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SCREENING TESTS FOR THYROID DYSFUNCTION; IS TSH SUFFICIENT?

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Abstract

There are different recommendations on how to screen for thyroid gland problems and TSH is the most ordered test. Anti TPO antibodies are usually tested when TSH is not within the normal range, but their presence before TSH changes has not been appreciated. This study aims to evaluate the role of anti-TPO and thyroid ultrasound for the early detection of thyroid pathologies, especially in the subclinical phase. This is a cross-sectional study in 458 individuals (80% females and 20% males). Thyroid laboratory tests and thyroid ultrasound was done. Statistical analysis was performed to assess the prevalence of thyroid dysfunction, thyroid antibodies and their correlation with thyroid ultrasound changes. 88.6 % (406) of subjects resulted in euthyroid. Subclinical *hypothyroidism and hyperthyroidism were observed in 5.5% and 1.7% of the population, respectively. The prevalence of positive thyroid antibodies was 26.5% in females and 11.8 % in males. Hypoechoic structure, heterogenicity and micronodular pattern in ultrasound were associated with significantly higher TPO antibodies activity p<.001. Undiagnosed biochemical thyroid dysfunctions were common in our country. Measurement of anti-TPO in individuals with normal TSH is valuable in determining individuals at risk for thyroid pathologies.*

Keywords

Thyroid, Ultrasound, TPO Antibodies, Hypothyroidism, TSH

1. Introduction

Thyroid pathologies are present in a significant part of the population (Tunbridge et al., 1977) (Vanderpump, 2011) (Canaris et al., 2000). Their prevalence varies from country to country depending on geographical factors, iodine intake and ethnic characteristics (Flynn et al., 2004), (Brochmann et al., 1988), (McGrogan et al., 2008). Autoimmune thyroid diseases such as Graves' disease or chronic Hashimoto's thyroiditis are more common in regions with adequate iodine levels. The prevalence of hypothyroidism is 1-2%. It is more common in women than in men, and its prevalence increases with age. The prevalence of hyperthyroidism in women varies from 0.5% to 2%. The prevalence of thyroid nodules is 1% in men and 5% in women and their frequency is higher in iodine-deficient regions and increases with age. (Vanderpump, 2019)

There are different recommendations on how to screen for thyroid gland problems and Thyroid Stimulating Hormone (TSH) is the most commonly ordered test. Screening for thyroid pathologies is not performed routinely. However, studies show that patients can benefit from early

detection and treatment of subclinical hypothyroidism (McDermott & Ridgway, 2001), especially in terms of lipid profile regulation and cardiovascular risk reduction (Palmieri et. al., 2004). Screening for thyroid dysfunction is more valuable for at-risk groups, including pregnant women. The presence of anti-TPO (Thyroid Peroxidase) antibodies or undetected subclinical hypothyroidism can cause infertility or pregnancy problems such as high blood pressure or toxaemia (Haddow et. al., 1999) (Allan et. al., 2000) (Thangaratinam et al., 2011). It is recommended that women who have problems conceiving and seeking a pregnancy be tested for thyroid, among other things, as dysfunction of the thyroid can lead to ovulation problems or infertility (Strickland, Whitted & Wians 1990). Anti TPO antibodies in clinical practice are tested when the results of TSH and FT4 (Free Thyroxine) are not within the normal range. But the role of the anti-TPO presence before TSH changes has not been appreciated.

2. Literature Review

Thyroid peroxidase (TPO) is a major antigen in autoimmune thyroid disorders and the titers of anti-TPO antibodies have a good correlation with the degree of lymphocytic infiltration of the thyroid gland in euthyroid individuals. The prevalence of anti-TPO antibodies in subjects with normal TSH is between 12% and 26%. Anti TPO titers also correlate with levels of TSH suggesting that they can be used for predicting thyroid failure in the future. (Prummel & Wiersinga, 2005). Anti TPO antibodies titers vary during and after pregnancy and their increase in euthyroid subjects is associated with alterations affecting mother and fetus. (Chuyu Li et al., 2020). According to some studies, anti-TPO antibodies are an early predictive marker of possible thyroid dysfunction and more than 50% of hypothyroid or hyperthyroid patients had positive anti-TPO 6 months before thyroid dysfunction onset. (Thushani et al., 2019). The risk of developing thyroid dysfunction in euthyroid female subjects, relatives of patients with autoimmune diseases, increases with higher anti-TPO antibody titers. (Strieder et al., 2008). Changes in thyroid structure during an ultrasound examination often are evident before the presence of abnormal TSH results. Ultrasound is helpful for the diagnosis of Hashimoto thyroiditis in anti-TPO positive subjects with normal thyroid hormone tests such as TSH and FT4. (Ceylan et al., 2014)

