Drug Saf (2013) 36:733–746
DOI 10.1007/s40264-013-0038-6

ORIGINAL RESEARCH ARTICLE

The Role of Metformin in Metformin-Associated Lactic Acidosis (MALA): Case Series and Formulation of a Model of Pathogenesis

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Published online: 3 April 2013

Abstract

Background Lactic acidosis is an adverse event associated with metformin usage. Patients with metformin-associated lactic acidosis (MALA), however, often have other conditions contributing to the event. The relative contribution of metformin is often unclear. MALA is usually diagnosed without measuring the plasma concentrations of metformin.

Objectives The objectives of this study were, first, to examine the plasma concentrations of metformin, lactate and creatinine and the arterial pH of patients with suspected MALA and, second, to review critically the mechanisms of MALA.

Methods Patients who were suspected of having MALA were identified during the period October 2008–September 2011. Repeated blood samples were collected to determine the plasma concentrations of lactate, metformin and creatinine. The pH of arterial blood was also measured on several occasions in each patient.

Results Patients ($n = 15$; 9 female, 6 male) were 70 ± 12 years of age. There was one acute metformin overdose (estimated dose 5 g). Metformin was undetectable in one patient and one patient had therapeutic concentrations of metformin on admission (<5 mg/L). There were ten patients with chronic kidney disease, whereby the estimated glomerular filtration rate (eGFR) was less than 60 mL/min/1.73 m^2 before the acidotic event. Metformin doses ranged from 1 to 3 g daily (excluding the deliberate overdose). On admission, the mean plasma concentration of metformin on admission was 29.8 ± 19.1 mg/L (mean ± SD), the mean lactate concentration was 12.9 ± 6.1 mmol/L and the mean pH was 7 ± 0.2. The mean creatinine concentration on admission was 481 ± 225 μmol/L. The main pre-admission symptoms were vomiting and diarrhoea ($n = 12$). There were linear

Electronic supplementary material The online version of this article (doi:10.1007/s40264-013-0038-6) contains supplementary material, which is available to authorized users.

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relationships between venous lactate, venous creatinine and arterial pH, with the venous plasma concentrations of metformin in most patients. Three patients died but metformin was unlikely to have been a significant factor.

Discussion and review Most patients with MALA presented to the hospital with high metformin concentrations. The following factors appear to have been involved in the development of MALA in these patients: vomiting and diarrhoea, acute kidney injury, high doses or excessive accumulation of metformin, and acute disease states leading to tissue hypoxia. The extent of metformin accumulation in patients with MALA can be determined by investigating the concentrations of metformin. We suggest that the development of MALA is due to a positive feedback system involving one or more of these factors. While nausea is a common adverse effect of metformin, vomiting and diarrhoea out of the ordinary is a clear first sign of MALA. In this condition, dosage with metformin should be stopped and patients should receive urgent medical attention.

1 Introduction

Metformin, a biguanide, is recommended as the first-line pharmacological agent for the treatment of type 2 diabetes mellitus (T2DM) [1]. Metformin is renally excreted and its accumulation in patients with chronic kidney disease (CKD) has been claimed to be a cause of lactic acidosis, which has a mortality rate that approaches 50 % [2].

Lactic acidosis is defined as an arterial blood lactate concentration greater than 5 mmol/L and arterial pH less than 7.35 [3]. Lactic acidosis during therapy with metformin is uncommon and a causal link with metformin is controversial [4–6]. The clinical presentation is commonly termed metformin-associated lactic acidosis (MALA). For brevity, we also use the term MALA while emphasising the often questionable causation of lactic acidosis by metformin. Some cases of what is termed MALA may be unrelated to metformin because the plasma concentrations of metformin may have been too low to cause lactic acidosis. There are many case reports of MALA but the concentrations of metformin have generally not been studied. In the few published surveys of the plasma metformin concentrations in MALA, samples of blood were mostly collected at unspecified times during the treatment [6–10]. The relationship between single plasma concentrations of metformin from each patient with plasma lactate or arterial pH was generally scattered and the correlation was not significant [6, 8, 10, 11]. In studies where serial blood samples were collected to examine concentrations of metformin, lactate and arterial pH [11, 12], possible correlations with measures of lactic acidosis were not examined.

Our studies commenced with a patient who was hospitalised twice with lactic acidosis. The association with metformin was not identified on the first episode (dose 1.7 g daily) and, consequently, the patient was recommenced on metformin and at a higher dose (2 g daily). The second episode of lactic acidosis occurred a year later. On this occasion the progress of the MALA was followed through multiple measurements of plasma metformin, lactate and creatinine concentrations and arterial pH. Fifteen further suspected cases of lactic acidosis were examined similarly with collection of multiple blood samples.

A crucial aspect of our arguments on the association between metformin and lactic acidosis is consideration of the therapeutic range of concentrations of metformin. Lalau et al. [13] suggested that plasma concentrations above 5 mg/L should be regarded "pragmatically" as markedly elevated. In agreement with this figure, the product label states that plasma concentrations of metformin generally have not exceeded 5 mg/L in clinical trials.

In this communication, we report our experience with the repeated measures of arterial pH and the venous concentrations of metformin, lactate and creatinine. The issues raised by the analysis of these factors prompted a detailed review of the literature and discussion of our findings. In turn, this allowed us/led us to propose a novel positive feedback scheme for the development of MALA. Newer or neglected aspects of literature on the handling of metformin, such as intra-patient variation in the oral absorption of metformin, the toxicology of metformin in animals, its effects on mitochondrial function and the potential influence of transporters of metformin, have been considered.

2 Materials and Methods

We performed a clinical review of 15 patients with suspected MALA. Patients were treated in various hospitals in Sydney and Canberra in the period October 2008–September 2011. St Vincent's Hospital Ethics Committee waived the need for formal approval of the study for this review of cases while the ACT Government Health Directorate Human Research Ethics Committee (HREC) granted approval to study a patient from Canberra Hospital (ETHR.11.224).

