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Evaluation of metformin use in non-critically hospitalized patients at a single tertiary hospital in Saudi Arabia: A cross-sectional study

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Abstract: The aim of this study was to assess the safety of metformin use in non-critically hospitalized patients. A cross-sectional study was performed at a single tertiary hospital in Saudi Arabia between January 2019 and June 2019. Patients aged >18 years with a confirmed diagnosis of type 2 diabetes who were taking metformin prior to admission were included. The primary outcome was the appropriateness of metformin use in non-critically hospitalized patients. A total of 251 patients were included in this study. Metformin was appropriate in 96 patients (38.2%). There were 14 (5.6%) incidences of absolute contra-indications and 141 (56.1%) incidences of precautions. Non-Saudi patients were about 1.856 times more likely to receive an inappropriate metformin dosage regimen compared to Saudi patients (AOR= 1.856; P= 0.022, 95% CI= 1.093, 3.151). Additionally, patients with chronic kidney disease (stage 3A) were approximately 2 times less likely to receive an inappropriate metformin dosage regimen than patients on stage 5 (AOR= 0.482; P= 0.035, 95% CI= 0.243, 0.835). This study highlighted a high rate of inappropriate metformin use in non-critically hospitalized patients. However, patients who were non-Saudi and at an advanced stage of chronic kidney disease were more likely to receive an inappropriate metformin dosage regimen.

Keywords: Metformin; Saudi Arabia; diabetes; hospitalization; evaluation

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INTRODUCTION

In hospitalized patients, the risk of hyperglycemia or hypoglycemia can be associated with serious complications, including death (Seisa *et al*., 2022; Wang *et al*., 2023). Therefore, appropriate management of hyperglycemia in hospitalized patients may have significant benefits for such populations. In addition, misunderstanding the correct management of hyperglycemia in hospitalized patients could be another factor contributing to the high number of complications (Mohajan and Mohajan, 2023). In most circumstances, insulin is the preferred treatment for hyperglycemia in hospitalized patients, which is in agreement with several guidelines, including the American Diabetes Association (ADA) and the clinical practice guidelines of the Endocrine Society (ADA, 2022; Korytkowski *et al*., 2022). The preference for insulin therapy in hospitalized patients is driven by its efficacy, rapid correction of hyperglycemia and ease of dose adjustment (Pasquel *et al*., 2021; Rosinha *et al*., 2022). However, oral glucose-lowering medications have not been widely tested in hospital settings to control hyperglycemia.

Although oral glucose-lowering medications can be used in some circumstances where hospitalized patients are able to eat, they have no change in medical condition or nutritional status, a stable outpatient regimen and stable kidney function (Pasquel *et al*., 2021, 2019). In addition, oral glucose-lowering medications may be continued safely in the absence of contraindications or precautions during hospital admission. The current guidelines have not favoured any oral glucose-lowering medications to be considered in hospital settings to manage hyperglycemia since most studies lack strong evidence to support such practice (ADA, 2022; Korytkowski *et al*., 2022). It should be noted that the decision to start oral glucose-lowering medications in hospitalized patients should consider drug availability and cost (Pasquel *et al*., 2019; van Vugt *et al*., 2020).

Metformin is one of the most prescribed medications for managing patients with type 2 diabetes. Furthermore, metformin is considered the first-line treatment after lifestyle modification to manage patients with type 2 diabetes and it should be continued in those populations if they do not have any contraindications (Korytkowski *et al*., 2022). Therefore, the widespread use of metformin in type 2 diabetes increases its availability in most hospitals. As an outpatient first-line therapy, metformin is safe and effective and might decrease cardiovascular outcomes and mortality (Gonzalez-Lopez and Wojeck, 2023; Mohammed *et al*., 2023; Ong *et al*., 2021). The most commonly reported side effects of metformin in outpatient settings include mild gastrointestinal intolerance, which can be decreased by dose titration. Metformin is cleared by the kidney and might be associated with rare cases of lactic acidosis if renal function is severely impaired or overdose (Squibb, 2018; FDA, 2016).

