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Thyroid dysfunction in type 2 diabetics seen at the University College Hospital, Ibadan, Nigeria

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Summary: Thyroid dysfunction complicates the metabolic derangement observed in Diabetes Mellitus (DM). It is necessary to recognize and treat it when present in order to achieve stability of metabolic control in these patients. The prevalence of thyroid dysfunction in type-2 diabetics in our environment is not known. This study was therefore designed to determine the prevalence of thyroid dysfunction in Type 2 diabetics seen at the Metabolic Research Unit of University College Hospital, Ibadan, Nigeria. Serum TSH, Free T3 & Free T4 assays were performed using Automated Enzyme Immunoassay platform on fresh sera from volunteers comprising 64 adult type 2 diabetics and 36, age matched, non diabetic controls; weight, height and blood pressures were measured in all subjects. In addition, past lipid profile results of type 2 diabetics were retrieved from medical records. Thyroid dysfunction was present in 19 (29.7%) of 64 type 2 diabetics and 1 (2.8%) of 36 non diabetic controls ($P< 0.05$). The prevalence of thyroid dysfunction is 32.4% in females and 25.9% in males. Secondary hypothyroidism was seen in 78.9%, sub-clinical hypothyroidism in 15.8%, and sub-clinical hyperthyroidism 5.2% of subjects with thyroid dysfunction. Abnormal lipid profiles were seen in 35.4% of euthyroid type 2 diabetics and 100% of hypothyroid type 2 diabetics ($P<0.05$). 87.5% of type 2 diabetics and 38.8% of controls were hypertensive ($P<0.05$). 7.8% of type 2 diabetics and 50% of controls were obese ($P<0.05$). The prevalence of thyroid dysfunction in type 2 is higher in type 2 diabetics than in controls. More of Type 2 diabetics were obese and more of them were hypertensive compared to controls. The approach of using TSH first in screening for thyroid dysfunction is not sufficient in type 2 diabetics. Routine screening for thyroid dysfunction should be carried out in type 2 diabetics.
Keywords: Thyroid dysfunction, Diabetes, Ibadan, Nigeria

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INTRODUCTION

Thyroid dysfunction is a spectrum of disorders of the thyroid gland which manifests either as hyper - or hypothyroidism and is reflected in the circulating levels of thyroid stimulating hormone (TSH) (Tunbridge et al, 1977).

Thyroid hormones, namely Tri-iodothyronine (T3) and Thyroxine (T4); either or both of which may be elevated or reduced have both direct and indirect effects on blood glucose homeostasis (Udiong et al., 2007). Elevated levels of free circulating thyroid hormones (hyperthyroidism) produce hyperglycaemia by causing polyphagia, enhancing glucose absorption from the gastro-intestinal tract, accelerating insulin degradation and stimulating glycogenolysis (Loeb, 1996). Reduced levels of the hormones (hypothyroidism) may cause hypoglycaemia (Loeb, 1996; Cooper, 2003).

The prevalence of thyroid dysfunction is higher in diabetics than in controls. This has been estimated to be between 10 to 15% in diabetes compared to 6% in the non-diabetic population (Wu, 2000; Johnson, 2006; Udiong *et al*, 2007). Numerous studies reported and justified this finding in type 1 diabetics (Cardoso et al., 1995; Wu, 2000; Sherman and Gagel, 2005; Johnson et al., 2006) and only two studies reported the same finding in type 2 diabetics (Perros et al., 1995; Radaideh et al, 2004).

Although autoimmunity, in which circulating antibodies exist to numerous body tissue components destroy such tissues was stated to be the underlying mechanism behind the increased prevalence of thyroid disorders in type 1A diabetes (Hawa et al, 2006), despite the fact autoimmune thyroid diseases are known to be highly prevalent in all forms of diabetes; no specific reason has been adduced for an increased prevalence of thyroid disorders in antibody negative (type 1B) or type 2 diabetics (Wu, 2000; Radaideh et al, 2004). However, insulin; the hormone required for transporting glucose from plasma across cell membranes into the cytosol of many cells (including those of the skeletal muscle) is absolutely deficient in type 1 diabetics and relatively deficient in type 2 diabetics. Some authors have postulated that insulin treatment in type 1 diabetics and insulin resistance with resultant high plasma insulin levels in type 2 diabetes may equally predispose both groups to deranged thyroid function (Radaideh et al, 2004; Udiong et al 2007; Pasupathi et al, 2008).

