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SHORT COMMUNICATION article

Metformin dosage and renal protection in type 2 diabetes mellitus: Impact on estimated glomerular filtration rate

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Abstract: Metformin is considered the first-line treatment as a monotherapy for patients with type 2 diabetes mellitus. Emerging evidence suggests that metformin may have a renoprotective role; therefore, understanding the impact of metformin dose and therapy duration on renal function may significantly improve renal outcomes in type 2 diabetes patients. This study aims to investigate the renoprotective effects of metformin by analyzing its dose-dependent impacts on the estimated glomerular filtration rate in patients with type 2 diabetes mellitus. A retrospective cross-sectional study design was used from September 2022 to October 2023. Data from 302 type 2 diabetes patients were collected from patient files at the Benghazi Diabetic Center and the Aljabal Al-Alkdar Diabetic Center, including all with type 2 diabetes mellitus patients on varying doses of metformin. The collected data included age, gender, metformin dose, duration of metformin therapy, urea, and creatinine. Exclusion criteria included patients with significant comorbidities such as chronic kidney disease (other than diabetic nephropathy), liver disease, heart failure, or malignancy; those taking nephrotoxic medications; individuals with recent acute illnesses or surgical procedures; pregnant or lactating women; participants with inadequate medical records; and patients who were non-adherent to metformin therapy. Survival analysis was conducted to evaluate the effect of different metformin doses on the estimated glomerular filtration rate. The study analyzed 302 diabetic patients, of whom 46.0% were male and 54.0% were female. The age was 58.3±11.9 years. The HbA1c was 7.7%±1.3%. The duration of diabetes was 11.4±8.1 years. The creatinine was 1.0±0.9 mg/dL, and the urea was 36.7±23.8 mg/dL. Data analysis revealed a statistically significant difference in survival distribution across the dose groups. Different metformin doses significantly impact the estimated glomerular filtration rate, suggesting that dosage plays a crucial role in maintaining renal function.

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Introduction

Metformin belongs to the biguanide class of medications, first used to treat type 2 diabetes mellitus (T2DM) in 1957 with the introduction of phenformin. However, phenformin was taken off the market in 1977 due to the risk of lactic acidosis [1]. The mechanism of action of metformin involves reducing glucose production in the liver, enhancing the body's insulin sensitivity, and decreasing insulin resistance [2-4]. Metformin is a key treatment for T2DM because of its effectiveness in reducing blood glucose levels and its minimal risk of causing hypoglycemia [5]. Additionally, metformin offers the advantages of being low-cost, having a favorable safety profile, and potentially providing cardiovascular benefits [6]. Despite its wide use, metformin's safety profile can be affected by the patient's renal function, as the drug is primarily excreted through the kidneys [7]. The concern about metformin accumulation leading to lactic acidosis in patients with renal impairment has been a topic of ongoing research. The clinical relevance of these observations remains uncertain, Still, the incidence of lactic acidosis among metformin users is estimated to be around 1 per 23,000 to 30,000 person-years compared to one per 18,000 to 21,000 person-years among patients with T2DM using other agents [8]. Metformin was approved by the Food and Drug Administration (FDA) in 1994, and it became the first-line treatment for T2DM in 2005, following the publication of the International Diabetes Federation guidelines [1]. Upon its approval, the FDA set strict prescribing guidelines for metformin based on kidney function [7]. According to these guidelines, metformin is contraindicated in patients with renal disease or dysfunction, defined by elevated serum creatinine levels (≥1.5 mg/dL [males] and ≥1.4 mg/dL [females]) or abnormal creatinine clearance (CrCl). Additionally, metformin should not be initiated in patients aged 80 years or older unless renal function is verified as normal [8]. The American Diabetes Association (ADA) and Kidney Disease Improving Global Outcomes (KDIGO) have established consensus statements for metformin use in patients with T2DM and chronic kidney disease (CKD). These statements recommend metformin for most patients with T2DM and CKD who have an estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2. They recommend careful patient selection and downward dose adjustment based on eGFR. They also suggest reducing the metformin dose to 1,000 mg daily for patients with an eGFR between 30 and 44 mL/min/1.73 m^2. They also recommend careful monitoring to mitigate the risk, particularly in patients with eGFR levels <60 mL/min/1.73 m^2. They advise about frequent monitoring of eGFR, with the frequency increasing when eGFR falls <60 mL/min/1.73 m^2. The ADA/KDIGO guidelines recommend sick day protocols, which involve holding metformin doses during acute illness to reduce the risk of lactic acidosis associated with acute kidney injury (AKI) and impaired metformin clearance [9]. Recent studies have shown that metformin poses renal protective properties which are influenced by dose and duration. Research indicates that metformin, when administered for 12 weeks at varying doses, significantly improves renal function by reducing inflammation and fibrosis in diabetic mice [10, 11]. Moreover, combining metformin with berberine enhances renal protection in diabetic nephropathy through anti-inflammatory pathways [11]. Also, clinical trials suggest higher doses of metformin are necessary for significant benefits in lipid regulation and glycemic control, contributing to overall renal protection [12]. This study aims to investigate the renoprotective effects of metformin by analyzing its dose-dependent impacts on eGFR in Libyan patients with T2DM.

