Author’s response to reviews

Title: Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long-term follow-up

Authors:
Andrea Angioi (andrea.angioi@gmail.com)
Gianfranca Cabiddu (gianfrancacabiddu@aob.it)
Maura Conti (mauraconti@aob.it)
Gianfranco Pili (gianfrancopili@aob.it)
Alice Atzeni (aliceatzeni@aob.it)
Valeria Matta (valeriamatta@aob.it)
Riccardo Cao (riccardocao@aob.it)
Matteo Floris (matteofloris@aob.it)
Marco Songini (marcosongini@aob.it)
Maria Franca Mulas (mariafrancamulas@aob.it)
Mitchell Rosner (MHR9R@hscmail.mcc.virginia.edu)
Antonello Pani (antonellopani@aob.it)

Version: 1 Date: 11 Sep 2017

Author’s response to reviews:

Editor Comments:

beside the important comments of the reviewers, please have the paper reviewed by a native language, skilled in scientific language.

R. Thanks for this comment. We sent the manuscript to a professional reviewer to be fixed as suggested.
Reviewer reports:

Reviewer 1: This article reviews all cases of metformin associated lactic acidosis at a single hospital in Italy. In recent years there have been large studies showing the incidence of lactic acidosis with metformin administration is very low and may be similar to other antihyperglycemic agents. However, there continues to be case reports of this condition. We need to give a chance to both sides of this debate to present their case. This article goes a long way in doing that and I think is clearly worthy of publication. I only have minor comments.

R. We are grateful for these kind comments.

1. The authors define MILA as lactic acidosis exclusively due to metformin and MALA as lactic acidosis with intake of metformin and other co-morbidities. The authors then go on to describe their patients as having MALA, however they fail to mention what are the other co-morbidities that have led to lactic acidosis in these patients. In my opinion this classification is not helpful as patients with diabetes very often have co-morbidities and it is difficult to state what has led to what. Also many of the co-morbidities can be caused by the lactic acidosis itself and there will be the question of the chicken and the egg.

R. Thank you for this comment. We reported comorbidities that alone can justify lactic acidosis in supplemental table 1. We fully agree with your opinion, thus we have modified the introduction as follows: “Metformin associated lactic acidosis (MALA) is defined as lactic acidosis in a patient with documented regular intake of metformin as well as comorbid conditions that increase the risk of lactic acidosis such as heart failure and kidney disease”.

2. The authors states that 86% of their patients were volume depleted as they had nausea and vomiting. But it is clear that severe lactic acidosis can also lead to nausea and vomiting. Do the authors have any solid data that the nausea and vomiting preceded the lactic acidosis? Were there other evidence for volume depletion (for example orthostatic hypotension)?
R. Thank you for this question. You are right, lactic acidosis and even metformin overload itself are able to generate nausea and vomiting. Unfortunately, we have not objective data about that. In fact, symptoms that preceded the admission come exclusively by the clinical history, which often had been collected by the emergency room. The timing of symptoms was reported by parents or friends in an empiric way. Moreover, our patients did not see any physician before being admitted, thus we were unable to review their acid-base balance at onset.

3. The authors talk about 57% of their patients had SIRS. Is the reason for SIRS just severe lactic acidosis or is there another cause for it?

R. Thank you for your question. We reported the prevalence of SIRS in our cohort especially for descriptive purposes. In fact, 2/4 criteria to define SIRS are overlapping with a pure metabolic acidosis condition (heart rate >90 beats per minute, respiratory rate of >20 breaths per minute). Fever of more than 38°C or less than 36°C and abnormal white blood cell count (>12,000/µL or < 4,000/µL) with elevated CRP were the only “specific” criteria available to document an inflammatory response.

4. In the patients with sepsis. Did all the patients have positive blood cultures and what did they grow?

R. Yes, we defined sepsis as a SIRS with the evidence of a positive blood culture. Unfortunately, actually we do not have the entire list of pathogens. We modified the manuscript as follows: “We defined systemic inflammatory response syndrome (SIRS) and sepsis as recommended by ACCP/SCCM (2012)[16]”. We also modified results as follows: “Systemic inflammatory response syndrome (SIRS) was frequently diagnosed (57.1%), and 10.7% of hospitalized patients had criteria diagnostic of sepsis (E. Coli was the most frequent pathogen (2/4 cases)).”

5. The patients with contrast exposure, did they receive contrast while on metformin without holding it?
R. Good question. Yes, unfortunately they were still taking metformin despite the recommendations. We modified results as follows: “Two patients developed AKI after administration of iodinated contrast medium, developing MALA because metformin had not been discontinued.”.

6. The authors state that hyperkalemia was corrected very slowly on the patients. It would nice to provide actual lab values on how slowly the potassium value was corrected and also what was the exact potassium bath that was used with hemodialysis?

