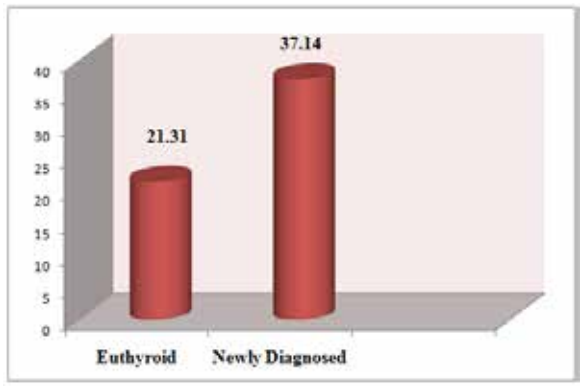


Fig.2 Comparison of mean values of Ox-LDL among the groups.

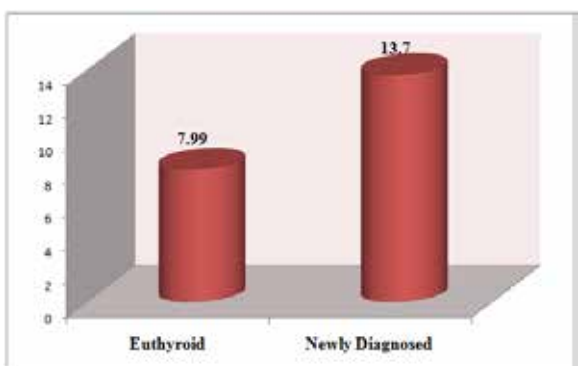
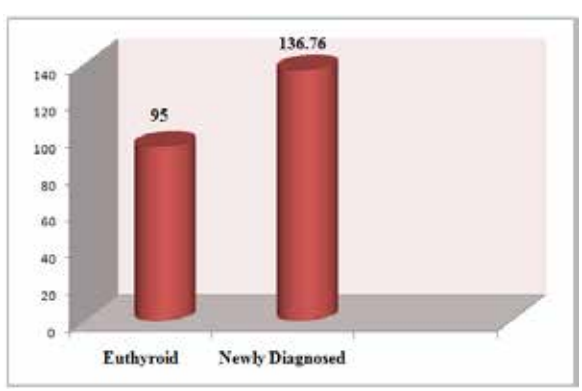


Fig.3 Comparison of mean values of Direct LDL among the groups.



Discussion
Dyslipidemia is a common finding in patients with thyroid disease because of the effects of thyroid hormones in almost all steps of lipid metabolism, consisting of high levels of total and LDL cholesterol.[8,9,10] The result observed in our study was similar to that of studies by Tzotzas et alwhere high lipid levels were found in hypothyroid patient.[11] LDL cholesterol is an independent and modifiable CVD risk factor. Mora et al have found LDL-C, Apo B-100, Apo B-100/A1 ratio to be useful marker for CVD risk.[12]

Overt hypothyroidism is characterized by hypercholesterolemia and a marked increase in low-density lipoproteins and apolipoproteins. Whereas the prevalence of overt hypothyroidism in patients with hypercholesterolemia is estimated to be 1.3% to 2.8%, 90% of patients with hypothyroidism had hypercholesterolemia. [13]

Specifically, some studies have demonstrated that LDL is increased in subclinical hypothyroidism and is reversed with thyroid hormone replacement.[14] In this study it was found in Overt hypothyroidism cases.The reported mechanisms for the development of hypercholesterolemia in hypothyroidism include decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver in addition to decreased receptor activity.[15]The catabolism of cholesterol into bile is mediated by the enzyme cholesterol 7-α hydroxylase.This liver-specific enzyme is negatively regulated by T_3 and may contribute to the decreased catabolism and increased levels of serum cholesterol associated with hypothyroidism.[16]The increased serum lipid levels in subclinical hypothyroidism as well as in overt disease are potentially associated with increased cardiovascular risk.[17] If untreated, the dyslipidemia together with the diastolic hypertension associated with hypothyroidism may further predispose the patient to atherosclerosis.[18-20]

It's been proven that LDL cholesterol has a major role in formation of atheromatous plaque and along with it another modified lipid which Lp(a) which has been considered as an emerging risk factor for atherosclerosis.[21]Because of the evidence linking raised Lp(a) concentrations with the development of atherosclerosis,[22] attention has focused on serum Lp(a) levels in thyroid diseases. This lipoprotein is synthesized mainly in the liver and consists of a LDL particle bound to an apoprotein that is structurally similar to plasminogen. The relationship between overt hypothyroidism and Lp(a) levels and the effect of levothyroxine therapy are still controversial.[23] The findings of this study is high level of Lp(a) along with high LDL cholesterol suggesting risk of atherosclerosis in patients of hypothyroidism. In this study Lipoprotein(a) level were high in Newly diagnosed cases and the levels reduced in on treatment group but the difference was not statistically significant. This suggests the predominance of genetic factors in Lp(a) metabolism, atleast in hypothyroidism, although thyroid hormones are proposed to play a role in Lipoprotein(a) metabolism.[24]hus screening for proatherogenic lipids should be done as early as possible in hypothyroid patients preferably at subclinical stage since in the changes which occurs due to high lipids in later stages .

Another aspect of the study was related to oxidative stress and hypothyroidism. In our study the Oxidised LDL levels were elevated in newly diagnosed hypothyroid patients. This finding was similar to the study done by Nanda et al[25]and Erdamar et al[26].Oxidized LDL (Ox-LDL) are known to promote atherogenesis through foam cell formation and inflammatory responses. The process involves receptor-mediated endocytosis of Ox-LDL which leads to lipid accumulation and vascular cell dysfunction including induction of apoptosis which represents major cause of plaque growth and rupture. The evaluation of the real effects of thyroid hormone on parameters of oxidative stress appears very difficult considering that thyroid hormone levels are influenced by diet, environmental factors, and reaction capacity to daily stress situations, in which cases, the parameters of oxidative stress are also modified.For this reason, the effect of thyroid hormone on oxidative stress parameters in women is not clear and depends on different variables.

This study was conducted to know the proatherogenic lipid levels in Hypothyroidism patient. Main reason for that is because of influence of thyroid hormones on the expression of enzymes involved in all steps of lipid metabolism leading to the development of qualitative and quantitative changes in lipid levels, in thyroid disease. Dyslipidemiacoexists with other metabolic abnormalities, including, hypertension, insulin resistance, oxidative stress, all of them being risk factors for cardiovascular disease. In addition, dyslipidemia induces insulin resistance and oxidative stress, via a vice- vicious cycle. The existing data support that there is an increased cardiovascular morbidity in patients with thyroid disease. However, more studies need to be done, especially prospective on larger no. of population, to elucidate the real significance of dyslipidemia or other metabolic changes to CVD morbidity and mortality in clinical thyroid disease.

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