

The Prevalence of Thyroid Dysfunction and Thyroid Autoantibodies Among Type 2 diabetic Patients in Nnewi, South Eastern Nigeria

Authors

Hope I. Nwokolo¹, Samuel C. Meludu^{2;3}, Chudi E. Dioka³, Christian E. Onah*

Florence O. Ikemefuna⁴, Obiageli B. Onyema-Ilo⁵.

^{1,4,5}Department of Chemical Pathology, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria.

²Department of Human Biochemistry, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University, Nnewi campus, Anambra State, Nigeria.

³Department of Chemical Pathology, Faculty of Medicine, Nnamdi Azikiwe University, Nnewi campus, Anambra State, Nigeria.

***Corresponding Author**

Onah Christian Ejike

Department of Chemical Pathology

Nnamdi Azikiwe University Teaching Hospital, Nnewi.

Email id: onamecwwide@yahoo.com

Abstract

Background: This study was carried out to determine the prevalence of anti-thyroid antibodies and Thyroid dysfunction (TD) among Type 2 Diabetic (T2DM) patients in our environment. **Methods:** The study comprises one hundred (100) known type 2 diabetic subjects attending out-patients diabetic clinics of Nnamdi Azikiwe University Teaching Hospital, Nnewi and one hundred (100) control subjects. Anti-thyroid peroxidase antibody (Anti-TPO Ab), Anti-thyroglobulin antibody (Anti-Tg Ab), Thyroid stimulating hormone (TSH), Total thyroxine (T4), Total triiodothyronine (T3), Free thyroxine (FT4), Free triiodothyronine (FT3), and Fasting plasma glucose (FPG) were assayed using standard methods. Age and body mass index (BMI) were also determined. **Results:** The comparison of the mean levels of BMI, T3, FT3, and FPG in T2DM and control subjects showed significant difference (0.02, <0.001, 0.03, and <0.001) respectively. However, there was no significant difference in the mean levels of Age, T4, FT4, and TSH in T2DM and control subjects ($p > 0.05$). The prevalence rate of TD was 16% in T2DM and 4% in control subjects. Female subjects had higher prevalence of TD than male in both T2DM (13%, 3%) and controls (3%, 1%) respectively. The prevalence of anti-TPO Ab positivity in T2DM and control subjects was 10% and 1% respectively, while that of anti-Tg Ab positivity was 48% and 2% respectively. **Conclusion:** This study reveals the association between autoimmune TD and T2DM with anti-Tg Ab being more associated with TD. We advocate at least an annual thyroid hormone screening of T2DM patients to detect asymptomatic TD, particularly those with positive anti-Tg Ab.

Key words: Anti-thyroid antibodies, Prevalence, Thyroid dysfunction, Type 2 diabetes mellitus.

INTRODUCTION

Diabetes affects over 150 million people worldwide and this number is expected to double by 2025,[1] 90% of whom are type 2.[2] The International Diabetes Federation (IDF) estimated in 2012 that 366 million adults, aged 20-79 years, of the world's 7 billion population have diabetes. This gives a comparative prevalence of 8.5%. In Africa, over 4.3% are estimated to have diabetes while 81.2% of Africans with diabetes are undiagnosed. This region has the highest mortality rate due to diabetes and it has been estimated that over the next 20 years, the number of people with diabetes in the region will almost double. According to the WHO standard, Nigeria has a comparative prevalence of 4.83% with over 88,681 Diabetes-related deaths.[3]

Diabetes mellitus and thyroid dysfunction have been reported to be the two most common endocrine disorders in clinical practice.[4] The association between diabetes mellitus and thyroid dysfunction was first studied by Papazafiropoulou et al.[5] This opened way for more studies in this area. Since then, several studies in different countries were conducted to estimate the prevalence of TD in diabetic patients. Several studies have shown that the prevalence of TD in T2D is greater than TD in general population.[6,-8] The prevalence of TD in general population varies, ranging from 6.6 to 13.4%.[8] In diabetic patients, the prevalence of TD is still higher and varies from 10 to 24%.[7,8] These differences can be explained by different diagnostic criteria of TD, the degree of iodine intake among different regions, different sensitivities of the TSH assays and the large population diversity.[9]

