LIPID LEVELS AND ATHEROGENIC INDICIS IN PRE- AND POSTMENOPAUSAL WOMEN WITH AUTOIMMUNE HYPOTHYROIDISM IN RELATION TO TSH VALUES

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Abstract

Introduction

According to current guidelines target levels of TSH below 2.5 mIU/l are recommended for the treatment of primary hypothyroidism but data on the benefits of this approach are inconclusive.

Aim

To compare lipid levels and atherogenic indices in pre- and postmenopausal women with autoimmune hypothyroidism on levothyroxine replacement therapy according to TSH values and evaluate their relationship with thyroid function tests.

Patients and methods

84 pre- and 54 postmenopausal women on levothyroxine replacement therapy in euthyroid state (TSH 0.4-4.2 mIU/l) were included in the study. Serum levels of TSH, free thyroxine, total cholesterol, HDL and triglycerides were measured; LDL values and atherogenic indicis were calculated.

Results

No differences between lipid parameters were found in premenopausal women with TSH below or above 2.5 mIU/l. No correlation between TSH levels and lipids and atherogenic indicis was observed. In postmenopausal women with TSH below 2.5 the levels of total ($p=0.022$) and LDL cholesterol ($p=0.016$) were significantly higher compared to those with TSH above 2.5 mIU/l. In addition, there was significant negative correlation between TSH and total cholesterol ($p<0.05$), LDL ($p<0.05$), I1, I2, AC ($p<0.05$) without relationship between the levels of FT4 and the studied parameters.

Conclusion

Our results suggest that there are no benefits in terms of lipid parameters in TSH below or above 2.5 mIU/l during treatment of autoimmune hypothyroidism. In postmenopausal women however a more unfavorable lipid profile may be observed raising the question whether TSH correctly reflects tissue thyroid hormone levels during levothyroxine treatment, particularly in older patients.

Key words: *autoimmune hypothyroidism, thyroid stimulating hormone, free thyroxine, lipids, atherogenic indicis*

Introduction

According to current guidelines target levels of thyroid-stimulating hormone (TSH) below 2.5 mIU/l are recommended for the treatment of primary hypothyroidism but data on the universal benefits of this approach is inconclusive [1].

Aim: To compare lipid levels and atherogenic indices in pre- and postmenopausal women with autoimmune thyroiditis (AIT) on levothyroxine (LT4) replacement therapy according to TSH values and evaluate their relationship with thyroid function tests.

Materials and methods: 84 premenopausal women (mean age 35.8±7.4 years) and 54 postmenopausal women (mean age 57.5±7.3 years) with autoimmune hypothyroidism were included in the study. All the patients were on stable replacement therapy with levothyroxine of at least 37.5 mcg daily with no changes in the dosage for the past 6 months. Serum levels of TSH, free thyroxine (FT4), total cholesterol, high-density lipoprotein cholesterol (HDL-C)

and triglycerides (TG) were measured in fasting state before the intake of levothyroxine. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. All the women included in the study were in euthyroid state with TSH between 0.4-4.2 mIU/l. Atherogenic index of plasma (AIP) = log triglyceride/HDL-C, Castelli's Risk Index (CRI) I = total cholesterol/HDL-C, CRI-II = LDL-C/HDL-C and atherogenic coefficient (AC) = (total cholesterol−HDL-C)/HDL-C were calculated for all subjects. The women included had no significant medical conditions, incl. diabetes mellitus and were not taking steroids, metformin, lipid lowering therapy or estrogen containing drugs. The statistical package for the social sciences (SPSS, Inc., Chicago, IL) version 21.0 was used to analyze the collected data. Significant level of p-value was considered less than 0.05. The major characteristics of the included patients are presented in tab. 1. The study is in compliance with the Helsinki Declaration.

Results and discussion: 48 of the premenopausal women had TSH < 2.5 mIU/l (mean level 1.64±0.50 mIU/l) and the rest 36 women had TSH > 2.5 mIU/l (mean level 3.47±0.52 mIU/l). The two groups did not differ in terms of age, body mass index (BMI) and FT4 levels (tab. 2). No differences between lipid parameters were found in premenopausal women with TSH below or above 2.5 mIU/l (tab. 2). No correlation between TSH levels and lipid parameters as well as atherogenic indicis was observed. FT4 showed negative correlation with total cholesterol (r= -0.385, p<0.001), LDL-C (r= -0.406, p<0.001) and TG (r= -0.263, p<0.005) as well as with CR-I (r= -0.323, p<0.001), CR-II (r= -0.324, p<0.001) and AC (r= -0.323, p<0.001). In addition, TSH levels had negative relation with FT4 (r= -0.256, p<0.05).

