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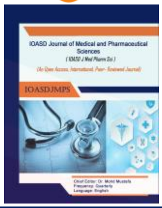

Evaluation of Estimated GFR as a Predictor of Diabetic Nephropathy among Type2 Diabetes Mellitus Patients at Zawia Region, Western Libya

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ABSTRACT

Background: Type2 diabetic mellitus (T2DM) patients with impaired renal function and diabetic kidney disease have a higher risk of mortality, and often progress to end-stage renal disease. ***Objectives:*** to estimate the glomerular filtration rate using the Cockcroft-Gault (CG) equation, and serum creatinine in the screening of reduced renal function in patients with T2DM in Zawia region Western Libya. ***Materials and Methods:*** A cross-sectional study was conducted among 68 type 2 diabetic patients and 67 healthy subjects as control group. Blood samples were tested for fasting blood glucose (FBG), blood urea, and serum creatinine for all patients and control subjects enrolled in this study in the period from January to March 2021. Then eGFR was calculated using Cockcroft- Gault (CG) equation for all patients and control individuals. ***Results:*** 68 patients aged 53.26± 13.52years were evaluated 58.8% were women. The mean of serum creatinine is 1.36 mg/dL which is significantly higher as compared with the controls (*P* value = 0.028). The mean of eGFR showed a significant decreasing in eGFR in diabetic patients compared to healthy subjects (*P*=0.000). Significantly increased risk of impaired GFR among T2DM patients was observed. 54.4% of patients (n,37) were classified as stage 1 and 27.9% (n,19) as stage 2 and 7.4% (n, 5) as stage 3A and 2.9% (n, 2) as stage 3 B and only 4.4% (n, 3) as stage 5. Study showed significantly decreased in eGFR with increasing of age and duration of diabetes type 2 (P= 0.000& 0.002), respectively. ***Conclusion:*** It can be concluded that patients with T2DM enrolled in this study had impaired GFR. This suggested that CKD was a major concern for patients with T2DM. Hence, age of the patient and duration of T2DM had a significant impact in decreasing eGFR.

Keywords: T2DM, eGFR, diabetic nephropathy, Cockcroft-Gault equation, Zawia Region.

Original Research Article

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1. INTRODUCTION

Hyperglycemia is a hallmark of diabetes mellitus, a collection of metabolic diseases linked to lipid abnormalities and caused by deficiencies in insulin action, secretion, or both. Every year, diabetes accounts for around 5% of all deaths worldwide [1]. The prevalence of T2DM has reached epidemic proportions and is estimated to afflict over 400 million people worldwide [2, 3].

T2DM manifests through the development of fasting and postprandial hyperglycemia, which is the primary contributor to the induction of numerous life-threatening complications and co-morbidities [4].

Kidneys are one of the important organs that are involved in diabetes. In most regions of the world, diabetes is the leading cause of end-stage renal disease (ESRD). In diabetes individuals, kidney involvement both directly and indirectly increases the involvement of other organs and raises morbidity and death. The most frequent cause of chronic kidney disease (CKD) nowadays is diabetic nephropathy. Chronic kidney disease and ultimately ESRD can result from either kind of diabetes. However, people with ESRD frequently develop T2DM since it is far more common than type 1 [5].

Diabetic kidney disease, also known as CKD owing to diabetes, is characterized by decreased kidney function or kidney damage for a minimum of three months, irrespective of renal function. Increased urinary indicators, such albuminuria, aberrant urine sediment, aberrant imaging tests, or kidney biopsy are all indicators of kidney disease. When a person with diabetes has high excretion of urine albumin without concomitant kidney disease, this is a major factor in the clinical diagnosis of diabetic kidney disease [6].

GFR may rise and then decline, and albumin or protein excretion may increase as diabetic kidney disease usually proceeds through several phases, sometimes leading to uremia or end-stage renal disease (ESRD) [7].

