SUBCLINICAL HYPOTHYROIDISM AND LIPID METABOLISM: TO TREAT OR NOT TO TREAT?

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SUBKLINIČKI HIPOTIROIDIZAM I METABOLIZAM LIPIDA: LEČITI ILI NE?

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Received/Primljen: 22.01.2019. Accepted/Prihvaćen: 28.07.2019.

ABSTRACT

Thyroid hormones have multiple complex effects on lipid synthesis and metabolism. These physiological actions are well documented in overt hypothyroidism where the elevated levels of total cholesterol, low density lipoporotein cholesterol and possibly triglycerides are reverted by levo-thyroxine therapy. Subclinical hypothyroidism, defined as elevated serum thyroid stimulating hormone in the presence of reference range of free thyroxine and free triiodothyronine concentrations, is a relatively frequent clinical conditions. Many clinical and epidemiological studies have evaluated lipid metabolism, markers of subclinical atherosclerosis and other cardiovascular risk factors in subclinical hypothyroidism as well as the need of replacement therapy in these patients. The available results are rather conflicting, with variable and inconclusive results. Moreover, no consensus still exists on the clinical significance and treatment of this mild form of thyroid failure. On the contrary, available evidences suggest that patients with plasma thyroid stimulating hormone levels above 10 mU/L should be treated with levo-thyroxine, since may have an increased risk of cardiovascular disease. However, the epidemiological evidences suggest being rather conservative in older people, since higher thyroid stimulating hormone is associated with lower risk of multiple adverse events in this population. In this review, we summarized the current evidences on the association between subclinical hypothyroidism and lipid metabolism and the effect of levo-thyroxine therapy on lipid parameters.

Keywords: *atherosclerosis, cardiovascular disease, levothyroxine, lipid metabolism, subclinical hypothyroidism, treatment*

SAŽETAK

Hormoni tiroide imaju multi kompleksne uticaje na sintezu lipida i metabolizma. Ove fiziološke aktivnosti dobro su prikazane kod primarnog hipotiroidizma, gde se povišeni nivoi holesterola, holesterola sa malom gustinom lipoproteina i mogućih triglicerida vraćaju u prethodno stanje pomoću terapije levotiroksinom. Subklinički hipotiroidizam, definisan kao povišen serum tireostimulišućeg hormona u prisustvu referentnog raspona slobodnog tiroksina i koncentracija slobodnog trijodotironina, relativno je često kliničko stanje. Mnoge kliničke i epidemiološke studije vršile su procenu metabolizma lipida, markera subkliničke aterosleroze i drugih kardiovaskularnih faktora rizika kod subkliničkog hipotiroidizma, kao i potrebu za promenom terapije kod ovih pacijenata. Dostupni rezultati su isuviše protivurečni, sa varijabilnim i neuverljivim rezultatima. Osim toga, ne postoji konsenzus po pitanju kliničkog značaja i lečenja ove blage forme poremećaja tiroide. Naprotiv, dostupni dokazi navode da pacijenti sa nivoima plazma tireostimulišućeg hormona iznad 10 mU/L treba da budu lečeni levotiroksinom, s obzirom na to da mogu imati povećan rizik od kardiovaskularne bolesti. Međutim, epidemiološki nalazi ukazuju, budući da se više susreću kod starijih, da je viši tireo stimulišući hormon povezan sa manjim rizikom od višestruko štetnih pojava kod ove populacije. U ovom pregledu, sumiramo trenutne nalaze o povezanosti između subkliničkog hipotiroidizma i metabolizma lipida, kao i uticaja terapije levotiroksinom na parametre lipida.

Ključne reči: *ateroskleroza, kardiovaskularna bolest, levotiroksin, metabolizam lipida, subklinički hipotiroidizam, lečenje*

ABBREVIATIONS

ATPase - sodium-potassium adenosine triphosphatase
CEPT - cholesterol ester transfer protein
CHD - coronary heart disease
cIMT - carotid intima-media thickness
CVD - cardiovascular disease
FT4 - free thyroxine
HDLc - high density lipoprotein cholesterol
HMG-CoA - hydroxymethylglutaryl coenzyme A reductase
LDLc - low density lipoprotein cholesterol
LDL-R - low density lipoprotein receptor
SH - subclinical hypothyroidism
SREBP-2 - sterol regulatory element-binding protein-2
TC - total choleterol
TG - triglycerides
TSH - thyroid stimulating hormone

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DOI: 10.2478/sjecr-2019-0069

