



## CKJ REVIEW

# Changes in metformin use in chronic kidney disease

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## Abstract

Metformin is one of the oldest and most widely prescribed antidiabetic medicines worldwide. It is the only such medicine that has shown a reduction of cardiovascular mortality in diabetes mellitus type 2. Since many diabetic patients have chronic kidney disease, its use is often curtailed by practitioners due to fear of lactic acidosis and the US Food and Drug Administration (FDA) warnings that, until recently, had been in place for decades. Current guidelines, though somewhat vague regarding dosages, clearly pave the way for spreading the use of metformin in patients with lower glomerular filtration rates. These guidelines also suggest moving away from just looking at serum creatinine to create a cut-off. Metformin's costs are lower, and in many underdeveloped countries this is the only medicine available for poor patients. More widespread use of metformin will further help with health care costs, as well as obesity. It will simplify the use of diabetes mellitus type 2 management with lower incidences of hypoglycemia. With all the mounting evidence, the FDA is finally requiring labeling changes regarding recommendations, to allow the use of metformin in patients with much reduced kidney function.

**Key words:** chronic renal insufficiency, diabetes mellitus, lactic acidosis, metformin

## Background

Glucose-lowering biguanides were discovered in the 1920s. One of these was metformin (dimethylbiguanide), but it was then forgotten [1]. The first human trial on biguanides that used the name Glucophage (glucose eater) was published in 1957 [2]. In the next couple of years reports were published on phenformin [3] and buformin [4]. However, due to their association with lactic acidosis (LA), both phenformin and buformin were withdrawn from many countries. Similar concerns were raised for metformin, but it remained on the market and has been available in the UK since 1958, although it only became available in the USA in 1994.

## Clinical benefits in diabetes mellitus type 2

Metformin acts primarily in the liver by reducing glucose output and also by enhancing peripheral uptake of glucose, mainly in muscles. It is not generally associated with a risk of

hypoglycemia unless there is excessive exercise, severe calorie reduction or when mixed with other antidiabetic medicine. There is absence of weight gain along with modest reductions in triglycerides [5]. It causes a reduction in mortality by decreasing cardiovascular complications [6].

Metformin has shown some effectiveness in polycystic ovarian syndrome, some gynecological cancers, nonalcoholic fatty liver disease and for premature puberty. However, its main role remains in the management of diabetes mellitus type 2 (DM2). The International Diabetes Federation lists it as one of the first antidiabetic medicines to be used for DM2 [7]. The World Health Organization lists it as one of two essential medicines for diabetes [8].

## Fear of LA

Metformin is chemically similar to phenformin, but has a different mechanism of action. Although the fear of LA remains, no

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absolute definitive causal relationship has been proven beyond doubt. Many reported cases of metformin-associated LA (MALA) did not measure metformin levels, whereas in others levels were not high, suggesting 'metformin coincident lactic acidosis' [9]. In 1998, Misbin *et al.* reported that after starting to use metformin, rates of LA in the USA were no different from prior to the approval of metformin [10]. Many reported cases of LA had multiple risk factors besides renal failure. Since DM2 is a risk factor, it is thought that many such cases may have been just from DM2. The putative risk factors for LA described in the literature include old age, decreased cardiac output, respiratory failure or hypoxic conditions, ethanol intoxication, fasting and decreased hepatic function.

In a nested case-control analysis that included 50 048 patients, six patients were identified with active use of metformin and LA. Out of those, five patients had sepsis and signs of end-organ damage, suggesting that LA most frequently occurs in acutely worsening clinical scenarios [11].

### Use of metformin in the presence of contraindications

There are many reports in the literature about continued use of metformin in the presence of contraindications. In a report of 47 patients who developed LA while on metformin, 43 had one or more risk factors including congestive heart failure (CHF) and renal insufficiency [10]. A Medline search for English language articles regarding metformin and CHF, published between January 1966 and May 2008, showed no new cases of LA [12]. In 2006, the US Food and Drug Administration (FDA) removed CHF as a contraindication for metformin use. A reduction in all-cause mortality with metformin use was even shown in diabetics with CHF [13]. In another study, there was no report of LA among 308 diabetic patients, even though 73% of patients had contraindications or risk factors [14].

Salpeter *et al.* conducted a Cochrane review in 2010. Three hundred and forty-seven prospective trials and cohort studies were included with more than 70 490 patient-years of metformin use. At least one contraindication was present in 97% of the studies. The conclusion was that metformin was not associated with increased risk of LA compared with other antidiabetic medicines. Instead, comorbidities causing tissue hypoxia were the main risks for LA [15].

