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Assessment of Thyroid Profile of Type 1 and Type 2 Diabetes Mellitus Patients and Patients with Diabetic Complications

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Assessment of Thyroid Profile of Type 1 and Type 2 Diabetes Mellitus Patients and Patients with Diabetic Complications

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Abstract

This study was undertaken to assess the thyroid profile of diabetes mellitus (DM) patients and patients with some associated complications in the Edo state, Nigeria. Blood samples from 267 subjects, consisting of 164 diabetic patients (24 type 1 DM and 140 type 2 DM) and 103 nondiabetic apparently healthy individuals (as controls), were analyzed. The thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels were determined using the enzyme linked immunosorbent assay (ELISA). From the result obtained, the T3 level was found significantly ($p < 0.05$) higher in diabetic-nephropathy (D-NEPHR) patients than the control subjects, while the TSH and T4 levels of D-NEPHR were insignificantly ($p > 0.05$) higher than those of the control group. The mean TSH level was significantly ($p < 0.05$) lower in diabetic hypertensive patients when compared with the control group, while the plasma T3 level was significantly ($p < 0.05$) higher in diabetic hypertensive patients when compared with the control group. There was no significant difference ($p > 0.05$) in the mean value of T4 of diabetic hypertensive patients when compared with the control subjects. The mean plasma T3 and T4 were significantly ($p < 0.05$) higher in diabetic neuropathy (D-NEUR) patients than those of control subjects. There were no significant ($p > 0.05$) differences in the mean plasma TSH level of D-NEUR patients when compared with those of control subjects. The mean plasma T3and T4 levels of diabetic patients with coronary heart disease (DM-CHD) were significantly ($p < 0.05$) higher than those of control subjects while the mean plasma TSH level of DM-CHD was significantly ($p < 0.05$) lower than that of control subjects. No significant ($p > 0.05$) difference in the mean plasma TSH, T4, and T3 levels of diabetic retinopathy subjects when compared with those of control subjects was obtained.

Keywords: Diabetes mellitus; Nephropathy; Thyroid; Hormone.

1. INTRODUCTION

One of the most common endocrine metabolic disorders is diabetes mellitus (DM). It is responsible for several mortalities worldwide [1]. It is characterized by hyperglycemia, resulting from various interactions of hereditary and environmental factors, and is due to insulin resistance (impairment in insulin-mediated glucose disposal) or defective secretion of insulin by pancreatic beta cells, or both [2]. The symptoms are characterized by excessive urine production (polyuria), excessive thirst, blurred vision, and increased intake of fluid. With mildly raised blood sugar levels, these symptoms will likely be absent.

Type 1, type 2, and gestational diabetes are the three forms of DM recognized by the World Health Organisation (WHO) [3]. Type 1 diabetes occurs as a result of destruction of the pancreatic beta cells by the autoimmune system, while type 2 diabetes is a result of insulin resistance in target tissues. This leads to a need for irregularly large amounts of insulin, and diabetes occurs when the demand cannot be met by the beta cells. There is a similarity between gestational diabetes and type 2 diabetes because both involve insulin resistance. In women who are genetically predisposed to developing this condition, the hormone of pregnancy, progesterone, can cause insulin resistance.

While type 1 and type 2 diabetes are chronic conditions, gestational diabetes usually resolves with delivery of the child. Although type 1 diabetes is inherited, lifestyle modifications, such as weight loss, exercise, and avoiding health problems like elevated cholesterol levels, obesity, and high blood pressure can help reduce it [4].

Several complications result from DM. Acute complications, such as hypoglycemia, nonketotic hyperosmolar coma, or ketoacidosis, could arise from poor control of the disease. Long-term complications include chronic renal failure

(nephropathy), cardiovascular disease, retinal damage (retinopathy) which can lead to blindness, nerve damage (neuropathy), and microvascular damage, which may cause impotence and poor healing. Since life expectancy is low in Nigeria (48 years), people aged 30 years and above should check their blood glucose level at least once a year [5], and this should be accompanied by blood pressure checks. Increasing incidence of metabolic syndrome also entails regular checks for serum lipids and renal function [6].

