Prevalence of Elevated Anti-Thyroid Peroxidase Antibodies in Subclinical Hypothyroidism

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ABSTRACT

Introduction: Autoimmune thyroiditis is a common cause of subclinical hypothyroidism (SCH). The progression of SCH to overt hypothyroidism depends on multiple factors of which elevated thyroid peroxidase antibody (anti-TPO) levels is one of the risk factors. There are sparse data on the prevalence of anti-TPO among Indian patients with SCH. So the aim of the present study was to determine the prevalence of anti-TPO positivity in SCH.

Material and Methods: We estimated anti-TPO levels in 215 patients of SCH between 18 to 60 years. Anti-TPO measurement was done by chemiluminescence method and a value of > 18 Iu/ml was considered as positive.

Results: The mean TSH value was 9.08 ± 2.63 µU/ml. The prevalence of anti-TPO antibodies in SCH was 49.7%. The TSH was significantly higher in anti-TPO positive group. The anti-TPO prevalence was significantly higher with TSH ≥8µU/ml.

Conclusion: There is a high prevalence of elevated anti-TPO in SCH patients which suggests an autoimmune aetiology. Since the subclinical hypothyroid patients with elevated anti-TPO titre are likely to develop overt hypothyroidism over a period of time, regular follow-up or initiation of replacement with levothyroxine is recommended.

Keywords: Subclinical Hypothyroidism, Thyroid Peroxidase Antibody, Autoimmunity, Thyroid Stimulating Hormone

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as an elevated thyroid stimulating hormone (TSH) with normal total (TT4) or free thyroxine (FT4).[1] It is a milder form of hypothyroidism. The prevalence of SCH varies from 4 -14%[2-5] in various population based studies. SCH is associated with increased cardiovascular risk[6], altered lipid profile[7], menstrual disorders[8], increased pregnancy loss[9] and infertility.[10] The most common underlying cause for SCH is chronic autoimmune thyroiditis and other causes include iodine deficiency, radio iodine therapy, infiltrative diseases like amyloidosis, sarcoidosis, hemochromatosis, Reidel's thyroiditis, subacute thyroiditis, partial thyroidectomy and external irradiation.[11]

SCH can be transient or permanent and can progress to overt hypothyroidism. The rate of progression to overt hypothyroidism is 3-18% of the affected patients per year.[1] The progression to overt hypothyroidism depends on multiple factors like the presence of anti-thyroid peroxidase antibodies (anti-TPO), radiation, radioactive iodine therapy and the initial TSH value.[11-14] The common antibodies identified are anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies (anti-TG). The sensitivity and specificity of anti-TPO is higher than that of anti-TG for identifying autoimmune thyroid disease.[15] Anti-TPO is an anti-microsomal antibody produced against a thyroid peroxidase (TPO) enzyme, a 100 kD glycosylated protein present in thyroid microsomes. The prevalence of anti-TPO in SCH varies from 12-70.2% in different studies.[4,16]

Many population based studies had shown that anti-TPO positivity is associated with higher rate of progression to overt hypothyroidism.[13,14] Some studies have shown that anti-TPO positivity in SCH is associated with increased pregnancy loss.[17] There is some evidence to suggest that antibody positive individuals may require higher dose of levothyroxine for normalisation of TSH compared to antibody negative individuals.[18] Indian data is sparse regarding prevalence of these antibodies in SCH. So, the aim of present study was to determine the prevalence of anti-TPO in Indian patients with SCH.

