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Relationship Between Thyroid Autoimmunity Status and Levothyroxine Dose in Hypothyroid Patients with or without Type 2 DM

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Abstract

Background:
Hypothyroidism is the most common thyroid problem in Bangladesh and worldwide. Autoimmune thyroid disease is the most common cause of hypothyroidism. Levothyroxine (LT4) dose requirements vary among patients and may be influenced by thyroid autoantibody status and metabolic comorbidities such as type 2 diabetes mellitus (T2DM) to achieve euthyroidism.

Objective:
To assess the relationship between thyroid autoantibody status and levothyroxine dose requirements in hypothyroid patients with or without T2DM.

Methods:
This cross-sectional study was conducted at the Department of Biochemistry, BIRDEM General Hospital, from July 2024 to June 2025 on 100 patients with hypothyroidism recruited from outpatient department of endocrinology, BIRDEM, Dhaka, and divided into two groups: Group 1 (Hypothyroid patients with T2DM, n=50) and Group 2 (Hypothyroid patients without T2DM, n=50). Data on demographic, physical, biochemical variables and dose of levothyroxine were collected. Thyroid peroxidase (TPO) antibody, thyroglobulin (Tg) antibody, TSH and HbA1c were measured. Statistical analysis was performed using SPSS version 29.0.

Results:
Among 100 patients with hypothyroidism, mean age was 49.66±11.19 years in Group 1 and 45.84±14.4 years in Group 2. TPO antibody positivity was significantly lower in hypothyroid patients with T2DM (36%) compared to those without T2DM (66%) (p=0.003).The mean levothyroxine dose was substantially higher among anti-TPO positive patients than anti-TPO negative patients (67.6±28.0 µg vs. 40.6±17.8 µg, p<0.001), with a similar pattern observed for anti-Tg positivity (74.1±32.3 µg vs. 46.7±20.3 µg, p<0.001).

Conclusion:
Thyroid autoantibody positivity is strongly associated with higher levothyroxine dose requirements in hypothyroid patients, irrespective of diabetes status. Recognition of thyroid autoimmunity is essential for individualized dose optimization.

Keywords: Hypothyroidism, Levothyroxine, Thyroid autoantibody, Type 2 diabetes mellitus.

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Introduction:

Hypothyroidism is a common endocrine disorder characterized by insufficient thyroid hormone production, leading to metabolic and systemic disturbances, most frequently caused by autoimmune thyroiditis.[1] Levothyroxine (LT4) remains the standard treatment, aimed at restoring euthyroidism with dosing traditionally based on body weight, age, and residual thyroid function. However, many patients require dose adjustments despite apparently adequate initial dosing.[2] Thyroid autoantibodies, particularly anti-thyroid peroxidase (anti-TPO) and anti- thyroglobulin (anti-Tg) antibodies, reflect ongoing autoimmune

destruction of thyroid tissue.[3] Persistent autoimmune activity may influence endogenous hormone production and peripheral thyroid hormone metabolism, potentially affecting LT4 requirements.[4] Type 2 diabetes mellitus (T2DM) commonly coexists with hypothyroidism, raising challenges for clinical care.[5] Insulin resistance, chronic inflammation, altered gastrointestinal absorption, and poly pharmacy in T2DM may further modify levothyroxine pharmacokinetics and pharmacodynamics.[6,7] Type 2 diabetes mellitus (T2DM) is frequently associated with hypothyroidism, and altered thyroid hormone metabolism in diabetics may further affect levothyroxine dosing.[6] The higher LT4 dose requirement in autoimmune hypothyroidism can be explained by progressive lymphocytic infiltration and destruction of thyroid follicular cells, leading to diminished endogenous hormone production and reduced thyroid reserve.[8,9] Anti-TPO antibodies, in particular, are known to mediate antibody-dependent cytotoxicity and complement activation, accelerating thyroid tissue damage.[10] Consequently, patients with higher antibody titers often experience a more severe and persistent form of hypothyroidism, necessitating higher replacement doses to maintain euthyroidism. Data on the combined impact of thyroid autoimmunity and T2DM on LT4 dose requirement are limited, particularly in Bangladesh. This study aimed to explore the relationship between thyroid autoantibody status and levothyroxine dose requirement in hypothyroid patients and to assess whether the presence of T2DM modifies this relationship.

