THE EFFECT OF GLYCAEMIC CONTROL ON CORTISOL LEVELS IN TYPE II DIABETICS IN UNIVERSITY OF CALABAR TEACHING HOSPITAL.

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ABSTRACT

Background: A high prevalence of subclinical hypercortisolism has been suggested in patients with type II diabetes mellitus with poor metabolic control and several observations have suggested that in type II diabetes patients, subclinical hypercortisolism may be more frequent than previously expected, however, results are inconclusive. **Objectives**: This study investigated the effect of glycemic control on serum cortisol levels in type II diabetics. **Materials And Methods**: The levels of serum cortisol, fasting plasma glucose and glycated haemoglobin were estimated in fifty five (55) type II diabetic patients attending the Diabetic Clinic of University of Calabar Teaching Hospital, Calabar and thirty three (33) non-diabetic controls. Consecutive sampling method was used. Serum cortisol was determined using enzyme immunoassay; fasting plasma glucose using colorimetric method and glycated haemoglobin using cation-exchange resin separation method. **Results**: The mean serum cortisol levels were significantly higher in diabetics as compared to the controls. The diabetics with poor glycemic control had significantly higher mean fasting plasma glucose and glycated haemoglobin compared to those with good glycemic control. However, there was no significant difference in the mean cortisol levels between the diabetics with poor control and those with good control. **Conclusion:** The diabetics in this study had elevated levels of serum cortisol. Cortisol levels in the diabetics were not affected by glycemic control.

KEYWORDS : Cortisol, type II diabetes, glycaemic control.

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INTRODUCTION

Diabetes is one of the major growing public health challenges, which threaten to overwhelm medical services in the near future[1]. The term diabetes mellitus describes a metabolic disorder of multiple etiology. It is characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin action and/or insulin secretion[2]. The degree of insulin deficiency determines largely the metabolic alterations. Regardless of the etiology of diabetes mellitus, the disease manifests in hyperglycemia and glycosuria[3]. The classical symptoms of diabetes mellitus include: thirst, polyuria, polydypsia, polyphagia, blurring of vision and weight loss. In its most severe form, a non-ketotic hyperosmolar state or ketoacidosis may develop leading to stupor, coma and in absence of effective treatment, death[3].

According to Shaw et al,[4] "The world prevalence of diabetes among adults (aged 20-79) was estimated at 6.4%, affecting 285million adults, in 2010, with variations from 10.2% in the Western Pacific to 3.8% in the African region. It was further predicted that by 2030, the prevalence of diabetes will increase to 7.7%, afflicting 439million adults. Between 2010 and 2030, the prevalence of diabetes was projected with a 6.9% increase in the number of adults with diabetes in developing countries and a 20% increase in developed countries"[4].

In Africa, continent–wise prevalence was estimated to be 3 million in 1994 and 7.1 million in 2000. This figure is expected to rise by 2030 to 18.6 million, in Nigeria, that the figure will rise to 4.8 million by the year 2030[5]. According to the Diabetes association of Nigeria (DAN), the national prevalence rate of diabetes is 2.2% [6].

The adrenal glands secrete cortisol, a primary stress hormone, in response to inflammation from infection, injury, reactive substances such as allergens or toxins and certain digestive disturbances[7]. Its primary functions are to increase blood sugar through glycogenolysis; aid in fat, protein and carbohydrate metabolism as well as suppress the immune system[8]

There is a renewed interest in adrenal function in diabetic conditions. This is because cortisol may play an important role in the development of type 2 diabetes; it is possible that even small increases in cortisol, within the range of normal, may have a detrimental influence by worsening diabetes itself and increasing the risk of diabetes-related complications[8]. Diabetes (mainly type 2 diabetes) have been shown to be associated with cortisol levels because hypothalamic-pituitary-adrenal activity is enhanced in patients with diabetes complications and the degree of cortisol secretion has been shown to be related to the presence and number of diabetes complications[9].

High levels of cortisol in the body, decreases the metabolism of glucose and increases mobilization and breakdown of fats. Decreased metabolism of glucose contributes to hyperglycaemia, and increased blood fat levels contribute to insulin resistance. Hyperglycemia and blood fats are classic symptoms of diabetes. An elevated level of cortisol antagonizes the effect of insulin on blood glucose[10].

A high prevalence of subclinical hypercortisolism has been suggested in patients with type II diabetes mellitus with poor metabolic control. Though several observations have suggested that in type II diabetes patients, subclinical hypercortisolism may be more frequent than previously expected, however, results are inconclusive[11]. This study therefore will investigate the effect of glycemic control on cortisol levels in diabetics.

