Review Article

Metformin and Intravascular Contrast Media: What to do in Patients Receiving Both: a Narrative Review

Moghadaseh Shams[1*], Pooneh Dehghan[2], Farhad Hosseinpanah[3]

[1] Department of Imaging, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Taleghani Hospital Research Development Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract

Metformin-associated lactic acidosis (M-ALA) is considered to be one of the complications caused by intravascular contrast media (CM) administration in diabetics especially those with coexisting renal or cardiac impairment. We focused on the necessity and duration of metformin suspension in diabetics with normal or impaired renal function scheduled for CT scan with IV contrast. Searching PubMed, Web of Science, and Scopus databases, we reviewed the latest relevant guidelines as well as articles published from 1994 to 2015. There is no global consensus among different guidelines on the duration of the Metformin suspension before CT scan with IV contrast. Also, lack of substantial evidence supporting M-ALA encourages specialists to take a less conservative approach.

It is safe to continue Metformin in patients with normal renal function who have no co-morbidities. In cases of equivocal renal function (30<GFR<60 mL/min/1.73 m^2) and also in patients with normal renal function and other co-morbidities, the decision should be made based on the patient's clinical status. In case of severe renal failure, the use of metformin should be reassessed. Due to the probability of contrast associated nephropathy, laboratory follow up seems to be necessary for all patients.

Keywords: Metformin, Lactic acidosis, Contrast media, CT scan

***Corresponding Author:** Moghadaseh Shams, Department of Imaging, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: (+98) 21 22432582; Email: mgdshams@gmail.com

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Introduction

Metformin is a biguanide used mainly as an oral hypoglycaemic agent in the treatment of type 2 diabetes mellitus[1]. The most significant adverse effect of metformin therapy is the potential for lactate accumulation and development of metformin-associated lactic acidosis (M-ALA). M-ALA occurs under circumstances include reduced lactate metabolism like hepatic dysfunction or alcohol abuse, increased anaerobic metabolism like cardiac failure or severe infection and renal impairment[2].

The incidence of M-ALA appears to be low[3,4]. In surveys from Europe, the US and Canada, the estimated incidence of M-ALA in patients with type 2 diabetes was 2–10/100,000 patient–years[5,6]. According to a Cochrane meta-analysis, considering an upper 95% confidence interval, the incidence of LA in 70,490 patient–years in metformin-treated patients and 55,451 patient–years in non-metformin-treated patients was 4.3/100,000 and 5.4/100,000, respectively[3]. The incidence of LA or elevated lactate concentrations in current metformin

users with renal impairment is estimated to be 7.4/100,000 person–years (vs 2.2/100,000 person–years in non-users)[7]. However, incidence of MALA accompany with cardiac or renal impairment might be higher up to 47 per 100,000 according to a more recent study[8]. Despite its rarity, M-ALA remains a concern because of its high mortality rate (50%), which mainly occurs in patients predisposed to hypoperfusion and hypoxaemia (acute or progressive renal impairment or heart failure, acute pulmonary decompensation, sepsis, or dehydration)[1,9].

Sedentary lifestyle and increased life expectancy in recent decades have led to greater consumption of metformin because of the increased prevalence of type 2 diabetes mellitus. There has been an increase in availability of advanced imaging technologies using intravascular contrast media (CMs), as wells as their indications and prescription[10]. Careful planning is required before using these procedures to avoid potential adverse reactions and complications arising from reckless use of intravascular contrast agents in susceptible patients. Patients taking metformin are encountered daily in busy imaging departments. There is no known interaction between metformin and intravascular CMs, and metformin itself is not a nephrotoxic agent[10]. The link between metformin, contrast medium and the risk of lactic acidosis (LA) is considered to be a potential factor which leads to renal impairment. Contrast-induced nephropathy increases the risk of metformin accumulation, thus the potential for LA; its incidence is estimated to range from 0.1% to 13% with preexisting renal impairment as an important risk factor[11].

The constantly changing nature of medicine and increase in research evidence mandates periodic revision and drafting of new guidelines for the safe use of intravenous CMs in special clinical scenarios, including patients on metformin. One of the most frequent questions asked by radiologists is whether metformin should be discontinued in patients receiving intravascular CMs. However, there is no general consensus in the literature and guidelines developed by different countries and no solid unequivocal evidence on the matter.

Methods

All relevant guidelines in the English-language medical literature were reviewed, including those of the American College of Radiology, Royal Australian and New Zealand College of Radiologists, Royal College of Radiologists, Canadian Association of Radiologists and European Society of Urogenital Radiology. We searched PubMed, Web of Science and Scopus for articles and guidelines on metformin discontinuation in patients receiving intravenous CMs and risk of LA. We analysed relevant articles in English, between 1994 and 2015, and focused on the necessity and duration of metformin suspension before administration of intravenous CMs in patients with diabetes with normal or impaired renal function. Key words were ‘metformin’, ‘lactic acidosis’, ‘contrast media’ and ’CT scan’.

Evidence for M-ALA after exposure to CMs: LA has been reported in patients with diabetes who do not taking metformin; typically secondary to underlying conditions in which there has been significant tissue hypoxia, such as acute left ventricular failure[10,12]. This implies that metformin is not the only factor to cause acidosis.