Methods:

A cross-sectional study carried out in the Department of Endocrinology at BIRDEM general hospital, Dhaka from July 2024 to June 2025. Ethical clearance was obtained from Institutional Review Board of BIRDEM General hospital before starting the study. Informed written consent was taken from each eligible person. Adult patients (≥25 years) with hypothyroidism receiving stable LT4 therapy for at least 3 months, having recent thyroid function tests and available thyroid autoantibody profile (anti-TPO and/or anti-Tg) were included. Any other thyroid disorder including thyroid surgery, radioactive iodine ablation, thyroid cancer, hyperthyroidism etc., any type of acute and chronic illness like ESRD, COPD, CVD, IHD etc., Type 1 diabetic patients, pregnancy and lactation, malignancy, use of drugs interfering with LT4 absorption (e.g., cholestyramine, rifampicin) unless dose stable were excluded. The demographic data of the patients include age, gender, weight, height, blood pressure, body mass index (BMI), waist-hip circumference (WHC) were recorded. The disease duration, smoking status and drug usage affecting levothyroxine absorption like proton pump inhibitors (PPI) were noted. All patients were receiving levothyroxine sodium tablets. The patients were on a standard fixed dose. After 8 to 10 hours overnight fasting blood sample were collected. Completion of sample collection, serum TSH and FT_4 levels was estimated at Hormone Laboratory and thyroid antibody (Anti TPO antibody and Anti Tg antibody) levels was estimated at Immunology Laboratory of BIRDEM General Hospital. TSH ,TPOAb and TgAb levels were measured by the same assay using the chemiluminescent microparticle immunoassay (CMIA) method. The serum TSH level for a euthyroid state was between 0.47-5.01μIU/L. The level of TPOAb was <60 U/mL and TgAb<4.5 IU/ml respectively. Values above these levels were considered positive for antibodies. All the results were compiled, and then statistical analysis was performed with the help of SPSS 29.0 version. Descriptive statistics were presented as Mean±SD, median and frequency (%). Group comparisons were performed using Chi-square test or Fisher exact test for categorical variables and Mann–Whitney U test for continuous variables. Correlations between thyroid autoantibodies and levothyroxine dose were analyzed using Spearman's rank correlation coefficient. A p-value <0.05 was considered statistically significant.

Results:

Among 100 hypothyroid patients, 50 had coexisting type 2 diabetes mellitus (Group 1) and 50 had hypothyroidism without T2DM (Group 2). The mean age of hypothyroid patients with T2DM was 49.66±11.19 years, while those without T2DM averaged 45.84±14.4 years. BMI was higher in the T2DM group (27.77±4.65 kg/m^2) compared to the non-T2DM group (26.04±3.78 kg/m^2), though this difference was not significant. There were no significant differences between the groups in terms of mean age, BMI or waist-hip ratio. Female patients predominated in both groups, and gender distribution was comparable (Table-I).

Anti-TPO antibody positivity was significantly higher in Group 2 compared to Group 1(66% vs 36%, p=0.003). Although anti-thyroglobulin antibody positivity was also more frequent in Group 2(36% vs 20%), this difference did not reach statistical significance (p=0.075) (Table-II).

Mean serum TSH and free T4 levels were comparable between the two groups (p >0.05). As expected, fasting blood glucose and HbA1c levels were significantly higher in Group 1 than in Group 2(p<0.001 for both).No significant correlations were observed between anti-TPO or anti-Tg antibody levels and glycemic or thyroid function parameters in patients with T2DM. In patients without T2DM, anti-Tg antibody showed a weak positive correlation with TSH (r=0.199, p=0.048). Patients with positive anti-TPO antibodies required significantly higher doses of levothyroxine compared to antibody-negative patients (67.6±28.0 µg vs 40.6±17.8 µg, p<0.001). Similarly, anti-Tg- positive patients required higher doses than anti-Tg-negative patients (74.1±32.3 µg vs 46.7±20.3 µg, p<0.001). Patients with overall positive thyroid autoimmunity status also required significantly higher levothyroxine doses than those without autoimmunity (66.5±28.1 µg vs 40.7±18.0 µg, p<0.001) (Table-III).

