



# THE PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN THE POPULATION OF ELDERLY NURSING HOME RESIDENTS IN ZAGREB

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**SUMMARY** – The aim of the study was to investigate the prevalence of thyroid dysfunction, positive thyroid peroxidase antibodies (TPOAb) and hypercholesterolemia in elderly and younger subjects, and the association of subclinical hypothyroidism with hypercholesterolemia. The study included 204 elderly (136 females and 68 males, age median 71, range 60-92 years), and 83 younger control subjects (63 females and 20 males, age median 45, range 19-55 years). Subjects with prior thyroid dysfunction were excluded. Serum thyrotropin (TSH), free triiodothyronine (FT3), free thyroxine (FT4), TPOAb, total cholesterol, height and weight were measured. Mann-Whitney,  $\chi^2$ -test and Student's t-test were used on statistical analysis. The prevalence of subclinical hypothyroidism (TSH >5 mU/L) in elderly was 7.4% *vs.* 3.6% in younger subjects, with the highest prevalence of 8.8% in elderly women *vs.* 4.8% in younger women, and 4.4% in elderly men. The prevalence of hypothyroidism and subclinical hyperthyroidism in elderly subjects was 0.5% and 1.5%, respectively. In women with subclinical hypothyroidism, the prevalence of TPOAb was 77% in elderly women and 67% in younger women (overall 19.9% in elderly and 14.3% in younger women). The mean FT3 level was lower in elderly women as compared with elderly men ( $p < 0.01$ ) and younger women ( $p < 0.05$ ). The mean cholesterol level was higher in elderly subjects in comparison with younger ones ( $p < 0.01$ ), and in elderly women *vs.* elderly men ( $p < 0.01$ ), but without difference between subclinical hypothyroidism and euthyroid subjects (6.0 mmol/L). In conclusion, subclinical hypothyroidism is the most prevalent thyroid dysfunction in elderly, with the highest prevalence in elderly women, and autoimmune thyroiditis is the most common etiology. Hypercholesterolemia was more related to older age, especially elderly females, but not influenced by subclinical hypothyroidism.

**Key words:** *Subclinical hypothyroidism; Prevalence; Elderly; Thyroid gland; Thyroid dysfunction; Thyrotropin; Cholesterol*

## Introduction

Subclinical hypothyroidism is a state associated with a mildly elevated serum thyrotropin (TSH) concentration and normal serum free thyroxine (FT4) and free triiodothyronine (FT3) concentration<sup>1</sup>. This condition is also known as mild thyroid failure. The

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prevalence of subclinical hypothyroidism ranges from 1% to 10% worldwide. It is the most common thyroid dysfunction in the elderly, especially in elderly women, with the prevalence of 5%-20% in this age group<sup>2</sup>. Subclinical hypothyroidism is usually asymptomatic state, defined by laboratory findings but not by clinical symptoms and signs. However, some of the patients may have symptoms of overt hypothyroidism such as fatigue, dry skin, and cold intolerance<sup>1-4</sup>. These symptoms are nonspecific and can be attributed to aging<sup>3</sup>. Patients with subclinical hypothyroidism may have adverse effects on cardiovascular system, especially due to the increased risk of ischemic heart disease and heart failure<sup>2,4</sup>. Mild abnormalities of serum lipoproteins<sup>5,6</sup>, higher mean total serum cholesterol level<sup>7,8</sup>, increased vascular resistance<sup>9</sup>, increased intima-media thickness<sup>10</sup>, as well as abnormalities of cardiac function<sup>11-13</sup> were recorded in these patients. Rotterdam Study has demonstrated that subclinical hypothyroidism is an independent risk factor for development of atherosclerosis and myocardial infarction in elderly women<sup>14</sup>. A panel of experts has divided patients with subclinical hypothyroidism into two categories according to the degree of TSH elevation, i.e., patients with mildly increased serum TSH level (4.5-10 mIU/L) and patients with serum TSH levels of more than 10 mIU/L because the progression of the disease and the adverse effects of increased serum TSH level are more pronounced in the latter group<sup>15</sup>. The most common etiology of subclinical hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease)<sup>1-3</sup>. The disease is associated with positive thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb). In the Wickham survey, 67% of women and 40% of men with subclinical hypothyroidism had increased antibody titers<sup>16</sup>. Other causes of subclinical hypothyroidism are treatment of Grave's disease with radioiodine, partial thyroid surgery, external radiation therapy to the head and neck, anti-thyroid drugs, inadequate replacement therapy for overt hypothyroidism, and use of medications such as amiodarone, lithium, iodine containing agents and tyrosine kinase inhibitor therapy<sup>1-4,17</sup>.