Type 2 diabetes is reported in association with hypothyroidism in the rare Crow-Fucase syndrome

(also called POEMS syndrome). This syndrome consists of polyneuropathy, organomegaly, endocrinopathies (which includes thyroid dysfunction), multiple myeloma and skin changes. One-third of patients with POEMS syndrome have type 2 diabetes mellitus (Mullai et al 2001). Type 2 diabetes accounts for > 90% of diabetes burden all over the world (ADA, 2007) despite the fact that it is grossly underdiagnosed(Sobnigwi et al, 2002). Because of the insidious nature of type2 DM, it often remains undiagnosed until late into the disease when complications have set in (Sobnigwi *et al*, 2002; Alvin et al, 2005; ADA, 2007). The prevalence of type 2 DM is rising faster than any other form of diabetes because of increased urbanization which encourages development of obesity due to reduced physical activity, increased consumption of refined foods and snacks globally (Zimmet, 1999; Zimmet et al, 2001).

Hypothyroidism, the most commonly diagnosed thyroid dysfunction in all studies conducted so far; has greater implications for type 2 diabetics in whom there is pre-existing dyslipidaemia and the risk of cardiovascular disease is increased (Cooper, 2003; Rama et al, 2003; Johnson, 2006). The only available studies of thyroid dysfunction in type 2 diabetics are from Portugal and Jordan (Perros et al, 1995; Radaideh et al, 2004). The study by Cardoso et al, (1995) was on type 1 diabetic Nigerians in Lagos while Udiong et al (2007) studied a mixed population of diabetic Nigerians in Calabar. There is the need to know the prevalence, the pattern and the effects of thyroid dysfunction in a purely type 2 diabetic population in Nigeria. The prevalence of thyroid dysfunction in type-2 diabetics in Nigera is not known. This study was therefore designed to determine the prevalence of Thyroid Dysfunction in Type 2 Diabetics seen at the Metabolic Research Unit of University College Hospital, Ibadan, Nigeria.

MATERIALS AND METHODS

This study was carried out at the Metabolic Research Unit of the University College Hospital, Ibadan, Nigeria between August 2008 and February 2009. Study subjects include 64 adult, known type 2 diabetic patients and 36 non diabetic controls of similar ages without evidence of thyroid disease, who gave voluntary informed consent to participate in the study. Questionnaires were administered to record findings on general physical examination, past medical, drug and family histories of volunteers. In addition, Type 2 Diabetics had their hospital files reviewed to verify their ages at diagnosis, their past lipid profile results, the adequacy of their glycaemic controls, the presence of complications and the medications they take. Type 2 diabetics diagnosed at ages below 30 years or those suffering from other acute illnesses/starvation/stress, those with previous evidence of thyroid disease or treatment for same, those on drugs known to affect thyroid function and pregnant women were excluded.

Diabetes Mellitus (DM) was ruled out in controls using Fasting Plasma Glucose (FPG). Those with FPG < 6.0mmol/L were accepted as controls if they are not on any hypoglycaemic medication. Ethical approval for this study was obtained from the joint Health Research Ethical Committee of the University of Ibadan and University College Hospital, Ibadan (UI/UCH-HREC).

Venous blood samples of participants were collected into plain serum bottles, allowed to clot and the serum was separated by centrifugation within 3 hours of collection. These sera were kept frozen at -20^{o}C until analysis. Frozen sera from the 64 Type 2 Diabetics and 36 controls were thawed and assayed for TSH, FT3 and FT4 in three runs, each on a different day using an automated immunoassay platform (AIA-600II) by TOSOH BioScience Inc. Japan.

