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ORIGINAL

Lipid Profiles in the Untreated Patients with Hashimoto Thyroiditis and the Effects of Thyroxine Treatment on Subclinical Hypothyroidism with Hashimoto Thyroiditis

TETSUYA TAGAMI, TAMIKO TAMANAHA, SATOKO SHIMAZU, KYOKO HONDA, KAZUTAKA NANBA, HIDENARI NOMURA, YORIKO SAKANE UEDA, TAKESHI USUI, AKIRA SHIMATSU AND MITSUHIDE NARUSE

Division of Endocrinology and Metabolism, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto 612-8555, Japan

Abstract. To evaluate the prevalence of dyslipidemia in the population of Hashimoto thyroiditis, we reviewed medical records on the consecutive 1181 cases with adult Hashimoto thyroiditis and 830 cases were adopted for the study. First, the serum TSH level increased and serum free T4 level decreased, slightly but significantly, with increasing age. There were significant positive correlations between serum TSH levels and lipid parameters such as total cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), non-HDL-C and LDL-C/HDL-C ratio (L/H). In contrast, there were significant negative correlations between serum free T4 levels and all of these lipid parameters. According to the thyroid function, the cases were classified into 4 groups such as thyrotoxicosis (TT), euthyroidism (EU), subclinical hypothyroidism (SH) and overt hypothyroidism (OH). TC, HDL-C, non-HDL-C and LDL-C of TT were significantly lower than those in EU. In contrast, TC, TG, non-HDL-C, LDL-C, L/H and age of OH were significantly higher than those in EU. Interestingly, LDL-C and L/H of SH were significantly higher compared with EU. Thirty-two of SH patients were treated with small doses of levothyroxine and the effects on the lipid profile were examined. The TC, non-HDL-C, LDL-C and L/H were significantly decreased after treatment. In conclusion, the prevalence of dyslipidemia increases along with hypofunction of the thyroid and T4 replacement therapy may improve lipid profile in the cases of SH with Hashimoto thyroiditis.

Key words: Dyslipidemia, Hashimoto thyroiditis, Subclinical hypothyroidism, Levothyroxine

HYPERCHOLESTEROLEMIA is a commonly experienced metabolic disorder and it causes arteriosclerosis. Recently, new therapeutic reagents such as statins have been created and primary hypercholesterolemia is effectively treated with these reagents. However, statins are not low priced and may induce rare but serious side effects such as rhabdomyolysis. Hypothyroidism induces hypercholesterolemia that accelerates arteriosclerosis, similarly that primary hypercholesterolemia does. Moreover, this secondary hypercholesterolemia is often resistant to the treatment with statins. In contrast, replacement of levothyroxine promptly improves cholesterol metabolism and, consequently, prevents cardiovascular events.

Subclinical hypothyroidism (SH) is defined as normal serum thyroxine (T4) level in the presence of high serum thyroid stimulating hormone (TSH). The etiology of SH is the same as that of overt hypothyroidism (OH) [1] and SH is most often caused by chronic lymphocytic thyroiditis (Hashimoto thyroiditis) [2]. Other factors that cause SH include thyroid injury (radioactive iodine treatment or external radiation therapy), drugs (iodine-containing compounds, lithium carbonate or interferon), thyroid infiltration (amyloidosis, sarcoidosis, hemochromatosis or lymphoma), a period of thyroiditis (subacute, postpartum or painless), a part of central hypothyroidism and TSH receptor gene mutations, among others [3]. The effects of SH on lipid metabolism are controversial and the significance of

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Correspondence to: Tetsuya TAGAMI, M.D., Ph.D., Clinical Research Institute, Division of Endocrinology and Metabolism, Kyoto Medical Center, National Hospital Organization, Mukaihata-cho 1-1, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan.
E-mail: ttagami@kyotolan.hosp.go.jp

T4 treatment for SH is not established [4], especially in Japanese population [5, 6] where the iodine intake is excess.