Glomeruli, clusters of blood vessels located in nephrons in the kidneys, filter waste from blood into urine for excretion. Uncontrolled diabetes mellitus can cause high blood glucose levels that can alter the nephrons, causing glomeruli to thicken and eventually destroy them. Greater levels of protein are permitted to go from the circulation into the urine for elimination when the glomerulus is impaired. At first, there is little protein in the urine (microalbuminuria), but as the damage gets worse, there is more protein, which leads to diabetic nephropathy. This explains how CKD can result from type 2 diabetes mellitus [8]. The eGFR is the most widely used parameter for the evaluation of fluctuations in renal function in clinical practice. Reduction in renal function is defined by a GFR <60 mL/min/1.73 m2, and renal failure by a GFR <15 mL/min/1.73 m2 [6].

Many formulas used to calculate estimated GFR such as Cockcroft and Gault (CG) (1976) where:
eCCr = (140 – Age) x Mass (kg) x [0.85 if female] / 72 x [Serum creatinine mg\dl]. [9]

And Modification of Diet in Renal Disease (MDRD) (1999) where:
GFR (ml/min/1.73 m2)=186×((serum creatinine (μmol/l)/88.4)−1.154)× age (years)×0.742 if female and ×1.21 if African American [10].

Also Chronic Kidney Disease Epidemiology Collaboration (2009) where: 141 * min (Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993^{Age} * 1.018 [if female] * 1.159 [if black].

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males.

The Chronic Kidney Disease-Epidemiology Collaboration equation does not improve the underestimation of Glomerular Filtration Rate (GFR) in people with diabetes and preserved renal function [11].

The degree of renal disease can be determined by changes in the GFR rate. The phases of renal disease are categorized as follows in the UK and many other countries:
Stage 1 - The GFR rate is typical. Nonetheless, there is indication of renal dysfunction.
Stage 2 - Evidence of renal disease has been found, and the GFR rate is less than 90 milliliters.
Stage 3 - GFR rate is lower than 60 milliliters, regardless of whether evidence of renal disease has been detected.
Stage 4 - Regardless of whether renal disease symptoms have been found, the GRF rate is less than 30 milliliters.
Stage 5 - Less than 15 milliliters is the GFR rate. There has been renal failure.

Rarely do most people with chronic renal disease advance past Stage 2. For significant harm to be avoided, kidney illness must be identified and treated as soon as possible [12].

2. OBJECTIVES

The current study aimed to investigate the effect of T2DM on estimated GFR and kidney function compared to the control group in Zawia city, and to find out if the age, BMI and gender of a diabetic patient has an effect on the estimated GFR, also to explore whether GFR changes according to duration of T2DM.

3. MATERIAL AND METHODS

3.1. Study groups

The current study was conducted on total number of 68 patients during the period of January to June 2021 in Zawia city (Zawia central lab). The patients were previously diagnosed as T2DM patients. 67 of healthy individuals were involved to this study for comparison. The objectives and procedures were verified to all subjects and patients as they express their consent and willingness to contribute to this study. Venous blood samples were withdrawn for both diabetic and control groups. A blood samples used for fasting glucose level, blood urea, serum creatinine measurement for all diabetic and control group. Both Patients and control subjects were interviewed at the Zawia central lab. The lead investigator conducted all interviews in-person, explaining any questions that participants could find challenging. Prior to their involvement, each subject provided their informed permission.

3.2. Equipment and Disposables

The following list of equipment and consumables were used to perform different experiments and measurements.
1- Cobas C 311 -Roche – made in Japan for measurement FBS, B. Urea, S. creatinine.
3- Centrifuge LSC4810-2015.
4- Pipettes (5μl, 75μl, 100μl, 1000μl) and disposable tips.

5- Plain Blood tube.
6- sodium fluoride blood tube.
7- Disposable sterile syringe 5 ml.

3.3. Blood Samples

After approximately 12 hours fasting period, 5 ml of venous blood samples were withdrawn with dry sterile syringe for all subjects (patients and controls). The blood was divided into 2 tubes; 2 ml in fluoride oxalate tube for blood glucose measurement, and 3 ml were allowed to clot in plain tube (free from any coagulant). Immediately all blood samples were centrifuged at 2000 r.p.m for 10 minutes to obtained sera and plasma.

