Risks of Metformin in Type 2 Diabetes and Chronic Kidney Disease: Lessons Learned from Taiwanese Data

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Key Words

Metformin · Biguanide · Lactic acidosis · Kidney dysfunction · Mortality

Abstract

Like other biguanide agents, metformin is an anti-hyperglycemic agent with lower tendency towards hypoglycemia compared to other anti-diabetic drugs. Given its favorable effects on serum lipids, obese body habitus, cardiovascular disease, and mortality, metformin is recommended as the first-line pharmacologic agent for type 2 diabetes in the absence of contraindications. However, as metformin accumulation may lead to type B non-hypoxemic lactic acidosis, especially in the setting of kidney injury, chronic kidney disease, and overdose, regulatory agencies such as the United States Food and Drug Administration (FDA) have maintained certain restrictions regarding its use in kidney dysfunction. Case series have demonstrated a high fatality rate with metformin-associated lactic acidosis (MALA), and the real-life incidence of MALA may be underestimated by observational studies and clinical trials that have excluded patients with moderate-to-advanced kidney dysfunction. A recent study of advanced diabetic kidney disease patients in Taiwan in *Lancet Endocrinology and Diabetes* has provided

unique insight into the potential consequences of unrestricted metformin use, including a 35% higher adjusted mortality risk that was dose-dependent. This timely study, as well as historical data documenting the toxicities of other biguanides, phenformin and buformin, suggest that the recent relaxation of FDA recommendations to expand metformin use in patients with kidney dysfunction (i.e., those with estimated glomerular filtration rates ≥ 30 instead of our recommended ≥ 45 ml/min/1.73 m²) may be too liberal. In this article, we will review the history of metformin use; its pharmacology, mechanism of action, and potential toxicities; and policy-level changes in its use over time.

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Introduction

Drug regulatory agencies play a key role in protecting and promoting public health through the rigorous regulation and supervision of various medications. Indeed, in 2010, the United States (US) Food and Drug Administration (FDA) honored Dr. Frances Oldham Kelsey by establishing the 'FDA Kelsey Award in Drug Safety Excellence [1]'. Upon announcing this annual award, the FDA leadership recognized the outstanding accomplishments

of pioneers in the field of drug regulation and safety, and summarized the historical implications of their contributions. Dr. Kelsey in fact received the first Kelsey Award for her perseverance against pressures from the medical community and industry to authorize the use of thalidomide in the United States in the early 1960s. While the drug had long been approved and was commonly prescribed in pregnant women across Canada and European countries, Dr. Kelsey refused to approve thalidomide use in the United States until rigorously reviewing additional safety data. During the few years that the drug was available on the world market, with the exception of the United States, thousands of children were born with thalidomide-related deformities. However, due to the work of Dr. Kelsey, the scale of such sequelae in the United States was extremely small by comparison [2]. Although the story of the oral anti-diabetic drug, metformin, may appear to be distinct from that of thalidomide, there are certain historical analogies that deserve focused attention. In this article, we review (1) the history of metformin use, (2) its pharmacology, mechanism of action, and potential toxicities, and (3) worldwide policy-level changes in its use over time, with a specific emphasis on (4) historical data from Taiwan that have added new insights into the consequences that may be observed with unrestricted use in moderate-to-advanced chronic kidney disease (CKD).

History of Biguanide Use

Metformin is a type of biguanide, a class of oral anti-hyperglycemic drugs that have been utilized in the treatment of diabetes mellitus for many years. In medieval times, *Galega officinalis*, also known as French lilac or goat's rue, was used for the treatment of diabetes [3–5]. In the 1920s, it was discovered that the active ingredient in French lilac extracts, which lowered blood glucose levels was guanidine (compound formula: $\text{HNC}(\text{NH}_2)_2$). By the 1950s and 1960s, 3 biguanide compounds became available for clinical use, namely, phenformin, buformin, and metformin. However, in 1976, phenformin was withdrawn from the US market and other countries due to high rates of fatal lactic acidosis. While buformin was never available in the United States, it was also removed from many industrialized nations due to lactic acidosis. In 1995, metformin use was approved by the FDA with the stipulation that (1) it would be contraindicated in kidney disease or kidney dysfunction, defined by a creatinine of ≥ 1.5 and ≥ 1.4 mg/dl in men and women, respectively, or an abnormal creatinine clearance, and (2) it should not

be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates normal kidney function [6, 7]. Notably, the aforementioned cutoff for kidney dysfunction was based upon conservative estimates of the threshold at which 3 g of metformin is removed at steady state levels in 24–48 h [8].

