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Original Article

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Status of Antibody Positivity and Antibody Titre after Six Weeks of Treatment with Levothyroxine in Primary Hypothyroid Patients

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Abstract

Background: Thyroglobulin antibody and thyroid peroxidase autoantibodies appear to be a secondary response to thyroid injury and are not thought to cause primary hypothyroidism themselves, although they may contribute to its development and chronicity. Anti-TPO-Ab, in particular, correlates well with thyroidal damage and lymphocytic infiltration. It is assumed that in Autoimmune Thyroid Disease (AITD), the injury process is persistently progressing unlike the NAITD group. There may be a difference of manifestation and response to treatment between the two goups. This part is not well estimated as yet and no definitive guideline about antibody status is as yet established.

Methods: A prospective observational study included 99 primary hypothyroid patients, newly diagnosed on the basis of clinical suspicion and biochemical confirmation. The patients were 18-60 years of age and included both sexes. Both the Anti-TPO Antibody and the anti-TG antibody were measured before initiation and after six weeks of levothyroxine treatment.

Results: 73 of the 93 patients who came at follow-up after 6 weeks were found anti-TPO (alone or along with anti-TG antibody) positive initially. After 6 weeks of treatment with levothyroxine, 70 (97.2%) of them remain anti-TPO antibody positive while 2 (2.8%) became anti-TPO antibody negative with p value of getting anti-TPO antibody negativity remaining non-significant (P=1.00). In case of anti-TG antibody, 55 of the 93 patients were positive before replacement (either alone or together with anti-TPO antibody). 49 (89.1%) of them remain positive after 6 weeks of treatment while 6 (10.9%) of the patients got anti-TG antibody negative with non significant p value (P=0.508). 77 of the patients were positive for either or both of the antibodies initially. All of them (100%) remain positive for either or for both of the antibodies after 6 weeks of treatment. Of the 16 patients who were antibody negative initially for both the antibodies, 3 (18.8%) got positive for at least one of the antibodies, while the other 13 (81.3%) remained negative for both the antibodies with insignificant p value(P=0.250). The median for anti-TPO antibody titre before

treatment was 659 with interquartile range between 106-1000, with post treatment median titre declining to 446 and interquartile range being between 73-1000 with p value being significant ($p<0.001$) for both the median titre and the interquartile range. The median of anti-TG antibody titre was 77 and the interquartile range was between 20-381 before initiation of treatment while the median of the titre was 52 and the interquartile range was between 20-238 after 6 weeks of levothyroxine replacement, both being statistically significant ($p<0.001$) as revealed by Wilcoxon matched pair signed rank test.

Conclusion: Though levothyroxine treatment in patients with antibody positive primary hypothyroid patients reduced the antibody titre significantly, there is no significant impact of treatment upon antibody positivity.

Keywords: Anti-TPO Ab, Anti-TG Ab, Primary hypothyro idism, Levothyroxine replacement.

