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ORIGINAL ARTICLE

Appropriateness of metformin prescription for type 2 diabetes mellitus patients with chronic kidney disease (Stages 3-5)

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Abstract

Introduction: Metformin is the first-line pharmacological therapy for type 2 diabetes mellitus (T2DM). Guidelines recommend metformin to be given at reduced dosages for those with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 and omitted in those with eGFR<30 mL/min/1.73m^2. Lactic acidosis is a known complication of those on metformin. This study aimed to determine the appropriateness of metformin prescription in T2DM patients with chronic kidney disease (CKD) stages 3-5 in a tertiary centre in Malaysia. *Materials and Methods:* A cross-sectional design using retrospective secondary data of T2DM patients on metformin attending nephrology and diabetic clinics in the year 2017. eGFR calculated using the CKD-EPI formula identified those in CKD stage 3-5 defined using the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative criteria. Metformin prescription was considered appropriate when the metformin maximum daily dosage does not exceed 1500 mg in CKD stage 3a and 1000 mg in CKD stage 3b and metformin stopped in CKD stages 4 and 5. *Results:* A total of 143 patients were included. Majority were in the elderly age group (62.9%), male (60.8%) and had concurrent hypertension (85.3%). Median HbA1c was 8.3% (67 mmol/mol) with most patients (88.8%) having HbA1c above 6.5% (48 mmol/mol). Majority (92.3%) were categorised as stage 3 CKD. Eleven (7.7%) subjects had inappropriate metformin prescription. Seven of nine (78%) subjects in CKD stage 4 were on metformin with a maximum daily dose of 500 mg to1000 mg. Three patients had serum lactate measured. *Conclusion:* The majority of CKD patients had appropriate metformin prescription. However, a considerable number of CKD stage 4 patients continued to be on metformin. The many benefits of metformin may be a reason why it is still continued against recommendations. Only three patients had lactate measured which, although may suggest that lactic acidosis is not a common occurrence, the potential for metformin-associated lactic acidosis especially in those at risk should be considered.

Keywords: metformin, chronic kidney disease, diabetes mellitus, lactic acidosis

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder resulting from a combination of exposure to genetic and environmental factors leading to insulin resistance characterised by hyperglycaemia.[1] Chronic hyperglycaemia is associated with long-term damage, categorised as micro- and macrovascular complications, with T2DM being a recognised risk factor for chronic kidney disease (CKD).[1,2] The reported prevalence of CKD among the Malaysian adult population is 9.07%.[3] In 2014, 61% of end-stage kidney disease in Malaysia was as a consequence of diabetes mellitus.[4] CKD is defined when there is presence of either kidney damage or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 for more than three months duration.[5] eGFR is commonly calculated in clinical practice either by the Modification of Diet in Renal Disease (MDRD) or the CKD-EPI formulae.[5] CKD staging is identified based on the National Kidney Foundation -Kidney Disease Outcome Quality Initiative (NKF-KDOQI) guidelines with lower

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eGFR indicating higher stage of CKD.[5]

Metformin is the first-line pharmacological therapy for T2DM.[6,7] It reduces glucose output from hepatocytes and induces peripheral glucose uptake in myocytes by the activation of AMP-activated protein kinase (AMPK).[8] Metformin reduces diabetes-related cardiovascular mortality and morbidity in overweight patients,[9] although recent evidence is equivocal on this matter.[10] Compared to other anti-diabetic therapy, it is associated with weight stability and the occurrence of hypoglycaemia is rare when used as a single therapy.[11] Metformin is eliminated unchanged primarily by the kidneys and thus, there were concerns regarding its use in those with CKD.[12] Being relatively cheap and effective in reducing hyperglycaemia as well as its possible benefits in improving macrovascular outcome has made metformin an attractive drug for many T2DM patients, including those with kidney disease.[12] The concerns were metformin-associated lactic acidosis in those with impaired kidney function. However, a recent systematic review reported an overall incidence varied between 3 and 10 per 100,000 person-years and generally was indistinguishable from the background rate of the overall population with diabetes.[12] Guidelines recommend metformin to be withheld in those with eGFR below 30 mL/min/1.73m (CKD stage 4 and 5).[2,6-7,11] For CKD stage 3a (45-59 mL/min/1.73 m^2) and 3b (30 – 44 mL/min/1.73 m^2), metformin may be continued with the recommended maximum metformin daily dose adjusted to 1500 mg for stage 3a and 1000 mg for CKD stage 3b.[13]

In the United States, 47.7% subjects with CKD stage 3a, 26.3% with CKD stage 3b and 1.3% in advanced CKD (stage 4 and 5) were on metformin.[14] In another study, 31.4% of elderly subjects with metformin prescription were in CKD stage 3 or greater.[15] We hypothesised that patients with CKD in Malaysia may also be on metformin despite advanced CKD or the metformin maximum daily dose are not adjusted in those with moderate CKD. Thus, the aim of this study was to determine the appropriateness of metformin prescription for T2DM patients with CKD (stages 3-5) in Hospital Serdang.

