

# Is there a link between Hashimoto's thyroiditis and primary hyperparathyroidism? A study of serum parathormone and anti-TPO antibodies in 2267 patients

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## Abstract

According to various authors, thyroid disorders like Hashimoto's thyroiditis (HT), diffuse goiter or multinodular goiter, Graves'disease, medullary or papillary carcinoma could be found in a number of patients with primary hyperparathyroidism (PHPT). This association is more common in elderly women. Neck irradiation, lithium treatment and elevated TSH levels have been suggested as some of the possible causes of this co-existence. *The aim* of this study was to investigate and determine the prevalence of patients having both HT and PHPT, and the possible relation between these two diseases. *We conducted a prospective study* during three and a half years. This study included 45,231 patients, which were referred by their general practitioner or endocrinologist, under suspicion of having thyroid and/or parathyroid disease. In these patients we measured serum levels of the following parameters: anti-thyroid peroxidase antibodies (antiTPO-Ab), anti-thyroglobulin antibodies (Tg-Ab), anti-TSH-receptor antibodies (TSHR-Ab), thyroid-stimulating hormone (TSH), parathyroid hormone (PTH) and calcium (Ca). *In 2,267 of these 45,231 patients (5.01%) we noticed elevated antiTPO-Ab (3542±3407IU/mL), with statistical significant difference from normal values (normal range 0-70IU/mL), P<0.05, and normal levels of other antithyroid antibodies (Tg-Ab, TSHR-Ab). All patients with elevated antiTPO-Ab were assumed to have HT. Within this group, 43 patients (1.89%) also had elevated serum levels of PTH (112.4±33.2pg/mL, normal range 8-76pg/mL) as well as elevated serum levels of calcium (2.92±0.06mmol/L, normal range 2.2-2.65mmol/L). These laboratory findings, accompanied with clinical symptoms, satisfied the criteria for PHPT. The mean age in this subgroup was 60.5±12.2 years. All 2,267 patients had normal or slightly elevated TSH levels. In conclusion, under the reported rate of prevalence of PHPT in the general population of about 0.3%, our results indicated a 1.89% occurrence of PHPT in 2267 patients with HT in central Serbia. This may be due to the autoimmune inflammatory process in HT supporting PHPT to PTH or calcium supporting HT or to common genetical predisposition of both entities.*

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## Introduction

Elevated serum levels of parathyroid hormone (PTH) are the result of hypersecretion from one or more parathyroid glands due to primary hyperparathyroidism (PHPT). In case of PHPT this excessive secretion of PTH is accompanied by hypercalcemia and hypophosphatemia. Less frequent causes of the elevated PTH are secondary and tertiary hyperparathyroidism, caused by a chronic calcium loss, which is characteristic for patients undergoing hemodialysis for chronic renal failure. Serum concentrations of PTH in these patients are elevated due to chronic hypocalcemia. While PHPT is accompanied by hypophosphatemia, in case of secondary HPT phosphate serum levels are elevated [1]. Tertiary hyperparathyroidism is a state of excessive secretion of parathyroid hormone (PTH) after a long period of secondary hyperparathyroidism and resulting in hypercalcemia. It reflects development of autonomous parathyroid function following a period of persistent parathyroid stimulation. Nevertheless, the parathyroid glands fail to respond to the normal signals for PTH secretion and regulation of calcium levels. In these patients, the PTH and the calcium level are both high [2]. Parathyroid hormone radioimmunoassay and serum calcium levels are sufficient for establishing the diagnosis of PHPT, according to various authors [1, 3, 4]. It should be kept in mind that some patients with PHPT especially those in early course of disease, may have serum PTH levels that fluctuate close to the normal range. In such case multiple PTH measurements by more than one PTH assay can help to resolve the differential diagnosis [5].

