

Evaluation of thyroid hormones alterations in diabetic subjects: A correlational study

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Abstract

Objective: Diabetes and thyroid disorders have been shown to mutually influence each other. The reported association of thyroid disorders with diabetes mellitus raises the risk of higher prevalence of thyroid disorder in patients with diabetes mellitus especially the type 2 and hence the exacerbation of the condition diabetes and its related complications. We evaluated thyroid hormones levels (T3, T4, TS and FT4) in diabetic patients attending University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu State, Nigeria.

Methods: A total of 142 subjects were recruited for this cross sectional and correlational study. Eighty (80) diabetic test subjects and sixty (60) non-diabetic control subjects. Anthropometric indices height (m), weight (kg) and blood pressure (mmHg) and the body mass index (kg/m²) were measured for all subjects. Fasting blood glucose (FBG) was determined colorimetrically. The thyroid hormones: Thyroxine (T4), thyroid stimulating hormone (TSH), triiodothyronine (T3) and free thyroxine (FT4) were estimated using Enzyme linked Immunosorbent Assay (ELISA). Data obtained was analyzed using statistical package for social sciences (SPSS) version 25 and results expressed as mean and standard deviation.

Results: There was a significance increase $p < 0.05$ in FBG (8.68 ± 9.94 , 4.64 ± 0.56 mmol/L), BM1 (25.49 ± 1.38 ; 24.42 ± 0.5), SBP (144.50 ± 7.50 , 112.0 ± 6.05 mmHg), DBP (99.22 ± 6.49 , 72.43 ± 7.30 mmHg) respectively for diabetic and non-diabetic subjects. For the thyroid function test, only triiodothyronine (T3) and thyroid stimulating hormones (TSH) of the diabetic subjects showed a significant low values when compared with that of the non-diabetic subjects ($p < 0.05$). Thyroxine (T4) and free thyroxine (FT4) showed no significance ($p > 0.05$). T3 (nmol/L) (0.055 ± 0.18 ; 1.6 ± 0.43), TSH (mIU/L) (3.39 ± 2.24 ; 5.01 ± 2.29), T4 (ng/dl) (10.90 ± 2.02 ; 9.79 ± 0.96), FT4 (ng/dl) (0.71 ± 0.16 ; 0.66 ± 0.18) respectively for diabetic and non-diabetic subjects. The results were correlated and there was a positive correlation between T4 and FT4 ($r = 0.609$, $p = 0.000$), T4 and BMI ($r = 0.350$, $p = 0.027$), FT4 and DBP ($r = 0.314$, $P = 0.049$) and T3 and BMI ($r = 0.846$), $p = 0.000$).

Conclusion: There is significant variation in the thyroid functions among the diabetic subjects and hence the need for regular thyroid function checks for diabetic patients.

Keywords: Thyroid-Hormones; Diabetics; Blood pressure; Enugu-Nigeria

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1. Introduction

Diabetes mellitus (DM), a common metabolic disease with rapidly increasing prevalence is characterized by hyperglycaemia and the metabolic disturbances of carbohydrates, proteins and lipids which is principally caused by pancreatic B-cell dysfunction, hyperglucagonaemia and increased renal glucose reabsorption, criteria that bring about imbalance in glucose level in the plasma [1].

In 2014, 8.2% of adults aged 20-79years (387 million people) were living with diabetes according to the International Diabetes Federation's Data [2]. The World Health Organization (WHO) has projected that the global prevalence of diabetes will rise to 300 million (7.8%) by 2030 [3]. Factors such as sedentary lifestyle, dietary indiscretions, ethnicity, hypertension and obesity are thought to be major contributions to this epidemic [2, 4].

The first reports showing the association between diabetes and thyroid dysfunction were published in 1979 [5]. Various studies have shown a high prevalence of thyroid disorders in patients with type 2 diabetes and hypertension [6]. Diabetes and thyroid disorders have been shown to mutually influence each other and an association between both conditions has been reported in literature [7].

