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Reviews

Metformin-associated lactic acidosis: Current perspectives on causes and risk

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ABSTRACT

Although metformin has become a drug of choice for the treatment of type 2 diabetes mellitus, some patients may not receive it owing to the risk of lactic acidosis. Metformin, along with other drugs in the biguanide class, increases plasma lactate levels in a plasma concentration-dependent manner by inhibiting mitochondrial respiration predominantly in the liver. Elevated plasma metformin concentrations (as occur in individuals with renal impairment) and a secondary event or condition that further disrupts lactate production or clearance (e.g., cirrhosis, sepsis, or hypoperfusion), are typically necessary to cause metformin-associated lactic acidosis (MALA). As these secondary events may be unpredictable and the mortality rate for MALA approaches 50%, metformin has been contraindicated in moderate and severe renal impairment since its FDA approval in patients with normal renal function or mild renal insufficiency to minimize the potential for toxic metformin levels and MALA. However, the reported incidence of lactic acidosis in clinical practice has proved to be very low (<10 cases per 100,000 patient-years). Several groups have suggested that current renal function cutoffs for metformin are too conservative, thus depriving a substantial number of type 2 diabetes patients from the potential benefit of metformin therapy. On the other hand, the success of metformin as the first-line diabetes therapy may be a direct consequence of conservative labeling, the absence of which could have led to excess patient risk and eventual withdrawal from the market, as happened with earlier biguanide therapies. An investigational delayed-release metformin currently under development could potentially provide a treatment option for patients with renal impairment pending the results of future studies. This literature-based review provides an update on the impact of renal function and other conditions on metformin plasma levels and the risk of MALA in patients with type 2 diabetes.

1. Introduction

Metformin is the most commonly prescribed oral antihyperglycemic medication in the world and is considered first line therapy for newly diagnosed type 2 diabetes by many professional diabetes organizations [1]. With approximately 50 years of accumulated real-world global clinical experience, metformin is generally regarded as safe with the most

Abbreviations: AUC, Area under the concentration–time curve; DR, Delayed release; eGFR, Estimated glomerular filtration rate; FDA, Food and Drug Administration; GLP-1, Glucagon-like peptide 1; MALA, Metformin-associated lactic acidosis; NDA, New Drug Application; XR, Extended release.

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frequent adverse effects being gastrointestinal in nature: diarrhea, nausea, and to a lesser extent, vomiting [2–4]. In particular, metformin is less well tolerated in patients with preexisting gastrointestinal conditions [5].

Metformin is contraindicated in patients with renal or hepatic insufficiency, in very elderly patients, and in patients with conditions of circulatory dysfunction such as congestive heart failure, due to increased risk of lactic acidosis [6]. Though metformin-associated lactic acidosis (MALA) is an extremely rare condition (most estimates are ≤10 events per 100,000 patient-years of exposure), cases continue to be reported and are associated with mortality rates of 30 to 50% [6–12].

At the time of initial US approval, the safety review and risk management of the New Drug Application (NDA) for metformin (Glucophage®) focused on the fact that MALA can be precipitated by drug accumulation, most notably in patients with chronic or newly acquired renal insufficiency or failure, complicated by lactate overproduction (from hypoxic tissues in respiratory and circulatory failure) and/or impaired lactate removal (in liver damage, which inhibits gluconeogenesis). Current metformin product labeling therefore includes warnings regarding lactic acidosis [6].

2. Biguanides and Lactic Acidosis

The biguanides, metformin, phenformin, and buformin, comprise a class of glucose-lowering drugs developed in the 1950s for the treatment of type 2 diabetes, although only metformin is approved for use today in most countries. Phenformin was approved in the US and Europe in the 1950s, while metformin and buformin were only approved in Europe at that time. By the end of the 1970s, evidence of an increased risk of lactic acidosis with phenformin use led to its withdrawal in most countries [3]. Although less widely used, buformin has largely been withdrawn from the market for the same reason.

