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METFORMIN-ASSOCIATED LACTIC ACIDOSIS IN A PATIENT WITH ACUTE KIDNEY INJURY: A CASE REPORT

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Abstract

Metformin-associated lactic acidosis is rare, but it carries a high mortality when it occurs alongside acute kidney injury. This review draws on published case reports, case series, cohort studies and pharmacological work to describe how a drug cleared unchanged by the kidney can accumulate when renal function falls abruptly, and how that accumulation interacts with hypoperfusion, sepsis and liver dysfunction. It covers mechanisms, epidemiology, the question of causality, clinical and laboratory presentation, extracorporeal treatment and prevention. Outcome appears to track the severity of the underlying illness, blood pH and lactate more closely than the metformin concentration. The evidence rests mainly on uncontrolled reports. No new patient or data are presented in this review.

1. INTRODUCTION

Metformin has been first-line oral therapy for type 2 diabetes for a generation, and few drugs can match its record. It lowers hepatic glucose output without causing weight gain or hypoglycaemia, and in the UK Prospective Diabetes Study it reduced diabetes-related endpoints in overweight patients [1]. Its labelling nevertheless carries a boxed warning for lactic acidosis, a legacy of the biguanide era, when phenformin was withdrawn from many markets after clusters of fatal cases [2]. Metformin-associated lactic acidosis (MALA) is rare. When it does occur, though, it tends to occur in sick patients, and it can move from vague malaise to profound acidaemia and multi-organ failure within hours [3, 4]. The commonest setting in published reports is a sudden fall in kidney function.

Acute kidney injury (AKI) is a frequent problem in hospital practice, and a large share of the people who develop it are already taking metformin. This is the setting that case reports keep returning to: a patient with diabetes, a dehydrating illness or another renal insult, a drug that depends on the kidney for its removal, and a prescription that is not stopped in time. This review reports no new patient and no new data. It draws on published case reports, case series, cohort studies, pharmacokinetic work and guidance to describe how MALA develops in AKI, how it is recognised, what the literature says about extracorporeal treatment, and how it might be prevented. The single-case framing of the title is treated as a prompt to review what many reported cases have in common, not as an account of one person.

2. PHARMACOLOGY AND MECHANISM

Metformin is a small, hydrophilic, strongly basic molecule that is not metabolised and is not bound to plasma proteins. Oral bioavailability is roughly half to two-thirds of the dose, and the drug leaves the body in urine through glomerular filtration and, more importantly, active tubular secretion, so that renal clearance exceeds creatinine clearance [5, 6]. Uptake into the tubular cell depends on organic cation transporters, and secretion into the lumen on multidrug and toxin extrusion proteins [6]. In people with normal kidneys the elimination half-life is a few hours. As filtration falls it lengthens several-fold, and the drug concentrates in tissues with high transporter expression, including kidney, liver and gut wall [5, 6]. An abrupt loss of renal function therefore leaves a patient still swallowing a dose that the body can no longer clear.

Some drug interactions act on the same transporters. Cimetidine reduces renal clearance of metformin and raises exposure, and trimethoprim, which inhibits extrusion proteins, has been reported to do the same [6]. Iodinated contrast has no pharmacokinetic interaction of this kind, but contrast-associated AKI produces the same accumulation by a different route, which is why contrast guidance appears in metformin labelling [6, 7]. Alcohol taken in excess changes the hepatic redox state, raises lactate, and is a recognised co-factor in published MALA cases [3]. Pharmacists screening a medicines list for a patient on metformin should therefore look beyond the obvious renal risks.

How metformin lowers glucose also suggests how it might raise lactate. Early work in hepatocytes and isolated mitochondria showed that the drug inhibits complex I of the respiratory chain, an effect that is indirect and depends on the drug accumulating inside the cell [8, 9]. The fall in cellular energy charge activates AMP-activated protein kinase (AMPK) and suppresses gluconeogenesis, and later work pointed to inhibition of mitochondrial glycerophosphate dehydrogenase as a further route [10]. At therapeutic concentrations the effect on respiration is mild and the cell compensates. At the concentrations reached in renal failure or overdose, inhibition is greater, oxidative phosphorylation falters, and pyruvate is diverted to lactate through glycolysis. The gut, which produces lactate from glucose even in healthy people, may add to the load. None of this requires tissue hypoxia, which is what makes the drug-related component distinctive.