In the present cross-sectional epidemiological study, we investigated the prevalence of thyroid dysfunction and autoimmune thyroiditis in elderly subjects, residents of old-age nursing home, and

middle-age subjects, employees of the nursing home from Zagreb, the capital of Croatia.

The primary aim of the study was to determine the prevalence of subclinical hypothyroidism in elderly subjects and compare it to the prevalence in younger subjects, as well as to investigate the main etiologic causes of subclinical hypothyroidism. The secondary aim of the study was to investigate the association of elevated total serum cholesterol level with subclinical hypothyroidism. The study hypothesis was that subclinical hypothyroidism is the most common thyroid dysfunction in the elderly, especially in elderly women, and that autoimmune thyroiditis is the most common etiology of subclinical hypothyroidism. Furthermore, subjects with subclinical hypothyroidism are expected to have higher mean total serum cholesterol level in comparison to euthyroid subjects.

## Subjects and Methods

We studied 204 elderly subjects (136 females and 68 males), residents of the Maksimir Elderly Nursing Home from Zagreb to determine the prevalence of subclinical hypothyroidism. Residents older than 60 (median age 71, range 60-92) years were included in the study. Control group included 83 subjects (63 females and 20 males aged 19 to 55, median age 45 years) working as employees in the nursing home. The study was approved by the Ethics Committee of the Maksimir Elderly Nursing Home in Zagreb and Ethics Committee of Sestre milosrdnice University Hospital Center, Zagreb. Informed consent was obtained from every study participant. Subjects with prior thyroid dysfunction and/or taking medications that deteriorate thyroid function were excluded from the study.

Serum TSH, FT4, FT3 and total cholesterol levels were measured in all participants. Serum TSH was determined by Immulite third generation TSH assay (DPC, Los Angeles, CA, USA) (reference range: 0.4-4.0 mIU/L). Serum FT3 and FT4 concentrations were measured by competitive Immulite Free T3 and Free T4 immunoassay (DPC, Los Angeles, CA, USA). Normal reference range is 2.3-6.3 pmol/L for FT3 and 10.3-24.5 pmol/L for FT4. Thyroid peroxidase antibodies (TPOAb) were measured by sequential immunometric assay. Normal values for TPOAb are less than 35 IU/mL.

Subclinical hypothyroidism was defined as serum TSH above 5.0 mIU/L and normal FT4 and FT3 levels. Hypothyroidism was defined as high serum TSH and low FT4. Subclinical hyperthyroidism was defined as serum TSH below the reference range of 0.4 mIU/L and normal FT3 and FT4 levels. Hyperthyroidism was defined as low serum TSH and high FT4 and/or FT3. Serum total cholesterol level was measured by spectrophotometric method with adult reference range from 3.8 to 5.7 mmol/L.

All participants answered a questionnaire with history data related to previous thyroid diseases, thyroid surgery, treatment of thyroid diseases with radioiodine, external head and/or neck radiotherapy, and medications. Physical examination was performed including thyroid gland palpation. Body height and weight were measured in all participants. Body mass index (BMI) was calculated according to the equation: BMI = body weight/body height<sup>2</sup> (kg/m<sup>2</sup>).

