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RESEARCH

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Thyroid hormones and glycaemic indices in euthyroid, hyperthyroid, hypothyroid, all type 2 diabetics and non-diabetic subjects

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Abstract

Background: Abnormal thyroid hormone levels have been reported in type 2, but the relationship between thyroid hormone levels and glycaemic indices: fasting plasma glucose (FPG), C-peptide (C-pep) and glycated haemoglobin (HbA_{Ic}), used in the management of type 2 is not well defined. This cross-sectional study examined the relationship between thyroid hormones and glycaemic indices in type 2.

Results: Positive correlations were observed between FPG and HbA_{Ic} in hypothyroid ($r=0.382$, $P=0.011$) and hyperthyroid group ($r=0.295$, $P=0.012$). FPG correlated with C-pep in hyperthyroid diabetics ($r=0.481$, $P<0.001$). HbA_{Ic} and TSH correlated positively in hypothyroid diabetics ($r=0.330$: $P=0.031$). HbA_{Ic} also correlated with T_4 in hypothyroid diabetics ($r=0.379$: $P=0.012$). C-peptide and TSH correlated positively in hyperthyroid diabetics only ($r=0.279$; $P=0.042$). C-peptide also correlated with T_3 and T_4 in euthyroid diabetics ($r=0.231$, $P=0.020$; $r=0.248$, $P=0.045$), respectively.

Conclusion: The presence of abnormal levels of thyroid hormones influenced glycaemic indices in type 2 population. This implies that thyroid hormones investigation can assist in proper diagnosis and management of diabetes mellitus.

Keywords: Thyroid hormones, Glycated haemoglobin, Diabetes mellitus, C-peptide

Background

Thyroid disease and diabetes mellitus are common endocrine disorders encountered in clinical practice. Both diabetes mellitus and thyroid disorders mutually influence each other (American Diabetic Association 2014). Researches indicate that there is increased incidence of type 2 globally, highlighting increased incidence of childhood type 2 diabetes mellitus (Jin et al. 2011). Predictions for the future are that in 2030 the number of persons suffering type 2 and the percentage of individuals with the disease will be more than double (Wilds et al. 2004). In developing countries, increasing morbidity of type 2 is reported (Smithson 1998). The increasing incidence of type 2 is compounded by reports of the coexistence of thyroid dysfunction with diabetes (Udiong et al. 2015). Furthermore, disturbing is the report that the thyroid disorders may present with low or raised levels of thyroid hormones (Ghazali and Abbingesuku 2010; Gursoy and Turkel 1999; O' Meara et al. 1993). Glycaemic index levels are commonly used for diagnosis and management of diabetes mellitus without due attention to the influence of thyroid hormone levels on those indices such as fasting plasma glucose (FPG), glycated haemoglobin (HbA1c) and C-peptide. Existing reports have shown that the associations between thyroid hormone and glycaemic indices are altered in diabetes mellitus (Ghazali and Abbingesuku 2010; O' Meara et al. 1993), the general notion being that thyroid hormone levels fluctuate with

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FPG. The physiological and biochemical interrelationship between insulin and thyroid hormone and the influence of both insulin and iodothyronines on the metabolism of carbohydrates proteins and lipids have been extensively studied and recorded (Additional file 1).

Endogenous production of glucose is enhanced by insulin and thyroid hormones since both FT_3 and FT_4 stimulate GLUT4 messenger RNA and protein expression in skeletal muscle and elevate glucose uptake (Kemp et al. 1997). In hyperthyroidism, increased level of thyroid hormones leads to increase GLUT4 and consequently increase hepatic output of glucose resulting in hyperglycaemia. Increased lipolysis which also occurs in hyperthyroidism results in increased levels of free fatty acid (FFA) (Maxon et al. 1975). Moreover, in hyperthyroidism, the non-oxidative disposal of glucose is enhanced resulting in overproduction of lactic acid which enters the Cori cycle and promotes further gluconeogenesis (Ghazali and Abbingesuku 2010). Hyperthyroidism is also associated with raised levels of growth hormone, glucagon and catecholamine which further impair glucose metabolism (Niki et al. 1992; Tosi et al. 2012). On the other hand, hypothyroidism also affects glucose metabolism through several mechanisms and reduced glucose production is reported. There is reduced rate of glucose production in hypothyroidism, a consequence of decreased production of GLUT4 (Kemp et al. 1997). Hypothyroidism has been recognized as insulin-resistant state due to impaired insulin-stimulated glucose utilization in peripheral tissues.