On the contrary, metformin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of < 30 ml/min/1.73 m^2, hypersensitivity to metformin and acute or

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chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Precautions for metformin use included age > 65 years, heart failure with hypoperfusion, acute kidney injury, hepatic impairment, contrast media with acute kidney injury and lactic acidosis (Squibb, 2018; FDA, 2016).

Evidence supporting the use of metformin in hospitalized patients is lacking and few studies have explored its safety during hospitalization in patients with type 2 diabetes (Alauddin and Petite, 2020; Alfayez *et al*., 2022). The use of metformin in hospitalized patients can be influenced by race/ethnicity, gender, basal insulin, body mass index and the stage of chronic kidney disease (CKD) (Alauddin and Petite, 2020; Elhussein *et al*., 2022; Miao *et al*., 2022) Race and ethnicity (Saudi and non-Saudi population) can potentially affect metformin use in hospitalized patients, as genetic variations in drug metabolism, differences in prevalence of conditions such as DM and CKD and varying socioeconomic factors may influence both prescribing patterns and drug efficacy (Ilias *et al*., 2022; Soric *et al*., 2016). The use of basal insulin in hospitalized patients can affect metformin use, as insulin therapy may be prioritized in cases of significant hyperglycemia or when oral agents are contraindicated (Soric *et al*., 2016).

A high body mass index (BMI) may influence metformin use, as the drug is often prescribed for overweight or obese patients due to its beneficial effects on weight control and insulin sensitivity (ADA, 2022; Alfayez *et al*., 2022) However, metformin is often contraindicated in advanced stages of CKD due to the increased risk of lactic acidosis, with gender differences in renal function further complicating safe use (ADA, 2022; Alfayez *et al*., 2022). Therefore, this study aimed to assess the safety of metformin use in non-critically hospitalized patients who were taking metformin prior to admission.

MATERIALS AND METHODS

This single-center cross-sectional study included patients admitted to a tertiary hospital in Saudi Arabia between January 2019 and June 2019. We included patients who were 18 years or older, on metformin prior to admission, received at least one dose of metformin at admission and had a confirmed history of type 2 diabetes. On the other hand, we excluded patients who were admitted to the intensive care unit (ICU), underwent any active surgery during admission, were pregnant, received metformin for other indications than type 2 diabetes and had a confirmed history of type 1 diabetes. All included patients were monitored throughout the hospitalization period for any potential unsafe use of metformin.

Since all patients who met the eligibility criteria within the predefined timeframe were included in the study, sample size calculation was not necessary. Furthermore, a previously published similar research demonstrated that the number of participants in the current study was sufficient (Alfayez *et al*., 2022).

The extracted data from the hospital records for each patient were nationality, age, sex, weight in kg, height in cm, serum creatinine, eGFR when medication was ordered for the first time, medication strength, dose, date of the initial dose, frequency and length of hospital stay. For data entry, we used Google Sheet and Microsoft Excel version 16.43. The primary outcome was the appropriateness of metformin use in managing hyperglycemia in non-critically hospitalized patients. The appropriateness of metformin use was assessed based on the recent metformin package insert regarding contraindications and precautions. According to the recent package insert, metformin is contraindicated in patients with eGFR less than 30 ml/min/1.73 m^2, hypersensitivity to metformin and acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Precautions for metformin use included age > 65 years, heart failure with hypoperfusion, acute kidney injury, hepatic impairment, contrast media with acute kidney injury and lactic acidosis (Squibb, 2018; FDA, 2016).

Descriptive statistics, such as mean and standard deviation (SD) for continuous variables, median and interquartile range (IQR) for non-normally distributed variables and numbers and percentages for categorical variables were used to summarize the data. The chi-square test was used to determine the association of independent variables (E.g., categorized age, gender, nationality, body mass index, stage of chronic kidney disease, etc) and dependent variable (appropriateness of metformin use). The appropriateness of metformin use was categorized into two, namely appropriate and inappropriate metformin use. The predictors of appropriate metformin use were determined using the binary logistic regression.

