point

Does metformin do more benefit or harm in chronic kidney disease patients?

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Metformin is one of most commonly prescribed medications for the treatment of type 2 diabetes mellitus. Metformin is a low-molecular-weight (129) cationic substance that is not metabolized and does not bind to serum proteins. Glomerular filtration combined with tubular secretion results in an efficient unchanged renal elimination (550 ml/min). Hence, until recently, guidelines discouraged the use of metformin in patients with acute and chronic renal failure (CKD G3–5) due to concerns that accumulation of metformin could substantially increase the risk of developing lactic acidosis (LA).

Metformin exerts control of glycemia by increasing peripheral glucose uptake and utilization and by decreasing hepatic gluconeogenesis. This agent enhances anaerobic metabolism and can also increase systemic lactate levels by inhibiting mitochondrial respiratory chain 1 (MRC1) and blocking pyruvate carboxylase, the first step of gluconeogenesis, in the gut, liver, and peripheral tissues. Hence, plasma lactate concentration may increase in a metformin dose/concentration–dependent way. Furthermore, inhibition of MRC1 results in activation of adenosine monophosphate–activated protein kinase (AMPk), a cellular metabolic sensor.

The most frequent clinical conditions related to metformin-associated LA are chronic renal failure (reduced metformin and lactate clearance), impaired hepatic metabolism (reduced lactate clearance), and increased lactate production, such as occurs in sepsis, severe dehydration, hypoxic states, cardiovascular insults, shock, liver failure, acute kidney injury (AKI), and chronic renal failure. Most cases of metformin-associated LA have metformin plasma levels >5 mg/l (therapeutic range <2 mg/l).

On the other hand, Friesecke *et al.*[1] and other authors have demonstrated that the survival rate of patients with severe LA associated with metformin accumulation, compared with controls not using metformin, is strikingly higher than expected based on the initial clinical evaluation and Simplified Acute Physiology Scores. In contrast to some publications, Bell *et al.*[2] found no evidence that metformin increases incidence of AKI and demonstrated that metformin was associated with higher survival after incident AKI.

Increased risk for metformin-associated LA is controversial. In a Cochrane Systematic Review of more than 347 trials, 43% of which did not exclude patients with kidney disease, evaluated the incidence of LA among patients prescribed metformin versus nonmetformin antidiabetes medications.[3] Of 100,000 people, the incidence of LA was 4.3 cases in the metformin group and 5.4 cases in the nonmetformin group, indicating that metformin is not associated with an increased risk for LA.

To compare the occurrence of LA between metformin and sulfonylureas, Bodmer and colleagues[4] conducted a nested, case-control analysis of 50,048 patients with type 2 diabetes receiving an oral antidiabetes agent. They found that in 100,000 patients, the crude incidence of LA in patients treated with metformin was 3.3, whereas the incidence in patients treated with sulfonylureas was 4.8. All patients who developed LA had underlying conditions that are known risk factors for LA.

Lazarus *et al.*[5] found in 2 real-world clinical settings that metformin was associated with acidosis only in patients with estimated glomerular filtration rate (eGFR) <30 ml/min per 1.73 m^2. Ekström *et al.*[6] found that metformin compared with any other treatment showed reduced risks of acidosis, serious infection, and all-cause mortality in patients

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with eGFR 45 to 60 ml/min per 1.73 m^2 and no increased risks in patients with eGFR 30 to 45 ml/min per 1.73 m^2. Eppenga *et al.*[7] found that the risk of LA or elevated lactate levels was significantly higher (7.4 vs. 2.2/100,000 person-years) in metformin-treated patients with moderate to severe CKD compared with those using other treatments. Inzucchi *et al.*[8] noted that the overall incidence for LA was low (35 events over 337,590 patient-years of follow-up) and that the incidence rate with worsening severity of kidney function was nonsignificant. With such small numbers of events, conclusions cannot be made.

Recently Hung *et al.*[9] reported that in Taiwan, where until recently metformin was authorized across the entire spectrum of CKD, among 12,350 patients with serum creatinine levels >6 mg/dl (>528 μmol/l; CKD5 patients) metformin users (n = 1005) had a 29% higher mortality than nonusers over a median period of 2.1 years. However, the number of reported metabolic acidosis events was small. This study did not provide data on the duration of metformin treatment, metformin levels, number of comorbidities, or HbA1 concentrations. Nevertheless, the message of this paper is a strong warning not to use metformin in CKD 5 patients characterized by their very fragile clinical situation and the fast accumulation of metformin.