The strong association of lactic acidosis with phenformin use resulted in a reluctance on the part of pharmaceutical companies to pursue regulatory approval for metformin in the US until the Glucophage NDA submission to the Food and Drug Administration (FDA) by Lipha Pharmaceuticals culminated in approval of the drug in 1995. Glucophage was subsequently marketed by Bristol-Myers Squibb [13].

In contrast to phenformin, which exhibits a well-defined hyperlactatemic effect, therapeutic doses of metformin used according to the current label cause little (usually less than 1–2 mmol/L) to no increase in basal and postprandial blood lactate levels [3,14,15]. The incidence of lactic acidosis with metformin is estimated to be 20 times less than with phenformin [16]. Preclinical studies also indicate that increased plasma lactate concentrations and lactic acidosis are related to biguanide dose and plasma levels, with phenformin being the most potent, followed by buformin, and metformin [7,17].

3. Metformin Pharmacokinetics and Metabolism

When metformin is administered orally, approximately 40% of the dose is absorbed in the upper small intestine (duodenum and proximal jejunum) and only ~10% is absorbed in the ileum and colon. Unabsorbed drug accumulates in the mucosa of the bowel [18] and is ultimately eliminated in the feces [19]. Current metformin formulations have a bioavailability of ~50%–60%; metformin circulates in the plasma unbound and is eliminated unchanged by the kidneys [3,19]. When metformin accumulates in the plasma to concentrations > 5 mg/L, elimination may be prolonged [20].

4. Risk Factors for MALA

Owing to the multiple and often nonspecific signs and symptoms of MALA, as well as the potential impact of other conditions and medications that can predispose a patient to lactic acidosis, MALA can be difficult to predict or diagnose [21–23]. This is true especially in the absence of knowing the circulating metformin concentration in a patient presenting with symptoms [24]. However, it is known that MALA occurs when there is an imbalance between increased lactate production and impaired metabolism/reduced clearance. Metformin plasma levels >5 μg/mL are generally found when metformin is implicated as the cause of lactic acidosis [6]. Such sustained very high elevations in plasma metformin concentrations (therapeutic range <2 μg/mL [19]) usually are observed in individuals with poor renal function (i.e., reduced metformin clearance), impaired hepatic metabolism (i.e., reduced lactate clearance) [25,26], and/or in the presence of increased production (i.e., sepsis, CHF, reduced tissue perfusion, or anoxia). Although not contraindicated for metformin use in either the US or other countries, other conditions that may increase the risk of lactic acidosis include severe dehydration, shock, alcohol use, hypoxic states, sepsis, and advanced age (because of age-related decline in renal function and increased risk for acute renal failure and other catastrophic medical conditions) [6,8,27–29]. However, MALA can occur in patients with even mild renal dysfunction [30] and patient outcome seems to be correlated with severity of the underlying disease, highlighting the need for judicious use of metformin even in otherwise lower-risk patients.

MALA is more likely to occur in patients who acutely develop renal impairment from dehydration, vomiting or diarrhea, surgery, etc., especially in elderly subjects who have a reduced glomerular filtration rate [31–38]. Dehydration can cause acute renal failure and reduce metformin clearance, resulting in increased plasma metformin levels, especially if metformin administration is continued [27]. The effect of metformin on plasma lactate concentrations in bariatric surgery patients has not been examined, but these individuals may be at higher risk for MALA due to increased metformin absorption and bioavailability [39].

Metformin plasma concentrations are approximately 2–4 fold higher in patients with type 2 diabetes and moderate to severe renal impairment (i.e., eGFR of 30 to <60 mL/min/1.73 m^2 or <30 mL/min/1.73 m^2, respectively) compared to healthy subjects [6,29]. Patients with type 2 diabetes are also at greater risk for hyperlactatemia, which is attributed to alterations in the redox potential [40]. As a consequence, patients with diabetes, especially those treated with

metformin, have a reduced threshold for the development of lactic acidosis in response to a secondary event [19,25,26,41]. This scenario is consistent with individual patient case reports [42,43]. While some publications report a lack of association between plasma metformin concentrations and prognosis in MALA [44–46] and metformin levels in patients with MALA [45], these findings likely reflect the multiple different clinical conditions associated with lactic acidosis and varying degree of certainty in the timing of collection of key data such as plasma lactate and metformin concentrations proximal to the event [47].