The demographics and clinical characteristics of the patients before and following their episode of lactic acidosis were collected. These data comprised metformin dose, comorbid diseases, condition on admission, treatments received and outcome. The plasma concentrations of creatinine and lactate and arterial blood pH were measured repeatedly according to routine clinical practice as markers of lactic acidosis. The assay for lactate concentrations was specific for L-lactic acid. Metformin concentrations were measured in one to 16 blood samples from each patient.

Plasma metformin concentrations were measured by a validated high-performance liquid chromatography assay with a Zorbax Cyano column [14]. The mobile phase consisted of methanol:acetonitrile:phosphate buffer (20:60:20, v:v; pH adjusted to 7.0 with acetic acid; flow rate of 2.0 mL/min; 40 °C). Quantification was achieved using UV detection (236 nm) and peak height ratios of six calibration standards (0.05–10 mg/L) with two quality control samples (QC; 1.0 and 3.0 mg/L).

Statistical analyses were performed using GraphPad Prism (Version 5; GraphPad Software Inc., San Diego, CA, USA). The data were presented as mean and standard deviation. In patients with sufficient plasma concentrations ($n \geq 5$) of metformin, a Pearson correlation was used to evaluate the association between metformin and concentrations of creatinine, lactate and pH. If the blood samples for metformin concentrations were collected at different times than samples for creatinine, lactate and pH, the plasma concentrations of metformin were then interpolated in the correlations of metformin with the biochemical markers of lactic acidosis.

3 Results

3.1 Patient Details

Fifteen patients with suspected MALA were examined, including patient 1 who was admitted twice for lactic acidosis (Sect. 1). Patients were 70 ± 12 years of age (mean ± SD), 9 females and 6 males, and were prescribed metformin 1–3 g daily (Table 1). Patient 15 was suspected to have MALA, but no metformin concentrations could be detected. This patient admitted to not taking his prescribed metformin doses for at least 3 months (Table 2). Thus, 14 patients had MALA and were admitted with metformin concentrations of 29.8 ± 19.1 mg/L, lactate concentrations of 12.9 ± 6.1 mmol/L and pH of 7 ± 0.2.

Most of the patients had CKD (eGFR <60 mL/min) and only five patients on long-term metformin therapy had eGFR values of 60 mL/min or more (Table 2). Patient 13 also had an eGFR greater than 60 mL/min but took an acute overdose of metformin. Seven of the 14 patients were also taking sulphonylurea drugs such as glipizide or glibenclamide.

3.2 Patterns of Plasma Concentrations of Metformin, Creatinine, Lactate and Arterial pH

Most MALA patients followed the pattern seen with patient 5 (Fig. 1; Supplementary Figure 1). In 11 patients, plasma concentrations of creatinine were much higher on admission (481 ± 225 μmol/L) than before the episode of MALA (118 ± 40 μmol/L; Table 2). In these 11 patients, the plasma concentrations of metformin, lactate and creatinine decreased approximately in parallel while the pH of arterial blood increased (Figs. 1, 2).

There were ten patients with sufficient plasma concentrations ($n \geq 5$) of both creatinine and metformin for the computation of the correlation coefficients (Supplementary Table 1). The correlations between metformin and creatinine concentrations were significant ($P < 0.05$) in eight of these ten patients. In three patients, the plasma concentrations of creatinine decreased initially but increased on cessation of haemodialysis (Supplementary Figure 1).

The correlations between plasma lactate and metformin were significant in six of nine patients with sufficient clinical data and approached significance ($0.1 > P > 0.05$) in two patients. For arterial pH, the correlation with plasma metformin was significant in seven of the nine patients. There were no significant correlations between the *peak* concentrations of metformin and either plasma lactate, plasma creatinine or arterial pH. At metformin concentrations of 10 mg/L or lower, the plasma lactate and pH of arterial blood generally returned to values within the normal range (Figs. 1, 2; Supplementary Figure 1).

There were three patients who did not follow the general trend. Patient 13 took an overdose of metformin and recovered from the episode of lactic acidosis within 30 h, with no significant changes in the creatinine concentrations (Fig. 1c; Table 2).

Patient 14 was admitted unconscious with low concentrations of metformin (<2.5 mg/L) and lactic acidosis developed subsequently (Table 2). This patient died 1 day after admission (Table 1).

Patient 8 had one of the lowest plasma metformin concentrations of the study cohort on admission (16 mg/L; Supplementary Figure 1). The plasma concentrations of creatinine were only slightly greater on admission (199 μmol/L) than before MALA developed (173 μmol/L; Table 2). This patient died 14 days after admission.

Patient 10 died 8 days after admission of respiratory complications associated with cancer of the lung. Plasma metformin, creatinine, lactate and arterial pH followed the general pattern and this patient no longer had lactic acidosis after 30 h (Fig. 1). Plasma lactate and creatinine subsequently increased at 4–5 days after admission.

Classification of the MALA in all patients is described in the section: there may be different forms of MALA.

3.3 Clinical Conditions and Outcomes

Most patients had risk factors other than metformin therapy for lactic acidosis (Table 1). The only clear exception was the patient who took an overdose of metformin (5 g) who

Table 1 Medical condition, treatment and survival of patients with lactic acidosis

