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METFORMIN ASSOCIATED LACTIC ACIDOSIS, OVERVIEW AND MANAGEMENT: A LITERATURE REVIEW

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ABSTRACT.

Background: Metformin is the first-line therapy for newly diagnosed type 2 diabetes mellitus. It accomplished glycemic control by gluconeogenesis inhibition in the liver and enhance glucose uptake in the peripheral tissues. Adverse effects commonly include gastrointestinal symptoms, such as nausea, vomiting, and diarrhea. A rare but life-threatening lactic acidosis could develop in the setting of metformin use. **Objective:** This study aims to understand the mechanism and the reality behind metformin-associated lactic acidosis, particularly in patients with chronic kidney disease. **Method:** We searched in the PubMed database for relative articles using two Mesh terms, "metformin" and "lactic acidosis." **Conclusion:** Metformin-associated lactic acidosis is a rare but serious consequence, especially in patients with chronic kidney disease, congestive heart failure, and chronic liver disease. Most of the cases have at least one predisposing factor other than metformin use. The link between metformin and lactic acidosis was previously overestimated, and there are growing data showing that metformin can be used in patients with mild to moderate renal impairment.

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Introduction

Metformin is an oral antidiabetic medication that belongs to the biguanide group used for type 2 diabetes mellitus (T2DM) to control blood glucose levels, and the commonest oral antidiabetic in Western countries [1-5]. Compared to other oral antidiabetic medications, metformin is less commonly cause hypoglycemia or weight gain and may be associated with lower mortality [1]. Metformin is strongly suggested to be highly effective in blood sugar control and body weight reduction [2]. Unlike insulin, metformin is considerably affordable and does not require patient education and training [1]. Metformin improves blood sugar by multiple mechanisms, including gluconeogenesis reduction in the liver, glycolysis increase, and glucose uptake increase in the skeletal muscle tissue [2]. Interestingly, it also reported to play a significant role in the gut via microbiota, the gut-brain-liver axis, or the gut-pancreas network [2]. Metformin has been approved for use in type 2 diabetic Mellitus in the United Kingdom since the 1960s, and in the United States in 1994 [6, 7]. In addition to the efficacy of metformin in type 2 diabetic patients, there is ongoing evidence of its effectiveness in cardiovascular diseases [6].

Lactic acidosis (LA) is a critical concern for diabetic patients taking metformin, particularly in people with impaired drug excretion such as chronic kidney disease (CKD), conditions with a tendency to accumulate lactate such as chronic liver disease (CLD) or Congestive Heart Failure (CHF), and overdose [2, 7]. However, there is an ongoing debate regarding the

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safety of metformin in patients with CKD, defined as an estimated Glomerular Filtration Rate (eGFR) of <60 ml/min/1.73m2 [6]. Guidelines concerning metformin use in CKD are variable [6]. The United States Food and Drug Administration (FDA) previously reported that metformin was contraindicated in males with a serum creatinine >132.6 umol/l and females above 123.8 umol/l [6]. Nevertheless, a recent literature review of these recommendations was concluded that metformin is considered to be safe in a patient with CKD and (eGFR is 40 - 60 ml/min/1.73m2), and in some patients with moderate renal impairment (eGFR <45 ml/min/1,73m2) [6]. The National Institute for Health and Care Excellence (NICE) in the UK recommends prescribing metformin in CKD patients with an eGFR <60 ml/min/1.73m2, but with adjustment of the dose in eGFR <45 ml/min/1.73m2 (or serum creatinine greater than 132.6 umol/l) and discontinue metformin if eGFR <30 or serum creatinine above 150.3 umol/l [6]. Following the FDA's approval, the European Medicines Agency (EMA) has also now approved that metformin can be safely used in patients with moderate renal impairment (eGFR 30-59 ml/min/1.73m2) [6]. Furthermore, recent literature has concluded that metformin produces beneficial effects on the kidney, and there is no clear association between metformin use and CHF [7, 8]. The FDA removed CHF as a contraindication for metformin use in 2006, although it remains considerably unsafe in case of acute or unstable CHF [7].

