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Cortisol and Electrolyte Levels in Type 2 Diabetic Patients Attending a State University Teaching Hospital, Ogun State, Nigeria

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ABSTRACT: The involvement of the Hypothalamic - Pituitary – Adrenal (HPA) axis activity in type 2 diabetes mellitus has been investigated by some studies. While some reported an enhanced activity of the axis, others showed no alteration. Disturbances of electrolyte homeostasis in uncomplicated diabetes have been reported and it is a known fact through basic knowledge that abnormalities of HPA axis also affect electrolyte homeostasis. The majority of diabetic patients eat diets that are rich in potassium (plantain, beans, etc) and this also has implication on the electrolytes.

This study was designed to establish cortisol and electrolytes levels among uncomplicated type 2 diabetic patients attending a University Teaching Hospital to know whether there is enhanced HPA axis or not in these patients and look at the pattern of the overall consequences on their electrolyte status. A total of 110 volunteers were used, 60 diabetics and 50 non-diabetics (control). Body Mass Index (BMI) and blood pressures were measured and blood samples taken at 8:00am for fasting plasma cortisol, fasting plasma glucose and electrolytes. The samples were analyzed using standard methods.

Results indicate that there was a statistically significant difference ($P < 0.05$) between the mean values of Waist/Hip Ratio (WHR) of the Diabetics and control but no statistically significant difference ($P > 0.05$) observed between the mean values of the BMI of the Diabetics compared with the control. The mean cortisol levels of the Diabetics and the control showed no statistically significant difference ($P > 0.05$) even though a higher percentage of the diabetics have higher serum cortisol levels. However, there were statistically significant differences ($P < 0.05$) in the mean values of the fasting plasma glucose, sodium and potassium comparing the Diabetics with the control, indicating a significant increase in plasma glucose, decrease in plasma sodium and increase in plasma potassium, comparing the diabetics with the control respectively.

Although a higher percentage of the Diabetic population had higher serum cortisol levels while a higher percentage of the control had lower levels, there was no significant correlation between the plasma cortisol levels and either the plasma glucose levels or any of the other biochemical parameters in both the Diabetics and control. Similarly, no significant correlation between cortisol level and either the BMI or WHR. However, there was a significant negative correlation between sodium and potassium ($\gamma = 0.601$, $P<0.05$).

The study showed that there was no alteration in the HPA axis activity of the type 2 DM subjects. Reduced sodium level and increased potassium level were observed in the Diabetics compared to the control subjects. This may be due to osmotic flux due to the hyperglycaemia in the diabetics or the effect of the peculiar diet they eat or both. It may even be the effect of medication. Studies to elucidate further on the electrolyte patterns in DM is advised and diabetics are also implored to be aware of possible electrolyte disturbances that may result from these factors.

Key words: Cortisol, Electrolytes, Type 2 Diabetic Patients, University Teaching Hospital

Introduction

Diabetes mellitus (DM) is the most common endocrine metabolic disease worldwide, a chronic condition resulting from inherited or acquired insulin deficiency which may be either of inadequate secretion or impaired action or both. Biochemically, it is characterized by hyperglycaemia, causing disturbances of carbohydrate, fat and protein which in turn damages body systems. As at 2014, an estimated number of 387 million were reported to have diabetes worldwide (IDF, 2014).

Interestingly only fifty percent (50%) of people living with diabetes are diagnosed (IDF, 2011). World health statistics indicate that Nigeria has the highest number of diabetics in sub – Saharan Africa (Chinenye & Ogbera, 2013). Type II DM is the major type of Diabetes in the world, constituting ninety to ninety five percent(90-95%) of cases (IDF, 2011) and the high incidence of Type II DM is a result of the pathophysiologic condition known as insulin resistance, which a study had shown to have a prevalence of 35% in Nigerian population (Ezenwaka, Akanji, Akanji, Unwin & Adejuwon, 1997). Diabetes mellitus has become a burden in the society because of its serious long – term complications which include cardiovascular disease, stroke, foot ulcers, damage to the eyes and chronic kidney failure (WHO, 2013).

