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ABOUT COVER
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AIMS AND SCOPE
The primary aim of World Journal of Diabetes (WJD, World J Diabetes) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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The WJD is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJD as 4.560; IF without journal self cites: 4.450; 5-year IF: 5.370; Journal Citation Indicator: 0.62; Ranking: 62 among 146 journals in endocrinology and metabolism; and Quartile category: Q2.

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Metformin toxicity: A meta-summary of case reports

Deven Juneja, Prashant Nasa, Ravi Jain

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**Abstract**

**BACKGROUND**

Metformin is arguably the most commonly prescribed oral hypoglycemic agent for the management of diabetes. Due to the lack of randomized control trials, most of the data pertaining to the clinical course, therapeutic interventions and outcomes of patients with metformin induced toxicity have come from case reports or series.

**AIM**

To analyse the symptomology, clinical interventions and outcomes of patients presenting with severe metformin toxicity by reviewing the published case reports and series.

**METHODS**

We performed a systematic search from PubMed, Science Direct, Reference Citation Analysis (https://www.referencecitationanalysis.com/) and Google Scholar databases using the terms “metformin” AND “toxicity” OR “overdose” OR “lactic acidosis” OR “hyperlactatemia”. The inclusion criteria were: (1) Case reports or case series with individual patient details; and (2) Reported toxicity or overdose of metformin in adults, published in the English language. Data regarding baseline demographics, clinical presentation, therapeutic interventions, intensive care unit course and overall outcome were collected.

**RESULTS**

Two hundred forty-two individual cases were analysed, from 158 case reports and 26 case series, with a cumulative mortality of 19.8%. 214 (88.4%) patients were diabetics on metformin. 57 (23.6%) had acute ingestion, but a great majority (76.4%) were on metformin in therapeutic doses when they developed toxicity.
Metformin associated lactic acidosis (MALA) was the most commonly reported adverse effect present in 224 (92.6%) patients. Most of the patients presented with gastrointestinal and neurological symptoms and a significant number of patients had severe metabolic acidosis and hyperlactatemia. The organ support used was renal replacement therapy (RRT) (68.6%), vasopressors (58.7%) and invasive mechanical ventilation (52.9%). A majority of patients (68.6%) received RRT for toxin removal, renal dysfunction and correction of MALA. Patients with lowest pH and highest serum lactate and metformin levels also had favourable outcomes with use of RRT.

CONCLUSION
Most of the reported cases were on therapeutic doses of metformin but developed toxicity after an acute deterioration in renal functions. These patients may develop severe lactic acidosis, leading to significant morbidity and need for organ support. Despite severe MALA and the need for multiple organ support, they may have good outcomes, especially when RRT is used. The dose of metformin, serum pH, lactate and metformin levels may indicate the severity of toxicity and the need for aggressive therapeutic measures but may not necessarily indicate poor outcomes.

Key Words: Extracorporeal toxin removal; Haemodialysis; Metformin associated lactic acidosis; Metformin overdose; Renal replacement therapy

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Core Tip: Metformin may be associated with significant toxicity, even when used in therapeutic doses, of which metformin associated lactic acidosis is the most commonly reported toxicity. These patients may have favourable outcomes in spite of consumption of high doses, severe acidosis, and high serum lactate and metformin concentrations. Early aggressive supportive care, use of renal replacement therapy for toxin removal and organ support may help in improving outcomes.

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DOI: https://dx.doi.org/10.4239/wjd.v13.i8.654

INTRODUCTION
Metformin is arguably the most commonly prescribed oral hypoglycemic agent (OHA) for the management of diabetes mellitus (DM). In addition to its hypoglycemic properties, it has the potential to reduce micro and macro vascular complications associated with DM and have a clinically beneficial role in reducing serum lipids levels and body weight[1,2]. Use of metformin in the management of type II DM has been shown to reduce all-cause mortality and risk of cardiovascular complications[3].