Renal dialysis to remove metformin (and correct metabolic acidosis) has been recommended to treat MALA [34,35,48,49], arguing in favor of a relationship between elevated plasma metformin and increased plasma lactate levels. Although individuals can develop lactic acidosis for other reasons, in the case of MALA, metformin exposure appears to be the main risk factor. This is consistent with the observation in several publications [46,50,51] that patients with lactic acidosis who are taking metformin often have better outcomes than those who are not, suggesting that less severe secondary events may be sufficient to result in lactic acidosis in the presence of metformin. One possibility is that metformin limits a patient's capacity to accommodate further increases in lactate induced by such secondary intercurrent events that ultimately trigger an event of MALA.

4.1. *History of Metformin Labeling Regarding Patients with Impaired Renal Function*

The specific criteria put forth in metformin labeling (serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) to contraindicate metformin use correspond roughly to an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 [6]. A creatinine clearance of 60 mL/min/1.73 m^2 is at the threshold of meeting the National Kidney Foundation's definition of chronic kidney disease, stated as "either kidney damage or GFR < 60 mL/min/1.73 m^2 for 3 months." This level falls between Stage 2 (kidney damage with mild decreased GFR) and Stage 3 (moderate decreased GFR). The specified serum creatinine levels in the metformin label reflect a then practical but imprecise estimate of GFR because calculation of GFR from serum creatinine levels by the Cockcroft–Gault, MDRD equation and similar approaches is highly dependent on age, sex, and body weight [52]. As an illustration from the National Kidney Foundation (Frequently Asked Questions about GFR Estimates), a serum creatinine of 1.2 mg/dL in a 22-year-old Black man, a 58-year-old white man, and an 80-year-old white woman result in calculated GFRs of 98, 66, and 46 mL/min/1.73 m^2, respectively. These values correspond to renal function categories of Stage 1, 2, and 3, respectively for those individuals.

Although not documented in detail in the FDA's Summary Basis of Approval for Glucophage, the appropriateness of these criteria was the subject of considerable discussion by both internal Agency staff and outside subject matter experts. Because of the concern about potential for MALA and the dependence on renal function for drug elimination, reviewers concluded that a conservative approach was warranted for metformin use in patients with renal insufficiency. Reviewers decided that any degree of renal insufficiency as reflected by the very rough proxy of serum creatinine should be contraindicated. The commonly listed upper limits of normal serum creatinine levels for men and women were used to define the contraindication with the understanding that these creatinine levels in some patients could reflect more than borderline renal dysfunction.

The contraindication thresholds limit metformin use to patients who could be treated without having metformin plasma concentrations significantly exceed the 'typical' therapeutic range of <2 μg/mL [19] and never reach or exceed 5 μg/mL, a concentration that has been associated with MALA. The FDA also encouraged the sponsor of the Glucophage NDA to continue to evaluate the effect of renal insufficiency and age on metformin clearance [53]. This led to subsequent efforts by FDA to identify other conditions associated with increased MALA risk such as congestive heart failure [9,54]. Labeling also includes recommendations that patients temporarily discontinue metformin before receiving radiocontrast medium, which can cause acute renal failure [6,55]. Additionally, patients with type 2 diabetes who have microvascular complications, especially diabetic nephropathy, are at increased risk for acute renal failure following administration of radiocontrast medium [4].

4.2. *Metformin Use in Contraindicated Populations*

Many individuals with diabetes continue to receive metformin, despite having conditions that place them at risk for lactic acidosis [56,57]. According to some estimates, approximately 25% of patients taking metformin have one or more contraindications [58,59].

For example, despite the contraindication for metformin use in diabetic patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73 m^2), metformin is often used off-label in patients with moderate renal impairment [60].