Glucocorticoid secretions have been suggested to cause insulin resistance in diabetes mellitus (Andrew, et, al, 1999), therefore, high level of cortisol may be an important factor amongst several factors responsible for the high prevalence of diabetes. Studies in the past have investigated the Hypothalamic – pituitary-adrenal (HPA) axis secretion in patients with type 2 diabetes extensively (Coiro, 1995), some studies reported an elevation of ACTH or serum cortisol (Cameron, 1984) and others did not show any alteration of pituitary-adrenal axis secretion. Chronic complications of type 2 diabetes have been associated with HPA axis activity. Cortisol is released in response to stress and low blood glucose concentration. It increases blood sugar through gluconeogenesis and aids the metabolism of fat, protein and electrolytes and also decreases bone formation (Chyun, et al, 1984). Cortisol inhibits sodium loss through the small intestine and excretes potassium in the intestine to regulate the body PH. Excess cortisol can lead to hypernatraemia and Hypokalaemia (Sandle, et al, 1981).

Electrolyte disturbances are common in patients with Diabetes and may be the results of an altered distribution of electrolytes related to hyperglycaemia induced osmotic fluid shifts or of total body deficits brought about by osmotic diuresis. plasma sodium in type 2 Dm is usually low as a result of the osmotic flux of water (kitabchi, 2009) and potassium is high due to redistribution of water from intracellular to extracellular (Palmer, 2010).

Furthermore, the need to investigate the levels of cortisol in diabetic patients cannot be overemphasized because enhanced HPA axis, otherwise called Hypercotisolism, has its own clinical manifestations even in the absence of diabetes. Incidentally, some of these manifestations also occur in diabetes mellitus. Hypercotisolism causes reduced libido and impotence in men, menstrual irregularities and infertility in women, insomnia and inhibited aromatase. Apart from inducing hepatic gluconeogenesis and decrease of bone formation, hypercotisolism has other metabolic effects. These include; inhibition of peripheral utilization of glucose (Brown and Brown, 2003) by decreasing the translation of glucose transporters to the cell membrane, inhibits collagen formation and protein synthesis (Manchester, 1964) to raise the serum free amino acids for gluconeogenesis, it suppresses the immune system to cause poor wound healing and susceptibility to superficial fungal infections and on electrolytes it transports potassium out of cells in exchange for an equal number of sodium ions (Knight, 1955). On the gastrointestinal tract it stimulates gastric acid secretion (Soffer et al, 1961) and finally, long term exposure to cortisol damages cells in the Hippocampus (McAuley, et al, 2009) and this damage results in impaired learning. Cortisol also inhibits memory retrieval of already stored information (de Quervein, et al, 2000).

The emphasis on diet of the diabetic patients also need be made in view of the electrolyte status. Many diabetic patient eat unripe plantain and beans and these have been reported in a study to be rich in plantain, among other minerals (Baiyeri, et, al, 2011), the metabolic effects of cortisol and diabetes need be considered along with dietary advice. There is paucity of information on the HPA axis activity in Type 2 Diabetics in this environment and the overall consequence of the several factors affecting electrolyte homeostasis in these patients.

Aim of the Study

This study therefore aims to determine cortisol and electrolyte levels in type 2 diabetic patients attending a state University Teaching Hospital in Ogun State, Nigeria, to know if there is alteration of the HPA axis activity in these patients and possibly the overall effect of this axis on electrolyte homeostasis.

Materials and Methods

This study involved a total of one hundred and ten (110) volunteers of both sexes, aged between eighteen and sixty-five years (18 – 65years). They were in two groups, group one (gp 1) comprised of 60 non – obese and non – hypertensive diabetic patients without complication selected randomly from the endocrinology clinic of Olabisi Onabanjo University Teaching Hospital (OOUTH) in Sagamu, group two (gp 2) comprised of 50 conrol volunteers (non – diabetic, non-obese and non-hypertensive) recruited from members of staff of the same Health Institution. Ethical approval for the study was obtained from the Health Research Ethics Committee of OOUTH and informed consent was obtained from all the volunteers after they had been intimated with the nature and relevance of the study. A questionnaire was used to collect the biometric data of the volunteers. Anthropometric measurements for the volunteers were taken using Camry mechanical scale for the weight (in kg) and Stadiometer for the height (in meters) and the Body Mass Index (BMI) determined. Waist and Hip circumferences were taken using non – stretch tape in centimeters and the Waist / Hip Ratio (WHR) determined. Finally, the blood pressure of each volunteer was taken to ensure that patient was not hypertensive.

