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Review

Dyslipidemia in patients with thyroid disorders

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ABSTRACT

Thyroid disorders are known to influence lipid metabolism and are common in dyslipidemic patients. Overt and subclinical hypothyroidism have an adverse effect on the serum lipid profile that may predispose to the development of atherosclerotic disease. Although thyroid substitution therapy is beneficial for patients with overt hypothyroidism, the question of whether subclinical hypothyroidism must be treated remains unanswered. The association between thyroid autoimmunity and lipoprotein (a) levels is controversial. Hyperthyroidism may be the underlying cause for acquired hypocholesterolemia or unexpected improvement of the lipid profile of a previously hyperlipidemic patient.

Key Words: Hypothyroidism, hyperthyroidism, dyslipidemia, thyroid autoimmunity, thyroid disorders, lipoprotein (a)

INTRODUCTION

It is well known that alterations in thyroid function result in changes in the composition and transport of lipoproteins[1-3]. In general, overt and subclinical hypothyroidism is associated with hypercholesterolemia mainly due to elevation of low density lipoprotein (LDL) cholesterol levels, whereas high density lipoprotein (HDL) cholesterol concentration is usually normal or even elevated[3-5]. On the other hand, hyperthyroidism (both overt and subclinical) is accompanied by a decrease in serum levels of total, LDL and HDL cholesterol[6]. These changes in the lipid profile are explained by the regulatory effect of thyroid hormones on the activity of some key enzymes of lipoprotein metabolism. Specifically, the thyroid hormone stimulates the hepatic de novo cholesterol synthesis by inducing the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase that catalyzes the conversion of HMG-CoA to mevalonate, the first step in the biosynthesis of cholesterol[7]. This results in an enhanced intracellular cholesterol concentration in hyperthyroidism and a decreased one in hypothyroidism. Additionally, thyroid hormones activate the LDL receptors (figure); 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[8]. Moreover, thyroid hormones stimulate the cholesteryl ester transfer protein (CETP), an enzyme which transports cholesteryl esters from HDL_2 to the very low density lipoproteins (VLDL) and triglycerides in the opposite direction[9] (figure). Finally, thyroid hormones stimulate the lipoprotein lipase (LPL), which catabolizes the triglyceride-rich lipoproteins, and the

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hepatic lipase (HL), which hydrolyzes HDL_2 to HDL_3[10] (figure). The alterations in the lipid profile observed in different thyroid abnormalities, the effect of treatment of these disturbances on the restoration of lipid metabolism, as well as the potential clinical implications and therapeutic guidelines are briefly discussed.

I. HYPOTHYROIDISM

Hypothyroidism is a common metabolic disorder in the general population, especially in older women; 9.5% of the participants of the Colorado prevalence study had elevated levels of thyroid stimulating hormone[3]. Levels of total and LDL cholesterol tend to increase as the thyroid function declines[3]. Therefore, hypothyroidism constitutes a significant cause of secondary dyslipidemia[11,12].

I A. OVERT HYPOTHYROIDISM

In hypothyroid patients, despite the reduced activity of HMG-CoA reductase, there is often an increase in the serum total cholesterol concentration, mainly due to raised levels of serum LDL cholesterol and intermediate density lipoprotein (IDL) cholesterol[4,12]. Decreased activity of LDL-receptors' resulting in decreased receptor-mediated catabolism of LDL and IDL is the main cause of the hypercholesterolemia observed in hypothyroidism[13-15]. Hypertriglyceridemia associated with increased levels of VLDL and occasionally fasting chylomicronemia are found less commonly in this population[15]. These changes are attributable to the decreased activity of LPL, which results in a decreased clearance of triglyceride-rich lipoproteins[16]. The VLDL and IDL particles in hypothyroidism are rich in cholesterol and apolipoprotein E,