Ethical approval

The Institutional Review Board of King Abdulaziz University approved the study (IRB number 596-18) before any data were collected. The authors obtained oral consent from all study participants prior to initiating the study. Oral consent was considered adequate as the study was neither invasive nor was it focused on a sensitive matter prone to discrimination. This study was conducted in accordance with the principles of the Declaration of Helsinki.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences SPSS Version 24. The institutional review board approved this study before data were collected (IRB number 596-18). Prior to study initiation and in accordance with the approved study protocols, all the participants provided oral consent.

RESULTS

Among the 347 patients screened, 251 were included in the final analysis (fig. 1). The patient characteristics are summarized in table 1. The mean age of the study subjects was 60.6 ± 14.6 years, while the mean weight was 76.9 ± 18.4 Kg. Most of our included subjects were females and Saudis, accounting for 54.6% and 57.4% of the study population, respectively. Regarding kidney function, the median serum creatinine was 74.3 ± (49.2 - 94.6) mmol/L and the median eGFR was 80.7 ± (57.5- 100.9) ml/min/1.73 m^2. The median total metformin dose in the current study was 1000 ± (500–1500) mg and the median length of hospital stay was 4 ± (2 -7) days.

Metformin use was appropriate in 96 patients (38.2%) and inappropriate in 155 patients (61.8%). Metformin use was contraindicated in 14 patients (5.6%) and all contraindications were metformin use while eGFR <30 ml/min/1.73 m^2. However, precautions for its use were identified in 141 patients (56.2%). The most reported precautions were age > 65 years in 90 patients (35.9%), heart failure in 25 patients (10%), 11 patients (4.4%), acute kidney injury (AKI) in 9 patients (3.6%), hepatic impairment in 4 patients (1.6%), contrast media with acute kidney injury, in 2 patients (0.8%) and lactic acidosis during admission (table 2).

Table 3 shows the binary logistic regression results identifying the predictors of appropriate metformin use. The findings revealed that the patient's nationality and stage of chronic kidney disease (CKD) significantly predicted the appropriate use of metformin. Specifically, non-Saudi patients have about 1.856 times higher odds of receiving an inappropriate metformin dosage regimen compared to patients of Saudi origin (AOR = 1.856; P = 0.022, 95% CI = 1.093, 3.151). In other words, non-Saudi patients had about 85.6% increased likelihood of receiving inappropriate metformin dosage regimens than patients of Saudi origin. The finding suggests that there might be a significant difference in the metformin dosage regimen prescribed for Saudi and non-Saudi patients. Additionally, patients on CKD stage 3A (Moderate Renal Impairment) were approximately two times less likely to receive an inappropriate metformin dosage regimen than patients on stage 5 (End Stage Renal Disease (ESRD)) (AOR = 0.482, P = 0.035, 95% CI = 0.243, 0.835). This finding implies that patients at an advanced stage of CKD (ESRD) have a higher risk of receiving an inappropriate metformin dosage regimen compared to those with moderate renal impairment.

DISCUSSION

Insulin therapy is the cornerstone for the management of hyperglycemia in non-critically hospitalized patients given its proven effectiveness and flexible dosing (ADA, 2022; Korytkowski *et al*., 2022). However, with the increasing number of oral glucose-lowering medications, several studies and strategies have been proposed to better manage hyperglycemia in non-critically hospitalized patients. Few randomized clinical trials (RCTs) have compared oral glucose-lowering medications with insulin in non-critically hospitalized patients with established type 2 diabetes (Fayfman *et al*., 2019; Garg *et al*., 2017; Vellanki *et al*., 2019). Notably, the findings of these previous trials suggested that oral therapy might be a good alternative for managing non-critically hospitalized patients with a history of type 2 diabetes (Fayfman *et al*., 2019; Garg *et al*., 2017; Vellanki *et al*., 2019) However, to the best of our knowledge, no RCT has investigated the efficacy or safety of metformin compared with insulin in non-critically hospitalized patients.