MATERIALS AND METHODS

Subjects

A total of 88 subjects of Nigerian origin were involved in this study. Fifty-five confirmed type II diabetic patients (males and females) attending the Diabetic clinic of the University of Calabar Teaching Hospital (UCTH) were recruited as test subjects. Thirty-three apparently healthy non-diabetic subjects were recruited from Calabar metropolis as controls. Consecutive sampling method was used. Ethical approval was obtained from the ethical committee of the University of Calabar Teaching Hospital. The purpose and nature of the research was explained to the participants and they gave their consent.

Inclusion criteria

All the subjects were 30years and above.

Exclusion criteria

Type I diabetics, terminally ill diabetics as well as anyone who did not consent to participating in the study were excluded.

Sample size calculation

The number of samples in this research was determined using the formular

$$N = \frac{Z\alpha^2 pq}{d^2}$$

where N = desired sample size

Zα = the α level of the coefficient interval at 95% (1.96)

p = proportion of non-occurrence

q = (1-p) proportion of non occurrence

d= precision

Substituting the expected occurrence of p= 2.2% i.e. 0.022 from DAN[6] we have

$$N = \frac{1.96^2 \times 0.022(1 - 0.022)}{(0.05)^2}$$

$$= 33$$

After calculating the sample size, a response rate of 80% was assumed and so the actual sample size was 33/0.8 = 41 cases.

Sample Collection

Fasting blood samples were collected between 8.00am and 9.00am owing to diurnal variation of cortisol secretion. With minimal constriction and stasis, 6 milliliters of venous blood was aseptically collected by venepuncture from each subject. Two milliliters of blood from each subject was dispensed into a tri-potassium ethylene diamine tetra-acetic acid (EDTA) bottle for glycated hemoglobin estimation and 2ml into a fluoride oxalate bottle for glucose estimation.

The remaining 2 milliliters of blood was collected into plain containers for serum extraction, which was used for cortisol assay. Serum not used immediately was kept frozen till used.

Glucose Analysis

Fasting plasma glucose was estimated using a test kit of glucose-oxidase-peroxidase method produced by Giesse Diagnostics Inc., Italy. Normal range 3.5 – 5.5mmol/L

Glycated Hemoglobin Estimation

Glycated hemoglobin was estimated using kits by Teco diagnostics, Anaheim, USA. The kit employed a weak binding cation-exchange resin for the rapid separation of glycohemoglobin (fast fraction) from non-glycated hemoglobin (HbA_o). Normal range : <6%

Serum cortisol Estimation

Serum cortisol was determined by the DRG cortisol enzyme immunoassay kit. It was obtained from DRG international Inc. USA. The DRG cortisol ELISA kit is a solid phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding. Absorbance was read at 450nm with an ELISA microtiter plate reader. Normal range of serum cortisol - 138nmol/L – 635nmol/L

Statistical analysis

This was done using the PAWstatistic 18, a statistical package from SPSS Inc, California, USA. The results were expressed as Mean ± SD. The data was analyzed by Student's t-test and Analysis of variance (ANOVA) followed by a post hoc test using least significant difference (LSD). The level of significance was set at 95% confidence interval, where p-value less than 0.05 ($p<0.05$) was considered as statistically significant.

Definition of terms

Good glycaemic control: was defined as HbA1c value of < 7% in the diabetic patients

Poor glycaemic control: was defined as HbA1c value of ≥7% in the diabetic patients[12]

RESULTS

A comparison of the mean values of fasting plasma glucose, glycated haemoglobin and serum cortisol levels in diabetics and control subjects showed that the mean fasting plasma glucose, glycated haemoglobin and serum cortisol levels were significantly (p =0.000)

higher in diabetics when compared to the control subjects. Among the physical parameters measured only the mean values of systolic BP in the diabetics was significantly higher (p=0.025) than that of the controls (Table 1). Table 2 shows a comparison of fasting plasma glucose, glycated haemoglobin, serum cortisol in diabetics and controls based on glycaemic control. The mean fasting plasma glucose, glycated haemoglobin and serum cortisol levels were significantly lower (p=0.000) in controls when compared with the two groups of diabetics. The diabetics with poor glycemic control had the highest levels of mean fasting plasma glucose (FPG) and glycated haemoglobin.

