Svetlana Jelić

Hypothyreosis and dyslipidemia – a chance association or causal relation

Hypothyroidism is one of the most common causes of secondary dyslipidemia. Strong association of hypothyroidism and atherosclerosis, as well as its clinical manifestations, is well-known (1, 2). Atherogenic lipid profile could be one of the possible mechanisms linking these entities (3, 4, 5). In fact, it is proved that hypothyroidism is accompanied by an increase in the serum total cholesterol concentrations, mainly due to elevated low density lipoprotein (LDL) cholesterol levels, as well as elevated levels of apolipoprotein B, lipoprotein (a) and, often, triglycerides. The Mayo Clinic annual report, which included 268 patients with primary and 27 with secondary hypothyreoidism, has shown normal lipid levels in only 8.5% of patients (5). Distribution of the most frequently encountered types of hyperlipidemia in these patients is displayed on Graph 1.

Graph 1. *The most frequently encountered types of hyperlipidemia in patients with hypothyroidism (according to the Reference 3)*
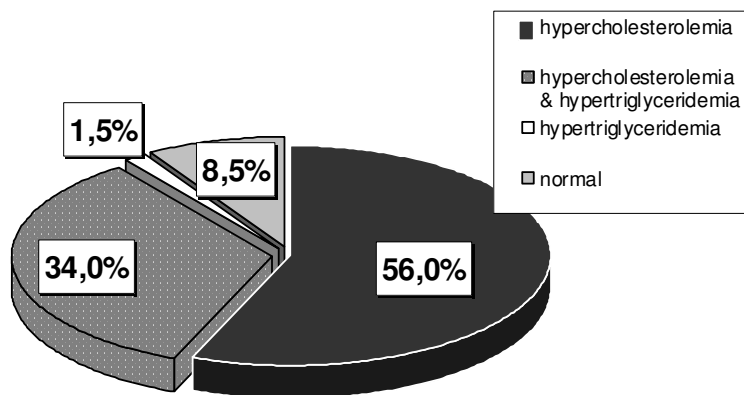
Type 2a hyperlipidemia was the most common lipid abnormality in patients with primary hypothyroidism, whereas type 2b was the most common in those with secondary hypothyroidism. In secondary hypothyroidism the lipid profile is more atherogenic because of the lower levels of protective high-density lipoprotein (HDL) cholesterol, in comparison with primary hypothyroidism (5).

If we turn the question of association between hypothyroidism and dyslipidemia upside-down, we shell start the search for the patients with hypothyroidism among patients with proven dyslipidemia. Results of several epidemiologic studies (6–9) suggest that such screening could be reasonable. In Sweden, among 782 subjects with serum total clolesterol leveles above 7.0 mmoL/L, 0.57% of males and 1.13% of females showed evidence of hypothyroidism (8). In the Netherlands and Greece, screening of the large number of referrals for dyslipidemia revealed

hypothyroidism in 2.8% i.e. 4.2% (6, 7), while its incidence was even 9.8–14.3%, according to the Brasilian investigators (9).

Mechanisms of development of dyslipidemia in hypothyroidism

It is well-known that thyroid hormones exert regulatory effects of on the activity of some key enzymes of lipoprotein metabolism:

1. by inducing the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, enzyme that catalyzes the conversion of HMG-CoA to mevalonate, the first step in the biosynthesis of cholesterol, thyroid hormones stimulate hepatic *de novo* cholesterol synthesis (10);

2. at the same time, thyroid hormones activate the LDL receptors due to the fact that the promoter of the LDL receptor gene contains a tri-iodo-thyronin (T3)–responsive element (TRE) which regulate the gene expression of this receptor (11);

3. the cholesteryl ester transfer protein (CETP), an enzyme which transports cholesteryl esters from HDL_2 to the very low density (VLDL)- and intermediary density lipoproteins (IDL) and triglycerides in the opposite direction, is also under the influence of these hormones (12);

4. thyroid hormones inhibit the LDL-oxydation due to the specific binding sites for thyroxine on apolipoprotein B (13);

5. thyroid hormones stimulate the lipoprotein lipase (LPL), enzyme which catabolizes the triglyceride-rich lipoproteins;

6. and the hepatic lipase (HL), which hydrolyzes HDL_2 to HDL_3 and catabolyzes IDL to LDL.

So, 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- and IDL-cholesterol (5), resulting from decreased activity of LDL-receptors and, consequently reduced catabolism of LDL i IDL. Decreased thyroid function not only increases the number of LDL particles but also promotes their oxidability making them even more atherogenic.

Hypertriglyceridemia associated with increased levels of VLDL and occasionally fasting chylomicronemia are attributable to the decreased activity of LPL, which results in a decreased clearance of triglyceride-rich lipoproteins in hypothyroid patients. Cholesterol- and apolipoprotein E-rich VLDL and IDL particles in hypothyroidism resemble â-VLDL particles of type III hyperlipoproteinemia. So, 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 (14).

Reduced transfer of cholesteryl esters from HDL to VLDL is the result of decreased activity of the CETP. Thus, increased HDL cholesterol levels as well as decreased catabolism of HDL_2 particles due to decreased activity of the hepatic lipase (HL) exist in hypothyroid patients.

The effect of levo-thyroxine replacement therapy on dyslipidemia in hypothyroidism

Benefitial effect of the replenishment of thyroid hormone on lipid disorders in overt clinical and/or biochemical hypothyroidism has been repetedly reported (6, 9, 14, 15, 16, 17). In meta-analysis of Danese et al. (15), reviewing 13 studies which included 247 patients, the mean decrease in the serum total and LDL-cholesterol concentrations, after the restoration of euthyroid state (TSH$\leq$2 mU/L), were –0.20 mmol/L and –0.26 mmol/L, respectively. This effect was more prominent in patients with higher pre-treatment cholesterol levels and in hypothyroid individuals taking suboptimal doses of levo-thyroxine. Diekman T et al. (6) verified statisticaly significant

decrease in serum concentration of total and LDL-cholesterol, following levo-thyroxine replacement therapy, only in patients with pre-treatment levels of TSH exceeding 10 mU/L.