Materials and methods

This study follows a retrospective cross-sectional study design that was used from September 2022 to October 2023. Data from 302 type 2 diabetes patients were collected from patient files at the Aljabal Al-Alkdar Diabetic Center and Benghazi Diabetic Center. All included patients with T2DM on varying doses of metformin. All the patients had T2DM and are receiving different doses of metformin (500, 850, and 100 mg). The data included

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age, gender, urea, creatinine, metformin dose, and duration of treatment. All medications taken by the patients were documented, and drugs that may affect renal function were excluded. The drugs generally included insulin, and other antidiabetic drugs besides metformin, statins, and antihypertensive drugs. All drug names and dosages were recorded to ensure a comprehensive analysis of the patient's medication regimens. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Exclusion criteria included patients with significant comorbidities such as CKD (other than diabetic nephropathy), liver disease, heart failure, or malignancy; those taking nephrotoxic medications; individuals with recent acute illnesses or surgical procedures; pregnant or lactating women; participants with inadequate medical records; and patients who were non-adherent to metformin therapy. According to the American Diabetes Association, eGFR <60 mL/min/1.73 m² is considered to decrease kidney function. Basic serum biochemical parameters, including urea, creatinine, and lipid profile (cholesterol, triglycerides, HDL, LDL), were assayed using the COBAS INTEGRA 400 plus analytical system, autoanalyzer. Based on the eGFR levels (mL/min/1.73 m²), the participants were divided into four groups: <30, 30-60, 61-90, and >90. These categories help us understand how efficiently the kidneys filter blood.

Statistical analysis: Patient characteristics are presented as mean±S.D. for continuous variables and percentage for categorical variables. The collected data were entered and analyzed using JASP version 0.18.3. Survival analysis was conducted to evaluate the effect of different metformin doses on eGFR. The log-rank test ($p<0.001$) confirmed significant differences in eGFR among the three dose groups, with the confidence intervals providing reliability to the statistical significance.

Results

Distribution of patients according to gender and age: As shown in **Figure 1**, among the 302 participants 46.0% were males and 54.0% were females with almost equal ratios. The average age of the 302 subjects as shown in **Table 1** was 58.3±11.9 years and the most prevalent age was more than 60 years old.

