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Evaluation of Thyroid Function in Normal, Pre-Diabetic and Diabetic Subjects attending University of Port Harcourt Teaching Hospital

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ABSTRACT

This study evaluated thyroid function in normal, pre-diabetic and diabetic subjects attending University of Port Harcourt (UPTH), using glycated haemoglobin (HbA1c) and fasting blood sugar (FBS)as glycemic indices for the discussion. The study compared the thyroid function, glycated haemoglobin and fasting blood sugar of the normal, pre-diabetics, and diabetics(three sets) so as to assess thyroid hormone levels. One hundred and twenty adult male and female human subjects comprising forty subjects each for three sets matched for age and sex were recruited into the study based upon specified criteria. Of the sets of human subjects, twenty were males and females respectively. Group A subjects were the non-diabetic, Group B were the pre-diabetic while Group C subjects were the diabetic. Blood serum samples were analyzed using Randox and Accubind kits, and an auto analyser for the tests. The overall results revealed a significant difference at 95% level of confidence interval ($p<0.05$) in the thyroid function parameters. The FBS and HbA1c showed a significantly increasing trend with values of 4.49±0.08 mmol/l, 6.00±0.11 mmol/l, and 10.84±0.96 mmol/l for FBS; and 4.75±0.05 mmol/l, 5.73±0.08 mmol/l, and 9.74±0.47 mmol/l for HbA1c, for the non-diabetics, pre-diabetics, and diabetics respectively. All values were significantly higher ($p<0.05$) across the groups for both FBS and HbA1c. The thyroid function profile showed progressive decrease in values for fT3 (free triiodothyronine) and fT4 (free thyroxine) respectively for the non-diabetics, pre-diabetics, and the diabetics while the thyroid stimulating hormone (TSH) values increased significantly when compared to the normal. This study revealed that thyroid function is significantly affected in the diabetic subjects.

INTRODUCTION

The thyroid gland is a small, butterfly-shaped gland located near the throat or is simply a gland located in the neck. Its function is to take iodine from the blood and combine it with an amino acid (one of the building blocks of protein) to form thyroid hormones. These hormones made by the thyroid functions in regulating energy use by the body. They also play important roles in regulating weight, body temperature, muscle strength and mood. One of the hormones, thyroxine is responsible for metabolism.[1]

Thyroid stimulating hormone (TSH), a progenitor of thyroxine and other thyroid-associated hormones, is made in a gland in the brain called the pituitary gland. When thyroid levels in the body are low, the pituitary gland makes more TSH. When thyroid levels are high, the pituitary gland makes less TSH. TSH levels that are too high or too low can indicate the thyroid is malfunctionin.[2] A TSH test is used to find out how well the thyroid is functioning[1].

Thyroid function tests help to determine if the thyroid is functioning effectively. Such tests include hyperthyroid (over-working thyroid) function and hypothyroid (poor thyroid) function[3].

High TSH levels can mean the thyroid is not making enough thyroid hormones, a condition called hypothyroidism. Low TSH levels can mean the thyroid is making too much of the hormones, often called hyperthyroidism. A TSH test may be needed if there are symptoms of too much thyroid hormone in the blood (hyperthyroidism), or too little thyroid hormone (hypothyroidism)[3].

Symptoms of hyperthyroidism, also known as overactive thyroid, include: feeling too hot, increased sweating, muscle weakness, fatigue, weight loss, tremors in the hands, increased heart rate, diarrhoea, irritability and anxiety, puffiness, bulging of the eyes, menstrual irregularities, and difficulty sleeping, while symptoms of hypothyroidism, also known as underactive thyroid are non-specific, but include: mild to moderate weight gain, tiredness, poor concentration, depression, hair loss, low tolerance for cold temperatures, irregular menstrual periods, and constipation[4].

Abnormal thyroid function is common. It is seen in two to three percent of the entire population[4].When the thyroid is not functioning effectively, it can cause changes in other blood tests as well. The normal range of TSH for an adult is 0.4–5.5 mU/ml[5].

Glycated Haemoglobin (HbA1c)is a blood test which does not require fasting, and indicates the average blood sugar level for the past two to three months. It measures the percentage of blood sugar attached to haemoglobin (Hb), the oxygen-carrying protein in red blood cells[6]. The higher the blood sugar levels, the more Hb will be present with sugar attached to it. A HbA1c level of $\geq$6.5 percent separate tests indicates diabetes. A HbA1c between 5.7 and 6.4 percent indicates pre-diabetes, and <5.7 percent is considered normal[7].