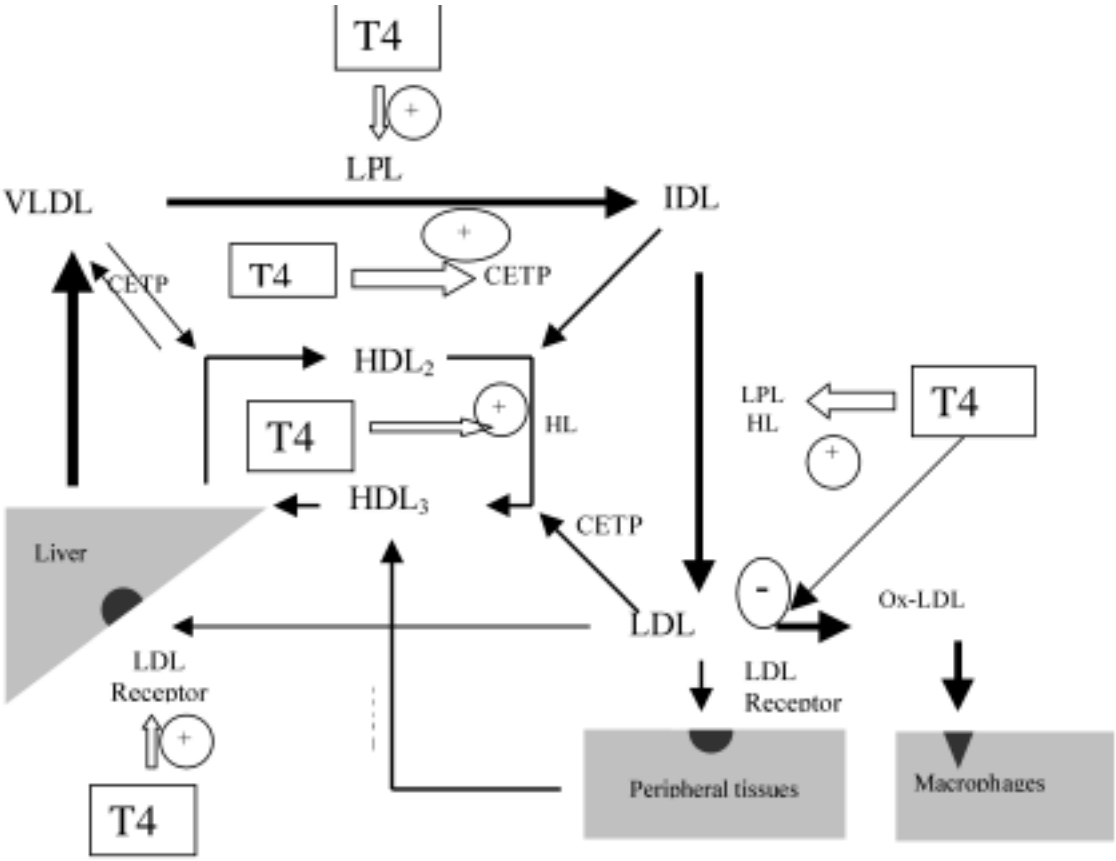

Figure. Thyroid hormones modulate lipid metabolism by a variety of ways: 1) upregulation of the low density lipoprotein (LDL) receptors, which results in enhanced catabolism of the LDL particles, 2) stimulation of the cholesteryl ester transfer protein (CETP), an enzyme which transports cholesteryl esters from high density lipoproteins 2 (HDL_2) to the very low density lipoproteins (VLDL) and the intermediate density lipoproteins (IDL), and triglycerides to the opposite direction, 3) activation of the lipoprotein lipase (LPL), which hydrolyses the triglyceride-rich lipoproteins, 4) stimulation of hepatic lipase (HL), which catabolizes HDL_2 to HDL_3 and IDL to LDL, and 5) inhibition of LDL oxidation. FC; free cholesterol, LCAT; lecithin cholesterol acyltransferase.

thus resembling β-VLDL particles of type III hyperlipoproteinemia[17]. It is not surprising that patients homozygous for the apolipoprotein E2 allele may develop the full-blown clinical syndrome of type III hyperlipoproteinemia if they become hypothyroid[18].

Hypothyroid patients usually exhibit elevated levels of high density lipoprotein (HDL) cholesterol mainly due to increased concentration of HDL_2 particles[19]. Decreased activity of the CETP results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL cholesterol levels[20]. Furthermore, decreased activity of the HL leads to decreased catabolism of HDL_2 particles[21]. Lipoprotein (a) [Lp(a)] levels, which are an independent risk factor for cardiovascular events, are also elevated in hypothyroid patients[22,23].