Mann-Whitney,  $\chi^2$ -test and Student's t-test were used on statistical analysis. The value of  $p \leq 0.05$  was considered statistically significant.

## Results

The characteristics of study subjects are presented in Table 1. Median age of elderly subjects was 71 (range 60 to 92) years. Median age of younger subjects was 45

(range 19 to 55) years. BMI was used as a measure of nutritional status. Mean serum TSH, FT3 and FT4 values with standard deviation and FT3/FT4 ratio are shown in Table 2. Mean serum TSH value was higher in elderly subjects, especially in elderly females. However, this difference was not statistically significant. Mean serum FT4 did not differ between the groups. Mean serum FT3 was significantly lower in elderly women in comparison to elderly men ( $4.4 \pm 0.9$  vs.  $4.9 \pm 0.9$  pmol/L,  $p < 0.01$ ), as well as in comparison to younger women ( $4.4 \pm 0.9$  vs.  $4.7 \pm 1.2$  pmol/L,  $p < 0.05$ ). The FT3/FT4 ratio was significantly lower in elderly women in comparison to elderly men ( $0.29$  vs.  $0.32$ ,  $p < 0.05$ ).

The prevalence of thyroid dysfunction in the study subjects is shown in Table 3. The prevalence of subclinical hypothyroidism (TSH >5 mIU/L) in the elderly was 7.4% vs. 3.6% in younger control subjects ( $p = 0.2$ ). The highest prevalence of subclinical hypothyroidism was recorded in elderly women (8.8%) vs. 4.8% in younger women ( $p = 0.3$ ) and 4.4% in elderly men. The majority of elderly subjects were euthyroid (90.6%). The prevalence of hypothyroidism in elderly subjects was 0.5% (one elderly woman) and of subclinical hyperthyroidism 1.5% (two elderly women and one elderly man). Serum TPOAb were positive in 77% of elderly women and 67% of younger

Table 1. Characteristics of elderly subjects and control group of younger subjects

	Control group			Elderly subjects		
	Female	Male	Total	Female	Male	Total
n	63/83	20/83	83	136/204	68/204	204
Age (yrs)	45 (19-55)	42 (23-53)	45 (19-55)	72 (60-92)	67 (60-89)	71 (60-92)
BMI	21.9±3.3	26.7±3.7	22.3±3.6	22.6±3.4	23.1±3.1	22.7±3.3

Age = median (min-max); BMI = body mass index (mean ± standard deviation)

Table 2. Serum thyrotropin, free triiodothyronine and free thyroxine concentrations in elderly and younger (control) subjects

	Control group			Elderly subjects		
	Female	Male	Total	Female	Male	Total
TSH <sup>†</sup> (mU/L)	1.9±1.5	1.8±0.9	1.9±1.4	2.5±4.7	1.9±1.4	2.3±4.0
FT3 <sup>†</sup> (pmol/L)	**4.7±1.2	4.7±0.9	4.7±1.1	**4.4±0.9	4.9±0.9	4.6±0.9
FT4 <sup>†</sup> (pmol/L)	15.1±3.4	15.4±2.1	15.2±3.2	15.3±3.1	15.0±2.4	15.2±2.8
FT3/FT4 ratio	0.31	0.31	0.31	0.29*	0.32*	0.30

TSH = thyrotropin; FT3 = free triiodothyronine; FT4 = free thyroxine (†mean ± standard deviation); \* $p < 0.01$ ; \*\* $p < 0.05$

Table 3. Prevalence of thyroid dysfunction in elderly and younger subjects

	Control group			Elderly subjects		
	Female	Male	Total	Female	Male	Total
Subclinical hypothyroidism, n/N %	3/63 4.8%	0/20 0%	3/83 3.6%	12/136 8.8%	3/68 4.4%	15/204 7.4%
Hypothyroidism, n/N %	0/63 0%	0/63 0%	0/83 0%	1/136 0.7%	0/68 0%	1/204 0.5%
Subclinical hyperthyroidism, n/N %	0/63 0%	0/20 0%	0/83 0%	2/136 1.5%	1/68 1.5%	3/204 1.5%
Hyperthyroidism, n/N %	0/63 0%	0/20 0%	0/83 0%	0/136 0%	0/68 0%	0/204 0%

