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## Administration of metformin in type 2 diabetes mellitus patients with chronic kidney disease; facts and myths

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### ABSTRACT

There are few publications reporting adverse effects of metformin for patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). Although some of these reports have made big claims about the adverse effects of metformin in patients with renal failure, the majority of studies showed a superior safety profile for metformin compared with other antidiabetic medications in these patients. Further, metformin use is not contributing to an increased incidence of acute kidney injury (AKI). In conclusion, we suggest that a low dose of metformin is safe to use in patients with or without CKD. Multicenter randomized trials are required to further discover the benefits of the risk of metformin therapy in different stages of CKD and its effect on progression of CKD.

### *Implication for health policy/practice/research/medical education:*

Some studies claim that the metformin use, precipitates lactic acidosis in patients with chronic kidney disease (CKD). But large majority of studies reported that the metformin is safe to use in patients with or without CKD. Low doses of metformin show superior safety profile beneficial in patients with renal failure.

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### Introduction

Metformin is a biguanide used in the treatment of type 2 diabetes mellitus (T2DM). Metformin has relevant pleiotropic effects on different organs specially the kidney. Numerous studies demonstrated that metformin mitigates the pathophysiological changes (such as fibrosis, inflammation and apoptosis) associated with chronic kidney disease (CKD). The renoprotective effects of metformin are mediated via 5' adenosine monophosphate-activated protein kinase (AMPK) pathway. Despite the fact that metformin has been in the market for about 60 years, new indications continue to occur about its administration. Using metformin in patients with moderate to advanced

renal damage has been a debatable subject since, with recommendations that seem contradictory in different guidelines (1). Consensus Report by the American Diabetes Association and European Association for the Study of Diabetes, discouraged the use of metformin in patients with an estimated glomerular filtration rate (eGFR) of 30–45 mL/min/1.73 m<sup>2</sup>. In contrast, the New Zealand Medsafe guidelines suggest metformin withdrawal when eGFR is less than 15 mL/min/1.73 m<sup>2</sup> (2). Further, the Food and Drug Administration (FDA) guidelines suggest that metformin should not be used in patients with an eGFR of <30 mL/min/1.73 m<sup>2</sup> (3). Although several experimental and clinical studies report

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the renoprotective effects and cardiovascular benefits of metformin, no prospective clinical studies on the effect of metformin on renal end-points in different CKD stages, are available. Therefore, controlled randomized clinical trials to detect the renoprotective effects of metformin on CKD progression should be conducted (4,5).

The reports on adverse effects of metformin for patients with T2DM and CKD are very few. A retrospective nationwide cohort study from Taiwan, using National Health Insurance Research Database (NHIRD) between 1996 and 2013, found that the use of metformin was independently associated with increased risks of end-stage renal disease (ESRD) and CKD in a dose-response relationship (6). Another retrospective nationwide cohort study from Denmark using a total of 168 443 drug-naïve T2DM patients with 50 years, after initiation of treatment the one-year risks of acute dialysis was found to be 92.4 per 100 000 for sulphonylurea and 142.7 per 100 000 for metformin (7). This increased 1-year risk of acute dialysis was providing evidence for increased risk of acute kidney injury (AKI) in patients using metformin (7). With Taiwanese T2DM and moderate CKD patients, continuous use of metformin showed adverse effect on renal function compared to the discontinued metformin treatment (8). In the Trial to Reduce Cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT), comparison of mortality and cardiovascular events in metformin users and non-users with T2DM and CKD demonstrated a significant reduction of death and cardiovascular events in stage 3 CKD patients (9). Further, a retrospective analysis of national health insurance research database showed that, in T2DM patients with serum creatinine concentration greater than 530 µmol/L, metformin use significantly increased risk of all-cause mortality compared with non-users (10).

To date, no review paper has provided the full scope of metformin therapy in CKD patients nor amalgamated their viewpoint. Therefore, the purpose of this review was to summarize more detailed information on metformin use in CKD patients.

## Materials and Methods

For this review, we conducted a systematic search of Web of Science, PubMed, Embase, Scopus and the directory of open access journals (DOAJ), using specific combination of keywords. In each database, we searched for metformin, end-stage renal disease (ESRD), T2DM, glomerular filtration rate, acute kidney injury (AKI), chronic kidney disease (CKD), lactic acidosis symptom, side effect, adverse effect and mortality.