Figure 1: Gender distribution of the patients

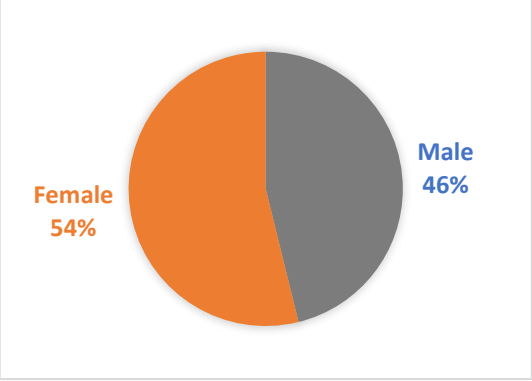

Table 1: Patients' distribution according to the age

N=312	Percentile %				
Variables	Mean &STD	Mode	25th	50th	75th
Age (Year)	58.3±11.9	60	51	59	66.25

Distribution of patients according to HbA1c and diabetes duration: **Table 2** shows that the mean HbA1c of the sample was 7.7%±1.3% and the mean diabetes duration was 11.4±8.1 years.

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Table 2: Mean $HbA1_C$ and diabetes duration

N=312	Percentile %				
Variables	**Mean &STD**	**Mode**	**25th**	**50th**	**75th**
HbA1C (%)	7.7±1.3	7.1	6.9	7.5	8.6
Diabetic duration	11.4±8.1	12	5	10	15

Distribution of patients according to urea and creatinine: The mean creatinine level was 1.0±0.9 mg/dL, with a mode of 0.6. Creatinine levels ranged from 0.6 mg/dl to 1.07 mg/dl. The mean urea level was 36.7±23.8 mg/dL. The most common result was 46.0 mg/dL (mode). The 75th percentile was 42 mg/dL (**Table 3**).

Table 3: Distribution of urea and creatinine

N=312	Percentile %				
Variables	**Mean &STD**	**Mode**	**25th**	**50th**	**75th**
Creatinine (mg/dl)	1.0±0.9	0.6	0.6	0.8	1.07
Urea (mg/dl)	36.7±23.8	46	25	32	42

Distribution of patients according to dose and frequency of metformin: In **Table 4**, the doses of metformin used by the participants were 500, 850, and 1,000 mg and the frequency of patients was once, twice, and three times per day. **Table 4** summarizes the metformin dose and duration among our sample.

Table 4: Dose and frequency of metformin (dose/day)

Metformin Dose/Form	**Once**	**Twice**	**Three times**	**Total**
500 mg	40 (22.7%)	136 (77.3%)	0.0	176
850 mg	06 (5.4%)	104 (92.9%)	02 (1.7%)	112
1-Gram	05 (21.7%)	18 (78.3%)	0.0	0.0
Total	51	258	02	288

Distribution of patients according to GFR: As in **Table 5**, the mean of the GFR was 89.5±85.5. The most frequent value was 99. Regarding the distribution of participants according to their GFR, the biggest group, which is 49.0% of the patients, had a GFR-R greater than 90, indicating normal or near-normal kidney function.

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Table 5: Distribution of the GFR

N=312	Percentile %				
Variables	**Mean &STD**	**Mode**	**25th**	**50th**	**75th**
Glomerular Filtration Rate (GFR) (mL/min)	89.5±85.5	99	65	89	104