Table I: Comparison of some physical parameters, fasting plasma glucose, glycated haemoglobin and serum cortisol in diabetics and non diabetics

Parameter	Diabetics	Non diabetics	Calc. t-value	Crit. t-value	p-value
Age (year)	47.2±10.10	44.8±10.65	1.076	2.00	0.285
BMI (Kg/m^2)	27.4±3.78	27.0±4.29	0.469	2.00	0.640
Systolic BP	140.2±22.98	129.6±17.07	2.282	2.00	0.025
Diastolic BP	83.1±17.20	79.6±13.0	1.014	2.00	0.314
Fasting plasma	8.42±3.30	4.25±0.53	7.187	2.00	0.000
HbA1c (%)	7.96±1.78	5.04±0.62	9.082	2.00	0.000
Serum cortisol (nmol/L)	442.9±179.68	296.3 ±88.36	5.110	2.00	0.000
n	55	33			

TableI I: Comparison of some physical parameters, fasting plasma glucose, glycated haemoglobin and serum cortisol in diabetics and non diabetics

Parameter	Diabetics with poor glycaemic	Diabetics with good glycaemic	Non Diabetics	Calc. F value	Crit. F value	p-value
Age (year)	45.5±10.65	50.4±10.11	44.8±10.65	2.042	3.103	0.136
BMI (Kg/m^2)	28.1±3.76	26.1±3.54	27.0 ±4.29	1.756	3.103	0.179
Systolic BP	140.7±24.22$^{\#}$	139.1±21.03	129.6±17.07	2.614	3.103	0.079
Diastolic BP	84.8±13.95	82.2±18.81	79.6±13.0	0.680	3.103	0.509
Fasting plasma	9.59±3.45$^{*\#}$	6.18±1.18	4.25±0.53	47.251	3.103	0.000
HbA1c (%)	8.91±1.38$^{*\#}$	6.15±0.70	5.04±0.62	130.427	3.103	0.000
Serum cortisol (nmol/L)	438.9±172.10$^{\#}$	450.5±197.91$^{\#}$	296.3 ±88.36	9.500	3.103	0.000
n	36	19	33			

KEY: *- higher than that of diabetics with good glycaemic control
- higher than that of controls

However, there was no significant difference (p= 0.790) in the mean cortisol levels between the diabetics with poor glycaemic control and those with good glycaemic control.

DISCUSSION

Given the documented deleterious role of glucocorticoids on glucose metabolism[13-16] it is possible to speculate that an increased cortisol secretion may contribute to a deterioration of the metabolic control of diabetes. In our study, the mean level of cortisol was significantly higher in type 2 diabetics when compared with controls. Elevated cortisol induces hyperglycemia. The value found in this study indicates that cortisol may be a contributor to the diabetic condition. Elevated cortisol is associated with increase hepatic gluconeogenesis and glycogenolysis and consequently hyperglycemia.

Cortisol is a glucocorticoid, which ensures that blood glucose level remains elevated. Its role in diabetes mellitus may however be undesirable as it tends to sustain hyperglycemia. This observation points to the need to measure this hormone in diabetics as part of monitoring and control. There are patients despite good management and treatment of diabetes do not respond to treatment. Management of some of these hormonal imbalances may help alleviate their particular situations.

Cortisol alters blood glucose levels by affecting glucose transporters in peripheral tissues such as skeletal muscle and fat[17]. Thus cortisol can contribute to elevated blood glucose levels by causing inefficient uptake of glucose in diabetics in the peripheral tissues. It is likely that even small increases in cortisol levels, within the normal range, may have an unfavourable influence by worsening diabetic condition and increasing complications[8]. Higher levels of cortisol in the body can increase glucose production in the liver, increase lipid accumulation, inhibit glycogen synthesis, and decrease insulin secretion[18,19]. This combination of events is a probable contributor to the development of type 2 diabetes.

In this study there was no significant difference in the mean cortisol levels between poorly controlled diabetics and diabetics with good glycaemic control. This suggests that in people with diabetes there may be altered cortisol secretion and/or metabolism irrespective of their glycaemic status. This may be an underlying reason for the increased susceptibility of diabetics to diabetic complications such as poor wound healing and hypertension.

A study carried out by Chiodini [20] reported that the degree of cortisol secretion as reflected by F24 was directly associated with both the type 2 diabetes and number of complications. However, they also reported that the patients in their study with diabetic complications showed higher glycated heamoglobin levels and longer duration of disease with respect to diabetic patients without chronic complications. Oltmanns *et al* [21] also reported that HbA1C to be directly associated with cortisol secretion in type 2 diabetic subjects with normal HPA activity.

These findings differ from those in this study. The differences observed may be a consequence of variation in study design.

Conclusion

The diabetics in this study had elevated levels of cortisol. There was however, no significant difference between the cortisol levels of diabetics with poor glycemic control and those with good glycemic control. ▬

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Cite this article as: Bassey IE, Ogbolu IA, Gali RM, Essien OE, Usoro CAO. The Effect of Glycaemic Control on Cortisol Levels in Type II Diabetics in University of Calabar Teaching Hospital. Bo Med J 2015; 12(1): 9 - 15. **Source of Support:** Nil, **Conflict of Interest:** None declared.