Blood Collection and Analytical Methods

Blood samples were collected at 8 am after 10 hours fasting overnight, 10ml of whole blood was collected, 2ml was dispensed into fluoride oxalate bottle for fasting plasma glucose (FBG), 3mls was dispensed into lithium heparin bottle for electrolytes and 5mls was dispensed into plain bottle for cortisol analysis. All samples were centrifuged at 2,500 for 5minutes and the supernatant (plasma) was stored at -20^0C until ready for analysis. Urine was collected into plain bottle for urinalysis to rule out overt nephropathy, using Dipstick method within 2hours of urine collection.

The blood samples were analyzed for fasting plasma glucose using enzymatic method (Randox Glucose Kit), fasting plasma cortisol using competitive immune – enzymatic method (Rapid Labs Cortisol ELISA Kit) and plasma electrolytes were measured using ion selective electrode (ion selective electrode reagent). All analytical assays were carried out according to the manufacturer's instructions.

Statistical Analysis

The data obtained was subjected to statistical analysis using statistical package for social sciences (SPSS), version 19. The mean, standard deviation and proportions were used as the descriptive statistics. Z –test was utilized as statistical measure for continuous variables. Pearson correlation was used to find the relationship between cortisol and other Biochemical parameters. The level of statistical significance for all tests was set at $P < 0.05$.

Results

Table 1 shows that there was no statistically significant difference ($p > 0.05$) in the mean age of the diabetics compared with the control, justifying the age matching. Also shown in this table is that there was no statistically significant difference ($p > 0.05$) in the body mass index of the diabetics compared with the control. However, there was a statistically significant difference ($p < 0.05$) in the waist to hip ratio of the diabetics compared with the control.

Table 1: Age and Anthropometric indices of the Diabetics and the Control group (Mean ± SD)

Parameters	DM Patients N – 60	Control N - 50	Z - Test	P- Value
Age	49.58 ± 11.2	47.00 ± 12.1	- .951	.524
BMI	26.47 ± 3.97	25.77 ± 4.85	- .833	.407
WHR	.9328 ± 0.41	0.9050 ± 0.08	- 2.284	.024*

Level of Significance $P < 0.05$

Key: BMI = Body Mass Index
WHR = Waist – Hip Ratio
S.D = Standard deviation

Table 2 shows the concentrations of cortisol and other Biochemical parameters (mean ± SD) in the diabetics and control group. This table shows that there was no statistically significant difference ($p > 0.05$) between the mean cortisol levels in the diabetics compared with the control. However, there were statistically significant differences ($p < 0.05$) in the fasting plasma glucose, sodium and potassium of the diabetics compared with the control.

Table 2: Concentrations of Cortisol and other Biochemical parameters (Mean ± SD) in the Diabetics and Control group

Parameters	**DM Pts Mean ± SD N = 60**	**Control Mean ± SD N =50**	**Z - Test**	**P - Value**
Cortisol (ng/ml)	125.5 ±43.20	121.5 ± 61.30	0.396	0.693
Fasting Plasma Glucose (mg/dl)	138.4 ± 78.70	82.5 ± 13.10	0.4.96	0.000*
Potassium (mmol/l)	5.2 ± 1.40	4.1 ± 0.53	5.009	0.000*
Sodium (mmol/l)	139.0 ± 8.40	142.4 ± 4.20	2.583	0.011*
Chloride (mmol/l)	99.3 ± 6.80	104.5 ± 5.00	4.400	0.000*
Bicarbonate(mmol/l)	21.7 ±3.10	22.0 ± **1.50**	0.658	0.512

Level of Significance $P < 0.05$
DM = Diabetes Mellitus
Pts = Patients

Table 3 shows that there was no significant correlation between cortisol and any of the other biochemical parameters in both the diabetics and control. However, there was a significant correlation between sodium and potassium in the diabetics only, none in the control.

Table 3**: Correlations between Cortisol and other Biochemical parameters in the Diabetics and the Control group**