The diagnosis of thyroid dysfunction in diabetic patients based solely on clinical manifestations can be difficult because poor glycaemic control can produce features similar to hyperthyroidism such as weight loss, fatigue, and irritability.[10] On the other hand, severe diabetic nephropathy can be mistaken for hypothyroidism because patients with this condition may have edema, fatigue, pallor and weight gain.[11] Uncontrolled hyperglycemia with ketosis alters the thyroidal blood profile by lowering the levels of T4 and T3 while that of Reverse-T3 is elevated. No change is observed in plasma TSH, and FT4 index is normal.[12,13] Therefore, caution should be exercised in interpreting thyroid function

screening tests in uncontrolled ketotic hyperglycemia.

The presence of anti-thyroid peroxidase (TPOAb) and anti thyroglobulin (TgAb) antibodies are helpful in predicting the development of autoimmune thyroid disorders, especially hypothyroidism and hyperthyroidism. The prevalence of positive thyroid peroxidase (TPO) antibodies has been reported in about 80% of patients with type 1 diabetes and elevated TSH levels and between 10 and 20% in those diabetic patients having normal TSH levels.[14,15] The prevalence of subclinical thyroiditis, ascertained by an elevated TSH level or TPO titer is reported to vary between 5 to 6% in both T2D and non-diabetic subjects.[16,17]

The determination of the prevalence of subclinical and clinical thyroid disease in diabetic patients and its implications in the course of diabetes in our environment is very imperative. However, data concerning the prevalence of TD in T2D in Nnewi south eastern Nigeria is very scanty hence the significance of this work. This study seeks to determine the prevalence of anti-thyroid antibodies and thyroid dysfunctions among type 2 diabetic subjects attending out-patient diabetic clinics of Nnamdi Azikiwe University Teaching Hospital, Nnewi.

METHODS

Study Population and Design:

This is cross-sectional study. The study comprises 100 T2DM patients attending out-patients diabetic clinics of Nnamdi Azikiwe University Teaching Hospital, Nnewi and 100 non-diabetic controls who are staff of the hospital. The diabetic patients were randomly recruited regardless of their diabetic complications, diabetic medications, and duration of diabetes except those that are not up to 30 years of age, and have used insulin in their first year after diagnosis, and/or history of ketosis or ketonuria. Both T2DM patients and Control subjects that are under thyroid hormone therapy or under any therapy that affect thyroid hormone levels were excluded. The diagnosis of diabetes mellitus was made based on WHO criteria.[18] The non-diabetic controls were also assessed of FPG and out of 104 individuals recruited 4 persons were disqualified based on their FPG being above 7.0mmol/l.

Written informed consent for the study was obtained from all the participants and the study

protocol was approved by the ethics committee of the Nnamdi Azikiwe University Teaching Hospital, Nnewi. The demographic data were obtained such as age, gender, and BMI.

5 ml of blood sample were obtained after a 12 hour overnight fast for biochemical analysis such as FPG, Anti-TPO Ab, Anti-Tg Ab, T3, FT3, T4, FT4, and TSH. The FPG was assayed using glucose oxidase method (Randox kit, USA), while thyroid hormones and anti-thyroid antibodies were assayed using Enzyme linked immunosorbent assay method (Biocheck immunoassay kit, USA). The reference ranges for the major thyroid hormones and the positivity range for Anti-thyroid antibodies for this test method according to the manufacturer were:

TSH = 0.4 – 6.0 μ IU/ml

FT3 = 1.4 – 4.2 pg/ml

FT4 = 0.8 – 2.0 ng/dl.