3.4. Laboratory measurements

Glucose and renal profile (blood urea ,serum creatinine) were measured by automated methods using Cobas C 311 –Roche instrument (Japan).

3.5. Estimated eGFR:

eGFR was calculated from the Cockcroft-Gault formula as follows.
eCCr = (140 – Age) x Mass (kg) x [0.85 if female] / 72 x [Serum Creatinine (mg/dL)]
The Cockcroft-Gault (C-G) formula uses a patient's weight (kg) and gender to predict CrCl (mg/dL), To account for the lower CrCl in females, the resultant CrCl is multiplied by 0.85 if the patient is female. Age is the primary predictor of CrCl in the C-G formula.

3.6. Statistical Analysis

Statistical analysis was performed using SPSS package version 23 (Statistical Package for the Social Sciences). The result was expressed as mean ± SD. Standard descriptive statistics, correlation coefficients, and significance tests were calculated. Differences between mean values were evaluated by Student's t-test. Also, for Correlation of eGFR with age, FBS, BMI, gender and duration of diabetes mellitus type2 we used. Simple regression. A P-value of less than 0.05 was considered to represent a statistically significant difference between groups.

4. RESULTS

4.1. Study group

A total number of 68 Patients (28 male, 40 female) previously diagnosed as type 2 diabetes mellitus, were randomly chosen to enrolled in this study from several medical centers in Zawia City-Western Libya, during the period of January to March 2021. On the other hand, a group of 67 healthy volunteers (38 male, 29 female) also studied as control group.The mean age of study group was 53.26±13.52year (26 to 91 year(, as mean age of control group was 42.61±16.84year (20 to90).

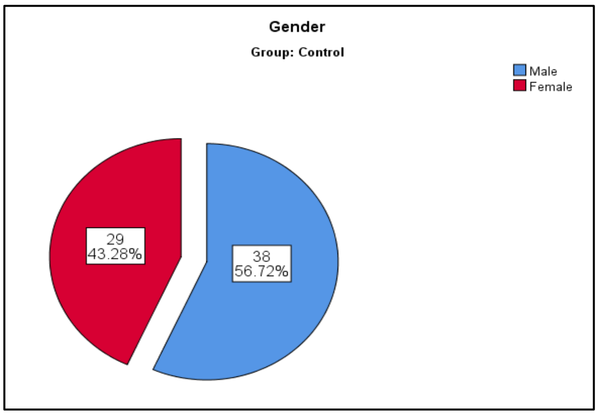

Figure 1: Gender in control group

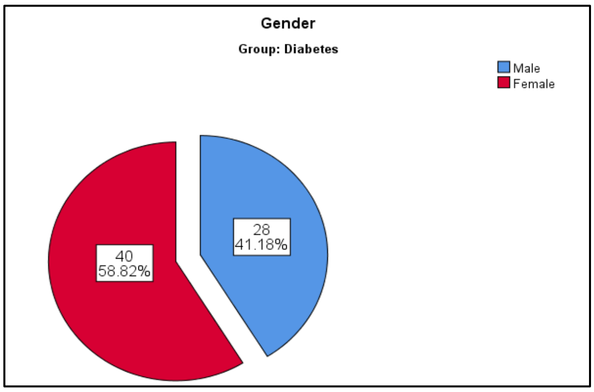

Figure 2: Gender in diabetics group

Table 1: Mean age of all study groups

Variable	Group	NO	Mean	SD	from	to
AGE	Control	67	42.61	16.84	20	90
	Diabetics	68	53.26	13.52	26	91

Table 2: Clinical characteristics of the participants

Group	Parameters	Frequency	Mean	SD
Control	FBS	67	90.01	27.22
	BU	67	26.01	16.62
	SC	67	0.89	0.72
	eGFR	67	126.76	44.52
Diabetics	FBS	68	201.60	79.77
	BU	68	38.35	22.61
	SC	68	1.36	1.54
	eGFR	68	90.79	36.97

4.2. Fasting blood glucose level (FBG) in diabetic patients compared with control group.

Table 2 and table 3. showed significant increasing in Fasting blood glucose level in diabetic patients compared with healthy volunteers (P= 0.000).

