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Original Research Article

Serum Apolipoprotein levels in Hypothyroidism

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Abstract

Dyslipidemia is a common finding in patients with thyroid disease, explained by the adverse effects of thyroid hormones in almost all steps of lipid metabolism. Clinical hypothyroidism, through different mechanisms, are associated with lipid alterations, mainly concerning total and LDL cholesterol and less often HDL cholesterol, triglycerides, lipoprotein (a), apolipoprotein A1, and apolipoprotein B. In addition to quantitative, qualitative alterations of lipids have been also reported, including atherogenic and oxidized LDL and HDL particles. In thyroid disease, dyslipidemia coexists with various metabolic abnormalities and induce insulin resistance and oxidative stress via a vice-vicious cycle. The above associations in combination with the thyroid hormone induced hemodynamic alterations, might explain the increased risk of coronary artery disease, cerebral ischemia risk, and angina pectoris in older, and possibly ischemic stroke in younger patients with overt or subclinical hyperthyroidism. This article presents a correlation study between hypothyroidism, Apo B and Apo A. It has been found that the 55 subjects enrolled in this study show a significant correlation between TSH and Apo B.

Keywords: Dyslipidemia, thyroid disease, metabolism, hypothyroidism.

INTRODUCTION

Thyroid disease, namely hypothyroidism and hyperthyroidism, constitutes the most common endocrine abnormality in recent years, diagnosed either in subclinical or clinical form. According to the 6-year duration NHANES III Study, the prevalence of hypothyroidism was 4.6% (0.3% clinical and 4.3% subclinical) and of hyperthyroidism 1.3% (0.5% clinical and 0.7% subclinical), in population aged at least 12 years, showing an age and sex dependence [1].

Thyroid disease is associated with various metabolic abnormalities, due to the effects of thyroid hormones on nearly all the major metabolic pathways. Thyroid hormones regulate the basal energy expenditure through their effect on protein, carbohydrate, and lipid metabolism. This might be a direct effect or an indirect effect by modification of other regulatory hormones such as insulin or catecholamines [2]. Dyslipidemia is a common metabolic abnormality in patients with thyroid disease, either in the overt or subclinical forms of the disease, and constitutes the end result of the effect of thyroid hormones in all aspects of lipid metabolism leading to various quantitative and/or qualitative changes of triglycerides, phospholipids, cholesterol, and other lipoproteins [3].

In thyroid disease, dyslipidemia and the coexisting metabolic abnormalities, in combination with the thyroid hormone-induced hemodynamic alterations, explain the high risk for cardiovascular disease [4, 5]. Thyroid hormones influence all aspects of lipid metabolism including synthesis, mobilization, and degradation [3]. Thyroid hormones stimulate cholesterol synthesis by inducing 3-hydroxy-3-methyl-glutaryl coenzyme A reductase in the liver [6]. Thyroid hormones affect lipoprotein lipase activity and thus, the hydrolysis of triglycerides into very-low, density lipoprotein (VLDL) and chylomicrons into fatty acids and glycerol [3]. In hypothyroidism, lipoprotein lipase activity in the adipose tissue has been found normal or decreased, in addition to decreased hepatic lipase activity resulting in normal or high levels of triglycerides [7].

In hyperthyroidism, although lipoprotein lipase activity is usually normal [8], an increased liver fatty acid synthesis and oxidation is observed due to enhanced acetyl-CoA carboxylase 1 and carnitine palmitoyl transferase-Ia expression leading to increased VLDL biosynthesis [9]. The observed abnormalities in total and LDL cholesterol are associated with the changes in the thyroid hormone levels in

hypothyroidism, as they are significantly improved after thyroxine replacement treatment [10]. However, triglycerides, apoB, apoA1, Lp(a) levels, and qualitative abnormalities might be normalized or remain unchanged after treatment, suggesting a more complex cause of dyslipidemia in hypothyroidism [11].