The primary mode of action of metformin is to reduce hepatic glucose production. In addition, it also exerts hypoglycemic effect through the neuroendocrine axis, enhancing cellular uptake of glucose and reducing insulin resistance[4]. It is considered a very safe drug and is generally not associated with hypoglycemia. Rarely patients may develop toxicity related to its use. Metformin associated lactic acidosis (MALA) has been defined as serum lactate levels above 5 mmol/L and arterial pH below 7.35 in association with metformin exposure[5]. It is a rare complication with a reported incidence of 1-30 cases per 100000 patient years but is associated with a high mortality rate of 25%-50%[6,7].

Despite severe acidosis, patients with MALA may have good clinical outcomes if it is recognised early and aggressive resuscitative measures are initiated[8]. In addition, certain therapeutic interventions like extracorporeal toxin removal (ECTR), if instituted timely, may improve survival in select patient subgroups and hence, it is currently recommended in patients with severe metformin toxicity[9]. Even though MALA remains the most dreaded complication associated with metformin use, other complications have also been reported that may require hospitalisation. Due to the lack of randomised control trials, most of the data pertaining to the clinical course, therapeutic interventions and outcomes of these patients have come from case reports and case series. Hence, we conducted this scoping review of case reports and series to analyse the symptomology, clinical interventions and outcomes of patients presenting with severe metformin toxicity requiring hospitalisation and acute intervention.
MATERIALS AND METHODS

We performed a systematic search for this review from PubMed, Science Direct, Reference Citation Analysis (https://www.referencecitationanalysis.com/) and Google Scholar databases from January 1, 1975 till December 31, 2021. The search terms used were “metformin” AND “toxicity” OR “overdose” OR “lactic acidosis” OR “hyperlactatemia”. The inclusion criteria were: (1) Case reports or case series with individual patient details; and (2) Reported toxicity or overdose of metformin. Further, it was filtered for the literature published in the English language and on adult (> 18 years) humans. We excluded: (1) Conference abstracts; and (2) Case reports or series which did not have individual biochemical data. The authors screened all the search results to include only the relevant literature for metformin toxicity. Duplicate articles from different search databases were excluded.

All the case reports and case series were evaluated, and the data were extracted for patient demographics, clinical symptomatology, clinical interventions including extracorporeal therapies (ECT), intensive care unit (ICU) course, need for organ support and outcomes. Concomitant use of nephrotoxic drugs including nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting-enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), aminoglycoside antibiotics and diuretics was also made. A datasheet for evaluation was further prepared.

Statistical analysis

The prepared datasheet was evaluated by Excel, Microsoft office 2019. Categorical variables were presented as frequency and percentage. Median (interquartile range) or mean ± SD was used for continuous variables. Qualitative correlation statistics were analysed by Chi-square test and Fisher’s exact test. A $P$ value of < 0.05 was deemed significant. Unless otherwise indicated, all the statistical analyses were done using SPSS (version 25.0, IBM SPSS Inc., Chicago, IL, United States). Tabulation and final documentation were done using MS Office software (MS office 2019, Microsoft Corp, WA, United States).

RESULTS

This review was performed using PRISMA 2009 checklist (Figure 1). Finally, 184 studies with 242 unique patients that met all the inclusion criteria were included (Supplementary material). Most of the included patients were from the United States of America (66, 27.3%) and the United Kingdom (30, 12.4%) (Figure 2). 185 (76.4%) patients developed toxicity while on chronic therapeutic doses of metformin while 57 (23.6%) patients developed toxicity after an acute overdose of the drug.

The commonly reported symptoms were gastrointestinal (vomiting 52.5%, abdominal pain 40%) and neurological (altered mental status 36%, loss of consciousness 11.6%). Two hundred fourteen (88.4%) patients had underlying diabetes and were on metformin (Table 1).

MALA was the most commonly reported adverse effect in 224 (92.6%) patients. Other reported isolated adverse effects were encephalopathy in 6 (2.5%) patients, hepatitis or acute liver failure in 5 (2.1%) patients, hypoglycemia in 4 (1.6%) patients, and psychosis, vitamin B12 deficiency and acute pancreatitis in 1 (0.4%) patient each.

