

Chronic Urticaria and Subclinical Hypothyroidism: A Cross-sectional Study

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Abstract

Introduction: Chronic urticaria or recurrent urticaria is defined as persistence of urticarial lesions for >6 weeks, with symptoms present at least 3 times in a week. About 30–45% of chronic spontaneous urticaria are related to autoimmune origin. The incidence of thyroid autoimmune conditions is about 4.3–57.4% in adults and 3.5–8% in children with chronic urticaria.

Aim and Objectives: The present study was undertaken to estimate the levels of anti-thyroid peroxidase (Anti-TPO) antibodies, T3, T4, thyroid-stimulating hormone (TSH), and to evaluate their use in early diagnosis of the sub clinical hypothyroidism in chronic urticaria.

Materials and Methods: A cross-sectional observational study was conducted in the Department of Biochemistry at Gandhi Medical College and Hospital over duration of 2 years after obtaining Institutional Ethics Committee. Fifty diagnosed chronic urticaria patients attending the dermatology outpatient department and 50 age and sex matched apparently healthy controls were included in the study. Blood samples were collected and analyzed for anti-TPO antibodies, T3, T4, and TSH by chemiluminescence immunoassay (CLIA) method.

Results: In the present study, the female to male ratio was 2.8:1 for cases and mean \pm SD for age was 27.04 ± 5.77 years. The serum anti-TPO antibodies levels were significantly increased in the chronic urticaria cases with mean \pm SD 43.10 ± 7.78 IU/ml compared to the controls with mean \pm SD, 13.72 ± 1.28 IU/ml. Serum T3 and T4 levels were significantly decreased in cases ($P < 0.01$ and $P < 0.037$) and serum TSH was higher (Mean \pm SD 5.55 ± 1.03 μ IU/ml) in cases than in controls (2.86 ± 0.31 μ IU/ml.) with significant ($P < 0.001$). Among the 50 chronic urticaria cases, 78 were euthyroid, 20% were subclinical hypothyroid, and 2% cases were clinical hypothyroid.

Conclusion: Chronic urticaria patients must be screened for subclinical hypothyroidism which would help in early diagnosis and change in treatment modalities thus improving the quality of life.

Key words: Anti thyroid peroxidase antibodies, Chronic urticaria, Serum thyroid-stimulating hormone, Subclinical hypothyroidism

INTRODUCTION

Chronic urticaria also called as recurrent urticaria is defined as persistence of urticarial lesions for >6 weeks, with symptoms present at least 3 times in a week with an annual incidence of about 1.4% in the general population.^[1,2] It is grouped as chronic inducible urticaria when the

urticaria occurs by external triggering stimulus such as food, pressure, and temperature and chronic spontaneous urticaria or chronic idiopathic urticaria when occurs without any specific triggering stimulus.^[3]

About 30–45% of chronic spontaneous urticaria are related to autoimmune origin^[4] and the autoimmune diseases associated with chronic urticaria are autoimmune thyroid diseases (Hashimoto's disease and Grave's disease), rheumatoid arthritis, type I diabetes mellitus, Sjogren's syndrome, Celiac disease, and systemic lupus erythematosus, among which thyroid autoimmune conditions are more commonly associated with incidence about 4.3–57.4% in adults and 3.5–8% in children.^[5]

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Anti-thyroid peroxidase (Anti-TPO) antibodies are most commonly associated thyroid antibodies in chronic urticaria.^[6] These are auto antibodies formed against TPO enzyme involved in the thyroid hormone synthesis. The anti-TPO antibodies act against high affinity receptor for immunoglobulin E(IgE) on mast cells and basophils resulting in histamine release and lead to urticaria^[7] and they also inhibit TPO enzyme activity and show cytotoxic effect on thyroid follicular cells leading to thyroid abnormalities such as hypothyroidism and hyperthyroidism.^[8,9] Due to these effects, the persons with the high-levels anti-TPO antibodies develop chronic urticaria and thyroid abnormalities.