Subclinical hypothyroidism is also associated with lipid abnormalities, including mainly increased total and LDL cholesterol in most [12, 13] but not all studies [14]. In contrast, HDL, triglycerides, Lp(a), apoB, and apoA1 levels did not exhibit any difference between patients with subclinical hypothyroidism and controls in the majority [15]. Rondeau et al. found that TSH was negatively correlated with HDL-C in euthyroid overweight or obese postmenopausal women [16].

Regarding the effects of treatment of subclinical hypothyroidism, the majority of studies suggest a normalization of total and LDL cholesterol levels after thyroxine substitution therapy [17]. However, there are few trials where LDL did not significantly fall after treatment [14, 16], especially if the pretreatment TSH levels were less than 10 mIU/L [18]. Triglycerides, HDL, apoA1, apoB, and Lp(a) levels are less influenced by thyroxine treatment in the majority of studies in subclinical hypothyroidism [19]. However, few studies exist that showed improved HDL, apoA1, apoB, and/or Lp(a) levels after treatment of subclinical hypothyroidism [20]. A quite recent study showed that the reduced transfer of triglycerides to HDL and phospholipids in subclinical hypothyroidism was fully reversed by achievement of euthyroidism [21].

MATERIAL AND METHOD

The present study was conducted in Department of Biochemistry, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India. Total 55 subjects out of which 32 suffering from euthyroidism and 23 from hypothyroidism were enrolled for this study. Samples collected from the patients was centrifuged at 3000 rpm and subjected to analyses using commercial kits. Apo A, Apo B and TSH were analyzed by chemiluminescence method on AU-480 Beckmann Coulter.All samples were treated in accordance with the Helsinki Declaration.

RESULTS AND DISCUSSION

The apo-lipo-protein B (Apo B100) is basically utilized, along with the other lipid kind of tests, to decide a person's danger of developing cardiovascular sickness (CVD). Apolipoprotein A (Apo A) helps in the movement and breakdown of lipids. It helps to estimate the level of high density lipoprotein in the blood.In the present study, the level of ApoA and ApoB had been studied in hypothyroidism patients. Table 1 and 2 shows that Apo B levels was significantly associated with serum TSH levels (r=0.493; p<0.001 on Spearman's correlation).

Table-1: The comparison of serum apoA and apoB levels in between euthyroid and hypothyroid subgroups

	No. of patients	TSH(µIU/ml) Median (IQR)		Apo A((mg/dl) Median (IQR)		Apo B (mg/dl) Median (IQR)	
Euthyroid	32	2.65 (1.82)		168.3 (60.69)		118.2(41.01)	
Hypothyroid	23	7.5 (8.21)	p<0.001	162.3 (43.74)	p=0.891	145.8 (49.57)	p=0.040*

Table-2: Spearman correlation of apoA and apoB with TSH

	Apo A		Apo B	
	r value	p value	r value	p value
TSH	-.006	0.967	0.493**	<0.001

Hypothyroidism has values and percentage of occurrence more in females than in males and the level of this disorder is severe in females of 31-40 yrs. Correlation and standard deviation were calculated for TSH, Apo A and Apo B and it was found that Apo B shows significant correlation with TSH as compared to Apo A under hypothyroidism condition. Thyroid hormones affect cholesteryl ester transfer protein and hepatic lipase activity, which are increased in hyperthyroidism and decreased in hypothyroidism, with consequent changes not only in total high-density lipoprotein (HDL) but also in HDL subfraction levels [22]. Furthermore, thyroid hormones, by binding to the thyroid hormone receptor, inhibit through a competitive action the liver X-receptor-mediated ATP-binding cassette transporter A1 gene expression resulting in decreased HDL levels in patients with hyperthyroidism and increased in hypothyroidism [23]. Experimental evidence suggests that thyroid hormones might also affect cholesterol-7alpha-hydroxylase in liver [24]. Thyroid hormones, especially tri-iodothyronine (T3), induce low-density lipoprotein (LDL) receptor gene expression in the liver, enhancing LDL clearance and explaining the decreased or increased LDL levels observed in hyperthyroidism and hypothyroidism, respectively [3]. Thyroid receptors seem to mediate the effects of thyroid hormones on lipid metabolism, and more specifically alpha 1 receptors control the lipogenesis in white adipose tissue, and β receptors regulate the activity of lipogenic and lipolytic enzymes in the liver [25]. The changes induced by thyroid hormones in enzyme activities, transfer proteins, and liver receptors involved in lipid metabolism are summarized in Table 3. Dyslipidemia is a common