Category	**CORTISOL (ng/ml)**	**FPG (mg/dl)**	**K^+ (mmol/l)**	**Na^+ (mmol/l)**	**Cl^- (mmol/l)**	**HCO_3^- (mmol/l)**
Control Cortisol (ng/ml)	1	0.180	.089	0.058	0.128	0.152
FPG (mg/dl)	0.180	–	0.087	0.322*	0.146	0.268
K^+ (mmol/l)	0.089	0.087	–	0.199	0.351	0.096
Na^+ (mmol/l)	0.058	0.322	0.199	–	0.483**	0.144
Cl^- (mmol/l)	0.128	0.146	0.351	0.483**	–	0.247
HCO_3^- (mmol/l)	0.152	0.268	0.096	0.114	0.247	–
DM patients						
Cortisol (ng/ml)	–	0.008	0.212	0.227	0.202	0.230
FPG (mg/dl)	0.008	–	0.051	0.056	0.128	0.045
K^+ (mmol/l)	0.212	0.051	–	0.377**	0.331**	0.053
Na^+ (mmol/l)	0.227	0.056	0.377**	–	0.070	0.239
Cl^- (mmol/l)	0.202	0.128	0.331	0.070	–	0.102
HCO_3^- (mmol/l)	0.230	0.045	0.053	0.239	0.102	–

****. Correlation is significant at the 0.01 level (2-tailed).**
*** Correlation is significant at the 0.05level (2-tailed)**

Figure 1 shows the distribution of the Diabetic population and Control group in the various levels of the fasting plasma glucose and indicates that only 55% of the Diabetics had good glyceamic control while 45% had poor glyceamic control.