4.3. Blood urea level in diabetic patients compared with control group.

Table 2, table 3 and figure 3 showed significant increasing in blood urea level in diabetic patients compared with healthy volunteers (P= 0.000).

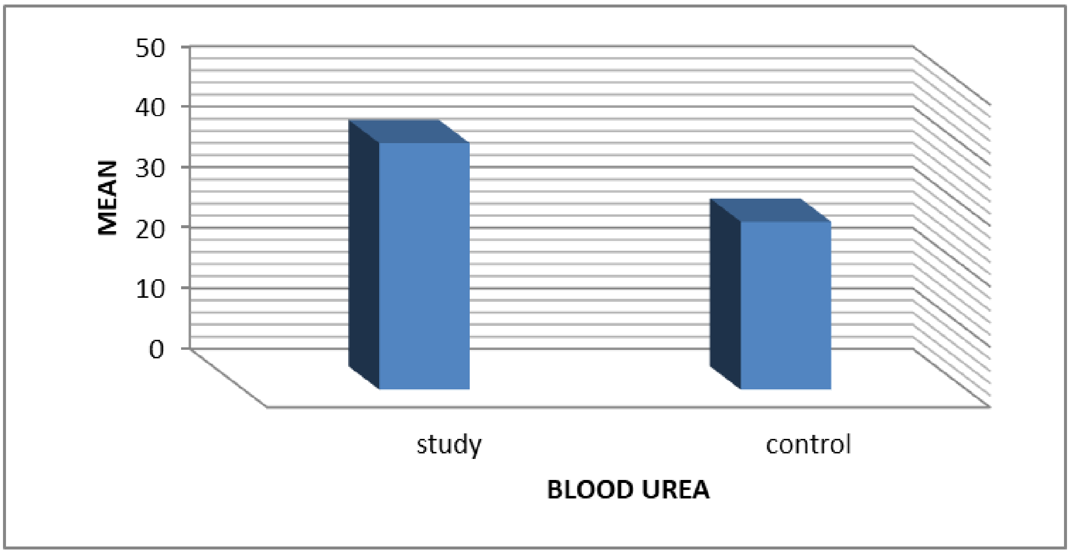

Figure 3: Comparison between B. urea in study & control

4.4. Serum creatinine level in diabetic patients compared with control group

Table 2, table 3 and figure 4 showed significant increasing in serum creatinine level in diabetic patients compared with healthy volunteers (P= 0.028).