The prevalence of PHPT is relatively low, but varies in different geographical regions. In Europe, the number of new cases of PHPT per 100,000 inhabitants is 100 annually

while in USA, this rate is 21.6 new cases per 100,000 inhabitants per year [6, 7]. In the general population the prevalence of PHPT in Europe is about 0.3% [8], while in the USA is 0.1% [7]. Over the last few decades, the epidemiology of PHPT has undergone marked changes. The introduction of routine serum calcium measurements in the 1970s, facilitated the diagnosis of asymptomatic PHPT. Epidemiological studies reported a higher prevalence than previously presumed. In a study analysing the changes in prevalence of newly diagnosed PHPT in Danish hospitals, the mean patient age at the time of diagnosis increased significantly from 1980 to 1999 [9], thus suggesting a change in age pattern of the disease. In Scandinavian and in other countries the prevalence of PHPT in 55-75 years old post-menopausal women rose to 2.1%-3% [4, 10]. Gender difference was documented by other researchers who reported a female predominance of 5:1 in elderly European PHPT patients [8].

Primary hyperparathyroidism is sometimes associated with disorders of other endocrine glands, especially of the thyroid gland [11-13], like Hashimoto's thyroiditis (HT) [11], multinodular or nodular goiter [11, 14], Graves' disease [13], papillary or medullary thyroid carcinoma [11, 12], multiple endocrine neoplasia (MEN syndrome) [15] and in other types of polyglandular syndromes [16].

It is known that in some cases of thyroid diseases, autoantibodies like thyroid stimulating hormone receptor antibodies (TSHR-Ab) may induce Graves' disease, and autoantibodies to thyroid peroxidase (TPO-Ab) may also induce chronic autoimmune HT [17]. According to some researchers, 73.5% to 99.3% of patients with HT have elevated levels of serum antiTPO-Ab [18-20].

Elevated serum levels of parathyroid hormone (PTH) in case of PHPT are accompanied by hypercalcemia [1, 3, 4]. According to some researchers PHPT is related to HT. In these studies, the rate of thyroid diseases coexisting with PHPT is reported to be 1.4%-10.9%, in different geographic regions [11, 21-26]. Additionally, no difference in calcitonin levels or in the frequency of elevated calcitonin was found at patients with and without HT, irrespective of sex [27]. Thus, we studied the prevalence of PHPT in patients with HT in central Serbia.

## Subjects and methods

This prospective study included 45,231 patients of both genders (1945 men and 43286 women). The average age of men was 52.4±19.1 years old, median age was 54 and the age range was 18-84 years. On the other hand, the average age of women was 50.4±14.2 years old, median age was 53, and the age range was 18-83 years. These patients lived in Sumadija region of central Serbia. The study was conducted from January the 1<sup>st</sup> 2009 to June the 1<sup>st</sup> 2012 at the Department of Nuclear Medicine, Clinical Center Kragujevac. All patients were referred by their general practitioner or endocrinologist, under clinical suspicion of having thyroid and/or parathyroid disease. Patients with Graves' disease (elevated serum antiTSHR-Ab), subacute thyroiditis (low uptake of <sup>131</sup>I), renal disease (elevated urea and creatinine were excluded from the study). Based on data from the personal history of the patient, we also excluded other autoimmune diseases, like Sjogren's syndrome, systematic lupus, rheumatoid arthritis, pernicious anemia, celiac disease, Addison's disease

and breast and lung cancers which may lead to secretion of parathyroid hormone-related protein.

The study was approved by the Ethical Board of the Clinical Center of Kragujevac, and all patients gave their written consent for this study.

Serum levels of TSH, antiTPO-Ab, anti-TSHR-Ab, antithyroglobulin (Tg-Ab) antibodies and PTH were measured by radioimmunoassay kits Company INEP, Serbia, for TSH, and Cisbio Bioassays, France for the rest of the measurements. Serum urea, creatinine and calcium were measured photometrically by Olympus AU 400 photometer, using kits of Olympus Life manufacturer and materials of Science Europa GmbH (Irish Branch) Lismeehen O' Callaghan's Mills, Co. Clare, Ireland. Table 1 provides data about used kits and reference values.

We divided our patients into two groups: Group I included patients with only HT (increased antiTPO-Ab) and Group II patients having HT and also elevated PTH.