Some health authorities, e.g., the National Institute for Health and Clinical Excellence (NICE) recommend initiation of metformin in patients with eGFR 45 to <60 mL/min/1.73 m^2 and continuation with additional caution and dose reduction if the eGFR decreases to 30 to <45 mL/min/1.73 m^2) [61]. Similar treatment guidelines are endorsed by the Canadian Diabetes Association and the Australian Diabetes Society [62] and the results of numerous studies support this measured approach to the use of metformin in patients with moderate renal impairment [63,64]. At the same time, recent safety alerts by some health authorities continue to highlight a more restricted use of metformin to minimize the risk of MALA [65,66]. Similarly, recent publications [67–69] continue to highlight the increased risk of MALA with metformin use in renally-impaired patients. While it has been suggested that using lower doses of metformin (eg, 500 to 1000 mg/day) could be safe even in patients with severe renal impairment [70], it is questionable whether such doses would provide meaningful glycemic control [71]. Recently, the US FDA has been in receipt of Citizen Petitions to ease the contraindication to allow use in patients with moderate renal impairment, similar to the clinical treatment guidelines in place in the United Kingdom. However, in the absence of controlled clinical trial data to support such a change it is unclear how

it could be justified, especially in light of continuing concern in the medical and health authority communities.

5. Incidence of MALA

MALA is an extremely rare event with an estimated incidence of 0.03 to 0.06 per 1000 patient-years [3,11]. However, the precise incidence of lactic acidosis in metformin users is not known, as event rates are very low and are based on spontaneous case reports. Decades of clinical experience have provided insight to clinicians and regulators about the optimal use of metformin to insure safety. Two years after metformin was introduced into the US market, the incidence of MALA was estimated at 5 cases per 100,000 patient-years based on 47 reported cases among an estimated 1 million users [9]. Similarly, MALA has been reported at a rate of 9 per 100,000 patient-years in Canada [72]. Other reports indicate a comparably low incidence of MALA, but all are consistent in that most cases occurred in patients with pre-disposing conditions or intercurrent precipitating events that predispose to lactic acidosis [3,8,9,27,28,72]. Cases of lactic acidosis with "normal" metformin levels have been reported in patients with [33,49,73–83] and without a history of diabetes [73,80,81,84–86].

A comparative outcomes study that examined patients with type 2 diabetes treated with metformin vs. patients treated with non-metformin antihyperglycemic therapies for 1 year reported no cases of lactic acidosis [87]. Analyses of two large clinical studies with metformin showed similar results [88,89]. A systematic review from the Cochrane library that included 347 comparative trials and cohort studies found no cases of fatal or non-fatal lactic acidosis and no difference in plasma lactate levels between metformin-treated and non-metformin-treated groups [88]. Another case–control analysis [89], which compared the incidence of lactic acidosis between metformin and sulfonylurea users in 50,048 patients, found no difference in the incidence of lactic acidosis between metformin and sulfonylurea (3.3 and 4.8 per 100,000 patient-years, respectively). All reports of lactic acidosis in this study occurred in patients with preexisting comorbidities. Some investigators have attributed the association between metformin and lactic acidosis to the fact that type 2 diabetes is itself a risk factor for lactic acidosis [44,88], although this likely reflects the accompanying deterioration in other organ systems (e.g., hepatic and renal) that in turn predisposes patients to a higher risk of MALA.

Estimates of the incidence of MALA are confounded by multiple factors. Data obtained from published trials, which typically exclude patients with risk factors for lactic acidosis and which are designed to provide standard of care, likely do not reflect actual rates in clinical practice [56,90]. Case-controlled studies reflect use of metformin as indicated on the label, thus excluding, in most cases, patients at higher risk of MALA. Furthermore, information on plasma metformin concentrations, serum creatinine levels, arterial lactate levels, and history of concurrent pathologies is inconsistently reported, complicating characterization of MALA vs. lactic acidosis of other etiologies [31].