This information has not defined the interrelationship between the glycaemic indices and the relationship between the individual thyroid hormones (T_3, T_4 and FT_3) and the different glycaemic indices, namely FPG, HbA1c and C-peptide/insulin. This study evaluates the relationship between thyroid hormone levels and glycaemic indices in type 2 diabetic subjects with euthyroid, hyperthyroid, hypothyroid hormone levels and in non-diabetic control subjects.

Methods

Study location/subject selection

This was a cross-sectional study involving one hundred and seventy type 2 diabetic subjects attending University of Calabar teaching hospital, University of Calabar Medical Centre, Luciama Memorial Specialist hospital and Mediscience laboratories Ltd. to monitor their glucose levels as the diabetic subjects. They were all residents of Calabar, Cross River State, Nigeria. All diabetic subjects were confirmed type 2 who previously had or were having fasting plasma glucose concentrations above 6.1 mmol/l and were receiving treatment for the ailment. Apparently healthy age (38–60 years) and sex match non-diabetic volunteers also residing in Calabar served as control subjects all of whom had fasting plasma glucose levels below 6.1 mmol/l. All subjects were briefed on the objectives of the study verbally, and informed consent was obtained. Very ill diabetics and patients with diabetic complications on admission were excluded from the study. The subjects under study were divided into 5 groups as follows: all type 2, euthyroid, hypothyroid, hyperthyroid type 2 diabetics and non-diabetic subjects. The parameters selected for thyroid profile were thyroid-stimulating hormone: TSH, triiodothyronine T_3, thyroxine, T_4 and free thyroxine, FT_4, which allowed assessment of TSH, FT_4, T_4 and T_3 under the 5 groups studied.

Sample collection

Criteria for selection of type 2 diabetic subjects were: age of onset of diabetic as greater than 37 years, type of treatment the patient was receiving and their physician's diagnosis on the patient records such diabetic subjects had fasting C-peptide levels of 0.38 ng/ml or above and were responding to treatment. Both the diabetic and non-diabetic control subjects were instructed to fast overnight (at least 8 h), before blood samples were collected from them. Ten millilitres of venous blood was collected from each subject and dispensed as follows: 2 ml into fluoride oxalate bottle for plasma glucose estimation, 2 ml into EDTA bottle for glycated haemoglobin (HbA_{1c}) and the remainder into a plain bottle from where serum was harvested and stored frozen at −20°C until use for thyroid hormones and C-peptide assays.

Laboratory methods

ELISA reagent kits obtained from Dslab Inc., California, USA, were used for the estimation of thyroid-stimulating hormone (TSH), total triiodothyronine (T_3), total thyroxine (T_4), free thyroxine (FT_4) and C-peptide. Reagent kits obtained from UNICO Inc., USA, were used for the estimation of HbA1c, while Trinder glucose oxidase method (Trinder 1969) was used for the measurement of FPG.

Statistical analyses

Statistical analysis was performed using SPSS version 18.0. Pearson's correlation was used for correlation analyses. Quality control of procedures was done using control sera at low, normal and raised levels as provided by the reagents' manufacturers. The results obtained were expressed as mean ± SD. The level of significance was set at $P<0.05$.

Results

FPG and HbA_{1c} were positively correlated in all type 2 diabetic group ($r=0.211$, $P=0.007$) and in the hypothyroid type 2 diabetic subjects ($r=0.382$, $P=0.011$) and hyperthyroid groups ($r=0.295$, $P=0.011$). FPG also correlated positively with C-pep in all type diabetics ($r=0.224$, $P=0.004$) and hyperthyroid type 2 subjects ($r=0.481$, $P=<0.001$). There was no significant correlation between FPG and HbA_{1c} or C-pep in the other group (Table 1). There were no significant correlations between FPG and all the thyroid hormones.

