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Complex interplay between metformin, AKI and lactic acidosis

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Abstract

Debate exists regarding the safety of metformin and the risk of metformin-associated lactic acidosis, particularly in the setting of kidney dysfunction. Data from two studies examining the interplay between metformin, acute kidney injury, and complications including lactic acidosis suggest that metformin should be used conservatively in patients with kidney dysfunction.

Biguanides are longstanding pharmacotherapeutics agents against diabetes mellitus. In early medieval times, *Galega officinalis* (also known as French lilac or goat's-rue) was used as a remedy for diabetes mellitus, and in the 1920s guanidino compounds were identified in French lilac extracts[1]. Oral biguanide agents became available for the treatment of diabetes mellitus in the 1950s, and metformin was approved as an antidiabetic drug by the FDA in 1995. Since then, metformin has had demonstrated efficacy in improving multiple metabolic end points, including insulin sensitivity, the metabolism of free fatty acids, dyslipidaemia, excess body fat and weight, and cardiovascular health. In a corollary study of the UK Prospective Diabetes Study, in which 1,704 overweight patients with diabetes mellitus were randomly assigned to receive conventional versus intensive therapy with metformin, insulin or the antidiabetic agents chlorpropamide or glibenclamide, those given metformin had a lower risk of myocardial infarction, all diabetes end points, diabetes-related death and allcause mortality than patients in other groups[2]. Thus, the American Diabetes Association and European Association for the Study of Diabetes recommend that metformin treatment is initiated when diabetes mellitus is diagnosed, barring no contraindications[3]. However, debate remains regarding the safety of metformin in the setting of impaired kidney function due to the risk of metformin-associated lactic acidosis (MALA). Two studies now examine metformin and the complications of acute kidney injury (AKI) and lactic acidosis in two well-characterized cohorts of patients with diabetes mellitus[4,5].

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Competing interests statement

The authors declare no competing interests.

In the 1970s, phenformin and buformin (antidiabetic drugs of the biguanide class) were withdrawn from the market in most countries due to complications of life-threatening lactic acidosis[1]. Although the frequency of lactic acidosis due to metformin is comparatively lower than that of phenformin, metformin use is restricted in kidney disease given the risk of MALA. In individuals with normal kidney function, metformin is filtered from the glomerulus and secreted from the proximal tubule in a non-metabolized and non-protein bound form, but its clearance decreases by 75% when estimated glomerular filtration (eGFR) falls to 30–59 ml/min/1.73 m^2 (REF. 6). The accumulation of metformin and the associated toxicity impairs mitochondrial function and oxygen consumption and diminishes gluconeogenesis and glycogenolysis, leading to the generation of lactate and a non-hypoxic type B lactic acidosis[1]. Whereas AKI is a key precipitant of MALA in patients on stable metformin therapy, sparse epidemiologic data exists on the inter-relationships between metformin use, AKI and lactic acidosis.

To address this gap in knowledge, Connelly *et al.* conducted a case-control study of 1,746 participants with type 2 diabetes mellitus and 846 individuals without diabetes, all of whom underwent lactate measurement between 1994 and 2014 in Tayside, Scotland[5]. Using the Genetics of Diabetes Audit and Research Tayside (GoDARTs) cohort, cases of lactic acidosis were defined as those with lactate >5 mmol/l and serum bicarbonate <18 mmol/l; controls were defined as those in the remaining source population with normal lactate levels; metformin users were defined as individuals who recieved a metformin prescription within 3 months prior to lactate measurement. Using mixed effects logistic regression models, the investigators observed a 2.3-fold higher risk of lactic acidosis among metformin users versus non-users. The presence of AKI (as judged using serum creatinine criteria from the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines) modified the metformin–lactic acidosis relationship; the association between these parameters increased with increased AKI severity. In the overall cohort, lactate concentrations were 0.34 mmol/l higher in metformin users versus non-users; a greater increase in lactate concentration was observed with increasing severity of AKI.

Bell *et al.* examined the interaction between metformin, AKI, and adverse outcomes in another cohort based in Tayside, Scotland[4]. By linking Health Informatics Centre electronic health record data from a population of ~400,000 residents in Tayside to the Scottish Care Initiative-Diabetes Collaboration (which includes records for 99% of patients with diabetes mellitus in Scotland), and to a prescription database of all community pharmacies in Tayside, the investigators identified 25,148 patients with type 2 diabetes mellitus for whom prescription data between 2004 and 2013 was available. They examined the association between metformin and the risk of hospital-based AKI, which was defined by creatinine-based KDIGO criteria, with the aim of using AKI as a proxy of lactic acidosis. Using time-updated medication data, they did not find an association between metformin and AKI. However, patients that had ‘ever’ used metformin had a 1.3-fold higher risk of AKI than those who had ‘never’ used metformin. Yet inference from these findings is limited by the fact that AKI is not a specific proxy for lactic acidosis, and by the lack of biochemical data confirming the presence of MALA. The investigators also found that metformin use versus no treatment at admission in patients with incident AKI was associated with a greater 28-day

survival. Finally, the baseline kidney function of patients predicted hospital-based AKI because incrementally higher rates of AKI were observed with increasingly lower eGFRs.