MATERIALS AND METHODS

A cross-sectional design using retrospective data of T2DM patients attending nephrology and diabetic clinics of Hospital Serdang, Malaysia from January 2017 to Jun 2017. Eligibility criteria for inclusion were adult T2DM patients aged at least 18 years old with eGFR <60 mL/min/1.73 m^2 undergoing follow up in the hospital's nephrology or diabetic clinics and received metformin prescription during this period. Exclusion criteria were those with incomplete data. Sample size determined using two proportion formula with standard error associated with a 95% confidence level, 80% power and 20% estimated non-response bias was 120. Ethical approval was obtained from the Medical Research Ethical Committee (MREC), Ministry of Health, Malaysia.

Data obtained from the electronic medical records included demographics (age, gender, and race), clinical characteristics (other comorbidities), laboratory parameters (HbA1c, serum creatinine and serum lactate), and metformin dosages (initial and current dosage). eGFR was calculated based on CKD-EPI formula using an online calculator at http://www.kidney.org/professionals/KDOQI/gfr calculator. CKD stages 3-5 were categorised based on the KDOQI criteria using eGFR cut-off values as shown in Table 1.[2]

TABLE 1: CKD stages categorised based on the KDOQI criteria

Stage	eGFR (mL/min/1.73m^2)
3a	45 – 59
3b	30- 44
4	15 – 29
5	<15

Metformin prescription was considered appropriate when the metformin dosage does not exceed 1500 mg in CKD stage 3a and 1000 mg in CKD stage 3b and metformin stopped in CKD stages 4 and 5.[13] The appropriateness was determined based on the eGFR at the time of latest metformin prescription. Inappropriate metformin use is when these criteria were not followed. Data analyses were performed using the IBM Statistical Package Social Science (SPSS) version 24.0. Descriptive analysis was reported as mean ± standard deviation (SD) for normally distributed continuous data or as median with interquartile range (IQR) for non-normally distributed data. Categorical data were presented as number (n) and percentage (%).

RESULTS

A total of 143 subjects were included in the study population (Table 2). More than half

TABLE 2: Characteristics of study subjects (n=143)

Variables	n (%)	Median (IQR)
Age (years)		
18-59	53 (37.1)	
≥60	90 (62.9)	
Gender		
Male	87 (60.8)	
Female	56 (39.2)	
Ethnicity		
Malay	65 (45.5)	
Non-Malays	78 (54.5)	
Hypertension		
Yes	122 (85.3)	
No	21 (14.7)	
HbA1c (%)		8.3 (2.7)
<6.5	16 (11.2)	
≥6.5	127 (88.8)	
Serum Creatinine (μmol/l)		126 (32)
Above gender specific URL*	22 (15.4)	
Below gender specific URL*	121 (84.6)	
CKD stage (eGFR mL/min/1.73m^2)		
3a (45 – 59)	82 (57.3)	
3b (30- 44)	50 (35.0)	
4 (15 – 29)	9 (6.3)	
5 (<15)	2 (1.4)	

*Based on Hospital Serdang URL (Female 97 umol/l; Male 115 umol/l)

were elderly (62.9%), male (60.8%) and having concurrent hypertension (85.3%). Majority (88.8%) of subjects had HbA1c values above the recommended target of 6.5% (48 mmol/mol) with median HbA1c of 8.3% (67 mmol/mol). The median for serum creatinine was 126 μmol/l, which was above the upper reference limit (URL) for both males and females. The majority were categorised with stage 3 CKD (92.3%).

Table 3 shows the maximum metformin daily dose given to the subjects according to the CKD stages. Seven subjects in CKD stage 4 (77.8%) were on metformin and thus, considered to have inappropriate metformin prescription. Two (4%) subjects in CKD stage 3b and two (2.4%) subjects in stage 3a had metformin prescription higher than the recommended 1000 mg and 1500 mg daily for stage 3b and stage 3a, respectively. Thus, the overall subjects with inappropriate metformin prescription were eleven (7.7%). A total of seven subjects had metformin stopped within the study period. Of 143 subjects, three (2.1%) had serum lactate measured (median 2.7 mmol/L) with two having raised lactate values

TABLE 3: Maximum metformin daily dose in study subjects

CKD stage	Maximum metformin daily dose (mg)						
	Stopped	250	500	850	1000	1500	2000
3a (n=82)	-	1	42	3	33	1	2
3b (n=50)	3	1	24	1	19	1	1
4 (n= 9)	2	-	3	2	2	-	-
5 (n=2)	2	-	-	-	-	-	-

(≥1.2 mmol/L). The two patients with raised lactate were in CKD stages 3a and 4, respectively.