Overall, 57 (23.6%) patients had acute ingestion, out of which 52 were suicidal, three were reported as accidental and in two cases the cause was not reported or was unclear. The reported median dose consumed by these patients was 42.5 gms (interquartile range 24.8–61.5 gms). Out of these 57 cases, there were 11 deaths with a cumulative mortality rate of 19.3%. Sixteen patients with acute intoxications had a history of co-ingestion of other drugs.

The mean duration of presentation after acute intoxication was 10.9 (± 13.8) hours. Activated charcoal (6.6%) and gastric lavage (5.8%) was rarely employed to reduce the absorption of metformin in patients with acute intoxication. Intravenous soda-bicarbonate was most commonly used among the other therapies employed in 65.3% of patients.

Arterial blood gas at presentation was available in 214 (88.4%) patients and serum metformin concentration was measured only in 58 (24%) cases (Table 2). Overall, 185 (76.4%) patients were on long-term therapeutic doses of metformin when they developed metformin toxicity. These patients were on metformin doses ranging from 250–3000 mg/day (median 1625 mg/day). The cumulative mortality was 37/185 (20%) in this group of patients. Out of these 185 patients, 38 patients had underlying chronic kidney disease (CKD) and 73 patients had documented reasons, which may have caused acute renal dysfunction precipitating metformin toxicity. These reasons included acute gastroenteritis leading to dehydration (36 patients), ACE-I inhibitors (22 patients), NSAIDs (18 patients), diuretics (16 patients), ARBs (8 patients), IV contrast (7 patients), post-operative (5 patients), acute urinary tract infection (5 patients), anti-retroviral drugs like tenofovir (4 patients), aminoglycosides (2 patients), and obstructive uropathy (1 patient). Several patients had multiple risk factors for acute kidney injury.