Introduction

Thyroid diseases are classified on the basis of presence of antithyroid antibodies into two groups: autoimmune thyroid disease (AITD) and non-autoimmune thyroid disease (NAITD). Reduced production of thyroid hormone is the cardinal feature of the clinical state called hypothyroidism[1]. Thyroglobulin antibody and thyroid peroxidase autoantibodies are considered to be a secondary response to thyroid injury. Though they are not thought to cause disease themselves, but they may contribute to its progression and chronicity. Anti-TPO antibody may be involved in antigen presentation, thus activating thyroid-specific T cells[2]. The other anti-Tg antibody may have complement-fixing cytotoxic activity. If the morphological aspects of abnormalities are kept aside, functional state alteration also may vary on the basis of autoimmune state of the disease, especially in regards to magnitude of functional decline and possibility of reversal towards normality. This part of the disease is not widely studied and yet poorly understood. Therefore, it is very rationale to see and compare these aspects for the benefit of the long term management of hypothyroidism. In a study by Hasanat M A et al in 2000 regarding the antithyroid antibody status of thyroid disorders in Bangladesh, positive antithyroid antibodies (anti TPO-Ab and anti-Tg-Ab) were frequently associated with patients with multinodular and diffuse goitre (43% and 36% respectively), hyperthyroid (37%) as well as hypothyroid (55%) patients[3]. It is to be mentioned that in some instances anti-TPO-Ab and anti-Tg-Ab may be triggered but do not persist for longer time and finally would not cause any alteration of functional status. Sub-acute thyroiditis is a good example of such condition. The best way to test thyroid function is to measure the thyroid stimulating hormone (TSH) and FT4 level in blood sample. TSH secretion is prettily sensitive to changes in serum free T4, and abnormal TSH levels occur before free T4 abnormalities are detectable during developing hypothyroidism and hyperthyroidism[4]. Levothyroxine is the main stay of treatment of hypothyroidism. As lean body mass is the best predictor of daily requirements, so ideal body weight is best used for clinical dose calculations[5]. The typical replacement dose of levothyroxine is approximately 1.6 to 1.8 µg per kg of ideal body weight per day[6]. If the patient with primary hypothyroidism is not having any known cardiac disease or symptom, a full starting dose of levothyroxine is safe and may be more convenient and cost-effective than a low starting dose regimen[7]. Thyroxine has a 7-day half life and approximately 6 weeks is required before there is complete equilibration of the FT4 and biologic effects of levothyroxine. So measuring Anti-TPO and anti-Tg antibody at 6 weeks after starting treatment is likely to reflect the antibody status in a biochemically euthyroid patient. In the present protocol, assessment of response to anti-TPO antibody and anti-TG antibody positivity status and to their titres were done at 6 weeks interval after initiation of thyroxine.

Materials And Methods

This study was carried out from May 2014 to April 2015 at the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The research protocol approval was taken from the Institutional Review Board (IRB) of the university. 99 newly diagnosed primary hypothyroid patients of both sexes aging 18-60 years were enrolled in the study. Biochemical confirmation for primary hypothyroid was done by measuring serum TSH (<0.8 ng/dL) and FT4 (>5.50 mIU/L) levels according to the laboratory's respective reference range. Patients beyond 18

to 60 years range, patients with other chronic or acute illnesses, with history of neck irradiation and thyroid surgery, patients who were receiving iodine containing drugs such as lithium and amiodarone, or already receiving treatment for hypothyroidism and who were pregnant & breastfeeding their babies were excluded from the study. Prior to enrollment, written informed consent was taken from each and every subject after complete explanation of the study. Structured Case Report Form (CRF) was filled-up after interviewing each patient and demographic data were recorded among others. Before starting replacement, blood samples were analyzed for anti-thyroid antibodies (Anti-TPO-Ab, Anti-Tg-Ab) using the chemiluminescent sequential immunometric assay with the IMMULITE 2000 system analyzers following manufacturer's instruction and the results were recorded in the Case Report Form (CRF). The cut-off for antibody positivity was ≥ 40 IU/ml for anti-TPO and ≥ 35 IU/ml for anti-Tg antibody according to the reference range of the specified laboratory. A standard dose of 1.6-1.8 µg/kg body weight/day of levothyroxine was prescribed based on measured ideal body weight and the patient was advised to take it one hour before breakfast, in empty stomach. The dose was approximated to the next half of a 25 microgram tablet for the convenience of the patient. The patients were followed up after 6±1 weeks and serum TSH, FT4 and anti-TPO and anti-Tg antibodies were measured from the same reference laboratory using the same procedure. 6 patients were excluded from the study either due to lack of or inappropriate follow-up. Information and records were kept maintaining anonymosity and confidentiality.

Results

72 of the 93 patients were found anti-TPO (alone or along with anti-TG antibody) positive initially. After 6 weeks of treatment with levothyroxine, 70 (97.2%) of them remain anti-TPO antibody positive while 2 (2.8%) became anti-TPO antibody negative (table 1) with p value (by McNemar test) of getting anti-TPO antibody negativity remaining non-significant (P=1.00).

Table 1: Anti-TPO antibody status before and after treatment (N=93)

Anti-TPO status		Before treatment		
		Normal	Raised	Total
After treatment	Normal	18 (85.7%)	2 (2.8%)	20 (21.5%)
	Raised	3 (14.3%)	70 (97.2%)	73 (78.5%)
Total		21 (100.0%)	72 (100.0%)	93 (100.0%)

P=1.00 by McNemar test (Within parentheses are percentages over column total)

In case of anti-TG antibody, 55 of the 93 patients were positive before treatment (either alone or together with anti-TPO antibody). 49 (89.1%) of them remain positive after 6 weeks of treatment while 6 (10.9%) of the patients got anti-TG antibody negative with non significant p value (P=0.508).