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INTRODUCTION

Cardiovascular disease (CVD) is a class of disease which involves a heart or blood vessels. Treatment of the CVD is a major goal for the public health due to its association with death in the general population. For this reason during last years many strategies have been designed for the treatment and prevention of the CVD (1-4). Aging is associated with a worsening of cardiovascular risks factors (5-8), including dyslipidemia (9) and hormones play a pivotal role in their regulation (10). The association between dysfunctions of thyroid and atherogenesis has long been acknowledged (11-13). This clinical relationship is partly related by the derangement of the lipid metabolism due to several changes in the synthesis, metabolism and mobilization of lipids. An increase in the total and low density lipoprotein cholesterol (LDL-C) levels is observed in the majority of patients with overt hypothyroidism (14). According to prevalence data of hypothyroidism in the general population, the milder clinical form (i.e. subclinical hypothyroidism) is significantly higher than overt hypothyroidism. Subclinical hypothyroidism (SH) is defined as an increase in serum thyroid stimulating hormone (TSH) level with normal free thyroxine (FT4) and free triiodothyronine levels, independent of the presence or absence of symptoms (15). Autoimmune thyroiditis, which recognized genetic and environmental factors (16-18), is the most common cause of the SH and is usually associated with other autoimmune diseases such as autoimmune diabetes, and celiac disease (19, 20). This clinical condition is relatively common, with a prevalence ranging from 4 to 15% in the general population, and up to 20% among females aged > 60 years (21-24). The SH has been associated with markers of cardiovascular risk (25) and different adverse outcomes, thus suggesting that the SH might be associated with a risk of increased prevalence of the CVD. As dyslipidemia and SH both increase with aging, it has also been hypothesized that the SH might worsen the effect of aging on serum lipid metabolism. However, despite the numerous population-based studies on the association of the SH and dyslipidemia, the causal relationships between the SH, lipid metabolism, and CVD remain incompletely understood. Moreover, benefits and risks of treating the SH still remain controversial. The aim of this review was to focus the clinical and biochemical aspects of the SH, the possible derangement of lipid profile and the potential risk factor of this clinical condition for the CVD and to establish whether the substitutive therapy with the levo-thyroxine (LT4) can reduce any associated cardiovascular risk.

MATERIAL AND METODES

In this review, published articles were searched on PubMed/Medline by using the search terms “subclinical hypothyroidism”, “cholesterol”, “lipoprotein”, “levo-thyroxine treatment”. A manual search of bibliographies of the found papers was also performed to meet objectives of this study.

Studies on lipids in subclinical hypothyroidism

Lipid metabolism is regulated by thyroid hormones through multiple mechanisms. Synthesis, metabolism and mobilization of lipoproteins are stimulated by thyroid hormones, In particular, the transcription of the low density lipoprotein receptor (LDL-R) gene and the hepatic expression of hydroxymethylglutaryl coenzyme A reductase (HMG-CoA), which result in the increased cholesterol synthesis are stimulated by thyroid hormones. Therefore, hepatic cholesterol synthesis is decreased in states of thyroid hormone deficiency. Thyroid hormone also increases the expression of the sterol regulatory element-binding protein-2 (SREBP-2) that in turn modulates the LDL-R expression. The decrease in LDL-R leads to reduce clearance of LDL-C from the serum (26, 27). Thyroid hormone may also reduce cholesterol through non-LDL-R mediated pathways, as demonstrated in the LDL-R gene knockout mice. The thyroid hormone effects on the LDL-R expression and cholesterol absorption outweigh the effects of decreased hepatic cholesterol synthesis, leading to hypercholesterolemia in overt hypothyroidism. Thyroid hormone may contribute to maintain cholesterol homeostasis through the conversion of cholesterol to bile acids and subsequent faecal excretion.

Thyroid hormone deficiency also decreases the cholesterol ester transfer protein (CEPT) concentrations, which may lead to alterations in high density cholesterol (HDL-C) plasma levels. Finally, lipoprotein lipase activity is increased by thyroid hormone. Higher serum triglycerides (TG) may also be observed in overt hypothyroidism because of the lower lipoprotein lipase activity.

The overall effects of thyroid hormones on serum lipids are well documented in overtly hypothyroid individuals. Overall, approximately 90% of overt hypothyroid have hyperlipidemia, whereas the TG, very low density lipoprotein and HDL-C may be normal or slightly increased resulting in an infavourable ratio of the LDL-C to HDL-C (28).