Patient	Age/sex	Metformin (mg/day)	Comorbidities	Condition on admission	Treatment	Outcome
1	63/F	1,700	Hyperthyroidism, recent urinary infection	Cyanosed, hypotensive, obtunded, sepsis	CRRT, IV fluids, inotropes, vasopressors, antibiotics	Survived
2	59/F	2,000	Atrial fibrillation, asthma, recent urinary infection	Anorexia, nausea, vomiting, fluid retention and oliguria	CRRT, IV fluids, inotropes, vasopressors and antibiotics	Survived
3	69/F	1,000	End-stage renal disease on haemodialysis, congestive cardiac failure	Vomiting, anorexia, epigastric	Intermittent HD, IV fluid, $NaHCO_3$, vasopressors	Survived
4	90/M	2,000	Atrial fibrillation, chronic obstructive pulmonary disease	Nausea, vomiting, diarrhoea, dehydrated, anorexia, hypoglycaemia, oliguria	CRRT, IV fluids, glucose, vasopressors	Survived
5	83/M	2,000	Coronary artery disease, interstitial lung disease	Anorexia, vomiting and diarrhoea	CRRT, IV fluids, glucose, vasopressors	Survived
6	77/F	2,000	Cerebrovascular disease	Lethargy, anorexia, nausea, vomiting	CRRT, IV fluids	Survived
7	67/F	2,000	Recent coronary artery bypass graft, atrial fibrillation, congestive cardiac failure	Lethargy, vomiting and diarrhoea	CRRT, IV fluids, $NaHCO_3$, inotropes, vasopressors	Survived
8	81/M	1,000	Prostate cancer, cardiac failure, chronic kidney disease, liver failure	Congestive cardiac failure, present with lethargy and general decline. Vomited once and 3 episodes of diarrhoea	CRRT, IV fluids, glucose,	Died, 14 days later
9	63/F	2,500	Hypercholesterolaemia	Vomiting	CRRT, IV $NaHCO_3$, inotropes	Survived
10	65/M	3,000	Ischaemic heart disease, cerebrovascular disease, gastro-oesophageal reflux disease, hypercholesterolaemia	Found unconscious	CRRT then intermittent HD, IV glucose	Died, 8 days later
11	82/M	3,000	Ischaemic heart disease, hypercholesterolaemia	Epigastric pain and a 2-week history of diarrhoea and anorexia	CRRT, intubation, ventilation, vasopressors, antibiotics	Survived
12	73/F	3000	Congestive cardiac failure with mitral regurgitation, pulmonary embolism	Lethargy, reduced appetite, respiratory distress	CRRT, IV fluids, $NaHCO_3$, inotropes	Survived
13	45/F	5,000[a]	Past gliclazide overdose, past intravenous drug use, alcohol abuse, hepatitis C, hypothyroidism	Deliberate self-poisoning with metformin, diarrhoea	CRRT, thiamine, insulin	Survived
14	74/F	2,000	Hepatitis C	Unconscious, hypotensive, septic shock	CRRT, antibiotics, vasopressors	Died 1 day after admission
15	61/M	1,000[b]	Atrial flutter, gout. No metformin for 3 months	Lethargy, vomiting and diarrhoea	CRRT, IV $NaHCO_3$, vasopressors	Survived

M male, *F* female, *IV* intravenous, *$NaHCO_3$* sodium bicarbonate, *CRRT* continuous renal replacement therapy, which includes continuous veno-venous haemodiafiltration and continuous veno-venous haemodialysis, *HD* haemodialysis

[a] Metformin overdose

[b] Patient was non-compliant

had no other risk factor. Twelve of the 14 patients with MALA experienced gastrointestinal symptoms (vomiting and/or diarrhoea) either on admission or in the days preceding hospital admission. The remaining four patients on admission were either obtunded or comatose and their prior acute conditions are unknown.

The most common form of treatment was renal replacement therapy. Either intermittent haemodialysis

Table 2 Biochemistry of patients before lactic acidosis compared to altered biochemical parameters during hospitalisation. The maximal concentrations of creatinine, lactate and anion gap are shown together with the minimal values of pH and plasma bicarbonate

Patient	Baseline		On admission						
	eGFR (mL/min/1.73 m^2)	Creatinine (μmol/L)	Metformin (mg/L)	Metformin half-life (h)	Creatinine (μmol/L)	Lactate (mmol/L)	pH	Anion gap	Bicarbonate (mmol/L)
1	43	119	–	–	862	12	6.8	47.4	4
		97	46	23	748	5.2	7.1	36.6	11
2	55	145	31	25	461	9.2	7.16	38.2	8
3	ESRD on dialysis	–	35	N/A	500	19	6.87	44	<10
4	>60	72	54	60	663	12.3	7.06	–	14
5	>60	80	52	69	740	5.5	7.14	–	<10
6	52	140	26	74	477	6.8	7.12	18.1	<10
7	>60	80	37	32	692	19.9	6.97	42.1	<16
8	33	173	16	13	199	9.9	7.2	19.8	16
9	50	97	25	16	740	11.7	6.75	41.9	6
10	28	160	27	22	653	7.8	7.31	29.6	19
11	50	121	60	13	462	17	6.83	37.3	<10
12	47	100	1.5[a]	N/A	235	19	6.73	28.2	6
13	>60	52	36	29	61	7.4	7.22		15
14	43	109	1.5	N/A	220	21	6.93	27.3	20
15	>60	93	0	N/A	368	22	6.6	57.6	<10

N/A not enough samples for half-life to be determined, *ESRD* end-stage renal disease

[a] Collected 40 h after admission

(IHD) or continuous renal replacement therapy (CRRT) was used in the management of 13 patients. Renal replacement therapy not only corrected the acidosis, but it also may have enhanced the elimination of metformin and creatinine. Sodium bicarbonate was also administered for correction of acidosis in six patients (Table 1).

4 Discussion and Review of MALA

The present study is, to date, the largest published case series of patients with MALA in which the time courses of venous concentrations of metformin, lactate and creatinine and the arterial pH were examined. There has been very little previous correlation between the plasma concentrations of metformin and creatinine, lactate and pH in individual patients. In addition, concomitant clinical conditions, treatment and outcomes of the patients were also recorded. The issue of 'causality' with respect to metformin and MALA has been debated widely. In this discussion, we have reviewed various factors that may be involved in the development of MALA. Some of these factors arose from the present study while others are hypothesized from recent work on transporters of metformin, which has yielded new insights into the possible aetiology of MALA. Dosage recommendations for metformin are also discussed.

4.1 The Timing of Blood Samples

Most previous studies on MALA did not report the times of blood collection for the measurement of metformin, creatinine, lactate and pH [6–9]. In the present series, we have examined the time course of concentrations of metformin in comparison to markers of lactic acidosis. This has yielded a much better analysis of lactic acidosis associated with metformin treatment (Figs. 1, 2). An important limitation is that the onset of the MALA is not evident to the patient and there is an inevitable and variable delay before hospitalisation.

Examination of the detailed time course of clinical and laboratory features of MALA is particularly important in understanding the processes involved after metformin overdoses because the episode of MALA may be missed. Patient 13 took a small overdose of metformin (5 g) and the associated lactic acidosis lasted for only about 24 h (Fig. 1). Measurement of plasma lactate or arterial pH at later times would have missed an association between metformin and the acidosis.

