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ASSESSMENT OF THE EFFECTIVENESS AND SAFETY OF METFORMIN ON EGFR IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Metformin hydrochloride is an hypoglycaemic drug that controls the level of blood glucose. It has been recognized as the first line of treatment for type 2 diabetic patients. Increasing burden on using metformin in patients with chronic kidney disease (CKD). Patients with CKD are at high risk of cardiovascular disease and mortality and they may benefit from using metformin as it improves cardiovascular outcomes and reduce mortality. However, current guideline restrict the use of metformin due to the risk of lactic acidosis. **Objectives:** The aim of our study was to examine the effectiveness and safety of metformin on kidney function in patients with CKD and type 2 diabetes mellitus and to evaluate the strength of evidence that prefers using metformin in patients with CKD over other glucose lowering agents. **Materials and Methods:** 133 type 2 diabetes mellitus patients with or without CKD were included for both sex (56 males and 77 females). **Results:** The results showed that 76.69% were diabetic for less than 5 years, 6.1% were diabetic for 5-10 years, and 17.29% were diabetic for more than 10 years. 41.35% of patients had (<6.5) HbA1C, whereas 58.64% had (>6.5) HbA1C. 36% of patients were treated with metformin and 24% treated with insulin, and 39.9% treated with other hypoglycemic agents. Metformin used twice a day by (33.33%) of patients and once per day by (66.66%) of patients. 68.42% of the patients have EGFR >90 mL/min/1.73m^2, 22.55% have EGFR 60-90mL/min/1.73m^2, and 9.02% have EGFR 45.59 mL/min/1.73m^2. Patients of more than 60 years old showed a lower EGFR level 92.1 mL/min/1.73m^2 than those of less than 60 years old 117 mL/min/1.73m^2. Duration of diabetes in patients of more than 10 years showed the lowest estimation of EGFR 89.1 mL/min/1.73m^2 compared to the duration of DM 5-10 (108.7 mL/min/1.73m^2) and less than 5 years (119.4 mL/min/1.73m^2) respectively. HbA1C was controlled in 41.35% of patients with EGFR level 119.2 mL/min/1.73m^2, while the uncontrolled HbA1C was in 58.64% of patients with EGFR 96.1 mL/min/1.73m^2. EGFR level in metformin treated patients was 91.7 compared patients treated with insulin, and other hypoglycemic agents 114.2mL/min/1.73m^2, 103.4mL/min/1.73m^2 respectively. Patients on metformin twice daily exhibit a lower EGFR level 93.3 mL/min/1.73m^2 compared to those using metformin once per day. **Conclusion:** The results of our study clearly indicates that EGFR level significantly influenced by dose frequency, diabetic duration and age despite being not fall much below normal level. It can be concluded that EGFR level was lower in metformin treated patients compared to patients on insulin or other hypoglycemic agents.

KEYWORDS: The effectiveness and safety of metformin, kidney function, CKD, type 2 diabetes mellitus.

INTRODUCTION

Metformin hydrochloride is an hypoglycaemic drug that controls the level of blood glucose by reducing hepatic glucose production and improving insulin sensitivity of the peripheral tissues by raising peripheral glucose uptake and utilization which results in reduction of FBS and HbA1C levels.[1] It has been recommended as a treatment of choice for type 2 DM patients due to its well established safety profile and its favorable adverse effect as well as its low cost.[2,3] However, emerging evidence confirms that metformin targets many path ways resulting to chronic kidney disease (CKD). The frequent use of metformin may also affect the rate of kidney function and progress to chronic kidney disease.[4] It is found that diabetes, hypertension, age, obesity and cardiovascular disease are the leading cause of CKD.[5] Chronic kidney disease been defined as the occurrence of structural and/or functional kidney damage with

glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 for approximately three months.[6] It is one of the leading causes of DM and considered a major panic to public health because of the increasing number of individuals affected which reach to approximately 850 million worldwide.[7] The rising incidence of diabetic kidney disease is predispose to the burden of CKD worldwide. It has elevated by 39.5% between 2005 and 2015 worldwide.[8] CKD is not only found to contribute to cardiovascular diseases but may also leads to health loss and premature death.[7] More importantly, the most disastrous consequence of CKD is its progression to kidney failure for the majority of affected patients. Metformin is a leading cause to lactic acidosis due to its accumulation and elevated concentration as a result of renal impairment and non metabolism propriety of metformin.[1]