Plasma concentrations in MALA tell a consistent story about accumulation. In people taking standard doses with normal renal function, steady-state concentrations are modest, whereas published MALA series report values many times higher, with the highest in patients with oliguric AKI [4, 6, 11]. Such figures should be read with caution because assays, sampling times and the interval since the last dose vary between reports. They nonetheless make a simple point: the kinetic change is large, and it happens in the same patients who have the least reserve in lactate disposal. Erythrocytes take up metformin slowly and release it slowly, which may explain why concentrations decline more gradually than plasma kinetics predict after the kidneys recover [6].

Lactate itself is not a poison, and the body handles very large amounts of it every day. It is produced by glycolysis in muscle, skin, red cells and gut, then taken up mainly by the

liver and the renal cortex, where it is oxidised or converted back to glucose [12, 13]. Clinicians usually divide lactic acidosis into type A, driven by hypoperfusion and hypoxia, and type B, driven by impaired oxidative metabolism without overt hypoxia. MALA does not sit neatly in either box. The drug impairs mitochondrial function, while the setting of AKI adds shock, reduced hepatic blood flow and loss of the kidney's own lactate clearance, so that production rises and removal falls together [12, 13]. Evidence that the effect is real in humans comes partly from overdose, where platelet mitochondria from poisoned patients showed measurable respiratory dysfunction [14].

3. INCIDENCE AND CAUSALITY

Reported frequencies are low. Surveillance in Sweden in the early 1990s, a health-plan cohort study in the United States and a Cochrane review of comparative trials all point to a few cases per 100,000 patient-years of use [15, 16, 17]. The Cochrane authors found no cases of lactic acidosis in the trial data and no difference in lactate levels between metformin and other treatments, although trial populations are selected and usually exclude people with renal impairment [15]. Cohort and case-control analyses of routine care give similar answers: rates in metformin users were not clearly different from those in users of sulfonylureas or other agents [17, 18]. These figures are reassuring on average. They say much less about the small subgroup with AKI, in whom the baseline rate of lactic acidosis is already high for reasons unrelated to any drug.

Whether metformin causes the acidosis or merely sits beside it has been argued for decades. A careful review of published case reports found that most patients had another serious condition capable of producing lactic acidosis by itself, such as sepsis, cardiac failure or shock, and questioned how often metformin was truly the cause [19]. A regulatory review of spontaneous reports reached a similar view of the accompanying conditions [20]. Others noted that in many reports the plasma metformin concentration was never measured, so that the label 'associated' described exposure and not proof [21]. A more recent view treats the question as a spectrum: in some patients accumulated metformin is the main driver, in others it adds to an existing insult, and in a few it is incidental [4, 22]. Case-series modelling supports the middle position, with metformin contributing when other mitochondrial or perfusion stresses are present [22].

Poisoning provides a cleaner view of the drug's effect, because renal function is often normal at the outset. In a series of acute metformin overdoses, survivors and non-survivors differed in arterial pH and lactate far more than in serum metformin concentration, and a review of biguanide toxicity makes the same point [23, 24]. A French analysis of severe MALA reached a similar conclusion: blood pH and lactate carried prognostic information, whereas the plasma metformin level, although usually very high, was a weaker guide to who would die [11]. Intensive care series add that circulatory failure and the severity of the underlying disease matter as much as acidaemia [25]. The practical lesson is that the patient's physiology, not a drug level that rarely returns in time, should steer decisions.

Individual reports, read side by side, share a recognisable outline. The patients are usually older, have had type 2 diabetes for years, and take metformin at a stable dose, often alongside a diuretic or a renin-angiotensin blocker. A few days of vomiting or diarrhoea, or an infection with poor oral intake, comes first. Creatinine is then found to be several times its baseline, and the blood gas shows a severe metabolic acidosis with a high lactate [19, 26, 27]. Some reports add hypotension that responded poorly to fluids, and many note that the dose had not been reviewed since the illness began. This pattern is useful because it describes who should trigger concern on a ward round. It is also a reminder that the typical case is a failure of medicines review during an acute illness, not a drug that behaved unpredictably.

Age is an under-appreciated element. Older adults have lower muscle mass, so serum creatinine can look normal while the true filtration rate is much reduced, and eGFR equations are less well validated in the very old [28, 29]. They are also more likely to take diuretics, renin-angiotensin blockers and

anti-inflammatory drugs, and to have reduced thirst. Whether age carries risk beyond its effect on kidney function and polypharmacy is not settled, and the case literature cannot answer it because denominators are missing.