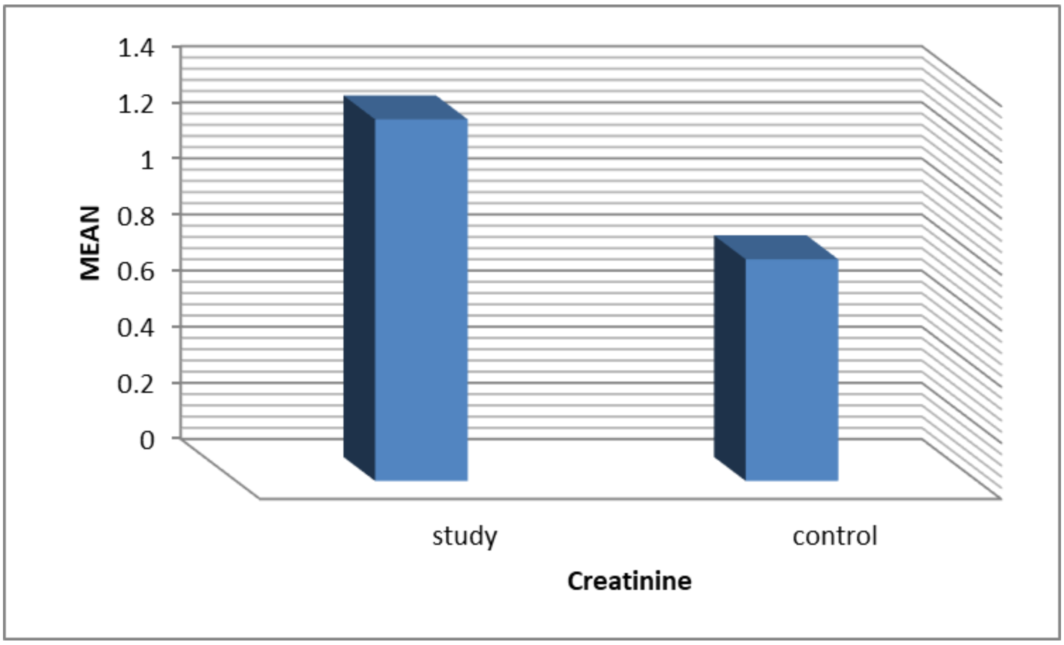

Figure 4: Comparison between S. creatinine in study& control

4.5. eGFR in diabetic patients compared with control group.

(Table 2, table 3 & fig 5) showed a significant decreasing in eGFR in diabetic patients compared to healthy subjects (P=0.000).

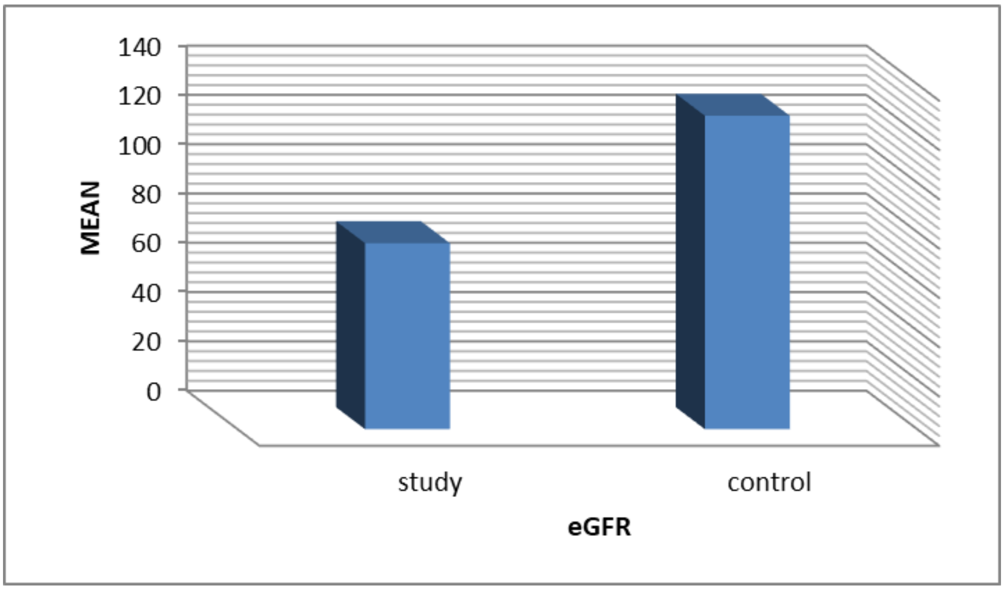

Figure 5: Comparison between eGFR in study & control group

Table 3. Comparison between various clinical data in study and control group

Parameter	Group	Frequency	Mean	SD	T - test	P value
FBS	Control	67	90.01	27.22	-10.908	0.000
	Diabetes	68	201.60	79.77		
BU	Control	67	26.01	16.62	-3.609	0.000
	Diabetes	68	38.35	22.61		
SC	Control	67	0.89	0.72	-2.236	0.028
	Diabetes	68	1.36	1.54		
eGFR	Control	67	126.76	44.52	5.110	0.000
	Diabetes	68	90.79	36.97		

4.6. Chronic renal failure stages in diabetic group according to eGFR

54.4% of patients (n,37) were classified as stage 1and 27.9% (n,19) as stage 2 and 7.4% (n, 5) as stage 3A and 2.9% (n, 2) as stage 3 B and only 4.4% (n, 3) as stage 5. (Table 4. & figure 6.)