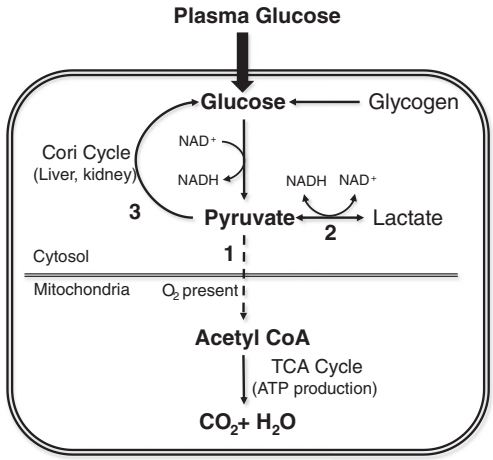

Fig. 1 – Biochemistry of lactate production. Pyruvate, the only precursor to lactate, is produced in the cytoplasm from metabolism of glucose via glycolysis. (1) When oxygen is available, pyruvate enters the mitochondria and is oxidized to CO_2 and H_2O in the TCA cycle. (2) Under anaerobic conditions, pyruvate is unable to enter the mitochondria to be oxidized and is reduced to lactate. (3) In the liver and kidney, pyruvate also can be converted to glucose. The Cori cycle describes a process by which lactate is produced by one tissue (muscle) and converted back to glucose in another tissue (liver). Lactate accumulates under anaerobic conditions. Adapted from Fall & Szerlip, 2005 [91].

6. Mechanism of MALA

Irrespective of its underlying etiology, lactic acidosis is a life threatening condition characterized by low blood pH (<7.35) and elevated arterial lactate (>5.0 mmol/L) levels [91]. Lactate is produced by the gut, liver, and peripheral tissues during glycolysis and can accumulate during hypoxic conditions (Fig. 1) [91]. The liver, kidney, heart, and skeletal muscle are the primary lactate metabolizers, while the liver and kidney account for ~60% and ~30%, respectively, of lactate clearance [92,93], although lactate clearance by the kidney does not correlate with renal function [94]. Lactate can either be oxidized to carbon dioxide and water by mitochondria to generate energy or converted back to glucose (gluconeogenesis) in the liver and kidney [17]. Lactic acidosis occurs during conditions of excessive lactate production and/or impaired hepatic lactate removal [91,92]. Hepatic lactate clearance can reach 320 mmol/h, which far exceeds the normal rate of lactate production [91]. Therefore, increased peripheral lactate production alone is rarely responsible for lactic acidosis. However, increased lactate production in the presence of impaired hepatic metabolism, such as occurs with cirrhosis, sepsis, or hypoperfusion, can result in sustained lactate accumulation and clinically significant lactic acidosis.

Lactic acidosis has been divided into two categories. Type A lactic acidosis results from the accumulation of lactate via glycolysis in the absence of oxygen. Type B lactic acidosis, exemplified by MALA, occurs during conditions when lactate

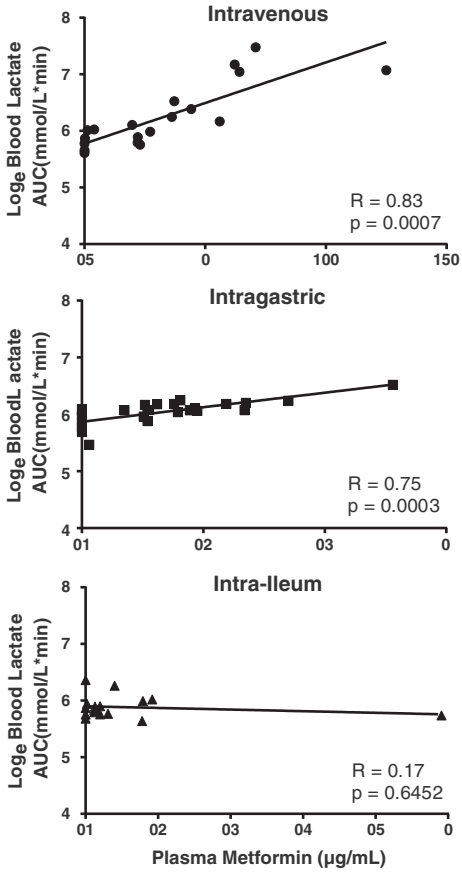

Fig. 2 – Relationship between blood lactic acid exposure (AUC) and plasma metformin concentration in normoglycemic rats. Rats received vehicle or metformin doses via the stomach, via the ileum and via a peripheral vein in randomized sequence. Blood glucose and lactic acid concentrations were determined before metformin administration (0 min) and at time points up to 4 h after administration. Plasma metformin concentration was measured at the 4-h time point.

production is increased at a time when clearance of lactic acid by oxidation or gluconeogenesis is reduced [91]. The remainder of this review will focus on MALA rather than the general topic of lactic acidosis.

