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Renal Function Assessment in Diabetics and Non-Diabetics Subjects at University of Gondar Specialized Referral Hospital, Northwest Ethiopia: A Comparative Study

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Abstract

Background: Diabetes mellitus (DM) contributes to the development of diabetic nephropathy (DN), the leading cause of chronic renal failure. Measurement of serum urea and creatinine is widely regarded as a test of renal function. Therefore, this study aimed at determining renal function tests in DM patients and their correlation with blood pressure and duration of illness in comparison with healthy controls.

Methods: A comparative cross-sectional study was conducted from February to May 2020 at the University of Gondar Specialized Referral Hospital, Northwest Ethiopia. A Simple random sampling technique was used to recruit 164 DM and 82 control participants. Five ml venous blood in the serum separation tube was collected and analyzed for blood urea nitrogen (BUN) and creatinine determination using BS-200E Mindray analyzer. Independent sample t-test and bivariate correlation were used to analyze continuous variables. A p-value <0.05 was considered as statistically significant.

Results: The mean value of creatinine (0.99 ± 0.40 vs. 0.75 ± 0.17 mg/dl) and BUN (16.1 ± 7 vs. 13.9 ± 6.6 mg/dl) was higher in DM patients as compared to the control group. However, the mean estimated glomerular filtration rate (eGFR) value was higher in the control group (158.83 ± 32 53.3 ml/min/1.73m^2) than the diabetic group (108 ± 45.4 ml/min/1.73m^2). The duration of illness has a significant positive correlation with creatinine and negative correlation with eGFR. Moreover, chronic kidney disease (CKD) is prevalent in 30.8% of DM patients.

Conclusion: Serum creatinine and BUN levels are significantly higher in DM patients than the controls, indicating renal complications in the former groups. All DM patients should regularly monitor their renal profile to avert complications associated with DM.

Keywords: ***Diabetes mellitus; Diabetic kidney disease; Ethiopia; Renal function tests***

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1. Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or in both conditions [1]. DM can be classified into Type 1 DM (T1DM) and Type 2 DM (T2DM) based on insulin dependency. T1DM is caused by an autoimmune reaction, where the body's defense system attacks the insulin-producing beta cells in the pancreas [2]. As a result, the body can no longer produce the insulin it needs. T2DM results from insulin resistance and is commonly seen in adults [3].

The chronic hyperglycemia of DM is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. After many years of DM, the delicate filtering system in the kidney becomes destroyed and this is more likely to occur if the blood sugar is poorly controlled [4]. Even when DM is controlled properly, the disease can lead to kidney failure [5]. DN is the kidney disease that occurs as a result of DM and it is the leading cause of chronic renal failure. The early detection of DN can improve long-term outcomes and retard progression to end-stage renal disease (ESRD). DN affects 30% of all DM patients and it is the major leading cause of ESRD in many countries [6].

In DN, several serum markers are known to be deranged with significant morbidity and mortality. Measurement of the plasma urea and creatinine is widely regarded as a test of renal function [4]. Changes in serum creatinine concentration more reliably reflect changes in GFR than do changes in urea concentrations, since urea formation is influenced by several factors such as liver function, protein intake, and rate of protein catabolism [7]. However, it has been demonstrated that normal serum creatinine levels may be accompanied by loss of renal function, making this a relatively late parameter for lesion detection [8]. Serum creatinine and BUN are easily available tests that can assist in the detection and prevention of diabetic kidney disease at an early stage thereby, limit the progression to ESRD [6]. These substances are normal metabolic waste products that are excreted by the kidneys. In kidney disease, these substances are not excreted normally, and so they accumulate in the body thus causing an increase in blood levels of urea [9]. Creatinine, the breakdown product of creatinine phosphate, is released from skeletal muscle at a steady rate. Serum creatinine correlates quite well with the percent of the body skeletal muscle. It is filtered by the glomerulus, and a small amount is also secreted into the glomerular filtrate by the proximal tubule [10].