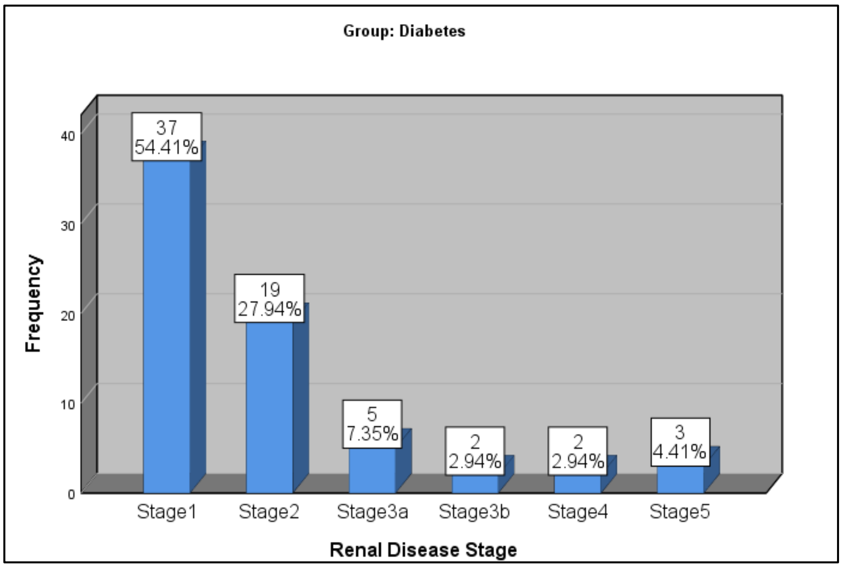

Figure 6. Stages of chronic failure in diabetic group

4.7. Chronic renal failure stages in control group according to eGFR.

79.1% of subjects (n,53) were classified as stage 1and 11.9% (n,8) as stage 2, only 3% (n, 2) as stage 3A. 4.5% (n, 3) as stage3b, and only 1.5% (n,1) as stage 5. (Table 4. & figure 7.).

Table 4. Stages of chronic failure in diabetic and control group.

Renal Stage	Control		Diabetics	
	Frequency	%	Frequency	%
Stage1	53	%79.1	37	54.4%
Stage2	8	%11.9	19	27.9%
Stage3a	2	%3.0	5	7.4%
Stage3b	3	%4.5	2	2.9%
Stage4	-	%0.0	2	2.9%
Stage5	1	%1.5	3	4.4%
Total	67	%100.0	68	100.0%