## Chronic kidney disease and metformin

Glycemic control helps in delaying the vascular aggression

and minimizing the risk of cardiovascular disease and progression to ESRD in diabetic kidney disease (11, 12). Hence glycemic control is considered; as the best solution to slowdown CKD progression in these patients. Several lines of evidence demonstrated that hyperglycemia suppresses the 5' AMP-activated protein kinase (AMPK) and amplifies activation of mammalian target of rapamycin (mTOR) pathway, that lead to simulation of kidney hypertrophy and renal injury contributing to diabetic nephropathy (13, 14). Conversely, metformin activates AMPK signaling pathways and attenuates mTOR pathway, contributing to its nephroprotective effects in CKD (15). In rat model with CKD-Mineral and Bone Disorder (CKD-MBD), metformin significantly reduced renal inflammation, cellular infiltration, and fibrosis and suppressed progression of CKD (16). Also in rats, metformin pretreatment inhibited inflammatory biomarkers, tumor necrosis factor-alpha and C-reactive protein and ameliorated diabetic nephropathy induced by a combination of high fat diet and streptozotocin in rats (17).

A double-blind, placebo-controlled, parallel design study for rosiglitazone versus placebo groups with T2DM patients showed that serum creatinine concentration was similar in placebo, rosiglitazone, and metformin groups (18). However, a cross sectional observational study demonstrated that metformin use could enable reduction of creatinine levels and provided unique cardiac and renal protection (19). A recent study demonstrated anti-inflammatory effects of metformin in gestational diabetes mellitus in mice (20). In this study metformin decreased body weight, blood glucose, micro-albumin, interleukin-6 and tumor necrosis factor-alpha levels in serum. This study also documented phosphorylation of mitogen-activated protein kinase (MAPK) in the kidneys of mice (20). Additionally, various studies also evaluated the effect of metformin on all-cause mortality in adult patients with T2DM and CKD. The large majority of studies showed that metformin administration was associated with lower mortality in comparison with non-metformin treatment group (21). Moreover, a new review compiling recent evidence of metformin treatment in T2DM-CKD patients suggested that the current contraindications of metformin use should be considered only in CKD stage 4. A single dose of 500 mg/d with some recommendations is suggested as appropriate for CKD stage 4 patients (22).

A well-adjusted risk-benefit examination of metformin, empagliflozin and liraglutide showed that metformin likely benefits patients with moderate CKD, resulting in many years of clinical use without side effects. However, there is an obvious performance for the newer drugs, mainly for those patients who require more than one drug to cure their hyperglycemia, or for those who can't

tolerate metformin (23). To study the effect of metformin or placebo on the progression of their renal function, a randomized controlled double-blinded trial (Renomet) on non-diabetic patients with early to moderate CKD is designed (ClinicalTrials.gov Identifier: NCT03831464). Currently there are many patients who do not use metformin in spite of the fact that it could be profitable. Discontinuation of metformin in CKD patients often causes poor glycemic control and may accelerate the progression of diabetic nephropathy, or cardiovascular events in high-risk patients.

### Metformin use in early CKD stages

The continued use of metformin in CKD patients lies in the adjustment dosage regimens based on level of CKD. But, it is essential to pay attention to the progression of lactic acidosis in various conditions such as heart failure and the risk of AKI. The metformin doses for different CKD stages are different: CKD stage 3A (eGFRs between 45-60 mL/min/1.73 m<sup>2</sup>) 1.5 g/d, CKD stage 3B (eGFRs between 30-45 mL/min/1.73 m<sup>2</sup>) 1 g/day and CKD stage 4 (eGFRs 15-30 mL/min/1.73 m<sup>2</sup>) 500 mg/d (24, 25). Some physicians prefer to prescribe metformin 250 mg/d to peritoneal dialysis, and 500 mg/d after each dialysis to hemodialysis patients (26). While some of the physicians in their clinical practice do not prescribe if eGFR of patient is below 30 mL/min (27). A large prospective cohort study on patients with diabetes and CKD stage 4 showed that treatment with low-dose metformin during one month revealed stable pharmacokinetics and was not associated with adverse effects (28). Measurement trough levels of metformin in serum using liquid chromatography-tandem mass spectrometry (LCMSMS) in patients with varying renal function showed a median trough level for metformin as 8.88 micromol/l in patients with eGFR <30 mL/min/1.73 m<sup>2</sup>, while a 20 µmol/l concentration is considered the upper safe therapeutic limit (29).