Whether mild thyroid hypofunction has a demonstrable effect on lipid metabolism is still unclear. Some population based studies demonstrated that serum lipids are elevated in patients with the SH (27). In particular, total cholesterol (TC), LDL-C and TG have been reported to be higher in the SH than in euthyroid subjects (13). Moreover, a linear and significant increase in serum lipoproteins following an increase in serum TSH has been reported (29). By contrast, in a cross-sectional study of 7000 thyroid clinic outpatients, there were no significant differences in serum TC, LDL-C, HDL-C, or TG serum concentrations between the SH and euthyroid subjects (30). Among 8586 adult patients from n NHANES III no significant differences in lipid parameters were found in the SH and controls (31). An atherogenic lipid pattern with small dense LDL-C particles was associated with higher values of TSH (10 mU/L), therefore suggesting that the increased TSH levels are associated with dyslipidemia without a clear cut-off threshold for this relation. Interestingly, the TSH has been reported to up-regulate

hepatic HMG-CoA expression, thus suggesting a potential mechanism for hypercholesterolemia involving a direct action of the TSH on the liver (32). Additional studies have reported the increased levels of lipoprotein (a) (Lp(a)), apolipoprotein B, or qualitative changes in lipoprotein composition in SH (33) although other Authors did not confirm this finding (34). Other studies (35, 36) reported that even in the mild form of hypothyroidism qualitative changes in lipoprotein composition (TG enrichment of LDL-C, altered metabolism of remnant lipoproteins) and metabolism might occur thus contributing to the atherogenic process. However, no differences in the LDL-C particle size have been found in the SH and age- and sex- matched euthyroid controls (37).

The association between subclinical hypothyroidism and lipids has been studied also in the context of metabolic syndrome. Studies showed that mild thyroid failure has not been clearly associated with an increased risk of metabolic syndrome, but, rather, an association with some of its component (25). In particular, previous studies found an inverse relation with waist circumference, raising the possibility of a link with adipocytokines (principally leptin and adiponectin), whose concentrations changed along with variation of the TSH levels (38, 39).

The different results found in scientific literature may be explained by sample size of the studies, gender and hormonal differences, and by the duration of SH, which is often unknown (27, 40, 41). Available data, taken together, do not allow a firm conclusion on this topic.

Subclinical hypothyroidism and cardiovascular disease

Thyroid hormones exert pleiotropic action, regulating different process in the body (42-44). The physiological importance of thyroid hormones to the cardiovascular system is well documented in humans (45). Thyroid hormones act on this system in complex metabolic pathways. In particular, the heart contains a high concentration of thyroid hormone receptors and represents the main target of these hormones both in normal and in states of hyper- and hypo-function of the gland. In overt hypothyroid patients the pericardial effusion, depression of ventricular function, congestive heart disease and electrocardiographic changes and, rarely, life-threatening arrhythmias may be observed. Bradycardia, reduced myocardial contractility and reduced myocardial oxygen consumption are also present. The thyroid hormone action on the heart and peripheral vasculature is clearly evidenced in hyperthyroidism where the increased heart rate, arrhythmias, atrial fibrillation, the increased myocardial contractility and decreased peripheral vascular resistance are almost always present (46). These effects are mainly mediated by the action of thyroid hormones on adrenergic and cholinergic receptors, sodium-potassium adenosine triphosphatase (ATPase), as well as calcium transport and cardiac myosin ATP-ase isoenzymes (47). Moreover, thyroid hormones directly affects myocardial contractility, whereas in hypothyroidism there is a reduced production of alpha chain in the myosin ATPase molecule with a lower capacity to convert the ATP to ADP, resulting in weak myocardial contractility. This aspect is related to the effects of thyroid hormone on the expression of alpha and β genes (48, 49).

The data on the risk for the CVD in SH are rather conflicting, since several studies, by evaluating the coronary heart disease (CHD) outcomes as well as markers of atherosclerosis, yielded variable and inconclusive results. A risk of CHD has been found to increase with the severity of thyroid hormone deficiency and was positively related to higher TSH levels (50). Other studies demonstrated that the SH is an independent predictor for the CVD in younger men, and an increased risk for coronary events was observed in patients with the SH compared with euthyroid individuals (51, 52). In addition, a meta-analysis of 15 studies showed the increased prevalence of CHD in SH compared with euthyroid subjects (53). On the contrary, other studies failed to confirm these data. The cardiovascular Health Study, and other population studies, showed no increased incidence of cardiovascular events or higher mortality risk also in older patients and postmenopausal women with SH (11, 54). Interestingly however, the association between the CHD and SH seems to be TSH-related, particularly in subjects with TSH levels of 10 mU/L or greater (54). Thus, high TSH levels might have a stronger beneficial effect on lipid parameters in moderately old subjects than in younger subject (55), since the SH seems to worsen the effects of aging on serum lipid profiles. Thus, treatment of the SH is recommended for all patients with serum TSH levels >10 mU/L. Given current evidence, the available data would suggest that hyperlipidemic patients with the SH and TSH >10 mU/L should be treated with LT4.