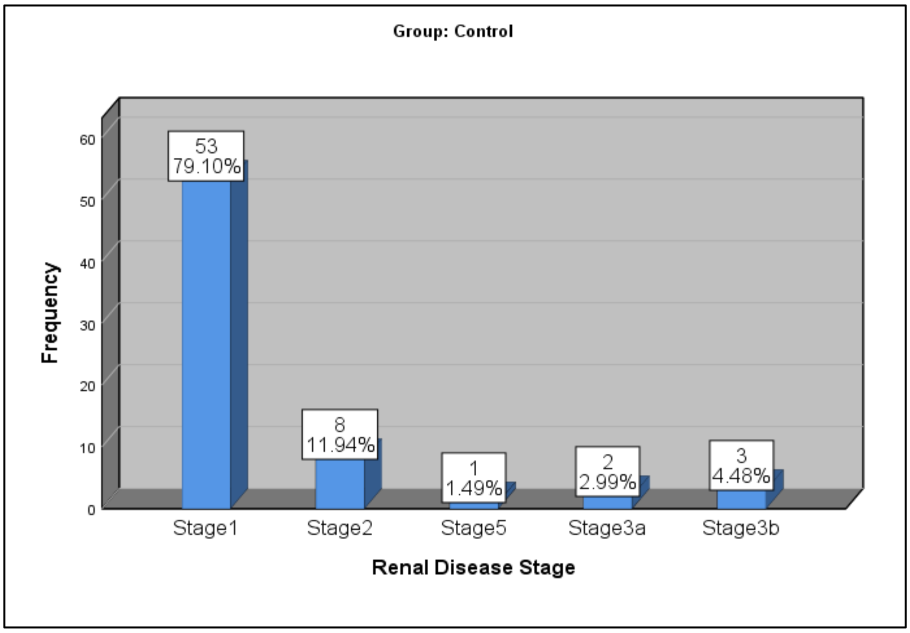

Figure 7: Stages of chronic failure in control group.

4.8. Variation of eGFR according to age, gender, BMI, duration of type 2 diabetes mellitus, and fasting blood glucose level (FBG).

eGFR was decreased significantly with increasing of age and duration of diabetes type 2 (P= 0.000& 0.002) respectively.

In contrast, eGFR was increased significantly with increasing of BMI (P = 0.004) as shown in table 5.

Table 5: Variation of eGFR according to age, BMI, and duration of type 2 diabetes mellitus

Variable	Parameter value	t	P value	Coefficient of determination R^2
Age	-1.342	-4.573	**0.000**	0.241
Duration of DM2	-1.781	-3.208	**0.002**	0.135
BMI	2.704	3.016	0.004	0.121

No correlation was observed between eGFR and gender (P =0.081) as shown in table 6.

Table 6. Variation of eGFR according to gender

variable	Gender	count	Mean	SD	t test value	P value
eGFR	male	28	100.14	38.52	1.773	0.081
	female	40	84.25	34.84		

No correlation was observed between eGFR and FBG (P =0.662) as shown in table 7.

Table 7: Variation of eGFR according to FBG

Variable	Parameter value	t	P value	Coefficient of determination R^2
FBG	-0.025	-0.439	0.662	0.003

5. DISCUSSION

The T2DM is a major health problem affecting 8.5% of the world population, and consuming about 1.8% of the global domestic [13]. The prevalence of T2DM has reached epidemic proportions and is estimated to afflict over 400 million people worldwide [2]. The most frequent cause of CKD nowadays is diabetic nephropathy. Chronic kidney disease and ultimately ESRD can result from either kind of diabetes. However, people with ESRD frequently develop T2DM since it is far more common than type 1[5].

GFR is the best estimate of number of functioning nephrons and functional renal mass. Precise measurement of glomerular filtration rate is a time consuming and expensive, thus measurement of the blood levels of the elements regulated by the kidneys can become useful in evaluating renal function especially where there are limited resources [14]. The estimated GFR is the most widely used parameter for the evaluation of changes in renal function in clinical practice (11). Reduced renal function is defined by a GFR <60 mL/min/1.73 m2, and kidney failure by a GFR <15 mL/min/1.73 m2 [6]. Aim of the current study, to investigate the effect of T2DM on estimated GFR and renal function compared to the control group.

Present study, showed significant increasing in fasting blood glucose levels in diabetics patients compared to healthy volunteers (P= 0.000) and this indicated that there is poor control of DM which lead to diabetes complication such as diabetic nephropathy [15]. Other study conducted in Jordan noted that the FBS and HbA1C estimates were consistently higher in type 1and T2DM diabetic patients [16].

Because of the increased demand, hyperglycemia is the primary cause of nephropathy. Additionally, the formation of harmful substances, advanced glycosylated end product (AGE), and elevated aldose reductase activity contribute to hyperglycemia. Controlling hyperglycemia, controlling blood pressure and glomerular pressure, controlling dyslipidemia, limiting protein consumption, and quitting smoking are the cornerstones of diabetic nephropathy care [17].