Thyroid hormones are essential for metabolism and energy homeostasis and participate in insulin action and glucose regulation [8]. In patients with DM, the nocturnal TSH peak is blunted or abolished; and the TSH response to TRH, from the hypothalamus, is impaired thus leading to hypothyroidism [9]. Low T3 levels have been observed in uncontrolled DM. This has been ascribed to the impairment in peripheral conversion of T4 to T3 which normalizes with improvement in glycaemic control [7]. Thyroid disorders such as subclinical hypothyroidism- a pathologic status defined as an elevated serum thyroid stimulation hormone (TSH) and low triiodothyronine (T3) syndrome are frequently observed in diabetic patients [10] and thus receiving increase concern in recent years. The possible reasons postulated for an association between diabetes mellitus and hypothyroidism could be genetic, biochemical or of hormonal origin [11]. Several reports have indicated a higher prevalence of thyroid disorders in diabetic patients with hypothyroidism being the most common disorder [12]. Hypothyroidism predisposes to hypoglycaemia and at the same time causes insulin resistance [13]. Subclinical hypothyroidism is characterised by normal free thyroxine (FT4) and increased thyrotropin (TSH) levels of which its prevalence increases with ageing ranging from 3 to 6% in individuals aged 60 years and above [9].

Thyroid functions investigation in most cases refers to follicular cell function including the measurement of secretions i.e. hormones of the gland and thyroid stimulating hormones, thyroxine and triiodothyronine [14]. Thyroid disease is a pathological state that can affect glycaemic control in diabetes adversely and also has the potential to affect the health.

Insulin and thyroid hormones are intimately involved in cellular metabolism and thus excess or deficit of either of these hormones result in the functional derangement of the other. The physiological and biochemical interrelationship between insulin and the influence of both insulin and iodothyronines on the metabolism of carbohydrates, proteins and lipids are recorded and thus indicates that iodothyronines are insulin antagonist with high levels being diabetogenic while absence of the hormone inhibits the development of diabetes [15]. Excessive thyroid hormones increases the rate of digestive tract absorption of glucose thereby increasing insulin resistance and degradation [16].

Insulin is an important hormone that carry out its action in some important sites such as skeletal muscles, liver and adipose tissue. Its action is mainly on the molecule glucose by promoting its facilitated diffusion from blood to skeletal muscles and adipose tissue after meals through the help of a glucose transporter known as GLUT 4 [2]. Carbohydrate and fat metabolism are interlinked; both synthesis and catabolism of fats depends on efficient glucose metabolism. Hence, any shift in the concentration of insulin affects the balance of glucose in the blood which will result in the disease called diabetes mellitus [2].

The reported association of thyroid disorders with diabetes mellitus raises the risk of higher prevalence of thyroid disorder in patients with diabetes mellitus especially the type 2 and hence the exacerbation of the condition diabetes and its related complications [16-17]. Screening for thyroid disorders in patients with diabetes mellitus can help in the early detection and better management of these disorders especially hypothyroidism. Hence, this study was conducted to determine the level of thyroid hormones in diabetic patients in the University of Nigeria Teaching Hospital Ituku-Ozalla, Enugu state and hopes to solve the problem of subclinical thyroid dysfunction in diabetic patients. Hence the need to incorporate thyroid hormone assay in routine checks of diabetic patients.

2. Materials and methods

2.1. Study Area

The prospective study was carried out in University of Nigeria Teaching Hospital (U.N.T.H.), Ituku-Ozalla, Enugu South-East Nigeria. The hospital is located 22 kilometers from Enugu capital along the Enugu-Port Harcourt expressway and covers an area of 200 acres and serves mainly the rural and urban areas of Enugu, as well as referrals from the neighboring local governments and States of Anambra, Abia, Ebonyi, Imo, Delta, Benue and Kogi.

2.2. Study Population and Design

2.2.1. Sample size

A structured questionnaire was used to get necessary data of the subjects that participated in the study. The study was a cross sectional study which involved about one hundred and forty individuals. Eighty were diabetic subjects who were recruited as test subjects and sixty non diabetic subjects recruited as control. The participants were recruited by simple random sampling technique once the inclusion criteria were met.

2.2.2. Subjects

The study was carried out on a total of one hundred and forty volunteers (Eighty test subjects and sixty control subjects) from University of Nigeria Teaching Hospital Ituku-Ozalla (UNTH) and Enugu metropolis between the age of 20 years and above. Informed consent was obtained from each participant.

2.2.3. Selection of the Study Group

The test group comprised of patients in endocrinology unit (Medical out Patients, MOP), at University of Nigeria Teaching Hospital, Ituku-Ozalla, who have been diagnosed of diabetes mellitus. Subjects that met with the inclusion criteria were shortlisted.