3. Research

Our study aimed to evaluate the role of anti-TPO antibodies and thyroid ultrasound in the early detection of thyroid dysfunction. The objectives of our study were:

- To assess the prevalence of thyroid dysfunction in a population not previously known or treated for thyroid disease
- To estimate the correlation between anti-TPO antibodies and thyroid dysfunction
- To estimate the correlation between thyroid dysfunction and ultrasound changes
- To evaluate the role of TPO antibodies and thyroid ultrasound as screening tests for thyroid dysfunction
- To identify in which categories the use of this test is cost-effective for early detection of thyroid dysfunction.

4. Methodology

This is a cross-sectional study performed during a 2year period (January 2019-January 2021) in Albania, which is considered a country with mild to moderate iodine deficiency. Measures such as the salt iodization program have been implemented in this country to prevent iodine deficiency (Zimmerman et al., 2006). We assessed the prevalence of thyroid disorders and the presence of thyroid antibodies in 458 individuals (80% females and 20% males). Individuals 18-70 years old, from different regions, were randomly included in the study. All subjects were tested for thyroid disorders for the first time. Those previously known or treated for thyroid problems were excluded from the study. Venous blood was taken and tested for TSH, FT4, FT3 (Free Tri-Iodothyronine), Anti TPO and anti-TG (Thyroglobulin) antibodies. These parameters were measured with ECLIA (Electrochemiluminescence) method with Cobas 6000 Roche Diagnostics. The following reference ranges for laboratory tests were used:

- TSH (0.2–4.5uUI/mL),
- FT3 (2–4.4 pg/mL),
- FT4 (0.9–1.7 ng/dL),
- anti TPO (<34 IU/mL),
- anti TG(<115 IU/mL).

Ultrasound (US) of the thyroid gland was done with Siemens Acuson NX2. We evaluated ultrasonographic parameters such as heterogenicity, hypoechoic structure, micronodular pattern and blood flow. Subjects were divided into two groups; positive for anti-TPO or anti-TG antibodies and negative for antibodies. Statistical analysis was performed to assess the prevalence of thyroid dysfunction, presence of thyroid antibodies and correlation with age, gender and ultrasonographic parameters mentioned above. The data were transferred to SPSS 25. Non-parametric tests (2-Tailed Mann-Whitney U Tests) and Chi-squared test were used to estimate if there was a difference between the two groups in thyroid function and ultrasound parameters. P values < 0.05 were considered statistically significant.

5. Results

The study involved 458 subjects of whom 80% were females and 20 % were males. In terms of the age group it turns out that 3.35% are under 20 years old, 38.9% are 20-40 years old, 41.2% are 41-60 years old and 16.65% are over 60 years old.Age varies from 14 years to 70 years with an average (M = 44.51, ds = 14.245).

Table 1: *Distribution By Gender*

	N	**%**
Female	365	79.7
Male	93	20.3
Total	458	100.0

(Source: Self)