Also, in a large randomized controlled trial, which was planned to assess the comparative outcomes of metformin use versus conventional approach, the researchers compared the outcomes in diabetics taking metformin with the outcomes in other people who underwent non-metformin monotherapy or combination therapy in one year interval; according to the results, no case of lactic acidosis was observed, and plasma lactate did not differ between patients undergoing these two methods. The COSMIC study suggests that metformin may be safely prescribed considering known contraindications[13].

This finding is in line with another meta-analysis on M-ALA, which used pooled data derivated from 347 prospective comparative trials and observational cohort studies. The authors found no cases of fatal or nonfatal LA in 70,490 patient–years of metformin use or in 55,451 patient–years in the non-metformin group. The mean blood lactate level during metformin treatment was not significantly different from that in patients receiving medications other than metformin. The authors concluded, compared to other anti-hyperglycemic treatments, there was no evidence suggesting a link between metformin and an increased risk of lactic acidosis, or increased lactate[3].

M-ALA is a rare event. Among about the first million patients who have received metformin in the United States, only 47 cases of confirmed lactic acidosis were reported to the Food and Drug Administration and of these just four patients were on metformin without any

other risk factors for lactic acidosis[10]. However, most patients in this study received metformin in the absence of routinely recommended contraindications.

Metformin use has increased especially among patients with renal impairment and heart failure, which carries the risk that more patients will have comorbidity associated with metformin consumption[5].

Inappropriate metformin prescription for patients with heart failure or serum creatinine levels ≥150 mg/L varied from 4.5% to 38%, and the prevalence of underlying disorders predisposing to hyperlactatemia was >50%[14,15].

In patients with heart failure, although the underlying condition can predispose to LA, existing evidence suggests that metformin is associated with improved outcome rather than increased risk[16]. When risk factors are present, LA is more frequently reported. One of the important factors in evaluating the possibility of LA is renal function. Renal impairment may be present before or induced by intravascular CM administration.

A cohort study compared 223,968 metformin users and 34,571 patients with diabetes (2004–2012) who had never used metformin[17]. The risk of LA or elevated lactate concentrations was significantly increased in patients with severe renal insufficiency (eGFR <60 mL/min/1.73 m^2), and this risk was further increased with long-term heavy metformin treatment. Similar results were achieved for an eGFR cutoff point of 45 mL/min/1.73 m^2.

In this study, there was a significantly increased risk of LA in patients with cumulative exposure to metformin of ≥730 g in the previous year, and in patients recently prescribed a daily dose of >2 g metformin. Compared with never users of metformin, there was a ~12-fold increased risk of LA in patients with reduced renal function and cumulative exposure to ≥730 g metformin in the preceding year. There was a ~13-fold increased risk of LA in patients with reduced renal function and recent exposure to >2 g/day metformin.

Renal impairment and high cumulative and daily use of metformin, which both cause higher drug concentrations, attributed to an increased hazard of LA or elevated serum lactate level[7]. It is particularly interesting that the risk was further increased when both reduced renal function and high intake of metformin were present. The authors reported that they were not able to identify and exclude the exact causes of LA.

In a cohort study with >51,000 patients with type 2 diabetes, the effect of different degrees of renal function on the safety of metformin was evaluated[17]. When metformin use was compared with any other treatment, the risk of acidosis or serious infection was not significantly increased in patients with eGFR ≤60 mL/min/1.73 m^2.

Another investigation used HPLC to measure plasma metformin level in 14 patients who experienced LA (pH <7.35 and lactate concentration >5 mmol/L) while they were on chronic metformin treatment[18]. There was a positive correlation between serum creatinine and plasma metformin concentration. However, arterial lactate increased significantly just in patients with metformin accumulation who had moderate to severe renal failure. Almost all 14 patients with M-ALA had an underlying hypoxic condition. Metformin accumulation did not predict survival; rather, the prognosis was dependent upon the severity of the associated comorbidities.

A similar recent study evaluating the prognostic effect of metformin serum concentration on M-ALA, confirmed this conclusion. Of 16 patients developing MALA while taking metformin, 11 (69%) had other risk factors for LA including renal failure or heart disease. Metformin serum concentration was higher in survivors whom had less sever concomitant underlying disorder. So the severity of such underlying disorders might have more significant prognostic influence than elevated metformin concentration itself[8].

M-ALA may occur in patients with previously normal renal function, even in young patients. Predisposing factors might be gastrointestinal discomfort or any concomitant disease that affects renal perfusion. In a study by Bruijstens et al., three patients with previously normal renal function developed serious M-ALA in the absence of chronic renal impairment[19]. The findings suggest that practitioners should keep any other contraindications of metformin in mind other than renal impairment or heart disease.