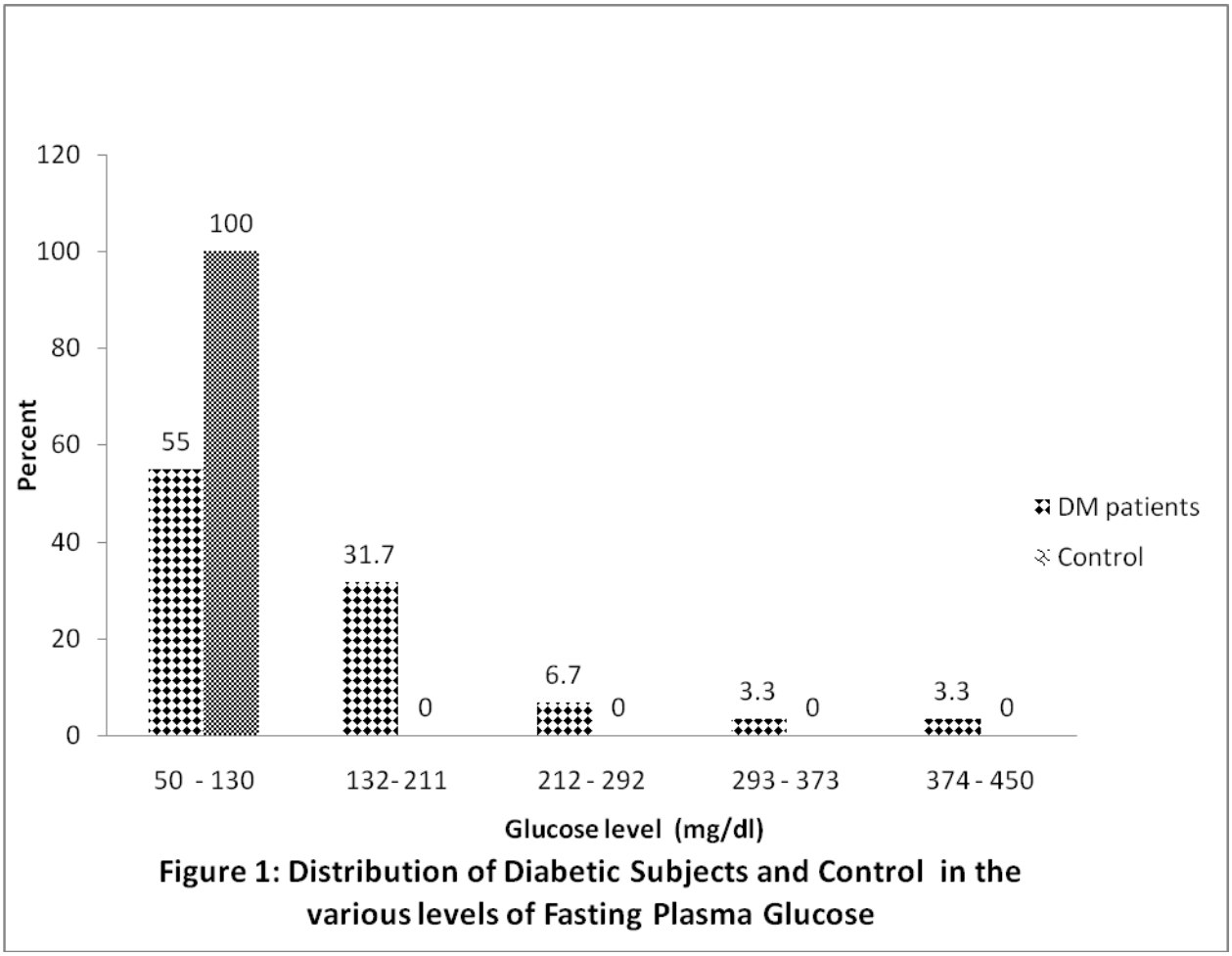

Figure 1: Distribution of Diabetic Subjects and Control in the various levels of Fasting Plasma Glucose

Figure 2: Distribution of the diabetic population and control group in the various levels of the fasting plasma cortisol and it indicates that there is no appreciable evidence that the Diabetics have higher cortisol levels than the control population.

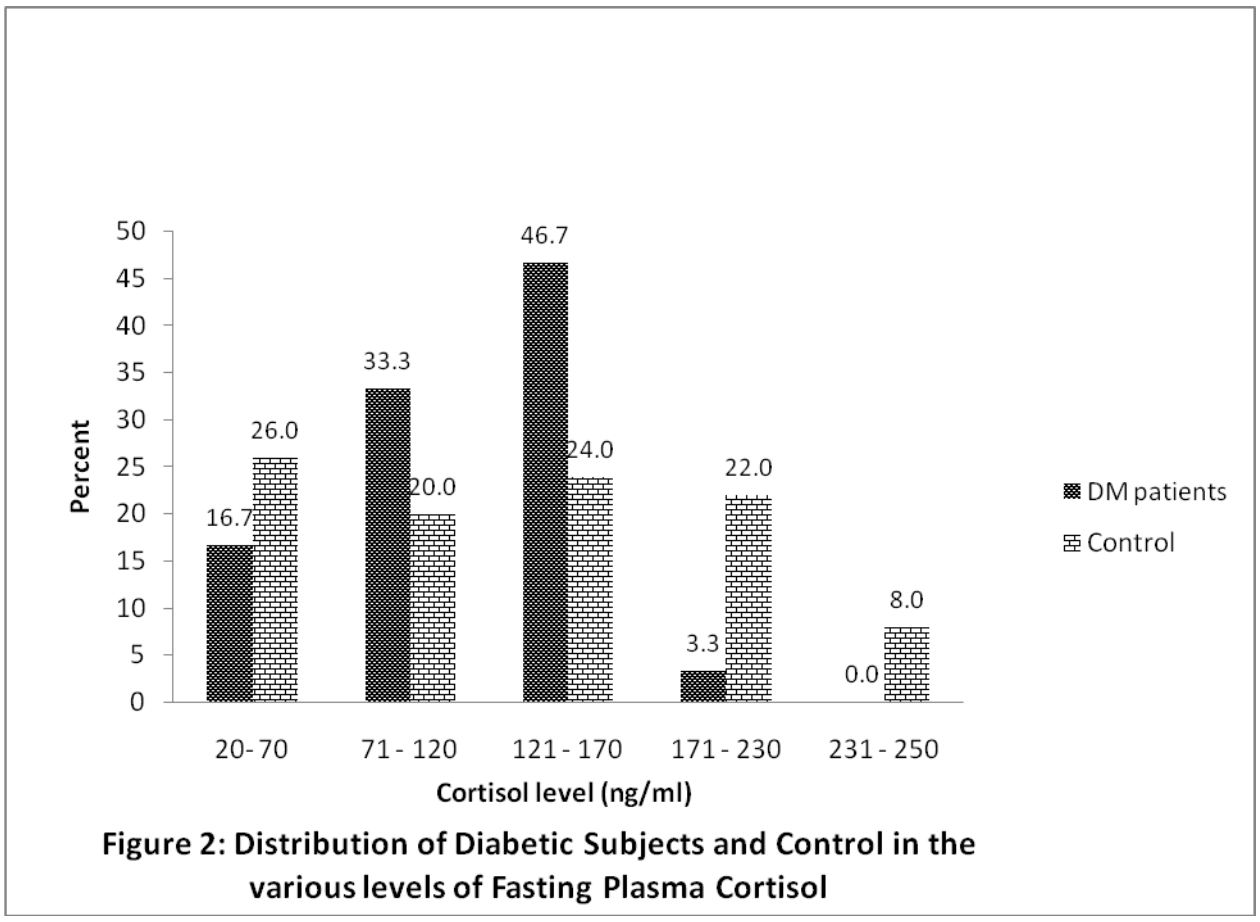

Figure 3: Distribution (proportion) of Diabetic subjects and Control group in the various levels of fasting plasma Cortisol