Pharmacology and Mechanism of Action

Metformin is rapidly absorbed from the small intestine, with peak plasma concentrations achieved after 2 h of ingestion [9]. It is filtered from the glomerulus and secreted from the proximal tubule in non-metabolized and non-protein bound form [10]. In normal kidney function, the clearance rate of metformin is 505 ± 129 ml/min (half-life 5–7 h) [9]. However, among patients with estimated glomerular filtration rates (eGFRs) of $30\text{--}<60$ ml/min/ 1.73 m^2 , known as stage 3 CKD, clearance rates are reduced by 75% [11].

As an anti-hyperglycemic agent, metformin promotes euglycemia (reduces fasting glucose concentrations and hemoglobin A1c levels by 20 mg/dl and 1.5%, respectively, on average [12–16]) and is less likely to cause hypoglycemia when used as monotherapy [17]. Metformin reduces glucose levels via several mechanisms, including (1) inhibition of hepatic gluconeogenesis, (2) augmentation of insulin sensitivity, (3) increased insulin-mediated uptake of glucose in peripheral tissues such as muscle and liver, and (4) reduction of free fatty acids as a substrate for gluconeogenesis [18, 19]. Metformin also favorably impacts dyslipidemia (reduces low-density lipoprotein and triglyceride levels and modestly increases high-density lipoprotein levels) [13, 14, 16], and promotes modest weight reduction and/or stabilization in obese patients [12, 20].

In the general population, metformin has also been shown to reduce cardiovascular morbidity and mortality. One of the early studies demonstrating cardiovascular benefit was the United Kingdom Prospective Diabetes (UKPDS) 34 trial, conducted among 1,704 overweight patients with incident type 2 diabetes [21], many of whom were in the UKPDS 33 trial [22], and which notably excluded patients with serum creatinine levels of >2 mg/dl (>175 $\mu\text{mol/l}$). In the UKPDS 34 study, patients were randomized to conventional therapy with diet vs. intensive glycemic control with metformin, insulin, chlorpropamide, or glibenclamide, which showed that, compared to the conventional arm, those in the intensive arm who received metformin had 32, 42, 36, and 39% lower risk of any diabetes-related endpoint, diabetes-related death, all-cause mortality,

Table 1. Adverse effects related to use of metformin

Adverse effect	Frequency	Comments
Lactic acidosis	Rare	<ul style="list-style-type: none"> – Typically in the context of AKI, CKD, and/or metformin overdose – High fatality rate in case series
Hypoglycemia	Rare to moderate	More common with kidney dysfunction
Pancreatitis	Rare	May be concurrent with lactic acidosis
Mortality (independent of lactic acidosis)	Rare, but more common in kidney dysfunction	Recent Taiwanese historical study suggests 35% higher death risk in patients with stage 5 CKD (creatinine >6.0 mg/dl)
Cardiovascular toxicity	Rare to moderate	<ul style="list-style-type: none"> – Guanidino compounds are known uremic toxins causing cardiovascular disease – Chest discomfort, flushing, and palpitations in up to 10% of patients – Worsening heart failure may be related to lactic acidosis or via independent mechanisms
Hormonal derangements	Rare	Studies in fish show intersex fish and other anomalies
Gastrointestinal	Common	Symptoms are usually mild, transient, and reversible after dose reduction or discontinuation of the drug: <ul style="list-style-type: none"> – Metallic taste, anorexia, soft stools/diarrhea, nausea, vomiting, flatulence
Vitamin B12 deficiency	Rare	<ul style="list-style-type: none"> – Metformin reduces intestinal absorption of vitamin B12 in up to 30% of patients and lowers serum B12 level in 5–10% of patients – Rarely causes megaloblastic anemia
Neurologic	Rare to moderate	Headache (6%), chills, dizziness, lightheadedness, myalgia, weakness, altered mental status

Adapted from Kalantar-Zadeh and Kovesdy [5].

and myocardial infarction, respectively [21]. In a secondary analysis, patients assigned to intensive glycemic control with metformin vs. other anti-diabetic drugs were found to have lower risk of any diabetes-related clinical endpoint, all-cause mortality, and stroke. Such data have augmented support for metformin as the preferred initial pharmacotherapy agent for type 2 diabetes in the absence of contraindications by various societal groups including the American Diabetes Association and European Association for the Study of Diabetes (grade A evidence) [23].