If the HbA1c test results are not consistent, the test is not available, or one has certain conditions that can make the HbA1c test inaccurate – as in pregnancy or uncommon form of haemoglobin (known as haemoglobin variant)[6]:

In addition to daily blood sugar monitoring, a doctor will likely recommend regular HbA1c testing to measure average blood sugar level for the past two to three months[6]. Compared with repeated daily blood sugar tests, HbA1c testing better indicates how well diabetes treatment plan is working overall. An elevated HbA1c level may signal the need for a change in oral medication, insulin regimen or meal plan[8].

The target HbA1c goal may vary depending on age and various other factors, such as other medical conditions that may be present. However, for most people with diabetes, the American Diabetes Association (ADA) recommends an HbA1c of below 7 percent[9].

Insulin is a hormone with strong association to diabetes. People with type 2 diabetes need insulin therapy to survive. Many types of insulin are available, including rapid-acting, long-acting and intermediate options. Depending on the needs, a doctor may prescribe a mixture of insulin types to use throughout the day and night[7]. Thus includes;

Insulin cannot be taken orally to lower blood sugar because stomach enzymes interfere with its action[10]. Often, insulin is injected using a fine needle and syringe or an insulin pen – a device that looks like a large ink pen[11]. An insulin pump also may be an option. The pump is a device about the size of a cell phone worn on the outside of the body. A tube connects the reservoir of insulin to a catheter that is inserted under the skin of the abdomen[12]. A tubeless pump that works wirelessly also is now available. The pump is programmed to dispense specific amounts of insulin. It can be adjusted to deliver more or less insulin depending on meals, level of activity and blood sugar level[13]. An emerging treatment approach is closed loop insulin delivery, also known as the artificial pancreas. It links a continuous glucose monitor to an insulin pump, and automatically delivers the correct amount of insulin when needed[14].There are a number of versions of the artificial pancreas, and clinical trials have had encouraging results. More research needs to be done before a fully functional artificial pancreas receives regulatory approval[15].

However, progress has been made towards an artificial pancreas. In 2016, an insulin pump combined with a continuous glucose monitor and a computer algorithm was approved by the Food and Drug Administration (FDA)[8]. Its shortcoming remains that the user still needs to tell the machine how many carbohydrates will be eaten[10].

ii. Oral or other medications: occasionally, other oral or injected medications, such as Glimepiride, Gliclazide, Glipizide, and Glyburide are prescribed. Some diabetes medications such as Glyburide, glipizide

and glimepiride (sulfonylureas) stimulate the pancreas to produce and release more insulin, while others, such as metformin undertake inhibitory role, indicating the need for less insulin to transport sugar into the cells[7].Other medications block the action of stomach or intestinal enzymes that catabolize carbohydrates or make the tissues more sensitive to insulin. Metformin (glucophage) is generally the first medication prescribed for type 2 diabetes[6].

iii. Fasting blood sugar (FBS) test: A blood sample is taken after an overnight fast. An FBS level <5.6mmol/l (100mg/dl) is normal, 5.6 to 6.9mmol/l (100 to 125mg/dl) is pre-diabetes and ≥7mmol/l (126mg/dl) on two separate tests, is diabetes[9].

The study was conducted to evaluate thyroid function in normal, pre-diabetic and diabetic subjects attending University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt. It was conducted on the premise that it could provide base-line data for physicians in the management of diabetes. It will, therefore, make available some scientific information on HbA1c, FBS and thyroid function (TSH, fT3, and fT4) statuses of normal, pre-diabetic and diabetic subjects, with the target population being normal individuals, pre-diabetic and diabetic human subjects designated for investigation of Thyroid Function (TSH, fT3, fT4), HbA1c, and FBS.

METHODOLOGY

This study was conducted in the UPTH, in Obio/Akpor Local Government Area of Rivers State, Nigeria. The study area is located in the Niger Delta region, bordering the Atlantic Ocean. It is a cosmopolitan environment with people of diverse culture and occupation. It is an experimental design and employed the following approach in grouping the human subjects.

GROUP A: The control group consisting of forty (40) normal (non-diabetic) subjects.
GROUP B: The test group consisting of 40 pre-diabetic subjects.
GROUP C: The test group consisting of 40 diabetic subjects.

The inclusion criteria is being aged between thirty six (36) to seventy six (76) years who agreed to participate, while the exclusion is co-infection with other metabolic disorders.
The sample size was by calculating the minimum sample size, employing the formula below:

$N = Z^2(pq) / e^{216}$

Where N = minimum sample size,Z = 1.96 at 95% confidence limits, so that $z^2 = 3.8416$, p = prevalence of increased normal and diabetic subjects' percentage average, q = 1-p and e = error margin tolerated at 5% = 0.05 ($e^2 = 0.0025$)
6.80% as the prevalence of increased normal subjects
10.20% as the prevalence of increased diabetic subjects
((6.80 + 10.20)/2)% = (17.00/2)% = 8.50%
8.50% as the prevalence of increased mean of normal and diabetic subjects
p = 8.50% = 0.0850
q = 1-p
= 1-0.0850
= 0.9150
N = ((3.8416(0.0850 x 0.9150))/0.0025 = 119.51 = approximately 120.