Hashimoto thyroiditis is an autoimmune disorder of the thyroid gland that is the most common cause of hypothyroidism. It is originally described as struma lymphomatosa, which is featured as the formation of lymphoid follicles, marked changes in the thyroid epithelial cells, extensive formation of new connective tissue, and diffuse infiltration of round cells [7]. An anti-thyroglobulin antibody prevalence of 10% and an anti-thyroid peroxidase antibody prevalence of 11% in the general population are reported [8]. Here, to evaluate the relationship between thyroid function and dyslipidemia, we chose the population of Hashimoto thyroiditis because it is one of the most common thyroid diseases that frequently cause various thyroid dysfunctions. Therefore, it is more efficient to study the patients with Hashimoto thyroiditis than to study the general population, to see the relationship between thyroid function and lipid profile. Because lymphocytic infiltration of the thyroid gland is present in up to 40% of healthy women [3], the majority of SH may be based on Hashimoto thyroiditis. Consequently, the results in this study may infer the prevalence of dyslipidemia due to thyroid dysfunction and the effects of thyroxine treatment on SH in the general population. Because hypercholesterolemia increases especially in postmenopausal women, correlations between age and thyroid function or lipid profile were also examined.

Patients and Methods

Patients

After Local Ethical Committee approval for the study was obtained, we analyzed the relationship between the thyroid function and lipid profile by reviewing the records of consecutive 1181 cases with adult Hashimoto thyroiditis, who visited the Endocrine and Thyroid Clinic of National Hospital Organization Kyoto Medical Center for the first medical examination from 1999 to 2008. A diagnosis of Hashimoto thyroiditis was based on the Japan Thyroid Association's guidelines for the diagnosis of Hashimoto thyroiditis (http://www.thyroid.umin.ac.jp/). Graves' disease was distinguished from painless thyroiditis using TBII and radioiodine thyroid scintigram [9, 10], if necessary, based on the Japan Thyroid Association's guidelines for the diagnosis of Graves' disease and painless thyroiditis (http://www.thyroid.umin.ac.jp/). The patients with familial hypercholesterolemia or the patients who were already having medical treatment for their dyslipidemia were excluded. The patients who had complications or conditions that affect lipid metabolism such as malignant tumor, chronic hepatic disease, uncontrolled diabetes mellitus, nephrotic syndrome, or pregnancy were also excluded. At the end, 830 cases (male 97 and female 733) were adopted for the analysis. In SH, the patients were counseled to abstain iodine-rich food such as kelp and reassessed their TSH after a few months. Because thirty-two patients had still SH, they were treated with low doses (25-50 μg/day) of levothyroxine and re-evaluated their lipid profiles after 3 months. The final mean daily dose of levothyroxine was 36 ± 17 μg.

Laboratory evaluation

The levels of total cholesterol (TC), triglyceride (TG) and HDL-cholesterol (HDL-C) were measured by enzyme assays. The non-HDL-C levels were calculated as TC − HDL-C. The LDL-cholesterol (LDL-C) levels were calculated by the Friedewald formula; TC − (HDL-C + TG/5) [11]. The patients whose TG was greater than 400 mg/dL, that might have limitation of the calculation of LDL-C, were excluded from the study. Serum concentrations of TSH (normal, 0.27-4.20 mU/L) and free T4 (normal, 1.0-1.8 ng/dL) were determined by electro-chemiluminescence immunoassay (ECLIA, Roche Diagnostics, Tokyo, Japan). According to the thyroid function, patients were classified into 4 groups such as thyrotoxicosis (TT; suppressed TSH), euthyroidism (EU; normal FT4 and TSH), SH (normal FT4 and elevated TSH) and OH (low FT4 and elevated TSH). The anti-thyroglobulin (Tg) antibodies and anti-thyroid peroxidase (TPO) antibodies were measured with commercial radioimmuno assays (RIA) (TgAb and TPOAb, Cosmic Corp., Cardiff, UK).