Table 2: Anti-TG antibody status before and after treatment (N=93)

Anti-TG status		Before treatment		
		Normal	Raised	Total
After treatment	Normal	35 (92.1%)	6 (10.9%)	41 (44.1%)
	Raised	3 (7.9%)	49 (89.1%)	52 (55.9%)
Total		38 (100.0%)	55 (100.0%)	93 (100.0%)

P=0.508 by McNemar test. (Within parentheses are percentages over column total)

Considering both the anti-TPO and anti-TG antibody together, 77 of the patients were positive for either or both of the antibodies. Of them, all (100%) remain positive for either or both of the antibodies after 6 weeks of treatment. Of the 16 patients who were antibody negative for both the antibodies, 3 (18.8%) got positive for at least one of the antibodies, while the other 13 (81.3%) remain negative for both the antibodies (table 3). P value is not significant (P=0.250)

Table 3: Combined antibody status before and after treatment (N=93)

Combined antibody status		Before treatment		
		Both Negative	Positive (any one or both)	Total
After treatment	Both Negative	13 (81.3%)	0 (0.0%)	13 (14.0%)
	Positive (any one or both)	3 (18.8%)	77 (100.0%)	80 (86.0%)
Total		16 (100.0%)	77 (100.0%)	93 (100.0%)

P=0.250 by McNemar test (Within parentheses are percentages over column total)

As far as the antibody titre is concerned, the median for anti-TPO antibody titre before treatment was 659 with interquartile range between 106-1000, with after treatment median titre declining to 446 and interquartile range being between 73-1000 with p value being significant (p<0.001) for both the median titre and the interquartile range. The

median of anti-TG antibody titre was 77 and the interquartile range was between 20-381 before initiation of treatment while the median of the titre was 52 and the interquartile range was between 20-238 after 6 weeks of levothyroxine treatment, both being statistically significant ($p<0.001$) as revealed by Wilcoxon matched pair signed rank test (table-4)

Table 4: Anti-TPO and anti-TG antibody titre before and after treatment (N=93)

Antibody	Antibody titre (median and interquartile range)		P-value*
	Before treatment	After treatment	
Anti-TPO	659 (106-1000)	446 (73-1000)	<0.001
Anti-TG	77 (20-381)	52 (20-238)	<0.001

*by Wilcoxon matched pair signed rank test (Within parentheses are interquartile ranges

Discussion

After 6 weeks of treatment, though many of the patients are likely to improve both clinically and biochemically as found in many other studies, but in this study, none of the anti-TPO or anti-TG antibody showed significant negativity. There was no significant negativity even when the anti-TPO and anti-TG antibodies were considered together. Moreover, 18.8% of the 16 patients who were negative for both the antibodies, became positive for at least one of the antibodies after 6 weeks of treatment, which implies that levothyroxine treatment couldn't prevent the development of antibody positivity in some of the patients. On the other hand, antibody titer reduced significantly for both the antibodies following treatment. As anti-thyroid antibodies are thought to contribute to the chronicity of primary hypothyroidism, it will be very interesting to know whether with continued treatment, the autoimmune hypothyroid patients get a cure or at least, the dose of levothyroxine decrease matching with the reduction of antibody titer. With the findings of the study, the importance of the conventionally used cut-off for positive and negative antibody status becomes diluted and exercise of mentioning the titer of the antibody is likely to become a part of good laboratory practice. The findings of the present study also create a scope of future long term studies to know more about the impact of thyroid auto-antibodies on the development of primary hypothyroidism and its probable cure.

Conclusion

Though levothyroxine treatment in patients with antibody positive primary hypothyroid patients reduced the antibody titre significantly after 6 weeks, there was no significant impact of treatment upon antibody positivity. But with such short time follow-up of 6 weeks it is not possible to evaluate the probable relation of lower antibody titre to functional improvement and possibility of reversal towards normality, if any. So a similar prospective study with the long term follow-up should be conducted to explore and resolve the issues relating to antibody titre, functional improvement of thyroid glands and reversal towards normality.

Conflict of Interest: None.

Source of Fund: Nil.

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