GFR is the best measure of kidney function since it measures the rate at which the kidney glomeruli filter plasma to process and remove waste products from the kidney. If the kidneys are injured by CKD, the GFR gradually declines, and the amount of remaining kidney function can be estimated by measuring or calculating the GFR. Although the best measure for GFR is obtained by techniques that involve infusion of exogenous substances, GFR is usually estimated in clinical practice by a various formulas based on serum creatinine concentration, since this is much less invasive and time-consuming [11]. The two most common methods for determining GFR are creatinine clearance and eGFR. Formula-derived eGFR results have become widely used in clinical practice. The most popular equation used today is the MDRD equation. It is anticipated that this process will aid early identification and therefore improve long-term outcomes for those with DN [9,12].

Blood urea and serum creatinine are good indicators of the normal functioning of the kidney and increased serum levels of these parameters are an indication of kidney dysfunction [13]. Therefore, this study aimed at determining renal function tests and their correlation with blood pressure and duration of illness in DM patients in comparison with apparently healthy controls in Gondar, Northwest Ethiopia.

2. Materials and Methods

The study group comprised of 164 DM subjects as study group attending the outpatient department of the University of Gondar specialized Referral Hospital, Gondar, Northwest Ethiopia. Eighty-two non-diabetic subjects participated in the study attending Gondar blood bank treated as a control group. Gondar town is found in Amhara regional state at 738 km from the capital city of Ethiopia, Addis Ababa. The University of Gondar Specialized Referral Hospital is a teaching hospital serving approximately 5-7 million people throughout most of the Amhara regional state and nearby regions. The facility has more than 500 inpatient beds and has a range of specialties including a chronic illness outpatient clinics.

All DM patients aged 18 years and above attending at the University of Gondar Specialized Referral Hospital in the time interval and volunteered to give informed written consent were included in the study. Apparently healthy volunteer non-remunerated blood donors who had no previous history of chronic diseases were included as control participants. Patients with urinary tract obstruction, hyperlipidemia, congestive cardiac failure, smokers, and critically troubled patients were excluded from the study. Thus, 246 study participants (164 DM and 82 controls) were selected by a simple random sampling technique in the study.

2.1 Data collection and laboratory methods

The variables collected were age, gender, Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of illness, blood urea, and serum creatinine levels of all the subjects. All aspects of the data collection process were supervised by the principal investigator to ensure data quality. Blood pressure was taken using a mercury sphygmomanometer in a sitting position after 15 min of rest and two measurements were averaged to be recorded. Five minutes interval is recommended between the two measurements. Anthropometric data were collected by recording the weight and height of the study participants. A portable weight scale and locally made stadiometer with a sliding headpiece were used to measure weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm), respectively. The BMI was calculated as weight divided by the square of height (kg/m^2).

Under aseptic conditions, 5 ml of collected whole blood in a serum separation tube was allowed to clot for 15 to 30 min and then centrifuged at 3000 rpm for 5 min and serum was separated. The separated serum was analyzed using a BS-200E Mindray chemistry analyzer (Shenzhen Mindray Bio-Medical Electronics Co. Ltd, China) for Creatinine and BUN determination. The GFR was estimated using the 4-variable modification of diet in renal disease (MDRD) equation (GFR in ml/min per 1.73 m^2 = 175 x Serum Cr-1.154 x age-0.203 × 1.212 (if patient is black) × 0.742 (if female). The normal range for BUN is 7-20 mg/dl, and 0.6 - 1.4 mg/dl and 0.5 - 1.2 mg/dl for serum creatinine for males/females, respectively. The normal value for GFR is 100-150 mL/min.

2.2 Data analysis and interpretation

Epidata version 4.6.02 and Statistical Package for Social Sciences (SPSS) version 20 (IBM Corporation, Armonk, NY, USA) software were used for data entry and statistical analysis, respectively. The data were tested for normality by performing Shapiro-Wilk and Kolmogorov-Smirnov tests. An Independent sample t-test was used to compare the difference between diabetic and non-diabetic control groups. The strength of association between the pairs of variables was assessed by Pearson's and spearman's correlation coefficient. A p-value of ≤ 0.05 was considered as statistically significant.