In the beginning, biguanide derivatives medications (phenformin and buformin) were introduced for DM treatment in the 1950s, followed by a withdrawal from the market two decades later in 1977 due to life-threatening Lactic Acidosis (LA) [7, 9]. The incidence of phenformin-associated lactic acidosis was nearly 129 cases per 100,000 patients annually, while the reported incidence of metformin-associated lactic acidosis (MALA) is around 3.3-9 cases per 100,000 patients annually [10]. Metformin was introduced in Europe as "Glucophage" by Jean Stern in 1957 and was approved in the US in 1995 [9]. It becomes the drug of choice for T2DM after introduction into the American market and the first-line treatment worldwide due to its effect on glycemic control and low risk of hypoglycemia [9-11]. Metformin can be used as a monotherapy or in combination with other oral and subcutaneous antihyperglycemic agents as long as tolerated well and no contraindications [9]. Over the years, metformin has been associated with a wide range of pleiotropic effects regardless of its antihyperglycemic effect [9]. Meanwhile, the associated risk of LA development becomes gradually less significant than previously thought [9]. The term "Lactic Acidosis" is defined as an event of acidosis, characterized by a decrease arterial PH to less than 7.35, high lactate level (plasma lactate level >5mmol/L), and increased anion gap [9-11]. It is important to note that LA cannot be ruled out by the absence of these factors, as the patient may present with normal PH due to concomitant acid-base disorder [11]. Immediate recognition and management of this condition are critical due to its poor clinical outcome [10]. Surprisingly, current studies suggest that metformin may be of a protective role in severe non-metformin-induced LA [10]. Moreover, Kamber et al. concluded in a longitudinal observational study that the incidence of LA induced by metformin use was about the same as those taking other anti-diabetic medications [10]. LA is divided into two categories, shown in **Table 1** [11].

Table 1. Lactic Acidosis Categories

Type A	Associated with hypoperfusion conditions and subsequent production of excess lactate by anaerobic glycolysis **e.g.**: Septic shock, advanced heart failure
Type B	Increase lactate in conditions other than hypoperfusion **e.g.**: Alcoholic, DKA, liver disease, and metformin use

DKA: Diabetic Ketoacidosis

Discussion

Metformin Mechanism of Action and Pharmacokinetics:

The primarily antihyperglycemic action of metformin is achieved by its inhibitory effect on glucose output from the liver and enhancing insulin-mediated glucose uptake in peripheral tissues [11, 12]. This effect has been attributed to multiple mechanisms by which the result is gluconeogenesis inhibition [11]. These mechanisms are listed in Table 2, and the mainstay of metformin inhibition of gluconeogenesis by decreased ATP/ADP ratio results in diminishing gluconeogenesis (by pyruvate carboxylase inhibition) [11]. Furthermore, metformin has been shown to reduce the activity of mGPD, results in inhibiting the conversion of glycerol-3-phosphate (G3P) to dihydroxyacetone phosphate (DHAP), thereby preventing the conversion of glycerol to gluconeogenesis [11]. Additionally, the inhibition mGDP would increase the cytosolic redox state, promoting the conversion of pyruvate to lactate to encourage the lactate/pyruvate ratio (Anaerobic metabolism), resulting in gluconeogenesis inhibition from lactate [6, 11]. Therefore, metformin inhibits the integral mitochondrial respiratory chain components (Complex 1 and mGDP) [11]. The end effect of metformin in hepatocyte is glucagon action inhibition and prevents endogenous glucose production from gluconeogenic precursors, pyruvate, and lactate [11].

