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Study of Antithyroid Peroxidase Antibodies in People with Normal Range Thyroid Stimulating Hormone

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Abstract

Aims and Objectives: *Hypothyroidism has become a common health issue in India, as it is worldwide. However, there is a lack of adequate information on the prevalence of hypothyroidism in the adult population of India. In this study we evaluated the presence of antithyroid peroxidase antibodies in people with high normal and low normal range thyroid stimulating hormone levels.*

Methods: *The staffs of Government Medical college, Thiruvananthapuram, with symptoms of thyroid dysfunction in the age group of 15-35 years were included in this study, with exclusion of those with other systemic illness and conditions which alter the thyroid stimulating hormone values. In this study, the normal range of thyroid stimulating hormone is taken as 0.36-5.49 µIU/ml The study population then divided into two groups based on the high(2.5-5.49 µIU/ml) and low(0.36-2.49 µIU/ml) normal range values of thyroid stimulating hormone. In both these groups all were evaluated for anti-TPO levels.*

Results: *In our study, even if it was done in a group of people with normal TSH levels, about 58.1 % have positive TPOAb values (> 75 U/ml) in which 70.3% is from the people with high normal TSH values (2.5-5.49 µIU/ml). In our study we observed that the people with thyroid related complaints are more in females and constitutes about 62.2 % in the study group. In the evaluation of TPOAb positivity also there is a strong female preponderance (74.4%) These findings carries a strong statistical significance.*

Conclusion: *Anti TPO antibody measurements in those with high normal range TSH value may be considered to identify the patients at risk of developing true hypothyroidism in future so that early commencement of LT4 therapy is possible to diminish the autoimmune thyroid destruction Or else we may reconsider the "normal range" of TSH so that most of the patients with high antibody titre will fall in the diagnosis of subclinical hypothyroidism.*

INTRODUCTION

A variety of disorders can plague the thyroid gland, including autoimmune disorders, goiter (an enlargement of the thyroid which caused by either over- or underproduction of thyroid hormone), benign and malignant tumors. Ever since India adopted the universal salt iodization program (1983), there has been a decline inthe prevalence of goiter in several parts of the country. And now, India is thought to be undergoing a transition from iodine deficiency to iodine sufficiency state.[1]In spite of this fact, the prevalence of hypothyroid-dism in developed world is about 4-5% and, the prevalence of subclinical hypothyroidism is about 4-15%.[1] Thyroid autoimmunity is being increase-ingly identified as the underlying cause of goitre in India, following the implementation of the salt iodization program in our country.[2] But, there is a

paucity of literature on the pathogenesis of AITD among the Indian population. Hashimoto's thyroiditis and Graves' disease are well characterized and interrelated autoimmune thyroid disorders with a variety of clinical manifestations. The diagnostic hallmark of autoimmune thyroid disorders is the presence in most patients of circulating antibodies and reactive T cells against one or another thyroid antigen. These varieties of thyroid autoantibodies are in common use and widely available in clinical diagnostic laborat-ories.[3] The pathogenesis of thyroid autoimmunity is believed to be multifact-orial, with contributions from both humoral as well as cell-mediated immune systems.[4] The role of iodine in triggering autoimmune thyroiditis has long been debated. Iodine supplementation in iodine-deficient areas increases the prevalence of lymphocytic infiltration of the thyroid 3-fold.[5] Also, the prevalence of thyroid autoantibody positivity in such areas rises to over 40% within 5 years of initiating supplementation.[6]Besides, in Hashimotos Thyroiditis several other putative triggering viruses have been implicated such as parvovirus, rubella, herpes simplex virus, Epstein Barr virus, and human T-lymphotropic virus type 1. Nevertheless, the evidences are scarce and further studies are required in order to confirm the role of infections as causative agents.[7]The exposure to environmental toxicants such as polyaromatic hydrocarbons or polyhalogenated biphenyls, both are commonly used in a variety of industrial applications, have been shown to provoke thyroid autoimmunity not only in experimental animals but also in humans.[8]*Several autoimmune disorders* have been reported to be associated with autoimmune thyroiditis and may coexist with other organ-specific autoantibodies.[9] Tolerance to self antigen is obtained by elimination of autoreactive T-cells[10] and defect in this mechanism leads to activation of these cells and consequent autoimmunity.[9] In areas with *selenium deficiency,* higher incidence of thyroid-itis has been reported.[11] It can be due to the decreased activity of selenium dependent glutathione peroxidase enzyme present in thyroid cells. Till now, the low levels of TPO-Ab and Tg-Ab found in many individuals are of uncertain significance in the presence of normal thyroid function; however, they remain a significant risk factor in families with autoimmune thyroid disorders.[3]