2.2.4. Selection of Control Group

The control group comprises sixty apparently healthy euthyroid individuals with no history of diabetes mellitus or hypertension and between the age of twenty years and above were selected based on free will. The individuals that met the inclusion criteria were shortlisted.

2.2.5. Inclusion Criteria

For diabetic patients

- Recent confirmation of increased blood sugar level.
- Exposure to diabetes for at least six months.

For non-diabetic patients.

- Must not have had any history of diabetes mellitus

Exclusion criteria

- A smoker. 2. An alcoholic. 3. Pregnant women

2.3. Method

2.3.1. Anthropometric Measurements

The following anthropometric data were measured: height, weight, and blood pressure. Standing height was measured to the nearest centimeter (cm) using a stadiometer with footwear removed. Weight was measured to the nearest kilogram (kg) with a manual Seca 761 scale (Vogel & Halke, Hamburg, Germany) after participants have removed outer garments, cell phone, and footwear. Body mass index (BMI) was calculated by weight in kilogram divided by height in meter square (kg/m^2). The readings of blood pressure (BP) and pulse rate were measured with an automated sphygmomanometer (OMRON HEM705CP, Omron Matsusaka Co, Matsusaka city, Mie-Ken, Japan) using appropriate cuff size after participants have sat undisturbed for at least 5 minutes then the average recorded for this study.

2.3.2. Blood collection and handling

Blood sample was collected from the volunteers by venipuncture using a sterile five millilitres needle and syringe. Two milliliters of blood was transferred into a fluoride oxalate bottle for glucose analysis and the rest transferred into a plain glass tube. Plain tube sample was allowed to clot and retract. The sample was centrifuged at 5000RPM for 5minutes and the serum was dispensed into a serum container well labelled for thyroid function analysis.

2.3.3. Biochemical Analysis

The glucose oxidase method [18] was used to determine the fasting blood glucose level. Thyroxine (T4), Thyroid stimulating hormone (TSH), free thyroxine (FT4), Triiodothyronine (T3) were tested using the Enzyme immunoassay (kit) method [19].

2.4. Statistical Analysis

Data obtained from this study were analyzed using the statistical package for social sciences (SPSS) version 22 for Windows Inc. Chicago, IL, USA. Student's independent T-test was used to calculate differences between means, and correlations were also done in all the parameters. P- value <0.05 was considered statistically significant.

3. Results

Results in table 1 show the anthropometric measurements and fasting blood glucose of diabetic and Non-diabetic subjects. There was a statistical significant higher values in the mean $\pm$ SD of the FBG (8.68 ± 9.94), SBP (144.50 ± 7.50), DBP (99.22 ± 6.49), and BMI (25.49 ± 1.38) in the diabetic subjects when compared with the FBG (4.64 ± 0.56), SBP (112.90 ± 6.05), DBP (72.43 ± 7.30) and BMI (24.42 ± 0.54) in the non-diabetic subjects ($p < 0.05$).

Table 1 Anthropometric measurements and fasting blood glucose levels of diabetic and non-diabetic subjects

Groups	Fasting blood glucose (FBG) (mmol/L)	Systolic BP (SBP) (mmHg)	Diastolic BP (DBP) (mmHg)	Body Mass Index BMI (kg/m ²)
Diabetic group N=80	8.68 ± 9.94	144.50 ± 7.50	99.22 ± 6.49	25.49 ± 1.38
Non-diabetic group N=60	4.64 ± 0.56	112.90 ± 6.05	72.43 ± 7.3	24.42 ± 0.54
t-statistics	2.152	17.33	20.41	3.568
p-value	0.040*	0.000*	0.000*	0.001*

Values are given as Mean $\pm$ Standard Deviation (SD) * = Significant value ($P < 0.05$)

Table 2 shows the thyroid hormone levels (T4, TSH, FT4 & T3) of the diabetic and non-diabetic subjects. There was a significantly decrease in the TSH (3.39 ± 2.24) and T3 (0.55 ± 0.18) of the diabetic subjects when compared with the TSH (5.01 ± 2.29) and T3 (1.60 ± 0.43) of the non-diabetic subjects ($P < 0.05$). The other parameters FT4 and T4 showed an increase in the diabetic subjects but not statistically significant ($P > 0.05$).