People with diabetes experience thyroid disorders more frequently than the general population [7]. Both diabetes and thyroid disease involve a group of glands called the endocrine system, which helps to regulate the body's metabolism. If the thyroid releases too much of thyroid hormone, metabolism speeds up (hyperthyroidism), but if it releases too little thyroid hormones, metabolism slows down (hypothyroidism). Almost one-third of people with type 1 diabetes have thyroid disease. This is because type 1 diabetes is an autoimmune disease in which the immune system attacks a gland or organ of the body. Patients with one kind of autoimmune disease are at risk of developing another type. The physiological and biochemical interrelationships between insulin and the influence of both insulin and iodothyronines (triiodothyronine [T3], thyroxine [T4]) on the metabolism of carbohydrates, proteins, and lipids are reported [8, 9], and such reports indicate that iodothyronines are insulin antagonists with high levels being diabetogenic, while absence of the hormones inhibits diabetes [10]. DM and hyperthyroidism are metabolic disorders that affect the level of carbohydrates, proteins, and lipids. Studies have also shown that the incidence of hypothyroidism seems to be increased in both type 1 and 2 diabetes, especially in women over the age of 40 years. People with diabetes who develop hypothyroidism may find it hard to manage their diabetes because the way their body utilizes glucose is affected. Thyroxine (T4) has been observed to increase the absorption of glucose from the gastrointestinal tract (GIT) and stimulate glycogenolysis. It also promotes an increase in blood glucose level by degrading insulin [11]. Therefore, for effective management of DM and its complications, the assessment of thyroid functions is necessary.

2. METHOD(S)

2.1. Study Area

The study was undertaken at the Irrua Specialist Teaching Hospital in Edo central and Edo north senatorial districts of Edo state, Nigeria, located between approximately Latitude 05° 44'N–07° 34'N and Longitude 05° 04'E–06° 43'E, covering an estimated area of 20,000 km^2.

2.2. Population of the Study

About 164 DM subjects within the age range of 23–83 years attending the clinic at the Irrua Specialist Teaching Hospital were randomly selected for the study, and 103 apparently healthy individuals within the age range of 20–53 years as controls were used for this study. This was obtained using the "precise prevalence" formula described by Araoye [12].

The 267 subjects for this study were divided into two major groups of 164 DM subjects (consisting of 24 type 1 and 140 type 2 DM patients) and 103 apparently healthy subjects as control group. The diabetic subjects were recruited from both inpatients and outpatients attending the diabetic clinic of the Irrua Specialist Teaching Hospital, which serves as the medical center for the study location. The selection of diabetic subjects was initially based on the physician's provisional diagnosis and then confirmed by the fasting plasma glucose of ≥126 mg/dl or random blood sugar of ≥200 mg/dl. The criteria used for separating type 1 DM from type 2 DM subjects were as follows: first, the clinical classification included the patient's history, age of onset of the DM (less than 35 years), and total dependence on insulin therapy alone to achieve normal plasma glucose concentration, and second, the laboratory classification using fasting C-peptide levels of less than 0.38 ng/ml (approximately 0.4 ng/ml) for type I DM [13]. The known DM subjects were already on drugs such as insulin and some oral hypoglycemic agents. Their thyroid conditions were not known. The criteria for diabetic complications were initially based on physician's provisional diagnosis and then confirmed by biochemical investigations of the organs that were being implicated. The diabetic nephropathies were confirmed with urea level above 55 mg/dl and creatinine level above 1.4 mg/dl. The diabetic hypertensions (DM-HTN) were based on the high blood pressure recorded. DM with coronary heart disease (DM-CHD) was confirmed based on the low concentration of high-density lipoprotein (HDL) or high concentration of low-density lipoprotein (LDL) cholesterol. The control subjects were selected from staff and students of the Irrua Specialist Teaching Hospital and Ambrose Alli University, Ekpoma, respectively, who were apparently healthy, free from thyroid disorders, and nondiabetic. The following guidelines for detection of thyroid dysfunctions were considered [14]. Normal function: when T3, T4, and thyroid stimulating hormone (TSH) were within normal range. Primary hypothyroidism: when TSH is increased, and T3 and T4 are less than the normal values. Secondary hypothyroidism: when T3 and T4 are less than normal values, but TSH is within normal. Subclinical hypothyroidism can be referred to as mild (TSH between 4 and 9.9 mIU/L) or severe hypothyroidism (TSH ≥ 10 mIU/L). Primary hyperthyroidism: when TSH is decreased, and T3 and T4 are more than normal values [15].

2.3. Sample Collection and Processing

Five milliliters of blood was obtained from the median cubital vein of both subjects and control and dispensed into plain bottles, which were allowed to cloth and centrifuged to obtain serum. Serum samples were stored at 4°C for 1 week; within this period, all the analysis was carried out.