MATERIAL AND METHODS

The present study was a cross sectional observational study done in the outpatient department of Endocrinology, Vydehi Institute of Medical Sciences and Research Centre (VIMS and RC), Bengaluru from July 2016 to February 2018. Subclinical hypothyroidism was defined as elevated TSH >4.2µU/L with normal thyroid hormones (TT4). Inclusion criteria was patients with subclinical hypothyroidism aged 18-60 yrs, whose TSH was elevated on at least two occasions done at the interval of three months. Patients on levothyroxine, antithyroid drugs, prior history of radioactive iodine ablation, hemithyroidectomy, antipsychotics were excluded from the study. Anthropometric data were recorded and thyroid examination was performed in all the patients. Body mass index (BMI) was calculated as weight/height². BMI is classified as follows: underweight < 18.5 kg/m²,

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How to cite this article: Atluri Sridevi, Boppana Rakesh, Goel Amit, Yalamanchi Aiswarya, Biswas Anupam, Shivaprasad Channabasappa. Prevalence of elevated anti-thyroid peroxidase antibodies in subclinical hypothyroidism. International Journal of Contemporary Medical Research 2018;5(3):C1-C4.

normal ≥ 18.5 kg/m² to < 25 kg/m², overweight 25kg/m² to <30kg/m², obese ≥ 30kg/m². Goitre is graded as absent if thyroid is not visible or palpable and is said to be present if it is visible or palpable. After examination 2 ml of blood was drawn and centrifuged to separate serum for estimation of anti TPO antibodies.

TSH, TT4 and Anti-TPO were estimated by chemiluminescent immune assay (CLIA) method in Beckman Coulter. The normative values for TSH was 0.4 - 4.2 µU/ml and total T4 was 5.5 -11.2 µg/dl. Anti-TPO >18 IU/ml was considered positive for the purpose of this study. The interassay and intraassay coefficient of variation is less than 5%.

STATISTICAL ANALYSIS

The age, BMI, TSH and Anti-TPO were expressed as mean and SD. The anti-TPO prevalence in relation to gender, age, BMI was expressed as absolute values or percentages as appropriate. The correlation between BMI and TSH was analysed using Pearson's correlation coefficient. Continuous variables between anti-TPO positive and negative were compared using unpaired 't'-test. The level of TSH and prevalence of anti-TPO significance was calculated using Fisher's exact two tailed significance using prism 7 software. P value < 0.05 is considered significant.

RESULTS

The present study was conducted in department of Endocrinology, VIMS and RC between July 2016 to February 2018. 530 patients presented with SCH of whom only 215 subjects satisfied the criteria. Of these 153 (71.16%) were females and 62 (28.84%) were males. The mean age of the subjects was 34.01 ± 10.17 years. The mean BMI of the subjects was 24.5 ± 3.75 kg/m². Fifty six subjects (26.04%) were overweight and fifteen subjects (6.9%) were obese and rest had normal BMI. Goitre was present in 30 (13.9%) of these patients. TSH ranged from 4.56 to 18 µU/ml with a mean TSH of 9.08 ± 2.63 µU/ml. Out of 215 patients, 136 had TSH between 4.5 to <10 µU/ml and in 79 patients it was between 10 to 18.56 µU/ml. No significant correlation was observed between TSH and BMI(r=0.04).

Anti-TPO and its distribution:

Anti-TPO above 18 IU/ml was considered positive. 107 (49.7%) patients had anti-TPO positivity. The antibodies were more prevalent between 20-40 years of age as shown in the Fig.1. The prevalence of antibody was higher in females (50.9%) than males (46.7%) though statistically not significant. Various parameters in anti-TPO positive and negative individuals were as summarised in table 1.

When Anti-TPO positivity was analysed in relation to the TSH level, subjects with a TSH cut off of ≥ 8 had significantly higher prevalence of antibody compared to those with TSH < 8 (Table 2).