These two reports are timely, given recent policy-level changes in metformin regulation. The US FDA has relaxed its recommendations to allow metformin use in patients with mild and moderate kidney dysfunction (eGFR 45–59 ml/min/1.73 m^2 and 30–44 ml/min/1.73 m^2, respectively)[6], and European Medicines Agency guidelines have been eased to allow metformin use in moderate kidney dysfunction (eGFR 30–59 ml/min/1.73 m^2)[4]. Although the metformin package insert advises against its use in conditions leading to AKI (including cardiovascular collapse or shock, myocardial infarction and sepsis), the FDA does not recommend with-holding metformin in this context[6]. However, the UK Renal Association and National Health Services England advocate that metformin be discontinued in AKI-predisposing illnesses[5].

Several findings from the studies discussed suggest that metformin should be more conservatively used in patients with kidney dysfunction. First, Connelly *et al.* present compelling data indicating that metformin should be discontinued in AKI-predisposing conditions given the heightened risk of MALA. Although Bell *et al.* showed that metformin use was associated with comparatively greater survival among incident AKI cases, the absence of a ‘new-user’ design may not have accounted for patients who stopped using metformin or died due to its adverse effects before study entry, biasing results towards a protective effect. Second, as Bell *et al.* demonstrated that underlying kidney dysfunction is a major predictor of AKI, metformin should be prescribed with caution to patients with chronic kidney disease (CKD). Third, although both studies add knowledge to the field, they also highlight the challenges of accurately identifying MALA by epidemiologic studies alone. For example, Connelly *et al.* observed a higher crude incidence rate of lactic acidosis as compared with other recent studies, possibly due to selection bias as non-protocolized lactate measurements were obtained from clinical data whereby metformin users may have undergone more frequent testing. Conversely, although systematic reviews suggest that MALA incidence is low, this low incidence may be due to the under-representation of high-risk populations in these studies (TABLE 1), non-sensitive and non-specific methods of outcome ascertainment (diagnostic codes) and residual confounding by non-indication. Rigorous studies, including clinical trials that examine the safety and effectiveness of metformin in CKD and/or other high-risk groups, should determine the eGFR threshold above which metformin use is safe. Meanwhile, we recommend reviewing the use of metformin in patients with eGFR 45–59 ml/min/1.73 m^2, discontinuing its use when eGFR is <45 ml/min/1.73 m^2, and discontinuing metformin in other AKI-predisposing conditions irrespective of eGFR[6].

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References

1. Kalantar-Zadeh K, Kovesdy CP. Should restrictions be relaxed for metformin use in chronic kidney disease? No, we should never again compromise safety! Diabetes Care. 2016; 39:1281–1286. [PubMed: 27330129]
2. 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). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352:854–865. [PubMed: 9742977]
3. Inzucchi SE, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015; 38:140–149. [PubMed: 25538310]
4. Bell S, et al. Risk of acute kidney injury and survival in patients treated with Metformin: an observational cohort study. BMC Nephrol. 2017; 18:163. [PubMed: 28526011]
5. Connelly, PJ., et al. Acute kidney injury, plasma lactate concentrations and lactic acidosis in metformin users: a GoDarts study. Diabetes Obes Metab. 2017. http://dx.doi.org/10.1111/dom.12978
6. Rhee CM, Kovesdy CP, Kalantar-Zadeh K. Risks of Metformin in type 2 diabetes and chronic kidney disease: lessons learned from Taiwanese data. Nephron. 2017; 135:147–153. [PubMed: 27760420]
7. Ekstrom N, 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.
8. Eppenga WL, 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. [PubMed: 24842984]
9. Richy FF, Sabido-Espin M, Guedes S, Corvino FA, Gottwald-Hostalek U. Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. Diabetes Care. 2014; 37:2291–2295. [PubMed: 24879835]
10. Hung SC, 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. [PubMed: 26094107]

Table 1

Metformin and the risk of lactic acidosis in patients with diabetes and CKD

Author (year)	Data source (country)	Study population	Findings
Ekstrom *et al.* (2012)[7]	National Diabetes Register (Sweden)	Overall cohort (n = 51,675), examined patients stratified by eGFR	• eGFR 45–59 ml/min/1.73 m^2 (n = 6,960): metformin users at decreased risk of acidosis and serious infection • eGFR <45 ml/min/1.73 m^2 (n = 2,044): metformin users trend towards an increased risk of acidosis and serious infection
Eppenga *et al.* (2014)[8]	Clinical Practice Research Datalink (UK)	• 223,968 metformin users • 34,571 patients naive to metformin	• eGFR <60 ml/min/1.73 m^2: metformin users had a 6.34-fold increase in risk of lactic acidosis • eGFR <45 ml/min/1.73 m^2: metformin users had a 6.74-fold increase in risk of lactic acidosis • Overall incidence rate low: 7 events per 29,751 person-years
Richy *et al.* (2014)[9]	Clinical Practice Research Datalink (UK)	77,601 metformin users	• Total of 35 non-fatal lactic acidosis events • Numerical trend for an increase in lactic acidosis events with eGFR <60 ml/min/1.73 m^2
Hung *et al.* (2015)[10]	Taiwan National Health Insurance Research Database	• Patients with Stage 5 CKD prescribed an erythropoietin-stimulating agent (coverage was restricted to those with creatinine levels of >530 μmol/l (>6 mg/dl)) • 813 metformin users matched to 2,439 non-users using propensity scores	Metformin users had a 35% increase in mortality risk

CKD; chronic kidney disease; eGFR, estimated glomerular filtration.