Subclinical hypothyroidism in chronic urticaria patients is more prone to develop clinical hypothyroidism due to cytotoxic effect of anti-TPO antibodies on thyroid follicular cells.^[8,9]

The present study was undertaken to estimate the serum levels of anti-TPO antibodies and T3, T4, and thyroid-stimulating hormone (TSH) in chronic urticaria patients. This would help in early diagnosis of subclinical hypothyroidism and changes in the treatment modalities of patients with chronic urticaria thus improving the quality of life.

Aim

The aim of the study was to estimate the serum levels of anti-TPO antibodies, T3, T4, and TSH in chronic urticaria patients.

Objectives

The objectives of the study are as follow:

1. To estimate anti-TPO antibodies, T3, T4, and TSH in chronic urticaria patients
2. To evaluate the use of anti-TPO antibodies and TSH in early diagnosis of subclinical hypothyroidism in chronic urticaria patients.

MATERIALS AND METHODS

A cross-sectional observational study was conducted in the Department of Biochemistry at Gandhi Medical College and Hospital from October 2018 to September 2020 after obtaining Institutional Ethics Committee.

Fifty patients attending the outpatient department of dermatology with complaint of urticaria >6 weeks, aged between 10 and 35 years of either sex were enrolled in the study.

Pregnant women, diagnosed cases of diabetes mellitus, chronic kidney disease, autoimmune thyroid diseases,

patients on thyroxine replacement therapy, and anti-allergic therapy were excluded from the study. Fifty apparently healthy age and sex matched individuals were enrolled as controls.

Sample Collection and Analysis

With prior instructions, 5 ml of fasting venous sample was collected; serum was separated and stored at – 200C. Anti-TPO antibodies and TSH were analyzed by chemiluminescent; sequential two-step immunoenzymatic (“sandwich”) assay and serum T3 and T4 were analyzed by chemiluminescent method.

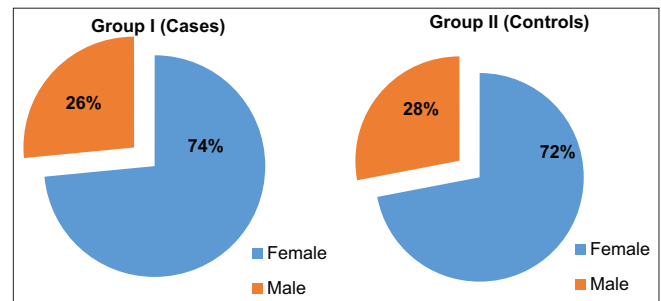


Chart 1: Sex-wise distribution of study groups

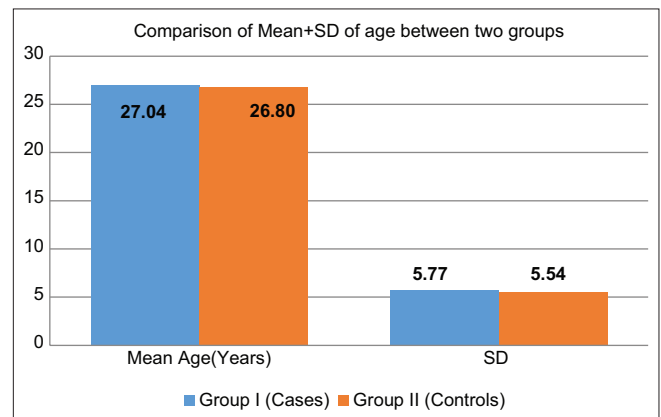


Chart 2: Comparison of mean and standard deviation two groups based on age

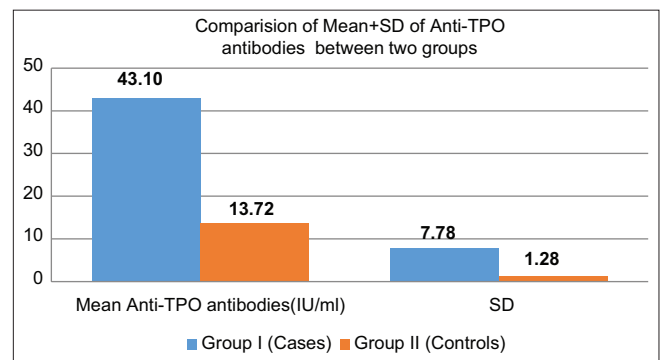


Chart 3: Comparison of serum anti-thyroid peroxidase antibodies between two groups

The results were tabulated in master chart and statistically analyzed using Microsoft Excel 2010 and SPSS software. $P < 0.05$ was considered as significant.