Analysis of plasma and effluent metformin and plasma lactate levels in patients receiving a daily dose in the range 0.5-1.0 g metformin before and after automated peritoneal dialysis therapy demonstrated no correlation between metformin dosage and lactate concentrations (30). Although this study showed the feasibility of metformin use in peritoneal dialysis, is not comprehensive enough to prove the safety of metformin administration in peritoneal dialysis. Further, CKD5 patients receiving 250-500 mg metformin per day did not show any side effects such as lactic acidosis, altered lactate levels, or raised plasma metformin (31). Hence a maximum metformin dose of 250 mg before dialysis and 500 mg after dialysis is recommended for peritoneal dialysis and hemodialysis patients (32).

### Other antidiabetic agents

Few clinical studies have compared different antidiabetic agents in patients with CKD. When metformin is discontinued, sulphonylureas or insulin may be used as substitutes. Clinical studies showed that sulphonylureas and insulin are both correlated with weight gain and hypoglycemic incidents and finally adverse cardiovascular events and increased mortality (33,34). Therefore, it is a challenge to continue metformin or to shift to an alternative hypoglycemic agent that reduces morbidity and mortality. Further, few retrospective and prospective cohort studies showed that metformin monotherapy is associated with lesser mortality than other hypoglycemic agents such as sulfonylureas such as glipizide, glyburide and glimepiride (35, 36). A study on the effect of metformin withdrawal on glycemic control of diabetic patients with deteriorating renal function showed that the continuous improvement in glycemic control using other agents resulted in further deterioration of renal function (37). This study suggests close monitoring of hypoglycemia in patients with deteriorated renal function.

A randomized controlled trial in patients from UK Prospective Diabetes Study (UKPDS) group showed that the intensive glucose control with metformin appears to decrease the risk of diabetes-related endpoints better than insulin and sulphonylureas (38). A large observational study comparing all-cause mortality in metformin group versus insulin group demonstrated a reduced risk of all-cause mortality in metformin group versus other oral hypoglycemic agents in patients with eGFR of 30 to 45 mL/min per 1.73 m<sup>2</sup> (39). Another prospective study on 13,238 veterans with baseline eGFR >60 mL/min showed that metformin initiation is associated with a reduced risk of diminished renal function or death compared to sulfonylureas (40). A systematic review of studies comparing the renal function outcome of metformin and those of sulfonylurea showed that metformin led to better renal outcome (41). Retrospective analysis of a cohort of veterans on intensified metformin monotherapy, the addition of insulin compared with a sulfonylurea was not associated with a higher rate of kidney outcomes (42). An open cohort study in primary care in the United Kingdom showed that patients using gliptin or pioglitazone monotherapy are exposed to a significantly higher risk of kidney failure against patients taking metformin monotherapy (43). Retrospective analysis of National Veterans Health Administration databases showed that initiating sulfonylurea had a higher risk of heart failure and cardiovascular death in male patients compared to similar patients initiating metformin (44). Comparison of the kidney function outcomes of metformin and sulfonylurea use in Italian T2DM patients showed that the metformin is not associated with fast progression to CKD (45).

### Metformin and lactic acidosis

Several observational studies have been conducted to explore the association between lactic acidosis and metformin use in T2DM and CKD patients. A nested case-control analysis using the UK based General Practice Research Database revealed that the lactic acidosis is a rare event in patients using oral antidiabetic agents and is associated with concurrent comorbidity (46). A Cochrane systematic review of prospective comparative trials and observational cohort studies showed that metformin is not associated with increased levels of lactate or with the risk of lactic acidosis (47). Retrospective analysis of Scottish Renal Registry data comprising 25 000 T2DM patients found no evidence for occurrence of metformin-induced AKI (as a proxy for lactic acidosis) or survival rate following AKI across different levels of renal function (48).

### Conclusion

Although some reports have made big claims on adverse effect of metformin on renal function, the volume of reports that display adverse effects of metformin for patients with CKD is very low. In contrast to this finding, there are many benefits that support prescription of metformin in early stages of CKD (stages 1 to 3). Further metformin use is not contributing to increased incidence of AKI. In conclusion, we suggest that a low-dose of metformin is safe to use in patients with or without CKD.

### Authors' contribution

MAS and RV searched the literature and prepared the first draft. LVKSB and SJK revised the manuscript and edited it. All authors read and approved the final paper.

### Conflicts of interest

The authors declared no competing interests.

### Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

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