

# The prevalence of thyroid nodular disease in patients with increased titers of anti-thyroidal peroxidase antibodies

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## Abstract

**OBJECTIVES:** The aim of our study was to evaluate the possible association between autoimmunity and thyroid nodular disease (TND).

**DESIGN AND SETTING:** We conducted a study on 58 patients who were treated in outpatient setting at the Department of Endocrinology, Metabolism and Internal Medicine. Serum samples were analyzed for TSH concentration and anti-TPO antibodies titers. Thyroid ultrasonography was performed in each subject in order to evaluate volume of the gland, and the number and size of nodules.

**RESULTS:** TND occurred in 70% of anti-TPO positive subjects and in 57.9% of anti-TPO negative subjects, but statistical analysis did not demonstrate a significant concordance between the presence of anti-TPO antibodies and prevalence of TND ( $p>0.05$ ). We showed that the mean (0.82 vs 0.75;  $p=0.49$ ), minimal (0.2 vs 0.3;  $p=0.89$ ) and maximal (2.7 vs 2.4;  $p=0.49$ ) diameters of a nodule were similar in both groups. Solely in anti-TPO positive patients, anti-TPO titers positively correlated with the number of nodules ( $p=0.04$ ).

**CONCLUSION:** Our results favor the role of autoimmunity in TND development although associations between thyroid nodules and thyroid autoimmunity are complicated and may be the subject of much controversy. Increased anti-TPO may influence the number of nodules rather than the presence of TND itself.

## Abbreviations:

TNT	- thyroid nodular disease
TSH	- thyroid stimulating hormone
ATD	- autoimmune thyroid disease
Anti-TPO	- anti thyroidal peroxidase antibodies
ECLIA	- electrochemiluminescence immunoassay

## INTRODUCTION

The presence of focal lesions in the thyroid gland detected on palpation, or incidentally discovered in ultrasound examination has been referred to as thyroid nodular disease (TND). This condition is one of the most frequent thyroid pathologies: approximately 4% to 7% of adults suffer from palpable thyroid nodules, and in up to 70% of adults thyroid nodules are found in ultrasonography, many of those lesions are less than 1 cm in diameter (Marqusee *et al.* 2000). In those patients, a functional status of the thyroid depends on an overall balance of each nodule's hormonal activity, and on the activity of normal thyroid tissue that surrounds the nodules. Thus, although most patients remain euthyroid, both hypo- and hyperthyroidism may also develop (Krohn *et al.* 2005).

In spite of high prevalence, the etiology of TND is not completely understood. Complex interactions between genetic predispositions and environmental influence play a crucial role in nodules formation (Knudsen *et al.* 2002). Siblings studies have shown that genes are substantial in developing inter-individual thyroid volume variation (Hansen *et al.* 2004). Furthermore, genome studies demonstrated several genetic loci, which were associated with TND risk (Teumer *et al.* 2011). In addition, gender seems to play an important role, as women are affected from 5 to 10 times more often than men in non-endemic goiter regions (Hegedüs *et al.* 2003). Numerous environmental factors may also influence TND development. For instance, iodine deficiency has long been considered a vital factor (Fountoulakis *et al.* 2007), although recently its role has diminished, especially in iodine-abundant areas, and as a consequence of iodine supplementation. Smoking, due to thiocyanate, which competitively inhibits iodine intake by thyroid, is important as well (Brix *et al.* 2000; Brauer *et al.* 2006; Ittermann *et al.* 2008). Moreover, ageing, increased body mass index and therapeutic or environmental radiation exposure may all be involved (Mitra *et al.* 2010), as well as some endocrine disorders including acromegaly (Ruchała *et al.* 2009). In addition, TND may be a manifestation of primary or metastatic malignancy (Owecki *et al.* 2004).

Interestingly, complex interactions between TND and thyroid autoimmunity may also influence nodular formation. Of question is, however, whether this autoimmunity is the cause of TND, or rather a secondary immunologic disturbance provoked by TND itself (Vasheghani *et al.* 2011). Moreover, Graves' disease and Hashimoto thyroiditis, which are both referred to as autoimmune thyroid disease (ATD), affect up to 5% of general population (Chistiakov & Turakulov 2003), and may lead to nodular formation in the course of disease, as ATD could develop, considering gland volume, in a goitrous or in an atrophic form (Chehade *et al.* 2010). One should be aware, however, that although the presence of thyroid auto-antibodies in ATD is the hallmark

for establishing a diagnosis (Prummel *et al.* 2004), those antibodies titers may be positive in approximately 5–10% of healthy population (Jarzab *et al.* 2010).

