Plasma Levels of Uric Acid, Urea and Creatinine in Diabetics Who Visit the Clinical Analysis Laboratory (CAn-Lab) at Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

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ABSTRACT

Introduction: Diabetes mellitus is one of the most common metabolic disorders worldwide. This metabolic disorder contributes greatly to the significant proportion of the burden of renal damage and dysfunction. The aim of the study was to investigate the renal function of the diabetic patients who visit the Clinical Analysis Laboratory (CAn-Lab) at the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana.

Materials and Methods: Demographic data as well as medical history were obtained through the administration of a questionnaire. Anthropometric measurements were taken and blood samples were analysed for glucose, uric acid, urea and creatinine. Data collected were analysed using SPSS version 16.0.

Results: A total of 34 diabetic patients, aged from 40-77 y were recruited, 22 (64.7%) of them were males with mean age of 57.40 ± 11.8 y (±SD), while 12 (35.3%) were females with mean age of 58.17 ± 7.47 y. There was a statistically significant difference between the mean duration of the disease, as the females had longer duration, 12.50 ± 6.95 y, as compared to 7.32 ± 4.48 y in males (p=0.033). The mean plasma creatinine level in the females was 84.17 ± 54.73 µmol/l. In the diabetic population, there was a positive correlation between age and plasma creatinine level, (r=0.375, p=0.029). In the female diabetics, there was a positive correlation between fasting blood sugar (FBS) and the measured metabolic end products (r>0.5, p<0.05), a positive correlation between body mass index (BMI) and uric acid (r=0.576, p=0.005) and a positive correlation between BMI and FBS (r= 0.625, p= 0.030).

Conclusion: Our results on the parameters measured; show that the diabetic population was experiencing mild kidney dysfunction, compared to non-diabetic controls.

INTRODUCTION

Diabetes mellitus, also called “sugar disease” by Ghanaians is one of the non-communicable diseases in the world. This metabolic disorder has increased in most tropical countries and is remarkably common among people, irrespective of their standard of living. Currently, about 217 million individuals all over the world live with diabetes mellitus and over 350 million people are likely to live with this condition by the year 2030 [1,2]. In sub-Saharan Africa the prevalence is about 4%, representing an estimated population of 12 million and it has been predicted that within the next 20 years, 24 million people would be living with the disease [3,4]. In Ghana, the prevalence of this metabolic disorder was 2% in the early 1990’s [5] and an increase of 0.4% to 6.3% was recorded within the period of 1950 and 2000 [6]. Approximately, 80-95% of all diabetics were type 2 diabetics in the Greater Accra region of Ghana [6]. In Kumasi, an urban city in the Ashanti region of Ghana, about 6% of all adults are diabetics [7].

Type 1 diabetes and type 2 diabetes are distinct disorders resulting primarily from either a lack of pancreatic insulin in the former or due to development of insulin’s ineffectiveness to maintain blood glucose within the physiologic range in the latter [8]. In genetically pre-disposed persons, the combination of excess caloric intake and less physical activity can lead to obesity which in turn, can induce a state of resistance to the action of insulin [9]. Reductions in β-cell mass and abnormalities of β-cell function can both be demonstrated in patients with type 2 diabetes mellitus and individuals at increased risk for diabetes [10]. Most type 2 diabetics are often obese [11].

The metabolic disease has been identified with some disorders such as mild kidney disease, endothelial dysfunction and oxidative stress [12]. In both developed and developing countries, chronic kidney disease (CKD) is one of the main causes of morbidity and mortality [13]. Since diabetes is closely associated with renal disease, there is the need to find out whether diabetics who visit the CAn-Lab are developing kidney dysfunction so that they can be offered timely advice.

This study was based on the hypothesis that diabetics are more prone to experience kidney dysfunction than non-diabetics. Therefore, the aim of this cross-sectional study was to investigate the renal function of the patients with diabetes mellitus, compared to age-matched non-diabetics. The specific objectives were to find out the symptoms of kidney diseases experienced by the diabetic patients through a questionnaire, to determine the prevalence of kidney disease, to determine the plasma levels of glucose, uric acid, urea and creatinine and to find the correlation between BMI, FBS, plasma uric acid, urea and creatinine and duration of the disease.