Statistical Analysis

Data are expressed as the mean ± SD. Independent Student's *t* test was used to compare age, thyroid function and lipid profile between euthyroid controls and other groups. Comparisons between the patients at the two time points were performed using paired *t* test for normally distributed data and Wilcoxon signed rank test for nonparametric distributions [6, 12, 13]. Pearson's correlation coefficients among age, thyroid

Table 1. Correlation between the age and the thyroid function or the lipid profile

	Total (n=830)	Correlation (r)[a]	EU+SH (n=505)	Correlation (r)[a]
Age (yr)	52.1 ± 16.4		51.2 ± 16.6	
TSH (mU/L)	18.4 ± 55.9	0.15[d]	2.67 ± 2.77	0.09[b]
Free T4 (ng/dL)	1.20 ± 0.80	-0.16[d]	1.18 ± 0.19	-0.10[b]
TC (mg/dL)	202.8 ± 49.4	0.22[d]	199.2 ± 38.2	0.32[d]
TG (mg/dL)	109.3 ± 60.1	0.25[d]	102.7 ± 53.5	0.28[d]
HDL-C (mg/dL)	68.0 ± 18.4	-0.10[c]	69.6 ± 17.0	-0.08
Non-HDL (mg/dL)	135.4 ± 45.6	0.29[d]	130.1 ± 36.5	0.38[d]
LDL-C (mg/dL)	113.3 ± 39.8	0.25[d]	109.6 ± 31.7	0.35[d]
LDL-C/HDL-C	1.79 ± 0.79	0.28[d]	1.69 ± 0.72	0.29[d]

Values are expressed as the mean ± SD.
[a]Pearson correlation coefficient *vs.* age.
Correlations were determined using log transformed values for TSH and free T4.
[b]$P<0.05$, [c]$P<0.01$, [d]$P<0.0001$.

Table 2. Correlations between the thyroid function and the lipid profile

Correlation (r)[a]	TSH	Free T4
TC	0.43[d]	-0.53[d]
TG	0.14[c]	-0.21[d]
HDL-C	0.13[b]	-0.13[c]
Non-HDL	0.41[d]	-0.51[d]
LDL-C	0.41[d]	-0.49[d]
LDL-C/HDL-C	0.26[d]	-0.32[d]

[a]Pearson correlation coefficient. Correlations were determined using log transformed values for TSH and free T4.
[b]$P<0.01$, [c]$P<0.001$, [d]$P<0.0001$.

function and lipid profile were determined by using regression analyses.

Results

Relationship between thyroid function and lipid parameters

The baseline profile is summarized in Table 1. The mean age of 830 cases was 52 years old (range 18-89). First, the relationships of age with thyroid function and lipid profile were examined. The correlation coefficients between the age and thyroid function or lipid profile are also shown in Table 1. The serum TSH level increased and serum free T4 level decreased, slightly but significantly, with increasing age. The lipid parameters such as TC, TG, non-HDL-C, LDL-C and the LDL-C to HDL-C ratio (L/H) increased, whereas HDL-C decreased with aging. Because TT and OH (see *Patients and Methods* about the classification) may greatly influence these parameters, we also examined these relationships within EU and SH, and the similar tendencies were observed. Next, we examined relationships between thyroid function and lipid parameters. There were significant positive correlations between serum TSH values and all of these lipid parameters (Table 2). In contrast, there were significant negative correlations between serum free T4 values and all of the lipid parameters.

Thyroid status and lipid profile

According to the thyroid function, patients were classified into 4 groups such as TT, EU, SH and OH (Table 3). SH was defined as normal serum free T4 level with high serum TSH (>4.20 mU/L). In the first place, the mean age of OH was significantly higher than that of EU. The TC, HDL-C, non-HDL-C, and LDL-C of TT were significantly lower than those of EU. In contrast, TC, TG, non-HDL-C, LDL-C, and L/H of OH were significantly higher than those of EU. Interestingly, LDL-C and L/H of SH were significantly higher compared with EU.

Effects of T4 treatment on lipid profile of SH

Thirty-two of SH patients were treated with small doses of levothyroxine and the effects on the lipid profile were examined (Table 4). The TC, non-HDL-C, LDL-C and L/H significantly decreased after treatment.