Table 2. Mechanism of Gluconeogenesis Inhibition by Metformin

1.	Inhibition of mitochondrial respiratory chain complex 1
2.	Inhibition of mitochondrial glycerophosphate dehydrogenase

3. AMP-mediated inhibition of adenylyl cyclase
4. Activation of AMP-activated protein kinase (AMPK)
5. AMPK-independent inhibition of glucose production

Metformin has specific pharmacokinetics: It is neither bound to plasma protein nor metabolized and eliminated primarily through active tubular secretion in the kidney [12]. Plasma metformin concentration is inversely related to eGFR, and this evidence emerges in all CKD stages [12]. Although metformin has been used for more than 50 years, the therapeutic range has never been clearly defined, and the exact level that is considered therapeutic or potentially harmed is unknown [12]. Besides, the pharmacokinetics of metformin is not adequately altered in patients with chronic liver disease (CLD) [13]. Although CLD and T2DM are associated with high plasma lactate levels, the pharmacokinetics of metformin in CLD were similar to T2DM patients and normal liver function [13].

Metformin-Associated Lactic Acidosis (MALA):

The term MALA first appeared in the literature in 1977 and was correlated with metformin due to difficulty in establishing its causal or coincidental effect [9]. Almost all cases with LA were observed in metformin prescribed patients [9]. There is growing evidence supporting the belief that metformin's therapeutic use may not be the primary cause of LA [10]. The mortality impaction by metformin remains unclear, although it has been published to be higher than 50% by several studies [9]. However, it has been noticed that most cases with MALA have at least one risk factor for LA other than metformin [10]. A retrospective study including 42 patients admitted to the intensive care unit has shown that LA related to intentional metformin overdose carries a better prognosis than LA secondary to metformin accumulation in the setting of concomitant medical illness [9]. Interestingly, in a cohort study involving 44 metformin users and 118 nonusers admitted to the emergency department due to severe LA and sepsis, the rate of the in-hospital mortality rate was significantly lower in patients using metformin, despite their high-risk comorbidities [9]. This study can outline a protective effect of metformin against LA due to its advantageous pleiotropic effects during acute disease [9]. Likewise, in a case reports review of MALA by Stades et al., almost 90% of the reviewed cases carried a risk factor for LA, concluding that LA might be coincidentally associated with metformin use [10].

The pathophysiology of MALA is not clearly understood, but it is suggested to result in excessive lactate production leading to protons release in the blood and thus leads to acidosis [10]. It is also caused by impaired hepatic lactate clearance by inhibiting mitochondrial respiratory chain complex 1 [14]. Moreover, MALA can occur in normal kidney function in the setting of massive metformin overdose [14]. In a case report of 14 years-old African girls who intentionally ingested an unknown metformin amount presented with severe lactic acidosis [14]. She was presented with acidotic breathing, sinus tachycardia, hypotension, and abdominal pain [14]. She was successfully treated with 45 cycles of peritoneal dialysis over five days [14]. In MALA patients with hemodynamic instability, intermittent hemodialysis, and sustained low-efficacy dialysis, SLED is the treatment of choice [14, 15], but in limited hemodialysis places, peritoneal dialysis can be used for MALA with a desirable outcome [15]. Metformin is generally safer than insulin and sulphonylureas due to the low risk of hypoglycemia [16]. Nevertheless, metformin overdose carries a higher mortality rate (6.1%) than sulphonylureas and insulin overdose (0.9% and 3.6%, respectively) [16]. There are poor prognostic factors for MALA, including advanced age > 60, arterial PH less than 7.35, the need for mechanical ventilation and vasopressors [15, 16]. Treatment monitoring for those people must be taken seriously, especially if preceded by digestive symptoms such as diarrhea, which can worsen LA [16].