Table 2 The thyroid hormone levels (T4, TSH, FT4 & T3) of the diabetic and non-diabetic subjects

Groups	Thyroxine (T4)(μ g/dl)	Thyroid stimulating hormone (TSH)(mIU/L)	Free thyroxine(FT4) (ng/dl)	Triiodothyronine (T3) (nmol/L)
Diabetic subjects N=80	10.90 ± 2.02	3.39 ± 2.24	0.71 ± 0.16	0.55 ± 0.18
Non-diabetic subjects N=60	9.79 ± 0.96	5.01 ± 2.29	0.66 ± 0.18	1.60 ± 0.43
t-statistic	1.667	-2.875	-0.107	-11.423
p-value	0.106	0.007*	0.916	0.000*

Values are given as Mean $\pm$ Standard Deviation (SD) * = Significant value ($P < 0.05$)

Table 3 shows the correlation of all the parameters in the diabetic subjects. The result showed that there was a positive correlation between T4 vs FT4 ($r=0.609$, $p<0.05$), T4 vs BMI ($r=0.350$, $p<0.05$), FT4 vs DBP ($r=0.314$, $p<0.05$), T3 vs BMI ($r=0.846$, $p<0.05$) while others show no correlation ($p>0.05$).

Table 3 The correlation of all the parameters in the diabetic subjects

Parameters	(r) person	P-value
T4 vs TSH	0.024	0.882
T4 vs FT4	0.609	0.000 *
T4 vs T3	0.237	0.140
T4 vs Age	-0.183	0.259
T4 vs FBG	0.271	0.091
T4 vs SBP	0.079	0.628
T4 vs DBP	-0.066	0.686
T4 vs BMI	0.350	0.027*
TSH vs FT4	-0.299	0.061
TSH vs T3	0.045	0.784
TSH vs Age	0.019	0.910
TSH vs FBG	0.278	0.083
TSH vs SBP	-0.197	0.224
TSH vs DBP	-0.238	0.139
TSH vs BMI	0.133	0.414
FT4 vs T3	0.095	0.560
FT4 vs Age	-0.033	0.839
FT4 vs FBG	-0.131	0.422
FT4 vs SBP	0.153	0.347
FT4 vs DBP	0.314	0.049*
FT4 vs BMI	0.171	0.291
T3 vs Age	0.166	0.306
T3 vs FBG	0.104	0.524
T3 vs SBP	0.002	0.991
T3 vs DBP	-0.306	0.054
T3 vs BMI	0.846	0.000*
Age vs FBG	0.115	0.480
Age vs SBP	0.173	0.287
Age vs DBP	-0.065	0.691
Age vs BMI	0.216	0.181
FBG vs SBP	0.120	0.461
FBG vs DBP	-0.234	0.146
FBG vs BMI	0.110	0.500

SBP vs DBP	0.100	0.540
SBP vs BMI	-0.114	0.484
DBP vs BMI	-0.312	0.050

*= Correlation is significant at the 0.05 level (2-tailed)

4. Discussion

Hypothyroidism and hyperthyroidism are known to have adverse effects on glycaemic control in diabetics with hyperthyroidism on its own resulting in diabetes. In this study, we screened for the levels of thyroid hormone in diabetic patients in University of Nigeria Teaching Hospital Ituku-Ozalla, Enugu State who have no symptom of thyroid disorders and in identical population of non-diabetics. This is in view of the widely reported effects of the various forms of thyroid dysfunction on blood glucose homeostasis.

In this study, comparison of results was made between test and control groups. Our findings showed significantly higher values of fasting blood glucose (FBG), systolic blood pressure (SBP), diastolic blood pressure (DBP) and body mass index (BMI) in the diabetic subjects when compared to non-diabetic subjects.

The significant increase in FBG in the test group was expected since they are diabetic hence, the regulation of plasma glucose concentration is impaired. This is due to either low plasma level of insulin as seen in type 1 diabetes or diminished effectiveness of insulin that is, the insulin receptors are down regulated in the membrane of target cells as seen in type 2 diabetes. This is not so for the apparently healthy individuals used as control.

The increase in SBP and DBP seen might be that diabetes over time, accumulated insulin causes the body to retain salt and fluids which damages the small vessels in the body causing it to stiffen thereby increasing the peripheral resistance which lead to high blood pressure.

