DOI：10.6314/JIMT.202606_37(3).04 內科學誌 2026：37：171-178

Rare but Fatal Metformin-Associated Lactic Acidosis: Challenges in Kidney Disease and Critical Illness

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Abstract

Metformin, the most widely prescribed oral hypoglycemic agent for type 2 diabetes, is generally regarded as safe and effective. Nevertheless, metformin-associated lactic acidosis (MALA) remains a rare but life-threatening complication, especially in patients with impaired renal function or acute intercurrent illness. This review aims to synthesize recent epidemiological evidence, mechanistic understanding, and clinical management strategies for MALA, drawing on large cohort studies, case series, and up-to-date guidelines. Although the incidence of MALA is low, the associated mortality remains substantial, underscoring the need for vigilant risk assessment, timely diagnosis, and prompt intervention. Recent data have refined our understanding of risk stratification, revealing that renal dysfunction, acute kidney injury, and critical illness are key predisposing factors. Advances in supportive care and renal replacement therapies have improved outcomes, but prevention through safe prescribing and patient education remains paramount.

Key Words: Chronic Kidney Disease, Dialysis, Metformin, Metformin-Associated Lactic acidosis

Teaching Points

1. Risk of MALA rises steeply when eGFR < 30 mL/min/1.73 m².
2. Sick day rule: Patients must be educated to temporarily suspend metformin during acute illness, severe dehydration, or before radiocontrast expo-

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sure to avoid precipitating a metabolic crisis.
3. Diagnostic criteria: Maintain high suspicion in patients with metformin exposure who present with a laboratory of pH < 7.35, lactate > 5 mmol/L.
4. Emergent dialysis criteria: Since metformin is highly dialyzable, initiate urgent dialysis if pH ≤ 7.0, lactate > 20 mmol/L, or in the presence of shock or altered mental status.

Introduction

Metformin has become the foundational therapy for type 2 diabetes mellitus worldwide, renowned for its efficacy, cardiovascular benefits, and favorable safety profile[1,2]. In Taiwan, the increasing prevalence of both diabetes and chronic kidney disease has resulted in a growing number of patients requiring complex glycemic management amidst declining renal function[3-5]. As this patient population expands and ages, clinicians are frequently confronted with the challenge of balancing optimal glycemic control with the risk of rare but serious adverse events such as metformin-associated lactic acidosis (MALA).

MALA is conventionally defined as the occurrence of laboratory-confirmed lactic acidosis, characterized by a serum lactate level > 5 mmol/L and an arterial pH < 7.35 in the presence of concurrent metformin exposure[6]. Although lactic acidosis related to metformin use is infrequent, the condition carries a high mortality once it occurs, particularly among those with significant renal impairment[7]. In real-world clinical practice, prescriptions for metformin have often continued in patients whose renal function has deteriorated beyond recommended safety thresholds, reflecting the inertia of chronic therapy and the subtlety of early CKD progression[8]. For decades, the association between metformin and lactic acidosis has been controversial, often complicated by confounding factors such as comorbid cardiovascular disease, infection, or the metabolic derangements seen in advanced CKD[5]. Nevertheless, the mechanistic basis for concern is clear: as renal function declines, the capacity to eliminate metformin is reduced, heightening the risk of drug accumulation and subsequent mitochondrial dysfunction that can trigger profound lactic acidosis.

Recent large-scale observational studies in Taiwanese clinical settings have provided compelling evidence that the risk of lactic acidosis rises steeply as renal function declines, and that this risk is not fully explained by the burden of comorbidities or age alone. Rather, the impaired renal clearance of metformin itself appears to play a pivotal role in the pathogenesis of MALA[5]. As CKD progresses from moderate to advanced stages, even minor acute insults, such as dehydration, infection, or perioperative stress, may further compromise metformin elimination and precipitate this life-threatening complication[9]. In this context, the safe and judicious use of metformin in patients with impaired kidney function has emerged as a major focus for clinicians. Heightened awareness, regular assessment of renal function, and timely discontinuation of metformin in at-risk individuals are now recognized as essential strategies for preventing MALA and safeguarding patient outcomes.