In the group of postmenopausal women 33 had TSH < 2.5 mIU/l (mean level 1.59±0.64 mIU/l) and in 21 TSH was above 2.5 mIU/l (mean level 3.28±0.58 mIU/l) without differences in the FT4 levels (11.90±1.65 vs 11.92±1.47 pmol/l, p=0.988). In women with TSH below 2.5 the levels of total cholesterol and LDL-C were significantly higher compared to those with TSH above 2.5 mIU/l (tab. 3). In addition, there was significant negative correlation between TSH but not FT4 levels and total (r= -0.293, p<0.05) and LDL-C (r= -0.304, p<0.05) (fig. 1, 2) and the atherogenic indicis CRI-I (r= -0.269, p=0.049), CRI-II (r= -0.284, p=0.037) and AC (r= -0.269, p=0.049). In those women TSH did not show correlation with FT4 levels.

Autoimmune thyroiditis is the most common cause of decreased thyroid function in iodine-replete areas. The annual incidence worldwide is estimated at 3.5 cases per 1000 people. Females are affected 10-15 times more often, with the highest incidence between 30 and 50 years [2]. The relation between thyroid function, lipid parameters and cardiovascular risk has been a matter of hot discussion for the past decades. With increasing age and especially after menopause changes in lipid profile are prominent characterised by increasing total and LDL cholesterol and lowering HDL cholesterol. Thus, menopause has been considered an independent risk factor for cardiovascular disease [3].

The generally accepted therapeutic strategy in the treatment of hypothyroidism is to restore clinical and biochemical euthyroidism by compensating for the reduced or absent thyroid hormones. The current approach for thyroid hormone replacement is based on the administration of LT4 [4]. Thus, in clinical practice it is widely accepted that monotherapy with LT4 at doses that normalize serum TSH levels is sufficient to restore the euthyroid state [5]. However, recently this concept has been questioned, as evidence show that a significant proportion of patients receiving LT4 continue to have some symptoms suggestive of hypothyroidism such as metabolic changes and psychological manifestations [6, 7]. Therefore, the usefulness of several markers reflecting the effects of thyroid hormones on target organs and tissues such as sex-hormone binding globulin (SHBG), osteocalcin, creatine kinase, ferritin, total cholesterol, LDL cholesterol, etc. has been examined [1]. The results of randomized controlled trials show that cholesterol and SHBG levels are most strongly

affected by the administration of LT4 [8]. It should be noted that the observed changes are within the range of variation in the healthy population, so these indicators may serve as an additional means of fine tuning treatment with LT4 in patients with TSH levels already within the reference range [8].

In our premenopausal patients there were no differences in lipid parameters and cardiovascular risk indices depending on TSH levels within the reference range. In these young healthy women, the studied parameters did not depend on TSH, but showed negative correlation with the levels of FT4, which is consistent with other findings on the metabolic effects of thyroid hormones. In the postmenopausal women, the discrepancy between lower TSH levels and lipid parameters is probably due to the effects of T3, which is supported by the lack of physiological negative correlation between TSH and FT4 in this group.

One possible explanation for this phenomenon is that serum T3 levels may not be completely normalized due to insufficient conversion of T4 to T3 in these patients [9]. Another hypothesis is based on the fact that in many tissues intracellular levels of T3 cannot be predicted using circulating thyroid hormone levels due to the action of type 2 and 3 deiodinases. Thus, in some tissues the relatively higher level of T4 may lead to increased hormone action without affecting circulating T3 levels [10]. However, in other tissues the relatively high serum T4 levels may reduce intracellular T3 production by decreasing deiodinase activity [11]. Recent evidence suggest that levothyroxine monotherapy cannot provide an euthyroid state in all tissues at the same time and that normal serum TSH levels in patients receiving levothyroxine reflect hormonal action only at the pituitary level [12].