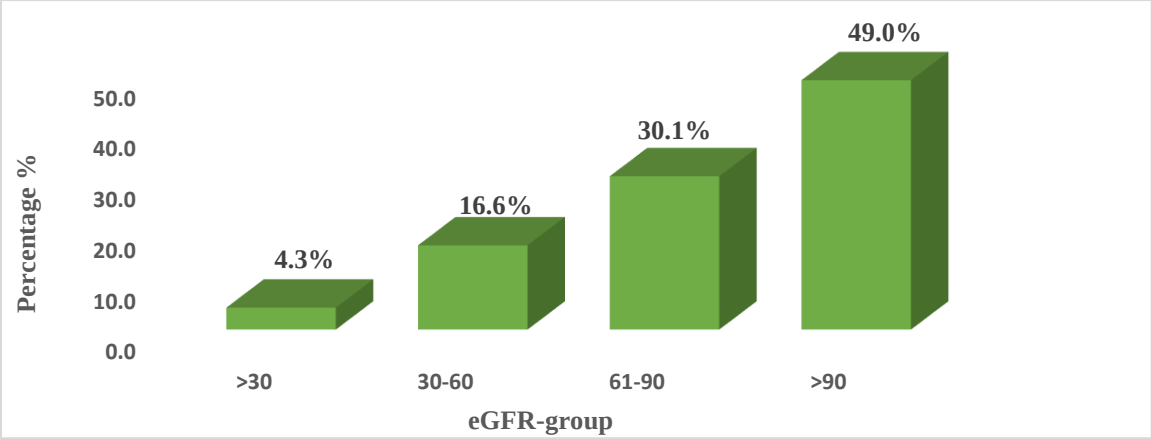

Figure 2: Distribution of the samples according to the estimated glomerular filtration rate (eGFR)

Distribution of EGFR according to gender: Regarding the EGFR distribution according to gender, **Table 6** shows a slight variation in eGFR in gender.

Table 6: EGFR levels according to patient gender

	Gender		**Total**	
EGFR mL/min/1.73 m^2	Male	Female	%	N.
<30	05 (3.6%)	08 (4.9%)	04.3	13
30-60	13 (9.4%)	37 (22.7%)	16.56	50
61-90	46 (33.1%)	45 (27.6%)	30.13	91
>90	75 (53.9%)	73 (44.8%)	49.01	148
Total	139	163	**100%**	302

Survival analysis and risk assessment of metformin dosage on eGFR

Survival table analysis: The survival analysis of different metformin doses on eGFR revealed significant variations across the groups. For patients receiving the 500 mg dose, which was the largest group with 167 patients, 46 experienced a decrease in GFR. The average survival time in this group was 18.1 years (standard error: 1.372). In the 850 mg dose group, which was the second largest with 109 patients, only seven experienced reduced GFR. This group had the highest mean survival time of 27.4 years (standard error: 1.006), suggesting better survival outcomes and indicating a potential protective effect of this dosage on renal function. The smallest group, consisting of 23 patients receiving the 1000 mg dose, had the highest number of events with 10 patients experiencing decreased GFR. The mean survival time in this group was 6.0 years (standard error: 0.873).

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Table 7: Survival table analysis of different metformin doses on eGFR

Strata **(Metformin)**	N	Events	Restricted Mean	Standard Error	Median Survival	Log-rank (Mantel-Haenszel)
Dose=500 mg	167	46	18.127	1.372	20	<0.001
Dose=850 mg	109	07	27.395	1.006		
Dose=1.000 g	23	10	6.006	0.873	05	

Event (decreased in GFR), N=number of patients used metformin

Risk table analysis: The risk table illustrated the number of patients at risk of decreased GFR over the years with the use of different metformin doses (500 mg, 850 mg, and 1000 mg) along with the 95% confidence intervals (CI). Metformin dose 500 mg: The initial number of patients at risk was 109, which gradually decreased over time. The confidence interval for the proportion of patients remaining in the study decreases slightly over time, indicating a relatively stable retention rate. Metformin dose 850 mg: The risk of decreased GFR starts with 167 patients, which reduces more rapidly compared to the 500 mg group. The confidence interval narrows significantly over time, suggesting a greater dropout or event rate. At zero time, the CI was [0.982, 1.0], while at 20 years, the CI was [0.251, 0.625]. Metformin dose 1000 mg: This group started with 23 patients and showed the steepest decline among the patients. The CI indicates a rapid decrease in the number of patients remaining at risk. At zero time, the CI was [1.0, 1.0], but at time 7, the CI was [0.145, 0.778].