Discussion

The study was to determine the involvement of the HPA axis in the incidence of Type 2 Diabetes mellitus and the overall consequence of the axis and other factors involved in electrolyte homeostasis on the electrolyte status of these patients. This is necessary to know if there is a relationship between the rising incidence of type 2 diabetes mellitus and the HPA axis in view of increasing emergence of stress related factors in our current socioeconomic environment, it will also be of value in guiding clinicians in giving dietary guidelines to diabetics in view of the several factors implicated in their electrolyte homeostasis.

The biophysical measurements revealed that there was no statistically significant difference ($P > 0.05$) in the Body Mass Index (BMI) of the Diabetics compared with the Control. However, the Waist / Hip Ratio (WHR) of the Diabetic group has statistically significant difference ($P < 0.05$) when compared with the Control, this reflects the fact that the WHR (which measures central Abdominal fat) has an implication in the etiology of Type 2 Diabetes mellitus, as a risk factor.

The mean cortisol levels of the Diabetics when compared with the control showed no statistically significant difference ($P > 0.05$) in this study. This is contrary to the reports of previous studies that reported elevation of serum cortisol in type 2 diabetes (Cameron, 1984 & Mamza, et al, 2013). On the other hand, it is in agreement with another study that reported that there was no alteration in the HPA activity in type 2 Diabetes (Roy, et, al, 1998). However, the fasting plasma glucose obtained in this study (table 2) for the Diabetics showed a statistically significant difference ($P < 0.05$) when compared with the control, being significantly higher in the diabetics. The implication of this is that many of the diabetic patients hardly attain a good therapeutic control. This is the usual trend in

subsaharan Africa due to several factors affecting the patients as previously reported (Chinenye & Ogbera, 2013). Some of these are poor economic status, sub-standard drugs, illiteracy and sociocultural practices.

The pattern of electrolyte status obtained in this study is also of interest. There was a statistically significant difference ($P < 0.05$) between the sodium levels of the Diabetics compared with the control, being significantly lower in the diabetics. This agrees with a previous work (Kitabchi, 2009) and the explanation is that the hyperglycaemia, characteristic of diabetes, causes increased plasma tonicity, creating an osmotic driving force that favours the movement of water from the intracellular space to the extracellular space thereby diluting the extracellular sodium concentration. On the other hand, the mean potassium concentration obtained in the diabetics in this study showed statistically significant increase when compared with the control ($P < 0.05$), this agrees with the report of a previous study (Palmer, 2010) in which it was explained that although insulin – mediated uptake of glucose is impaired in type 2 diabetes, the cellular uptake of potassium remains normal. However, the observed hyperkalaemia is a result of increase in plasma tonicity that results in potassium redistribution from intracellular to extracellular space.

Finally, the study showed that in both Diabetics and Control there was no statistically significant correlation between serum cortisol and fasting plasma glucose ($P > 0.05$). Also, no statistically significant correlation between cortisol and either serum potassium or sodium. However, a negative statistically significant correlation was observed ($r = - .601$, $P < 0.01$) between the sodium and potassium levels in the Diabetics, similar finding had been reported by some workers (Biff, et al, 2015).

Conclusion

The study has shown that there is no significant enhanced activity of the Hypothalamic – Pituitary- Adrenal axis in type 2 diabetics in the study environment. Although many of the patients with diabetes showed higher levels of plasma cortisol than the control, this is not statistically significant, however it may require that further studies with a larger sample size be done to elucidate further on this finding.

Another important finding of this study is that there is some degree of electrolyte derangement ((hyponatraemia and hyperkalaemia) in uncomplicated type 2 diabetes in this environment. This means clinicians and the diabetics have to be aware of this and make it a necessary factor to guide against developing more metabolically significant electrolyte derangement when prescribing drugs or diet in the control of diabetes mellitus. Lastly, this study indicated central obesity (WHR) as risk factor in the incidence of type 2 diabetes and also revealed that achieving the therapeutic goal in the management of diabetes mellitus in this environment is still an issue of concern like other places in sub- sahara Africa.

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