Given the absence of high-quality studies, the Endocrine Society Clinical Practice Guideline suggests a future area of research to investigate the role of oral glucose-lowering medications in hospitalized non-critically ill patients (Korytkowski *et al*., 2022). Although metformin is widely used to manage patients with type 2 diabetes in outpatient settings and to control blood glucose levels, metformin use in inpatient settings requires more data to support its use. Few observational studies have examined the safety and efficacy of metformin in noncritically hospitalized patients (Alauddin and Petite, 2020). However, some studies have reported that metformin use in inpatient settings can be as high as 50% in some countries (Al-Rubeaan *et al*., 2020; Kim *et al*., 2024; Oktora *et al*., 2023).

The most important finding of our study was that metformin use was inappropriate in a large number of patients (61.8%). Most of the inappropriate use came from the precautions criteria for metformin use (56.2%), while (5.6%) of the included patients had absolute contraindications to its use. The findings of our study regarding absolute contraindication, defined as eGFR <30 ml/min/1.73 m^2 were in concordance with Alauddin and Petite, where there was (1%) of absolute contraindication to metformin use in hospitalized non-critically-ill-patients (Alauddin and Petite, 2020).

Regarding the precautionary use of metformin, our findings were comparable to those of Alauddin and Petite (2020). The most reported precaution was related to the use of metformin in patients aged > 65 years (47%), compared to only (35.9%) in our included subjects. This slight difference might be due to the difference in mean age between the two studies. The second most frequently reported precaution was the use of metformin in patients with a history of heart failure and hypoperfusion. They identified (7.5%) who used metformin with a confirmed history of heart failure, which was similar to our findings for the same indication (10%). The third reported precaution was the use of metformin within 48 h of contrast media, as they reported in (6%) of the population. In contrast, our findings identified only (1.6%) who used