Peterson et al. in a large population study found that patients with hypothyroidism and normal TSH treated with LT4 had lower T3 and higher T4 levels and lower T3:T4 ratio respectively compared to healthy controls [13]. In addition, differences between levothyroxine-treated and healthy individuals were seen in terms of BMI, total cholesterol, caloric intake and physical activity. These findings suggest that a normal TSH level may not be sufficient as a single criterion used to determine the exact levothyroxine dose for each patient [13]. TSH values in the lower reference range in patients on LT4 were associated with higher FT4 levels without differences in free and total T3. Those subjects had higher HDL-C and lower LDL-C, TG and C-reactive protein (CRP) [13].

The distribution of TSH in subjects with hypothyroidism was significantly shifted to higher values and in patients after thyroidectomy to lower values compared to the normal distribution in euthyroid controls (14). There was a dissociation between TSH and FT4 in hypothyroidism expressed by higher levels of FT4 and higher matched TSH [14]. 5% of hypothyroid patients and 10 % of patients after thyroidectomy normalized TSH values only in a state of hyperthyroxinemia. Serum T3 was lower in both groups of patients and did not respond to higher LT4 dose and higher serum T4 concentration in patients after thyroidectomy. The authors concluded that decreased serum T3 is a major cause of impaired feedback between TSH and thyroid hormones in patients with hypothyroidism treated with LT4 [14].

Despite recent trends toward lowering the upper limit of TSH reference interval, the results of this 12-month study do not support the view that the goal of treating primary hypothyroidism should be keeping low normal TSH [15]. No differences in a number of metabolic parameters, incl. lipid profile between patients on LT4 therapy with low normal (0.4-2.0) or high normal (2.0-4.0) TSH levels were found during 12 months follow-up [15]. Other investigators did not find differences in energy expenditure or body composition in hypothyroid patients treated with LT4 and TSH levels below or above 2.5 mIU/l [16].

Hoermann et al. investigated the relationship between TSH and thyroid hormones in more than 1900 patients. The results showed a high degree of individuality, influenced by

demographic factors such as gender, age and BMI [17]. TSH, FT4 and FT3 have both individual and interrelated roles in the regulation of thyroid activity. Equilibrium patterns characteristic of healthy individuals are not constant, but can be modulated, for example, by treatment with LT4 [17]. The thyroid gland and peripheral tissues are integrated into the physiological process of T3 homeostasis through TSH which coordinates peripheral and central regulatory mechanisms. Disorders in these mechanisms lead to altered T3 balance in LT4 treated patients [18]. Moreover, recent genetic studies have established associations between common genetic variations and serum levels of thyroid hormones [19, 20].

Our study has strengths and some limitations. All of the women included are selected according to strict criteria in order to minimize the possible impact on the studied parameters of concomitant drugs, incl. estrogen-containing and lipid-lowering medications, diseases, conditions, etc. The limitation of the study is not measuring the serum levels of FT3 which would have helped to clarify the interaction between thyroid hormones and lipids.

In summary, TSH levels for most non-pregnant patients with primary hypothyroidism on levothyroxine replacement should be within the population-specific reference range and one should not necessarily increase the dose of levothyroxine in asymptomatic people with TSH in the upper half of the normal range [21].

Conclusion: Our results suggest that there are no benefits in terms of lipid parameters in TSH below or above 2.5 mIU/l during treatment of autoimmune hypothyroidism. In postmenopausal women however a more unfavorable lipid profile may be observed raising the question whether TSH correctly reflects tissue thyroid hormone levels during levothyroxine treatment, particularly in older patients.

Statement for Potential Conflicts of Interest: None

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Figure legends

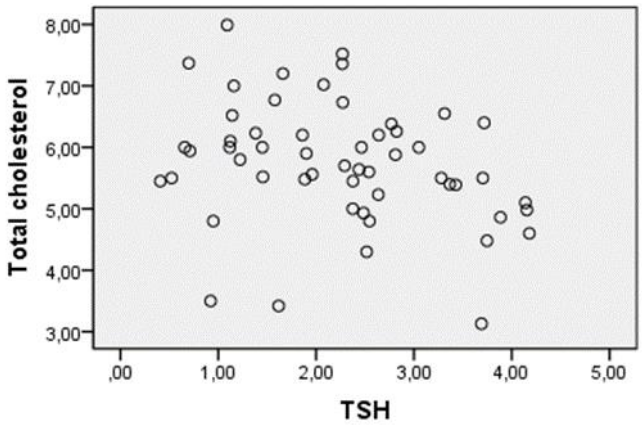

Figure 1. Correlation between TSH and total cholesterol levels in postmenopausal women.