Renal dysfunction was the most common organ dysfunction (74%), followed by cardiac (59.5%) and pulmonary (47.1%). One hundred sixty-six (68.6%) patients underwent renal replacement therapy (RRT)
### Table 1 The commonly reported symptoms (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients (n = 242)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>59.3 (16) yr</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Females, 126 (52.1)</td>
</tr>
<tr>
<td></td>
<td>Males, 115 (47.5)</td>
</tr>
<tr>
<td></td>
<td>Not mentioned, 1 (0.4)</td>
</tr>
<tr>
<td><strong>Clinical presentation, n (%)</strong></td>
<td>Vomiting, 127 (52.5)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain, 96 (40)</td>
</tr>
<tr>
<td></td>
<td>Altered mental status, 87 (36)</td>
</tr>
<tr>
<td></td>
<td>Shock, 43 (17.8)</td>
</tr>
<tr>
<td></td>
<td>Breathlessness, 41 (16.9)</td>
</tr>
<tr>
<td></td>
<td>Loss of consciousness, 28 (11.6)</td>
</tr>
<tr>
<td></td>
<td>Anuria, 22 (8.3)</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrest, 5 (2)</td>
</tr>
<tr>
<td></td>
<td>Others, 15 (6.2)</td>
</tr>
<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td>Diabetes, 214 (88.4)</td>
</tr>
<tr>
<td></td>
<td>Hypertension, 94 (38.8)</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease, 34 (14.1)</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease, 41 (16.9)</td>
</tr>
<tr>
<td></td>
<td>Chronic liver disease, 6 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Others, 24 (9.9)</td>
</tr>
<tr>
<td></td>
<td>None, 22 (9.9)</td>
</tr>
<tr>
<td></td>
<td>Not mentioned, 2 (0.8)</td>
</tr>
<tr>
<td><strong>History of psychiatric illness, n (%)</strong></td>
<td>30 (12.4)</td>
</tr>
<tr>
<td><strong>History of metformin use, n (%)</strong></td>
<td>214 (88.4)</td>
</tr>
<tr>
<td><strong>Type of ingestion, n (%)</strong></td>
<td>Chronic use, 185 (76.4)</td>
</tr>
<tr>
<td></td>
<td>Suicidal, 52 (21.5)</td>
</tr>
<tr>
<td></td>
<td>Accidental, 3 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Unclear, 1 (0.4)</td>
</tr>
<tr>
<td></td>
<td>Not mentioned, 1 (0.4)</td>
</tr>
<tr>
<td><strong>Urine toxicology screen, n (%)</strong></td>
<td>15 (6.2)</td>
</tr>
<tr>
<td><strong>Time to presentation after acute intoxication (h)</strong></td>
<td>10.9 ± 13.8</td>
</tr>
<tr>
<td><strong>Hypoglycemia, n (%)</strong></td>
<td>59 (24.4)</td>
</tr>
<tr>
<td><strong>Therapies to reduce absorption, n (%)</strong></td>
<td>Activated charcoal, 16 (6.6)</td>
</tr>
<tr>
<td></td>
<td>Gastric lavage, 14 (5.8)</td>
</tr>
<tr>
<td></td>
<td>Whole bowel irrigation, 1 (0.4)</td>
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<tr>
<td><strong>Need for organ support, n (%)</strong></td>
<td>RRT, 166 (68.6)</td>
</tr>
<tr>
<td></td>
<td>Vasopressors, 142 (58.7)</td>
</tr>
<tr>
<td></td>
<td>Invasive mechanical ventilation, 128 (52.9)</td>
</tr>
<tr>
<td></td>
<td>Extracorporeal membrane oxygenation, 2 (0.8)</td>
</tr>
<tr>
<td><strong>Type of RRT, n (%)</strong></td>
<td>Haemodialysis, 83 (34.3)</td>
</tr>
<tr>
<td></td>
<td>Continuous RRT, 60 (24.8)</td>
</tr>
<tr>
<td></td>
<td>Slow low-efficiency dialysis, 13 (5.4)</td>
</tr>
</tbody>
</table>
for underlying renal dysfunction, metabolic acidosis correction, or metformin removal. Intermittent haemodialysis (IHD, 34.3%) was the most commonly employed method of RRT followed by continuous RRT (CRRT, 24.8%), which included both continuous veno-venous hemofiltration and continuous veno-venous hemodiafiltration. Overall, 41 (16.9%) patients had underlying CKD and were already on dialysis support. Only 17 survivors, who did not have pre-existing CKD, required RRT after hospital discharge, rest all showed complete recovery of renal function.
Records identified from PubMed database (n = 3590)
Science direct database (n = 10856)
Other sources, reference citation analysis and Google scholar (n = 76800)

Records removed before screening:
Duplicate records removed (n = 78006)

Records screened
PubMed (n = 291)
Science direct (n = 149)
Reference citation analysis and Google scholar (n = 12800)

Records excluded by filter:
(non-human, paediatric, and language other than English) (n = 12950)

Reports sought for retrieval (n = 290)

Reports removed after manually sorting for relevance: (n = 106)

Total studies included in review
(n = 184, case reports = 158, case series = 26)

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Figure 1 PRISMA flow diagram of the selected literature for this Meta summary. The inclusion criteria were (1) Case reports or case series with individual patient details; and (2) Reported toxicity or overdose of metformin.

Figure 2 Geographical distribution of the patients reported with metformin toxicity.

**DISCUSSION**

This review evaluated data of 242 individual patients from 158 case reports and 26 case series. Most of the patients had gastrointestinal or neurological symptoms at presentation. A great majority of patients (76.4%) developed metformin toxicity on chronic therapeutic doses. The most commonly reported side effect was MALA (92.6%). These patients had severe metabolic acidosis with hyperlactatemia and required multi organ support. RRT was employed in 68.6% of patients, and the cumulative mortality rate was 19.8%.