4.2 Acute Overdoses of Metformin Can Cause Lactic Acidosis

The clearest finding linking metformin causally to lactic acidosis is following acute overdoses [9, 15–19].

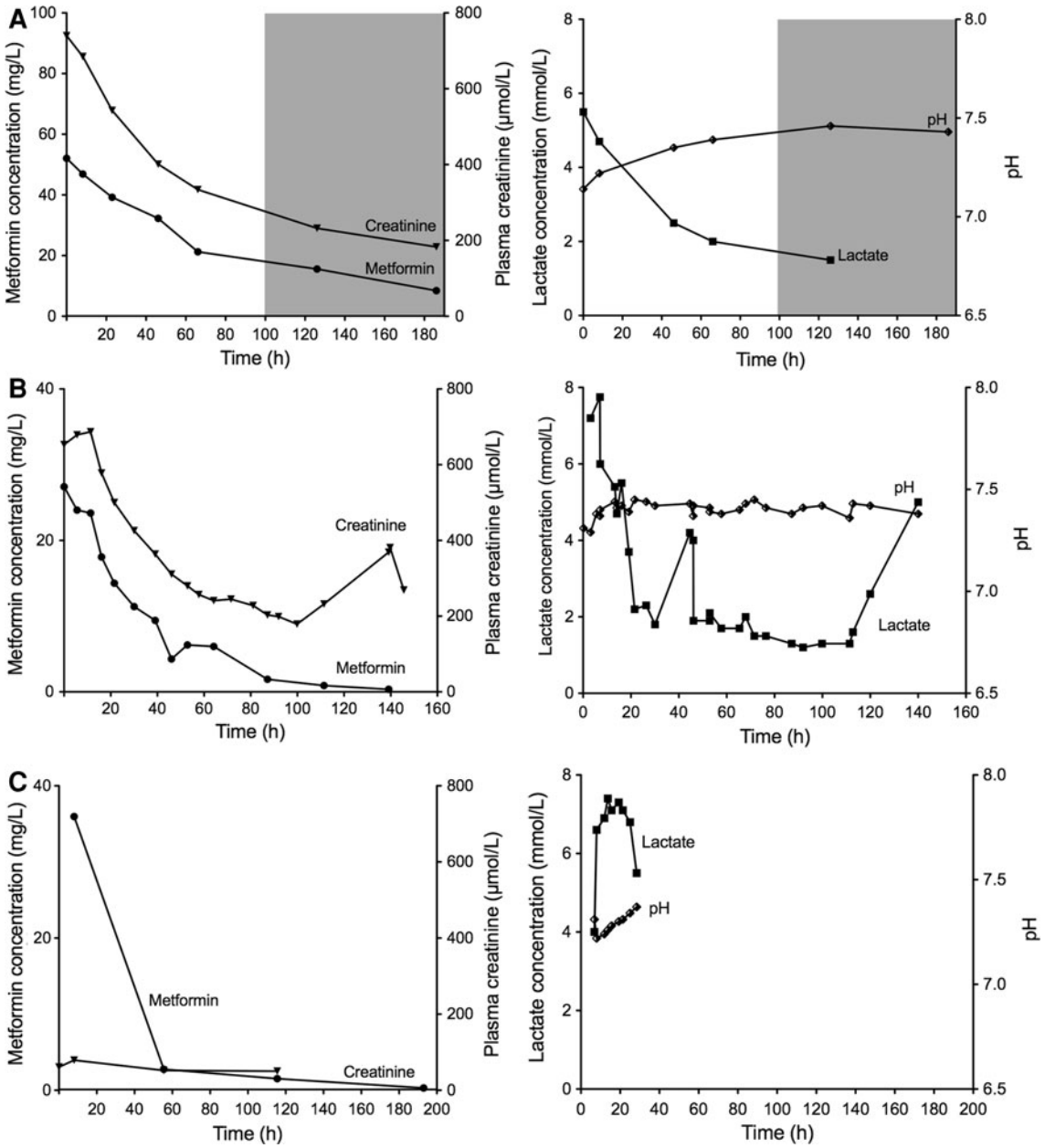

Fig. 1 Metformin, creatinine, lactate and pH concentration-time profiles in **a** typical patient with metformin-associated lactic acidosis (patient 5), **b** patient who died (patient 10) and **c** patient who took an overdose (patient 13). The *grey shaded area* represents the duration of the dialysis session for patient 5

4.3 Lactic Acidosis is Frequently Associated with Supratherapeutic Plasma Concentrations of Metformin

As discussed above, plasma concentrations up to 5 mg/L are considered to be therapeutic. Excluding patient 12 for whom the concentration of metformin was not determined on admission, only patient 14 had metformin concentrations below 5 mg/L. It is of note that, apart from the patient who took an overdose of metformin, the two patients with the lowest plasma metformin concentrations (patient 8, 16 mg/L; patient 14, 1.5 mg/L) had the lowest plasma creatinine concentrations, indicating a lesser degree of acute renal impairment during their episodes of MALA. It is also possible that these patients missed metformin doses because of their illness.