2.4. Sample Analysis

The plasma TSH was quantitatively determined using enzyme linked immunosorbent assay (ELISA), according to Uotila *et al*. [16], and Drg-diagnostics [17]. Plasma total T3 was quantitatively determined using enzyme immunoassay [18] and Drg-diagnostics [19]. Plasma T4 level was determined using enzyme immunoassay (EIA) [18] and Drg-diagnostics [20]

2.5. Ethical Consideration

Approval for this research was obtained from the Research and Ethics Committee of the Irrua Specialist Teaching Hospital, Irrua, (ISTH/ETHICS COM/7). Informed written consent was obtained from the test (case) and control subjects; also questionnaires were given to them to fill for obtaining the required personal information and data that were necessary for the study.

2.6. Statistical Analysis

Data obtained were statistically analyzed using the SPSS version 20 statistical software package to carry out the analysis of variance (ANOVA). Data obtained were expressed as mean ± SD, with a p-value < 0.05 considered significant.

3. RESULTS

Table 1 shows that the T3 level was significantly ($p < 0.05$) higher in diabetic-nephropathy (DM-NEPHR) patients than the control subjects, while the TSH and T4 levels of DM-NEPHR were insignificantly ($p > 0.05$) higher than those of the control group. The mean TSH level was significantly ($p < 0.05$) lower in diabetic hypertensive patients when compared with the control group, while plasma T3 level was significantly ($p < 0.05$) higher in diabetic hypertensive patients in comparison with the control group. No significant difference ($p > 0.05$) in the mean value of T4 of diabetic hypertensive patients when compared with the control subjects was observed. The mean plasma T3 and T4 levels were significantly ($p < 0.05$) higher in diabetic neuropathy (D-NEUR) patients than those of control subjects. There were no significant ($p > 0.05$) differences in the mean plasma TSH level of D-NEUR patients when compared with those of control subjects. The mean plasma T3and T4 levels of DM-CHD were significantly ($p < 0.05$) higher than those of control subjects, while the mean plasma TSH level of DM-CHD was significantly lower ($p < 0.05$) when compared with the control subjects. There were no significant ($p > 0.05$) differences in the mean plasma TSH, T4, and T3 levels of diabetic retinopathy subjects when compared with those of control subjects.

Table 1. Comparisons of the mean thyroid profiles of diabetes mellitus, diabetic complications, and control group using analysis of variance (ANOVA).

Groups	*TSH (Miu/ml)*	*T3 (ng/ml)*	*T4 (µg/dl)*
Control (*N*=103)	1.77 ± 0.73^{a}	1.50 ± 0.50^{a}	7.81 ± 1.60^{a}
Type 2 DM (*N*=140)	1.14 ± 0.97^{b}	1.80 ± 0.80^{b}	8.80 ± 3.01^{a}
Type 1 DM (*N*=24)	0.93 ± 0.76^{b}	1.51 ± 0.76^{a}	7.71 ± 2.57^{a}
DM-NEPHR (*N*=25)	2.34 ± 3.54^{c}	2.07 ± 0.99^{b}	8.45 ± 2.73^{a}
DM-HTN (*N*=42)	0.96 ± 0.69^{b}	1.70 ± 0.64^{b}	8.31 ± 1.90^{a}
DM-CHD (*N*=22)	0.94 ± 0.98^{b}	2.34 ± 0.87^{bc}	14.34 ± 20.91^{b}
DM-NEUR (*N*=8)	1.48 ± 0.85^{ab}	2.34 ± 0.81^{b}	9.80 ± 2.30^{a}
DM-RETIN (*N*=5)	1.00 ± 0.86^{b}	2.00 ± 1.17^{b}	7.68 ± 4.44^{a}
DM Only (*N*=62)	1.04 ± 0.86^{b}	1.53 ± 0.71^{a}	8.05 ± 2.81^{a}
F-Value	3.63	4.31	3.31
***P*-Value**	0.000	0.000	0.001
Remark	S	S	S

Note: Values in a column with different superscripts are significantly different at $p < 0.05$ using post hoc test; S, significant.

4. DISCUSSION

The thyroid profiles observed in this study for DM subjects without complications show a significant decrease ($p < 0.05$) for TSH in comparison with the control group, but no significant differences ($p > 0.05$) were observed for the thyroid hormones (T3 and T4). This pattern of thyroid profiles was also observed in type 1 DM, and it is a manifestation of subclinical hyperthyroidism. Degreef *et al.* [21] and Suzuki *et al.* [22] reported that thyroid releasing hormone (TRH) synthesis decreases in DM. Decreases in TRH secretion will lead to decrease in TSH secretion by the anterior pituitary. Also, Celani *et al.* [23], Suzuki *et al.* [22], and Udiong *et al.* [13], in their separate studies, found and reported altered thyroid hormones levels of different magnitudes in diabetic patients.