Table 3. The lipid profiles in patient groups classified with the thyroid function

	Thyrotoxicosis (n=100)	Euthyroidism (n=426)	Subclinical Hypothyroidism (n=79)	Overt Hypothyroidism (n=225)
Age (yr)	48.5 ± 16.4	50.7 ± 16.6	53.5 ± 16.4	55.6 ± 15.3[c]
TSH (mU/L)	0.04 ± 0.07[c]	1.8 ± 1.0	7.5 ± 4.1[c]	62.5 ± 94.8[c]
Free T4 (ng/dL)	2.62 ± 1.48[c]	1.19 ± 0.19	1.11 ± 0.14[c]	0.62 ± 0.29[c]
TC (mg/dL)	163.4 ± 33.0[c]	198.4 ± 37.2	203.9 ± 44.0	228.7 ± 62.4[c]
TG (mg/dL)	100.3 ± 56.1	102.4 ± 54.2	104.1 ± 50.2	127.9 ± 71.1[c]
HDL-C (mg/dL)	59.4 ± 14.7[c]	70.1 ± 16.5	66.8 ± 18.7	68.4 ± 21.7
Non-HDL (mg/dL)	105.3 ± 30.4[c]	128.7 ± 35.3	137.7 ± 42.2	161.3 ± 56.4[c]
LDL-C (mg/dL)	85.6 ± 27.5[c]	108.3 ± 30.6	116.8 ± 36.8[a]	134.7 ± 49.5[c]
LDL-C/HDL-C	1.52 ± 0.61	1.64 ± 0.64	1.91 ± 0.93[b]	2.13 ± 0.93[c]

Thyrotoxicosis, Euthyroidism, Subclinical hypothyroidism and Overt hypothyroidism were determined with suppressed TSH, normal FT4 and TSH, normal FT4 and elevated TSH, and low FT4 and elevated TSH, respectively.
Values are expressed as the mean ± SD.
[a]$P<0.05$, [b]$P<0.01$, [c]$P<0.0001$ *vs.* euthyroidism.

Table 4. The thyroid functions and lipid profiles in patients with SH before and after levothyroxine replacement therapy

	L-T4 replacement (n=32)	
	Before	After
TSH (mU/L)	8.4 ± 5.8	3.4 ± 1.9[c]
Free T4 (ng/dL)	1.08 ± 0.15	1.32 ± 0.23[c]
TC (mg/dL)	205 ± 32	195 ± 27[a]
TG (mg/dL)	106 ± 54	125 ± 74
HDL-C (mg/dL)	66 ± 19	65 ± 16
Non-HDL (mg/dL)	140 ± 30	131 ± 31[a]
LDL-C (mg/dL)	118 ± 27	106 ± 26[b]
LDL-C/HDL-C	1.98 ± 0.79	1.76 ± 0.64[a]

Values are expressed as the mean ± SD.
[a]$P<0.05$, [b]$P<0.01$, [c]$P<0.0001$ *vs.* before treatment, respectively.

Discussion

The prevalence of SH in the general population was estimated as 4.3% [8] and that in the thyroid antibodies positive population was 19% in the U.S. [14]. The prevalence of SH in Hashimoto thyroiditis in this study was 9.5%. Because the subjects with TT or OH may have visited our hospital with some complaints, it might be better to exclude TT and OH, in order to compare the percentage in this study with that in the thyroid antibodies positive general population. Then, the prevalence of SH in Hashimoto thyroiditis in EU and SH in this study becomes 16.6%.

The results that TC, TG, HDL-C and LDL-C were negatively correlated with free T4 levels, obtained in our study. TC, HDL-C, non-HDL-C and LDL-C levels were lower in TT than those in EU, and TC, TG, non-HDL-C and LDL-C levels were higher in OH than those in EU. Alternatively, the TG level in TT and the HDL-C level in OH were not different from EU. Although only LDL-C was significantly higher in SH, the mean levels of TC, TG and non-HDL-C in SH were also relatively higher than those in EU. In contrast, the mean level of HDL-C in SH was relatively lower than that in EU. Interestingly, although the grouping of SH from EU was done based on the TSH levels, the mean free T4 values in SH were significantly lower than those in EU (Table 3). Several reports have been made about the association between TSH and serum cholesterol levels. Higher serum cholesterol levels are found in subjects with high-normal TSH levels [15]. There was a significant positive correlation between serum TSH and serum TC and LDL-C levels in men and women [16]. The serum non-HDL-C and the L/H ratio have been used as better predictors of cardiovascular disease [17-20]. Ito *et al*. [6] first demonstrated decrease of the serum non-HDL-C in SH by T4 treatment. The L/H ratio was significantly high in SH [21] and T4 treatment de-

creased the ratio in one study [22] but not in another [23]. However, because T4 treatment unchanged serum levels of HDL-C in SH in most studies, decreases in the L/H ratio can be simply explained by the decrease in serum levels of LDL-C.