HbA_{1c} correlated positively with TSH in all type 2 ($r=0.211$, $P=0.012$) and in hypothyroid subjects ($r=0.330$, $P=0.031$), and there was positive association between HbA_{1c} and T_4 in all types ($r=0.194$, $P=0.038$) and the hypothyroid groups ($r=0.379$, $P=0.012$). There were no observed correlations in other groups (Table 2).

Table 3 shows a positive correlation between C-peptide and FT_4 only in the hyperthyroid group ($r=0.279$, $P=0.042$) and negative correlation between C-pep and T_4 in the euthyroid group. There were also significant positive correlations between C-peptide and T_3 in all type 2 and euthyroid diabetic groups. C–peptide did not correlate with TSH in any of the five groups of subjects.

Discussion

The coexistence of both low and raised levels of thyroid hormones in type 2 diabetic subjects I has been reported in many studies (Gursoy and Turkel 1999; O' Meara et al. 1993; Kemp et al. 1997; Maxon et al. 1975), but currently, glycaemic indices: FPG, HbA_{1c} and C-peptide levels, are frequently used for the diagnosis, evaluation and management of diabetic subjects without due attention to the possible effects of the coexistence of low or raised thyroid hormone levels alongside type 2 diabetes in those subjects.

In this study, FPG correlated positively with HbA_{1c} in all type 2, hypothyroid and hyperthyroid groups. Glycation is said to be a non-enzymatic catalysed reaction (Udiong et al. 2007), and thus, our current findings suggest that

Table 1 Correlation analysis between FPG and C-pep, HbA_{1c} and thyroid profile in all type 2 diabetics, euthyroid, hypothyroid, hyperthyroid diabetic and non-diabetic control subjects

Subjects	All type 2 diabetics		Euthyroid diabetics		Hypothyroid diabetics		Hyperthyroid diabetics		Non-diabetic controls	
n	170		80		50		40		110	
Analysis	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
FPG vs HbA_{1c}	0.221	0.007*	0.163	0.104	0.382	0.011*	0.295	0.011*	0.295	0.709
FPG vs C-pep	0.224	0.004*	0.111	0.850	0.194	0.076	0.481	0.001**	0.018	0.606
FPG vs TSH	0.101	0.233	0.610	0.118	0.118	0.136	0.132	0.281	0.048	0.688
FPG vs FT_4	0.127	0.133	0.133	0.315	0.055	0.580	0.153	0.160	0.003	0.973
FPG vs T_4	0.072	0.333	0.093	0.341	0.093	0.341	0.137	0.204	0.163	0.104
FPG vs T_3	0.049	0.562	0.027	0.176	0.027	0.176	0.132	0.104	0.003	0.973

FPG fasting plasma glucose, *HbA_{1c}* glycated haemoglobin, *C-pep* C-peptide, *TSH* thyroid-stimulating hormone, *FT_4* free thyroxine, *T_4* total thyroxine, *T_3* total triiodothyronine

Table 2 Correlation analysis between HbA_{1c} and C-pep and thyroid hormones in all type 2, euthyroid, hypothyroid, hyperthyroid diabetics and non-diabetic subjects

Subjects	All type 2 diabetics		Euthyroid diabetics		Hypothyroid diabetics		Hyperthyroid diabetics		Non-diabetic controls	
n	170		80		50		40		110	
Analysis	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
HbAlc vs C-pep	0.111	0.107	0.021	0.832	0.155	0.322	0.011	0.935	0.029	0.709
HbAlc vs TSH	0.211	0.012*	0.051	0.251	0.330	0.031*	0.175	0.104	0.009	0.929
HbAlc vs FT4	0.083	0.326	−0.133	0.312	0.023	0.186	−0.133	0.312	0.023	0.786
HbAlc vs T4	0.194	0.038*	−0.099	0.610	0.379	0.012*	0.137	0.204	0.018	0.856
HbAlc vs T3	0.020	0.808	−0.162	0.218	−0.055	0.580	−0.066	0.551	0.055	0.580

