Original Article

Subclinical Hypothyroidism is Associated with Atherogenic Lipid Profile in Postmenopausal Women

Subklinik Hipotiroidizm Menopoz Sonrasında Aterojenik Lipid Profiliyle İlişkilidir

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Abstract

Purpose: To determine the prevalence and association of atherogenic lipid profile in postmenopausal women with subclinical hypothyroidism.

Materials (Subjects) and Methods: This as a prospective clinical study included 140 postmenopausal women. In all subjects, basic sociodemographic and anthropometric data, hormonal status of the thyroid gland, and lipid profile were determined. The subjects were followed for a period of 30 months.

Results: The subclinical hypothyroidism in postmenopausal women was significantly associated with higher levels of serum cholesterol, triglycerides, LDL-C, and lower HDL-C (p=0.009, p=0.01, p=0.023, p=0.001, respectively). Furthermore, the analysis of repeated measures showed that subclinical hypothyroidism, irrespective of age and duration of postmenopause, was associated with higher levels of serum cholesterol (adjusted beta: 0.43, CI: 0.12, 0.74, p=0.007), triglycerides (adjusted beta: 0.52, CI: 0.21, 0.84, p=0.001) and LDL-C (adjusted beta: 0.35, CI: 0.03, 0.67, p=0.03), and lower levels of serum HDL-C (adjusted beta: -0.48, CI: -0.81, 0.15, p=0.004)

Conclusion: Subclinical hypothyroidism is associated with atherogenic lipid profile in postmenopausal women.

Keywords: Subclinical hypothyroidism; atherogenic lipid profile; postmenopause

Özet

Amaç: Subklinik hipotirodizmi olan postmenopozal kadınlarda aterojenik lipid profilinin prevalansını ve ilişkisini belirlemektir.

Gereç (Olgular) ve Yöntemler: Prospektif klinik çalışma 140 postmenopozal kadını içermiştir. Tüm olgularda temel sosyodemografik ve antropometrik verileri, tiroid bezinin hormonal durumu ve lipid profili belirlenmiştir. Olgular 30 ay süreyle takip edilmiştir.

Bulgular: Postmenopozal kadınlarda subklinik hipotiroidizm daha yüksek serum kolesterol, trigliserid, LDL-C düzeyleri ve daha düşük HDL-C düzeyleriyle anlamlı düzeyde ilişkilidir (sırasıyla, p=0,009, p=0,01, p=0,023, p=0,001). Dahası, tekrarlanan ölçümlerin analizleri subklinik hipotiroidizmin, yaş ve menopoz süresinden bağımsız olarak; daha yüksek serum kolesterol (uyarlanmış beta: 0,43, CI: 0,12, 0,74, p=0,007), trigliserid (uyarlanmış beta: 0,52, CI: 0,21, 0,84, p=0,001) ve LDL-C (uyarlanmış beta: 0,35, CI: 0,03, 0,67, p=0,03) ve daha düşük serum HDL-C (uyarlanmış beta: -0,48, CI: -0,81, 0,15, p=0,004) düzeyleriyle ilişkili olduğunu göstermiştir.

Sonuç: Subklinik hipotiroidizm postmenopozal kadınlarda aterojenik lipid profiliyle ilişkilidir.

Anahtar kelimeler: Subklinik hipotiroidizm; aterojenik lipid profili; postmenopozal

Introduction

Subclinical hypothyroidism (SH) is defined as an elevated serum level of thyroid stimulating hormone (TSH) with the normal levels of free thyroxine (FT4) and free triiodothyronine (FT3) (1). Most patients are symptomless and have serum TSH levels <10 mU/L. In the studies conducted on the general population, the prevalence of subclinical hypothyroidism ranges from 4% to 15% (2). The preva-

38   Godinjak et al.
      Subclinical Hypothyroidism and Lipid Profile

Turk J Endocrinol Metab
2017;21:37-41

lence increases with age and is higher among women than men (3). Some authors define SH when TSH concentration is higher than 3.6 mU/L (4), while others define it when TSH is higher than 4.0 mU/L (5) or even 5.7 mU/L (6).

Dyslipidemia is defined as an increase in the levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides (7). The patients with dyslipidemia have an increased risk of atherosclerosis, which might lead to cardiovascular disease—reported as the main cause of death in a younger age (8).

Menopause is defined as having occurred when a woman has not had any vaginal bleeding for more than one year due to a decrease in ovarian hormone production. Menopause occurs most often between 49 and 52 years of age (9). Postmenopausal phase has a high risk of cardiovascular diseases that indicates progression of ageing. Postmenopausal women, as compared to premenopausal women, have a higher prevalence of metabolic syndrome (10). Waist circumference, waist-to-hip ratio, blood pressure and the levels of fasting glucose are higher in postmenopausal women compared to women before menopause (11). Compared to premenopausal women, postmenopausal women have higher total serum cholesterol and LDL-C levels (12).