Several other isolated serious complications, in the absence of MALA, were also reported in many case reports. These included encephalopathy[10-14], psychosis[15], vitamin B12 deficiency[16], acute pancreatitis[17] and acute liver failure[18-22]. In our analysis, many patients (24.4%) developed hypoglycemia, attributed to sulphonylureas or other OHA that the patients were co-prescribed.
As metformin is primarily excreted by the kidneys, it is generally recommended not to use metformin in patients with underlying renal dysfunction[28]. Nonetheless, in our review we observed that 16.9% patients who developed metformin related side effects had underlying CKD. However, emerging literature supports the use of metformin in patients with mild to moderate renal dysfunction, when used in reduced dosage and regular monitoring[29].

Even though renal dysfunction is a major contributing factor for metformin toxicity, other factors like hypotension, dehydration, sepsis, ischemia, and liver impairment, which lead to increased production or impaired clearance of lactates, may also contribute to lactic acidosis. In our analysis, most of the patients on therapeutic doses of metformin who developed toxicity had some insult causing acute renal dysfunction which could have precipitated metformin toxicity. This acute insult included concomitant use of nephrotoxic drugs, acute infection, post-operative state or dehydration secondary to severe diarrhoea. Hence, it may be suggested that patients on long-term metformin should be closely monitored for the development of any side-effects in case of any acute renal insult, and concomitant use of nephrotoxic drugs should be avoided in these patients.

Patients with MALA had severe metabolic acidosis and hyperlactatemia, with the reported nadir of pH being 6.28[30]. The mainstay of therapy for MALA remains early aggressive resuscitation and organ support, as there is no specific antidote. In our analysis, intravenous soda-bicarbonate was used in a large proportion of patients (65.3%). Even though it may help in the correction of acidoses, it may lead to electrolyte imbalance and fluid overload. In addition, it does not help in the correction of the underlying cause. However, it may be reasonable to use intravenous bicarbonate in patients with severe acidemia and patients with an arterial pH less than 7.20 in the presence of underlying cardiovascular disease or hemodynamic compromise[31].

Low serum pH levels, and high lactate and metformin concentration have been associated with severe toxicity and higher mortality[32]. However, in our review, the patients with the lowest pH and highest serum lactate and metformin levels survived. All three patients with acute ingestion of massive doses of metformin (more than 100 g) survived after the institution of ECTR with complete recovery of renal functions[33-35]. In addition, patients with the highest serum metformin levels (2020 and 678 mcg/mL)[36,37] and patients with the highest presenting lactate levels (40.2 and 35.3 mmol/L)[38,39] also had favourable outcomes. The lowest pH reported was 6.28, in a post-operative diabetic CKD patient on prolonged metformin therapy, who survived after aggressive intensive care[30]. Similar findings have also been reported by other authors who found that blood pH, lactate and metformin levels were poor predictors of mortality in patients with MALA[40].

Even though metformin has a relatively large volume of distribution (1-5 L/kg), but its small molecular size (165 Da) and lack of protein binding makes it amenable for removal through ECTR. Hence, it may be suggested that patients on long-term metformin should be closely monitored for the development of any side-effects in case of any acute renal insult, and concomitant use of nephrotoxic drugs should be avoided in these patients.

However, in a few case reports no other cause could be ascertained and hypoglycemia was attributed to metformin toxicity[23-26]. The reported incidence for development of moderate to severe hypoglycemia is 60 per 100000 for patients on metformin therapy, with an odds ratio of 1.42[27].

As metformin is primarily excreted by the kidneys, it is generally recommended not to use metformin in patients with underlying renal dysfunction[28]. Nonetheless, in our review we observed that 16.9% patients who developed metformin related side effects had underlying CKD. However, emerging literature supports the use of metformin in patients with mild to moderate renal dysfunction, when used in reduced dosage and regular monitoring[29].