Lactate concentrations in non-diabetic critically ill patients are raised in a large proportion of cases, and the prognostic weight attached to them was built largely on such populations, not on MALA [12, 13]. That matters when a patient with diabetes and AKI arrives with a lactate of 8 mmol/L: the number alone does not separate metformin accumulation from sepsis. Clinical context, a history of recent doses and the pattern of response to resuscitation help, but neither is definitive [11, 19].

4. KIDNEY INJURY AS PRECIPITANT

Consensus definitions of AKI have evolved from the RIFLE criteria through the Acute Kidney Injury Network staging to the KDIGO guideline, which uses a rise in serum creatinine or a fall in urine output over defined periods [30, 31, 32]. Whichever definition is used, the clinical triggers are familiar: volume depletion from vomiting or diarrhoea, sepsis, hypotension, iodinated contrast, and drugs that alter renal haemodynamics such as non-steroidal anti-inflammatory drugs, diuretics and renin-angiotensin system blockers. In published intensive care series of MALA, AKI was present in most of the patients [25, 26]. Often the illness that caused the injury, a gastrointestinal infection for instance, was also the reason intake had fallen while the metformin dose went on being taken.

The reason AKI is so hazardous lies in the speed of the change. In stable chronic kidney disease (CKD), the dose can be reduced in step with the estimated glomerular filtration rate (eGFR) and the patient settles at a new, lower steady state. In AKI the filtration rate may fall by half in a day, creatinine lags behind, and the prescribed dose continues unchanged, so exposure climbs for days before anyone adjusts it [6, 33]. Population studies show that the risk of lactic acidosis rises as eGFR falls, although they cannot cleanly separate chronic from acute decline [28]. A systematic review of metformin in CKD, heart failure and chronic liver disease found the evidence thin, with few events and low-quality data, which cuts both ways: it neither proves harm nor excludes it [34].

Two large analyses illustrate the gradient. A population-based cohort from the Netherlands found that lactic acidosis or raised lactate became more frequent as renal function declined among metformin users [28]. A community cohort in the United States, covering the whole range of kidney function, found that risk rose progressively as eGFR fell, with the steepest increase below 30 mL/min/1.73 m^2 [29]. A systematic review of metformin in kidney disease had earlier taken a more permissive view of moderate impairment, noting that observational data did not show harm at an eGFR of 30 to 45 and that dose reduction was a reasonable response [35]. Together these studies describe a gradient and not a cliff. They also share a limitation: a single baseline eGFR says little about the day-to-day kinetics of a patient whose kidneys are failing acutely.

Other factors tilt the balance in the same direction. Hypoperfusion from heart failure or septic shock reduces hepatic and renal lactate uptake, acute or chronic liver disease limits clearance, heavy alcohol intake impairs gluconeogenesis, and hypoxaemia from lung disease increases anaerobic metabolism [3, 36, 37]. Reviews of contraindications list these conditions beside renal impairment, and the older age of most affected patients adds to the burden [36, 37]. The main published findings on mechanism, epidemiology, causality, treatment and prevention are drawn together in table 1, and the way those findings divide across themes is shown in fig. 1. Mechanism and renal handling account for the largest single group of entries, a reflection of where the strongest evidence lies. The clinical management entries rest mostly on case series and expert consensus.

5. PRESENTATION AND DIAGNOSIS

Presentation is rarely specific. Reported patients describe nausea, vomiting, abdominal pain, diarrhoea and malaise, often for a day or two, followed by fast deep breathing, hypotension, drowsiness and sometimes hypothermia [19, 27]. Because

gastrointestinal illness is frequently what triggered the AKI, the early symptoms may be attributed to the primary illness and the acid-base disturbance noticed only when a blood gas is taken. Diagnostic definitions in the literature vary, but most require a lactate above about 5 mmol/L with arterial pH below 7.35 in a patient exposed to metformin [3, 4]. Values in severe reports are much more extreme, with lactate above 15 or 20 mmol/L and pH below 7.0 [26, 27]. Blood glucose may be low, normal or high, a reminder that ketoacidosis has to be excluded and that a normal glucose does not argue against the diagnosis.