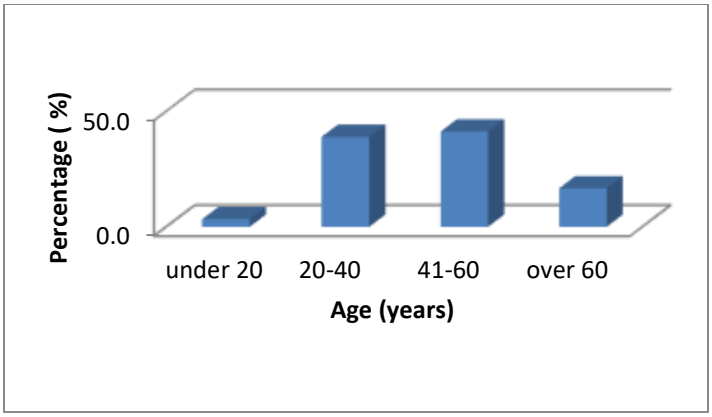

Figure 1: *Distribution By Age (Source: Self)*

Out of 458 patients analyzed, 88.6 % (406) of subjects resulted in euthyroid. Prevalence of hyperthyroidism was 1.1% and hypothyroidism 3.1%. Subclinical hypothyroidism and subclinical hyperthyroidism were present in 5.5% and 1.7% respectively. 97 % of subjects who tested negative for antibodies had normal thyroid function compared to 73 % in the antibodies positive group. There was a significant difference between subclinical hypothyroidism and other thyroid disorders between the antibodies positive and the antibodies negative groups (p-value <0.00001). 21 % (96 Individuals) from 458 examined had normal thyroid function and resulted positive for anti-TPO or anti-TG.

Table 2: *Population Characteristics And Laboratory Data*

Population Characteristics and Laboratory Data	
Parameter	**Value**
Patients n	458
Age y	44.51 ± 14.2
Female/male n (%)	365/93 80/20
TSH uUI/ml	3.2 ± 7.9 (0-67.4)
Anti TPO or anti-TG positive in females (%)	26.5
Anti TPO or anti-TG positive in males (%)	11.8

(Source: Data from the Study)

Table 3: *Prevalence Of Thyroid Dysfunction And Thyroid Antibodies*

Prevalence of Thyroid Dysfunction and Thyroid Antibodies	
Euthyroid n (%)	406 (88.6%)
Overt Hyperthyroidism n (%)	5 (1.1%)
Overt Hypothyroidism n (%)	14(3.1%)
Subclinical Hyperthyroidism n (%)	8 (1.7%)

Subclinical Hypothyroidism n (%)	25 (5.5%)
Prevalence of Positive Antibodies in the Population Examined (%)	25.3%
Prevalence of Positive Antibodies in Euthyroid Individuals (%)	25.5%

(Source: Data from the Study)

The prevalence of positive thyroid antibodies, at least one of them was 26.5% in females and 11.8 % in males (2,2:1 ratio). Anti TPO antibodies were present in 78% of individuals who had a family history of Hashimoto thyroiditis compared to 23% who did not. There was not found a significant statistical difference between age and presence of antibodies ($p>0.05$)

Hypoechoic structure, heterogenicity and micronodular pattern were associated with significantly higher TPO antibodies activity $p<.001$. The hypoechoic structure had 96% sensitivity and 89.3% specificity. The micronodular pattern was the most specific parameter with a specificity of 99.4%. There were significant correlations for changes in blood flow $p<.001$ between the two groups.