Serum HDL cholesterol levels tend to decrease with thyroid replacement therapy (18), but this finding in inconsistent (15). Serum Lp (a) levels also tend to decrease with restoration of euthyroidism (7, 19).

Usually, it takes 4-6 weeks of replacement therapy with thyroxine to correct dyslipidemia in overt hypothyroidism. Changes in serum lipoproteins in hypothyroid patients are correlated with changes in free thyroxin (FT4) (20). However, the variability of the response of dyslipidemia to the levo-thyroxine replacement therapy is partially related to the variations in the expression of hepatic LDL-cholestrol receptor genes (21). If dyslipidemia persists despite successful restoration of euthyroid state it could represent unrelated co-morbidity which needs additional treatment options (9). These patients could benefit from combination of the levo-thyroxine replacement therapy, life-style changes and/or hypolipemic drugs.

Subclinical hypothyroidism and dyslipidemia

Subclinical hypothyroidism, defined by the mildly elevated serum TSH levels (up to 10 mU/L) with normal levels of thyroid hormones, is a far more common disorder than overt hypothyroidism in general population (22). In a classical epidemiological study of Tunbridge WM et al., including 2779 subjects, the prevalence of subclinical hypothyroidism was 2.8% in men and 7.5% in women (23). In the recent years this disorder was observed with the increasing frequency, particularly in women older than 60 years (17%) (14, 15, 24).

Association of subclinical hypothyroidism and dyslipidemia remains controversial as well as the effect of thyroxine administration on serum lipoprotein levels in these patients. Part of the difficulty stems from the variations in the range and design of studies addressing these topics (15).

When lipid disorders are concerned, it is most widely accepted that subclinical hypothyroidism is accompanied with the elevated serum total and LDL-cholesterol concentrations (15, 22, 25, 26), that are significantly higher than in healthy euthyroid individuals (27–31). Elevated cholesterol levels were observed even in subjects with high normal TSH levels (2-4 mU/L) but with positive anti-thyroid antibodies (32). Numerous opservational studies also noted higher prevalence of subclinical hypothyroidism among hypercholesterolemic than in normocholesterolemic individuals (33–36).

Certain investigations indicated also that patients with subclinical hypothyroidism had significantly higher levels of apolipoprotein B and Lp(a), whereas levels of triglycerides, HDL cholesterol and apolipoprotein AI did not differ significantly compared to euthyroid controls (37).

However, results of some studies have completely ruled out the association between subclinical hypothyroidism and dyslipidemia (38–41).

It is well-known that subclinical hypothyroidism could be present for many years before hypothyroidism became clinically evident. Available data showed that patients with subclinical hypothyroidism develop overt hypothyroidism with the approximate rate of 2.6–4.3% per year (15, 23, 42). Therefore, it is very important to know whether the tretment of mild thyroid failure with levo-thyroxine has the potential to improve lipid profiles consequently reducing the risk for development and progression of atherosclerosis and its complications.

Evidence-based medicine and clinical guidelines do not recommend routine administration of levo-thyroxine in patients with minimally raised serum TSH (4.5 i 10 mIU/liter) (42).

More than 20 intervention studies, at least 2 meta-analyzes (15, 43) and several reviews (44) addressed the issue of the effect of thyroxine administration on serum lipoprotein levels in patients with subclinical hypothyroidism. Despite the fact that half of intervention trials reported statistically significant improvement in serum lipid levels, all of those studies that stratify TSH levels unanimously indicated that levo-thyroxine administration did not influence lipid levels significantly if the pre-treatment level of TSH was below 10 mU/L (6, 37, 45). Moreover, some

of them demonstrated significant decrease of HDL level and consequent worsening of total cholesterol/HDL holesterol index, an indicator of cardiovascular risk (44, 45).

However, significant response or decrease of total and LDL cholesterol was observed after levo-thyroxine administration in those patients with mild thyroid failure in whom pre-treatment total cholesterol level were higher than 5.7 mmol/L (44) or 6.2 mmol/L (37), as well as in those with positive anti-thyroid antibodies (46). In the study of Meier C et al, an important risk reduction of cardiovascular mortality of 9–31% could be calculated from the observed improvement in LDL–cholesterol (–0.17 to –0.60 mmol/L (16).

Possible directions for the future research

There has been extensive interest in using thyroid hormones for treating a variety of indications, including obesity and familiar hypercholesterolemia. This interest is based on experimental and clinical studies, meticulously reviewed by Tulloch BR in 1974. (47). Clinical use of thyroxine analogue, D-thyroxine, was limited due to an increased incidence of cardiovascular complications. This problem could not be solved even by combining thyroxine analogue and â-blocking agents.

Recent identification of two different types of the thyroid hormone receptors (TRá i TRâ), as well as the synthesis of compounds with TRâ-selective actions, made possible hypolipemic effects without adverse effecs on heart rhythm and rate. GC-1 represents such compound with approximately a 10 times higher affinity to TRâ compared with TRá (48). Result of its selective receptor binding as well as of selective uptake of this compound by the different tissues is its 14 times greater potency on lowering serum cholesterol than on heart rate. GC-1 has similar or greater effects than T3 on triglyceride levels and diminished effects relative to T3 on weight gain and heart rate.