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted at the CAn-Lab of the Department of Biochemistry and Biotechnology (KNUST). Data were collected from diabetic patients and non-diabetics from the month of January 2013 to March 2013.
Sampling Procedure

Diabetic and non-diabetic persons who visited the laboratory within the period of the study were recruited after they had given their verbal informed consent. The CAN-Lab is run by the Department of Biochemistry and Biotechnology of KNUST for undertaking clinical biochemistry tests. Apart from using this laboratory for teaching and research, it is also used for income generation, as the clientele visit the Lab for tests, pay for the services rendered. Some of the patients who go to the University Hospital and other hospitals/clinics near the University patronise this laboratory. In addition, apparently healthy persons who have no overt clinical condition, go there to have periodic check-ups on their state of health. In 2013 the clientele who visited the laboratory were 3,203. Both the diabetics and non-diabetic were part of those who visited the place. The non-diabetics status was confirmed by the measured FBS, which was between 4.1-6.4 mmol/l. The age range of the diabetics and non-diabetics was within the 40-80 y range. The diabetics were out-patients but not in-patients. They were known type 2 diabetics, taking anti-diabetic drugs.

Prior to undertaking the study, permission was sought from the Laboratory Management Committee.

Data Collection

After explaining the aim of study to the subjects and obtaining informed consent, a questionnaire seeking information on the age, sex and duration of the disease was administered to the subjects. The questionnaire was also used to gather information about medical history, like the presence of some signs and symptoms of kidney disease.

A calibrated meter rule was used to measure heights of patients, while weights were measured using a scale (Camry, China) and the body mass indices were calculated. The criteria adopted for the classification of body weight in this study was as follows; BMI less than 20kg/m\(^2\) falls within the underweight group, 20–25kg/m\(^2\) are within the normal range. Those that fall within the range of 25–30kg/m\(^2\) and beyond are overweight or obese.

Blood samples were collected from the patients and analysed at the laboratory for plasma fasting blood glucose, uric acid, urea and creatinine. All reagents were obtained from Fortress Diagnostics Limited, United Kingdom.

All criteria used for the determination of hyperglycemia, hyperuricemia, hyperuremia and hypercreatininemia were based on the following reference ranges given by Fortress Diagnostics Limited (2011); plasma uric acid: Males 202.3 - 416.5 µmol/l, Females 142.8 - 339.2 µmol/l; plasma creatinine: Males 53 -97 µmol/l, Females 44 -80µmol/l; plasma urea: for both males and females 2.1 - 7.1mmol/l; plasma glucose: for both males and females 4.1 - 6.4mmol/l.

Analysis of Blood Samples for Glucose, Uric Acid, Urea and Creatinine

Five millilitres of blood sample was collected from each subject by venepuncture after an 8-12 h overnight fast. The collected specimens were centrifuged to obtain serum samples. The separated serum samples were analysed for uric acid, urea and creatinine. Creatinine was determined by the alkaline picrate method, urea, by the urease-hypochlorite method and uric acid, by the uricase-peroxidase method. Serum from specimen in fluoride tubes were also analysed for glucose, using the glucose oxidase method. All these methods were based on manufacturer's instructions of Fortress Diagnostics Limited.

Statistical Analysis

Data was analysed using SPSS version 16.0. The student t-test was used to compare means of measured variables in the diabetics. A p-level of less than 0.05 was reckoned statistically significant. Bivariate analysis was used to determine the relationship between BMI and the various measured parameters. FBS, duration of the disease and age were also compared to the measured parameters using the bivariate analysis. Pearson correlation analysis was used to calculate the correlation coefficients (r), for determining the relation between the variables (age, duration of the disease) and the metabolic parameters (uric acid, urea and creatinine).