Table 4. Mean total serum cholesterol and range in younger and elderly subjects

	Control group			Elderly subjects		
	Female	Male	Total	Female	Male	Total
Cholesterol, mean <sup>†</sup>	5.5±1.3	6.0 0.4	5.6±1.3	6.3*±1.1	5.2±0.7	6.2±1.1
Cholesterol, range	3.2-9.4	5.7-6.6	3.2-9.4	3.4-9.8	3.9-6.4	3.4-9.8

<sup>†</sup>mean ± standard deviation; \*p<0.0005

women with subclinical hypothyroidism indicating autoimmune thyroiditis as the main etiologic cause of hypothyroidism. The overall prevalence of positive TPOAb was 19.9% in elderly women and 14.3% in younger women.

The mean total serum cholesterol level in elderly subjects was significantly higher in comparison to younger subjects (6.2±1.1 *vs.* 5.6±1.3 mmol/L, p<0.0005), as well as in elderly women *vs.* elderly men (6.3±1.1 *vs.* 5.2±0.7 mmol/L, p<0.0005). There was no difference in the mean serum cholesterol level between subjects with subclinical hypothyroidism and euthyroid subjects (6.0 mmol/L). Furthermore, younger males had a higher mean total serum cholesterol level in comparison to younger females, but the difference was not statistically significant (p=0.132) (Table 4).

## Discussion

This was the first epidemiological study investigating the prevalence of subclinical hypothyroidism in the elderly in Croatia. Furthermore, the prevalence of subclinical hypothyroidism was also investigated in a smaller group of middle-aged subjects of the same ethnic group for comparison.

Subclinical hypothyroidism is quite common in the elderly. Previous studies from the United Kingdom and the United States have reported rates of subclinical hypothyroidism from 3% to 12% in elderly people<sup>16,18-21</sup>. A similar prevalence has been reported in studies from Europe (Netherlands) of 5%<sup>14</sup> and 10.8%<sup>22</sup>. A study from Japan has reported rates of 5.5% in women over age 40 and 3.2% in men<sup>23</sup>. In a study from South Africa, elevated TSH was found in 6.2% of old-age home residents in Cape Town<sup>24</sup>. In all these studies, the prevalence of subclinical hypothyroidism was higher in women than in men. The highest prevalence was reported in Colorado (USA), i.e., 21% in women and 16% in men older than 74<sup>7</sup>.

Similar results were recorded in our study with the prevalence of subclinical hypothyroidism of 7.4% in the elderly, being more prevalent in elderly women (8.8%) in comparison to elderly men (4.4%). However, subclinical hypothyroidism was also found in 4.8% of younger women. The prevalence of overt hypothyroidism in the elderly was 0.5% (one elderly woman), and of subclinical hyperthyroidism 1.5% of elderly women and men. Aging is associated with the rise in TSH level<sup>25,26</sup>. Elderly subjects from our

study had a higher mean serum TSH concentration in comparison to younger subjects, especially females. Large epidemiological study from the United States (NHANES III) demonstrated that the percent of patients with elevated TSH gradually increased with age, and hypothyroidism was more prevalent in women of all ages in comparison to men. The same age-related increase has been reported for TPOAb, but only in women. At the age of 70, every fourth woman had positive TPOAb<sup>27</sup>. In our study, TPOAb were positive in 77% of elderly women and 67% of younger women with subclinical hypothyroidism. Therefore, Hashimoto's thyroiditis is the most common etiology of subclinical hypothyroidism, as expected. The overall prevalence of positive TPOAb was 19.9% in elderly women and 14.3% in younger women.