The increase in BMI can be as a result of increase in weight of the diabetic patients. Overweight and obesity are among the risk factors for diabetes because when fat metabolism is disrupted, it causes fat tissues to release fat molecules into the blood which affects insulin responsive cells leading to reduced insulin sensitivity. Hence, there will be increased level of free insulin in the body which retain more salts and fluid. Diabetics in this study are significantly heavier than non-diabetics.

All these findings are in the line with the works done by [2, 4, 20] which stated that there is positive relationship between fasting blood glucose, BM1 and blood pressure.

This study also observed a significantly low levels of triiodothyronine (T3) and thyroid stimulating hormones (TSH) and a slight but non-significant increase in thyroxine (T4) and free thyroxine (FT4) in the diabetic subjects when compared with non-diabetic subjects.

The low level of T3 as seen in this study might be due to poor glycaemic control in diabetic patients leading to impairment of T4 conversion to T3. This is in line with [21] in their study on the "effects of diabetic control on the level of circulating thyroid hormones".

Also, the low level of TSH as seen in this study may be due to the use of an oral hypoglycaemic medication metformin and L-T4 substitution. Cappelli *et al* in their study evaluated thyroid hormone profiles by studying the interaction between metformin and circulating thyroid function parameters in patients who were started on metformin and they showed a significant fall in TSH level after 6 months [22]. Similarly, a large cohort study carried out by Vigersty *et al* on diabetic patients showed a significant fall in TSH level in diabetic patients on L-T4 substitution [23]. The insignificance in T4 and FT4 might be due to negative feedback mechanism of T4 on the pituitary and the hypothalamus to stop the production of thyroid hormones or might be because T4 is an inactive form of thyroid hormone. Though Pasupathi *et al.* in their investigation of the effect of diabetes on thyroid hormone levels and other biochemical variables found that the levels of TSH were significantly decreased whereas the levels of T4 and FT4 were significantly increased and the T3 and FT3 levels did not differ significantly in diabetic patients compared with control subjects [24]. This is almost in accordance with our work as there was a significant decrease in TSH while T4 and FT4 increased but not statistically significant.

However, T3 decreased significantly. Islam *et al.* in their works reported that patients with type 2 diabetes had significantly lower serum FT4 levels compared with the control [16]. This is not in accordance with our work as FT4 level was not significant.

The notable differences observed in these studies may be explained by racial, sex and age differences between the populations studied. Racial factors are recognized causes of variation in epidemiology of diseases. While this study was carried out on Nigerian subjects in Enugu state, Udiong *et al* [14] studied subjects in Calabar, Radaideh *et al*, [25] studied subjects in Jordan, Bal *et al* [26] was in Indian, Pasupathi *et al* [24] in India and Islam *et al* [16] in Asia.

Methodological differences between this study and the other studies:

TSH, T4, T3 & FT4 were assayed using Enzyme linked Immunosorbent assay (ELISA) while the Jordanian study used a manual technique based on ELISA principle. Modern analysing method have better analytical performance characteristics compared to manual methods.

Correlation of the work was done and it was found that there was a positive correlation between T4 and FT4, T4 and BMI, FT4 and DBP and T3 and BMI. Hence as one parameter is increasing, the other is also increasing and vice versa.

Studies done have unequivocally stated that testing for thyroid dysfunction in diabetic patients is necessary and should be carried out more often. The American Thyroid Association guidelines for type 2 diabetes patients require frequent testing for thyroid dysfunction. They recommend testing at 35 years of age, and every 5 years thereafter in adults with high risk persons frequently tested [27].

5. Conclusion

There is growing evidence of an association between thyroid dysfunction and diabetes. This study hence concludes that thyroid dysfunction is known to be more prevalent in diabetics when compared to the general non-diabetic populations. It is therefore important to diagnose thyroid dysfunction in diabetic patients and this practice should be inculcated in clinical settings hence there should be regular checks. This would encourage further understanding of the relationship between thyroid function and diabetes, thereby reducing morbidity and mortality from these conditions.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Statement of ethical approval

Ethical approval was duly obtained from Research Ethics Committee of University of Nigeria Teaching Hospital Health, College of Medicine Ituku Ozalla Enugu State, (UNTH/CSA/329/Vol.5).

Statement of informed consent

Informed consent was also obtained from each of the participants before enrollment into the study.

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