2.3 Ethical consideration

Ethical clearance for the study was obtained both from the Ethical Review Committee of the School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar. An informed consent was taken from all the subjects to participate after explaining the objective of the study. Then those who were willing to participate were included in the study. To ensure the confidentiality of data, study participants were identified using codes and unauthorized persons had no access to the collected data. Only the principal investigator had access to the computerized data.

3. Results

3.1 Socio-demographic, clinical, and anthropometric characteristics of study participants

A total of 246 (164 DM patients and 82 controls) participants were included in this study. The results showed that the mean levels of BMI and SBP were significantly higher (P, 0.05) in patients with DM compared to controls. The mean duration of illness since diagnosis (years) was 6.25 ± 4 in DM patients (TABLE 1).

TABLE 1. **Demographic, clinical, and anthropometric characteristics of diabetic and non-diabetic controls at University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020 (n=246).**

Variables	DM Mean ±SD	Control Mean ± SD	p-value
Age (years)	48.23 ± 15.3	46.5 ± 11.4	0.268
BMI (Kg/m^2)	25.5 ± 3.4	23.9 ± 3.30	<0.001*
SBP	126.2 ± 16.9	114.8 ± 11.6	<0.001*
DBP	76.3 ± 9	75.6 ± 5.2	0.665

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation
*statistically significant at p, 0.05

The male diabetic subjects had significantly higher creatinine levels (1.05 ± 0.42) (p-value = 0.012) compared to female subjects (0.89 ± 0.37). However, the mean values of BUN and eGFR don't show a significant difference among males and females (Table 2). The mean values of serum creatinine, BUN, and eGFR are significantly higher in DM patients as compared to the control group (TABLE 3).

Table 2. **Gender-wise correlation of renal function test in DM patients at University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020 (n=246).**

Variables	Male Mean ± SD	Female Mean ± SD	p-value
Creatinine	1.05 ± 0.42	0.89 ± 0.37	0.012*
BUN	16.1 ± 7	13.9 ± 6.6	0.057
eGFR	112.8 ± 46.4	101.3 ± 43.5	0.111

Abbreviations: BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; SD, standard deviation
*statistically significant at p, 0.05

TABLE 3. **Comparison of renal function tests in diabetic and non-diabetic controls at University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020 (n=246).**

Variables	DM Mean ± SD	Controls Mean ± SD	p-value
Creatinine	0.99 ± 0.4	0.76 ± 0.17	<0.001*
BUN	15.2 ± 6.9	12.7 ± 3.49	0.003*
eGFR	108 ± 45.4	139.1 ± 38.7	<0.001*

Abbreviations: BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; SD, standard deviation

*statistically significant at p, 0.05

Out of the total 164 DM subjects, 30.8% had CKD (stage 2-5). Of them with CKD, 23.9%, 6.3%, and 0.6% was in stage 2, 3, and 4, respectively. Not a patient that develop renal failure (Stage 5) (TABLE 4).

TABLE 4. **Staging of CKD among DM patients based on eGFR value at University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020 (n=164).**

Staging of CKD	Description	GFR (ml/min)	Frequency
Stage 1	Kidney damage with normal GFR	90 and above	69.2%
Stage 2	Kidney damage with a mild decrease in GFR	60 to 89	23.9%
Stage 3	Moderate decrease in GFR	30 to 59	6.35%
Stage 4	Severe reduction in GFR	15 to 29	0.6%
Stage 5	Kidney failure	Less than 15	0%

Abbreviations: CKD; chronic kidney disease; GFR, glomerular filtration rate

Respecting the correlation of renal function tests with blood pressure and duration of illness, creatinine was found to be positively correlated with the duration of illness (p-value, 0.005). The eGFR was found to be negatively correlated with duration of illness (p-value, 0.003) and SBP (p-value, 0.025). There was no significant correlation between renal function tests and blood pressure in the control group **(**TABLE 5). Serum Creatinine concentration changes inversely with changes in eGFR and therefore useful in gauging the degree of renal dysfunction (FIG. 1).