Control samples provided in the reagent packs were analysed daily with each run of these analytes according to manufacturer's instruction. Co-efficient of Variations (C.V) for TSH, FT3 and FT4 are presented in table 1. The reference ranges for the analytes measured are presented in table 2. TSH and FT4 assays were performed before and after spiking three serum samples with three different levels of both analytes, recovery values ranged between 96.7% and 109.4% for all assays. The above procedure was repeated with serial dilutions of serum samples containing high concentrations of TSH and FT4, recovery values ranged between 98.3% and 101.3%.

TSH below 0.38mU/L is regarded as low and TSH above 4.31mU/L is regarded high. Similarly, FT3 below 3.2pmol/L or above 5.9pmol/L are regarded low and high respectively and FT4 below 10.6pmol/L and above 21.0pmol/L are regarded low and high respectively. An elevated TSH is interpreted as hypothyroidism, in this condition, if FT4 is low it is overt hypothyroidism, if FT4 is normal it is referred to as mild (subclinical) hypothyroidism, if FT4 is high it is secondary hyperthyroidism or thyroid hormone resistance. A low FT4 which in this setting is not artefactual, when seen in association with a low or normal TSH is regarded as secondary hypothyroidism whether FT3 is low or not. When TSH is low, it is regarded as overt hyperthyroidism which may be primary if FT4 is high, mild

hyperthyroidism if FT4 is normal and secondary hypothyroidism if FT4 is low (table 3).

The glycaemic control was assessed by the average values of their fasting and 2 hour post prandial glucose (2HPPG) levels in the 6 months preceding this study which is available for all of them (glycated haemoglobin was not readily available). The Glycaemic Control (GC) was graded as "good" if average FPG in the past six months is ≤ 7.2mmol/l(130mg/dl) and 2HPPG is ≤ 10.0mmol/l (180mg/dl), and "poor" if either FPG average is >7.2mmol/l or 2HPPG average is >10.0mmol/l.

Body Mass Indices (BMIs) were calculated from their weights measured in kilograms (kg) and heights in metres (m) using the standard formular. Subjects were classified "normal weight" if BMI is <25 or "abnormal weight" (Overweight/Obese) if BMI is 25 or higher. Blood Pressure (BP), measured with a manual sphygmomanometer was taken on two occasions; and the average of two readings (each taken on a different day at least a week apart after initial evaluation) following standard procedure was recorded. Normal BP was defined as a Systolic BP < 140mmHg and/or Diastolic BP < 90mmHg in an adult who is not on treatment for hypertension. Subjects who fail to satisfy these criteria were considered to have a high BP (Table 4).

Lipid profile results were categorised as either Normal or Dyslipidaemic according to the World Health Organisation (WHO) risk categorisation of plasma lipid values. Those with Total Cholesterol and/or Low Density Lipoprotein (LDL-) Cholesterol and/or triglyceride above the optimal level, or High Density Lipoprotein (HDL-) Cholesterol below the optimal level for individuals at risk of developing cardiovascular disease were classified "dyslipidaemic".

Statistical Analysis was done using SPSS Version 13 for windows. The differences observed between cases and controls with regards to qualitative variables (sex, lipid profile, and glycaemic control) were assessed using Pearson's Chi-Square test while the differences observed in the two groups with regards to quantitative variables (age and BMI) were tested for significance using Student's t-test. Statistical significance was defined by a P-value < 5% (0.05).

RESULTS

The general clinical characteristics and demographic features of the study population (n=100) are presented in Table 4. Sixty-four patients (27 males and 37 females) are type 2 diabetics who are the study subjects and the remaining 36 are the control subjects. The mean ages ± (2SD) of study subjects and controls are 50.1±18.9years (range 32-66years) and 53.8±24years (range 30-70years) respectively. Thyroid dysfunction was found in 29.7% out of type 2 DM patients, and in 2.8% of controls (P=0.002).

Table 1. Precision profile for TSH, FT3 FT4 assays.