Risk factors for LA include any disease state that has the potential either to increase the production or decrease the removal of lactic acid. A recent retrospective study, demonstrated that metformin use in advanced CKD patients, especially those with CKD 3B, decreased the risk of all-cause mortality and incident end-stage renal disease.[10] Additionally, metformin did not increase the risk of LA.

Checking metformin dosages in plasma is still not a common practice in the majority of hospitals, and thus metformin intoxication should be considered as probable when LA and renal failure are pronounced, other primary explanations are not evident, and chronic metformin use is reported.

Renoprotection

Cumulative evidence from *in vitro* and *in vivo* models suggests that the nephroprotective impact of metformin is much larger than its antihyperglycemic effect. In a rat model of cyclosporin A (CsA)–induced renal fibrosis, a 4-week treatment of metformin effectively prevented CsA-induced renal dysfunction with (i) increased creatinine clearance rate, (ii) reduced renal fibrosis, and (iii) lower proteinuria compared with the control CsA group. The antifibrotic effects of metformin were associated with a decreased phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2).[11] In another classical rat model of nondiabetic CKD based on subtotal 5/6th nephrectomy, metformin gavage (250 $mg \cdot kg^{-1} \cdot day^{-1}$) improved the glomerular filtration rate (measured by clearance of ^{3}H-inulin in Ringer solution) within 7 days and reduced kidney fibrosis and structural alterations within 30 days.[12] These benefits may be related to the AMPK, as suggested by the similar beneficial exposure to 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), a classical AMPK activator.[12] AMPK is a critical cellular energy sensor.[13] Several uremic factors were shown to inactivate AMPK *in vitro* and in *ex vivo* preparations of kidney tissue, which may explain the cellular/tissular energy mismatch in case of CKD.[14] A failure to sense 5'-adenosine monophosphate (AMP) may be regarded as the pivotal mechanism of the vicious cycle of energy depletion and CKD progression.[14] Hence, the AMPK-mediated phosphorylation of the acetyl-CoA carboxylase helps to restore fatty acid oxidation in tubular epithelial cells from kidneys with tubulointerstitial fibrosis, thereby increasing energy supply and limiting renal lipotoxicity.[15] Similarly, in rats with CKD induced by a 0.25% adenine diet for 8 weeks, metformin administration (200 $mg \cdot kg^{-1} \cdot day^{-1}$ from 1 week after CKD induction onward) was associated with less cellular infiltration, fibrosis, and inflammation in the renal parenchyma.[16] Furthermore, metformin preserved calcium/phosphorus homeostasis in these CKD rats, thereby preventing the development of vascular calcification and high bone turnover disease.[16] Of note, metformin had previously been shown *in vitro* to prevent vascular calcification in female rat aortic smooth muscle cells via the AMPK pathway.[17] Interestingly, AMPK also participates in the negative regulation of the biosynthesis of fibroblast growth factor 23 (FGF23), which is a proteohormone regulating renal phosphate transport and vitamin D metabolism.[18] The AMPKα1-deficient mice showed high FGF23 levels and cardiac hypertrophy, which resemble those seen in patients with CKD. The inhibitory effect of AMPK on FGF23 production is partly mediated by the store-operated calcium ion entry through the calcium selective ion channel Orai.[19]