Risk Factors and Prognosis

Over the past decades, large-scale registry analyses and comparative cohort studies have firmly established that the absolute incidence of MALA is extremely low among the general diabetic population, particularly in those with preserved renal function. For example, Canadian and US national databases have documented incidence rates of 5-9 cases per 100,000 patient-years, with virtually all episodes occurring in patients with overt risk factors such as CKD, hepatic dysfunction, or acute systemic illness[10,11]. Despite these reassuring statistics, comparative studies reveal a stark paradox: although rare, the onset of MALA carries an alarmingly high case-fatality rate[12,13].

Recent population-based studies and meta-analyses have refined our understanding of MALA risk stratification. Richy et al. and Eppenga et al. demonstrated that, while the risk for lactic acidosis is negligible in patients with an estimated glomerular filtration rate (eGFR) above 30 mL/min/1.73 m², the incidence rises dramatically with more advanced renal impairment[14,15]. In these strata, the risk can be two- to three-fold higher, underscoring the central role of renal function in metformin safety. These findings were echoed in both Western and Asian populations, including the REMIND-TMU study in Taiwan, which revealed an independent association between declining eGFR and lactic acidosis in metformin users, even after adjusting for age and comorbidities[5].

Additional risk modifiers, such as sepsis, congestive heart failure, advanced age, and drug interactions (notably with cimetidine or nephrotoxic agents), hepatic dysfunction, excessive alcohol consumption, have also been consistently reported[16]. These factors either reduce metformin elimination, increase lactate production, or both, compounding the vulnerability of patients with already compromised metabolic reserve. The weight of comparative literature supports current guidelines recommending discontinuation of metformin in patients with persistent eGFR < 30 mL/min/1.73 m² and in those experiencing acute illness or hemodynamic instability[1]. Despite these recommendations, inappropriate prescribing and system-level gaps remain a global concern, as highlighted by several national audits and population registries[15].

Despite the consensus regarding the rarity and high risk of MALA, key studies vary considerably in methodology. Large registry analyses often rely on administrative coding and voluntary adverse event reporting, which may undercapture true incidence and lack uniform diagnostic definitions[10,11]. Retrospective cohorts differ in their biochemical criteria for lactic acidosis and may introduce selection bias by including only patients with comprehensive laboratory and prescription data.[14,15] Meta-analyses (e.g., Salpeter et al.) aggregate heterogeneous study designs, while case series (e.g., Lalau et al., Kim et al.) are inherently limited to more severe, often hospitalized cases[8,12,15]. Furthermore, most published studies are based on Western populations, with limited generalizability to Asian cohorts. These methodological differences highlight the challenges in directly comparing incidence rates and risk factors for MALA across studies (Table 1).

Collectively, while the absolute incidence of MALA remains low, ranging from 2.4 to 39 cases per 100,000 patient-years, the clinical impact is disproportionately severe, with mortality rates spanning 10% to 50%[5,6]. This significant clinical burden is most pronounced when independent risk factors, specifically eGFR < 30 mL/min/1.73 m², advanced age, hepatic dysfunction, excessive alcohol consumption, or acute systemic illness, intersect with metformin therapy.

Pathophysiology

Metformin (129 Daltons) is a highly water-soluble organic cation that is negligibly bound to plasma proteins and does not undergo hepatic metabolism, being excreted unchanged in the urine via glomerular filtration and active tubular secretion (renal clearance approximately 3.5 times greater than creatinine clearance)[17]. Due to its low molecular weight and negligible protein binding, metformin is readily dialyzable.[18] In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and renal clearance is decreased, increasing the risk of toxic accumulation.

