Review Article

Lipid Abnormalities and Cardiometabolic Risk in Patients with Overt and Subclinical Thyroid Disease

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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. Not only overt but also subclinical hypo- and hyperthyroidism, 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.

1. 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 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 [4–7].

2. Effects of Thyroid Hormones on Lipid Metabolism

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 [8]. Thyroid hormones affect lipoprotein lipase activity and thus, the hydrolysis of triglycerides into very-low, density lipoprotein (VLDL) and chylomicrons into fatty
3. Lipid Abnormalities in Hypothyroidism

Dyslipidemia is a common finding in patients with clinical hypothyroidism, consisting of high levels of total and LDL cholesterol [3, 28–30]. 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 [3, 22, 28–34] (Table 2). 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, 35].

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 [29, 30, 36–40]. However, triglycerides, apoB, apoA1, Lp(a) levels, and qualitative abnormalities might be normalized or remained unchanged after treatment, suggesting a more complex cause of dyslipidemia in hypothyroidism [29, 31, 36–43].

Subclinical hypothyroidism is also associated with lipid abnormalities, including mainly increased total and LDL cholesterol in most [3, 28–30, 44–53], but not all [54–57], studies. 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 [29, 44–57], but not all [33, 44–48, 50, 55, 58–61], studies. In the majority of studies in subclinical hypothyroidism and controls in the majority [29, 44–48, 50, 55, 58–61]. A quite recent study showed that transfer of triglycerides to HDL and phospholipids was lower in patients with subclinical hypothyroidism than that in controls while transfer of free and esterified cholesterol to HDL, HDL particle size, and paraoxonase 1 activity did not exhibit any difference [63] (Table 2).

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 [28, 30, 40–43, 48, 49, 52, 53, 64–67]. However, there are few trials where LDL did not significantly fall after treatment [29, 46, 51], especially if the pretreatment TSH levels were less than 10 mIU/L [49, 68]. Triglycerides, HDL, apoA1, apoB, and Lp(a) levels are less influenced by thyroxine treatment in the majority of studies in subclinical hypothyroidism [28–30, 38, 43–49, 52, 53, 58, 65, 66]. However, few studies exist that showed improved HDL, apoA1, apoB, and/or Lp(a) levels after treatment of subclinical hypothyroidism [46–48, 51, 52, 58, 61, 67]. 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 [69].

4. Lipid Abnormalities in Hyperthyroidism

Most of the existing studies support lower total and LDL cholesterol levels in patients with hyperthyroidism [3, 32, 39, 68–73], while only a few data support no change [21]. Lower triglycerides, HDL, apoA1, apoB, and Lp(a) levels have been

### Table 1: 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 palmitoyltransferase Ia | ↑ |
| 7alpha-hydroxylase | ↑ |
| LDL receptor | ↑ |

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 [9–11].

In hyperthyroidism, although lipoprotein lipase activity is usually normal [10, 12], an increased liver fatty acid synthesis and oxidation is observed due to enhanced acetyl-CoA carboxylase 1 and carnitine palmitoyltransferase Ia expression leading to increased VLDL biosynthesis [13, 14]. Thyroid hormones affect cholesteryl ester transfer protein 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 [12, 15]. 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 [14, 16]. Experimental evidence suggests that thyroid hormones might also affect cholesterol-7alpha-hydroxylase in liver [17, 18]. Thyroid hormones, especially triiodothyronine (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 beta receptors regulate the activity of lipogenic and lipolytic enzymes in the liver [3, 14]. The changes induced by thyroid hormones in enzyme activities, transfer proteins, and liver receptors involved in lipid metabolism are summarized in Table 1.
found in patients with hyperthyroidism compared with euthyroid controls, which is questionable by other reports [21–23, 32, 68–72] (Table 2).

In hyperthyroidism, qualitative lipid changes, including increased levels of oxidized LDL, higher contents of thiobarbituric acid-reactive substances and dienes in LDL, low paraoxonase activity in HDL particles, and lower LDL content in antioxidant vitamin E and β-carotene have been found [21, 23, 24, 35].