Metformin Toxicity

Metformin may contribute to various adverse effects (table 1), the most common of which are gastrointestinal in etiology, affecting up to 30% of patients [5, 14]. However, the major toxicity of metformin is metformin-associated lactic acidosis (MALA), a type of non-hypoxemic type B lactic acidosis (table 2) [24]. MALA may result from metformin accumulation in the setting of acute kid-

Table 2. Types A and B lactic acidosis

	Type A	Type B
Pathogenesis	Tissue hypoperfusion	Toxin-induced impairment of cellular metabolism Regional areas of ischemia
Etiology	Cardiogenic shock Cardiopulmonary arrest Sepsis	Diabetes Chronic alcohol intake Human immunodeficiency virus Malignancy D-Lactic acidosis Mitochondrial dysfunction Drugs Metformin Anti-retrovirals Linezolid

ney injury (AKI), CKD, and/or metformin overdose, leading to (1) impaired mitochondrial function leading to reduced gluconeogenesis and glycogenolysis and increased glycolysis, and (2) activation of anaerobic metabolism in the intestine [5, 24, 25]. If severe, MALA may

have dire consequences on multiple end-organs including the cardiovascular (decreased ventricular contractility and output, arrhythmias, hypotension), respiratory (pulmonary edema), and central nervous systems (delirium, coma) [24], with case series reporting a MALA fatality rate as high as 45–48% [26, 27].

In the general population, there have been multiple large studies that have systematically examined the risk of MALA. In a systematic review of 347 randomized controlled trials and observational studies comparing metformin vs. placebo vs. other anti-diabetic drugs in the treatment of type 2 diabetes by Salpeter et al. [28], no cases of fatal or non-fatal lactic acidosis were observed following 70,490 patient-years of follow-up in the metformin group and 55,451 patient-years of follow-up in the non-metformin group. Although exclusion of participants with kidney dysfunction may have resulted in the low observed MALA rates, 43% of the 334 trials that were pooled did not exclude patients with kidney disease at baseline. In a study of 51,675 patients from the Swedish National Registry, a higher risk of MALA was not observed in patients with CKD [29]. Similarly, in a study of 50,048 type 2 diabetic patients from the United Kingdom General Practice Research Database, occurrence of lactic acidosis was rare (6 cases total), and did not differ between those who received metformin vs. other oral anti-diabetic agents [30].

However, 2 recent studies utilizing data from the United Kingdom General Practice Database have suggested a heightened risk of MALA among patients with kidney dysfunction. In the first of these studies, Eppenga et al. [31] compared the risk of lactic acidosis among 223,968 and 34,571 patients using metformin vs. other oral anti-diabetic agents over the period of 2004–2012. Using an outcome defined by clinical codes and elevated lactic acid levels, investigators found that metformin use was associated with a six to seven-fold higher risk of lactic acidosis compared to metformin non-use among those with eGFRs <60 ml/min/1.73 m² but not in those with eGFRs ≥60 ml/min/1.73 m². Among patients with eGFRs <45 ml/min/1.73 m², metformin users had a six to nine-fold higher risk of lactic acidosis compared to non-users. It should be noted that the overall incidence rate of lactic acidosis was low (7.4 vs. 2.2 events per 100,000 person-years of follow-up in metformin users vs. non-users, respectively) and that kidney function was not documented in 25% of patients. Using the same database, Richy et al. [32] examined 77,601 type 2 diabetic patients treated with metformin who had at least one kidney function value over the period of 2007–2012. While the overall incidence rate for lactic acidosis was low (35 events over 337,590

patient-years of follow-up), there was a trend toward a numerically higher incidence rate with worsening severity of kidney function, albeit non-significant.