It has already been established that estrogens have a profound effect on the endothelium and smooth muscle cells in the vascular wall, thereby causing vasodilatation (13). Estrogens also exert some effect on hepatic cells by decreasing LDL-C and increasing HDL-C concentrations in blood (14). A decrease in the level of estrogens is related to an increase in fatty tissue in postmenopausal women (15). The decrease in estrogen results in atherogenic lipid profile in postmenopausal women (16,17). The process of subclinical atherosclerosis can be well controlled and even reversed if diagnosed on time and treated by improving hormonal and metabolic control.

Recent studies suggest that subclinical hypothyroidism can be a potentially modifiable risk factor for cardiovascular disease. Since subclinical hypothyroidism is more prevalent in older women than in any other population group (3), it is important to investigate the association between SH and lipid profile in postmenopausal women.

Objective

The aim of this study was to determine the prevalence and association of atherogenic lipid profile in postmenopausal women with subclinical hypothyroidism.

Materials and Methods

Study design and data collection

This prospective case-controlled clinical study included 140 postmenopausal women at the clinic for endocrinology, diabetes and metabolic diseases, Clinical Center of Sarajevo University. Sixty-one postmenopausal women with SH were compared with 79 age and BMI- matched euthyroid controls. Menopause was considered when a woman did not have vaginal bleeding for more than one year. SH was defined as TSH greater than 4.2 mU/L with normal FT4 and FT3. Dyslipidemia was defined as serum levels of LDL-C

>4.30 mmol/L, total cholesterol >5.20 mmol/L, triglycerides >1.70 mmol/L, and HDL-C <1.06 mmol/L. A smoker was defined as a person who smokes tobacco regularly. Physical activity was defined as any movement of the body that requires energy expenditure (walking, gardening, climbing the stairs, running, other forms of physical exercise) for at least 30 min on a daily basis. Exclusion criteria were renal failure, hepatic failure, diagnosed or already treated hypothyroidism. After signing an informed consent, all postmenopausal women in the study were subject to a thorough physical examination and the following data were collected: age, duration of postmenopause, basic lifestyle factors (smoking habits, physical activity), thyroid gland (TSH, FT3, FT4), lipid profile (cholesterol, triglycerides, HDL-C, LDL-C). The parameters of the thyroid gland (hormonal status) and lipid metabolism were determined by ELISA (Cobas e411 and Cobas 6000 Biochemistry Analyzer Roche Diagnostics GmbH, Japan, 2009).

The study was conducted in accordance with the World medical association Declaration of Helsinki on ethical principles for medical research involving human subjects (2008, Revised), and was approved by the Ethics Committee of the Clinical Center of Sarajevo University.

Statistical analysis

The data for continuous variables were presented as means, median, and standard deviation, and for categorical variables as absolute and relative frequencies. In order to determine the difference of means between the two groups, continuous variables were compared using either t-test (normal distribution) or the Mann-Whitney test (non-normal distribution). The role of subclinical hypothyroidism was examined using the multivariate logistic regression analysis. The odds ratio was calculated with the corresponding index of confidentiality. Wherever the sample permitted, an appropriate modeling was done for the evaluation of predictors in relation to the dependent variable logistic regression analysis. A statistical significance was interpreted as $p \leq 0.05$. The data were presented in the form of tables and figures. SAS (Statistical Analysis system) software Version 9 for Microsoft Windows (SAS Institute Inc., Cary, NC, USA) was used for data processing and all statistical analyses.

Results

The study included 140 postmenopausal women (61 with confirmed subclinical hypothyroidism and 79 euthyroid controls). Table 1 presents reference values of laboratory tests used in the study.

The mean value of TSH in the women with subclinical hypothyroidism was significantly higher compared to the mean value of TSH in the euthyroid women (6.4 ±1.2 mU/L vs. 2.4 ±1.1 mU/L; P = 0.0001).

The period of postmenopause in women with subclinical hypothyroidism was longer but the difference was not statistically significant compared to euthyroid women (7.0 ±3.3 vs. 6.1 ±3.5 years; P = 0.099). The number of non-smokers was higher in both groups compared to smokers. In the group with subclinical hypothyroidism, 91.8% of the women were non-smokers, while in the euthyroid group 78.5% of the women were non-smokers (P = 0.032).