Anti-TPO Ab = (<60 IU/ml)

Anti-Tg Ab = (<100 IU/ml)

Thyroid dysfunction was classified thus:

Clinical Hypothyroidism – when TSH level is greater than the upper limit of the reference range and FT4 is lower than the lower limit of the reference range.

Subclinical Hyperthyroidism – when TSH level is lower than the lower limit of the reference range and FT4 is within the reference range.

Subclinical Hypothyroidism – when TSH level is greater than the upper limit of the reference range and FT4 level is within the reference range.

Secondary Hypothyroidism – when both FT3 and FT4 levels are lower than the lower limit of their reference range and TSH level is within the reference range.

Statistical Analysis

Statistical analyses were performed using SPSS for windows, version 20 (Chicago, USA). Data are presented as mean \pm SD. Two independent samples were compared by student's t-test while qualitative variables were assessed using Pearson's Chi-Square test. Statistical significance was defined by a P-value < 0.05. Graphical presentation was done using SigmaPlot for window, version 12 (Systat software, USA).

RESULTS

The total number of subjects studied was 200, 100 T2DM patient comprising 63 females and 37 males with mean age of 57.43 \pm 11.59 years (range 26-76) and 100 non-diabetic controls comprising 61 females and 39 males with mean age of 55.85 \pm 11.97 (range 26-76). The comparison of the mean levels of BMI, T3, FT3, and FPG in T2DM and control subjects showed significant difference (0.02, <0.001, 0.03, and <0.001) respectively. However, there was no significant difference in the mean levels of Age, T4, FT4, and TSH in T2DM and control subjects ($p>0.05$) (Table 1).

A total of 16 (16%) T2DM subjects had a thyroid dysfunction while 4 (4%) of the non-diabetic control subjects had a thyroid dysfunction. Thyroid dysfunction was more prevalence in female subjects 13(20.6%) than in male 3(8.1%). Of all the categories of thyroid dysfunction, subclinical hyperthyroidism had the highest prevalence of 8(50%) with female also taken the lead. Secondary hypothyroidism had the second highest prevalence of 4(25%) with more female than male. Subclinical hypothyroidism had 3 female but no male while clinical hypothyroidism had 1 female but no male (Table 2).

The prevalence of anti-thyroid antibodies positivity (anti-TPO Ab and anti-Tg Ab) was higher in T2DM than in non-diabetic controls. 10 (10%) T2DM subjects had positive anti-TPO Ab while 1(1%) male non-diabetic control had positive anti-TPO Ab. Out of 10 T2DM that had positive anti-TPO Ab, 8 were female while 2 were male subjects. However, anti-Tg Ab had higher prevalence in both T2DM and non-diabetic control than anti-TPO Ab. 48 (48%) of T2DM subjects had positive anti-Tg Ab. 30 females had positive anti-Tg Ab while 18 males had positive anti-Tg Ab. In the control group, 1 male and 1 female had positive anti-Tg Ab (Figure 1).

Of all the 16 T2DM that had thyroid dysfunction, 2 had positive anti-TPO Ab while 14 had negative anti-TPO Ab. Also the positive cases of anti-TPO Ab in euthyroid T2DM subjects were 8 while 76 had negative anti-TPO Ab. However, 10 out of 16 thyroid dysfunction T2DM subjects had positive anti-Tg Ab while 38 out of 84 euthyroid T2DM had negative anti-Tg Ab. This showed that anti-Tg Ab is more associated with thyroid dysfunction than anti-TPO Ab (Figure 2).

Table 1: Comparison of Laboratory/demographic data in T2DM and Control subjects.