Most recently, in a systematic review of 65 studies that rigorously examined the risk of MALA in CKD patients over the period of 1950–2014, Inzucchi et al. [6] concluded that (1) lactic acid levels were typically normal among patients taking metformin with eGFRs >30 ml/min/1.73 m²; (2) the incidence of MALA across studies was low (3–10 events per 100,000 person-years) and similar to the background rate in the overall diabetic population; (3) data suggesting heightened risk of MALA in CKD were limited, with no trials to date testing safety in advanced CKD; and (4) that there should thus be cautious expansion of metformin in mild-to-moderate CKD (table 3). The investigators also acknowledged that conclusions were based on small studies; there may have been underestimation of MALA risk due to confounding by indication; and that, conversely, ascertainment of MALA using lactate levels may have overestimated risk.

MALA in CKD: Lessons Learned from Taiwan Prior to the Implementation of Policy Changes

A recent study of diabetic kidney disease patients by Hung et al. [33] using historical data from Taiwan in *Lancet Endocrinology and Diabetes* provides unique insight into the potential toxicities of metformin in a setting where use of this anti-diabetic agent was previously unrestricted. Until 2009, metformin could be prescribed to all patients in Taiwan irrespective of kidney function. In this study, investigators examined 12,350 type 2 diabetic patients with stage 5 CKD from the Taiwan National Health Insurance Database who had an ICD-9 code for CKD and were prescribed an erythropoietin-stimulating agent (ESA; in whom coverage was restricted to those with creatinine levels of >6 mg/dl (>530 μmol/l) and anemia); among this source population, 1,005 of patients were metformin users and 11,345 were non-users. In rigorous analyses that matched 813 metformin users to 2,439 non-users using propensity scores, metformin users demonstrated a 35% higher mortality risk compared to non-users: adjusted hazard ratio (HR) 1.35 (95% CI 1.20–1.51). While the overall incidence of metabolic acidosis was small (1.6 events per 100 patient-years of follow-up), point estimates suggested a higher risk of metabolic acidosis in metformin users vs. non-users. However, the association between metformin use and metabolic acidosis was not statistically significant: adjusted HR 1.30

Table 3. Comparisons of recommendations for metformin use in kidney dysfunction

eGFR, ml/min/1.73 m ²	US FDA recommendations [34]	Inzucchi et al. [6] recommendations	Our recommendations [32]
45–<60	No change in use	<ul style="list-style-type: none"> – Avoid if kidney function is expected to become unstable – Consider cautious follow-up of kidney function – Maximum total daily dose: 2,000 mg 	<ul style="list-style-type: none"> – Review use – Referral to nephrologist for accurate eGFR assessment
30–<45	Review use Do not initiate	<ul style="list-style-type: none"> – Do not initiate therapy, but drug may be continued – Avoid if kidney function is expected to become unstable – Consider more cautious follow-up of kidney function – Maximum total daily dose: 1,000 mg 	<ul style="list-style-type: none"> – Withhold until further risk-benefit evaluation – Referral to nephrologist for accurate eGFR assessment
<30	Discontinue	Discontinue	<ul style="list-style-type: none"> – Discontinue – Referral to nephrologist for accurate eGFR assessment
Any illness with risk of AKI	No change in use	Discontinue	<ul style="list-style-type: none"> – Withhold until further risk-benefit evaluation – Referral to nephrologist for prevention and monitoring of AKI

(95% CI 0.88–1.93). Secondary analyses also showed that there was also a dose-dependent increase in mortality risk with incrementally higher metformin doses defined by the (1) cumulative defined daily dose (DDD), categorized as ≤ 15 , 16–40, and >40 DDD (1 DDD equivalent to 2,000 mg of metformin over a 90-day exposure period), and (2) prescribed daily dose, categorized as ≤ 500 , 501–1,000, and $>1,000$ mg/day. There were a number of strengths of this study, such as its national representativeness (85% of pre-dialysis CKD patients received prescriptions for ESA in Taiwan), extended follow-up period, and detailed patient-level data on comorbidities, medications, and laboratory results.

Emerging Data on Additional Metformin Benefits

Among type 2 diabetic patients who were newly prescribed metformin vs. other anti-diabetic drugs from the National Health Insurance reimbursement database in Taiwan, the incidence of kidney cancer among metformin users was substantially lower compared to non-users: 80 vs. 190 cases per 100,000 person-years, respectively [34]. Furthermore, metformin use was associated with 72, 40, 72, and 90% lower risk of developing kidney cancer after <14.5 , 14.5–45.8, and >45.8 months of follow-up compared to non-metformin users. These findings may have

particular relevance in diabetic kidney disease patients, given the heightened risk of kidney cancer associated with CKD [35]. Given the relatively low event rate of MALA (<10 events per 100,000 person-years) observed in the aforementioned Hung et al. [33] study, further studies are needed to determine whether the risks of metformin outweigh its potential benefits upon cancer risk and cardiovascular outcomes as shown in the UKPDS 34 study [21].