Turk J Endocrinol Metab
2017;21:37-41

Godinjak et al.
Subclinical Hypothyroidism and Lipid Profile

39

Table 1. Laboratory tests and reference values for lipid and thyroid gland hormonal status.

Laboratory parameters	Referent values
Thyroid gland hormonal status	
TSH	0.3–4.2 mU/L
FT3	3.1–6.8 pmol/L
FT4	12.0–22.0 pmol/L
Lipid status	
Total cholesterol	3.1 – 5.2 mmol/L
Triglycerides	0.11 – 1.70 mmol/L
HDL – C	1.06 – 1.94 mmol/L
LDL – C	2.00 – 4.30 mmol/L

There was a statistically significant difference between the groups regarding their physical activity, with 91.8% of the women with subclinical hypothyroidism being physically active, compared to 74.7% of the euthyroid women (P = 0.009).

The mean values of serum cholesterol were significantly higher in postmenopausal women with subclinical hypothyroidism compared to the euthyroid postmenopausal women (6.12 ±0.91 mmol/L vs. 5.68 ±1.02 mmol/L; P=0.009). The mean values of serum triglycerides were significantly higher in postmenopausal women with subclinical hypothyroidism compared to euthyroid postmenopausal women (1.90 ±0.49 mmol/L vs. 1.57 ±0.58 mmol/L; P=0.01).

The mean values of serum HDL-C were significantly lower in postmenopausal women with subclinical hypothyroidism compared to euthyroid postmenopausal women (1.20 [1.03 – 1.38] mmol/L vs. 1.41 [1.21 – 1.63] mmol/L; P=0.001). The mean values of serum LDL-C were significantly higher in postmenopausal women with sub-

clinical hypothyroidism compared to euthyroid postmenopausal women (4.20 [3.67 – 4.65] mmol/L vs. 3.91 [3.19 – 4.34] mmol/L; P=0.023).

The postmenopausal women were followed for a period of 30 months. The laboratory parameters of lipid status were determined at the beginning and at 6th, 18th, and 30th months. Follow-up measurements are shown in Table 2.

The analysis of repeated measures showed that subclinical hypothyroidism, independent of age and duration of postmenopause, is associated with higher levels of serum cholesterol (adjusted beta: 0.43, CI: 0.12, 0.74, p=0.007), triglycerides (adjusted beta: 0.52 ,CI: 0.21, 0.84, p=0.001) and LDL-C (adjusted beta: 0.35 ,CI: 0.03, 0.67, p=0.03), and lower levels of serum HDL-C (adjusted beta: –0.48 ,CI: –0.81, 0.15, p=0.004), as shown in Figure 1.

Discussion

Several studies have shown that the morbidity due to cardiovascular disease is approximately six times lower in women of reproductive age compared to the men in the matched age groups (18).
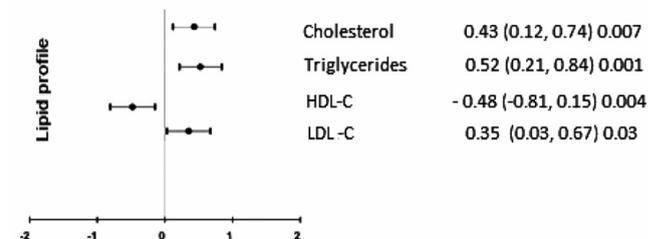

Figure 1: Parameters of lipid profile in postmenopausal women with regard to thyroid gland function (n=140).

Table 2. Follow-up of lipid status parameters in postmenopausal women with subclinical hypothyroidism (SH group) and euthyroid state (EU group)

	Control of lipid status	SH group (n=61)	ET group (n=79)
Total cholesterol (mmol/L)	First measurement	6.12 ±0.91	5.68 ±1.02
	6 months	6.09 ±1.11	5.78 ±0.55
	18 months	6.14 ±0.87	5.65 ±0.79
	30 months	6.16 ±1.02	5.68 ±1.01
Triglycerides (mmol/L)	First measurement	1.90 ±0.49	1.57 ±0.58
	6 months	2.06 ±0.99	1.55 ±1.05
	18 months	1.88 ±1.09	1.61 ±0.77
	30 months	1.95 ±0.67	1.59 ±1.03
HDL-C (mmol/L)	First measurement	1.20 (1.03–1.38)	1.41 (1.21–1.63)
	6 months	1.18 (1.01–1.34)	1.44 (1.25–1.67)
	18 months	1.24 (1.03–1.39)	1.39 (1.20–1.60)
	30 months	1.19 (1.04–1.36)	1.52 (1.22–1.74)
LDL-C (mmol/L)	First measurement	4.20 (3.67–4.65)	3.91 (3.19–4.34)
	6 months	4.22 (3.88–4.71)	4.02 (3.45–4.42)
	18 months	4.31 (3.99–4.70)	3.99 (3.21–4.25)
	30 months	4.26 (3.89–4.61)	4.14 (3.61–4.39)