Lactic acidosis is when plasma lactate level become higher than 5mmol/L and pH lower than 7.35 and may associated with dysfunction in multisystem organ in severe conditions.[5] However, Several studies argued that small percentages of patients hospitalized with lactic acidosis associated with metformin exposure.[9] Beneficial effects of metformin on diabetic treated patients such as reduced risk of CVD and all case mortality have been stated in numerous studies. Roussel,. et al examined the effect of metformin in 19691 patients with diabetes and advanced CVD and demonstrated that the risk of mortality reduced significantly in metformin treated patients.[10]

Metformin contraindications to patients with CKD was previously labeled at serum creatinine level greater than 1.5mg and 1.4mg/dl in men and women respectively.[11] Recently the US (FDA) changed the metformin contraindications to be labeled at eGFR level instead of serum creatinine. FDA do not recommend the use of metformin at eGFR less than 45 mL/min/1.73m^2 and its contraindicated its use at eGFR less than 30mL/min/1.73m^2[12]. On the other hand, other guidelines permitted the use of metformin with caution at eGFR 30-60 mL/min/1.73m^2[13]. eGFR is the most significant functional parameter of the kidney, it is equal to total amount of fluid filtrated through the glomeruli per unit per time.[14]

The current international guidelines stated that decreased eGFR of less than 60 mL/min/1.73m^2 is defined as CKD, whereas eGFR of less than 15 mL/min/1.73m^2 is nominated as the final stage of renal failure which occurred when the kidney function become inefficient to face body requirements.[5,15] The aim of our study was to examine the effect of metformin on kidney function in patients with CKD and type 2 diabetes mellitus and to evaluate the strength of evidence that prefers using metformin in patients with CKD over other glucose lowering agents.

MATERIAL AND METHODS

This cross sectional observational study includes 133 of adult participants of both male and female diagnosed with diabetes mellitus and with or without CKD to assess the ratio of eGFR in those participants based on the type of medication they receive. Patients visited Alweqaia and Alreiada privet laboratories in the city of Sabratha and Surman between April and July 2024 were included in this study. We divided those patients into three groups: metformin treated patients, insulin treated patients and patients on other hypoglycemic agents. We included diabetic patients without established CKD because diabetes is a major cause of kidney failure especially those treated with metformin. patients age, sex were included as well as their detailed medical history. FBS, HbA1C, blood creatinine, eGFR and EPI-CKD was used for electronical calculation of eGFR. The patients were informed about the study and agreed to participate.

Statistical analysis

All data are expressed as means and standard deviations. The results were analyzed using SPSS software package version 20 to apply one-way ANOVA test to find out the statistical significance between variables. All results were considered to be significant at p value < 0.01.

RESULTS

In the present study 133 type 2 diabetes mellitus patients with or without CKD were included for both gender (56 males and 77 females) (Figure.1). Their age ranged from 20-75 years old. Approximately 76.69% were diabetic for less than 5 years, 6.1% were diabetic for 5-10 years and 17.29%) were diabetic for more than 10 years. The use of metformin was studied in terms of combination with other glucose lowering treatments such as insulin, age, dose frequency and duration of diabetes. HbA1C was controlled (<6.5) in 41.35%) of patients whereas 58.64% had uncontrolled HbA1C (6.5%**).** In the present study 36% of our participants were treated with metformin and 24% treated with insulin and 39.9% treated with other hypoglycemic agents. Metformin 850 mg used twice a day by (33.33%) of patients and once per day by (66.66%) of patients. We investigated the EGFR of our patients who were classified into three groups based on the severity of CKD. 68.42% of the patients have eGFR >90 mL/min/1.73m^2, 22.55% have eGFR 60-90mL/min/1.73m^2 and 9.02% have eGFR 45.59 mL/min/1.73m^2 (Table.1).