The data were processed by the statistical program SPSS, version 13. Statistical significance was defined as  $P < 0.05$ . The age of the patients, the antiTPO-Ab, TSH, PTH and calcium levels were expressed by the mean±SD, and also by the median (Me), since the data were not evenly distributed.

## Results

Group I included 2267 patients (5.01%) with HT, who had elevated serum levels of antiTPO-Ab, without elevated concentration of antiTSHR-Ab or antiTg-Ab. This Group included 96.7% women and 3.3% men, with a mean age of 47.3±12.2 years. The average value of serum antiTPO-Ab was 3542±3407IU/mL and Me was 2209IU/mL, (range from 135-11231IU/mL) quite above the upper limit of normal range with statistical difference between normal and abnormal values of antiTPO-Ab ( $P < 0.05$ ). Our normal range of serum antiTPO-Ab is 0-70IU/mL. In all patients of Group I, serum TSH level was slightly elevated or within the normal range. Mean value of TSH was 3.41±3.29mIU/L, Me 2.4mIU/L, with a range of 0.3-10.2mIU/L (normal range for TSH: 0.3-5.5mIU/L). There was no statistical difference between normal TSH level and TSH level in Group I.

Patients in Group II included 43 out of the 2267 patients with HT (1.89%), where we found increased serum PTH, with a mean value of 112.4±33.2pg/mL, Me 89.6pg/mL and range 79.2-238pg/mL (the normal range for PTH is 8-76pg/mL). All patients in Group II also had hypercalcemia. The average value of serum calcium was 2.92±0.06mmol/L, Me 2.81mmol/L, range 2.73-2.98mmol/L (reference range: 2.20-2.65mmol/L). Serum PTH and calcium concentrations were significantly higher ( $P < 0.05$ ) than in Group I, and were also significantly higher ( $P < 0.05$ ) than the reference values for PTH and calcium. In Table 2 and Figure 1, the concentrations of TSH, antiTPO-Ab, PTH and calcium are shown. The prevalence of patients with PHPT in the population of patients with HT was 1.89% and significantly higher than the prevalence of PHPT in the general population, which is 0.3% ( $P < 0.05$ ). In Group II, concentrations of antiTPO-Ab and TSH were elevated (antiTPO-Ab=3025±1058IU/mL, Me 3828IU/mL, range 1131-6109IU/mL; TSH=3.9±3.5mIU/L, Me 2.65, range 0.4-12.1mIU/L). These values were not significantly different from the Group I, with statistical difference between normal and abnormal values of antiTPO-Ab ( $P < 0.05$ ). There was no statistical dif-

**Table 1.** *The used kits and reference values*

Kit	Methodology	Manufacturer	Device	Reference range
TPO-AB-CT	RIA			0-70IU/mL
TR-AB-CT	»		Wallac 1470 Automatic Wizard	0-1IU/mL
TGAB one step	»	Cisbio Bioassays, France		0-30IU/mL
ELSA-PTH	»			8-76pg/mL
IRMA TSH	IRMA	INEP, Serbia		0.3-5.5mIU/L
Urea				3.5-7.5mmol/L
Creatinin	photometric color test	Olympus Life and material Science Europa GmbH (Irish Branch) Lismeehan O' Callaghan's Mills, Co. Clare, Ireland	Olympus AU 400	49-106µmol/L
Calcium ARSENAZO III				2.2-2.65mmol/L

\*TPO-Ab-CT: anti-thyreoperoxidase antibody kit; TRAB-CT: antiTSHR-Ab kit; Tg-Ab one step: antiTgAb kit, ELISA-PTH kit; IRMA TSH kit; RIA: radioimmunoassay; IRMA: immunoradiometric assay

**Table 2.** *Concentrations of antiTPO-Ab, TSH, PTH and Ca in Groups I and II*

	Group I	Group II	P
antiTPO-Ab	3542±3407 IU/mL	3025±1058IU/mL	ns
TSH	3.30±3.17mIU/L	3.9±3.5mIU/L	ns
PTH	40.5±17.2pg/mL	112.4±33.2pg/mL	P<0.05
Ca	2.2-2.65mmol/L	2.92±0.06mmol/L	P<0.05