Table 1: Published findings on metformin-associated lactic acidosis in kidney injury

Topic	Published finding	Ref.
Renal elimination unchanged drug	Cleared by filtration and tubular secretion; half-life lengthens several-fold as glomerular filtration falls.	[5, 6]
Mitochondrial effect complex I	Inhibition of respiratory chain complex I reduces oxidative phosphorylation and shifts pyruvate towards lactate.	[8, 9]
Hepatic gluconeogenesis glucose lowering	Suppression via glycerophosphate dehydrogenase explains glucose lowering and may limit lactate handling at high concentrations.	[3, 10]
Incidence population data	Reported at a few cases per 100,000 patient-years; rates in users of other agents not clearly lower.	[15, 17, 18]
Renal function gradient eGFR	Risk rises as eGFR falls, with the steepest increase below 30 mL/min/1.73 m^2.	[28, 29]
Causality case reviews	Severe comorbidity in most reports; metformin often a contributor and not the sole cause.	[19, 21, 22]
Prognostic markers pH, lactate	Blood pH and lactate predict outcome better than plasma metformin concentration.	[11, 23]
Extracorporeal treatment haemodialysis	Clears metformin and lactate; recommended when lactate exceeds 20 mmol/L or pH is 7.0 or lower.	[38]
Intensive care series outcome	Early renal replacement therapy linked with survival despite severe acidaemia, though confounded by illness severity.	[25, 26, 39]
Labelling eGFR rules	Contraindicated below 30; review below 45; stop around contrast or acute illness.	[7, 40]
Sick-day guidance withholding	Pausing during dehydrating illness, sepsis and surgery is widely advised; evidence is consensus-based.	[33, 37]

Interpreting the blood gas takes a little care when the picture is mixed. Vomiting generates a metabolic alkalosis that can partly offset the acidosis, so a pH that looks only moderately low may hide a very large anion gap. Respiratory compensation should lower the carbon dioxide tension by an amount predictable from the bicarbonate, and a value higher than expected suggests fatigue or sedation and warns of imminent respiratory failure [12, 13]. Hyperkalaemia is common when AKI and acidaemia coexist, and it is a frequent reason for urgent dialysis independent of the metformin question [12]. Serial gases every one to two hours in the early phase give a clearer view of trajectory than any single value, and a rising lactate despite resuscitation is itself an argument for early renal replacement.

Laboratory interpretation has its own traps. Lactate samples should be drawn without prolonged tourniquet time, collected in the correct tube and analysed promptly or kept on ice, otherwise glycolysis in the sample inflates the result [12]. The anion gap is usually raised, but a low albumin can mask it, and a gap not fully explained by lactate should prompt a search for ketones, toxic alcohols, salicylate and uraemic acids [12, 13]. A plasma metformin concentration confirms exposure and its magnitude, yet it needs a specialist assay and seldom returns within the time in which treatment is decided [4, 11]. The differential diagnosis includes sepsis, mesenteric ischaemia, cardiogenic shock, thiamine deficiency and diabetic ketoacidosis, any of which can coexist with MALA. Treatment therefore starts on the

clinical picture, and metformin is assumed to be contributing until proved otherwise.

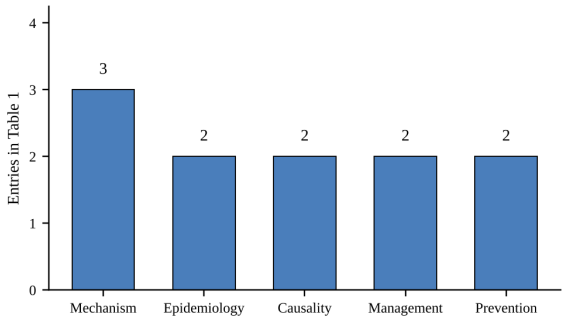


Fig. 1: Number of entries in table 1 by theme

Outcomes in the literature vary widely, mostly because the populations do. The classic review of biguanide-treated patients reported mortality of about half [2], while later intensive care series of MALA reported lower but still substantial death rates [25, 26]. Some individual reports describe striking recoveries from pH values below 7.0 with prompt renal replacement therapy [39]. In the larger series, death was associated with shock, higher lactate, lower pH and greater overall illness severity, not with the metformin dose or concentration [11, 25, 26]. Publication bias probably shapes this picture, because dramatic survivors are more likely to be written up than quiet deaths. Even so, the consistent message is that MALA in a patient with AKI is survivable if recognised early and treated as a medical emergency.

Intentional overdose presents differently from accumulation in AKI. After a large ingestion, lactate can rise within hours in patients whose kidneys are still working, and gastrointestinal symptoms are prominent. Some patients with modest overdoses develop only mild hyperlactataemia [23, 24]. The patient with AKI, by contrast, is often accumulating an ordinary daily dose over several days, so the drug concentration may be lower than in overdose while the capacity to clear lactate is also much reduced. The two situations should not be assumed to carry the same prognosis [11, 23].