The progressive systemic accumulation of metformin eventually precipitates a metabolic crisis by disrupting cellular respiration. Metformin, particularly when accumulated due to impaired renal clearance, exerts its deleterious metabolic effects predominantly by inhibiting complex I of the mito-

Table 1. Summary of Methodologies and Findings from Major Studies on Metformin-Associated Lactic Acidosis

Study/Source	Study Design / Population	Main Findings	Risk Factors or Mechanisms
Stang et al., 1999[10]	National registry, Canada; > 1 M user-years	Incidence of MALA estimated at 9/100,000 patient-years	Most cases with predisposing conditions
Misbin et al., 1998[11]	FDA report, US market, 1M users	MALA rare; incidence ~5/100,000 patient-years	Often occurs in renal or hepatic dysfunction
Richy et al., 2014[14]	Retrospective cohort; CKD and non-CKD	No significant difference in lactic acidosis between metformin and non-metformin users in CKD with proper selection	Risk rises as eGFR decreases
Eppenga et al., 2014[15]	Population-based cohort; eGFR stratified	Lactic acidosis rare in eGFR > 30; risk increases in eGFR < 30	Renal impairment is key risk
Salpeter et al., 2010[16]	Meta-analysis, 347 trials/ cohorts	No cases of fatal/non-fatal lactic acidosis in > 70,000 pt-years	Properly selected patients safe
Lalau et al., 1999[12]	MALA case series	High metformin and lactate levels associated with worse outcome; Mortality 30-50%	Blood pH and lactate are prognostic
Kim et al., 2015[8]	Case series, Korea; 24 MALA pts	Most had acute kidney injury or sepsis as triggers; Mortality 41.7%	AKI, sepsis, dehydration most common triggers
DeFronzo et al., 2016[13]	Narrative review, translational research	Metformin inhibits mitochondrial complex I, impairs hepatic gluconeogenesis, especially when accumulated in renal impairment; MALA mortality up to 50%	eGFR < 30, acute illness, liver dysfunction, drug interactions, overdose

Abbreviation: AKI: Acute kidney injury, CKD: Chronic kidney disease, DKA: Diabetic ketoacidosis, eGFR: Estimated glomerular filtration rate, FDA: Food and Drug Administration, MALA: Metformin-associated lactic acidosis, RRT: Renal replacement therapy

chondrial respiratory chain in hepatocytes and other tissues. This inhibition disrupts oxidative phosphorylation, leading to impaired ATP generation, increased anaerobic glycolysis, and consequent lactate overproduction[19,20]. Moreover, metformin's interference with mitochondrial function reduces the hepatic and renal capacity for lactate clearance, further amplifying the risk of systemic lactic acidosis.

Studies employing animal models and cellular systems have demonstrated that metformin-induced lactic acidosis is associated not only with increased plasma lactate concentrations, but also with profound disturbances in mitochondrial bioenergetics[21]. Wang et al. (2014) also identified a role for organic cation transporter 1 (OCT1) in mediating metformin's entry into hepatocytes and subsequent mitochondrial toxicity[22]. This molecular insight helps explain why patients with compromised drug elimination or mitochondrial reserve, such as those with CKD or acute illness, are at particularly high risk for MALA. Importantly, these mechanistic findings corroborate clinical observations and underscore the need for heightened vigilance when prescribing metformin in populations with impaired mitochondrial or metabolic function (Figure 1).

Clinical Presentation and Diagnostic Approach

Across case series and registry reports, the clinical presentation of MALA is consistently described as nonspecific, often manifesting with gastrointestinal symptoms, malaise, confusion, tachypnea, and hypotension[4]. These symptoms overlap significantly with other causes of high-anion gap metabolic acidosis, such as sepsis or diabetic ketoacidosis, which frequently coexist in the critically ill. Lalau et al.'s case series and related literature emphasize the need