### Rates and incidence of LA

Compared with a baseline rate of 9.7 per 100 000 patient-years when no biguanides were available in the USA, LA rates were about 40–129 per 100 000 patient-years once phenformin was available [16–18]. However, metformin's package insert reports a rate of 3 per 100 000 patient-years [19]. The 2010 Cochrane review found that based on statistical inference, the incidence of LA was 4.3 per 100 000 patient-years, as compared with 5.4 cases per 100 000 patient-years in the non-metformin group [15].

### Metformin in chronic kidney disease

Abnormal kidney function remains the biggest contraindication for metformin. Until early 2016, US FDA guidelines contradicted its use with a serum creatinine (Cr) >132.63  $\mu\text{mol/L}$  (1.5 mg/dL) in men and >123.79  $\mu\text{mol/L}$  (1.4 mg/dL) in women. It is well known that serum Cr measurements are not an accurate reflection of the glomerular filtration rates (GFRs) [20]. Lalau *et al.*

compared a group of patients receiving 850 mg metformin daily with creatinine clearance (CrCl) of 30–60 mL/min with another group that received 1700 mg of metformin daily with CrCl >60 mL/min. There was no significant difference in serum levels of metformin and lactate between the two groups [21]. In a study of 24 patients with CrCl 15–49 mL/min, no correlation was found between lactate and metformin levels. Two of their patients were even on dialysis [22]. In another study, 393 patients with serum Cr ranging from 132.63  $\mu\text{mol/L}$  (1.5 mg/dL) to 221.05  $\mu\text{mol/L}$  (2.5 mg/dL) were divided into those who continued metformin and those who did not. After a follow-up of 4 years, no cases of LA were found in either group [23].

At the usual dosages, the steady-state plasma concentrations of metformin are generally <7.8  $\mu\text{mol/L}$ . The precise level of serum metformin that is unsafe is not known. A study by Frid *et al.* showed that even at lower GFR levels, metformin levels rarely exceed 20  $\mu\text{mol/L}$ . It seems that this may be the safe level [24]. However, it is not yet fully known if measurement of metformin levels predicts LA. Also, no correlation between renal function, metformin levels and LA has been shown.

Individual Cr levels were not available in the last Cochrane analysis. However, 45% of the studies did not exclude patients with Cr >132.63  $\mu\text{mol/L}$  (1.5 mg/dL). This equated to 37 360 patient-years of metformin use in chronic kidney disease (CKD) patients that did not lead to any LA [15].

A large observational study of >19 000 subjects with a history of atherothrombotic disease was conducted by investigators in the Reduction of Atherothrombosis for Continued Health (REACH) study. In this study, 1572 patients were on metformin, despite GFRs 30–60 mL/min/m<sup>2</sup>. After adjustment for baseline factors and propensity score, metformin was associated with a significant reduction in 2-year mortality, including in those with CKD. Mortality reduction was 36% in moderate renal impairment (CrCl 30–59 mL/min/1.73 m<sup>2</sup>) [25].

A cohort study from the Swedish National Diabetes Register reviewed 51 675 patients with DM2. Mean follow-up was 3.9 years. Compared with any other treatment, metformin showed a 13% reduction in all-cause mortality in those with a GFR 45–60 mL/min/1.73 m<sup>2</sup>. Although similar benefits were not observed with a lower GFR of 30–45 mL/min/m<sup>2</sup>, neither was any increased risk of acidosis noted [26].

Since April 2016, the FDA is finally requiring labeling changes for metformin. It is recommending measuring GFR instead of serum Cr, before starting metformin. In established patients it allows for the use of metformin up to a GFR of 30 mL/min/1.73 m<sup>2</sup>, but recommends not starting metformin in patients with a GFR between 30–45 mL/min/m<sup>2</sup>.

### Current guidelines

Evidence of safety is mounting regarding the use of metformin with a GFR as low as 30 mL/min/1.73 m<sup>2</sup>. Hence, many nations have already adopted this as a recommendation. In Australia, National Evidence Based Guidelines for blood glucose control in DM2 have suggested that metformin, although contraindicated if GFR is <30 mL/min/1.73 m<sup>2</sup>, can still be used with caution in those with a GFR of 30–45 mL/min/1.73 m<sup>2</sup> [27]. Canadians have a similar guideline with a reduced dosage recommended at a GFR of 30–59 mL/min/m<sup>2</sup> [28]. The joint position statement of the American Diabetes Association and European Association for the Study of Diabetes agrees that it is reasonable to use metformin down to a GFR of 30 mL/min/1.73 m<sup>2</sup>, with further dose reduction at a GFR of 45 mL/min/1.73 m<sup>2</sup> [29]. However, frequent checking of GFR is always recommended in such cases, while it

should be stopped in cases of worsening clinical condition, dehydration and hypoxemia [30]. A maximal daily dose of 2000 mg and 1000 mg with a GFR 45–60 mL/min/1.73 m<sup>2</sup> and 30–45 mL/min/1.73 m<sup>2</sup>, respectively, was proposed by Inzucchi et al., with the warning to avoid metformin completely if kidney function is expected to become unstable [31].