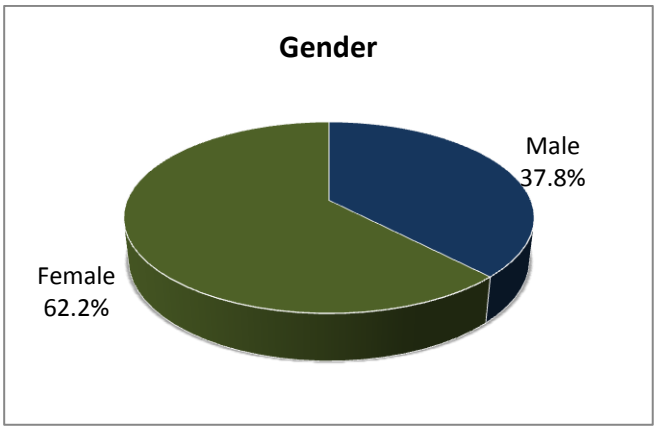
Keeping these data in mind and the numerous reports of increased thyroid autoimmunity, incidence of thyroid autoimmunity cannot be ignored and refuted anymore.

PRIMARY OBJECTIVE

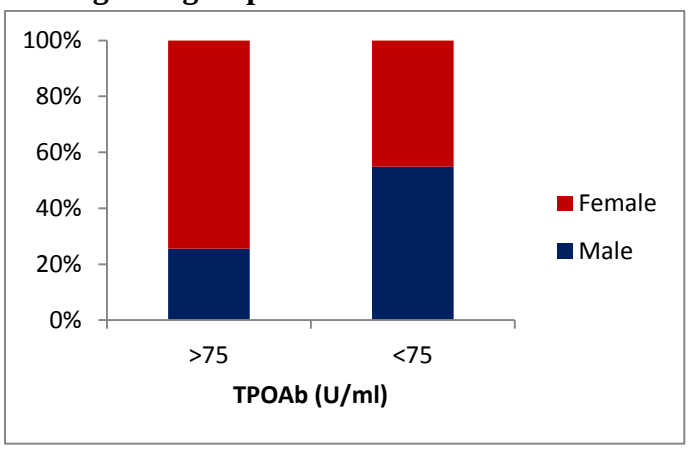
To study the presence of antithyroid peroxidase antibodies in people with high normal and low normal range thyroid stimulating hormone levels.

RESULTS

Here, we have studied a group of people with normal thyroid function (37 people with high normal TSH and 37 people with low normal TSH) irrespective of the previous history of thyroid dysfunction and thyroxine supplementation. Some of the people were diagnosed previously as subclinically hypothyroid but not on any medication at present. At the same time some are symptomatic but due to the normal levels of thyroid hormones not yet started any medication.



Sex distribution among the TPOAb positive and negative groups.

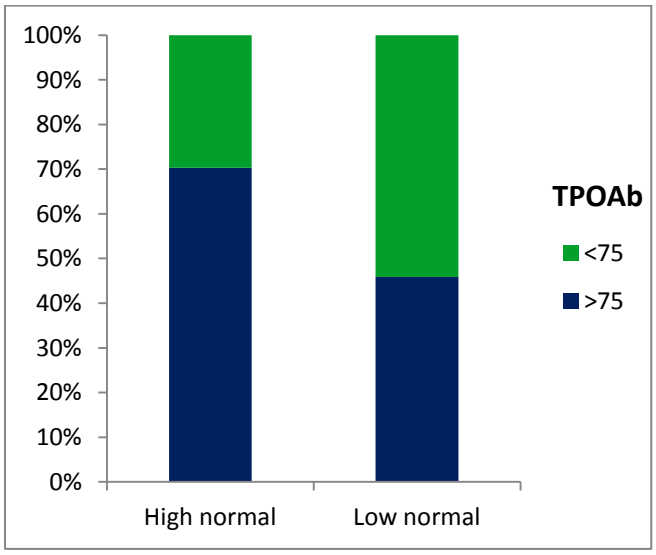


Percentage of TPO Ab positivity in high normal and low normal TSH groups

TPOAb (U/ml)	Category				Total	
	High normal TSH (µIU/ml)		Low normal TSH (µIU/ml)			
	N	%	N	%	N	%
>75	26	70.3	17	45.9	43	58.1
<75	11	29.7	20	54.1	31	41.9
Total	37	100.0	37	100.0	74	100.0