The above described abnormalities of lipid metabolism associated with overt hypothyroidism may predispose to the development of atherosclerotic coronary artery disease (CAD)[24,25]. Furthermore, hypothyroidism may contribute to the development of atherosclerosis by other mechanisms as outlined below: a) Decreased thyroid function not only increases the number of LDL particles but also promotes LDL oxidability[26,27] (figure); an obvious reason being that T4 has three specific binding sites on apolipoprotein (apo) B and inhibits LDL oxidation in vitro[26] b) Thyroid failure is accompanied by an increase in plasma homocysteine levels[28,29] with its known adverse effect on the cardiovascular system c) Hypothyroidism is strongly associated with arterial hypertension (especially diastolic)[30,31] via sympathetic and adrenal activation[30], and increased aortic stiffness[31] d) The insufficient concentration of thyroid hormones induces a hypercoagulable state[32]. A precise relationship between overt hypothyroidism and CAD has not been confirmed although data linking these two conditions have been demonstrated in autopsy studies[24,25].

Substitution therapy with L-thyroxine significantly improves the above described abnormalities of lipid metabolism and increases the previously low biliary cholesterol excretion[33]. In a recent meta-analysis, the mean decrease of serum total and LDL cholesterol levels after T4 substitution was -7.9 mg/dl and –10 mg/dl, respectively[34]. The reduction was larger in individuals with higher pre-treatment cholesterol levels and in hypothyroid individuals previously taking suboptimal T4 doses[34]. Serum HDL cholesterol levels tend to decrease with thyroid replacement, but this is a less consistent finding[35]. Serum Lp(a) levels also tend to decrease with restoration of euthyroidism[11,23]. In general, changes in serum lipoproteins in hypothyroid patients are correlated with changes in free thyroxin (FT4)[36]. Normally, it takes 4-6 weeks of replacement therapy with thyroxin to correct dyslipidemia in overt hypothyroidism. Superimposed dyslipidemia should be taken into account in cases of failure of substitution therapy to normalize the lipid profile, despite the restoration of euthyroidism[1].

Prevalence of overt hypothyroidism in patients with dyslipidemia is not low; in one of our studies, 2.8 % of the patients who were examined in our outpatient lipid clinic had elevated levels of TSH and reduced levels of FT4[11]. After restoration of euthyroidism with levothyroxine therapy, a significant decrease of serum levels of total and LDL cholesterol, apolipoprotein B and Lp(a) was observed while levels of HDL cholesterol, triglycerides and apolipoprotein AI were not changed significantly[11].

I B. SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism (SH), defined as the clinical status of mildly elevated serum TSH levels (up to 10 mU/L) with normal levels of FT_4 and FT_3, is a far more common disorder than overt hypothyroidism with a higher prevalence among women and older subjects[34,37]. Patients with SH tend to have higher levels of serum total and LDL cholesterol[34,38,39]. Even subjects with high normal TSH levels (2-4 mU/L) but with positive antithyroid antibodies may present with elevated cholesterol levels[40]. Among 248 patients who were followed in our outpatient lipid clinic for a period of 2 years, 11 patients (4.4%, 9 female, 2 male) had SH[11]. In a cross-sectional study we evaluated the serum lipid parameters of 66 patients with SH and 75 age- and sex-matched euthyroid controls[41]. Patients with SH had significantly higher levels of total cholesterol, LDL cholesterol, apolipoprotein B and Lp(a), whereas levels of triglycerides, HDL cholesterol and apolipoprotein AI did not differ significantly compared to euthyroid controls[41].

Certain studies have indicated that subclinical hypothyroidism has been associated with increased risk of CAD, especially in women with antibodies to thyroid peroxidase as well as in smokers, the SH-induced lipid abnormalities offering the most obvious expla-

nation for this association[42,43]. Moreover, SH impairs ventricular function as well as cardiovascular and respiratory adaptation to effort and, decreases heart rate variability impairs flow-mediated vasodilation, which is a marker of endothelial function[43]. Smoking may deteriorate the lipid profile in women with SH and aggravate the degree of thyroid failure, thus contributing to the development of atherosclerosis[44,45].

Several studies have shown conflicting results concerning the effect of levothyroxine substitution therapy on lipid parameters in patients with SH[23,25,34,39,40,46,47]. In a reanalysis, total cholesterol was decreased by 15 mg/dl irrespective of the initial level[39]. In another follow-up study, restoration of euthyroidism in 37 patients with SH resulted in no significant changes in serum lipid parameters except for a significant decrease in HDL cholesterol concentration by 6.8%[41]. However, patients with high pre-treatment total cholesterol levels (TC > 240 mg/dl) as well as high pretreatment levels of serum TSH (> 10 mU/L) exhibited a significant reduction in both total and LDL cholesterol levels following thyroid substitution therapy[41]. On the other hand, levothyroxine replacement did not produce any significant changes in Lp(a) concentrations in any of the studied groups[23,41].