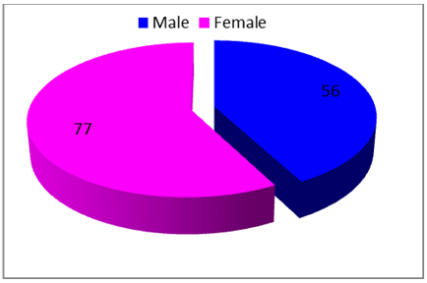

Figure 1: Distribution of patients according to gender.

Table 1: General distribution of frequencies of diabetic patients.

Characteristics	Subgroups	Frequencies	%
Age (years)	< 60	86	64.66%
	60>	47	35.33%
Duration	<5 years	102	76.69%
	5-10 years	8	6.01%
	> 10 years	23	17.29%
HbA1c %	Controlled diabetic patientsHbA1c < 6.5%	55	41.35%
	Non controlled diabetic patients bA1c > 6.5%	78	58.64%
Treatment use	Insulin	33	24.81%
	Metformin	48	36.09%
	Other drugs	52	39.09%
Dose of metformin/ day	Once	32	66.66%
	Twice	16	33.33
EGFR ml/ min/ 1.73m^2	Normal kidney function > 90 ml	91	68.42%
	Mild loss of kidney function 60-90 ml	30	22.55%
	Moderate loss of kidney function 45-59 ml	12	9.02%

In the present study patients of more than 60 years old showed a lower eGFR level 92.1 mL/min/1.73m^2 than those of less than 60 years old 117 mL/min/1.73m^2 (table2 and figure2). This difference was statistically significant at p value 0.01. Duration of diabetes in patients of more than 10 years showed the lowest estimation of eGFR 89.1 mL/min/1.73m^2 compared to the duration of DM 5-10 (108.7 mL/min/1.73m^2) and less than 5 years (119.4 mL/min/1.73m^2) respectively (table3 and figure3). This difference was statistically significant at p value 0.01. HbA1C was controlled in 41.35% of patients with eGFR level 119.2 mL/min/1.73m^2, while the uncontrolled HbA1C was in 58.64% of patients with eGFR 96.1 mL/min/1.73m^2. This difference was statistically significant at p value 0.01 (Table1 and figure4).

In the present study eGFR level in metformin treated patients was (91.7) compared to patients treated with insulin and other hypoglycemic agents 114.2mL/min/1.73m^2, 103.4mL/min/1.73m^2 respectively. This difference was statistically significant at p value 0.01 (table5 and figure5). Patients on metformin twice daily exhibit a lower eGFR level 93.3 mL/min/1.73m^2 compared to those using metformin once per day. This difference was statistically significant at p value 0.01 (table 6 and figure 6).

Table 2: The means and standard deviations of EGFR levels according to ages.

Parameter	Ages in years		*P-value*
	<60	> 60	
eGFRml/min/1.73ml	117.2±3.73ml	92.1±3.11ml	< 0.01

All data are expressed as means and standard deviations. The results were analyzed using SPSS software package version 20 to apply one-way ANOVA test to find out the statistical significance between variables. All results were considered to be significant at p value < 0.01.

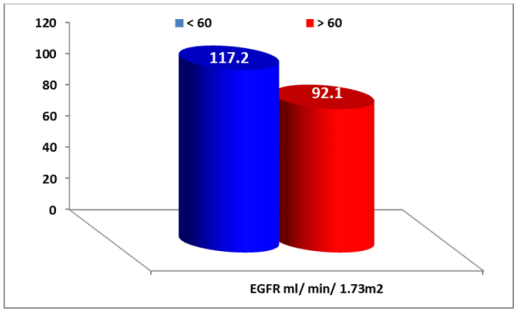

Figure 2: shows eGFR levels according to ages.