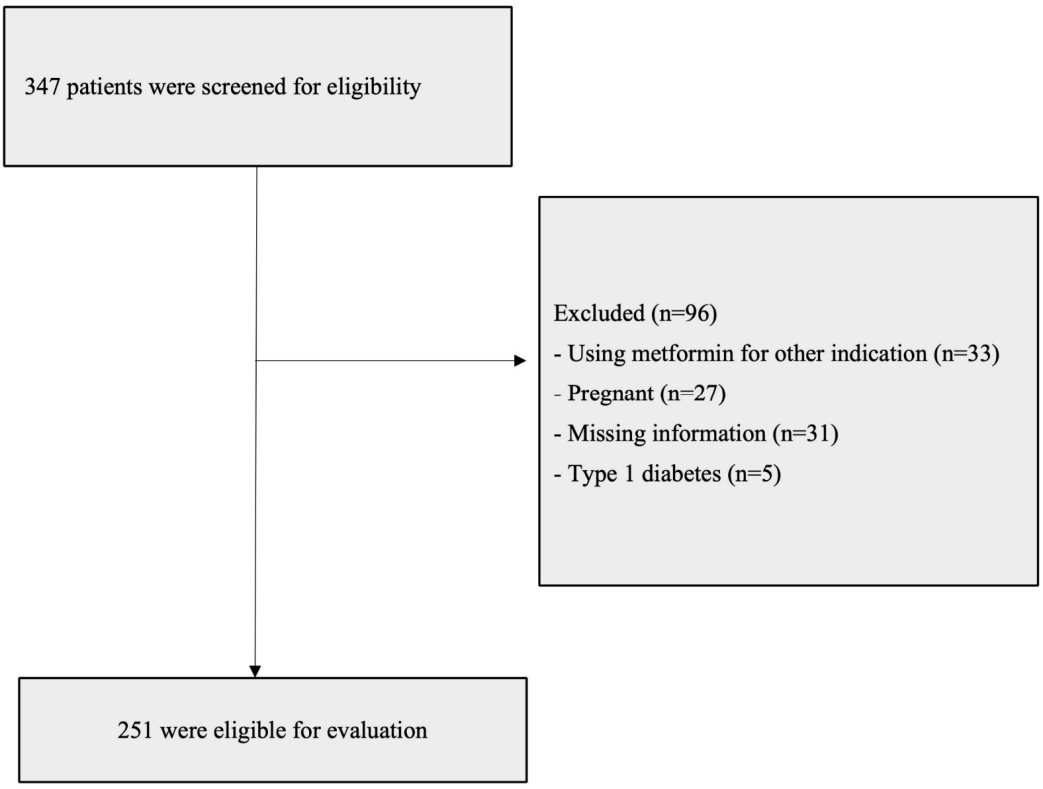

Fig. 1: Patients' Flowchart

metformin for the same indication. This difference might be due to inconsistencies in practice between the two institutions. The fourth reported precaution in their study was related to the use of metformin for AKI, as they recognized only (1%) of the included subjects. In contrast, we identified (4.4%) who used metformin while they had AKI during hospitalization. The final reported precaution in their study was the use of metformin in patients with hepatic impairment (0.5%), which was recognized in (3.6%) of the included patients. Lastly, Alauddin and Petite did not identify any patients who used metformin while developing lactic acidosis, but we found that there were two patients (0.8%) who were on metformin while they had lactic acidosis (Alauddin and Petite, 2020).

The present study also found that patients of non-Saudi origin have increased chances of misusing metformin than patients who are of Saudi descent. Our finding is supported by a previous cross-sectional study in Sweden, in which patients of Swedish origin had better health outcomes, including health literacy, compared to immigrants (Wångdahl *et al*., 2014). This finding suggests that cultural factors affect how patients interact with their healthcare providers. Factors such as difficulty communicating in the local language, differing healthcare norms and health literacy, access to healthcare facilities and availability of resources might contribute to the disparity in metformin use between Saudi and non-Saudi patients (Al-Rubeaan *et al*., 2020). Non-Saudi patients may also need help accessing healthcare services owing to insurance problems, financial limitations and systemic barriers. Therefore, healthcare providers should be adequately trained on cultural sensitivity and effective communication strategies, which could help ensure that all patients in the hospital are well taken care of, irrespective of their country of origin.

Additionally, using interpreters as mediators between clinicians and patients could improve communication between non-Saudi patients and healthcare professionals, as this will minimize the likelihood of misunderstanding metformin dosage. There may be a need to review relevant national practice guidelines, ensure they are culturally sensitive and ensure equal access to available healthcare resources for all patients, whether Saudi or of non-Saudi descent. However, future studies could explore the contributing factors to the observed difference in metformin use between Saudi and non-Saudi patients.

Patients with moderately impaired kidney function were more likely to use metformin inappropriately compared to patients with ESRD. It is well known that metformin is mainly eliminated through the kidney and tends to accumulate in patients with compromised renal functions (Li *et al*., 2020; Orloff *et al*., 2021). A possible explanation for this finding could be that healthcare practitioners might be more cautious when prescribing metformin for patients at an advanced stage of CKD due to the increased risk of metformin accumulation and toxicity than for patients with moderately impaired kidney function.

Table 1: Baseline characteristics

Age, years (mean ± SD)	60.6 ± 14.6
Weight, Kg, (mean ± SD)	76.9 ± 18.4
Height, cm, (mean ± SD)	165.7 ± 64.4
Gender, N (%)	
Male	114 (45.4%)
Female	137 (54.6%)
Nationality, N (%)	
Saudi	144 (57.4%)
Non-Saudi	107 (42.6%)
Serum creatinine, mmol/L, (median ± IQR)	74.3 ± (49.2 - 94.6)
GFR, mL/min/1.73m^2, (median ± IQR)	80.7 ± (57.5- 100.9)
Total metformin daily dose, mg, (median ± IQR)	1000 ± (500 - 1500)
Length of stay, day(s), (median ± IQR)	4 ± (2 -7)
Stage of CKD, N (%)*	
Stage 1	77 (30.7)
Stage 2	78 (31.1)
Stage 3A	29 (11.6)
Stage 3B	11 (4.4)
Stage 4	10 (4.0)
Stage 5	3 (1.2)