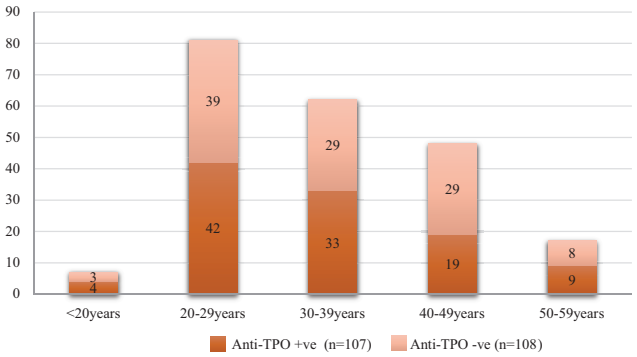

Figure-1: Distribution of cases according to age and anti-TPO status

DISCUSSION

In the present study we have evaluated the prevalence of anti-TPO positivity in patients with SCH and its correlation with TSH levels. We found a prevalence of 49.7% of anti-TPO antibody positivity in SCH in patients of Indian origin. Anti-TPO positivity status in SCH has both diagnostic and prognostic significance. Anti-TPO positivity in SCH confirms the autoimmune pathology. Prognostically, it signifies a higher risk of progression to overt hypothyroidism. Hence, patients with SCH who have positive anti-TPO need regular follow up to detect the progression to overt hypothyroidism. The results of our study are comparable to that reported from the previous studies. Asvold et al[19] reported a prevalence of 52.2% and Cappola et al.[20] reported a prevalence of 40.8% anti-TPO positivity in SCH. An Indian study done by Deshmukh et al[4] showed a similar prevalence of 47.6%.

Parameter	Anti-TPO +ve (n=107)	Anti-TPO –ve (n=108)	P Value
Age (years)	33.2 ±9.4	34.8 ±10.8	0.26
Gender (F:M)	2.6:1	2.3:1	
BMI (kg/m²)	25.7 ± 5.8	25.6 ± 3.9	0.84
TSH (µU/ml)	9.45 ± 2.4	8.7 ± 2.8	0.036
Total T4 (µg/dl)	8.24 ± 1.8	8.3 ± 1.4	0.68
Anti-TPO (IU/ml)	337.0 ± 384.2	5.0 ± 4.3	0.0001
BMI – Body mass index, TSH - Thyroid stimulating hormone, Total T4 – serum total thyroxine			

Table-1: Comparison of clinical and biochemical parameters in relation to anti-TPO positivity

TSH Level	TPO+VE	TPO –VE	P value*#
TSH ≥8	78	55	0.0012
TSH <8	29	53	
* Fisher's exact two tailed test, # P < 0.05 significant			

Table-2: Anti-TPO positivity in relation to a TSH cut-off value of 8

Meta-analysis done by Collett TH et al[6] reported an average prevalence of 45.8% which was similar to the results of our study.

However, a few studies have shown a higher rate of anti-TPO positivity in SCH. An Australia Busselton Health Study by Walsh JP et al showed a prevalence of 67.4%.[21] An Indian study by Mohanthy et al.[16] had also reported a prevalence of 72%. However, the sample size of this study was small precluding generalization. In contrary, some studies like Vanderpump et al.[22] and a Japanese Study by Imaizumi M et al[23] reported lower frequencies of 33.1% and 20% respectively. Wickham survey had taken TSH cut off as 6 to 15µU/ml to define SCH and antibodies were assayed with radio immune assay and raising titres was considered positive rather than an absolute value. Japanese study used hemagglutination method instead of immunoassay. The difference in the prevalence rates could also be attributed to ethnic variations, iodine intake, patient characteristics, lab assays, cut off value of TSH and background frequency of autoimmune thyroid disease in general population.

The present study had significantly higher TSH in TPO antibody positive group than antibody negative group which was similar to observations made in Tehran Thyroid Study (TTS) and the HUNT Studies.[14,24] Anti-TPO were more prevalent in females compared to males which as similar to the finding in HUNT study. The prevalence of anti-TPO was significantly higher with TSH $\geq$ 8. This finding could potentially suggest a progressive increase in TSH over a period of time and higher risk of developing overt hypothyroidism.

The limitations of the study are it is a cross-sectional study, and a follow up study is required to confirm the findings. It's a hospital based study and a referral bias could have impacted the results.

CONCLUSION

We conclude that there is a high prevalence of TPO antibody in SCH patients which suggests an autoimmune aetiology. Since the subclinical hypothyroid patients with elevated anti-TPO titre are likely to develop overt hypothyroidism over a period of time, regular follow-up or initiation of replacement with levothyroxine is recommended.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 22-02-2018; **Accepted:** 20-03-2018; **Published:** 04-04-2018