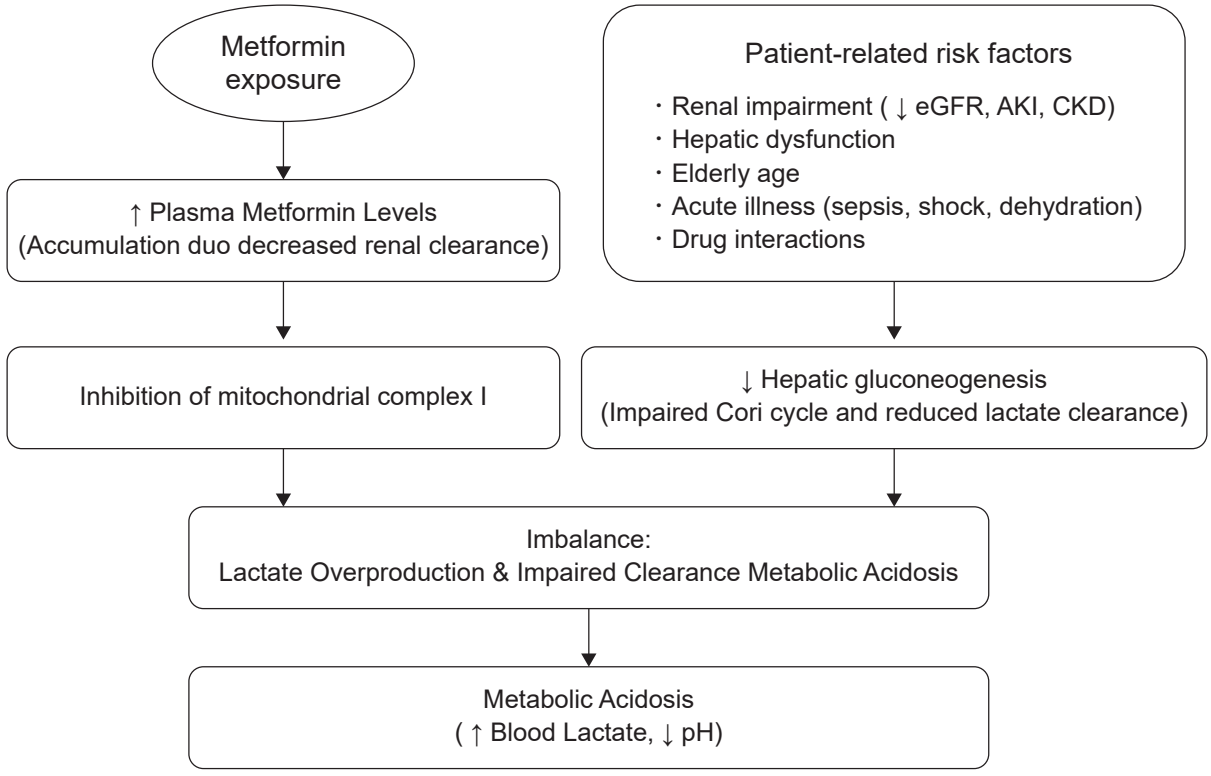

Figure 1. Mechanisms of metformin-associated lactic acidosis

Predisposing factors, including CKD, AKI, and reduced eGFR, impair metformin clearance and promote drug accumulation. In the presence of acute illness or hemodynamic instability, this leads to mitochondrial dysfunction, impaired lactate metabolism, and ultimately lactic acidosis.

Abbreviation: AKI: Acute kidney injury, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, MALA: Metformin-associated lactic acidosis, RRT: Renal replacement therapy

for a high index of suspicion, especially in patients with recent or ongoing metformin use and concomitant renal impairment or acute illness[23].

Laboratory findings pivotal to diagnosis include severe metabolic acidosis (pH < 7.35), low serum bicarbonate (< 22 mmol/L), and markedly elevated serum lactate (> 5 mmol/L). Although measurement of plasma metformin concentration (> 5 mg/L) may support the diagnosis, the literature consistently notes that this assay is rarely available in real-time and thus has limited utility for acute management. Therefore, clinical context and the exclusion of alternative etiologies remain paramount for timely recognition and intervention. Notably, several studies, including Kim et al., have correlated both blood pH and lactate levels with patient outcomes, reinforcing their prognostic relevance[8].