DISCUSSION

Majority of the study population was in CKD stage 3, which was expected as metformin may be continued in this group of patients at reduced dosage with the caveat of being cautious and frequent monitoring of complications. A median HbA1c of 8.3% was obtained, in parallel to a reported median HbA1c of 7.9% in another tertiary centre in Malaysia.[16] This was also comparable to the Malaysian National Diabetes Registry (NDR) 2009-2012 report where the mean obtained was 8.1%, with 23.8% achieving the glycaemic target of HbA1c <6.5%.[17] In contrast, only 11.2% of our study population had achieved this target which could be explained by the more complex cases of diabetes being referred and managed in a tertiary centre compared to government primary care centres from which the data for NDR was derived. The majority (85.3%) also had concurrent hypertension similar to Malaysian NDR 2009-2012 where 70.1% of patients with T2DM were noted to have hypertension.[17]

Metformin is widely prescribed in patients with moderate, but not advanced renal impairment. Christiansen *et al*. 2015 reported that majority of subjects continued on metformin within 90 days after persistent decline in eGFR from a value of above 60 to 45–59 mL/min/1.73 m^2.[18] Even when the first eGFR decline was <30 mL/min/1.73 m^2, 59% continued on metformin within 90 days after the decline date.[18] Only 6.3% and 1.4% of our study subjects were in CKD stages 4 and 5, of which four out of 11 had metformin stopped. Most subjects in CKD stage 4 were continued on metformin. In a French study, 33% of advanced CKD patients were continued on metformin with some at a daily dose of 2000 mg.[19] Inaccurate assessment of renal function and under-recognition of CKD are possible explanation for inappropriate metformin use in CKD patients.[20] In a hospital setting where there is lack of automated reporting of eGFR may to some extent contribute to patients still on metformin despite being in CKD stages 4 and 5. Automated reporting of eGFR each time serum creatinine is ordered immediately highlights the presence of abnormal eGFR rather than the need for clinicians to calculate eGFR. Lack of application to the recommended prescribing guidelines in CKD, rather than lack of knowledge has also been suggested as a possible explanation for the continued use of metformin.[20,21]

The cautiousness of using metformin in CKD patients is related to the risk of lactic acidosis although a systematic review highlighted that the data from which this is derived are limited.[12] Despite a proportional decrease in metformin clearance with declining eGFR, metformin remains within therapeutic range with no significant increase in lactate levels in mild to moderate CKD (eGFR 30 – 60 ml/min/1.73 m^2).[12] The incidence of metformin-related lactic acidosis is low, and if lactic acidosis does occur, the medication may not necessarily be responsible.[12] The authors of the systematic review proposed that metformin should be withheld for CKD stage 4 and 5 but may be continued with caution in those with CKD stage 3a (maximal total daily dose of 2000 mg/day) and stage 3b (maximal total daily dose of 1000 mg/day) even though the dosage was never validated in clinical trials.[12] Only three patients had lactate measured in our study which may suggest that lactic acidosis is not a common occurrence in these CKD patients particularly considering the widespread use of this anti-diabetic drug although this cannot be truly ascertained from a retrospective study. Although, the risk of lactic acidosis may not be common, there is a 35% increased mortality risk from all causes for patients in stage 5 CKD on metformin compared to those not treated with metformin.[21]

Huang *et al*. 2014, states that older age (OR = 1.13, 95% CI 1.08-1.19) and female sex (OR = 2.51, 95% CI 1.44-4.38) were associated with increased odds of inappropriate metformin prescription in CKD.[15] Wu *et al*. 2014, on the other hand, noted that Hispanic residents with CKD were more likely to receive appropriate anti-diabetic medications as recommended by guidelines compared to other races.[22] It was also suggested that concordance with the recommended guidelines for anti-diabetic drugs prescription could be affected by the type of practice, i.e., specialists versus general practitioner.[23] Another factor that should be considered is the method of calculating eGFR. Muller *et al* 2016 state that the distribution in and outside of the recommended guidelines for oral anti-diabetic use was significantly impacted by the equation used to estimate GFR, either by CKD-EPI, MDRD or Cockgroft-Gault formula.[23] Specifically for metformin, the person out of recommendations was 45.6%, 66.9% and 49.3% for Cockgroft-Gault, CKD-EPI and MDRD

formulas, respectively (p=0.02). No comparison was performed using either the MDRD or Cockgroft-Gault formula, which may be a limitation of our study. This will be assessed hopefully in future study. Being a retrospective study, there was no documented explanation on why dosage alteration or omission of metformin by physicians was not implemented as deemed appropriate.

CONCLUSION

In general, the majority of the CKD patients had appropriate metformin prescription. However, a considerable number of CKD stage 4 patients continued to be on metformin. The many benefits of metformin may be a reason why it is still continued against recommendations. Only three patients had lactate measured which, although may suggest that lactic acidosis is not a common occurrence, the potential for metformin-associated lactic acidosis especially in those at risk should still be considered.

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