TABLE 5. **Correlation of renal function tests with blood pressure and duration of illness in diabetic and non-diabetic control subjects at University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020 (n=246).**

Variables	DM			Controls	
	Duration of illness rho (p)	DBP rho (p)	SBP rho (p)	DBP rho (p)	SBP rho (p)
Creatinine	0.225 (0.005)*	0.055 (0.485)	0.128 (0.104)	-0.02 4(0.837)	0.073 (0.526)
BUN	0.151 (0.070)	0.063 (0.452)	-0.032 (0.705)	-0.079 (0.489)	-0.204 (0.073)
eGFR	-0.230 (0.003)*	-0.064 (0.417)	-0.176(0.025)*	0.052 (0.656)	0.013 (0.190)

Abbreviations: BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure

*statistically significant at p, 0.05

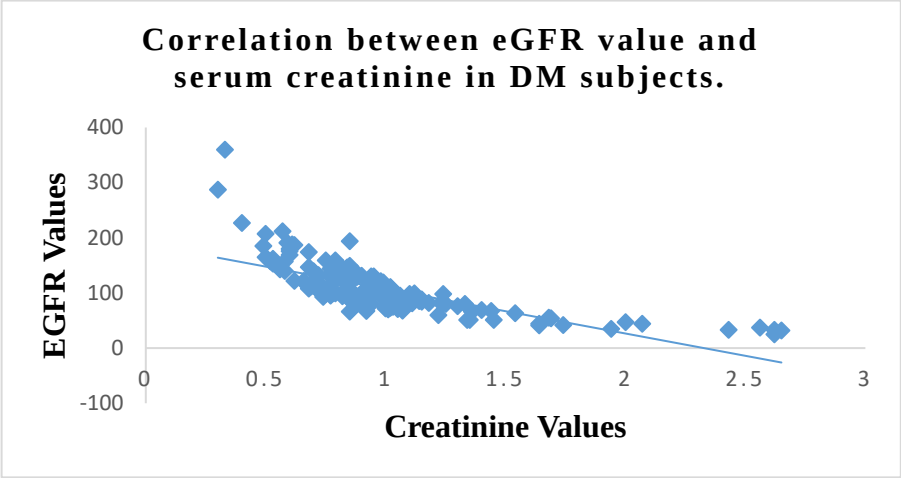

FIG. 1. **Correlation between eGFR value and serum Creatinine in DM subjects.**

4. Discussion

Assessment of renal function in DM patients is extremely important since DN constitutes a major cause of CKD in the world [14]. Serum levels of urea and creatinine can be used as useful prognostic markers and predictors of renal damage in DM patients [15]. Serum creatinine is filtered by the Glomerulus; therefore, serum creatinine level is used as an indirect measure of glomerular filtration. Serum creatinine is a more sensitive index of kidney function compared to serum urea level. This is because creatinine fulfils most of the requirements for a perfect filtration marker [6,15].

In this study, the mean ± SD values of creatinine and BUN were significantly higher among DM patients than controls. The finding of this study was in harmony with other studies conducted in India, Bangladesh, and the Caribbean [4,6,10,16,17]. This might be explained by the fact that, in DM subjects, increased BUN and creatinine level is seen when there is damage to the kidney or the kidney is not functioning properly [4]. This increased mean value said that there may be slight obstruction in kidney disease patients in excreting urea and also showed that there was an impairment of renal function [13]. A study conducted in India in 2017 showed that an increase of blood urea with the increment of blood sugar level clearly indicates that long-standing high blood sugar levels cause damage to the kidney [6]. Therefore, an increased blood urea and serum creatinine levels in DM patients indicates irretrievable damage to the nephrons of the kidney [18]. The tendency of occurrence of renal function tests values at the higher reference limits in cases of DM reflects the initiation of nephropathy changes.