In animals [95] and humans [96,97], biguanide administration is associated with an increase in blood lactate levels. The increase in plasma lactate concentration with therapeutic doses of metformin is small, usually <2 mmol/L [3,14,15,98,99], although higher levels may occur [100]. Metformin also elevates plasma lactate levels during exercise [101,102]. The small magnitude of increase in plasma lactate with metformin under typical conditions most likely explains why elevated plasma lactate levels have not been observed in some studies [13,103].

One mechanism via which metformin increases plasma lactate levels relates to the inhibition of mitochondrial respiration in tissues (i.e., liver and muscle) responsible for lactate removal [17,26,104–107]. This results in both accelerated lactate production and reduced lactate metabolism. In isolated hepatocytes, metformin inhibits complex 1 of the mitochondrial respiratory chain in a concentration-dependent manner and impairs gluconeogenesis [17,26,107]. The increase in plasma lactate concentration observed with metformin exposure in vivo correlates with the inhibition of mitochondrial oxidative phosphorylation in vitro [17].

6.1. *Evidence from Metformin Overdose Cases*

Reported cases of metformin overdose provide insight about the mechanisms linking metformin accumulation, increased plasma lactate levels, and the development of lactic acidosis. A retrospective analysis of metformin overdose cases [50] demonstrated a strong correlation between increased circulating metformin concentrations (as would be expected to occur in subjects with renal impairment receiving effective doses of current metformin formulations) and decreased arterial pH. High plasma lactate concentrations and pH were both predictors of fatal outcomes; patients who died had 100% higher circulating plasma metformin levels, 30% higher plasma lactate concentrations, and lower arterial pH compared to those who survived. In addition, individual overdose case studies indicate that metformin alone, in the absence of an intercurrent precipitating event, can cause MALA in instances of a major overdose, even in healthy individuals [108].

7. Relationship Between Metformin and Increased Lactate: Results of Novel Studies

We performed both nonclinical and clinical studies to better understand the relationship between systemic metformin exposure and increased plasma lactate concentrations.

7.1. *Results of Preclinical Studies*

In a nonclinical study [109], normoglycemic rats were administered vehicle or metformin by infusion through chronic indwelling catheters implanted into the stomach (intragastric), into the ileum (intra-ileum), or into a peripheral vein (intravenous) (Fig. 2).

Plasma metformin concentrations following intra-ileum administration were very low (≤10 μg/mL) compared to intravenous administration, which resulted in plasma levels that were up to 10 times higher. The increase in plasma metformin levels with intragastric administration was intermediate between intra-ileum and intravenous metformin administration. The increase in blood lactate concentration following metformin administration varied as a function of (i) metformin dose, (ii) circulating metformin concentration, and (iii) route of administration. While the lowest metformin dose tested (300 mg/kg) did not produce a significant increase in lactate AUC for the intragastric and intra-ileum routes of administration, it did result in a significant increase following intravenous administration.

Intravenous and intragastric administration of metformin produced statistically significant increases in lactate AUC at the higher metformin doses tested (500 and 750 mg/kg), but intra-ileum administration did not produce an increase in

lactate AUC relative to vehicle at either dose. Importantly, while it has previously been shown that metformin increases lactate concentration in the intestine [18], administration of metformin directly into the ileum did not produce an increase in blood lactate concentration even at very high doses. In contrast, with both intravenous and intragastric administration, the blood lactate concentration increased significantly and the rise was strongly correlated with the increase in plasma metformin concentration. There was no relationship between the plasma metformin concentration and blood lactate level following ileum infusion, most likely because that route of administration produced very low plasma metformin concentrations.