The impact of treatment of hyperthyroidism on the lipid levels is not clear. Treatment with antithyroid drugs has been associated with elevated total and LDL cholesterol levels in some but not all studies [12, 21, 22, 68, 74–76]. Triglycerides are not affected by antithyroid treatment [21, 42, 70, 74, 76]. HDL, apoB, apoA1, Lp(a) levels have been found increased or unchanged after treatment [21, 22, 31, 42, 70–76]. The issue of lipid abnormalities in patients with subclinical hyperthyroidism has not been fully addressed. The existing data support normal levels of total LDL and HDL cholesterol, triglycerides, Lp(a), apoA1 and apoB while lower total and LDL cholesterol have also been reported [77, 78].

Table 2: Lipid abnormalities in clinical and subclinical thyroid disorders.

|                      | Clinical hypothyroidism | Subclinical hypothyroidism | Clinical hyperthyroidism | Subclinical hypothyroidism |
|----------------------|-------------------------|----------------------------|--------------------------|---------------------------|
| Total cholesterol    | Increased               | Increased or unaltered     | Decreased (rarely unaltered) | Decreased or unaltered     |
| LDL                  | Increased               | Increased (rarely unaltered) | Decreased (rarely unaltered) | Decreased or unaltered     |
| HDL                  | Unaltered or increased | Unaltered (rarely decreased) | Unaltered or decreased | Unaltered? (a few data exist) |
| Lipoprotein (a)      | Unaltered or increased | Unaltered (rarely increased) | Decreased? (a few data exist) | Unaltered? (a few data exist) |
| Triglycerides        | Unaltered or increased | Unaltered (rarely increased) | Decreased? (a few data exist) | Unaltered? (a few data exist) |
| Apolipoprotein B     | Unaltered or increased | Unaltered or increased     | Decreased? (a few data exist) | Unaltered? (a few data exist) |
| Apolipoprotein A1    | Unaltered or increased | Unaltered (usually)        | Unaltered or decreased    | Unaltered? (a few data exist) |

5. Thyroid Disease and Cardiovascular Risk

Most of the existing data supporting that thyroid disease is associated with increased cardiovascular risk which is mainly attributed to hemodynamic alterations as well as to a high risk of atherosclerosis [4–7].

5.1. Thyroid Disorders and Hemodynamic Changes. In hypothyroidism, the main functional cardiovascular disturbances involve decreased heart rate, elevated peripheral vascular resistance, increased diastolic blood pressure and cardiac afterload, reduced blood volume and cardiac preload, and diminished cardiac output. Impaired left ventricular systolic contractility at least during exercise and delayed left ventricular diastolic relaxation at rest and during exercise are common in both overt and subclinical hypothyroidism. Hypothyroidism is also associated with diastolic heart failure in the elderly [4, 7].

In hyperthyroidism, hemodynamic changes result mainly from increased β1-adrenergic activity. Increased triiodothyronine levels exert positive inotropic and chronotropic effects, leading to enhanced heart rate and systolic contractility and, consequently, increased cardiac output. Increased triiodothyronine stimulates sarcoplasmic reticulum Ca2+-ATPase, leading to systolic and diastolic dysfunction. Moreover, triiodothyronine reduces peripheral vascular resistance, causing a decrease in diastolic blood pressure and cardiac afterload, which further raises cardiac output. Decreased vascular resistance accounts for activation of renin-angiotensin-aldosterone system, which increases blood volume and cardiac preload, augmenting cardiac output even more [5, 7]. Biondi et al. found that even patients with subclinical hyperthyroidism had significantly higher average heart rate, enhanced systolic function, impaired diastolic function with prolonged isovolumic relaxation time, and increased left ventricular mass compared with euthyroid subjects [79].

5.2. Thyroid Disease and Atherosclerosis. As mentioned above, thyroid disease is related to the development of dyslipidemia which is a well-known atherogenic factor. Dyslipidemia induces insulin resistance oxidative stress, via a vicious cycle [19–24, 35]. Insulin resistance, hypertension, inflammation, oxidative stress, and coagulation deficits are also promoted by thyroid disease, independently of dyslipidemia [4–7]. The above associations support a multifactorial origin of atherosclerosis in thyroid disease, with dyslipidemia playing an important role [4–7].