Table 1 | Metformin in patients with CKD

- Metformin was and still is an important drug in the treatment of diabetes type 2.
- The risk of lactic acidosis is essentially nil in the context of clinical trials, including those that did not specify kidney disease as an exclusion criterion.
- The incidence of lactic acidosis in the setting of metformin (MALA) therapy is very low, and the drug is not necessarily responsible when lactic acidosis occurs in patients taking this medication. In almost all cases, associated pathology particularly acute kidney injury has to be considered as a triggering factor.
- As long as kidney function is stable, the patient is followed at regular intervals, and metformin is prescribed in a CKD-adapted dose, it is unlikely to measurably increase the risk of LA in patients with moderate CKD (i.e., eGFR 30–60 ml/min per 1.73 m^2).
- Recent studies support the use of metformin at adapted doses in CKD 3A: 1500 mg/d, CKD 3B: 1000 mg/d, and CKD 4: 500 mg/d.[26]
- The use of metformin in renal failure patients is increasingly acceptable but never without risk: congestive heart failure, sepsis, acute renal failure, acute-onset chronic renal failure, liver insufficiency, pulmonary infectious diseases, dehydration, decreased plasma volume, for example, dramatically change the pharmacokinetics of the drug.
- Stop before or at the time of intravenous or intraarterial iodinated contrast procedures. Control eGFR after procedures.
- Frequent monitoring of the renal function (eGFR) in CKD patients using metformin is mandatory.
- Lactate should be measured in fragile patients (CKD 3 or 4) particularly in the context of intercurrent disease. A value of $\geq$3 mmol/l of lactate means that metformin must be withdrawn and restarted after lactate value has decreased to $<$2.5 mmol/l.
- CKD 5 remains a contraindication because of instability of the clinical situation and increased risk of drug accumulation.
- Renoprotection of metformin in different experimental models and information in the context of clinical studies warrants randomized controlled trials investigating the renoprotection of metformin in CKD.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LA, lactic acidosis.

In line with these preclinical observations, observational clinical studies also support a renoprotective role of metformin.[20] Compared with sulfonylureas, metformin has been associated with a lower risk of kidney function decline or death, independent of changes in body mass index, systolic blood pressure, and glycated hemoglobin.[21] Furthermore, a meta-analysis of 17 observational studies concluded that metformin use is associated with reduced all-cause mortality in CKD patients.[22] Similar observations have been reported in incident kidney transplant recipients.[23] Particularly, the retrospective analysis of the Scientific Registry of Transplant Recipients in the United States showed that metformin is associated with lower adjusted hazards for living and deceased donor allograft survival at 3 years post-transplantation and with lower mortality.[23]

In a very recent study, Charytan *et al.*[24] found that metformin may be safer for use than previously considered and may lower the risk of death and cardiovascular events in individuals with diabetes and stage CKD 3.

Clinical trials repurposing generic therapeutics such as metformin, which have shown their potential of attenuation CKD progression (in both animals and clinical observations) through mechanisms related to decreasing the oxidative stress and antifibrotic effect should be prioritized where there is sufficient scientific evidence and limited, controllable side effects.[25]

We have currently reached that point concerning the use of metformin as a renoprotective agent in CKD patients (Table 1).[26] Some interesting randomized controlled trials (Renomet Eudrac Clinial Trial number 2019-000134-18, "Renoprotection of metformin in non-diabetic CKD patients"; Clinical Trials number NCT TO 3831464, "To treat autosomal dominant polycystic kidney disease") have begun, and ideally we will read their promising results within a few years.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Friesecke S, Abel P, Roser M, et al. Outcome of severe lactic acidosis associated with metformin accumulation. *Crit Care*. 2010;14:R226.
2. Bell S, Farran B, McGurnaghan S, et al. Risk of kidney injury and survival in patients treated with metformin. *BMC Nephrol*. 2017;18:163–171.
3. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010;4:CD002967.
4. Bodmer M, Meier C, Krähenbühl S, et al. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care*. 2008;31:2086–2091.
5. Lazarus B, Whu A, Shin JI, et al. Association of metformin use with lactic acidosis across the range of kidney function. *JAMA Intern Med*. 2018;178:903–910.
6. Ekström N, Schiöler L, Svensson AM, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of