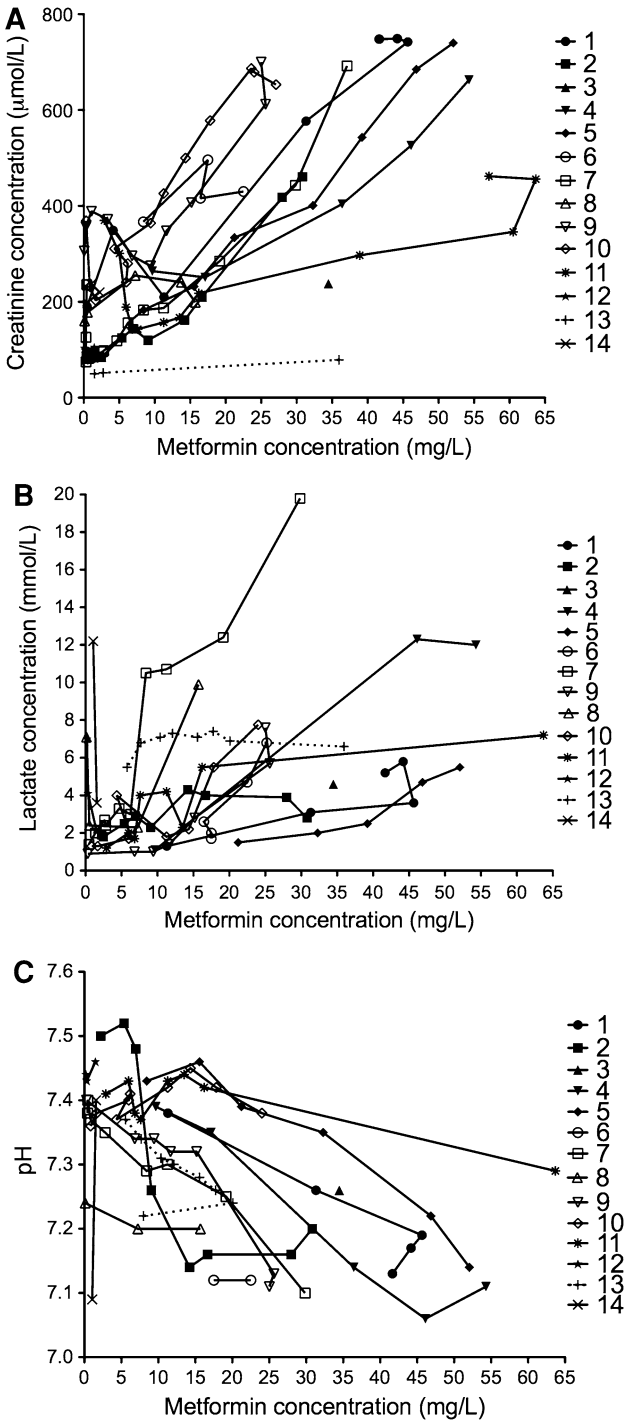

Fig. 2 Plasma concentrations of creatinine, lactate and pH concentrations plotted against metformin concentrations

4.4 Plasma Lactate, Creatinine and Arterial pH Correlate with Plasma Concentrations of Metformin in Many Patients with MALA

Previous studies on single plasma concentrations in individual patients have yielded poor or no significant correlations between the plasma metformin and the plasma concentrations of creatinine or lactate or arterial pH. This has been taken to indicate that metformin is not a major cause of MALA except after acute overdoses [6].

The present study also found that the peak plasma concentrations of metformin did not correlate with plasma creatinine, lactate or arterial pH. By contrast, a substantial finding in the present study was that the plasma concentrations of lactate and creatinine decreased approximately in parallel with the plasma concentrations of metformin, while the arterial pH increased in many patients. There was sufficient data (5 blood samples) on one patient in a published study to examine the relationships between plasma metformin and measures of lactic acidosis [12]. Our analysis of this published case showed significant correlations between plasma metformin and both plasma creatinine and arterial pH but not plasma lactate (Supplementary Table 1; Supplementary Figure 2).

Correlations certainly do not prove causation but the significant correlations in several patients is consistent with metformin being a major contributor to MALA. Furthermore, these correlations indicate the value of collecting multiple samples of blood in studying the mechanisms of MALA.

4.5 Toxicological Studies in Animals Indicate that Metformin Increases the Plasma Concentrations of Lactate

During infusion of metformin to rats, lactate concentrations begin to increase when plasma metformin concentrations reach about 20 mg/L [20]. Similarly, most patients from the present study had metformin concentrations above 20 mg/L. In pigs, lactic acidosis developed following acute overdoses of metformin (about 6 g) [21]. Furthermore, the concentrations of metformin were associated with the severity of MALA, whereby the pig with the lowest concentration (3 mg/L) did not develop significant lactic acidosis.

4.6 Overdoses of Metformin May Decrease Renal Function

Increases in plasma creatinine levels have been noted in two overdosed patients with MALA [15, 16]. This was not seen in patient 13 who took a small overdose with an associated short period of lactic acidosis.

4.7 Patients Generally Take Metformin for Long Periods Before the Development of MALA

Prolonged dosage with metformin before MALA develops has been noted in several reports [5, 7, 22]. This was

confirmed in the present case series where patients had been taking metformin for many months before developing lactic acidosis. This is of particular note in the index case (patient 1) in the present series. This patient had an episode of probable MALA and then was dosed with metformin for a year before the second proven episode of MALA.

An interesting but contrasting report [23] involves a patient who, after metformin therapy for an unspecified time, developed lactic acidosis. The significance of this report is that the patient did not have risk factors for lactic acidosis and plasma lactate increased a week after reinstitution of dosage with metformin. The case also provides evidence for metformin being, at least in some instances, a direct cause of lactic acidosis, even at the low plasma concentrations of metformin (2.1 and 1.3 mg/L) in this patient. While the times of blood collection during a dosage interval were not stated, it is still surprising that toxicity was produced at such low concentrations of metformin. It would be of interest to determine whether this patient has a deficient organic cation transporter (see later discussion of transporters).

4.8 Vomiting and Diarrhoea Are Often Associated with Lactic Acidosis

Vomiting and diarrhoea were recorded prior to admission in 10 of 13 patients in the present series and have been noted previously in several reports of MALA [22, 24, 25]. Nausea, vomiting or diarrhoea has also been reported after acute overdoses of metformin [26, 27] and may be a response to acidosis or be caused by the accumulation of metformin within the gut wall. In the present case series, vomiting and diarrhoea were also reported in patient 13 who took a small overdose of metformin (Table 1). Vomiting and diarrhoea if sustained and severe are expected to lead to dehydration and hypovolaemia and, in turn, impaired renal function, especially in patients with pre-existing cardiac and/or renal disease [23, 28, 29]. Overall, vomiting and diarrhoea may be causes *or* symptoms of MALA. Nausea is a common adverse effect of metformin but more severe gastrointestinal adverse effects appear to be signs of current or impending lactic acidosis in many patients presenting with MALA.