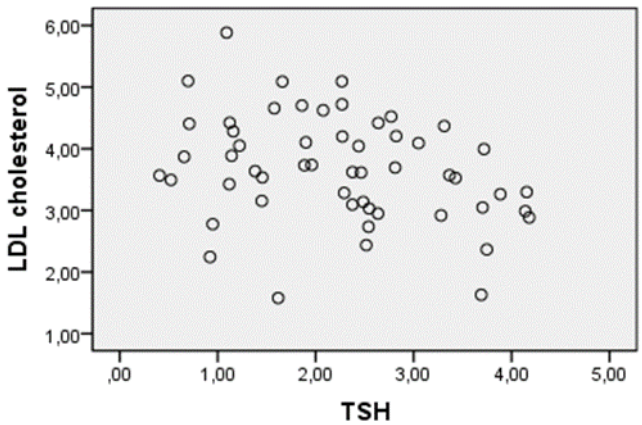

Figure 2. Correlation between TSH and LDL-C levels in postmenopausal women.

Table 1. Characteristics of the studied women.

Parameter		**Premenopausal (n=84)**	**Postmenopausal (n=54)**
Age	years	35.8±7.4	57.5±7.3
BMI	kg/m^2	25.3±5.6	28.5±4.7
TSH	mIU/l	2.43±1.04	2.23±1.04
FT4	pmol/l	11.50±1.44	11.91±1.57
Total cholesterol	mmol/l	4.87±0.88	5.74±0.99
HDL cholesterol	mmol/l	1.40±0.38	1.43±0.33
LDL cholesterol	mmol/l	3.04±0.73	3.68±0.86
Triglycerides	mmol/l	0.95±0.48	1.38±0.72
Dose of LT4	mcg/d	70.7±26.5	76.2±27.7
Calculated AIP, CRI-I,CRI-II and AC			

Table 2. Comparison between parameteres in premenopausal women with TSH below and above 2.5 mIU/l.

Parameter		**TSH < 2.5 (n=48)**	**TSH > 2.5 (n=36)**	**p**
Age	years	35.4±1.0	36.5±1.3	0.482
BMI	kg/m^2	24.6±0.8	26.2±1.0	0.197
FT4	pmol/l	11.7±0.2	11.2±0.3	0.089
Total cholesterol	mmol/l	4.81±0.87	4.95±0.89	p>0.05
HDL cholesterol	mmol/l	1.37±0.33	1.44±0.43	
LDL cholesterol	mmol/l	3.00±0.75	3.08±0.72	
Triglycerides	mmol/l	0.95±0.47	0.95±0.50	
AIP		-0.19±0.24	-0.20±0.27	
CRI-I		3.67±0.93	3.66±1.1	
CRI-II		2.32±0.80	2.31±0.84	
AC		2.67±0.13	2.66±1.1	

Table 3. Comparison between parameteres in postmenopausal women with TSH below and above 2.5 mIU/l.

Parameter		**TSH < 2.5 (n=33)**	**TSH > 2.5 (n=21)**	**p**
Age	years	57.3±1.2	57.9±1.7	0.772
BMI	kg/m^2	28.4±0.8	28.7±1.1	0.835
FT4	pmol/l	11.90±0.28	11.91±0.34	0.988
Total cholesterol	mmol/l	5.99±1.02	5.36±0.84	0.022*
HDL cholesterol	mmol/l	1.44±0.35	1.42±0.31	0.834
LDL cholesterol	mmol/l	3.90±0.86	3.33±0.76	0.016*
Triglycerides	mmol/l	1.41±0.68	1.33±0.79	0.684
AIP		-0.04±0.25	-0.07±0.28	0.629
CRI-I		4.30±0.92	3.88±0.82	0.098
CRI-II		2.82±0.79	2.41±0.63	0.054
AC		3.30±0.92	2.88±0.82	0.098