\* antiTPO-Ab: anti-thyreoperoxidase antibody; TSH: thyroid-stimulating hormone; PTH: parathyroid hormone; Ca: calcium; HT: Group of patients with HT; HT+PHPT: Group of patients with HT and PHPT; ns: non-significant

ference between normal TSH level and TSH level in Group II. The average age of patients in Group II was 60.5±12.2 years, range from 19-78 years. From the 43 patients in the Group II, 41 (95.4 %) were females, and only two (4.6%) were males. The average age of women was 60.9±12.6, and the age of the two male patients was 45 and 68 years.

## Discussion

Hashimoto's thyroiditis is characterized by chronic immunological damage of thyrocytes which leads to hypothyroidism [28]. Prevalence of HT in the general population ranges from 0.1% to 5%, making it the most common autoimmune disease of the thyroid gland, mainly in women from 45 to 65 years old (ratio women: men 10-20:1) [29, 30]. In our study prevalence of HT was 5.01%, as elevated level of antiTPO-Ab was present at 2267 patients (ratio women: men 29:1). This disease is characterized by the presence of circulating antibodies specific for thyroid peroxidase in the serum (antiTPO-Ab, previously called "anti-microsomal antibodies") [18]. Most of our patients with HT have no typical signs or symptoms. In some cases, patients with elevated serum TSH level, depending on the severity of the hormone deficiency, had

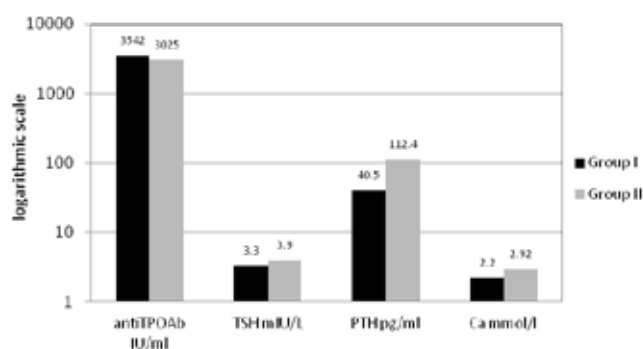
signs or symptoms of hypothyroidism, such as dry skin, a pale, oedematous face and constipation (8.16% were symptomatic).

Serum antiTPO-Ab could also be detected in 50%-90% of patients with Graves' disease where antibodies to other structures of the thyroid gland could also be found. On the contrary, in HT other antibodies are rarely found [17, 20]. The link between HT and PHPT was not explored in sufficient detail so far, although it was first described in 1947 [31]. Various authors investigated the association of simultaneous pathology in the two glands,

to determine the best surgical approach [11, 12, 32-34]. These researchers found that the significant association of simultaneous pathology in the two glands justifies preoperative and intraoperative thyroid examination in patients with PHPT to avoid misdiagnosis or delayed diagnosis of thyroid pathologies and to determine the best surgical approach for patients [11, 12, 32-34].

According to the results of our research, PHPT prevalence in patients with diagnosed HT was 1.89%. Patients also had been observed and referred by their primary care physician or endocrinologist under the suspicion of dysfunction of parathyroid glands. Most of them had nonspecific symptoms like getting easily tired, weakness and forgetfulness. Only seven patients (16.27%) had signs and symptoms of advanced clinical stage of PHPT like loss of appetite, nausea, vomiting, constipation, bone and joint pain. This finding is in agreement with the literature, where about 80% of people with PHPT were having few or no symptoms [35].

In the general population, in Europe the prevalence of PHPT is reported to be about 0.3% [8]. Our results indicated that in HT patients, PHPT is significantly more frequent 1.89%. Other studies confirmed our results and also showed that the incidence of thyroid disease is higher in patients with PHPT than in the general population [11-14, 25, 26, 32].