RESULTS

In the present study, 50 clinically diagnosed patients of chronic urticaria were categorized as cases (group I) and 50 apparently healthy subjects as controls (group II).

In the present study, the female to male ratio in group I was 2.8:1 and in group II was 2.6:1.

The Mean Age of the Study Population

In the present study, the mean age of group I (cases) was 27.04 years and of the group II (controls) was 26.80 years with standard deviation (SD) ± 5.77 and ± 5.54 , respectively (as shown in chart 2).

As shown in Chart 3, the anti-TPO antibodies were significantly increased in group I subjects as compared to group II subjects. As shown in Chart 4, the serum T3 levels were decreased in cases than in group I (cases) as compared to group II (controls).

As shown in Chart 5, serum T4 levels were increased in group I (cases) than in group II (controls). As shown in

Chart 6, serum TSH levels were increased in group I (cases) than in group II (controls).

Euthyroid, Subclinical Hypothyroid, and Clinical Hypothyroid Status in Patient Group

Among the 50 chronic urticaria cases, 39 cases were euthyroid, 10 cases were with subclinical hypothyroidism, and one case was with clinical hypothyroidism.

As shown in Chart 7, 78% cases were euthyroid, 20% cases were subclinical hypothyroid, and 2% cases were clinical hypothyroid.

DISCUSSION

Chronic urticaria is a common dermatological problem in India and is a distressing disorder that has significant impact on the quality of life of the patient. The most of the chronic urticaria cases remain idiopathic and are associated with systemic autoimmune diseases, most commonly with thyroid autoimmunity that results in thyroid dysfunction.

Anti-TPO antibodies have two-way effect; they show effects both on thyroid gland and skin. They can stimulate dermal mast cells and cause onset of urticaria and at the same time they show cytotoxic effect on thyroid follicular cells results in abnormalities in thyroid hormone levels

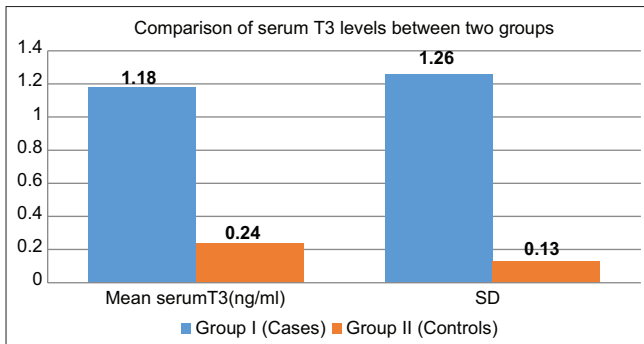


Chart 4: Comparison of serum T3 levels between case and control groups

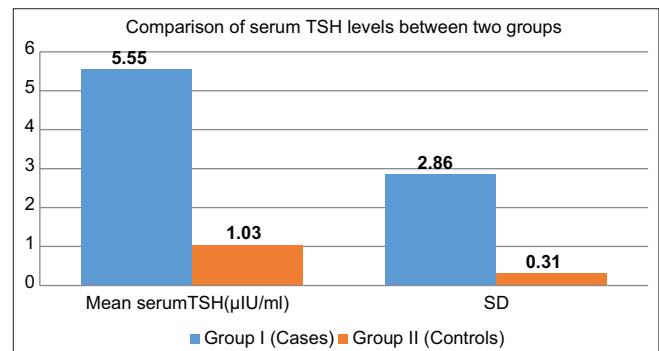


Chart 6: Comparison of serum thyroid-stimulating hormone levels between cases and controls