In spite of high prevalence of ATD and TND, it is not clear whether high titers of anti-thyroidal antibodies are more common in TND, and numerous conflicting results have been published by now. As shown previously, antibodies stimulating thyroid hypertrophy are found in approximately 80% of patients with a toxic multinodular goiter (Macchia *et al.* 1989).

On the other hand, low incidence of non-toxic goiter and autoimmunity was demonstrated (Bottazzo *et al.* 1982). To add some new knowledge to this controversial issue, in this study we examined the prevalence of TND in a population of patients with increased titers of anti-thyroidal peroxidase antibodies. In this setting, we were able to evaluate a frequency of TND amongst patients with thyroidal autoimmunity.

## SUBJECTS AND METHODS

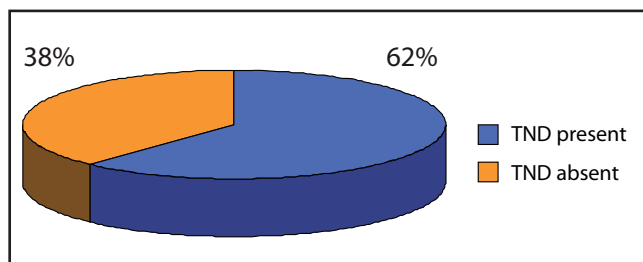
The study group consisted of 56 women and 2 men aged from 18 to 91 years, with mean age of  $45.5 \pm 16.9$  years. In all cases, they were referred to Endocrine Outpatient Clinic by their General Practitioners for thyroid evaluation or for thyroid disorder treatment. Fourteen patients received L-thyroxin as substitutional therapy for hypothyroidism, and one person was treated with methimazole for hyperthyroidism. In all patients, venous blood samples for the assessment of anti thyroidal peroxidase antibodies (anti-TPO) and serum thyrotropin concentrations (TSH) were obtained in the morning after an overnight fast. TSH levels and anti-TPO titers were measured with electrochemiluminescence immunoassay (ECLIA) with a sensitivity of  $0.005 \mu\text{IU/mL}$ , and  $5 \text{ IU/mL}$ , respectively (Roche TSH III gen. and Roche Anti-TPO; analyzer: Roche Cobas e 601, year of production: 2009). A value of anti-TPO titers of less than  $34 \text{ IU/mL}$  was considered negative, and consequently, patients were divided into two groups: anti-TPO positive and anti-TPO negative.

Subsequently, ultrasonography of the thyroid gland was performed in each subject. A diagnosis of thyroid nodular disease was established on the basis of focal lesions revealed by ultrasonography: here, solid and mixed cystic and solid nodules were included, as well as simple cysts larger than 5 mm.

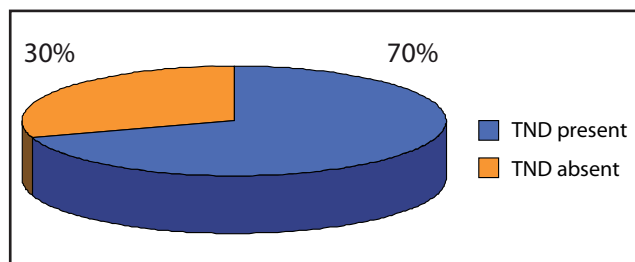
## RESULTS

The mean serum concentration of TSH was  $2.55 \text{ IU/mL}$  ( $\text{SD} \pm 3.74$ ), ranging from  $<0.01$  to  $24.92$ . In the whole group examined, anti-TPO serum level was positive ( $>34 \text{ IU/mL}$ ) in 20 patients (34.5%) and negative in 38 subjects (65.5%).

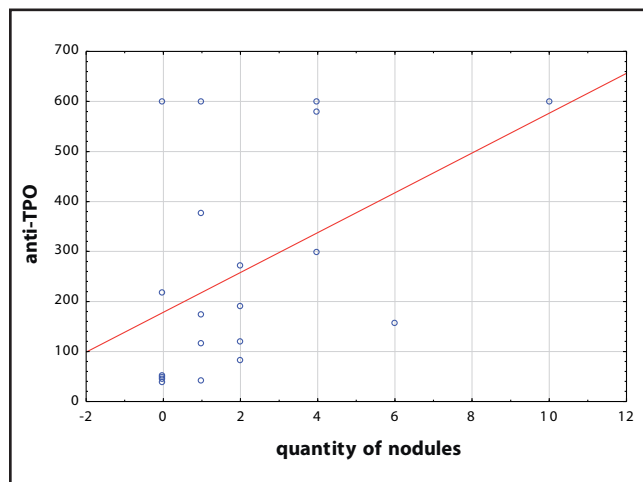
Altogether, ultrasound imaging revealed thyroid nodules in 36 patients, whereas 22 were diagnosed with other structural abnormalities: decreased or het-