Before commencing sample collection (blood sample), the subjects were issued or given the informed consent form to complete or fill out after listening to a detailed explanation from the researcher. This was followed by taking five (5) ml of blood from the phlebotomy department of UPTH using 5 ml syringe for each subject. Two (2) ml was put into Lithium heparin bottle, 2 ml into plain bottle and one (1) ml into Fluoride oxalate bottle.

The samples were placed in sample racks and left to stand for at least thirty (30) minutes at room temperature. The sample was then centrifuged for 5 minutes at 320 rpm (Hettich Universal) at room temperature and a completely cell free non-haemolysed sample was obtained. The samples were then separated into a 1 ml sample container which was labeled with the serial number of the subject, and left to refrigerate before use.

Whole blood sample was also collected from the subjects by intravenous means (collected intravenously) and the samples were collected into plain and heparinized bottles respectively, which were allowed to stand for 30 minutes to clot, centrifuged at 3,000 rpm for 10min for proper separation, separated into plain bottles and labeled accordingly. This was stored frozen, until when needed for biochemical analysis.

Published studies that evaluate thyroid function, HbA1c, and FBS in normal, pre-diabetic and diabetic subjects (especially type 2 diabetes mellitus [T2DM]) were searched in MEDLINE, EMBASE and Pub Med databases covering the period from year 2000 to 2018. Literature search was then carried out using the combination of terms "thyroid", "thyroid function", "HbA1c","Blood sugar", "FBS", "diabetes", "diabetes mellitus", "type 2 diabetes","T2DM", "type 2 DM", "epidemiology", and "review". The reference lists of the retrieved articles and reviews of this field[17,18,19], were also searched. The search was limited to human studies and English publications.

In the course of the study, collecting information about normal subjects and persons suffering from diabetes was difficult. Two issues were addressed at the outset: the kind of data collection instrument that would be used and the unit of measurement that would be employed. Generally, the instruments used for collecting information about normal and diabetic subjects were: sample surveys(general social surveys/specific health surveys) and administrative collections and registries.

Each of these tools was used to measure aspects of diabetes in the study population.

Sample surveys are shorter surveys designed to be administered to the study sub-population selected by some other instrument (often a census) that focus on specific issues; normal and diabetic subjects in this case. They were put into the field to answer specific questions about the study population. As such, they were provided the opportunity to ask more detailed questions about being normal and being diabetic. More detailed information was useful in itself, of course, and it helped to reduce the number of false positive and negative responses, therefore offering a more accurate prevalence measure of being normal and being diabetic. The sample survey was an independent survey focusing entirely on normal and diabetic subjects.

Administrative collections and registries are composed of information that is collected as part of the normal operation of some service or programme. In this case, it is the information found on the participant's informed consent form. These collections provided useful information on the characteristics of people accessing normal routine and diabetes services as well as details about the services provided. They do not guarantee an accurate measure of non-diabetes and diabetes prevalence since there would be no coverage of events. The quality of this type of administrative register information is closely related to the quality of administrative system, in particular, how well it has been maintained and how closely the concepts align with the normal and diabetic subjects' concept of interest. In this work, most of the diabetic subjects were drawn from members of the Diabetic Society of Nigeria (DAN), who already have established meeting days and documented records.

The second preliminary issue that was addressed was the unit for which the diagnostic parameters were measured. The selection unit was a collection of normal and diabetic subjects. The measurement unit was mmol/l for the blood sugar and percent (%) for HbA1c.

For the analysis, the diabetic indices comprising the FBS were analyzed using Randox Kits (RANDOX, USA) while HbA1c test was analyzed using Wondfo Finecare System (WONDFO, CHINA). Thyroid Function was analyzed using Accubind Elisa Kits (ACCUBIND, USA).

The quantitative determination of TSH concentration in human serum was done by a Microplate Immunoenzymometric assay[20].

The quantitative determination of fT3 concentration in human serum was done by a Microplate Enzyme Immunoassay[21].

The quantitative determination of fT4 concentration in human serum was done by a Microplate Enzyme Immunoassay[22].

HbA1c was determined using the Fine care™ HbA1c Rapid Quantitative Test which is a fluorescence immunoassay used for quantitative determination of HbA1c in human blood[23].

The quantitative *in vitro* determination of FBS in serum and/or plasma was done on the Randox (Rx) Monza analyser.