finding in patients with clinical hypothyroidism, consisting of high levels of total and LDL cholesterol [26]. Data regarding triglycerides, lipoprotein (a) (Lp (a)), HDL, apolipoprotein B (apoB), and apolipoprotein A1 (apoA1) components are scarce, reporting either higher or similar to euthyroid subjects levels [27]. Qualitative changes of various lipid components have also been reported in clinical hypothyroidism, such as the enhanced LDL oxidation, reflected on the increased levels of markers of lipid peroxidation, such as MDA and thiobarbituric acid-reactive substances [19, 24].

Table-3: Changes in enzyme activities, transfer proteins, and receptors involved in lipid metabolism induced by thyroid hormones

Enzymes, transfer proteins, and liver receptors	Thyroid hormone effect
3-hydroxy-3-methyl-glutaryl coenzyme-A reductase	↑
Adipose lipoprotein lipase	Usually normal (may be ↓ in hypothyroidism)
Hepatic lipase	
Cholesteryl ester transfer protein	↑
ATP-binding cassette transporter A1	↑
Acetyl-CoA carboxylase 1	↓
Carnitine palmitoyl transferase-Ia	↑
7-alpha-hydroxylase	↑
LDL receptor	↓
	↑

Studies have shown the association of hypothyroidism with diastolic hypertension, hyperhomocysteinemia and possible coagulation deficits [26-28] Insulin resistance and increased intima media thickness of the common carotid artery are some of the severities developed by hypothyroidism patients in their lifetime [29]. Dyslipidemia is a common finding in patients with clinical hypothyroidism, consisting of high levels of total and LDL cholesterol [30]. Data regarding triglycerides, lipoprotein (a) (Lp(a)), HDL, apolipoprotein B (apoB), and apolipoprotein A1 (apoA1) components are scarce, reporting either higher or similar to euthyroid subjects levels [30]. Qualitative changes of various lipid components have also been reported in clinical hypothyroidism, such as the enhanced LDL oxidation, reflected on the increased levels of markers of lipid peroxidation, such as MDA and thiobarbituric acid-reactive substances [31]. Serum TSH levels should be screened while evaluation of dyslipidemia. Since many cases may go unrecognized and statins (drugs used to lower serum cholesterol) are known to cause myopathy more in cases with hypothyroidism.

The findings of our study are in line with these studies as we have shown significant correlation between Apo B and hypothyroidism, which suggests that the subjects enrolled in our study were dyslipidemic and had higher chances of developing the abnormalities associated with hypothyroidism as found in other studies. Since dyslipidemia is one of the severe conditions leading to cardiovascular disorders hence the subjects in our study may also have higher chances of developing cardiovascular disorders in their lifetime if left untreated.

CONCLUSION

Thyroid hormones regulate the expression of enzymes involved in all steps of lipid metabolism leading to the development of qualitative and quantitative changes of lipids, in thyroid disease. Dyslipidemia coexists with other metabolic abnormalities, including, hypertension, insulin resistance, and 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 and possibly mortality that is in part mediated by the dyslipidemia or the dyslipidemia-induced metabolic abnormalities. Since our study consisted of a limited number of patients, more studies need to be done, especially prospective, to elucidate the real significance of dyslipidemia or other metabolic changes to CVD morbidity and mortality in clinical and, even more, in subclinical thyroid disease.

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