40   Godinjak et al.
Subclinical Hypothyroidism and Lipid Profile

Turk J Endocrinol Metab
2017;21:37-41

The incidence of cardiovascular diseases in women increases after 50 years of age (19). This increased risk can be attributed to a decline in the estrogen levels after the menopausal transition (20). The studies carried out in postmenopausal women have reported an inverse relation between estrogen levels, dyslipidemia, and atherosclerosis (21,22). The improvements in lipid profile following hormonal replacement therapy have been established in postmenopausal women (23).

Lipid status was evaluated among the subjects. The mean values of serum total cholesterol, triglycerides, and LDL-C in postmenopausal women with subclinical hypothyroidism at the baseline were significantly higher than the mean values of serum cholesterol, triglycerides, and LDL-C of euthyroid postmenopausal women. The mean value of serum HDL-C in women with subclinical hypothyroidism at the baseline was significantly lower than the mean serum value of HDL-C in euthyroid postmenopausal women. Furthermore, our analysis of repeated measures showed that subclinical hypothyroidism independent of age and duration of postmenopause is associated with an increase in serum total cholesterol, triglyceride and LDL-C values, and a decrease in HDL-C values.

The cross-sectional study of Meuwese et al. showed that patients with mildly elevated TSH (between 5.1 and 10.0 mU/L) had significantly higher levels of cholesterol than those who were euthyroid (3). Posadas-Romero et al. (24) found that patients with subclinical hypothyroidism have significantly higher triglyceride levels and decreased HDL-C.

Similar results were observed by Siemiński et al. (25), who found elevated serum concentrations of cholesterol and triglycerides, while HDL-C was lower in women with subclinical hypothyroidism compared to the euthyroid postmenopausal women. Heima et al. (26) also established the association between dyslipidemia and subclinical hypothyroidism.

The exact pathophysiological mechanism accounting for the effects of TSH on lipid profile has not been fully established. Tian et al. (27) proposed that TSH upregulates the expression of hepatic 3-hydroxy-3-methyl-glutaryl co-enzyme A reductase (an enzyme that limits cholesterol synthesis) by acting on the TSH receptor on liver cells. Gagnon et al. (28) showed that TSH stimulates lipolysis in cultured adipocytes and elevates serum-free fatty acid levels.

The elevated TSH levels in the serum of patients with SH suggest that, although apparently normal, serum thyroid hormones are insufficient. Thyroid hormone deficiency, therefore, represents a well-known cause of dyslipidemia, both in overt and subclinical hypothyroidism (29).

Our study has several limitations such as a small sample size and the relatively short follow-up time. The inconsistencies between our and previous studies may be explained by the differences in the study design, sample size, population characteristics, as well as the criteria used to define the dysfunction of the thyroid gland.

Larger cohort studies with a longer duration in our population are required in order to evaluate the further consequences of subclinical hypothyroidism as the mildest form of thyroid gland dysfunction. This study has several advantages, including a longitudinal design and implication of repeated measures. Also, we were able to control our analysis for the age and duration of postmenopause. Additionally, all measurements were valid and the data were collected using the recommended modern equipment. To the best of our knowledge, this is the first study with multiple measurements related to the subclinical hypothyroidism and its consequences carried out on Bosnia and Herzegovina population.

Conclusion

Subclinical hypothyroidism is significantly associated with higher levels of serum total cholesterol, triglycerides, LDL-C, and lower HDL-C. Our analysis of repeated measures during the 30-months follow-up showed that subclinical hypothyroidism independent of the age and duration of postmenopause is associated with higher levels of serum cholesterol triglycerides, LDL-C, and lower HDL-C. Our study confirms that elevated serum TSH in patients with subclinical hypothyroidism is associated with atherogenic lipid profile and increases the risk of developing cardiovascular diseases, regardless of other known risk factors.

Ethics

Research was aproved by the Ethics Committee of Clinical Center University of Sarajevo.

Authorship Contributions

Concept: Amina Godinjak, Design: Zelija Velija-Asimi, Data Collection or Processing: Azra Burekovic, Analysis or Intrepretation: Amina Godinjak, Selma Jusufovic, Literature Search: Adisa Brgulja, Amela Bostandzic, Writing: Amina Godinjak.

Conflict of Interest: No conflict of interest was declared by the authors

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Turk J Endocrinol Metab
2017;21:37-41

Godinjak et al.
Subclinical Hypothyroidism and Lipid Profile

41

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