Table-I: Comparison of demographic variables among study subjects (N=100)

Variables	Group-1 (n=50) Mean±SD no. (%)	Group-2 (n=50) Mean±SD no. (%)	p-value
Age (years)	49.66±11.19	45.84±14.4	0.064[a]
BMI (kg/m)	27.77±4.65	26.04±3.78	0.071[a]
Waist-Hip Ratio	0.86±0.027	0.86±0.025	0.735[a]
Gender			
Female	45(90)	44(88)	0.749[b]
Male	5(10)	6(12)	

Values are expressed as Mean±SD, Frequency (%) shows within parenthesis.
[a]Mann-Whitney U test, [b]Chi-square test. p-value is significant <0.05.

Table-II: Comparison of thyroid autoantibodies among study population (N=100)

Variables	Group-1 (n=50) no.(%)	Group-2 (n=50) no. (%)	p-value*
Thyroid peroxidase (TPO) antibody			
Positive	18(36)	33(66)	0.003
Negative	32(64)	17(34)	
Thyroglobulin (Tg) antibody			
Positive	10(20)	18(36)	0.075
Negative	40(80)	32(64)	

Values are expressed as Frequency (%) shows within parenthesis.
*p-values are obtained by Chi-square test. p-value is significant <0.05.

Table-III: Dose of thyroxin by antibody and autoimmunity status of study population (N=100)

Variables	Category	Dose of Thyroxin (µgm) (Mean±SD)	Median (µg)	p-value*
Anti-TPO	Negative	40.6±17.8	50.0	<0.001
	Positive	67.6±28.0	50.0	
Anti-Tg	Negative	46.7±20.3	50.0	<0.001
	Positive	74.1±32.3	75.0	
Thyroid Autoimmunity Status	Negative	40.7±18.0	50.0	<0.001
	Positive	66.5±28.1	50.0	

Values are expressed as Mean±SD, Median.
*Mann-Whitney U test. p-value is significant <0.05.

Discussion:

In this study, the mean age of hypothyroid patients with T2DM was 49.66±11.19 years, while those without T2DM averaged 45.84±14.4 years, with no statistically significant difference (p=0.064). BMI was higher in the T2DM group (27.77±4.65 kg/m^2) compared to the non-T2DM group (26.04±3.78 kg/m^2), though this difference was not significant. A case-control study of 302 T2DM patients and 310 non-diabetic controls, observing no significant age differences but a notable difference in BMI, which contrasts with the current study.[11] The waist-hip ratio in this study showed no intergroup differences, another study found central obesity more frequent in diabetics.[11] Gender distribution was similar between the groups (female 90% vs. 88%, p=0.749), consistent with other study, who reported no significant gender differences (58.9% vs. 58.4%, p=0.95).[11]

The present study found that the prevalence of TPO antibody positivity was significantly lower in hypothyroid patients with T2DM (36%) than in those without T2DM (66%) (p=0.003). Thyroglobulin antibody (Anti-Tg) positivity was higher in non-diabetic hypothyroid patients (36%) compared to T2DM patients (20%), but this difference was not statistically significant. This finding suggests that chronic hyperglycemia and insulin resistance in T2DM may modulate immune activity, resulting in attenuated thyroid autoimmunity.[12,13] Similar studies indicate that while hypothyroidism is common in T2DM, thyroid autoantibody expression may vary.[13,14] These findings align with reports that autoimmune markers, particularly TPO Ab, serve as reliable indicators of thyroid autoimmunity, but their prevalence may be attenuated in diabetic populations due to immune dysregulation.[5] The higher autoimmune positivity in non-diabetic hypothyroid patients highlights the importance of screening for thyroid autoantibodies, particularly in this group. Another study reported that 23.3% of T2DM patients with hypothyroidism were positive for thyroid autoantibodies.[15] Only a few studies have explored thyroid autoimmunity in hypothyroid patients with or without T2DM.