6. MANAGEMENT

Initial management is supportive and differs little from that of other severe lactic acidosis. Metformin and other nephrotoxic or renally cleared drugs are stopped, volume is restored, sepsis is sought and treated, and vasopressors are used for shock, with attention to oxygen delivery and ventilation. Intravenous sodium bicarbonate remains controversial. Studies in lactic acidosis have not shown a clinical benefit, and it can raise carbon dioxide and lower ionised calcium, yet in profound acidaemia with AKI many clinicians use it as a temporary measure while dialysis is arranged [12, 13]. There is no antidote for metformin. Activated charcoal has a role only after recent large ingestions, which is not the usual scenario in accumulation due to AKI [24].

Haemodynamic support deserves more thought than it usually receives in toxicology-oriented reviews. Many patients with MALA and AKI are hypovolaemic, and early restoration of circulating volume improves renal perfusion, which may itself restore some metformin clearance and lactate disposal [12, 13]. Vasopressors that increase splanchnic vasoconstriction can worsen hepatic lactate handling, and adrenaline infusions raise lactate through beta-adrenergic stimulation of glycolysis, so a rising value on adrenaline does not always signal worsening perfusion [12]. Titrating therapy to perfusion markers beyond lactate, such as capillary refill, urine output and central venous oxygen saturation, avoids both over- and under-treatment [13].

Extracorporeal treatment is the one specific intervention. Metformin has a low molecular weight and negligible protein binding, features that favour removal by haemodialysis, and dialysis also removes lactate and supplies bicarbonate buffer [6, 38]. The EXTRIP workgroup reviewed the literature on metformin poisoning and recommended extracorporeal treatment when lactate is above 20 mmol/L, when pH is 7.0 or lower, when standard therapy fails, or when shock or impaired consciousness is present, and suggested it for lactate of 15 to 20 mmol/L or pH of 7.0 to 7.1 [38]. Intermittent haemodialysis was the preferred modality, with continuous techniques acceptable when it is unavailable, and treatment was advised to continue until lactate falls below 3 mmol/L and pH rises above 7.35 [38]. In AKI most such patients have an independent indication for renal replacement therapy (RRT) anyway.

Practical details matter. Because metformin has a large apparent volume of distribution, plasma concentrations can rebound after a session as the drug leaves the tissues, and lactate may climb again, so a second session or prolonged treatment is sometimes needed [6, 38]. Haemodynamically unstable patients are often started on continuous venovenous haemofiltration or haemodiafiltration, which clears the drug more slowly but is better tolerated, and case series report reversal of acidosis with both approaches [25, 26]. Timing is an open question. Reports from intensive care units (ICU) suggest that earlier initiation, before refractory shock develops, is associated with better outcomes, but this is confounded by the fact that sicker patients are more likely to die before any treatment starts [25, 26]. No randomised trial exists, and none is likely, so the recommendations rest on case series and pharmacokinetic reasoning [38].

What happens after the acute phase receives less attention in the literature than it deserves. Where AKI had a haemodynamic or prerenal cause, kidney function often recovers over days to weeks once perfusion is restored, and survivors of intensive care series generally left hospital independent of dialysis [25, 26]. The decision to restart metformin then rests on the recovered eGFR, the stability of the underlying illness and the availability of alternatives, and guidance suggests it be resumed only when function is stable and above the labelled threshold [40, 41]. Where recovery is partial, a lower dose or another glucose-lowering class is the safer path. Patients and general practitioners need to be told that a pause happened and why, so that a later infection prompts the same response.

7. PREVENTION AND PRACTICE

Prevention is where the evidence translates most directly into practice. In 2016 the US Food and Drug Administration (FDA) revised its metformin labelling to base decisions on eGFR instead of serum creatinine. The drug is contraindicated below 30 mL/min/1.73 m^2, starting is not recommended between 30 and 45, benefit and risk should be reassessed if eGFR falls below 45 during treatment, and metformin should be stopped around iodinated contrast in patients with an eGFR of 30 to 60, liver disease, alcoholism or heart failure [7]. The KDOQI guideline on diabetes in chronic kidney disease, and the KDIGO guideline on diabetes in CKD, give similar thresholds and advise dose reduction when eGFR is 30 to 44 [40, 41]. Earlier UK advice listed much the same contraindications [37].