Results

A total of 34 diabetic patients aged 40 to 77 y were involved in this study. The number of males was 22 (64.7%) and the females, 12 (35.3%). The mean age of the total population of diabetics was 57.68 ±10.39 (±SD) y. The mean ages for males and females were 57.41 (± 11.8) y and 58.17 ± 7.47 y respectively. Of the nine non-diabetics drafted into the study, four (44.4%) were males, while five (55.6%) were females. The mean age of the non-diabetic females was 61.0 ± 3.32 y and the mean age of the non-diabetic males was 50.75 ± 8.10 y.

Table/Fig-1 shows the mean values of the measured parameters in the diabetics. The females were non-significantly older (mean age, 58.17 ± 7.47 y) than the males (mean age, 57.41 ± 11.8 y; p=0.843). There was also no significant difference between their body mass indices (p=0.256), FBS (p=0.975), uric acid (p=0.191), urea (p=0.905) and creatinine (p=0.769), all at 95% confidence level. There was however, a significant difference between their mean durations of the metabolic disease (p-value<0.05). Females recorded a higher mean duration of the disease (12.50 ± 6.95 y) than males (7.32 ± 4.48 y). The mean plasma creatinine level in the female diabetics (84.17± 54.73 µmol/l) was outside the reference range (44-80 µmol/l). For the males, the mean values of all parameters were within the reference ranges with the exception of their mean FBS (8.56 ± 3.42 mmol/l).

According to Table/Fig-2, there were no differences in the prevalence of obesity, hyperglycemia, hyperuremia, hyperuricemia and hypercreatininemia between the male and female diabetics.
p=0.018), plasma creatinine levels (r=0.375, p=0.029). Also, in the diabetics, there was a weak positive correlation between BMI and plasma uric acid levels (r<0.5, p=0.043). In [Table/Fig-4], the bivariate analysis shows that, there was a strong correlation between the BMI and FBS (r>0.5, p=0.030) as well as the BMI and uric acid (r>0.5, p=0.05) in the diabetic females. There was also a strong positive correlation between their FBS and the plasma levels of the measured blood parameters, uric acid, urea and creatinine and this gave r>0.5 and p<0.05.

In [Table/Fig-5], the comparison of the prevalence of some symptoms of kidney disease between male and female diabetics showed there was no statistical difference (p-value > 0.05).

Prevalence of some common symptoms of kidney disease in the non-diabetics:

In the non-diabetics, two females (40%) experienced lower back pain. There were no symptoms like abdominal pains, urgency in urination and difficulty in urination in the non-diabetic females. Also, there were no symptoms of kidney disease in the non-diabetic males. Prevalence of obesity, hyperglycemia, hyperuricemia, hyperuremia, hypercreatininemia in the non-diabetic females.

In the non-diabetic population, none of them was obese. There was also no case of hyperglycemia, hyperuricemia and hypercreatininemia. However, two non-diabetic females (40%) had high blood levels of uric acid while all the non-diabetic males had normal blood levels of uric acid. From [Table/Fig-6] however, there was a significant difference between the mean BMI and mean fasting blood glucose of the diabetic females and that of the non-diabetic females, p-value =0.05 at 95% confidence level. There was no significant difference between the mean age, mean plasma uric acid, mean plasma urea and mean plasma creatinine levels of the diabetics and non-diabetics, ( p-value >0.05).

**DISCUSSION**

This study looked at the effect of diabetes mellitus on renal function in some diabetics who visit the CAN-Lab at KNUST, Kumasi, Ghana. From [Table/Fig-1], though there was no significant difference (p=0.843) between the mean ages of male and female diabetics, there was a significant difference (p=0.033) between the mean duration of the metabolic disease; that is, 7.32 ± 4.48 y and 12.50 ± 6.95 y, for the male and female diabetics, respectively. This suggests that there was an early onset of the metabolic disease in the females than in the males.