χ^2 =4.497 df =1 p=0.034

Graph:6



Positive TPOAb is present in 70.3% of high normal TSH groups and 45.9% of low normal TSH groups. It is found to be statistically significant (0.034).

The mean value of TSH is 3.67 in the high normal TSH group and it is 1.44 in the low normal TSH group

The mean value of TPOAb in high normal TSH group is 560.76 and in the low normal TSH group is 164.69. This is found statistically significant (p value: 0.004).

TSH and TPOAb are positively correlated (.384**) and is highly significant (.001).

DISCUSSION

Advances in diagnostic techniques and knowledge in molecular biology have provided valuable insights in understanding the epidemiology and pathogenesis of various diseases including the highly prevalent thyroid disorders in the population worldwide. There is an evident rise in the prevalence of all the thyroid disorders including subclinical hypothyroidism in India, in the post iodization era. However, screening studies have a scarcity in India and there is only scanty literature on prevalence of these disorders in all regions of India.[12]

The most common complaints of people included in this study were weight gain, lethargy, hair loss, increased sleepiness and menstrual irregularities. The age group we studied included people in the age group of 15-35 years since we can easily exclude the postmenopausal women who have a higher chance of developing thyroid dysfunction and autoimmunity. There is usually an age-wise increase in prevalence of hypothyroidism. It is probably due to thyroid autoimmunity, which is known to increase with age as reported in the Wickham survey.[13] Besides, prevalence was more in females and increased with age, which is similar to that observed by Parle et al.[14] Prevalence was also more in postmenopausal women. But in this study TSH level showed a gradual decrease as the age advances whereas most of the TPOAb positive people are in the age group of 26-30 years of age. This may be because of the autoimmunity developed in the body affected the thyroid as well as other organ systems especially pituitary so that the regulatory feedback mechanism itself can get affected. A detailed study is needed to find out the causes for this fact with a large population so that the bias is avoided.

There is no such studies to support this finding. In our study we observed that the people with thyroid related complaints are more in females and constitutes about 62.2 % in the study group. In both the TSH groups, female predominates with 67.6% (32.4% males) in the high normal TSH group and 56.8% (43.2% males) in the low normal TSH group. In the evaluation of TPOAb also there is a strong female preponderance (74.4%), which can be explained by the above finding of high normal TSH levels in females. The female predominance in thyroid disorders is supported by numerous studies which includes a 'PolSenior' multicentre crossover study,[15] in which thyroid dysfunction was revealed in more than 10% of participants, where hypothyroidism was in 7.95%, and hyperthyroidism in 2.95%. Both types of dysfunction were more prevalent in women, and more than 80% of both dysfunctions were subclinical. They have studied 1,542 participants and concentrations of TPOAb were measured in them. Increased levels of TPOAb was revealed in 19% of the cohort and the prevalence of thyroid autoimmunity was higher in women and also more often found in participants with hypothyroidism.[15] So screening for Subclinical hypothyroidism needs to be considered in reproductive group females in view of high prevalence of raised serum TSH and thyroid autoimmunity after the age of 21 yearsas seen in our study population.In our study, even if it was done in a group of people with normal TSH levels, about 58.1 % have positive TPOAb values (> 75 U/ml) in which 70.3% is from the people with high normal TSH values (2.5-5.49 µIU/ml[197]). This suggests a high prevalence of autoimmune etiology in the development of hypothyroidism in our population. The mean TPOAb value in the low normal TSH group is less (164.69 U/ml) compared to the mean value of 560.76 U/ml in the high normal TSH group, which shows a statistical significance. That means even if there is TPOAb positivity in the low normal TSH group (45.9%), it may be restricted around the normal range. This TPOAb positivity in the low normal group may be contributed by the Grave's disease or by an otherwise normal population. According to the study of Unnikrishnan et al, anti-TPO antibodies suggesting autoimmunity were detected in 21.85% patients of their study group which included the general population.[16] And in their study the prevalence of hypothyroidism was high, affecting approximately one in 10 adults in the study population. Subclinical hypothyroidism and anti-TPO antibody positivity were observed in their study. This gives evidence that autoimmune mechanisms appear to play an etiological role in a significant proportion of patients.[16] There is also another study which is similar to the present study in which they selected a group of people with high normal and low normal TSH to study the TPOAb levels, and found out that around 3% of the low normal TSH group was anti TPO positive, while 18.6% of the high normal TSH group had a positive test for antiTPO.[17]And from their study they suggested to lower the upper limit of TSH to 3.49 IU/ml so that about 20% more patients can be identified as hypothyroid with the help of suggesting TPOAb check. Our study revealed another finding that there is not much significant difference in the mean of TSH in TPOAb positive and negative groups, which may indicate that the importance is in the positivity of TPOAb and not in the numerical value. Considering the serum T3 levels in our study, it does not vary much among the high normal and low normal TSH groups(mean 1.20 and 1.12 respectively). The mean T3 level in the TPOAb positive and negative groups is also suggests that the change in T3 values is relatively sluggish. This can be due to the fact that the biologically active form of thyroid hormone is T3 and for the same reason its level in the blood is highly regulated by the hypothalamo-pituitary axis.