Table 8: Risk table analysis of different Metformin doses on eGFR

Metformin Dose	**500**			**850**			**1G**		
Time/year	**At Risk**	**95% CI**		**At Risk**	**95% CI**		**At Risk**	**95% CI**	
		Lower	**Upper**		**Lower**	**Upper**		**Lower**	**Upper**
00	109	01	01.0	167	0.982	01.0	23	01.0	01.0
03	90	0.939	01.0	139	0.918	0.987	09	0.523	0.981
07	53	0.871	0.987	79	0.66	0.825	04	0.145	0.778
10	40	0.871	0.987	55	0.539	0.733	01		
13	17	0.8	0.986	20	0.459	0.676			
17	10	0.8	0.986	11	0.423	0.658			
20	07	0.8	0.986	08	0.251	0.625			
23	02	0.8	0.986						
27	01	0.8	0.986						
30	01	0.8	0.986						

Survival curve analysis: The survival curves compared the survival probabilities among the different metformin dose groups over up to 30 years. 850 mg dose: Patients using the 850 mg dose showed the highest survival probability, indicating a better GFR rate over time. This suggests that the 850 mg dose had a protective effect with fewer adverse events. The number of subjects at risk decreases steadily but remains the highest among the three groups. 500 mg dose: This dose group showed a moderate decrease in GFR probability, lower than the 850 mg dose but higher than the 1000 mg dose, suggesting that this dose may be less effective or associated with poorer outcomes.

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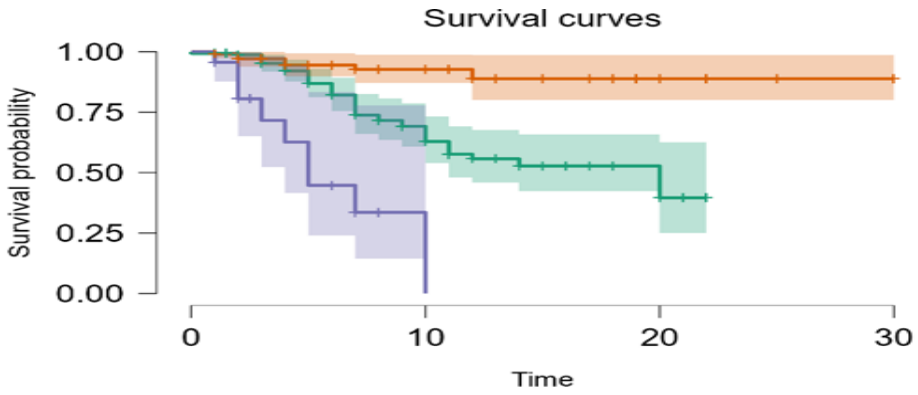

Figure 3: Kaplan–Meier curves for survival (normal GFR) over time in years

Discussion

As renal function naturally declines over time due to the aging process, the impact on metformin clearance becomes increasingly significant. Given the kidneys' vital role in eliminating metformin from the body, any changes in renal function can influence its presence in the bloodstream, potentially leading to accumulation and heightened risks with prolonged use. Nevertheless, our study suggests a potential correlation between metformin duration and declines in renal function. We observed that longer periods of metformin usage were linked to a slower rate of decline in renal function. These findings align with a retrospective cohort study by in Chicago [13], revealing a decelerated decline in the estimated glomerular filtration rate among individuals in the metformin group compared to non-users. Similarly, a retrospective cohort study involving veterans with impaired kidney function demonstrated that metformin treatment during the initial 360 days of reduced kidney function was associated with a decreased incidence of kidney-related events or death compared to sulfonylurea treatment [14]. Continuation of metformin beyond 361 days further reduced the risk of kidney events or death. Furthermore, the present findings are consistent with a study conducted by Boddepalli and others [15], analyzing data from 2001 to 2022 across eight cohort studies. This study highlighted metformin's superiority over sulfonylurea monotherapy in various outcomes, including reduced all-cause mortality, improved glomerular filtration rate, decreased end-stage renal disease incidence, and fewer cardiovascular events.

Conclusion: Different metformin doses significantly impact the estimated glomerular filtration rate, indicating that appropriate dosage is crucial for maintaining renal function in patients with type 2 diabetes. The findings suggest that careful dose management of metformin can enhance renal protection and prevent declines in eGFR.

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Authors' contributions: HMA conceived and designed of the study. HA, SA SG & MAN collected data and GH analyzed data. HAE performed data analysis and interpretation. HMA &AMA drafted and revised the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for its contents.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission were completely observed by the authors.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.