Thresholds only help if someone applies them to the individual in front of them. Case reviews repeatedly note that metformin had been continued despite recognised contraindications, or that an acute illness had not prompted a pause [19, 27]. Sick-day rules, which tell patients to stop metformin, with some other medicines, when vomiting, diarrhoea or fever lead to poor intake, are widely advocated but have little trial evidence behind them [33]. A pharmacist can add value at several points: reviewing the medicines list at admission, flagging combinations with diuretics, anti-inflammatory drugs and renin-angiotensin blockers, checking eGFR before discharge, and making sure metformin is restarted only after renal function has stabilised. Kidney function should be rechecked at least yearly in all users and more often when eGFR is below 60 or the clinical picture is unstable [33, 40].

8. LIMITATIONS AND FUTURE DIRECTIONS

The limits of this literature need stating plainly. Case reports and series are uncontrolled, selected for severity and subject to publication bias. Definitions of MALA differ between papers, so that a lactate threshold of 5 mmol/L in one report is 10 in another. Metformin concentrations are measured in a minority of cases, with sampling at inconsistent times relative to dialysis and the last dose [4, 21]. Observational cohorts rely on diagnostic codes for lactic acidosis, which may capture sepsis-related cases as well as drug-related ones, and confounding by indication is hard to remove because clinicians already avoid metformin in the sickest patients [19, 28]. Estimates of absolute risk in AKI are therefore uncertain, and claims that metformin is either dangerous or harmless in that setting should be read with caution.

Reporting standards would improve the usefulness of future case reports. A minimum

dataset would record the metformin dose and duration, the date and time of the last dose, baseline and peak creatinine, urine output, arterial pH and lactate at presentation and at fixed intervals, concomitant drugs, the modality and timing of renal replacement therapy, plasma metformin where measured, and the outcome at discharge and at follow-up [4, 26, 38]. Journals could ask for this as a checklist. Even a modest increase in consistency would allow pooled analysis of reports that currently cannot be compared, and would let readers judge whether an apparent association with a given comorbidity reflects the drug or the general severity of illness [19, 21].

Several gaps could be closed with better data. Prospective registries that record metformin concentration, dose timing, renal function trajectory and outcome using common definitions would allow a proper analysis of dose-response in AKI. Population pharmacokinetic models of metformin in unstable renal function could test whether eGFR-based dose rules are adequate when creatinine is not at steady state [6]. Transporter variants affecting renal secretion might explain why a few patients accumulate the drug disproportionately [6]. Finally, the growing use of newer glucose-lowering agents with kidney and cardiovascular outcome data may change how often metformin is the drug a patient with advancing kidney disease is left on, and kidney guidelines already encourage such choices [40, 41].

9. CONCLUSION

Published reports describe metformin-associated lactic acidosis in acute kidney injury as a rare event with a serious course. The drug is eliminated by the kidney, accumulates when filtration collapses, and at high concentrations interferes with mitochondrial respiration, so that lactate production rises just as clearance by the injured kidney and often by a poorly perfused liver falls [3, 6, 8]. Whether metformin is the cause, a contributor or a bystander differs from patient to patient, and prognosis follows the severity of the underlying illness, the pH and the lactate more closely than it follows the drug level [11, 19, 23]. Population data show a gradient of risk with falling eGFR and not a sharp threshold [28, 29].

For practice, the evidence supports a short list of actions: stop metformin during dehydrating illness, sepsis or contrast exposure when kidney function is threatened, apply eGFR-based limits, recognise the acid-base picture early and involve intensive care and nephrology without delay, and use haemodialysis along the lines of the EXTRIP recommendations when lactate and pH reach the published thresholds [7, 38, 40]. Pharmacists are well placed to catch the risk at admission and at discharge. What is missing is prospective, standardised data, and until it exists the literature should be read as strong on mechanism and weak on the exact size of the risk [4, 21].

10. ABBREVIATIONS

AKI-Acute kidney injury, AMPK-AMP-activated protein kinase, CKD-Chronic kidney disease, eGFR-Estimated glomerular filtration rate, EXTRIP-Extracorporeal Treatments in Poisoning workgroup, FDA-US Food and Drug Administration, ICU-Intensive care unit, KDIGO-Kidney Disease: Improving Global Outcomes, MALA-Metformin-associated lactic acidosis, RRT-Renal replacement therapy

11. FUNDING

Nil

12. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

13. CONFLICT OF INTERESTS

Declared none

14. REFERENCES

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