The most common presenting symptoms of MALA is gastrointestinally related, such as nausea, vomiting, and diarrhea, followed by an altered conscious level, breathlessness, hypothermia, and hypotension [15]. MALA symptoms may mimic sepsis with gastroenteritis, high blood lactate levels, and PH less than 7.35 [15]. In a case report of a 60 years-old lady presented to the emergency room with abdominal pain, nausea, vomiting, and diarrhea was suspected of having severe acute mesenteric ischemia [17]. She underwent an urgent exploratory laparotomy and found no evidence of bowel ischemia and intact pulsation in the superior mesenteric artery [17]. The diagnosis of MALA was made presumptively after taking a full history, and the continuous renal replacement was rapidly performed [17]. Another case report of a 68-year-old man presented with acute reversible binocular blindness preceded by nausea and vomiting secondary to severe lactic acidosis [18]. His symptoms were resolved entirely after hemodialysis and correction of acidosis [18].

MALA in Chronic Kidney Disease:

Since circulating metformin is unchangeably eliminated in the urine, the use of metformin in CKD is an area of controversy due to the risk of developing a rare, but life-threatening lactic acidosis [9, 19, 20]. Therefore, it is considered contraindicated in patients with eGFR below 30ml/min [19]. Current studies showed that metformin use does not increase the risk of lactic acidosis [19]. The recommendation for patients with eGFR between 30-60 ml/min remains ambiguous [19]. Some observational studies have shown that the risk of LA mainly in eGFR below 45ml/min [19]. Furthermore, a recent trial by the European Medicine Agency (EMA) had assessed the safety of metformin in patients with or without renal failure showed a higher risk of LA in metformin users compared to other antidiabetic agent users [19]. Afterward, in October 2016, the EMA safety review recommended that metformin can be used in patients with moderate renal function (eGFR 30-59

ml/min) [19]. Studies of renal dysfunction patients had shown no association between metformin use and lactic acidosis when metformin concentration was maintained below 5mg/L [20]. Besides, there are case reports of high metformin concentration without LA [20]. A recent retrospective observational study in T2DM and Stage 5 CKD patients found that all-cause mortality was significantly raised in metformin dose of >1000mg/d, the adjusted mortality hazard ratio for patients taking <500mg/d or 500-1000mg/d were not remarkable [20]. Over the years, novel clinical trials have continued to confirm metformin's safety in CKD patients [9]. Moreover, metformin showed a renoprotective positive effect on both in vitro and animal models representing different renal disease stages, from acute kidney injury to CKD [9]. Finally, Ravindra et al. concluded in his study that metformin could be safely used in Stage 3 CKD and Stage 4 and 5 with close monitoring of plasma lactate level [21]. Due to the remarkable efficacy and the uncertainty of metformin safety in CKD patients, a large controlled clinical trial is strongly needed to establish the safety profile and potential harms of metformin in those populations. Those patients might get cardiovascular and renal benefits from using metformin regardless of glycemic control.

Conclusion

Metformin is one of the oldest and most prescribed antidiabetic drugs for type 2 diabetic patients worldwide. It belongs to the biguanide group and favored over other agents due to the low risk of hypoglycemia and weight gain. It is the first-line medication for type 2 diabetes mellitus, showing a significant control of blood glucose level, HbA1C, and enhancing insulin resistance in peripheral tissues. Previously, metformin was thought to be directly associated with lactic acidosis development due to its original action in the hepatocyte. It inhibits gluconeogenesis and, therefore, promotes the accumulation of lactic acid in the blood. Over the years, growing studies suggest that lactic acidosis in metformin users can be correlated to other predisposing factors, such as chronic kidney disease, dehydration secondary to gastrointestinal symptoms, or sepsis. Furthermore, metformin has shown some protective effect in lactic acidosis patients compared to non-metformin users. The use of metformin in CKD is an area of caution due to the fear of rare, but life-threatening lactic acidosis development. Metformin plasma concentration is inversely related to the eGFR. Thus, the use of metformin is contraindicated in patients with eGFR below 30ml/min, while in moderate renal impairment (eGFR 30-59ml/min), it can be used with caution and dose adjustment. Further large clinical trials are recommended to establish the efficacy and safety of metformin in the CKD population.

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