The European Medicines Agency and the advisory board of European Renal Best Practice have also concluded that metformin can be used with a GFR as low as 30 mL/min/1.73 m<sup>2</sup>. The dose should be adapted depending on the renal function, but there are no specific dosing recommendations [32, 33]. KDIGO recommends that metformin's use should be reviewed in those with a GFR 30–44 mL/min/1.73 m<sup>2</sup> [34].

However, even the cut-off of 30 mL/min/1.73 m<sup>2</sup> GFR is arbitrary and Mani has reported its use in more than 1000 poor patients in India with CKD Stages 3 and 4 with no cases of LA [35].

## Conclusion

Use of metformin in DM2 makes management of blood sugars somewhat simpler as it has been shown that the incidence of hypoglycemia from oral hypoglycemics like glibenclamide was significantly greater than that of LA [36]. Metformin is rarely the sole cause of LA and even the prognosis seems better in LA occurring in the presence of metformin [37]. Even the overall mortality rate for MALA was down to 25% in a recent review by Kajbaf and Lalau as compared with around 50% during the period 1966–2000 [38]. After the widespread adoption of various formulas for the measurement of estimated GFR, the nephrology community has come to regard the use of serum Cr in isolation as irrelevant for the assessment of renal function. A simplified and pragmatic set of guidelines will facilitate the more widespread use of metformin [39]. The latest recommendations from the FDA will further help promote the use of metformin [40].

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## Conflict of interest statement

None declared.

## References

1. Werner E, Bell J. The preparation of methylguanidine, and of  $\beta\beta$ -dimethylguanidine by the interaction of dicyanodiamide, and methylammonium and dimethylammonium chlorides respectively. *J Chem Soc Trans* 1921; 121: 1790–1795
2. Sterne J. Du nouveau dans les antidiabetiques. La NN dimethylamine guanyl guanide (N.N.D.G.). *Maroc Med* 1957; 36: 1295–1296
3. Ungar G, Freedman L, Shapiro SL. Pharmacological studies of a new oral hypoglycaemic drug. *Proc Soc Exp Biol Med* 1957; 100: 190–192
4. Mehnert H, Seitz W. Weitere Ergebnisse der diabetesbehandlung mit blutzuckersenkenden biguaniden. *Munch Med Wschr* 1958; 100: 1849–1851
5. Campbell IW, Howlett HCS. Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. *Diabetes Metab Rev* 1995; 11: S57–S62

6. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352: 854–865
7. International Diabetes Federation. Clinical Guidelines Task Force. *Global Guideline for Type 2 Diabetes*. 2012. <http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf> (18 December 2015, date last accessed)
8. World Health Organization. [http://www.who.int/medicines/publications/essentialmedicines/18th\\_EML.pdf](http://www.who.int/medicines/publications/essentialmedicines/18th_EML.pdf) (18 December 2015, date last accessed)
9. Terpening C. MALAdaptive: Do we avoid metformin unnecessarily? *J Am Board Fam Med* 2014; 27: 136–141
10. Misbin RI, Green L, Stadel BV et al. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998; 338: 265–266
11. Bodmer M, Meier C, Krähenbühl S et al. Metformin, sulfonylureas, or other antidiabetics drugs and the risk of lactic acidosis or hypoglycemia. *Diabetes Care* 2008; 31: 2086–2091
12. Swift TMM. Metformin use in patients with diabetes and heart failure: cause for concern? *Diabetes Spectr* 2009; 22: 18–20
13. Taharani AA, Varughese GI, Scarpello JH et al. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? *BMJ* 2007; 335: 508–512
14. Holstein A, Nahrwold D, Hinz S et al. Contra-indications to metformin therapy are largely disregarded. *Diabetic Med* 1999; 16: 692–696
15. Salpeter SR, Greyber E, Pasternak GA et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus (Review). *Cochrane Database Syst Rev* 2010; 1: CD002967. DOI: 10.1002/14651858.CD002967.pub4.
16. Heaf JG, Biesen EV. Metformin and chronic renal impairment: A story of choices and ugly ducklings. *Clin Diabetes* 2011; 29: 97–101
17. Aguilar C, Reza A, Garcia JE et al. Biguanide related lactic acidosis: incidence and risk factors. *Arch Med Res* 1992; 23: 19–24
18. Stang MR, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. *Diabetes Care* 1999; 22: 925–927
19. *Metformin Package Insert*. Princeton, NJ: Bristol-Myers Squibb, 2008
20. National Kidney Foundation. KDOQI Clinical practice guidelines for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012; 60: 850–886
21. Lalau JD, Vermersh A, Hary L et al. Type 2 diabetes in the elderly: an assessment of metformin (metformin in the elderly). *Int J Clin Pharmacol Ther Toxicol* 1990; 28: 329–332
22. Duong JK, Roberts DM, Furlong TJ et al. Metformin therapy in patients with chronic kidney disease. *Diabetes Obes Metab* 2012; 14: 963–965
23. Rachmani R, Slavachevski I, Levi Z et al. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. *Eur J Intern Med* 2002; 13: 428–433
24. Frid A, Sterner GN, Löndahl M et al. Novel assay of Metformin levels in patients with type 2 diabetes and varying levels of renal function: clinical recommendations. *Diabetes Care* 2010; 33: 1291–1393
25. Roussel R, Travert F, Pasquet B et al. Reduction of atherosclerosis for continued health (REACH) registry investigators. Metformin use and mortality among patients with diabetes and atherothrombosis. *Arch Intern Med* 2010; 170: 1892–1899
26. Ekström N, Schiöler L, Svensson A-M et al. Effectiveness and safety of metformin in 51675 patients with type 2 diabetes

- and different levels of renal function: a cohort study from Swedish National Diabetes Register. *BMJ Open* 2012; 2: e001076
27. Colagiuri S, Dickinson S, Girgis S et al. *National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes*. Canberra: Diabetes Australia and the NHMRC, 2009. [http://www.nhmrc.gov.au/\\_files\\_nhmrc/publications/attachments/di19-diabetes-blood-glucose-control.pdf](http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/di19-diabetes-blood-glucose-control.pdf) (18 December 2015, date last accessed)
  28. Canadian Diabetic Association. *Clinical Practice Guideline*. 2013 [http://guidelines.diabetes.ca/App\\_Themes/CDACPG/resources/cpg\\_2013\\_full\\_en.pdf](http://guidelines.diabetes.ca/App_Themes/CDACPG/resources/cpg_2013_full_en.pdf) (18 December 2015, date last accessed)
  29. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35: 1364–1379
  30. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care* 2011; 34: 1431–1437
  31. Inzucchi SE, Lipska KJ, Mayo H et al. Metformin in patients with type 2 diabetes and kidney disease. A systemic review. *JAMA* 2014; 312: 2668–2675
  32. European Medicines Agency, London, UK. *Use of Metformin to Treat Diabetes Now Expanded to Patients with Moderately Reduced Kidney Function*. 2016 EMA/603690/2016. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Referrals\\_docu](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_docu)ment/Metformin\_31/WC500214235.pdf (5 December 2016, date last accessed)
  33. Clinical practice guidelines on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR  $\leq$  45ml/min). *Nephrol Dial Transplant* 2015; 30: ii1–ii142.
  34. Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group. KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; 3: 1–150.
  35. Mani MK. Metformin in renal failure: weigh the evidence. *Nephrol Dial Transplant* 2009; 24: 2287–2288
  36. Campbell IW. Metformin and glibenclamide: comparative risks. *BMJ* 1984; 289: 89
  37. Lalau JD, Arnouts P, Sharif A et al. Metformin and other anti-diabetic agents in renal failure patients. *Kidney Int* 2015; 87: 308–322
  38. Kajbaf F, Lalau D. Mortality rate in so-called ‘metformin-associated lactic acidosis’: a review of the data since the 1960s. *Pharmacoepidemiol Drug Saf* 2014; 23: 1123–1127
  39. Imam TH. Metformin and kidneys-A contentious relationship. *Austin J Nephrol Hypertens* 2014; 1: 1012
  40. US Food and Drug Administration, Silver Spring, MD. *FDA Drug Safety Communication: FDA Revises Warnings Regarding Use of the Diabetes Medicine Metformin in Certain Patients with Reduced Kidney Function*. 2016 <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf> (5 December 2016, date last accessed)