The normal levels of creatinine were considered 0.8 to 1.4 mg/dL. However, Females usually have a lower creatinine values (0.6 to 1.2 mg/dL) [5]. In this study, high serum creatinine level was seen in males (1.05 ± 0.42) than females (0.89 ± 0.37), which could be because of storage of creatinine as a waste product in muscle mass and the presence of high muscle mass in males [19]. The finding of this study showed that there is no significant variation in BUN between males and females. This

result is supported by another study who showed that gender-wise variation occurs only in serum creatinine level but not urea level [5].

The prevalence of CKD among DM patients in this study was 30.8% (stage 2 and above) and this was lower than a study in Japanese (46%) [20] and Kenya (82.6%) [21]. However, the prevalence of CKD in this study is higher than that of 21.3% reported in Ethiopia [22], 25.3% in Brazil [8], and 27.9% in Spain [23]. These differences in the prevalence of CKD might be because of the differences in study design and/or due to the use of MDRD equation for GFR estimation that led to a higher prevalence of CKD.

In this study, the duration of illness positively correlated with serum creatinine levels and negatively correlated with eGFR. At the onset of DM, the kidney grows large and the GFR becomes disturbed [9]. GFR increases during the early stages of DM due to high blood sugar and decreases during the later stages of DM, reflecting a decline in renal function [24].This finding is in accordance with the fact that serum creatinine is established markers of GFR. As GFR diminishes, there is a rise in plasma concentrations of serum creatinine and BUN. Raised serum creatinine and reduced GFR has become fairly reliable indicators of kidney dysfunction [6]. SBP negatively correlated with eGFR in DM patients. High blood pressure is a leading cause of CKD. The prevalence ranges from 60% to 90% depending on the stage of CKD and its cause. The mechanisms of hypertension in CKD include volume overload, sympathetic over activity, salt retention, endothelial dysfunction, and alterations in hormonal systems that regulate blood pressure. Hypertension remains a leading attributed cause of ESRD [25, 26]. High Blood pressure may develop early in the course of CKD and can be associated with adverse outcomes such as worsening renal function and development of cardiovascular disease. Hypertension is a major promoter of the decline in GFR in both diabetic and non-diabetic kidney disease [27]. In a retrospective study done by Klag et al it was found that elevations of blood pressure are a strong independent risk factor for ESRD and that interventions to prevent the disease need to emphasize the prevention and control of both high blood pressure [28].

5. Conclusion and Recommendation

Serum creatinine and BUN levels are significantly higher in DM patients than the controls, indicating renal complications in the former groups. Moreover, significant correlation was found between renal function tests in relation with duration of illness and blood pressure. All DM patients should regularly monitor their renal profile to avert complications associated with the disease.

6. Abbreviations

BMI: Body Mass Index; BUN; Blood Urea Nitrogen; CI: Confidence Interval; CKD: Chronic Kidney Disease; DBP: Diastolic Blood Pressure; DM: Diabetes Mellitus; DN: Diabetic Nephropathy; DBP: Diastolic Blood Pressure; eGFR: Estimated Glomerular Filtration Rate; ESRD: End-Stage Renal Disease; GFR; Glomerular Filtration Rate; SBP: Systolic Blood Pressure; SOPs: Standard Operation Procedures

7. Declarations

Ethical approval and consent to participate: The study was conducted after it had been reviewed and approved by the Ethical Review Committee of the School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar.

Consent for publication: Not applicable

Competing interests: None declared

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Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contribution: TA designed and implemented the study, undertook statistical analysis, performed data interpretation, drafted the manuscript. ZG and FA undertook statistical analysis and reviewed the manuscript. The author agrees to be accountable for all aspects of the work.

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