Table 3: The means and standard deviations of EGFR levels in relation with the duration of diabetes mellitus.

Parameter	Duration groups of diabetes mellitus			P- value
	<5 years N = 53	5-10 years N = 8	> 10 years N = 23	
Duration of diabetes mellitus	2.66±1.07	7.59±1.47	16.48±2.25	
eGFR ml/ min/ 1.73m^2	119.4±4.22 ml	108.7±3.87ml	89.1±4.11ml	< 0.01

All data are expressed as means and standard deviations. The results were analyzed using SPSS software package version 20 to apply one-way ANOVA test to find out the statistical significance between variables. All results were considered to be significant at p value < 0.01.

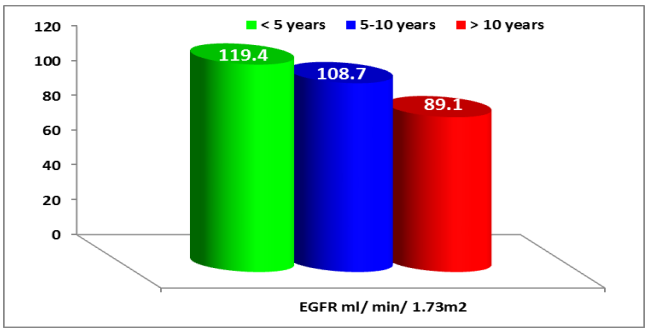

Figure 3: reveals EGFR levels in relation with the duration of diabetes mellitus.

Table 4: The mean and standard deviations of EGFR levels according to glycemic control.

Parameter	Controlled diabetic patients HbA1c < 6.5%	Non-controlled diabetic patients HbA1c > 6.5%	*P- value*
HbA1c %	6.1±2.13	10.9±2.91	
eGFR ml/ min/ 1.73m^2	119.2±2.73ml	96.1±2.41ml	<0.01

All data are expressed as means and standard deviations. The results were analyzed using SPSS software package version 20 to apply one-way ANOVA test to find out the statistical significance between variables. All results were considered to be significant at p value *<0.01*.

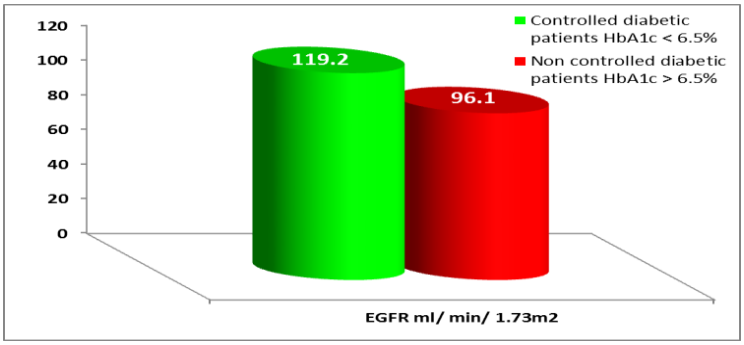

Figure 4: illustrates eGFR levels according to glycemic control.

Table 5: The means and standard deviations of EGFR levels in relation with the treatments.

Parameter	Treatments			*P- value*
	Insulin	Metformin	Other drugs	
EGFR ml/ min/ 1.73m^2	114.2 ± 2.78 ml	91.7 ± 3.12 ml	103.4±2.91ml	< 0.01

All data are expressed as means and standard deviations. The results were analyzed using SPSS software package version 20 to apply one-way ANOVA test to find out the statistical significance between variables. All results were considered to be significant at p value < 0.01.