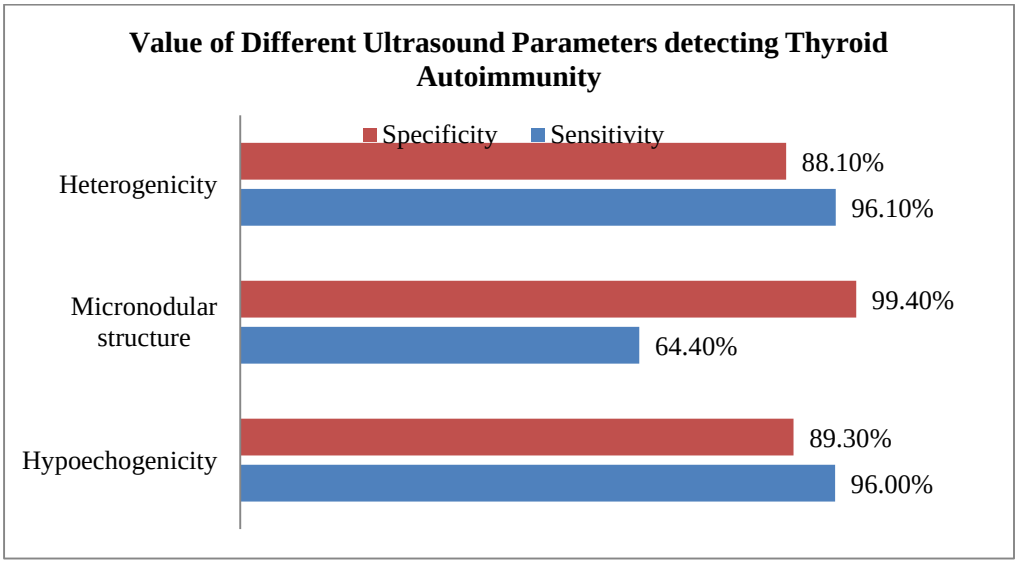

Figure 2: *Ultrasound Changes Detecting Autoimmune Thyroid Disorders*

(Source: Data from the Study)

6. Discussion

A low prevalence of overt thyroid dysfunction was observed; respectively, hyperthyroidism was 1.1% and hypothyroidism was 3.1%. Subclinical hyperthyroidism was rare with a frequency of 1.1%. These data are similar to those reported in other studies. Subclinical hypothyroidism was the most common thyroid pathology occurring with a frequency of 5.5%. Most of the patients with subclinical hypothyroidism do not manifest any specific symptom and pass without being diagnosed. Screening for thyroid dysfunction is important especially in individuals with risk factors. (McDermott & Ridgway, 2001).

The presence of high antibodies (anti-TPO or anti-TG) was relatively high in females 26.5%. The presence of a high frequency of thyroid antibodies is influenced by different factors, but initiation of salt iodization in our country may be one of the contributing elements to be considered. Studies show that autoimmune thyroid problems are more common in countries with adequate iodine intake. Consider here the example of Denmark where the prevalence of anti-TPO before and after iodization of salt was respectively 14.3% and 23.8% (Pedersen et al., 2011). The level of anti-TPO also correlates with the degree of lymphocytic infiltration of the thyroid gland of persons who have normal TSH and FT4 values, considered euthyroid. In these individuals, the prevalence of anti-TPO positive varies from 12 to 26% in different populations (Prummel & Wiersinga 2005). The ultrasound can serve as a screening test for early detection of autoimmune thyroid gland disorders in groups considered at risk. Decreased ultrasound echogenicity represents the most common and sensitive finding in Hashimoto's thyroiditis, while the micronodular pattern is the most specific parameter. Testing for TPO antibodies in euthyroid subjects can be used to identify people at risk for developing thyroid dysfunction in the future. Many subjects do not seek medical advice since the symptoms develop gradually over time, are not specific or may be confused with other problems such as vitamin D deficiency, iron deficiency, emotional problems etc.

7. Conclusions

Considering the results of our study and data from the literature review we conclude that the presence of thyroid autoantibodies is more frequent in females, people with a family history of autoimmune thyroid disorders, people with other autoimmune diseases and people with decreased echogenicity of the thyroid gland in ultrasound examination. In addition, euthyroid subjects with

positive anti-TPO antibodies have higher TSH levels near the upper reference range compared to those with negative antibodies. These categories are considered at risk for developing thyroid dysfunction in the future and we suggest testing for anti-TPO antibodies in these individuals besides TSH as the screening first test. When access to ultrasound equipment is possible it can give a lot of information on the risk for developing thyroid dysfunction especially findings of hypoechoic structure or micronodular pattern. Our research limitations consist of the small number of individuals included in the study. Larger population data are needed in the future to evaluate the role of anti-TPO antibodies as screening tests for thyroid dysfunction. Furthermore remains to be evaluated the cost, access and implementation in practice of the laboratory technology for anti-TPO test and thyroid ultrasound equipment in different geographic regions. Other factors such as smoke, different treatments and nutrition habits that may influence thyroid function should be taken into consideration. Our scope for future research is the follow up of euthyroid subjects with positive thyroid antibodies included in this study for deterioration of thyroid function. The aim is to estimate the number of subjects that develop a decrease of thyroid function, the average time from positive anti-TPO detection or ultrasound changes to the installation of hypothyroidism and the risk factors that predispose for that. It would be of great value the development of a predictive model to stratify individuals based on risk for thyroid function deterioration in the future.

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