7.2. *Results of Clinical Studies*

We examined the relationship between metformin exposure and lactate production across the spectrum of renal function ranging from normal to severely impaired in patients with type 2 diabetes [110]. In this study, we used an investigational delayed-release metformin formulation (Metformin DR) designed to release metformin in the distal small intestine, thereby restricting metformin exposure to the distal bowel where it activates L cells resulting in the release of hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY [111]. This formulation differs from currently available IR and XR metformin products that are absorbed mainly in the proximal small intestine, resulting in high plasma metformin levels (Table 1). We have demonstrated that Metformin DR retains the full glucose lowering capacity of currently available metformin preparations [112].

Results from this study showed that, although plasma metformin concentrations increased with decreasing renal function, the metformin plasma AUC was significantly reduced (by ~25%-50%) after administration of a single 1000 mg dose of Metformin DR compared to a 1000 mg dose of Metformin XR (Fig. 3). In addition, Metformin XR, administered as a single 1000 mg dose, resulted in a significant relationship between the plasma metformin concentration and the change in placebo-corrected plasma lactate concentration from baseline ($p < 0.0001$) (Fig. 4). No relationship between plasma metformin and plasma lactate levels was observed when metformin was administered to the distal small intestine with Metformin DR ($p = 0.94$), most likely because metformin plasma concentrations were not high enough.

It should be noted that the change in plasma lactate concentration with Metformin XR was relatively small, consistent with the low dose used and the lack of opportunity for metformin accumulation due to the single dose administration. However, based on the observed relationship between plasma metformin and lactate concentrations, repeated Metformin XR dosing in patients with renal impairment could result in metformin concentrations that cause a clinically significant increase in circulating plasma lactate levels. The results of this study are consistent with those in rats discussed earlier.

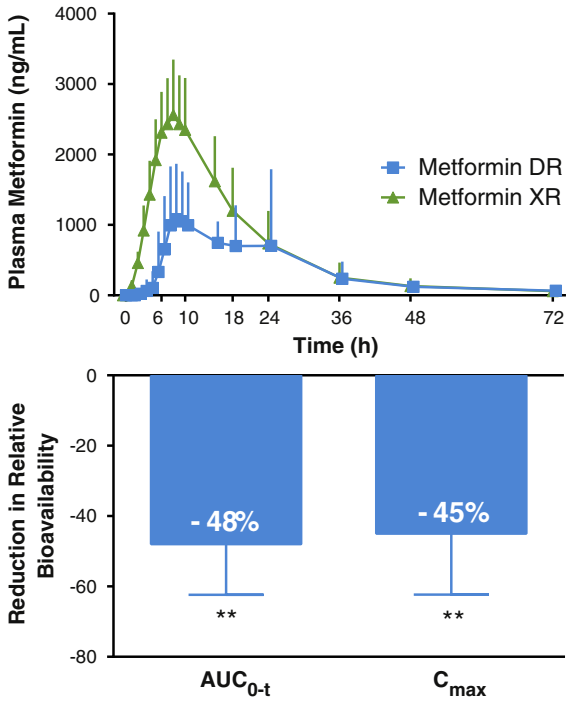

Fig. 3 – Plasma metformin concentrations following a single dose of metformin DR and metformin XR in patients with type 2 diabetes and severe renal impairment. Patients with severe renal impairment (eGFR < 30 mL/min per 1.73 m^2) were administered single doses of 1000 mg Metformin DR, 1000 mg Metformin XR, and Placebo in a cross-over study design. Top panel: Time-course plasma metformin concentration after a single administration of Metformin DR or Metformin XR. Bottom panel: Reduction in metformin bioavailability (C_{max} and AUC) with Metformin DR relative to the same dose of Metformin XR.

Table 1 – Characteristics of the Metformin Delayed-Release (Metformin DR) formulation.