renal function: a cohort study from the Swedish National Diabetes Register. *BMJ Open*. 2012;2:e001076.
7. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care*. 2014;37:2218–2224.
8. Inzucchi SE, Lipska KJ, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA*. 2014;312:2668–2675.
9. Hung SC, Chang YK, Liu JS, et al. Metformin use and mortality in patients with advanced chronic kidney disease: national, retrospective, observational, cohort study. *Lancet Diabetes Endocrinol*. 2015;3:605–614.
10. Kwon S, Kim YC1, Park JY, et al. The long-term effects of metformin on patients with type 2 diabetic kidney disease. *Diabetes Care*. 2020;43:948–955.
11. Lin CX, Li Y, Liang S, Liang S, Tao J, et al. Metformin attenuates cyclosporine A-induced renal fibrosis in rats. *Transplantation*. 2019;103:e285–e296.
12. Satriano J, Sharma K, Blantz RC, et al. Induction of AMPK activity corrects early pathophysiological alterations in the subtotal nephrectomy model of chronic kidney disease. *Am J Physiol Renal Physiol*. 2013;305:F727–F733.
13. Hardie DG. AMPK: positive and negative regulation, and its role in whole-body energy homeostasis. *Curr Opin Cell Biol*. 2015;33:1–7.
14. Rajani R, Pastor-Soler NM, Hallows KR. Role of AMP-activated protein kinase in kidney tubular transport, metabolism, and disease. *Curr Opin Nephrol Hypertens*. 2017;26:375–383.
15. Lee M, Katerelos M, Gleich K, et al. Phosphorylation of acetyl-CoA carboxylase by AMPK enhances anaerobic metabolism reduces renal fibrosis and is essential for the anti-fibrotic effect of metformin. *J Am Soc Nephrol*. 2018;29:2326–2336.
16. Neven E, Vervaet B, Brand K, et al. Metformin prevents the development of severe chronic kidney disease and its associated mineral and bone disorder. *Kidney Int*. 2018;94:102–113.
17. Cao X, Li H, Tao H, et al. Metformin inhibits vascular calcification in female rat aortic smooth muscle cells via the AMPK-eNOS-NO pathway. *Endocrinology*. 2013;154:3680–3689.
18. Komaba H. Energy sensor as a new regulator of FGF23 synthesis. *Kidney Int*. 2018;94:453–455.
19. Glosse P, Feger M, Mutig K, et al. AMP-activated kinase is a regulator of fibroblast growth factor 23 production. *Kidney Int*. 2018;94:491–501.
20. Lalau JD, Arnouts P, Sharif A, et al. Metformin and other antidiabetic agents in renal failure patients. *Kidney Int*. 2015;87:308–322.
21. Hung AM, Roumie CL, Greevy RA, et al. Kidney function decline in metformin versus sulfonylurea initiators: assessment of time-dependent contribution of weight, blood pressure, and glycemic control. *Pharmacoepidemiol Drug Saf*. 2013;22:623–631.
22. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in enhances anaerobic metabolism populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. *Ann Intern Med*. 2017;166:191–200.
23. Stephen J, Anderson-Haag TL, Gustafson S, et al. Metformin use in kidney transplant recipients in the United States: an observational study. *Am J Nephrol*. 2014;40:546–553.
24. Charytan DM, Solomon SD, Ivanovich P, et al. Metformin use and cardiovascular events in patients with type 2 diabetes and chronic kidney disease. *Diab Obes Metab*. 2019;21:1199–1206.
25. Levin A, Tonelli M, Bonventre J, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet*. 2017;390:1888–1937.
26. Lalau JD, Farshad K, Youssef B, et al. Rationale for the prescription of metformin in patients with CKD 3A, 3B, and 4. *Diabetes Care*. 2018;41:547–555.

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counterpoint

Metformin in chronic kidney disease: a strong dose of caution

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Metformin is a biguanide anti-hyperglycemic that inhibits hepatic gluconeogenesis, decreases enterocyte intake of glucose, and attunes cells for peripheral glucose uptake.[1] It has become a nearly universally used first-line agent in the treatment of diabetes mellitus and impaired glucose tolerance.[2] Metformin is a historic treatment for diabetes mellitus, with lilac goat's rue used in French herbal therapy in the Middle Ages.[1] The active ingredients, guanidino compounds, were identified and chemically isolated in the 1920s.[1] These compounds do have a potentially hazardous side because they are also uremic toxins, which can result in hypoglycemia as their concentrations rise in acute kidney injury and chronic kidney disease (CKD). It is in the context of this background that we discuss a derivative of these compounds, metformin, which was officially approved by the US Food and Drug Administration in 1995.

The benefits of metformin in improving insulin sensitivity, promoting weight loss, and improving hepatic steatosis have been useful, and millions of patients have been exposed to this agent worldwide. Cardiovascular benefits have been reported,[2] although these positive findings are not unique to biguanides and are increasingly being duplicated and surpassed in studies of patients receiving sodium glucose cotransporter (SGLT2) inhibitors.[3] The trade-off has been the development of life-threatening metformin-associated lactic acidosis (MALA) in patients with impaired estimated glomerular filtration rate (eGFR),