Control	Sample	Within-Run C.V	Between Run C.V
TSH	A	2.9%	5.0%
	B	2.3%	4.8%
	C	2.5%	4.4%
FT3	A	4.7%	6.9%
	B	3.9%	4.8%
	C	2.4%	3.6%
FT4	A	3.3%	4.9%
	B	2.7%	3.5%
	C	1.8%	2.4%

C.V=Coefficient of Variation

Table 2.
Reference values for TSH, FT3 & FT4 using AIA-600II (TOSOH)

ANALYTE	REFERENCE RANGE
TSH (mU/L)	0.38-4.32
FT3 (pmol/L)	3.2-5.9
FT4 (pmol/L)	10.6-21.0

TSH = Thyroid Stimulating Hormone, FT3 = Free Tri-iodothyronine, FT4 = Free Thyroxine

Those with thyroid dysfunction consists of 12(32.4%) out of 37 diabetic females and 7(25.9%) out of 27 diabetic males. This puts the overall prevalence of thyroid dysfunction in type 2 diabetics at 32.4% and 25.9% in females and males respectively (Tables 5).

Table 3. Criteria for diagnosis of thyroid dysfunction in this study

TSH	FT4	FT3	Diagnosis
→	→	→	Euthyroid
↑	→	→	SCl. Hypothyroidism
↓	→	→	SCl. Hyperthyroidism
→	↓	↓	2^0 hypothyroidism

SCl = sub clinical, 2^0 = secondary, ↑= High, → = Normal, ↓= Low

The pattern of thyroid dysfunction observed in the Type 2 DM Patients and the controls is presented in table 3. Fifteen (78.9%), out of 19 study subjects with thyroid dysfunction have secondary hypothyroidism and these include 10 females and 5 males whose TSH values were within the stipulated reference range and FT3 & FT4 were both low (table 4), three (15.8%) of them have mild (sub-clinical) hypothyroidism with high TSH while both FT3 & FT4 were normal. One person (5.2%) has subclinical hyperthyroidism (table 5). Seven (25.9%) of twenty seven type 2 diabetic males, and twelve (33.6%) of thirty seven female type 2 diabetics have thyroid dysfunction (table 5).
Fifty (71.8%) of sixty four type 2 diabetics and eighteen (50%) of thirty six controls were either overweight or obese (P = 0.004), while 87.5% of type 2 diabetics versus 38.8% of controls were hypertensive (P=0.000).

Lipid profile results were available for 43 out of 64 study subjects, these include 31 out of the 45 euthyroid type 2 diabetics and 12 out of the 19 type 2 diabetics with thyroid dysfunction (see table 6). Eleven (35.48%) of the 31 results of the euthyroid type 2 diabetics show dyslipidaemia as against their twelve (100%) hypothyroid counterparts (P = 0.001). Lipid profile result was not available for the single patient with subclinical hyperthyroidism (Table 6).

The mean age and BMI across diagnostic groups in type 2 diabetics were presented in table 3. There is no significant age and BMI difference between the thyroid type 2 diabetics and those with thyroid dysfunction. The only control subject with thyroid dysfunction (subclinical hyperthyroidism) is a 43year-old, normotensive female with a normal weight.

Table 4.
Demographic and Physical Characteristics of the Study Population.

Characteristics		Diabetics	Controls
Sex:	male	27	13
	female	37	23
mean age (years)		50.06	53.78
BMI	normal	14	18
	obese	50	18
BP:	normal	8	22
	high	56	14
Diagnosis	Eu	45	35
	Dys	19	1

BP = Blood Pressure, BMI = Body Mass Index, Eu = Euthyroid, Dys =. Thyroid Dysfunction

Table 5.
Thyroid function pattern in Type 2 Diabetics and Controls

Thy. function		Diabetics	Controls	Total
Euthyroid	male	20	15	35
	female	25	20	45
	Total	**45(70.3%)**	**35((97.2%)**	**80**
2^0 Hypo	male	5	------	5
	female	10	--------	10
	Total	**15(23.4%)**	---------	**15**
SCl. Hypo	male	1	----------	1
	female	2	----------	2
	Total	**3(4.7%)**	----------	**3**
SCl. Hyper	male	1	----------	1
	female	–	1	1
	Total	**1(1.6%)**	**I(2.8%)**	**2**
Grand total		**64(100%)**	**36(100%)**	**100**

2^0 Hypo.= Secondary Hypothyroidism, SCl. Hypo = Subclinical Hypothyroidism, SCl. Hyper = Subclinical Hyperthyroidism.