In our study, there was no age- or sex-related difference in the mean FT4 concentration between the groups. Similar findings of TSH rise with age and no change in FT4 concentration have been reported in the large Australian Busselton Health Survey longitudinal study<sup>26</sup>. Low levels of FT3 are recorded in the elderly<sup>28</sup>, especially in old centenarians<sup>29</sup>. In our study, significantly lower FT3 levels were recorded in elderly females in comparison to elderly males, as well as in comparison to younger females.

Subclinical hypothyroidism is more prevalent in the areas of iodine sufficiency. In studies from Hungary, the prevalence ranged from 4.2% in iodine deficient areas to 23.9% in areas of increased iodine intake, despite a similar prevalence of patients with high serum antibody concentrations in these areas<sup>30</sup>. In a comparative epidemiological study conducted in an area of adequate iodine intake of Iceland and mild iodine deficiency region of Jutland (Denmark), the prevalence of subclinical hypothyroidism in Iceland was 18.0% in women, but only 3.8% in Jutland<sup>31</sup>. In the past, Croatia was a iodine deficient country<sup>32</sup>. Mild to moderate iodine deficiency was present in Croatia until the early 1990s. In 1996, the new act on salt iodination with 25 mg of potassium iodide *per* kg of salt was introduced in Croatia. Nowadays, Croatia is a iodine sufficient country<sup>33,34</sup>.

Subclinical hypothyroidism is most commonly an early stage of overt hypothyroidism<sup>1-4</sup>. Progression to overt hypothyroidism occurs in patients with both mildly elevated TSH and high thyroid antibody concentrations. The rate of progression ranges from

5% to 20% *per* year in different studies<sup>1-4</sup>. In the study from the UK, patients were followed-up at 20 years. Women with mildly elevated serum TSH and high thyroid antibody concentrations developed overt hypothyroidism at a progression rate of 4.3% *per* year<sup>35</sup>. In a study with elderly patients, the rate of progression was 20% *per* year<sup>36</sup>. Besides autoimmune thyroid disease, another important cause of progression to overt hypothyroidism is radioiodine ablative therapy or high-dose external radiotherapy<sup>1-4</sup>. The state of mildly elevated TSH may remain unchanged, or TSH may return to normal values. This situation is more likely in younger patients<sup>2</sup>. Many studies investigated the influence of mildly elevated serum TSH level on serum lipid and apoprotein concentrations. The reports were different and contradictory. In the largest study to date with 25 862 participants, patients with mildly elevated serum TSH level (5-10 mU/L) had significantly higher mean total serum cholesterol concentrations than those who were euthyroid<sup>7</sup>. In a large cross-sectional study, an increase of TSH by 1.0 mU/L raised the mean total cholesterol level by 0.09 mmol/L in women<sup>37</sup>. In our study, there was no difference in the mean total serum cholesterol level between patients with subclinical hypothyroidism and euthyroid subjects. However, the number of patients with subclinical hypothyroidism in our study was too small to draw any conclusions from comparison. The mean total serum cholesterol level in our study was more age- and gender-related than influenced by subclinical hypothyroidism. In elderly subjects, total serum cholesterol level was significantly higher in comparison to younger subjects ( $6.2 \pm 1.1$  *vs.*  $5.6 \pm 1.3$  mmol/L,  $p < 0.005$ ), as well as in elderly women *vs.* elderly men. A randomized double-blind cross-sectional study demonstrated that treatment of subclinical hypothyroidism patients with L-thyroxine significantly reduced total serum cholesterol level by 5.5%, reduced cardiovascular risk, and improved the quality of life<sup>38</sup>. According to the European and American guidelines, treatment with L-thyroxine is justified in all patients with TSH level above 10 mU/L<sup>4,39</sup>.