R. As a general rule, we avoided an excessive correction of potassium that may be cause of arrhythmias. As an example, for a serum potassium of 7 meq/l, we started with a K5 bath in order to obtain a slower correction than less concentrated baths. However, this was done only for patients with severe hyperkalemia. Interestingly, despite a severe acidosis, most of patients did not have severe hyperkalemia. We modified the manuscript as follows: “Of note, severe hyperkalemia was gradually corrected to ensure hemodynamic stability and avoid sudden drops of the serum concentration of potassium. In particular, if serum potassium was high (≥6.5 meq/l), we first corrected it with a potassium concentration of 5 in the bath and then subsequently lowered the potassium with less concentrated solutions”.

7. It would be nice to supply lactate and bicarb values right before and after SLED if available.

R. Good point. We did not report trends from time 0 (T0) to end of SLED (T1) since SLED had been interrupted only when lactates and bicarbonate got normal values (lactates <5 mmol/L; bicarbonate >21 mmol/L). Thus, normal values of lactates and bicarbonates are achieved to T1. T0 values had been reported in table 2. We preferred to report the values after 36 hours since T0, to demonstrate the rapid reversal obtained after metformin had been removed. Conversely, lactates in heart failure, intestinal hypoxia, septic shock, etc does not reverse after 36 hours or if it happens, it is extremely unlikely.
8. The authors state 21% of the patients died after the first hemodialysis treatment. Did anyone die prior to the first hemodialysis treatment?

R. Thanks for the question. We considered only patients that started hemodialysis. Thus, we do not know how many patients died before our evaluation (e.g. in Emergency Room or before).

9. The English needs to be improved a little.

R. We provided an extensive revision by a native professionist.

10. On Table 2. can the authors fill in the second column for hemoglobin, potassium, glycemia and CRP.

R. We reported the values after 36 hours as you rightly suggested.

11. The authors states that the serum lactate was 13.7 and the anion gap 36 at time zero. Was the serum lactate and anion gap drawn at exactly the same time on all of the patient? In our experience the two values usually coincide pretty well.

R. Thank you for this question. Yes, it is the same sample. It seems to underline the presence of other negative circulating charges.

Darren Roberts (Reviewer 2):

Thank you for the opportunity to review this manuscript which describes clinical outcomes in 28 patients with a clinical diagnosis of MALA, and temporal changes in the incidence of MALA in a region. I have the following comments to make.
Major comments

1. Abstract, conclusion: mortality of 21.4% does not sound particularly "acceptable" to me. Upon what criteria was this assessment made? It may not be reasonable to compare to some of the other studies listed in the paper because these may reflect a different patient group to those presented here (based in ICUs or drug company which are highly selective/biased).

R. Thanks for this comment. We are in agreement with your comment. We would like to underline that instead of proposing CRRT or IHD, we treated our cohort with SLED, which is actually not covered by literature in MALA and semi-intensive environments (a nephrology division), except for scattered case reports (Teutonico A et al. Treatment of metformin associated lactic acidosis with sustained low-efficiency daily dialysis. Clinical Kidney Journal. 2008; 1: 380-381) or publications in not peer reviewed journals (Baro-Serra A et al. The importance of early hemodiafiltration in the treatment of lactic acidosis associated with the administration of metformin. Nefrologia. 2012; 32: 664-669). Thus, as you correctly wrote in your comments, it is hard to draw any direct comparison. As reported by the EXTRIP group, this condition is extremely heterogeneous. Furthermore, the existing recommendations are suboptimal since are based on case reports (160), few cohort studies (11) and 3 pharmacokinetic studies (Colello et al. Crit. Care 2015).

However, we compared our cohort with results published by ICU groups where, in most of cases, patients have similar comorbidities but arrived too late to clinical attention. Probably our cohort had better metabolic parameters since, from the beginning, our protocol was very aggressive, especially if we compare it with other very conservative recommendations (e.g. EXTRIP guidelines, UPTODATE Aug. 2017). However, this does not mean that our patients had a better prognosis. If left conservatively, our patients were exposed to extremely poor outcomes, in particular death. They had been admitted with AKI stage III and most of them were oliguric/anuric, thus they did not have any possibility of metformin clearance and were exposed to increasing serum concentrations of metformin due to a continuous absorption of drug from intestine since they had taken metformin until their last meal before admission. Rising concentrations of metformin, even with good starting parameters, will result in profound acidosis, shock and thus access in ICU. We did not waste time and treated our patient to prevent the evolution to shock. Concluding, we are convinced that prognosis depends by time of
intervention. In every patient MALA evolves from the same starting point. We never treated our patients conservatively, and this is probably the best explanation for this result.