LT4 therapy on serum lipids and cardiovascular risks in subclinical hypothyroidism.

Different studies have tested the effect of the LT4 on lipids and other markers of the CVD in subjects with SH, since LT4 replacement therapy might be beneficial. However, some evidences suggested this hypothesis, other did not. Razvi et al. reported a reduction of the TC and LDL-C (56), with a direct proportion to the respective baseline values reported by other Authors (57). Another study showed the decrease of only LDL-C, which was more pronounced in patients with higher LDL-C baseline values and in those who had TSH > 12 mU/L. Conversely, other authors reported no effect of LT4 replacement therapy of lipids, as reported in Table 1. Kong et al. randomly assigned 40 women with SH to either LT4 treatment or placebo (58). After 6 months of therapy, there was no significant change from the baseline for any of lipid measurement (TC, LDL-C, TG, HDL-C, ApoA, and ApoB). Moreover, a Cochrane review of LT4 replacement in SH concluded that there was no significant evidence of treatment on lipid levels (59).

Since thickening of the carotid arterial wall is an early marker of atherosclerosis and is associated with the increased prevalence of myocardial infarction and stroke (60), other studies have evaluated other surrogate markers of atherosclerosis such as a carotid intima media thickness (cIMT). Data

from the Brazilian Longitudinal Study of Adult Health showed that patients with the SH had higher cIMT (61). In addition, there are also some evidences suggesting a beneficial effect of LT4 replacement therapy on cIMT in the SH (62-66). On the other hand, no improvement in cIMT values has been found in other studies (67). Furthermore, it should be remarked that a recent study on the association between cIMT and thyroid function failed to support the concept that the TSH and FT4 are related to the IMT (68). Recently, a meta-analysis included all published randomized controlled and self-controlled trials, which evaluated the effect of LT4 replacement therapy of c-IMT (69). This study included 117 patients with the SH coming from 3 randomized controlled trials and results of analyses clearly showed the decrease of development of c-IMT. In addition, the estimated decrease of cIMT was -0.04 mm, in particular among female patients with a longer treatment (> 6 months). Authors hypothesized that the ameliorating effect of LT4 on cIMT could be due to the reduction of TC, TG, LDL-C and blood pressure.

Table 1. Studies that failed to demonstrate beneficial effects of levothyroxine replacement therapy on lipids

	Studies
TC	34, 35, 58, 67, 74, 77-88
LDL-C	34, 35, 58, 67, 74, 77, 78, 80-84, 86-91
HDL-C	34, 35, 57, 58, 62, 67, 74, 78-80, 82-85, 87, 88, 90-102
TG	34, 35, 57, 58, 62, 67, 74, 77-91, 93, 95-104

Abbreviations: TC, total cholesterol; LDL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; TG, Triglycerides.

SH has been also associated with the increased arterial stiffness, which is an independent risk factor for the development of the CVD (70). It has been also demonstrated that thyroid hormone could modify arterial stiffening also in subjects with a normal thyroid function (71, 72). However, other researchers found a positive association between FT4 and carotid-femoral pulse wave velocity, suggesting that the increased level of FT4 might have detrimental effect on the aging of the vascular system (73). Treatment of SH had beneficial effect on arterial stiffness (74) and log-term LT4 therapy targeting TSH in the reference range did not cause adverse effect on the central hemodynamic (75).

Several studies have also examined other CVD risk (such as endothelium-related molecules or inflammatory and thrombotic adipokines and chemokines) in the SH and the effect of replacement therapy on them. However, no significant amelioration and benefit has been demonstrated (33, 58). Moreover, no clinical trial to date has examined cardiovascular events or cardiovascular mortality before and during LT4 therapy in patients with the SH. Finally, the role of thyroid hormone receptor β agonists is still not clear (76).

CONCLUSIONS

The role of LT4 replacement on lipid synthesis and metabolism in patients with overt hypothyroidism is well documented. The relationship of the SH with serum lipids together with the effects of LT4 in these patients is less clear. Since the SH may progress in overt hypothyroidism, many studies have been addressed to ameliorating the markers of subclinical atherosclerosis. So far there are insufficient data to support an unequivocal benefit of LT4 in term of the CVD prevention, as well as lipid parameters. Therefore no consensus still exists on the clinical significance and treatment of this mild form of thyroid failure. Since high TSH levels are associated with an increased risk of the CVD, treatment of the SH is recommended for all patients with TSH levels > 10 mU/L, especially if they are young. On the contrary, in older people the policy is to be rather conservative. However, specific lipid lowering drugs should be instituted in dyslipidemic patients with SH, regardless the administration or not of LT4.

CONFLICTS OF INTEREST

Nothing to decleare.

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