Individual approach is probably most important for decision whether to treat or not to treat patients with mildly elevated TSH (5-10 mU/L)<sup>4,39,40</sup>. However, follow-up of patients with mildly elevated serum TSH is mandatory. Older patients require lower dosages of L-thyroxine and therapy should be

instituted slowly because the half-life of T4 increases with age. Recommendations for thyroid screening are inconsistent and are not generally accepted. The US Preventive Services Task Force does not recommend routine TSH screening<sup>41</sup>. Screening costs could be significant when applied at the population level, but without clear benefit. It seems reasonable to determine TSH level in patients with nonspecific complaints, positive family or personal history of thyroid disease, presence of thyroid antibodies, radiation therapy to head, neck or chest, other autoimmune diseases, therapy with lithium, amiodarone or iodine, and in elderly<sup>42</sup>. The Croatian Thyroid Society recommends TSH screening of all pregnant women at the beginning of pregnancy, and screening of women older than 50 seeking medical care due to nonspecific complaints (case finding)<sup>43</sup>.

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## Sažetak

## UČESTALOST SUBKLINIČKE HIPOTIREOZE U POPULACIJI ŠTIĆENIKA DOMA ZA STARIJE I NEMOĆNE OSOBE U ZAGREBU

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Cilj istraživanja bio je utvrditi učestalost poremećaja funkcije štitnjače, pozitivnih protutijela na tireoidnu peroksidazu (TPOAt) i hiperkolesterolemije u starijih i mlađih ispitanika te povezanost subkliničke hipotireoze s hiperkolesterolemijom. U istraživanje su bila uključena 204 starija ispitanika (136 žena i 68 muškaraca, medijan dobi 71, 60-92 godine) i 83 mlađa ispitanika kao kontrolna skupina (63 žene i 20 muškaraca, medijan dobi 45, 19-55 godina). Ispitanici s ranije otkrivenim poremećajem funkcije štitnjače bili su isključeni iz istraživanja. Određivani su serumski tireotropin (TSH), slobodni trijodtironin (FT3), slobodni tiroksin (FT4), TPOAt i ukupni kolesterol. Ispitanicima su izmjereni visina i težina. U statističkoj analizi primijenjeni su Mann-Whitneyev test,  $\chi^2$ -test i Studentov t-test. Učestalost subkliničke hipotireoze (TSH >5 mU/L) u starijih osoba iznosila je 7,4%, a 3,6% u mlađoj kontrolnoj skupini, s najvećom učestalošću od 8,8% u starijih žena, zatim 4,8% u mlađih žena, a potom 4,4% u starijih muškaraca. Učestalost hipotireoze u starijih osoba iznosila je 0,5%, a subkliničke hipertireoze 1,5%. Učestalost pozitivnih TPOAt u žena u subkliničkoj hipotireozu iznosila je 77% u starijih i 67% u mlađih (sveukupno 19,9% u starijih i 14,3% u mlađih žena). Srednja vrijednost FT3 u starijih žena bila je niža u odnosu na starije muškarce ( $p < 0,01$ ) i mlađe žene ( $p < 0,05$ ). Srednja razina kolesterola u serumu starijih osoba bila je viša u odnosu na mlađe ( $p < 0,01$ ), kao i u starijih žena u odnosu na starije muškarce ( $p < 0,01$ ), ali bez razlike između osoba u subkliničkoj hipotireozu i eutireozu (6,0 mmol/L). Subklinička hipotireoza je najčešći poremećaj funkcije štitnjače u starijih osoba, uz najveću učestalost u starijih žena, a autoimuni tireoiditis je najčešći uzrok poremećaja. Hiperkolesterolemija u našem istraživanju nije bila povezana sa subkliničkom hipotireozom, ali je utvrđena njena povezanost sa starijom životnom dobi, osobito u starijih žena.

*Ključne riječi: Subklinička hipotireoza; Učestalost; Starije osobe; Poremećaji funkcije štitnjače; Tireotropin; Kolesterol*