According to [Table/Fig-6], the mean value for BMI of the female diabetics (29.8 ± 7.36 kg/m²) was significantly higher (p= 0.033) than that of the non-diabetic females (24.30 ±2.12 kg/m²). The prevalence of obesity in the female diabetics was 33.3% and in the male diabetics, it was 22.7% [Table/Fig-2] but among the non-diabetic females, the prevalence of obesity, hyperglycemia, hyperuricemia, hyperuremia, hypercreatininemia in the non-diabetic females.

According to Caprio and Tamborlane [11], unhealthy dieting, such as intake of foods rich in saturated fats, is a risk factor to obesity.
The observation that 83.3% of the diabetics and 68.2% of males were hyperglycemic is an indication of the general, poor glycemic control in diabetics. Lack of exercise, unhealthy diet and poor compliance in the use of diabetic drugs are the possible factors for the poor glycemic control. The incidence of type 2 diabetes mellitus has increased over the years, and this seems to be driven by growing rates of obesity [14]. Obesity is a multifactorial condition and the causes include genetic and environmental factors [14]. Glucose homeostasis is critically dependent on a finely regulated balance between insulin sensitivity and output in the pancreas [10,11]. In hyperglycemic conditions prior to insulin resistance, there should be a corresponding rise in insulin output in order to maintain normal glycemia [14]. However, this compensation is lost in individuals predisposed to type 2 diabetes mellitus, resulting in overt hyperglycemia [10,11].

Hyperglycemia is known to be involved in inflammation and vascular complications associated with diabetes, arising from reactive oxygen species (ROS) generation and action [15]. Chronic hyperglycemia induces the production of ROS, through the glycation reaction [16], in many tissues. ROS increase levels of protein oxidation, DNA oxidation and lipid peroxidation. Consequently, oxidative stress originating from hyperglycemia would be a major cause of impaired islet function at the level of insulin synthesis and secretion [10].

From Table/Fig-1, since the mean plasma creatinine level in the diabetic females falls outside the reference range, while the males had a value within the reference range, this implies that the clearance of creatinine from the blood by the kidneys is more impaired in the diabetic females than males. This finding is backed by a previous report that, serum creatinine level is one of the basic markers for renal function examination [17]. The poor clearance of creatinine in the females could also be linked with the longer duration of the diabetes.

The prevalence rates of hyperuricemia and hypercreatininemia in the females were 16.7% and 25%, respectively, and in the males, 9.1% and 22.7%, respectively. In the non-diabetics, there were no cases of hyperuricemia and hypercreatininemia. This also implies that, renal excretion rate of urea and creatinine is slower in some of the diabetics. Urea is produced from the oxidative deamination of amino acids in which ammonia generated is transported to the liver for the formation of urea through the urea cycle. Azotemia (a condition associated with abnormal elevation of blood nitrogen), may indicate renal disease or a disorder that causes a secondary increase of blood urea [18]. Uremia is a condition in which there is an elevated blood urea level as a result of kidney malfunction [19].

According to Table/Fig-2, the prevalence of hyperuricemia (45.5%) in the male diabetics was higher, than that of the female diabetics, 41.7%, (p-value= 0.832). This could not convincingly confirm a report in literature that blood uric acid levels are usually higher in men under sixty-five years than in females of the same age category [20]. Coincidentally, 40% of the non-diabetic females were hyperuricemic (results not shown). Moreover, the mean uric acid level in non-diabetic females (376.80 ± 113.74 µmol/l) was outside the reference range (142.8-339.2 µmol/l). Information obtained from an interview with the non-diabetics was that some of them were hypertensive and were on some diuretic drugs. This result may be due to the possible excessive loss of water due to the intake of the diuretics [21].

Creatinine is produced after the pyrophosphate cleavage of phosphocreatine to produce energy for muscle activity [22]. Serum creatinine level is one of the markers for renal function examination. Age, gender, protein intake, and muscle mass influence serum creatinine levels [17]. From Table/Fig-2, apart from uric acid in which the males have greater elevation, for all the other parameters, females had the higher elevations (though nonsignificant). The longer duration of the condition could be responsible. If the sample sizes were larger, a clearer picture would have been seen.