TABLE 6.
Qualitative Variables and Thyroid Function in Type 2 Diabetics

Variable		**Eu**	**2^0 Hypo**	**SCl. Hypo**	**SCl. Hyper**
LP :	Total	35	9	3	--
	Dyslip	11 (35.5%)	9 (100%)	3(100%)	--
GC:	Total	45	15	3	1
	Poor	18(40%)	11(63.6%)	2(66.7%)	1(100%)
Sex:	Male	20	5	1	1
	Female	25	10	2	--
BMI:	Total	45	15	3	1
	>25	37	10	1	1
Age (yr):	Total	45	15	3	1
	≥50	37	15	2	1

L.P = Lipid Profile, G.C = Glycaemic Control, OHA = Oral Hypoglycaemic Agents, Dyslip = Dyslipidaemia, Insul.= Insulin.Eu = Euthyroid; 2^0Hypo = Secondary Hypothyroidism; Scl. Hypo = Subclinical Hypothyroidism = Scl. Hyper = Subclinical Hyperthyroidism.

DISCUSSION

Thyroid dysfunction is known to be more prevalent in type 1 diabetics compared to the general non diabetic populations. The prevalence of thyroid dysfunction

had also been reported to be higher in type 2 diabetics in Jordan and in the United Kingdom but it is still not clear which event precedes which. This is so because type 2 diabetics are not routinely screened for thyroid dysfunction upon diagnosis. The hyperglycaemia seen in diabetics is known to have negative effects on thyroid function precisely blunting the pituitary TSH response to stimulation by hypothalamic TRH. This may be due to possible alteration of post translational glycosylation of TRH thus affecting the biological activity. This mechanism suggests that diabetes may predispose to thyroid dysfunction.

However, both hypothyroidism and hyperthyroidism are known to have adverse effects on glycaemic control in diabetics with hyperthyroidism on its own resulting in diabetes. This study entails screening for biochemical evidence of thyroid disease in a purely type 2 diabetic Nigerian population who did not have symptoms or signs of thyroid dysfunction; and an 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.

The findings in this study include; an overall thyroid dysfunction prevalence significantly higher ($p<0.05$) in type 2 diabetics than in controls. This finding agrees with those of Radaideh et al (2004) and Smithson (1998) both of whom reported similar findings in Jordan and in the UK respectively. However the prevalence rate of 29.7% found in type 2 diabetics in this study is much higher than 10.8% reported by Smithson (1998) in the UK and 12.5% reported by Radaideh et al (2004) in Jordan.

The notable differences in prevalence observed in these studies may be explained by the (1) racial, sex and age differences between the populations studied and (2) methodological differences between this study and the other studies. Racial factors are recognized causes of variation in epidemiology of diseases. While this study was carried out on Nigerian subjects, Radaideh et al (2004) studied Arabian subjects in Jordan and The Smithson (1998) studied British subjects in the UK. TSH, FT3 & FT4 were assayed on an Automated Immunoassay Analyser (AIA) format while the Jordanian study used a manual technique based on ELISA principle. Modern AIAs have better analytical performance characteristics compared to manual methods.

The finding of a sex related prevalence rate of 32.4% in female and 25.9% in male type 2 diabetics in this study also agrees with the previous works of Tunbridge et al (1977), Udiong et al (2007), Wu (2000), Johnson (2006) and Rama (2003) who reported higher prevalence of thyroid dysfunction in females than in males not only in diabetics but also in the non-diabetic population. None of these studies gave reasons other than age because the prevalence of both disorders i.e. thyroid dysfunctions and type 2 diabetics increase with age.

Hypothyroidism found in 18 out of 19 Type 2 Diabetics with thyroid dysfunction in this study is also in agreement with all previous studies cited above including the Wickham survey(Tunbridge et al, 1977) and the Colorado study (Sobnigwi et al, 2002) which reported hypothyroidism as the most prevalent form of thyroid dysfunction observed in all the studies.

However, the finding of secondary hypothyroidism in the majority (78.9%), of those with thyroid dysfunction with subclincal hypothyroidism constituting only 15% of cases in this study; coming only next to secondary hypothyroidism in prevalence, is in sharp contrast with the earlier studies of Cooper (2003), Johnson (2006), Radaideh et al (2004), Rama et al (2003), Weetman (1997), all of which reported subclinical hypothyroidism as the most prevalent thyroid dysfunction. Of all these, only Radaideh et al (2004) studied purely type 2 diabetic patients who are of Arab extraction.