Recent Policy Changes in the United States

Across the world, clinical practice guidelines have recommended various kidney function thresholds for restriction of metformin use in CKD [36]. However, epidemiologic data show that there is suboptimal adherence to these recommendations. In a study of 83,850 US veterans age ≥ 65 with creatinine clearances of 15–49 ml/min, metformin was among the 3 medications that together accounted for 76% of renally misprescribed medications among patients with creatinine clearances of 30–49 ml/min [37]. In the systematic review by Inzucchi et al. [6], it was also shown that among patients with a renal contraindication, as many as one-third may still be prescribed metformin.

In April 2016, the FDA revised its warnings regarding the use of metformin, now supporting expanded use in

patients with kidney dysfunction, namely, those with eGFRs ≥ 30 ml/min/1.73 m² (table 3) [38]. However, given the higher likelihood of potential toxicity associated with more liberal metformin prescribing and given a high prevalence of non-adherence to clinical practice recommendations, it is our opinion that there should be continued restraint of metformin use in patients with moderate to advanced CKD. Population-based studies have suggested that there is heightened MALA-risk below various eGFR thresholds of <45 or <60 ml/min/1.73 m² [31, 32]. As the precise eGFR threshold for metformin toxicity remains uncertain, we recommend that (1) metformin use be reviewed in patients with eGFRs 45– <60 ml/min/1.73 m², (2) metformin be withheld among patients with eGFRs <45 ml/min/1.73 m² and those with any illness with risk of AKI, and that (3) diabetic kidney disease patients who receive metformin be referred to a nephrologist for accurate assessment of eGFR [36]. In addition to United Kingdom General Practitioner Database findings from Eppenga et al. [31] and Richy et al. [32] and Taiwanese data from Hung et al. [33], there are several points that dissuade us from more liberal prescription of metformin: (1) MALA has been associated with high death rates; (2) the real-life incidence of MALA is likely underestimated by observational studies and clinical trials; (3) it is likely that the low observed incidence of MALA has been influenced by the previous FDA-mandated renal restrictions of metformin; (4) CKD patients have a lower threshold for kidney function deterioration, including greater susceptibility to AKI and accelerated kidney function decline; and (5) CKD patients have multiple concomitant risk factors for MALA including AKI, sepsis, and hypoxia [5, 25–27, 36]. Prior to lifting restrictions, multiple knowledge gaps regarding the safety and tolerability of metformin in CKD should be addressed including: (1) At what eGFR threshold should metformin doses be reduced and/or restricted altogether? (2) At what dosage and blood levels is metformin toxic? (3) How frequently should eGFR be monitored while on metformin? (4) What are the short- and long-term comparative effectiveness of traditional and emerging anti-diabetic medication alternatives in comparison to metformin? [6, 33, 36, 39].

Conclusions

In the absence of renal contraindications, metformin is the first-line oral agent in the treatment of type 2 diabetes [23]. However, given data by Hung et al. [33] show-

ing a higher mortality risk with metformin use in advanced CKD that is dose-dependent, case reports describing the gravity of metformin-related adverse events, along with historical data on the toxicities of other biguanides, it may be premature to liberalize the use of metformin in patients with kidney dysfunction [5, 24, 25, 27, 33, 36]. Furthermore, since the real-life incidence rate of MALA may be underestimated, there remains poor adherence to renal prescribing guidelines, and treatment options remain limited and largely supportive. It is possible that previous restrictions have protected many patients from a heightened risk of lactic acidosis and mortality. Thus, rigorous observational studies and randomized controlled trials of metformin in mild-to-moderate CKD will be imperative in informing future evidence-based guidelines. Until then, the renal restrictions of metformin should be maintained, given the utmost priority of practicing safe and conservative medicine. The story of Frances Oldham Kelsey reinforces our ‘never again’ motto [1, 2].

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