From Table/Fig-3, the positive correlation between age and plasma creatinine levels supports the study of Cholongitas et al., [17], who reported that plasma creatinine level is influenced by age. The association between the age and plasma creatinine levels in the diabetics also suggests that diabetics are at risk of developing end stage renal disease (ESRD) as they age.

There was a weak positive correlation between BMI and uric acid levels (r=0.350; p=0.043) in the diabetics. Obesity influences reabsorption of salts in proximal convoluted tubules [23]. Obesity decreases the uptake of glucose into target cells like muscle cells and adipocytes, by suppressing insulin signalling molecules in these cells; hence, blood glucose levels become elevated and glucose gets spilled into urine. The decrease in urine pH that results from the high levels of glucose in the urine causes salts of weak acids like uric acid to be reabsorbed into the blood [23].

In the diabetic females, there was a stronger positive correlation between FBS and BMI (r=0.625 and p= 0.030). Obesity causes insulin resistance in target cells [11]. In the obese female diabetics, the high deposition of fats in adipose tissue suppresses insulin signalling molecules in target cells. This causes the reduced uptake of glucose by the target cells in response to insulin secretion, therefore blood levels of glucose increase. Often, individuals with normal blood glucose levels have normal blood uric acid levels [24].

In diabetic females, there was a strongly positive correlation between FBS and uric acid (r=0.754; p=0.005). This means that the increased FBS levels in the blood of the diabetic females results in an increase in their plasma uric acid levels. According to Eckel et al., [25], the presence of glucose in urine due to its elevated levels in the blood, decreases the pH of the urine which influences the reabsorption of uric acid in the proximal convoluted tubules into the blood.

Feig et al., [26] have shown that there is an association of high levels of uric acid with diabetes mellitus. Obesity which is a common feature of type 2 diabetics influences the reabsorption of salts in the proximal convoluted tubule or the loop of Henle and this results in increased glomerular capillary pressure and glomerular filtration rate [24]. Again, insulin resistance which is a feature of type 2 diabetes causes low urine pH due to a defect in ammoniagenesis. Such a lowered urine pH (acidic urine) favours formation of uric acid stones, [25]. Hyperuricemia is an underlying risk factor for type 2 diabetes mellitus, as it causes proinflammatory endocrine imbalance in vascular smooth muscle cells and adipose tissue which lead to cell surface morphological changes and insulin resistance [27].

The occurrence of lower back pain in the non-diabetics, despite their normal plasma levels of uric acid, urea and creatinine could be attributed to aging which is a risk factor for osteoporosis and other bone and joint diseases or particularly, the nature of their work. Apart from this, the other symptoms of kidney disease were absent in the non-diabetics.

The presence of some of the symptoms of kidney disease in the diabetics may be due to the elevated levels of uric acid and creatinine. Lower back pain could be associated with kidney dysfunction, due to infection of the urinary tract and formation of uric acid stones that deposit in the renal tubules. Though urgency in urination is a common symptom associated with kidney disease, this should however, not be used as a yardstick to determine renal dysfunction in the diabetics because, increase in urination (polyuria) is a characteristic of diabetes mellitus. This results from the increased levels of glucose in the urine which influences loss of water from the body.

Some limitations of this study are the small sample sizes used and the cross-sectional design. There are also differences in the numbers of males and females, as well as diabetics and control subjects. All these affect the statistical power of the study, so our findings cannot be generalised.
CONCLUSION
Renal function of diabetics has been investigated through this study. Some of the diabetics were having kidney dysfunction due to their elevated blood creatinine and uric acid levels. The study has also shown that the BMI of some of the diabetics fell in the range of overweight and obese; thus, confirming a correlation between BMI and diabetes mellitus. In the diabetic females, there was a strong positive correlation between FBS and BMI (r=0.625 and p= 0.030).

REFERENCES