The serum concentrations of free T4 and TSH seem to change little with increasing age [24], but the prevalence of SH seems to increase with aging [14, 25]. In our study with Hashimoto thyroiditis, there was a significant positive correlation between the age and serum TSH level, and a negative correlation between the age and serum free T4 level. The correlations were retained within EU and SH as well. The age-related increases of TC, TG, non-HDL-C and LDL-C may result from age-related decrease of thyroid function because thyroid function decreased with aging. In contrast, HDL-C decreased with aging and this is an opposite direction of age-related decrease of thyroid function because there was a negative correlation between HDL-C and thyroid function. To be emphasized is that there was no significant difference in the mean age between SH and EU.

There are several studies about the replacement therapy of SH. Among them, 8 studies were done with double-blind placebo controlled, recently. There were no changes in TC levels in earlier two studies [26, 27]. In other two studies, TC, LDL-C and HDL-C were unchanged [28, 29]. In contrast, TC and LDL-C but not HDL-C improved in the remaining four studies [12, 13, 23, 30]. In our study with Hashimoto thyroiditis, TC, non-HDL-C, LDL-C and L/H ratio were significantly decreased after treatment in the SH patients, indicating that our results not only support the positive effects of replacement therapy for SH on dyslipidemia but also provide the effects on additional cardiovascular markers such as non-HDL-C and L/H ratio.

There are some possible limitations in the present study. Because the subjects visited our hospital with some complaints, the prevalence of dyslipidemia in Hashimoto thyroiditis may have some bias. Indeed, the prevalence of OH in Hashimoto thyroiditis in this study was 27% and it was much higher than that in the general population [8]. With the same reason, the prevalence of OH may have exceeded that of SH in this study. It might be more suitable to investigate its prevalence on the occasion of a nation-based health examination. It is necessary, however, to examine enormous number of subjects in such a population. The design of replacement therapy was not prospective placebo-controlled and sample size was relatively small. Properly controlled prospective studies with a larger sample size are necessary to demonstrate whether replacement therapy alters several cardiovascular markers in patients of SH with Hashimoto thyroiditis.

In conclusion, the prevalence of dyslipidemia increases along with the decrease of thyroid function in Hashimoto thyroiditis. The compensation of SH can improve lipid profile, not only LDL-C but also non-HDL-C and L/H, as indicators for atherosclerosis and cardiovascular risk.

References

1. Cooper DS (2001) Clinical practice: subclinical hypothyroidism. *N Engl J Med* 345: 260-265.
2. Ayala AR, Dance MD, Landenson PW (2000) When to treat mild hypothyroidism. *Endocrinol Clin North Am* 29: 399-415.
3. Biondi B, Cooper DS (2008) The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 29: 76-131.
4. Surks MI, Ortiz EO, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 291: 228-238.
5. Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M, Usa T, Ashizawa K, Yokoyama N, Maeda R, Nagataki S, Eguchi K (2004) Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab* 89: 3365-3370.
6. Ito M, Arishima T, Kudo T, Nishihara E, Ohye H, Kubota S, Fukata S, Amino N, Kuma K, Sasaki I, Hiraiwa T, Hanafusa T, Takamatsu J, Miyauchi A (2007) Effect of levo-thyroxine replacement on non-high density lipoprotein cholesterol in hypothyroid patients. *J Clin Endocrinol Metab* 92: 608-611.
7. Hashimoto H (1912) Zur Kenntniss der lymphomatosen Veranderung der Schilddruse (Struma lymphomatosa). *Arch Klin Chir* 97: 219-248.
8. Hollowell JG, Staehling NW, Flanders WD, Hannon