**Fig. 1.** Distribution of thyroid nodular disease (TND) in both study groups analyzed together.



**Fig. 2.** Distribution of thyroid nodular disease (TND) in anti-TPO positive group.



**Fig. 3.** Correlation between anti-TPO titers and the quantity of nodules in anti-TPO positive group.

**Tab. 1.** The size and number of nodules in both groups of patients.

Parameters of thyroid nodules	Anti-TPO positive subjects	Anti-TPO negative subjects	p-value
Min. diameter (cm)	0.20	0.30	0.89
Max. diameter (cm)	2.70	2.40	0.49
Mean diameter (cm)	0.82	0.75	0.49
Average number of nodules per patient	2.05	2.21	0.84

erogeneous echogenicity, or cystic structures of less than 5 mm in diameter (Figure 1). In the group with anti-TPO positive titers, 14 (70%) patients were diagnosed with TND, as compared with 22 patients (57.9%) in anti-TPO negative subjects (Figure 2). Statistical analysis did not demonstrate a significant concordance between laboratory findings and the prevalence of TND ( $p>0.05$ ).

Next, we analyzed whether the presence of positive anti-TPO antibodies was associated with the size of nodules. We showed that the mean, minimal and maximal diameters of a nodule were similar in both groups.

In addition, we calculated the average number of nodules per patient, and compared it between the groups (Table 1).

Furthermore, we investigated whether anti-TPO titers showed any association with the number of nodules per patient. We demonstrated that anti-TPO titers positively correlated with the number of nodules solely in anti-TPO positive patients (Figure 3), whereas this correlation was absent in the entire group and in anti-TPO negative individuals.

## DISCUSSION

As we show here, the presence of increased anti-TPO antibodies did not influence the overall rate of TND in patients examined. However, we demonstrate that the average number of nodules per patient increases accordingly to anti-TPO titers in individuals with confirmed autoimmunity. The last finding might be, at least partially, explained by the theory of thyroid nodules origin. This theory is based on a sequence of events beginning with hyperplasia and resulting in focal, autonomous growth. First, autoimmunity, goitrogens and iodine deficiency may lead to diffuse thyroid hyperplasia. In addition, increased mitotic index enhances the probability of somatic mutations affecting cellular growth and function. Finally, cells divide and form clonal and focal lesions, *ie.*, nodules (Paschke 2011). Under these circumstances, the autoimmune process triggers nodular formation, and the presence of thyroid autoantibodies in serum may reflect the degree of autoaggression. Thyroid peroxidase, which is a membrane-bound glycoprotein enzyme involved in synthesis of thyroid hormones, acts as a main target autoantigen (Fortunato *et al.* 2010).

Although elevated anti-TPO serum level along with hypoechogenicity in sonography and hypothyroidism are the hallmarks for Hashimoto thyroiditis (Slatosky *et al.* 2000; Ruchała, Szczepanek 2010), increased anti-TPO alone can be either present in healthy subjects. For example, a Spanish study conducted on patients without personal or family history of thyroid disease revealed 43% of anti-TPO positive samples (Lanas *et al.* 2010). Other similar researches performed on larger groups in Japan (Tajiri *et al.* 1984) and Sweden (Bjoro

*et al.* 2000) disclosed the prevalence of positive thyroid autoantibodies in 6.1% and 13.9% of patients, respectively. Some divergence between those studies can be easily explained by different population samples that have obviously various iodide intake and genetic profile.

Increased titers of anti-TPO can be also detected in subjects diagnosed with thyroid nodular disease. Research on Nigerian population revealed that 12.5% of patients suffering from toxic nodular goiter were anti-TPO positive (Okosieme *et al.* 2007). Moreover, in another study a raised serum concentration of anti-TPO was detected significantly more frequent in connection with pathological ultrasound, than without it. The latter study has also proven significant correlation between anti-TPO level and the presence of TND (Döbert *et al.* 2008). Additionally, the association of thyroid nodular disease with anti-TPO in a Swedish study concerning thyroid structure, functional status and autoimmunity was positive ( $p < 0.001$ ) (Bülow *et al.* 2005).

Noteworthy, we observed a tendency for increased prevalence of nodules in anti-TPO positive subjects (70%), as compared with negative ones (57.8%), although it was not significant. However, even in spite of the lack of statistical significance, this tendency indicates a possibility of some relationships in a larger population.

In conclusion, as we demonstrate in this paper, the associations between thyroid nodules and thyroid autoimmunity are complicated and may be the subject of much controversy: here, although anti-TPO antibodies did not influence the size and number of nodules, they did correlate with the number of nodules per patient in anti-TPO positive individuals. The latter finding points to the role of autoimmunity in TND development.

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