2. Inclusion criteria state AKI stage 3, but Table 1 states that 3.6% had AKI stage 2.

R. Thanks for your comment. Yes, we included only patients with AKI stage III that developed MALA. At the admission, only 3.6% of patients had AKI stage II, but after 24h had criteria for AKI stage III. We modified the manuscript as follows: “However, after the first 24 hours of observation, all patients met criteria for AKI stage III.”

I note that metformin levels were not measured - how did the authors exclude alternative diagnoses of lactic acidosis?

R. This is a crucial question, and we thank you for your comment. Essentially, MALA was a clinical diagnosis and by definition. MALA is a lactic acidosis were metformin and other conditions able to give lactic acidosis are coexisting, thus by definition we cannot rule out confounding variables.

The clinical reliability of metformin dosage is an open debate in literature. We report some issues raised by the EXTRIP group against metformin dosage: 1) pharmacokinetic studies are lacking (only three are actually published); 2) a high metformin concentration (>20–50mg/L) was predictive of poor outcome in two studies (Duong et al. Drug Saf 2013; Dell’Aglio et al. Ann Emerg Med 2009) while others did not show this correlation (Lalau JD et al. Diabetes Care 1995; Vecchio S et al. Clin Toxicol (Phila) 2014; Seidowsky et al. Crit Care Med 2009; etc). 3) A very high metformin concentration may predict a precipitous clinical decline in an otherwise asymptomatic patient following an intentional poisoning. 4) it is likely that publications that did perform metformin sampling incorrectly classified some cases as MALA.

We add also that very few institutions in Europe are dosing serum metformin according to this debate. Concluding, every case included in our cohort was spurious, thus accountable as MALA.
3. Please clarify that the key indications for inclusion in this study were the same as the indications for dialysis (given that 100% of patients received dialysis, as per Table 1). These criteria indicate minor illness based on markers of acidemia. Further, they are conservative indications for dialysis, particularly when compared to those criteria proposed by others previously, notably by the EXTRIP group (Crit Care Med. 2015 Aug;43(8):1716-30). I note that the EXTRIP guidelines were published after the patients reported here were treated, but it may be interesting to compare the indications in this study to those in the EXTRIP document.

R. These are excellent questions and comments. We already reported in the manuscript (methods) the following “In all cases, patients were treated with a sustained low-efficiency dialysis (SLED) using bicarbonate buffer to ensure appropriate removal of metformin and the electrolyte/metabolic equilibration”.

We had been largely more aggressive in the treatment of these patients compared with EXTRIP guidelines. In fact, our experience suggests that clinical conditions, acid-base and electrolyte balances reach rapidly clinical criteria that fulfill EXTRIP guidelines. This is theoretically justified by the fact that in our cohort AKI stage III with or without anuria/oliguria did not allow metformin to be properly expelled, thus allowing a further worsening of the metabolic status. Moreover, every patient included continued to take of metformin even in desperate conditions, thus allowing a further increase of serum concentrations. As suggested, we modified the manuscript accordingly: “We believe that the improved mortality seen in our cohort is due to aggressive use of SLED along with more gradual correction of metabolic derangements. Interestingly, recent guidelines had been published by the EXTRIP workgroup, that are much more conservative compared with our approach. In fact, hemodialysis is indicated if any of the following conditions (lactate concentration greater than 20 mmol/L; pH less than or equal to 7.0; shock; Failure of standard supportive measures; decreased level of consciousness) were present. Instead, we preferred to be more aggressive with the use of dialysis, prescribing SLED in every patient taking metformin with lactic acidosis (metabolic acidosis with an increased anion gap and lactate concentration ≥5 mmol/L) and AKI stage III”. 

4. The findings of a change in incidence of MALA following the educational campaign, which is currently in the discussion, is very interesting. I suggest that this be incorporated into the methods and results and not the appendix. Was there a change in the number of prescriptions of metformin during this period, too?

R. We really thank you for this comment. We included our data in methods and results. Unfortunately, we do not have this information for our local area. However, in Italy, prescriptions of metformin rose every year and are still growing according to ARNO observatory for diabetic prescriptions. We modified the manuscript as follows:

METHODS: “Educational campaign. In 2010 we observed the peak of a progressive annual rise in the incidence of MALA. This triggered us to organize several dedicated courses on MALA for specialists and general practitioners, and specific sessions in local congresses held by diabetologists, internists and nephrologists”.

RESULTS: “Considering that our operative area accounts for 552,303 inhabitants and that 1.55 individuals out of every 100 have a prescription for metformin, we estimated that in our district there are about 8,560 patients taking metformin. Thus, in 2010, we had a peak incidence of MALA of 76.8 cases per 100,000 patients on metformin, that fell after an education campaign conducted by specialists on its usage in patients at risk of MALA (supplemental figure 1). Although the fall in incidence after the educational program is not necessarily causal, in 2014 the incidence was 32.9/100,000, while prescription rate remained almost stable in this period”.