It is notable that patient 15, in whom metformin was not found, reported gastroenteritis before lactic acidosis was detected. In 1925, lactic acidosis was reported in several children with gastroenteritis [30]. Vomiting and diarrhoea are also quite common early symptoms in the acidosis associated with HIV treatment (see below) and may be a general precursor *or* symptom of lactic acidosis. Of course, vomiting and diarrhoea are commonly caused by infection and may not be caused by metformin. However, the common occurrence of vomiting and diarrhoea in patients taking metformin who develop MALA indicates that these symptoms are danger signals for possible lactic acidosis.

4.9 Lactic Acidosis Is Often Associated with Acute Renal Impairment

A common finding in cases of MALA is that the plasma concentrations of creatinine are high on admission and higher than in routine clinical biochemical tests prior to the MALA episode [6, 10, 31]. This was also found in the present study where plasma creatinine was markedly higher in 11 patients than measured previously when the patients were well.

The plasma concentrations of creatinine may also be acutely elevated in patients who have taken acute overdoses of metformin [15, 16, 32]. No such elevation was seen in patient 13 but, as mentioned, this patient had taken a much smaller dose of metformin. By contrast, in previously reported cases, estimated doses ranged from 13 to 77 g [16, 32].

The acute renal impairment observed in most patients with MALA will have a marked effect on plasma metformin because metformin is excreted unchanged in urine [28]. Consequently, any acute decrease in renal function will lead to accumulation of metformin, which may, in turn, contribute towards induction of lactic acidosis if metformin dosage is continued.

4.10 The Clinical State of Patients Has a Variable Influence on the Development of MALA

It is widely recognised that many patients who develop MALA have medical conditions that may lead to tissue hypoxia and hence to lactic acidosis. This was the case in the present series where most patients had concurrent disease states such as ischaemic cardiac disease, cardiac failure, atrial fibrillation and asthma (Table 1). However, the long delay between the start of metformin treatment and the development of MALA indicates that the chronic risk factors are not immediate causes of lactic acidosis and that there must still be a precipitating cause of the episode. Possibly, an acute exacerbation or decompensation of one of these conditions may be the precipitating factor [33].

Heart failure is listed as a contradiction to the use of metformin in the product information and is a frequent reason for not using the drug. However, three recent observational studies found that, in patients with chronic heart failure, there was less cardiovascular mortality in patients treated with metformin than in patients treated with sulphonylureas [34–36] while no such effect was shown in a fourth study [37]. Health Canada has removed heart failure as a contraindication to metformin use [38] while the UK National Institute for Health and Clinical

Excellence guidelines (NICE) document does not give a clear opinion [39].

4.11 Chronic Kidney Disease (CKD)

Acute kidney injury is common in patients who develop MALA [7, 10]. This has led to renal impairment being listed as a risk factor for the development of MALA. As shown in the present studies and that by Lalau et al. [10], many patients with MALA do have CKD before the development of MALA.

Renal clearance of metformin is proportional to the clearance of creatinine and hence it is widely recommended that the dose of metformin should be reduced in renal impairment [28, 40]. Furthermore, it is commonly stated that metformin should only be prescribed if creatinine clearance or GFR is above a defined lower limit. The problems for prescribers are that many patients with renal impairment have been documented as receiving metformin (see below) and also that recommendations on the limiting renal function are inconsistent. The product information [41] states that metformin should not be prescribed when creatinine clearance is below 60 mL/min. Other references include a lower limit of 30 mL/min [42]. The NICE guidelines [39] advise against using metformin when estimated GFR is <30 mL/min/1.73 m^2 or, according to the FDA guidelines, if the serum creatinine concentration is elevated [male, ≥1.5 mg/dL (134 μmol/L); female, ≥1.4 mg/dL 124 μmol/L)] [43].

As a guide, we suggest that the maximal dose of metformin should be adjusted approximately in proportion to the creatinine clearance. As the maximal recommended dose of metformin is 3 g daily in patients with good renal function, then, at a creatinine clearance of 60 mL/min, the maximal dosage should be approximately 1.5 g daily and 0.75 g daily at 30 mL/min. As is widely recommended, however, patients should still start at a lower dosage and gradually increase the dosage depending on their response and tolerance. However, many patients with renal impairment have received excessive doses as judged by their renal function. For example, Lalau and Race [7] reported that three patients with acute kidney injury were taking total daily doses of 2.6 g metformin, while from the present study, of the patients with eGFR values less than 60 mL/min/1.73 m^2, four patients were receiving 2 g daily; one patient was dosed with 2.5 g daily and three patients were receiving 3 g daily. Thus, we suggest that the 11 patients with significant renal impairment were receiving excessive daily doses of metformin. The plasma concentrations of metformin may have been already high and even a small decrease in renal function may result in plasma concentrations that are sufficient to trigger the lactic acidosis. This concept is discussed further in our suggested positive feedback mechanism of MALA (see Sect. 5).

4.12 Patients with Impaired Renal Function can and do Take Metformin

The dosage of metformin should, on average, be lower or decreased in patients with renal impairment. Surveys indicate that metformin is commonly prescribed for patients with eGFRs down to 30 mL/min [23] and, in small numbers of patients, at even lower creatinine clearances [44]. We have recently administered metformin to five patients with creatinine clearances ranging from 15 to 35 mL/min and to two patients with creatinine clearance <10 mL/min (patients were receiving dialysis). No patient developed lactic acidosis [45]. These studies indicate that metformin, at reduced doses, can be administered to patients with CKD provided that kidney function is stable [46].

4.13 MALA Can Occur in Patients Without Significant Prior Renal Impairment

MALA can occur in the absence of CKD [12, 47]. Similarly, although most patients in the present studies had substantial renal impairment, three patients had eGFR values above 60 mL/min before MALA developed. All three had acute renal failure during their episodes of MALA.

4.14 MALA May Be Triggered by Iodinated X-ray Contrast Agents

MALA has occurred in patients taking metformin and who were given iodinated X-ray contrast agents [48]. The occurrence of MALA is not surprising given that the contrast agents can produce acute renal failure, especially in patients with CKD. There are inconsistencies in the guidelines in the administration of contrast medium to patients who are taking metformin [49]. However, it is generally recommended that if patients have CKD, metformin should be ceased 48 h before administration of the contrast medium [50], whilst, if patients have eGFR <30 mL/min, iodine-based contrast media should be avoided. Also, the use of non-ionic contrast media and adequate hydration prior to these investigations have reduced the risk of acute renal failure substantially.