The thyroid profiles observed in type 2 DM showed a significant ($p < 0.05$) decrease in TSH level but a significant ($p < 0.05$) increase in T3 and T4 levels when compared with the control group. This is a clear indication of primary hyperthyroidism in type 2 DM. By inhibiting the hepatic conversion of T4 to T3, it is known that insulin is capable of raising the levels of TSH and suppressing the levels of T3 [24]. This could account for the significant decrease in TSH with a significant increase in the thyroid hormones because of the significant decrease in insulin levels in DM as observed in this study. This finding is in line with the report of the Canadian Diabetes Association [24] in that there appears to be a higher than normal occurrence of thyroid disorders in people with type 2 DM.

From the study, the patterns of thyroid profiles for some diabetic complications were revealed. There was significant increase ($p < 0.05$) in the level of T3 for patients with diabetic nephropathy, when compared with the control subjects, but no significant differences ($p > 0.05$) in the levels of T4 and TSH. The significant increase in T3 level could be due to the decreased level of insulin observed in this study, since insulin is capable of raising the levels of TSH and suppressing the levels of T3 [24]. The slight increase in T4 level and significant increase in T3 level without a corresponding effect on TSH are suggestive of secondary hyperthyroidism in diabetic nephropathy. For the diabetic subjects with hypertension (DM-HTN) in this study, there was a significant ($p < 0.05$) decrease in TSH level and significant increase ($p < 0.05$) in T3 level, when compared with the control group. But there was no significant difference in T4 when compared with the control group, though there was a slight increase. This pattern of thyroid profiles is indicative of primary hyperthyroidism or T3-toxicosis in DM-HTN. It should be noted that T3 is a more potent and biologically active thyroid hormone than the T4 because of the higher percentage of free fraction of T3. In the study, the mean TSH level of DM-CHD was significantly ($p < 0.05$) lower than that of the control subjects, while the T3 and T4 levels were significantly ($p < 0.05$) higher than those of the control subjects. This pattern of thyroid profiles with significant decrease of TSH level but significant increase of T3 and T4 levels as observed in this study is a clear indication of primary hyperthyroidism among DM-CHD. By inhibiting the hepatic conversion of T4 to T3, it is known that insulin is capable of raising the levels of TSH and suppressing the levels of T3 [24]. This could account for the significant decrease in TSH with significant increase in the thyroid hormones because of the significant decrease in insulin level in DM as observed in this study. In the study, there were significant ($p < 0.05$) increases in the levels of T3 and T4 for D-NEUR when compared with the control group; but insignificant ($p > 0.05$) decrease in TSH level for DM-NEUR. This pattern of thyroid profiles is suggestive of secondary hyperthyroidism. There was no obvious thyroid disorder observed in diabetic retinopathy.

5. CONCLUSION

This study confirms that DM, both type 1 DM and type 2 DM, are associated with thyroid disorders. It was observed that type 1 DM is mostly associated with secondary and subclinical hyperthyroidism while type 2 DM is mostly associated with secondary and primary hyperthyroidism. But more importantly, the study revealed and distinguished the type of thyroid disorders that are associated with different diabetic complications and proved that the type of thyroid disorders depends also on the type of diabetic complications and not only on the type of DM. It was observed that patients with D-NEPHR and D-NEUR are associated with secondary hyperthyroidism, DM-HTN is associated with T3-toxicosis, while DM-CHD is associated with primary hyperthyroidism. There was no obvious thyroid disorder observed in diabetic retinopathy. The study also confirms that DM, especially type 2 DM, is associated with dyslipidemia, cardiovascular disease, renal failure, hypertension, overweight, and obesity, which are also risk factors for metabolic syndrome.

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Authors' Contributions
This research was carried out with the collaboration and contribution of all the authors. FKI was responsible for the conceptualization and execution of the research. GRAO was responsible for supervision and quality control. EOD was responsible for the development of the manuscript. LFD was responsible for the research logistics. IKA was responsible for the clinical evaluation of the patients used as test subjects. BNO and OO were involved in the laboratory analytical process.

Conflict of Interest
None.

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