HbA_{1c} glycated haemoglobin, *TSH* thyroid-stimulating hormone, *FT_4* free thyroxine, *T_4* total thyroxine, *T_3* total triiodothyronine, *FPG* fasting plasma glucose, *C-pep* C-peptide, *r* correlation coefficient, *p* probability, *n* sample size

*Significant

Table 3 Correlation analysis between C-peptide and thyroid hormones in all type 2, euthyroid, hypothyroid and hyperthyroid type 2 diabetics and non-diabetic subjects

Subjects	All type 2 diabetics		Euthyroid diabetics		Hypothyroid diabetics		Hyperthyroid diabetics		Non-diabetic controls	
n	170		80		50		40		110	
Analysis	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
C-pep vs TSH	0.151	0.071	0.145	0.735	0.034	0.672	−0.072	0.444	0.024	0.808
C-pep vs FT4	0.221	0.013*	0.074	0.572	0.094	0.341	0.279	0.042*	0.034	0.672
C-pep vs T4	0.127	0.135	0.248	0.045*	0.119	0.226	0.156	0.150	0.094	0.341
C-pep vs T4	0.172	0.049*	0.231	0.020*	0.024	0.808	0.038	0.774	0.119	0.226

C-pep C-peptide, *TSH* thyroid-stimulating hormone, FT_4 free thyroxine, T_4 total thyroxine, T_3 total triiodothyronine, *r* correlation coefficient, *p* probability, *n* sample size
*Significant

altered thyroid hormone levels may play a role in glycation in type 2 since there was no significant association in both non-diabetic subjects and euthyroid type 2 diabetic subjects. But the positive correlations between FPG and HbA_{lc} were observed in both diabetic subjects with low and raised thyroid hormone levels prompting a conclusion that the positive association between FPG and HbA_{lc} is not driven by abnormal thyroid hormone levels; otherwise, the direction of correlation would have been opposite. The correlations observed in all type 2, hypothyroid diabetics would then depend on the FPG levels and the percentage of subjects in those groups that had raised glucose levels and the period, the hyperglycaemia lasted (Dimitriadis et al. 1985).

FPG and C-peptide were positively correlated in all type 2 and hyperthyroid groups. There were no significant correlations between the two parameters in the euthyroid, hypothyroid diabetics and non-diabetic subjects. It may thus be reasoned that raised thyroid hormone levels enhance association between FPG and C-peptide and that the positive correlation found in all type 2 diabetic group is due to the presence of diabetes with raised thyroid hormone levels in that group. Raised thyroid hormone levels promote hyperglycaemia (Beer et al. 1989) and would aggravate existing hyperglycaemia in type 2. In type 2 diabetes subjects, the raised levels of FPG trigger increased secretion of C-peptide/insulin (Beer et al. 1989; Levin and Symth 1963). The correlation between FPG and C-peptide is enhanced by hyperthyroidism which increases glucose absorption in the gut (Levin and Symth 1963), alters pro-insulin processing (Matty and Seshadri 1963) and reduces the half-life of insulin by increasing the rate of degradation and enhancing release of biologically inactive insulin precursors (Arshad and Hussain 2013). FPG levels did not correlate with TSH, FT_4, T_4 or T_3 levels in any of the 5 groups of subjects studied though positive correlation was reported between glucose and T_4 in streptozotocin-induced diabetic rats (Hage et al. 2011), and the disparity may be due to differences in the cause and intensity of diabetes in diabetic humans and induced diabetic rats. Our results imply that thyroid hormones levels are not influenced by glucose levels or vice versa. HbA_{lc} did not correlate with C-peptide in all type 2, hypothyroid, hyperthyroid and euthyroid diabetic and also in non-diabetic controls. Rather, glycated haemoglobin correlated positivity with TSH and T_4 in all type 2 and hypothyroid diabetic groups. Raised TSH levels are associated with hypothyroidism and low TSH with hyperthyroid states (Lai et al. 2011) in non-thyroidal illness state such as type 2 mellitus; the findings are not different even in the presence of complicating factors.