4.15 The Variable Oral Absorption of Metformin May Contribute to MALA

An important aspect of the pharmacokinetics of metformin is its incomplete and variable absorption. In a study of four healthy subjects, Tucker et al. [40] found that oral absorption ranged from 25 to 80 %. The within-subject, fractional absorption varied by no more than 20 % in three

of the four subjects but two studies on one subject yielded oral availabilities of 24 and 54 %, respectively. While further work is required, it is possible that a large increase in the oral availability of metformin could increase the risk of MALA. This may be the case, particularly in patients with chronic renal impairment who are taking high doses, as judged from their creatinine clearances.

4.16 Transporters of Metformin Are pH Sensitive and Acidosis May Alter the Absorption, Distribution and Elimination of Metformin

Metformin is a highly ionised, water-soluble drug and is absorbed, distributed and excreted by organic cation transporters (OCTs), the plasma membrane monoamine transporter (PMAT) and the multidrug and toxin extrusion transporter 2-K (MATE2-K) [28].

The rate of cellular uptake of organic cations in vitro by OCT1 and OCT2 is reduced as pH decreases [51], while, by contrast, the transport by PMAT is increased [52]. The MATE2-K is a hydrogen ion antiporter, i.e. it transports organic cations, including metformin, with an associated exchange of H^+. A lower pH should, therefore, favour the slower transport of metformin into cells [53, 54].

The effect of an acidotic episode on the pharmacokinetics of metformin in vivo is not known, but we suggest that acidosis could alter the absorption, distribution and/or elimination of metformin. Alternatively, high concentrations of metformin may lead to acidosis. In experimental animals, these are testable hypotheses, which may give insight into the association between metformin and lactic acidosis.

4.17 Creatinine Is Transported by the OCT2 and There May Be Competition Between Metformin and Creatinine

Recent work on the transport of organic cations indicates a further complexity. A feature of patients with high plasma concentrations of metformin is the very high plasma concentrations of creatinine. Elevated creatinine is taken to indicate acute renal failure; however, there may be an alternate mechanism. As is very well known, creatinine is largely excreted in urine by filtration in the glomerulus. Consequently, the renal clearance of creatinine is used widely as a measure of the glomerular filtration rate. However, some creatinine is cleared by secretion and OCT2 appears to be important in this process [55]. Metformin is also a substrate of OCT2 [28] and there may be a competitive interaction between metformin and creatinine. The in vivo consequences are unknown but massive plasma concentrations of metformin attained by many patients with MALA may inhibit the renal secretion of creatinine. Conversely, high plasma concentrations of creatinine may inhibit the renal secretion of metformin such that the calculated GFR may underestimate the true value. Again, these are testable hypotheses.

4.18 Inhibition of Mitochondrial Electron Transport by Metformin Is a Major Cause of MALA

Metformin is an inhibitor of mitochondrial electron transport, an effect that favours anaerobic metabolism and the accumulation of lactate [21]. The level of inhibition is dose-dependent in vitro and has been well demonstrated at supratherapeutic concentrations [56]. However, the inhibition of mitochondrial electron transport also increases with time in in vitro studies at metformin concentrations of 50 μM (6.5 mg/L) [56]. Consequently, it is difficult to make meaningful correlations between toxic concentrations in plasma and mitochondrial-suppressive concentrations in vitro. However, a recent study of metformin overdoses in pigs showed decreased oxygen consumption, consistent with inhibition of electron transport in the mitochondria in vivo [21]. Furthermore, isolated mitochondria from heart, liver, kidney and skeletal muscle in the overdosed animals showed depressed electron transport (particularly complex 1).

4.19 The Lactic Acidosis Seen During Antiviral Treatment for HIV Infection Is Similar to the Lactic Acidosis Seen with Metformin

Lactic acidosis is an uncommon adverse effect of treatment with nucleoside reverse transcriptase inhibitors (NRTI), such as stavudine and zidovudine [57]. As is the case with MALA, the patients have malaise, nausea, vomiting and diarrhoea [58, 59]. The lactic acidosis associated with NRTIs has a high mortality [59], again, as is the case with MALA. The lactic acidosis seen with NRTIs appears to be due to inhibition of mitochondrial electron transport [59], and, therefore, may have a similar metabolic basis to most cases of MALA.

The mitochondrial deficit produced by NRTIs may be due to loss of mitochondrial enzymes following depletion of mitochondrial DNA [60]. No such mechanism has been suggested for metformin. Acute increases in serum creatinine do not appear to be common in cases of lactic acidosis due to NRTI, in contrast to MALA.

4.20 Lactic Acidosis Is Not Associated with Sulphonylureas

Many patients in the present series were also taking sulphonylurea hypoglycaemic drugs. These were ceased during the episodes of MALA and the plasma concentrations

of the sulphonylureas would have been decreasing. However, it is unlikely that such decreases contributed to recovery from MALA. In one previous study lactic acidosis been claimed to develop during treatment with sulhonylureas. However, three of the four patients who developed lactic acidosis during sulphonylurea therapy in that previous study were also taking metformin [61]. An association between sulphonylureas and lactic acidosis cannot be supported.

4.21 Variable Incidence of MALA Has Been Reported

It should be remembered that MALA is uncommon. Not a single case of lactic acidosis was recorded in clinical trials of metformin, involving more than 70,000 patient-years of metformin treatment [62]. In epidemiological studies, the incidence of MALA has been estimated to occur at rates of 1 to 15 per 100,000 person years [63], 3.4 [61], 22 [64], 30 [65] and 47 [8] to 57 [66] cases per 100,000 patient years. The reported incidence is thus variable but the higher figures for metformin (about 1 per 2,000 patient years) are particularly worrisome given its increasingly widespread usage. MALA clearly requires more detailed study so that the risks are better understood.

4.22 There May Be Different Forms of MALA

Classification of MALA is difficult. Lalau and Race [7] have suggested that there are three possible scenarios. Our results support this categorisation.