This study demonstrates a significant association between thyroid autoantibody positivity and increased levothyroxine dose requirements in hypothyroid patients. Patients with positive anti-TPO, anti-Tg, or overall thyroid autoimmunity required substantially higher doses of levothyroxine compared to antibody negative patients. These findings highlight the clinical importance of autoimmune status when managing hypothyroidism. Autoimmune thyroiditis leads to progressive destruction of thyroid tissue, resulting in diminished endogenous hormone production. Persistent autoimmune activity, reflected by the presence of thyroid autoantibodies, may explain the increased reliance on exogenous levothyroxine.[16]

In this study, the mean levothyroxine dose was substantially higher among anti-TPO positive patients than anti-TPO negative patients (67.6±28.0 µg vs. 40.6±17.8 µg, p<0.001), with a similar pattern observed for anti-Tg positivity (74.1±32.3 µg vs. 46.7±20.3 µg, p<0.001). Furthermore, patients classified as having positive thyroid autoimmunity (both antibody) required significantly higher LT4 doses than those without autoimmune thyroid disease (66.5±28.1 µg vs. 40.7 ±18.0 µg, p<0.001). These results strongly suggest that the autoimmune process itself, rather than thyroid hormone levels alone, influences levothyroxine requirements.

A previous study done in Turkey of about 303 patients (273 females and 30 males with the mean [SD] age of 46.6 [13.2] years), and had found antibody-positive group (n=210) average daily levothyroxine dose was significantly higher than in the antibody-negative group (n=93) (mean of 78.8 [36.7] vs 64.2 [27.1] mg/day, P=.001, respectively). There was a low but significant positive relationship between the TPOAb (r=0.217, P<.01) and TgAb levels (r=0.158, P<.05) and levothyroxine doses in the antibody-positive group.[17]

Although thyroid autoimmunity was significantly more prevalent among hypothyroid patients without T2DM in this study, the relationship between antibody positivity and levothyroxine dose remained consistent across the entire study population. This suggests that diabetes status does not substantially modify the impact of thyroid autoimmunity on LT4 requirements. Notably, serum TSH and FT4 levels did not differ significantly between antibody-positive and antibody-negative groups, indicating that higher LT4 doses were required to achieve comparable biochemical control in autoimmune hypothyroidism.

From a clinical perspective, these findings highlight the importance of assessing thyroid

autoimmunity at the time of diagnosis of hypothyroidism. Identification of anti-TPO and anti-Tg antibodies may help clinicians anticipate higher levothyroxine dose requirements, closer monitoring, and more frequent dose adjustments. This is particularly relevant in resource-limited settings, where delayed achievement of euthyroidism can contribute to persistent symptoms and increased cardiovascular risk.

In summary, the study provides robust evidence that thyroid autoimmunity is a key determinant of levothyroxine dose requirement in hypothyroid patients. Positive thyroid autoantibodies and autoimmune thyroid status are associated with significantly higher LT4 doses, independent of T2DM status. Incorporating thyroid autoantibody testing into routine evaluation may facilitate more individualized and effective management of hypothyroidism.

Limitations:

This study has some limitations. All the patients were already under LT4 replacement therapy. Our study has fewer sample and hence cannot be generalized. Cross-sectional design limits causal inference.Single-center study may reduce generalizability. Lack of longitudinal follow-up for dose adjustments.

Conclusion:

Thyroid autoimmunity and T2DM independently contribute to higher levothyroxine requirements in hypothyroid patients. Individualized dosing strategies considering these factors may optimize treatment outcomes. The findings of this study suggest that clinicians should consider both autoimmunity status and comorbid diabetes when titrating levothyroxine in Bangladeshi patients. Personalized dosing may improve symptom control and reduce the risk of under- or over treatment.

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