Parameters	T2DM N=100	Controls N=100	P-value
Age (year)	57.43±11.59	55.85±11.97	0.34
BMI (kg/m ²)	25.95±5.45	24.44±3.34	0.02
T3 (ng/ml)	1.55±0.49	1.21±0.31	<0.001
FT3 (pg/ml)	1.78±0.67	2.16±1.54	0.03
T4 (µg/dl)	9.12±2.35	9.69±2.28	0.08
FT4 (ng/dl)	1.10±0.33	1.15±0.32	0.39
TSH (µIU/ml)	1.66±0.54	1.41±0.79	0.34
FPG (mmol/l)	9.84±4.03	4.12±0.49	<0.001

Table 2: Thyroid function pattern in T2DM and control subjects

Thyroid Functions		T2DM N=100	Controls N=100	Total
Euthyroid	Male	34	38	72
	Female	50	58	108
	Total	84	96	180
Secondary Hypothyroidism	Male	1	-	1
	Female	3	-	3
	Total	4	-	4
Subclinical Hypothyroidism	Male	-	-	-
	Female	3	1	4
	Total	3	1	4
Clinical Hypothyroidism	Male	-	-	-
	Female	1	-	1
	Total	1	-	1
Subclinical Hyperthyroidism	Male	2	1	3
	Female	6	2	8
	Total	8	3	11
Total Thyroid Dysfunction	Male	3	1	4
	Female	13	3	16
	Total	16	4	20

Figure 1: Percentage positivity of anti-TPO Ab and anti-Tg Ab of male and female in T2DM and percentage positivity of anti-TPO Ab and anti-Tg Ab in T2DM and Control subjects.

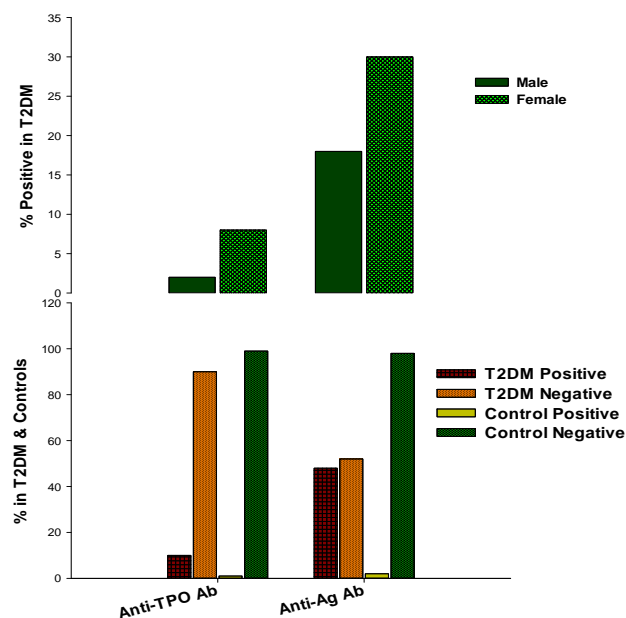
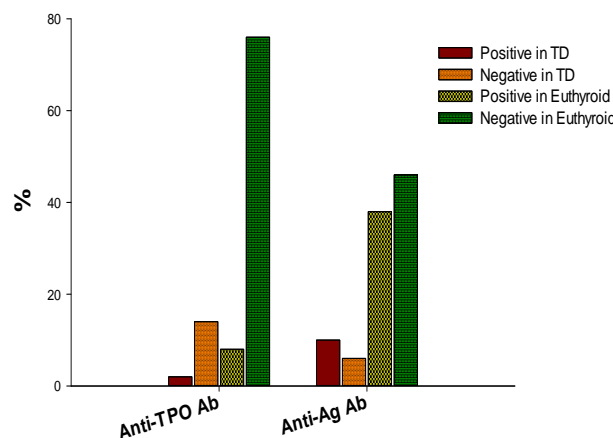


Figure 2: Percentage positivity of anti-TPO Ab and anti-Tg Ab in Thyroid dysfunction (TD) and Euthyroid subjects of T2DM.