1. The first is when low metformin or creatinine concentrations in plasma are detected. In these cases, lactic acidosis may be caused by tissue hypoxia related to comorbid conditions such as sepsis or acute heart failure. We consider that metformin is not the cause of the lactic acidosis [5]. As Lalau and Race [7] have recorded, deaths are very common in this group. Patients 8 (little increase in plasma creatinine and relatively low plasma metformin) and 14 (low plasma metformin) in the present series are in this category. Both these patients died.
2. The second form is uncommon. This is lactic acidosis in the presence of high plasma concentrations of metformin but without any associated factors other than renal failure. Overdosed patients are in this category and their renal failure may be due to metformin (see Sect. 4.6), possibly because of the vomiting and diarrhoea that may be caused by metformin. Patient 13 in the present series is in this category but did not have renal impairment because the acidosis was short-lived.
3. The third scenario is lactic acidosis due to accumulation of metformin, together with acute impairment of renal function and organ decompensation such as acute on chronic heart failure, induced by sepsis and/or dehydration [7]. This is by far the most common scenario. Mortality in this group is low if there is early recognition and adequate treatment [7], as was confirmed in the present studies. As we have shown, plasma metformin and creatinine concentrations decrease and the arterial pH increases approximately in line with the decreasing plasma concentrations of metformin with adequate treatment of this group.

5 Conclusions

It is likely that several mechanisms contribute to MALA. Figure 3 summarises our views on the development of MALA in categories 2 and 3. We suggest that there is a positive feedback cycle that may be triggered at any of the four steps in the cycle. Vomiting and diarrhoea may be caused by infection and, if severe, can lead to dehydration and an acute decrease in the glomerular filtration rate [24, 29, 67]. Non-steroidal antiinflammatory drugs (NSAIDS) can also cause acute renal impairment [68]. Consequently, in patients taking metformin, the drug accumulates because of its continued dosage in patients with decreased renal clearance. In turn, the accumulation of metformin can cause lactic acidosis through inhibition of mitochondrial function. The development of lactic acidosis can lead to further vomiting and diarrhoea and renal impairment. Exacerbations of comorbid conditions, such as heart failure, lead to decreased oxygenation of the liver and other tissues. Tissue concentrations of metformin could also increase because of the acidosis (see Sect. 4.16).

Lessening of the lactic acidosis may be associated with several measures used in the treatment of MALA.

- Improved cardiovascular function by intravenous fluids and inotropic agents.
- Removal of metformin by improved renal function and dialysis.
- Decreased acidosis by dialysis with media containing bicarbonate or infusion with sodium bicarbonate can be used. However, infusion with sodium bicarbonate must be managed carefully as it can cause hypernatraemia, hyperosmolality, volume overload, decreased cardiac contractility and even alkalosis [47].

Repeated measurements of plasma metformin, lactate and pH will not only assist in the characterisation of MALA but also help its management. These measures should assist in informing when dialysis should be started or stopped.

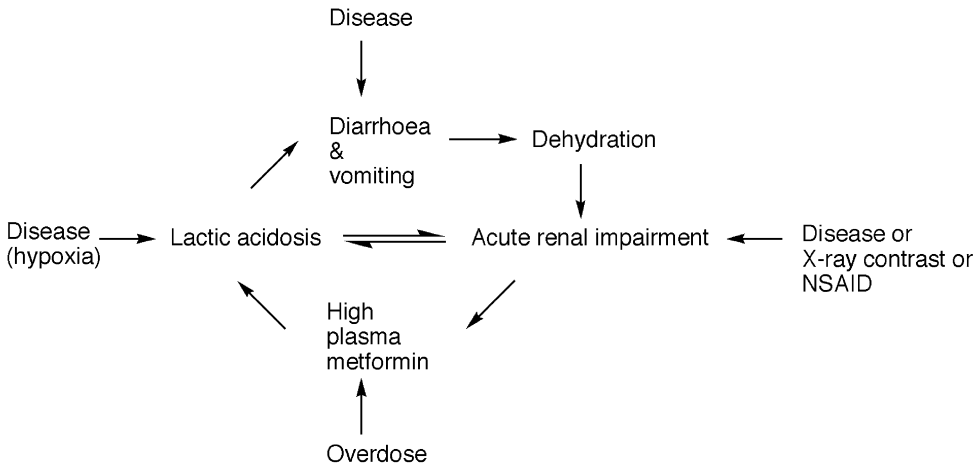

Fig. 3 Proposed mechanism and triggers for metformin-associated lactic acidosis in categories 2 and 3 of MALA. Lactic acidosis may commence with relatively small changes in hydration, kidney function, plasma concentrations of metformin or tissue oxygenation leading to positive feedback and severe lactic acidosis

In patients taking metformin, it is critical that treatment with the drug should be stopped, at least temporarily, if a patient develops gastroenteritis or other cause of vomiting and diarrhoea. Mild vomiting and/or diarrhoea may not be clinically relevant but severe vomiting and/or diarrhoea is a clear indication for medical attention. This is an important message and should be emphasised in all information on the prescription for metformin. For safety, it is recommended that the dosage should also be stopped in a variety of acute conditions such as worsening cardiac failure or myocardial infarction, respiratory failure, pulmonary embolism, shock, significant blood loss, sepsis, gangrene, pancreatitis and elective major surgery. All are conditions that can potentially lead to an increased tendency to lactic acidosis and, furthermore, to impaired renal perfusion. Patients with substantial renal impairment can take low doses of metformin but their renal function must be stable and their metformin dosage must also be reviewed if their renal function decreases. We also suggest that the plasma concentrations of metformin should be monitored during therapy, particularly in patients with renal impairment. Plasma concentrations over 5 mg/L [13] should lead to thorough investigation including measurement of plasma creatinine and lactate [45].

Acknowledgments The authors would like to thank Dr. Hari Nandakoban, Dr. Meg J. Jardine and Dr. Mary-Ann Kulh for contributing cases to this case series. Funding for this study was provided by the NH&MRC Program Grant 568612 and the Australian Research Council Grant LP 0990670.

Conflicts of interest All authors have no conflicts of interest to declare that are directly relevant to the content of this study.

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