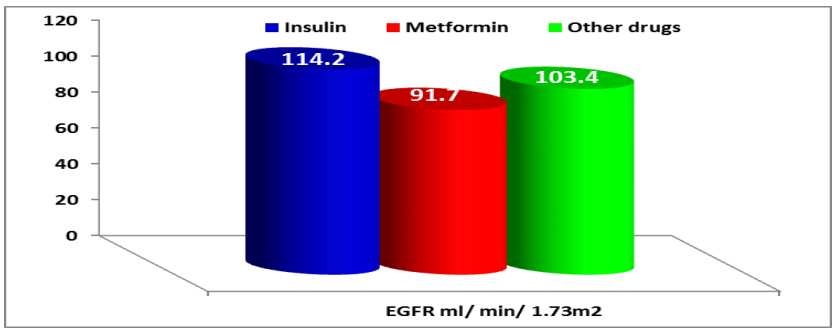

Figure 5: illustrates EGFR levels in relation with the treatments.

Table 6: The mean and standard deviations of EGFR levels according to doses of metformin per day.

Parameter	Doses of metformin per day		P-value
	Once	Twice	
1.73m^2/ min/EGFR ml	111.4±2.23ml	93.3±2.11ml	< 0.01

All data are expressed as means and standard deviations. The results were analyzed using SPSS software package version 20 to apply one-way ANOVA test to find out the statistical significance between variables. All results were considered to be significant at p value < 0.01.

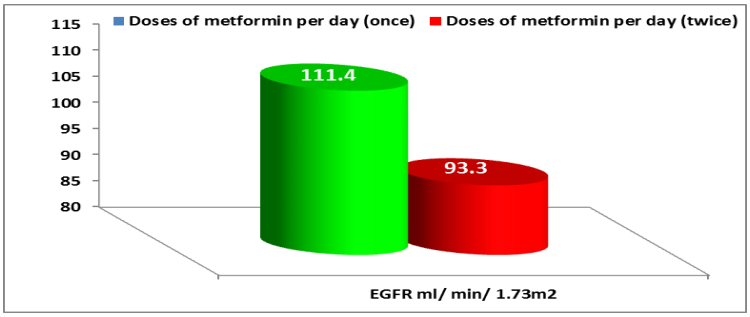

Figure 6: shows eGFR levels according to doses of metformin per day.

DISCUSSION

In order to examine the effectiveness of metformin on kidney function in patients with type 2 diabetes mellitus and CKD, we conducted this study on patients with DM and different levels of renal function treated with metformin or other drugs. In this study metformin treated type 2 DM patients showed a lower eGFR level compared to patients treated with insulin or other glucose lowering agents. 48 out of 133 were metformin treated, those patients had lower eGFR level 91.7 mL/min/1.73m^2 whereas patients treated with insulin or other hypoglycemic agents had higher eGFR levels 114.2 mL/min/1.73m^2 and 103.4 mL/min/1.73m^2 respectively. Several observational studies were in agreement with our study and reported a reduced risk of metformin compared to other hypoglycemic drugs including insulin. Ekstrom,. et al claimed that metformin exhibit a reduced risk of CVD, acidosis, total mortality compared with insulin in monotherapy.[16] Also patients with impaired renal function showed no increased risk of severe outcomes.

Therefore, metformin could have a beneficial effect on patients with normal or mild to moderate renal function. Hung, et al. reported that metformin use was associated with reduced risk of cardiovascular death and cardiovascular complications in patients with CKD stages 2-4.[17] Patients with diabetes and CKD are at a high risk of CVD and using metformin may reduce this concern and decreases mortality in contrast to other glucose lowering agents including insulin that may associate with weight gain and hypoglycemic episodes.[18] Furthermore, insulin found to be a leading cause of an increasing risk of CVD and mortality as a consequence of the higher severity of the disease. These findings were reported by several studies in which insulin found to increase the risk of CVD and mortality.[19-21] However, Hung et al. claimed that there was a correlation between metformin and mortality in patients with advanced CKD.[17] This rises the concern that patients receiving metformin with a decrease in renal function and moderate CKD may elevate the risk of metformin toxicity.[1] Cases with severe loss of kidney function were not reported in our study and only low percentages of mild and moderate CKD were found, both groups were eligible to continuing metformin medication as clarified in recent guidelines.