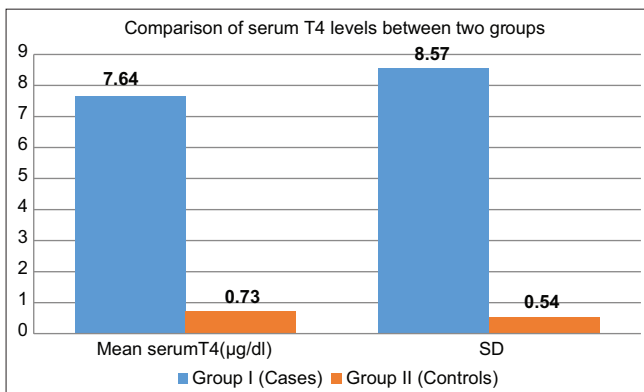


Chart 5: Comparison of serum T4 levels between cases and controls

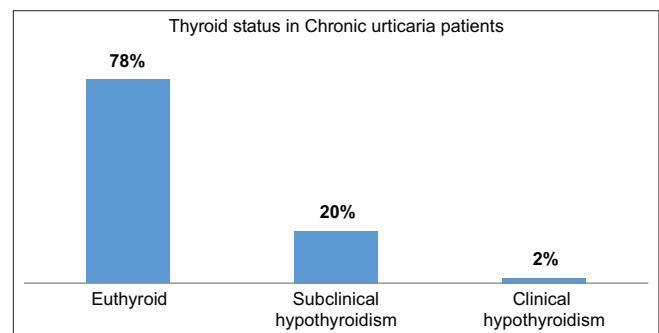


Chart 7: Distribution of euthyroid, subclinical hypothyroid, and clinical hypothyroid status in patient group

leading to hypothyroidism or hyperthyroidism. Hence, chronic urticaria and thyroid disease are considered as associated and parallel autoimmune events.

Chronic urticaria is more common in the age group of 20–35 years (27.04 ± 5.77 years) (as shown in Table 1) and more common in females than in males (74% were females and 26% were Males, as shown in chart 1) with female to male ratio of 2.8:1. In the present study, the statistical analysis of the obtained values showed that the serum anti-TPO antibodies levels were significantly increased in the chronic urticaria cases with mean \pm SD 43.10 ± 7.78 IU/ml compared to the controls with mean \pm SD 13.72 ± 1.28 IU/ml. The mean difference was statistically highly significant at $P < 0.001$ as shown in table 2. The majority of cases with increased levels of serum anti-TPO antibodies were in the age group of 25–35 years and the duration of disease ranged from 3 months to 2 years. Out of 50 cases, 60% cases had significantly increased levels of serum anti-TPO antibodies.

The cases with increased levels of serum anti-TPO antibodies were associated with thyroid abnormalities and subclinical hypothyroidism was the most common thyroid abnormality found in our study.

Work done by Turktas *et al.*,^[10] Palma-Carlos *et al.*,^[11] and Kasumagic-Halilovic *et al.*,^[12] detected increased levels of anti-TPO antibodies in chronic urticaria patients. A retrospective longitudinal chart review study done by Amin *et al.*^[13] in chronic urticaria patients found that 28.3% of patients had high-levels of serum anti-TPO antibodies. In the present study, serum anti-TPO antibodies levels were significantly increased in cases when compared to controls, thus correlating with above studies.

The statistical analysis of the obtained values showed that (as shown in table 2) mean \pm SD of serum T3 levels for cases was 1.18 ± 0.24 ng/ml and for controls was 1.26 ± 0.13 ng/ml and was significantly decreased in cases compared to controls and the mean \pm SD of serum T4 levels for cases was 7.64 ± 0.73 μ g/dl and for control was 8.57 ± 0.54 μ g/dl and was significantly decreased in chronic urticaria patients compared to healthy controls.