Although it is clear that thyroid replacement therapy has beneficial effects on the serum lipid profile and on the risk of CAD in patients with overt hypothyroidism, the question of whether SH should be treated or not is still pending. It seems that thyroid substitution, if used, would be most beneficial in patients with prominent thyroid dysfunction (TSH levels > 10 mU/L), higher initial cholesterol levels and in smokers[44]. On the other hand, a possible thyroid substitution-induced decrease of HDL cholesterol concentration could undermine the beneficial effect of total and LDL cholesterol reduction in these patients. When treating people with angina pectoris or heart disease, one should be very cautious since thyroxin therapy may exacerbate angina or promote cardiac arrhythmia.

In conclusion, subclinical hypothyroidism is relatively common among hypercholesterolemic patients. Thus, the measurement of serum TSH levels should be included in the screening of patients with dyslipidemia[1,46,47]. Hypercholesterolemic patients with SH may be treated with thyroxin substitution therapy since the restoration of euthyroidism can effectively lower the lipid levels, relieve certain symptoms and may prevent progression to overt hypothyroidism[48].

II. THYROID AUTOIMMUNITY AND LIPOPROTEIN (a)

It has recently been reported that euthyroid males and postmenopausal females with evidence of thyroid autoimmunity (increased titers of thyroperoxidase and/or thyroglobulin autoantibodies) have increased Lp(a) levels[49]. In one study, the levels of Lp(a) in 22 euthyroid subjects (9 males and 13 postmenopausal females) with thyroid autoimmunity were compared with those of 64 age- and sex-matched controls without thyroid autoimmunity[50]. There were no significant differences in the values of lipid parameters, including Lp(a), between the two groups even when apo(a) phenotypes, which are known to influence Lp(a) levels, were taken into account[50]. Moreover, no significant difference in the Lp(a) levels was found in euthyroid patients with chronic renal failure regardless of the presence of thyroid autoimmunity, the apo(a) phenotype, the stage of renal failure and the mode of dialysis in end stage patients[51]. Finally, the presence of thyroid autoimmunity does not influence the serum lipid parameters even in patients with SH[41].

III. OVERT AND SUBCLINICAL HYPERTHYROIDISM

Despite the increased activity of the HMG-CoA reductase, levels of total cholesterol, LDL cholesterol, apolipoprotein B and Lp(a) tend to decrease in patients with clinical or subclinical hyperthyroidism due to increased bile excretion of cholesterol and mainly to increased LDL receptor gene expression resulting in enhanced LDL receptor-mediated catabolism of LDL particles[6,52]. Furthermore, HDL cholesterol levels are also decreased in hyperthyroidism due to increased CETP-mediated transfer of cholesteryl esters from HDL to VLDL and increased HL-mediated catabolism of HDL_2[6,52]. Triglyceride levels remain unchanged. Therapy of hyperthyroidism results in restoration of the above mentioned alterations of lipid metabolism[6,52]. Furthermore, hyperthyroidism results in enhanced LDL oxidability, which is strictly related to FT4 levels[27].

The incidence of hyperthyroidism is lower than that of hypothyroidism in the general population (2.2 vs 9.5%)[3], as well as in patients attending a lipid clinic,

since only 3 out of the 248 patients of our study had thyrotoxicosis[11]. However, hyperthyroidism constitutes not only a significant cause of acquired hypobetalipoproteinemia but can also be the underlying cause of unexpected improvement of the lipid profile of hyperlipidemic patients[53]. In the latter case, therapy of thyrotoxicosis restores the lipid parameters to the previously elevated levels[53].

CONCLUSION

Biochemical screening for thyroid dysfunction is of paramount importance in all dyslipidemic patients, as well as in all patients with unexpected improvement or worsening of their lipid profile. Underlying thyroid disorders should be recognized and treated in this setting. On the other hand, there is an absolute need for large studies designed to answer the question as to whether thyroid abnormalities (and especially SH) are associated with increased risk for CAD and whether therapy of these disorders might influence cardiovascular mortality.

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