Overt hypothyroidism has been associated with diastolic hypertension [4, 6, 7, 80, 81] and hyperhomocysteinemia [82–85]. Increased levels of high-sensitivity C-reactive protein and coagulation deficits have been reported in patients with hypothyroidism [83, 86–88]. Higher levels of homeostasis model assessment and lower levels of Matsuda indexes, suggesting insulin resistance, have been found in
patients with overt hypothyroidism compared with euthyroid subjects in some [25, 26, 89, 90] but not all [91, 92] studies. Impaired intracellular glucose catabolism and GLUT4 translocation, decreased glycerogen synthesis and glucose oxidation, and altered blood flow, have been proposed as underlying mechanisms [25, 26, 90, 93, 94]. Increased intima-media thickness of the common carotid artery has been reported in some studies in patients with overt hypothyroidism [53, 95, 96]. A higher frequency and/or severity of coronary heart disease [4, 97, 98] and an increased ischemic stroke risk [99] have been reported in patients with overt hypothyroidism.

Subclinical hypothyroidism has been also associated with diastolic hypertension in most but not all studies [48, 60, 89, 100–103]. A few but not all studies have reported hyperhomocysteinemia [48, 83, 104–108], higher but also normal levels of high-sensitivity C-reactive protein [56, 57, 83, 104, 107, 109–111], and possible coagulation deficits [86, 87] in patients with subclinical hypothyroidism. Higher levels of homeostasis model assessment and lower levels of Matsuda indexes, suggesting insulin resistance, have been found in patients with subclinical hypothyroidism in some but not all studies [25, 26, 89, 104, 111]. Increased intima-media thickness of the common carotid artery has been found in some studies in subclinical hypothyroidism [45, 53]. In the Whickham Survey, an association was found between incident coronary heart disease and related mortality in patients with subclinical hypothyroidism over the 20 yrs of followup, which was attenuated after levothyroxine treatment [112]. In support of this, 3 meta-analyses suggested that subclinical hypothyroidism is associated with a significant risk of coronary heart disease and cardiovascular mortality [113–115]. Another meta-analysis by Razvi et al. showed that the incidence and prevalence of coronary heart disease and the risk of cardiovascular mortality were higher in subclinical hypothyroidism, in patients younger than 65 years old and more prevalent in women [116]. Subclinical hypothyroidism has been associated with cerebral ischemia [117]. Although Jeong et al. in a study of 382 patients with ischemic stroke found no difference in the prevalence of subclinical hypothyroidism (4.5%) compared to the general population, low-normal free T4 levels in euthyroid patients were independently associated with a higher percentage of ischemic stroke [118]. In addition, it has been demonstrated that patients with subclinical hypothyroidism (especially those with TSH ≥ 10 μU/mL) and acute ischemic stroke exhibited a better level of consciousness, a milder neurological deficit at presentation, and more favorable outcomes on the 30th and 90th day compared with euthyroid patients [119, 120]. However, Rodondi et al. found no association between subclinical hypothyroidism and risk for stroke [121].

On the other hand, clinical hyperthyroidism has been associated with systolic hypertension, increased pulse pressure, and possibly hyperhomocysteinemia [6, 7, 122, 123] Additionally, patients with overt hyperthyroidism have a hypercoagulable state and an increased risk of thrombosis [86]. Higher levels of homeostasis model assessment and lower levels of Matsuda indexes have been reported, suggesting insulin resistance. [25, 27, 71, 91–93] Decreased fractional postprandial glucose uptake in adipose tissue, increased fasting lipolysis, increased interleukin 6, and tumour necrosis factor alpha may be associated to its development [25, 93, 124, 125]. Angina pectoris is a frequent disorder, especially in older patients with hyperthyroidism and underlying cardiac disease, and is due to increased heart rate and contractility and high myocardial oxygen demand [5]. Some cases of patients with hyperthyroidism due to Graves’ disease presenting with coronary artery spasm have been reported [126–128]. Hyperthyroidism has been associated with a higher risk for ischemic stroke among young adults during a 5-year followup which was probably associated with atrial fibrillation (AF), hypercoagulability and rarely antiphospholipid antibody syndrome [129–132].

Subclinical hyperthyroidism has been also associated with hypertension in some but not all studies [102, 103, 133]. Higher HOMA, lower Matsuda indexes [27], and increased carotid intima thickness [134] have been found in patients with subclinical hyperthyroidism. However, the association of subclinical hyperthyroidism with coronary heart disease risk and cardiovascular mortality is still unclear. Ochs et al. found a possible association, while the meta-analysis by Singh et al. found no significant association [113, 115]. Jeong et al. in a study of 382 patients with ischemic stroke found no difference in the prevalence of subclinical hyperthyroidism (1.6%) compared to the general population [118].

6. 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 which is in part mediated by the dyslipidemia or the dyslipidemia-induced metabolic abnormalities. However, 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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