Glycated haemoglobin also correlated positively with T_4 in all type 2 and those with low thyroid hormone levels similar to the relationship between HbA_{lc} and TSH even though TSH levels would normally be expected to be inversely related to T_4 levels in primary thyroid disorders (Ghazali and Abbingesuku 2010). In type 2, where glucose, insulin and thyroid hormone levels are raised, there is also increased binding protein levels such thymoglobulin (TBG) level leading to raise total T_4 levels. Prolonged hyperglycaemia prompted by diabetes or hyperthyroidism will give rise to raise HbA_{lc} and correlation with T_4 as observed in the study. Moreover, the rate of conversion of T_4 to T_3 is reduced or inhibited by raised levels of insulin found in type 2 resulting in raised T_4 levels (American Diabetic Association 2014; Jin et al. 2011). There were no significant correlations between HbA_{lc} and TSH or T_4 in the euthyroid, hypothyroid and non-diabetic subjects. FT_4 and T_4 did not correlate with HbA_{lc} in any of the 5 groups of subjects. This again shows that thyroid hormones do not influence glycation process, and hence, glycated haemoglobin results can be interpreted without reference to thyroid hormone levels.

C-peptide correlated positively with FT_4 in hyperthyroid diabetic group, positively with T_4 in the euthyroid

diabetics and positively with T_3 in all type 2 and euthyroid group. The associations observed between C-peptide and FT_4, T_4 and T_3 are similar. T_3 is biologically more potent than T_4 (Niki et al. 1992), but in type 2, FT_4 increases, while T_3 decreases. In spite of the disparity in activity, the observed association between T_4, T_3 and C-peptide in diabetics with euthyroid hormones level shows that C-peptide levels are influenced by thyroid hormone levels. In type 2, insulin resistance leads to hyperglycaemia and increased C-peptide/insulin levels which may trigger thyroid hormone increase to enhance glucose metabolism, hence the correlation between C-peptide and the thyroid hormones (FT_4 and T_3). There was a positive correlation between C-peptide and T_3 in all type 2 group, but the association between C-peptide and FT_4 was not significant. The disparity may be due to the levels of and number of subjects in each of FT_4 and T_3 in the hyperthyroid group. Our study suggests that C-peptide levels are positively associated with thyroid hormones levels.

Conclusions

This study has shown that the presence of low or raised levels of thyroid hormones in the diabetic population influenced the levels of glycaemic indices in the general type 2 diabetic population. This implies that inclusion of thyroid hormonal profiling may be useful in proper diagnosis and management of diabetes mellitus.

Abbreviations

FPG: Fasting plasma glucose; HBA_{1c}: Glycated haemoglobin; C-pep: C-peptide; GLUT4: Glucose transporter type 4; FT_4: Free thyroxine; TSH: Thyroid-stimulating hormone; T_3: Triiodothyronine; T_4: Total thyroxine; ELISA: Enzyme-linked immunosorbent assay; EDTA: Ethylenediaminetetraacetic acid.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42269-022-00897-8.

Additional file 1: STROBE Statement—Checklist for cross-sectional studies.

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Author contributions

CEJ conceptualized the research, data collection and laboratory analyses and reviewed manuscript. IK conceptualized the research and data collection and contributed to initial manuscript writing and review. UO was involved in data collection, statistical analysis, drafting and final review of manuscript. All authors have read and approved the manuscript for submission.

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Availability of data and materials

Data obtained from this study will not be shared as it is against the ethical policies of Cross River State Ministry of Health on research carried out on human subjects as well as maintained the participants' confidentiality.

Declarations

Ethics approval and consent to participate

All experiments were performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975, as revised in 2000. Ethical approval was given by the Health and Ethics committee of the Ministry of Health, Cross River State, Nigeria. Informed written consent was given by the participants before being enrolled into the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interest.

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