WH, Gunter EW, Spencer CA, Braverman LE. (2002) Serum TSH, T4, and thyroid autoantibodies in the United States population (1988-1994): National health and nutrition examination survey (NHANES III). *J Clin Endocrinol Metab* 87: 489-499.
9. Tagami T, Hagiwara H, Kimura T, Usui T, Shimatsu A, Naruse M. (2007) The incidence of gestational hyperthyroidism and postpartum thyroiditis in the treated patients with Graves' disease. *Thyroid* 17: 767-772.
10. Tagami T, Usui T, Shimatsu A, Naruse M. (2007) Toxic thyroid adenoma presenting as hypokalemic periodic paralysis. *Endocr J* 54: 797-803.
11. Rifai N, Warnick RW, McNamara JR, Belcher JD, Grinstead GF, Frantz Jr ID (1992) Measurement of low-density-lipoprotein cholesterol in serum: a status report. *Clin Chem* 38: 150-160.
12. Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR, Drewe J, Huber P, Herzog R, Muller B (2001) TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). *J Clin Endocrinol Metab* 86: 4860-4866.
13. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU (2007) The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 92: 1715-1723.
14. Surks MI, Hollowell JG (2007) Age-specific distribution of serum thyrotropin and antithyroid antibodies in the U.S. population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab* 92: 4575-4582.
15. Michalopoulou G, Alevizaki M, Piperingos G, Mitsibounas D, Mantzos E, Adamopoulos P, Koutras DA (1998) High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical hypothyroidism? *Eur J Endocrinol* 138: 141-145.
16. Iqbal A, Jorde R, Figenschau Y (2006) Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: the Tromso Study. *J Intern Med* 260: 53-61.
17. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, et al. Lipid alternations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 260: 641-651.
18. Frost PH, Havel RJ (1998) Rationale for use of non-high density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol* 81: 26-31.
19. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, Bush TL (2001) Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med* 46: 55-56.
20. Kannel WB (2005) Risk stratification of dyslipidemia: insight from the Framingham Study. *Curr Med Chem Cardiovasc Hematol Agents* 3: 187-193.
21. Althaus BU, Stab JJ, Ryff-De Leche A, Oberhansli A, Stahelin HB (1988) LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. *Clin Endocrinol (Oxf)* 28: 157-163.
22. Caron P, Calazel C, Parra HJ, Hoff M, Louvet JP (1990) Decreased HDL cholesterol in subclinical hypothyroidism: the effect of L-thyroxine therapy. *Clin Endocrinol (Oxf)* 33: 519-523.
23. Caraccio N, Ferranini E, Monzani F (2002) Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. *J Clin Endocrinol Metab* 87: 1533-1538.
24. Sawin CT (2005) In: Age-related changes in thyroid secretion. Braverman LE, Utiger RD (eds) Werner & Ingbar's The Thyroid, a fundamental and clinical text, 9th ed. Lippincott Wikkiams & Wilkins, Philadelphia, 214-219.
25. Canalis GJ, Manowitz NR, Mayor G, Ridgway EC (2000) The Colorado thyroid disease prevalence study. *Arch Intern Med* 160: 526-534.
26. Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway ECL (1984) Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Ann Intern Med* 101: 18-24.
27. Nystrom E, Caidahl K, Fager G, Wikkelso C, Lundberg PA, Lindstedt G (1988) A double-blind cross-over 12-month study of L-thyroxine treatment of women with 'subclinical' hypothyroidism. *Clin Endocrinol (Oxf)* 29: 63-67.
28. Jaeschke R, Guyatt G, Gerstein H, Patterson C, Molloy W, Cook D, Harper S, Griffith L, Carbotte R (1996) Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med* 11: 744-749.
29. Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, Crook M, Dore CJ, Finer N (2002) A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med* 112: 348-354.
30. Monzani F, Caraccio N, Kozakowa M, Dardano A, Vittone F, Virdis A, Taddei S, Palombo C, Ferrannini E (2004) Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo- controlled study. *J Clin Endocrinol Metab* 89: 2099-2106.