This study, showed significant increasing in serum creatinine and blood urea levels in patients with DM compared to the controls (P= 0.000). Study observations found that blood glucose concentration, plasma creatinine and urea concentrations were noticed to be greater in type 2 DM subjects [18]. In previous study findings which found that hyperglycemia is the main reasons for progressive kidney damage [19].

In present study, we found that the mean of eGFR calculated by CG formula was significantly decreased in diabetic patients when compared with non-diabetics subjects (P=0.000). Previous study done in Thailand, noted that the prevalence of impaired GFR in a T2DM population was 39.2% were discovered to be connected to a significantly increased risk of impaired GFR among T2DM patients (20). Distinct sets of risk variables were revealed by eGFR reduction, indicating that various pathways contribute to the development of this aspect of diabetic kidney disease.

In this study, 54.4% of patients (n,37) were classified as stage 1and 27.9% (n,19) as stage 2 and 7.4% (n, 5) as stage 3A and 2.9% (n, 2) as stage 3 B and only 4.4% (n, 3) as stage 5. Classification depends on eGFR using MDRD and Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012.

About 4 to 17% of people with type 2 diabetes develop the condition 20 years after their diagnosis, and 16% do so 30 years later. Some research indicates that nephropathy is becoming less common in people with type 1 diabetes (21).
Rarely do most people with chronic renal disease advance past Stage 2. For significant harm to be avoided, kidney illness must be identified and treated as soon as possible. Every year, diabetic patients should undergo a test to check for microalbuminuria, or trace quantities of protein in their urine. Early diabetic nephropathy, or kidney disease associated with diabetes, can be identified by this test (12).

Early identification and appropriate management of CKD are important measures to slow its progression. Present study revealed a significant decreasing in eGFR according to duration of T2DM, and age of patient (P= 0.002& 0.000) respectively. Previous study noted that the current findings are consistent with elderly diabetic patients with impaired renal function who had been diagnosed with type 2 diabetes for a long time (22). In individuals with type 2 diabetes and intact renal function, a number of modifiable risk variables predict an annual reduction in eGFR.

The patient's gender and eGFR did not correlate, according to our study (P = 0.081). A prior research identified the elements that influence the annual decline in eGFR. In all individuals, the yearly GFR decrease was 2.3±5.4 mL/min/1.73 m2. With no discernible sex difference, that was 2.5 ± 5.4 mL/min/1.73 m2 for male patients and 2.0 ± 5.4 mL/min/1.73 m2 for female subjects [23].

The GFR in healthy people falls between 90 and 120 mL/min/1.73 m2, remains constant until mid-adulthood, and then drops by about 1 mL/min year after the age of 50 [24]. This study noted that eGFR was increased significantly with increasing of BMI(P = 0.004).In contrast, previous study noted that the mean estimated (eGFR) was lower in obese children (122.7 ± 21.6 versus 129.4 ± 23.1, P < 0.001).(18)Weight reduction to a BMI of <25 is beneficial [25].

Additionally, this study found no association between FBG level and eGFR (P = 0.662). While it would seem to have little clinical significance with relation to the risk of low eGFR, an Italian study found that poorer glycemic control also influenced the beginning of albuminuria, with an increased risk of 7% for every 1% increase in HbA1c [26].

6. CONCLUSION

In conclusion, GFR was compromised in T2DM patients who were recruited in this research. This suggested that CKD was a significant worry for T2DM patients. Therefore, the patient's age and the length of T2DM had a major effect on the decline in eGFR. Patients with type 2 diabetes should routinely have their falling eGFR detected in order to prevent CKD. To ensure that the eGFR deficit is due to diabetic kidney disease and not to other causes of nephropathy, microalbuminurea measurement should be incorporated into the diabetes treatment plan. We recommend more extensive nationwide research with a sizable sample size that takes into account additional variables as blood pressure, HBA1C, diet, and kind of therapy. For comparison, we recommend calculating eGFR using multiple formulas.

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