Among 50 chronic urticaria cases, one case had significantly decreased levels of serum T3 and T4 and 49 cases had serum T3 and T4 levels in within the normal limits but were nearer to the lower limit value. The statistical analysis of the obtained values showed that mean \pm SD for levels of serum TSH for cases was 5.55 ± 1.03 μ IU/ml and for controls was 2.86 ± 0.31 μ IU/ml as shown in table 2. Mean \pm SD of serum TSH levels was higher in cases than in controls and $P < 0.01$ which was statistically significant.

Table 1: Sample distribution according to the age group, n=100

Age group (years)	Group I (Cases) n=50		Group II (Controls) n=50		Total
	X	%	Y	%	
10–15 years	01	2	01	2	2
16–20 years	06	12	06	12	12
21–25 years	12	24	12	24	24
26–30 years	14	28	15	30	29
31–35 years	17	34	16	32	33
Total	50	100%	50	100%	100

X: Number of cases. Y: Number of controls. N: Total cohort

Table 2: Comparison of mean \pm SD of serum anti-TPO, T3, T4, and TSH between two Groups, n=100

Mean \pm SD	Group I (Cases) (n=50)	Group II (Controls) (n=50)	P-value
Serum anti-TPO (IU/ml)	43.10 \pm 7.78 IU/ml	13.72 \pm 1.28 IU/ml	<0.001
Serum T3 (ng/ml)	1.18 \pm 0.24	1.26 \pm 0.13	<0.01
Serum T4 (μ g/dl)	7.64 \pm 0.73	8.57 \pm 0.54	<0.05
Serum TSH (μ IU/ml)	5.55 \pm 1.03	2.86 \pm 0.31	<0.001

TPO: Thyroid peroxidase, TSH: Thyroid-stimulating hormone

Table 3: Distribution of euthyroid, subclinical hypothyroid, and clinical hypothyroid status in patient group

Thyroid status	No. of female	No. of male	%
Euthyroid	29	10	78
Subclinical hypothyroidism	7	3	20
Clinical hypothyroidism	1	0	2
Total	37	13	100

Among 50 chronic urticaria cases, 11(22%) cases had significantly increased levels of TSH and 39 (78%) cases had serum TSH levels in within the normal limits but were nearer to the upper limit value. As shown in the table 3, among 11 cases with thyroid abnormalities, one case had clinical hypothyroidism and 10 cases had subclinical hypothyroidism.

In a study done by Mallick *et al.*^[5] with 55 chronic urticaria cases, 45.5% patients had significantly increased levels of anti-TPO antibodies and 18.2% had hypothyroidism and our study results were consistent with above studies.

A case-control study performed by Diaz-Angulo *et al.*^[14] from Spain detected increased levels of serum anti-TPO antibodies in 20.4% of chronic urticaria patients with $P < 0.001$. They also reported that 14.9% patients were detected with thyroid dysfunction and the most common thyroid abnormality was subclinical hypothyroidism (5.8%). In consistent with this study, in our study, also the most common thyroid abnormality in cases was subclinical hypothyroidism.

These findings may provide stimulus to further investigate the relationship between anti-TPO antibodies and thyroid abnormalities in chronic urticaria patients and also help in finding the subclinical hypothyroidism in chronic urticaria cases with high anti-TPO antibodies as the available data regarding these in our county is less.

CONCLUSION

This study revealed a significant association between chronic urticaria and serum anti-TPO antibodies. Serum anti-TPO antibodies and serum TSH levels were significantly increased and serum T3 and serum T4 levels were significantly decreased in chronic urticaria patients as compared to controls.

As the anti-TPO antibodies show slow cytotoxic progression, the most of the cases present as subclinical hypothyroidism and later on they progress to clinical hypothyroidism if left untreated. Hence, early detection of anti-TPO antibodies and thyroid dysfunction and periodic follow-up with proper management may help in better control of urticaria and prevent patients from going into disease related complications. This would help to improve the quality of life of the patients.

Hence, it is beneficial to consider testing for serum anti-TPO antibodies along with the primary thyroid markers serum T3, T4, and TSH to prevent long-term morbidity in chronic urticaria.

Limitations of the Study

Small sample size, follow-up, and response of the patient to the treatment were not taken into account.

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