**Figure 1.** \*Concentration of TPO-Ab, PTH, TSH and Ca in Groups I and II.

\*antiTPO-Ab: anti-thyroperoxidase antibody; TSH: thyroid-stimulating hormone; PTH: parathyroid hormone; Ca: calcium.

The underlying mechanism that possibly links HT to PHPT is not quite clear. Data from animal experiments indicated that chronically elevated TSH in the advanced stage of HT may cause hyperplasia of parathyroid glands [36], especially if hypothyroidism arises. We found an increased serum TSH in 8.16% of patients but the difference in TSH levels between Groups I and II was not significant, indicating that TSH could not be the factor that linked these two diseases. Human [14] and animal [37] research studies reported increased endogenous calcium concentrations in PHPT as a growth factor for the development of goiter. These studies concluded that elevated serum PTH [14] and elevated calcium [37] are the main factors that associate PHPT with HT. All our patients from Group II had elevated both serum PTH and calcium levels, which imposed the theoretical possibility of this being the cause of HT. Direct experimental evidence is lacking in humans [37]. The speculation about the possible role of PTH acting by itself as a goitrogenic factor in hyperparathyroid patients is undetermined, by the observation that the prevalence of concurrent thyroid disease was significantly lower in patients with secondary HPT, in whom the average serum PTH concentrations were greater than those in patients with primary HPT [14].

Considering that a small number of patients with HT had elevated serum PTH and serum calcium, development of HT in these patients could be due to genetic and environmental factors [38-40].

Serum antiTPO-Ab were elevated in both groups of our patients and varied in a wide range of several thousand IU/mL. There are reports in the literature that in certain PHPT patients anti-parathyroid-Ab were found, so it seems that an immunological relation between HT and PHPT exists [41]. For published data, we could speculate that in some HT patients, increased PTH secretion is due to chronic inflammation, as during HT thyroid cells participate in the immune response, due to their ability to produce cytokines and to react on their presence. In the HT, serum interleukins IL-1, IL-6 and IL-8 were found elevated and in PHPT IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were also found elevated [42-45].

Some researchers suggested that previous lithium treatment and also neck irradiation especially in childhood were a possible cause of the association of HT and PHPT [4, 18, 46]. According to the past histories of our patients, none was exposed to these two factors.

It is widely known that thyroid gland diseases are more common in women. According to the literature, after the age of 50, 1/10, and after the age of 60, 1/6 woman will become hypothyroid [33]. Our results showed that simultaneous ele-

vation of both serum antiTPO-Ab and PTH were mainly found in women at the age of  $60.9 \pm 12.6$  and that the prevalence of PHPT in this age group was significantly higher than in the general population. This is in accordance with the findings of others [3, 9]. Aging may lead to an increase in PTH levels and a decrease in vitamin D concentrations in postmenopausal women [47, 48].

This may be due to change of regulatory mechanisms, such as estrogen levels, especially the estrogen withdrawal at menopause, that might cause or trigger autoimmune diseases in women. The production of cytokines IL-6, IL-1 and TNF- $\alpha$  increased after menopause, as does the physiological response to those cytokines during and after menopause [49]. These serum interleukins were found elevated in HT [42, 44, 45] and also tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-6 were also found elevated in PHPT [43-45]. This may explain the connection between menopause and these diseases.

In our study the average age of patients of Group II was  $60.9 \pm 12.6$ , and that of patients of Group I was  $47.3 \pm 12.2$  years, so the influence of age on these two diseases can be further investigated. Besides, socio-medical factors shouldn't be disregarded, since others have shown that older women undergo more often medical check-ups [50].

*In conclusion*, under the reported rate of prevalence of PHPT in the general population of about 0.3%, our results indicated a 1.89% occurrence of PHPT in 2267 patients with HT in central Serbia. This may be either due to the autoimmune inflammatory process in HT causing PHPT or due to PTH or calcium hyperproduction causing HT or due to common genetic predisposition of both entities.

*The authors declare that they have no conflicts of interest.*

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