Although secondary hypothyroidism is believed to be very rare in the general population, there is no report on its prevalence in a special population like type 2 diabetics. Age 50 years or above, female sex, pituitary disease, surgery or irradiation and Sheehan's syndrome are some of the predisposing factors to secondary hypothyroidism. Hypothalamic TRH deficiency (tertiary-hypothyroidism) is a differential diagnosis which may be discountenanced in this situation because hyperglycaemia itself is known to induce a low T3 state and absence of TSH response to TRH. Chronic hyperglycaemia in these patients via the above mechanism results in atrophy of the thyroid gland. Most (66.7%) of these patients are females above 50 years of age and suffer from chronic hyperglycaemia as a result of poor glycaemic control. One of them is a 56year old woman with Sheehan's syndrome diagnosed about 20 years ago. For these reasons, trying a TRH stimulation of TSH to distinguish a secondary from a tertiary hypothyroidism may not be worthwhile.

The single hyperthyroid TSH 2.8 mU/l, FT4 24.5 pmol/l and FT3 3.6pmol/l) type 2 diabetics in this study is a male and this agrees with Udiong et al, (2007) who reported a higher prevalence of hyperthyroidism in male diabetics in Calabar.

Dyslipidaemia is present in 100% of hypothyroid type 2 diabetics with lipid profile results as compared to 35.48% of their euthyroid counterparts ($P=0.001$) This finding agrees with that of and Rama et al (2003) who found a significant association between hypothyroidism and dyslipidaemia in Hyderabad, but

differs from Nobre et al, (2002) who found no difference between hypothyroid and euthyroid type 2 diabetics in Portugal. Type 2 DM on its own is associated with atherogenic dyslipidaemia the way hypothyroidism also is; that may explain the finding of dyslipidaemia in 100% of hypothyroid dyslipidaemia in this study. Apart from this, type 2 diabetes is found in association with atherogenic dyslipidaemia, central obesity and hypertension in the insulin resistance syndrome (Metabolic Syndrome). More than 25% of type 2 diabetics in the US have this syndrome (Zimmet et al, 2001).

Type 2 diabetics in this study are not significantly heavier than non diabetic controls ($P>0.05$); this is contrary to the findings of Zimmet et al (2001) who reported an increased prevalence of overweight and obesity in type 2 diabetics. However, the average blood pressure which is significantly higher than that of controls ($P<0.05$) in this study agrees with Zimmet et al (2001) and many other studies which reported an increased prevalence of hypertension in type 2 diabetics.

The index of glycaemic control used in this study is plasma glucose average in the last 6 months preceding this assay, only one of those with good glycaemic control and 2 of those with poor glycaemic control had an HbA1c result to confirm the FPG-average based categorization as "good" or "poor" control. Forty percent of euthyroid, 63.6% of secondary hypothyroid, 66.7% of of subclinical hypothyroid and 100% of subclinical hyperthyroid type 2 diabetics in this study respectively show poor glycaemic control ($P>0.05$). This shows, contrary to the view of some authors; that glycaemic control may not be influenced by thyroid function status in this study. No significant association was found between medications used and thyroid function status in type 2 diabetics in this study. The limitation here is that many other (confounding) variables, notably treatment compliance which influence glycaemic control cannot be monitored.

In summary, the prevalence of thyroid dysfunction is higher in Type 2 DM (as it is in Type 1 DM) than that in the general population, more females are affected than are males. Secondary hypothyroidism is the commonest thyroid dysfunction in type 2 diabetics here in Ibadan. Dyslipidaemia is almost always present in hypothyroid type 2 diabetics. Routine screening and regular monitoring of type 2 Diabetics for thyroid dysfunction is warranted. The TSH- first approach to screening for thyroid dysfunction is not adequate for type 2 diabetics. There is the need to determine method specific reference intervals for local application to allow an unbiased interpretation of thyroid function tests in our citizens

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