5. Table 1

a. Suggest ordering the content into demographics, status on admission, treatment received. At present it seems a bit haphazard. For example, % hemodialysis (which I assume to be "post-admission" and this should be stated) is listed prior to mean baseline creatinine. Also, I don't know why it is necessary to list status which were not present (eg "0%")

R. We absolutely agree with your comment, we modified table 1 accordingly.
b. "before the event" should be clarified - before admission? Before the 6 day prodrome?

R. We absolutely agree with your comment, we modified table 1 accordingly.

c. What proportion were treated in ICU? This is important to understand severity. At present, based on the BP listed, can we assume that vasopressors/inotropes were not required?

R. In this cohort we considered only patients that had a sufficient clinical stability to perform SLED in our semi-intensive ward (see methods), thus inotropes were not required.

6. Table 2

a. Some laboratory results are here and in Table 1. Suggest turning Table 1 into demographics and baseline characteristics, and Table 2 into admission and followup clinical and laboratory status

R. We agree with your comment, although we reported quantitative data in table 1 only to show how was the baseline of these patients before MALA.

Minor comments

1. Please include both SI and conventional units (notably for creatinine)

R. Thanks for your comment. We reported quantitative data with their units according with Journal guidelines (“SI units should be used throughout (liter and molar are permitted, however)”).

2. Page 5, line 48: The endpoints for dialysis treatment would allow a patient to be more medically unwell than when they started on the basis of bicarbonate.
R. We thank you for your comment. Most of our patients had a significant improvement of clinical conditions after and during dialysis. This scheme is still in use in our Division and its main goal is to reduce metformin levels and allinicate acid base and electrolytes according to physiological values, but it is helpful to relieve the symptoms of high azotemia too.

3. Page 7, line 12-14: at present, it looks like the results provided are from admission, but they are actually from a later time point?

R. Thanks for this comment. We clarified the sentence as follows: “Metabolic parameters also normalized significantly within the same time frame (pH [7.36 ± 0.072], HCO3- [22.71 ± 6.44 mmol/L], lactate levels [2.6 ± 2.65 mmol/L]).” and remained stable and within range during follow-up.

4. Further discussion of the causes of death would be of interest to help the reader understand if this applies similarly to their own hospital.

R. Thanks for this comment. We would like to add many details of our experience, but we have limitations according with authors guidelines. Causes of death were probably due to acidosis itself, probably due to the deep levels of pH. All patients died for cardiovascular arrest due to refractory arrhythmias. We modified discussion as follows: “A review of electrocardiographic data in these deaths revealed ventricular tachycardia first, then followed by ventricular fibrillation”.

5. Page 8, line 23: add "despite ongoing dosing" to the end of the sentence after "metformin excretion".

R. We modified the text accordingly.

6. Page 8, lines 40+: I don't follow these comments about Salpeter's work
R. We modified the sentence as follows: “However, the work by Salpeter estimated the incidence of the so called MILA, thus a lactic acidosis generated by a metformin poisoning alone in the absence of other predisposing factors, instead of MALA. In fact, it differs significantly from the “real world” experience, where several comorbidities able to generate lactic acidosis easily coexist in diabetic patients”.

7. Page 9, line 43: is this talking about incidence of fatal cases? Also, "to be explained" can be "to explain".

R. We modified the text accordingly.

8. Page 9, line 56-58: it is stated that renal function returned to normal in 3 days. Please confirm that this was the case in 85% of patients (given that in 15% of patients did not return to baseline)?

R. We modified the text as follows: “The use of these strategies led to an improvement in renal function within 3 days of admission in most of our patients (85.2%), thus allowing patients to be weaned from replacement therapy”.

9. English review would be useful. For example:

a. Abstract, "clinical restoration" could be "clinical recovery"

b. Page 4, line 16: "finest" could be "detailed". Does "mechanisms" refer to "mechanisms of action"?

c. Page 6, line 4: "discharged" could be simply "discharge"

d. Page 8, line 17: "profound interactions" could be "detailed mechanisms of toxicity"

R. We modified the manuscript accordingly.
10. Page 4, line 50: Lalau 2015 (ref 14) was not the first to describe MILA vs MALA. For example, this was discussed in Duong 2011 (Drug Saf. 2013 Sep;36(9):733-46.)

R. We partially agree with your comment. In the manuscript we cited an updated paper of JD Lalau, the first to propose the distinction between MALA and MILA in 2001 (Lalau JD, Race JM. Lactic acidosis in metformin therapy: searching for a link with metformin in reports of 'metformin-associated lactic acidosis'. Diabetes Obes Metab. 2001 Jun;3(3):195-201). We changed the reference with the original one.