*Some data were missing; SD: Standard deviation; N: number; GFR: Glomerular filtration rate; IQR: Interquartile range

Table 2: Study Outcomes

eGFR < 30 mL/min/1.73m^2, N (%)	14 (5.6%)
Age > 65 years old, N (%)	90 (35.9%)
Heart failure, N (%)	25 (10.0%)
AKI, N (%)	11 (4.4%)
Hepatic impairment, N (%)	9 (3.6%)
Iodinated contrast media with AKI, N (%)	4 (1.6%)
Lactic acidosis, N (%)	2 (0.8%)

N: number; eGFR: estimated glomerular filtration rate; AKI: acute kidney injury

Table 3: Predictors of appropriate use of metformin

Variable	Adjusted Odds Ratio	P-value	95% Confidence interval	
			Lower	Upper
Nationality				
Non-Saudi	1.856	0.022*	1.093	3.151
Saudi	Reference			
Gender				
Female	0.804	0.412	0.478	1.353
Male	Reference			
Insulin Basal Dose				
No	1.325	0.527	0.554	3.171
Yes	Reference			
Body mass index				
Underweight	3.272	0.352	0.269	39.753
Normal weight	1.353	0.535	0.520	3.516
Overweight	0.927	0.870	0.374	2.300
Obese	Reference			
Stage of CKD				
Stage 1	2.516	0.311	0.987	3.552
Stage 2	4.098	0.789	1.110	8.042
Stage 3A	1.882	0.035*	1.243	5.435
Stage 3B	2.001	0.653	0.809	5.024
Stage 4	1.099	0.845	0.227	2.900
Stage 5	References			

*Logistic regression is significant at P < 0.05

Healthcare practitioners may be more inclined to monitor metformin dosage and adjust the drug regimen when necessary for patients with severe impairment of renal function than for patients whose kidney function has been moderately compromised (Orloff *et al*., 2021). Healthcare practitioners should, therefore, provide proper attention and monitoring to every diabetic patient on metformin who is known to have impaired kidney function regardless of the stage of the disease. Following this step would ensure that all kidney-impaired diabetic patients receive appropriate treatment.

Study limitations

Our study had several limitations. First, it should be noted that the study design might not have been able to identify all eligible patients who were on metformin during the study period. However, we used a pharmacy record review to identify all patients who received metformin in inpatient settings, but this did not include patients who received metformin in the emergency department because this was not retrievable. Second, some information regarding lactic acidosis was not available to all included subjects because it is not a regular test to be performed in inpatient settings. Third, our findings cannot be generalized to other hospitals in Saudi Arabia because prescribing patterns might not be the same among different institutions. Fourth, it was not our focus to follow those included patients in outpatient settings, which could result in changing their regimen based on the new findings in their admission. Lastly, since the current study utilized a cross-sectional design, a cause-effect relationship between the variables and changes in the prescribing behaviour over time could not be ascertained, hence the need for a future experimental or longitudinal study.

CONCLUSION

Our findings highlight the high rate of inappropriate metformin use in noncritically hospitalized patients. However, patients who are non-Saudi and at an advanced stage of CKD were more likely to receive an inappropriate metformin dosage regimen. Thus, appropriate interventions such as continued education for healthcare practitioners would likely improve metformin use in hospital settings. A prospective study evaluating metformin safety in non-critically hospitalized patients is warranted.

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Data sharing statement

All data were retrieved from databases and are available from the corresponding author upon reasonable request.

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Conflict of interest

The authors declare that they have no conflict of interest.

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