Contemporary Management

The consensus across all comparative studies and reviews is that successful management of MALA depends on early recognition, immediate cessation of metformin, and the rapid correction of underlying precipitating factors. In addition to conventional supportive treatment, including fluid resuscitation and hemodynamic optimization, urgent renal replacement therapy (RRT) is a cornerstone of management, particularly in cases with critical drug accumulation or life-threatening acidemia. According to the EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup, hemodialysis should be initiated when pH ≤ 7.0, serum lactate

> 20 mmol/L, or in the presence of shock, renal/hepatic failure, or altered mental status[24].

Adjunctive therapies, such as intravenous sodium bicarbonate, should be reserved for cases of severe and refractory acidemia, as their routine use has not demonstrated significant benefit in less severe presentations. In critically ill patients, mechanical ventilation may be required for respiratory failure, and extracorporeal life support may be considered as a rescue measure in select catastrophic cases. Importantly, measurement of plasma metformin concentrations is seldom available in real time and, as consistently emphasized in the literature, rarely impacts immediate clinical management[25]. As such, reliance on clinical judgment and rapid laboratory assessment remains central to effective intervention.

Despite its rareness, outcome analyses by Lalau et al. and Kim et al. highlight the dramatic impact of clinical context and timely intervention. Delays in recognition and RRT, the presence of oliguric AKI, profound acidemia, older age, and coexisting hepatic dysfunction all independently predict poor prognosis[8,12]. Conversely, when MALA is rapidly identified and managed, particularly with early RRT in hemodynamically unstable patients, survival can be substantially improved, emphasizing the need for prompt, protocol-driven care.

Prevention and Risk Mitigation

Given the overwhelming evidence that MALA is largely preventable, the literature strongly advocates for rigorous risk assessment, ongoing monitoring, and patient education as the cornerstone of prevention. Baseline and periodic assessment of renal function is recommended for all patients prescribed metformin, and the drug must be carefully re-evaluated during episodes of acute illness, dehydration, or before exposure to nephrotoxic agents or radiocontrast. Education of patients and healthcare providers, ensuring that “sick day” rules and early warning signs are well understood, is highlighted as an essential, but often overlooked, aspect of care[26].

At the institutional level, system-based interventions such as electronic alerts, pharmacy oversight, and standardized protocols can further reduce inappropriate prescribing. Resumption of metformin following an acute event must always be preceded by reassessment and confirmation of adequate renal recovery.

Conclusions

In summary, early recognition, prompt discontinuation of metformin, and timely escalation of supportive care, including RRT, are essential for optimizing outcomes in patients at risk for MALA. Despite advances in epidemiological understanding, clinical stratification, and critical care, MALA remains a rare but devastating complication. Future research priorities include the development of individualized risk prediction tools, exploration of novel metformin formulations with reduced systemic exposure, and implementation of real-time clinical decision support to guide therapy in complex, rapidly evolving clinical settings.

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罕見卻致命的二甲雙胍相關乳酸中毒：腎臟病與重症照護中的挑戰

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摘要

二甲雙胍是全球治療第二型糖尿病最廣泛使用的口服降血糖藥物，普遍被認為安全且有效。然而，二甲雙胍相關乳酸中毒 (metformin-associated lactic acidosis, MALA) 仍是一種罕見但致命的併發症，尤其發生於腎功能受損或急性重症患者。本綜述綜合了近期流行病學證據、機轉性研究及臨床管理策略，引用大型世代研究、病例系列及最新臨床指引。雖然 MALA 的發生率極低，但一旦發生，死亡率卻相當高，顯示必須高度警覺、及時診斷與快速處置。近年來資料進一步釐清了危險因子的分層，指出腎功能障礙、急性腎損傷與重症為主要的易感族群。支持性治療及腎臟替代治療雖已改善部分預後，然而預防仍以安全用藥與病人衛教為首要目標。