In our study metformin treated patients were also affected with the frequency of the doses per day. Patients treated with metformin twice a day showed a lower eGFR level 93.3 mL/min/1.73m^2 compared to those treated once per day 111.4 mL/min/1.73m^2. These findings were in agreement with a study conducted in Benghazi/Libya and claimed that patients on frequent doses of metformin showed lower eGFR level and are at a higher risk of lactic acidosis.[1] A crucial inverse correlation between eGFR and the concentration of metformin 12 h after the last dose after one week of using treatment.[15] Therefore, patients in our study were eligible to use metformin and no contraindications on being required as their eGFR level was > mL/min/1.73m^2 in all metformin treated patients and they were not at risk of lactic acidosis even with frequent doses of metformin.

Several studies highlighted that the incidence of lactic acidosis in metformin treated patients is rarely occurred and this medication may not responsible when treated patients develop lactic acidosis.[22] It is reported that large proportion of patients with CKD and treated with metformin but rarely to develop lactic acidosis.[23] Additionally, *Fung L,. et al* suggested that lactate level does not increase substantially in metformin users with reduced eGFR level.[24] Therefore, the risk of lactic acidosis on metformin treated patients may be overstated. On the other hand, metformin treated patients with advanced kidney dysfunction are at higher risk of lactic acidosis or increased lactate level compared with

users of other glucose lowing agents despite the risk of incidence is absolutely low.[22] It is therefore one would accept the minor risk of lactic acidosis with continuing metformin than mortality and morbidity that may develop from using an alternative therapy.[18]

In the present study patients above 60 years old with uncontrolled HbA1C 96 mL/min/1.73m^2 exhibit lower eGFR level compared to those below 60 years old with controlled HbA1C, both values. Normal eGFR level usually decreases with age even in people with normal kidney function.[1] Inverse correlation between metformin and patients age has also been reported in this study. We found that patients who were above 60 years old had a lower eGFR level than those below 60 years old. These findings supported by another study in which EGFR after the age of forty decreases by approximately 10 mL/min/1.73m^2 every 10 years. Thus, it is advised to monitor the renal function in metformin treated diabetic patients as 90% of renal function might be lost before the appearance of clinical symptoms of renal failure.[1]

In our findings eGFR level was not only influenced by HbA1C, dose frequency and patients age but also the diabetic duration found to significantly alter the eGFR level. Patients of more than 10 years exhibited a lower eGFR level 89.1 mL/min/1.73m^2 whereas diabetic patients of less than 5 years and those from 5-10 years were 119.4 mL/min/1.73m^2 and 108.1 mL/min/1.73m^2 respectively. Therefore, we indicate that diabetic duration crucially affects EGFR level despite the fact that most of studies we reviewed focused only on metformin use or not and no adjustments were made on other important covariates including HbA1C and diabetic duration.[16] Present guidelines recommend to reduce the metformin dose when eGFR is less than 45 mL/min/1.73m^2 and metformin ought to be stopped when eGFR is below 30 mL/min/1.73m^2[12]. However, a recent report highlighted an improvement in mortality and cardiovascular outcomes even in a population with eGFRs below 20 mL/min/1.73m^2[25]. Also, possibly in assessing the risks and benefits of using metformin with a lowered eGFR in a population, the risk of lactic acidosis may not to carry so much panic as it is thought in current guidelines.[26]

CONCLUSION

Our study clearly indicates that eGFR level significantly influenced by dose frequency, diabetic duration and age despite being not fall much below normal level. Patients currently unlikely to be at risk of developing CKD and therefore are eligible to use metformin. The beneficial effects of metformin to reduce mortality, improve CVD outcomes and its low risk of lactic acidosis rises the calls to reconsider current recommendations of reducing metformin doses in severe CKD cases as patients may deprived from such benefits of this glucose lowering treatment. Further larger and longer studies are required to provide a solid basis for the use of metformin in those patients.

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