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have happened after EXtracorporeal TReatments In Poisoning guidelines, released in 2015, recommending ECTR for metformin toxicity[9]. Yeh et al[45], also included conference abstracts from the EMBASE database and included publications in all languages, explaining their relatively higher case numbers[45]. On the other hand, we included only English language papers and excluded conference abstracts. In addition, we also included all patients with metformin toxicity and even those in whom ECTR was not employed.

**Strength and limitations**
This review compiled 184 global studies involving 242 unique patients who had developed metformin toxicity. In addition, we included only studies with individual patient’s details to compare demographics, therapeutic interventions and outcomes.

The included studies were only case reports and case series without a control arm. Hence, the efficacy and cost-benefit analysis of ECTR compared to pharmacological therapy could not be performed. The studies were heterogeneous, with a high risk of bias and missing data, which may impact the generalisability of the results. As we excluded case reports or series which did not have individual biochemical data, we might have missed some relevant case reports or series.

**CONCLUSION**
Metformin is associated with significant toxicity, of which MALA is most commonly reported. Most of the reported cases were on therapeutic doses of metformin but developed toxicity after an acute deterioration in renal function. These patients may develop severe lactic acidosis, leading to significant morbidity and need for organ support. However, in spite of severe lactic acidosis and need for multiple organ support they may have good outcomes, especially when RRT is used for toxin removal. The dose of metformin, serum pH, lactate and metformin levels may indicate the severity of toxicity and the need for aggressive therapeutic measures but may not necessarily indicate poor outcomes.

**ARTICLE HIGHLIGHTS**

**Research background**
Metformin is arguably the most commonly prescribed oral hypoglycemic agent for the management of diabetes. Due to the lack of randomized control trials, most of the data pertaining to the clinical course, therapeutic interventions and outcomes of patients with metformin induced toxicity has come from case reports or series.

**Research motivation**
Despite severe acidosis, patients with metformin associated lactic acidosis (MALA) may have good clinical outcomes, if it is recognized early and aggressive resuscitation measures are initiated.

**Research objectives**
This study aimed to analyse the symptomology, clinical interventions and outcomes of patients presenting with severe metformin toxicity by reviewing the published case reports and series.

**Research methods**
We performed a systematic search from PubMed, Science Direct, Reference Citation Analysis (https://www.referencecitationanalysis.com/) and Google Scholar databases using the terms “metformin” AND “toxicity” OR “overdose” OR “lactic acidosis” OR “hyperlactatemia”. The inclusion criteria were case reports or case series with individual patient details; and reported toxicity or overdose of metformin in adults, published in the English language. Data regarding baseline demographics, clinical presentation, therapeutic interventions, intensive care unit course and overall outcome were collected.

**Research results**
Two hundred forty-two individual cases were analyzed, from 158 case reports and 26 case series, with a cumulative mortality of 19.8%. 214 (88.4%) patients were diabetics on metformin. 57 (23.6%) had acute ingestion, but 76.4% were on metformin in therapeutic doses when they developed toxicity. MALA was the most commonly reported adverse effect present in 224 (92.6%) patients. Patients with lowest pH and highest serum lactate and metformin levels also had favorable outcomes with use of renal replacement therapy.

**Research conclusions**
Most of the reported cases were on therapeutic doses of metformin but developed toxicity after an acute
deterioration in renal function. These patients may develop severe lactic acidosis, leading to significant morbidity and need for organ support. Despite severe MALA and the need for multiple organ support, they may have good outcomes, especially when renal replacement therapy is used. The dose of metformin, serum pH, lactate and metformin levels may indicate the severity of toxicity and the need for aggressive therapeutic measures but may not necessarily indicate poor outcomes.

Research perspectives

Larger trials may be required to identify the risk factors associated with poor outcomes in patients with MALA.

FOOTNOTES

Author contributions: Juneja D contributed to acquisition of data, analysis and interpretation of data, drafting the article, final approval; Nasa P contributed to acquisition of data, analysis and interpretation of data, drafting the article, final approval; Jain R contributed to interpretation of data, revising the article, final approval.

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