Status	Investigational new drug in development
Delivery Target	Lower Bowel (Ileum)
Systemic Exposure	~50% lower than metformin immediate- or extended-release at equivalent doses
Glucose Lowering Effect	Using ~50% lower dose, appears to be comparable to metformin immediate- or extended-release based on Phase 2 clinical trials. Needs to be confirmed in Phase 3 trials.
Gastrointestinal Tolerability	To be determined
Utility in Treating Patients with Renal Impairment	To be determined

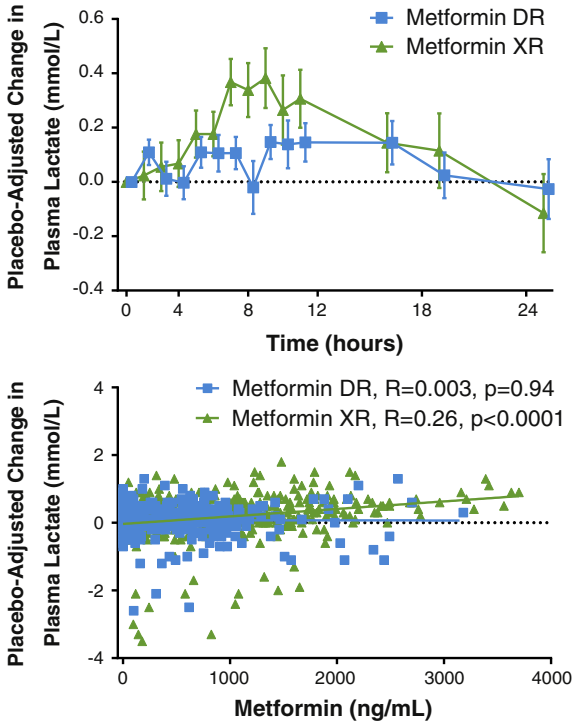

Fig. 4 – Plasma lactate concentration during a single-dose metformin administration in patients with type 2 diabetes. Patients with normal or impaired renal function were administered single doses of 1000 mg Metformin DR, 1000 mg Metformin XR, and Placebo in a cross-over study design. Top panel: Placebo-adjusted change in plasma lactate concentration after a single-dose administration of Metformin DR or Metformin XR. Time 0 to 24 h post-dose. Study medication administered at t = 0 h; meals administered at t = -0.33, 5.5, 8.5, 12.5, and 15.5 h. Bottom panel: Placebo-adjusted change in plasma lactate and metformin concentrations after a single-dose of Metformin DR or Metformin XR. Evaluable population. Time 0 to 24 h post-dose.

7.3. Strengths and Weaknesses of Metformin DR Studies and Translational Potential

The premise that Metformin DR acts substantially through activation of the L cell in the lower bowel is supported by the rodent data and early clinical data. The precise efficacy and safety profile of Metformin DR relative to existing metformin formulations remain to be confirmed with further clinical studies, as does the important potential use in patients with renal impairment who currently cannot benefit from metformin owing to the appropriate contraindications currently in place.

8. Conclusions

The fear of MALA and the contraindication for metformin in renally-impaired patients are rooted in the history of biguanide-associated lactic acidosis, in particular the experience with phenformin. While prudence has appropriately dictated caution in prescribing practices, judicious use of metformin in moderate renal impairment is common and is sanctioned by several health authorities, including those in the United Kingdom, Canada, and Australia. However, the success of metformin as the first-line diabetes therapy may be a direct consequence of conservative labeling, the absence of which could have led to excess patient risk and withdrawal from the market as was done with earlier biguanide therapies. Given that excessive plasma metformin accumulation is a necessary predisposing condition for MALA, alternative methods of delivering metformin to high-risk diabetic patients that minimize systemic exposure while maintaining glycemic efficacy are desirable. Limiting exposure by simply administering lower doses is likely not to provide optimal glycemic control. However, investigational formulations of metformin that target the lower bowel [112] potentially could impact the ability to treat currently contraindicated (e.g., renally impaired) or otherwise metformin-intolerant patients who could benefit from this biguanide.

Contributions of Authors

All authors contributed equally to the conception and writing of the manuscript.

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Conflicts of Interest

T.A.B. and K.C. hold stock or stock options in Elcelyx Therapeutics, Inc. R.D. is a member of Elcelyx Therapeutics, Inc.'s Clinical Advisory Board. The authors declare no other conflicts of interest.

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