DISCUSSION

Our study revealed a significant difference when compared the level of T3 and FT3 in T2DM and control subjects. This is not in line with the work of Udiong et al who observed no significant difference in the level of T3 in T2DM and controls.[19] This may be as a result of diabetic medication especially insulin. Insulin has been reported to enhance the levels of FT4 while it suppresses the levels of T3 by inhibiting hepatic conversion of T4 to T3.[20] The level of TSH in

this study was not statistically significant in T2DM than in controls. This is in line with the work of [19] but differed from other studies such as [21,22] that showed significant difference in the mean levels of TSH in T2DM and controls. The present study showed that in a sample of Nigerian diabetic patients the prevalence of thyroid dysfunction was 16%. This is consistent with the previous studies that showed an association between T2DM and thyroid

dysfunction though with some variations.[23]-[25] A study done by Akbar et al, reported a prevalence of 16% in Saudi T2DM patients.[23] Smithson et al. in their study revealed a prevalence of 10.8% of thyroid dysfunction in diabetic patients[24] while another study of 1,310 randomly selected diabetic patients by Perros et al showed a prevalence of thyroid dysfunction at 13.4%.[25] However, a study carried out by Ghazali and Abbiyesuku in south west Nigeria observed a higher prevalence of 29.7% in T2DM.[26]

This present study observed greater prevalence of TD in female than in male T2DM. This is in line with other previous studies.[25,26] Our study also showed 8% of hypothyroidism and 8% of hyperthyroidism in T2DM subjects. Out of 8 diabetic subjects that had hypothyroidism, 4 individuals had secondary hypothyroidism while 3 had subclinical hypothyroidism and 1 female had clinical hypothyroidism. These results showed that secondary hypothyroidism had the highest prevalence among hypothyroidism group. This is consistent with the work of Ghazali and Abbiyesuku, who reported higher prevalence of secondary hypothyroidism among T2DM in Nigeria.[26] The effect of diabetes on TRH and the negative effect of hyperglycaemia on T3 and absence of TSH response to TRH might cause secondary hypothyroidism.[27,28] Our results also showed that 7 out of 8 T2DM that had hypothyroidism were female showing that the prevalence of hypothyroidism is greater in female than in male subjects. All the T2DM subjects that had hyperthyroidism belong to subclinical hyperthyroidism group comprising 6 female and 2 male subjects.

The study result showed high prevalence of Anti-TPO Ab (10%) and Anti-Tg Ab (48%) positivity in T2DM than in control subjects (1% and 2%) respectively. This is consistent with several other studies that reported higher autoimmunity in T2DM than in control subjects though with varying results.[6,23],[29]-[31] Akbar et al who studied the same population size like ours (100 T2DM and 100 controls) detected 10% of autoimmunity in T2DM and 5% in controls.[23] Some studies could not find any differences in autoimmunity between T2DM and control subjects. For example, Ortega-Gonzalez in his study showed that the frequency of TPO Ab was similar in T2DM and control subjects.[32] The

variations in the results of the prevalence of autoimmunity in T2DM in many studies could be due to geographical/ethnic factors, large population diversity and possibly laboratory assay methods.

Majority of the subjects (62.5%) that had TD were also positive for Anti-Tg Ab as against 12.5% for Anti-TPO Ab. This suggests that Anti-Tg Ab is more associated with TD than Anti-TPO Ab. This is not consistent with the work of Afkhami-Ardekani et al. who reported lower specificity of Anti-Tg Ab in TD diagnosis.[29] 76 out of 84 euthyroid T2DM subjects were negative for anti-TPO Ab while only 46 out of 84 euthyroid T2DM subjects were negative for Anti-Tg Ab. This shows that Anti-TPO Ab has lower specificity in thyroid dysfunction diagnosis.

CONCLUSION

This study reveals the association between autoimmune TD and T2DM with anti-Tg Ab being more associated with TD. We suggest at least an annual thyroid hormone screening of T2DM patients to detect asymptomatic TD, particularly those with positive anti-Tg Ab. Future research on this topic should involve HbA1c and other clinical/laboratory data such as duration of sickness, blood pressure and lipid profile in order to understand fully the role of TD in T2DM and the risks involve.

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