All data were subjected to statistical analyses. Statistical analysis was performed using SPSS version 21 (IBM, U.S.A). The data was analyzed using one-way analysis of variance (ANOVA) and significant differences were determined using post Hoc Duncan multiple comparison test ($p<0.05$). The results were considered significant at 95% confidence level. The values were represented as mean ± standard deviation (SD) and data obtained was analyzed using the SPSS. Data was shown as mean $\pm$ SD and displayed in figures. Qualitative variables of gender categories were summarized as proportions. Quantitative variables such as age were summarized as mean. Difference in mean of parameters was compared using analysis of variance (ANOVA).

RESULTS

Glycemic indices and thyroid function of subjects

The results obtained for the glycemic indices and thyroid function levels are shown in Table 1.

FBS and HbA1c (Glycemic indices), and Thyroid Function profile (TSH, fT3, and fT4) of the subjects are shown in Table 1.

The FBS and HbA1c showed a significantly increasing trend with values of 4.49±0.08 mmol/l, 6.00±0.11 mmol/l, and 10.84±0.96 mmol/l for FBS; and 4.75±0.05 mmol/l, 5.73±0.08 mmol/l, and 9.74±0.47 mmol/l for HbA1c, for the non-diabetics, pre-diabetics, and diabetics respectively. All values were significantly higher ($p<0.05$)across the groups for both FBS and HbA1c. The fT3 and fT4 showed progressive decrease in values having values of3.22±0.11pmol/L, 3.0±0.12pmol/L, and 2.61±0.09pmol/L for fT3; and 1.11±0.05ng/dL, 1.07±0.06ng/dL, and 0.97±0.05ng/dL for fT4; respectively for the non-diabetics, pre-diabetics, and the diabetics while the TSH values increased significantly when compared to the normal. TSH for the pre-diabetic group was however slightly higher than that for the diabetics as shown in Table 1 below.

Table 1 Fasting Blood Sugar and HbA1c (Glycemic indices), and Thyroid Function profile of the subjects.

GROUP	FBSmmol/l	HbA1c mmol/l	TSH mU/ml	fT3 pmol/L	fT4 ng/dL
NON-DIABETIC	4.49±0.08[bc]	4.75±0.05[bc]	1.55±0.15[bc]	3.22±0.11[bc]	1.11±0.05[c]
PRE-DIABETIC	6.80±0.11[ac]	5.73±0.08[ac]	3.97±0.09[a]	3.05±0.12	1.07±0.06
DIABETIC	10.84±0.96[a]	9.74±0.47[a]	3.72±0.08[ab]	2.61±0.09[ab]	0.97±0.05[ab]

Data are expressed as Mean ± Standard deviation (SD), n=120 where n represents the number of subjects. Values in the same column with similar superscript letter a, were significantly higher ($p<0.05$) than that of the non-diabetic. Values with the superscript b, were significantly lower ($p<0.05$) than that of the pre-diabetic. Values with the superscript c, were significantly lower ($p<0.05$) than that of the diabetic group.

Where: FBS – Fasting Blood Sugar, HbA1c – Glycated Haemoglobin, TSH – Thyroid Stimulating Hormone, fT3 – Free Triiodothyronine, fT4 – Free Thyroxine

DISCUSSION

Analysis of thyroid function (TSH, fT3 and fT4) in the subjects showed that the thyroid function of pre-diabetics and diabetics differed significantly from that of the normal non-diabetic subjects. There was a significant increase in the TSH of the pre-diabetic and diabetic subjects and this increase was highest in the pre-diabetic subjects which suggest that the diabetic subjects may have already taken intervention measures. On the other hand, fT3 and fT4 were decreased in the pre-diabetic and diabetic state. The decrease in fT3 and fT4 followed the glycaemic state as indicated by the FBS and HbA1c levels and was lowest in the diabetic subjects. Thyroid dysfunction is widely reported in diabetes[24].

Diabetes mellitus and thyroid dysfunctions are two commonly encountered endocrine disorders encountered in the hospital clinic. In a hospital-based study in India, 20% of diabetic subjects were found to have hypothyroidism[24,25].

Our study was in agreement with this as we found fT3 and fT4 to be lower in the diabetic compared to the pre-diabetic and normal groups with increased Glycaemia as represented by the FBS and HbA1c concentrations.

CONCLUSION

This study assessed thyroid hormone levels and the findings largely corroborated previous studies. The study revealed that thyroid function is altered in diabetic subjects.

RECOMMENDATIONS

It is recommended that the thyroid function levels of subjects attending clinics for diabetic care should be checked routinely. This research should be further carried out using larger population of subjects. The research should also be conducted in various geographical locations as variations in different locations affect the genetic factor and limit the generalization of the research findings.

CONTRIBUTION TO KNOWLEDGE

The return of some diabetic markers assayed through the administration of varying doses of the standard drug shelped in the control of diabetes mellitus by ameliorating its effect.

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