CONCLUSION

Subclinical hypothyroidism is defined as high serum TSH concentration with normal serum Free Thyroxine (FT4) and Free Triiodothyronine (FT3) concentrations, associated with few or no signs

and symptoms of hypothyroidism.[18]It is the most prevalent thyroid disorder affecting 3–15% of the adult population. Its incidence increases with advanced age, female gender, and greater dietary iodine intake.[18]An important issue is whether serum concentrations of T4 and T3 are normal for the individual in subclinical thyroid disease. In order to make a decision whether or not subclinical hypothyroidism should be treated, it is indeed important to know whether the disorder has any adverse effects and/or how often overt hypothyroidism will develop.[18]Autoimmune Thyroid Diseases (AITD) are composed by a spectrum of thyroid disorders, the two extremes being Graves' Disease, characterized by hyperthyroidism, and Hashimoto's Thyroiditis characterized by hypothyroidism.[19,20] The pathogenesis of thyroid autoimmunity is believed to be multifactorial, with contributions from both humoral as well as cell-mediated immune systems.[4] Thyroid autoimmunity is being increasingly identified as the underlying cause of goitre in India, following the implementation of the salt iodization program in our country.[2]But, there is a paucity of literature on the pathogenesis of AITD among the Indian population. Many organ-specific autoimmune diseases are preceded by a long pre-clinical phase, and several longitudinal cohort studies[21] revealed that patients may carry autoantibodies many years before they manifest clinical symptoms. Detecting these antibodies in the serum has been shown to have strong predictive value, and it is depending on the particular autoantibody, test method, and disease at the time of presentation.[21]It was suggested that even in normal thyroid hormonal states, without distinguishable inflammation or destruction of thyroid tissue compared with normal subjects, subsequent thyroid destruction of HT might already be indicated through heterogeneity of the thyroid tissue.[22] The understanding of the thyroid peroxidase (TPO) antigen as the main antigen of the thyroid microsomal fraction has enlightened the development of a sensitive and specific assay for detection of the corresponding autoantibodies.[23]

Selenium substitution has a significant effect on the inflammatory activity of thyroid specific autoimmune disease. It would be of interest to determine whether early supplementation of selenium in patients with newly developed autoimmune thyroiditis may delay or even prevent the natural course of the autoimmune diseases.[11]A number of studies have shown that the serum levels of anti-thyroid peroxidase antibodies (TPO-Ab) in patients with Hashimoto's thyroiditis declinedafter the levothyroxine treatment. So to conclude, there is a diminution of serum TPO-Ab levels in most patients with Hashimoto's thyroiditis those who underwent treatment with levothyroxine, but after a mean of 50 months. [24] So the serum TPOAb values may be considered as a screening test to evaluate the thyroid function in euthyroid symptomatic patients, so that the L-T4 replacement can be initiated at an early stage to decrease the severity of thyroid auto-destruction and also can be used as a prognostic indicator to adjust the dosage of thyroxine supplementation.

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