Evidence of LA in patients on metformin receiving intravascular CM is based on some case reports and case series. Some authors believe that if renal function is normal, concomitant metformin use with intravascular CM might not be challenging. In a case series of 33 patients receiving metformin, serum creatinine level did not increased in none of 29 patients with normal renal function post angiography[20]. In contrast, four patients who had an abnormal serum creatinine level before the procedure died. Two of the deaths were because of acute renal failure and LA. .In another group of 97 patients

receiving metformin, the serum creatinine levels were measured to determine the appropriate time for evaluation of renal function after CM administration. 0f 97 patients with diabetes mellitus and normal renal function who received contrast media, 8 patients (~8%) had minor increase in creatinine level which required further monitoring and evaluation of metformin therapy and of them 4 patients (~4%) developed contrast induced nephropathy [21]. In a clinical trial on a small group of 50 patients exposed to CM with normal serum creatinine level, no accumulation of metformin was observed by ultra-high-performance chromatography tandem mass spectrometry [22]. Also, there was no significant difference between the calculated creatinine clearance before and 48 h after exposure. According to this patient population, interruption of metformin therapy during exposure to CM might not be necessary.

Concerns about MALA after exposure to intravascular CMs in patients with normal serum creatinine level are raised by some case reports. Some alarming issues remain in such cases, like excess dose of CM, which might be a risk factor for MALA, as it induces a higher rate of contrast nephropathy. Jain et al. reported one fatal M-ALA that was triggered by CM-induced nephrotoxicity in a patient who had normal renal function before imaging. The patient underwent two CT scans with intravenous and a digital subtraction angiography with intra-arterial CM administration to evaluate the cause of subarachnoid haemorrhage. Overload of CM used in a rather short duration of 36h is probably responsible for such a poor outcome[23,24].

There is little evidence suggesting that metformin is a determining cofactor for the development of LA in patients with known predisposing conditions like renal or heart failure[5]. It is also suggested that in many cases of MALA that occurred after administration of intravascular CM, there was either pre-existing poor renal function or another contraindication to metformin usage[25].

Goergen et al. carried out a systematic review of guidelines evaluating the risk of LA after administration of CM in patients receiving metformin[24]. There was no evidence to discontinue metformin or retest renal function after CM administration in patients with normal baseline renal function who received a moderate load of CM.

As the results of researches and guidelines are inconsistent, there are variable clinical practices. In a survey on UK physicians, 88% routinely suspended metformin prior to coronary angiography, irrespective of baseline renal function, and 28% felt that discontinuing metformin did not make a significant effect on outcome. Of those who discontinued metformin, there was no consensus about the discontinuation period, accordingly of all, 9% stopped taking metformin over 48 hours prior to procedure, 45% stopped 48 hours prior to procedure, 17% stopped 24 hours prior to procedure, and 28% stopped on the day of the procedure. Of all, 94% did not routinely check renal status post-procedure unless there was an abnormal pre-procedural result, for instance in a pre-admission clinic measurement. Re-continuation time ranged from 24 hours (17%) to more than 48 hours (19%) post-procedure. The mentioned study demonstrated wide variations in clinician uptake and implementation of guidelines[26].

Guidelines: American College of Radiology guidelines classifies patients taking metformin based on their renal function status and presence of comorbidities including causes of decreased metabolism of lactate (like liver dysfunction and alcohol abuse) and causes of increased anaerobic metabolism (such as cardiac failure, myocardial or peripheral muscle ischemia and sepsis or sever infection). Patients with normal renal function and without known comorbidities can continue taking metformin while receiving intravenous iodinated contrast medium and there is no need to recheck serum creatinine level following the procedure. Patients with multiple comorbidities and normal renal function should discontinue metformin at the day of the procedure and suspend it for 48 hours. A repeat serum creatinine is not necessary, although the follow-up procedure should be considered. Patients who are known to have renal dysfunction should stop metformin at the time of contrast injection, and cautious follow-up of kidney function should be done[27].

According to Royal College of Radiologist guideline, there is not necessary to stop metformin in patients with normal serum creatinine and/or eGFR>60 ml/min/1.73 m^2. in other cases, any decision to suspend metformin for 48 hours should be made in "consultation with the referring physician"[28].

Table 1: Summary of guidelines on administration of contrast media in diabetic patients taking metformin[7-31].

	ACR	CAR	ESUR	PCR	RANZCR
What is definition for renal impairment?	SCr>1.5mg/dL	eGFR <45 mL/min/1.73 m2	eGFR <60 mL/min/1.73 m2	eGFR <60 mL/min/1.73 m2	eGFR <60 mL/min/1.73 m2
When metformin should be discontinued in patients with normal renal function?	No need If multiple comorbidities are present discontinue at the day of procedure	No need (if contrast volume≤100 mL)	No need	No need	No need (if contrast volume≤100 mL)
When metformin should be discontinued in patients with abnormal renal function (pre-exposure to contrast administration)?	just at the time of contrast exposure	1. eGFR<45 mL/min/1.73 m2: at the time of contrast exposure 2. eGFR mL/min/1.73 m2<30 or AKI: 48 hours prior to non-urgent contrast exposure	1.eGFR≥45 mL/min/1.73 m2 (intravenous): no need 2.30≤ eGFR<59 mL/min/1.73 m2 (intra-arterial) And 30≤ eGFR<44 mL/min/1.73 m2 (intravenous): 48 hours before exposure 3. eGFR<30 mL/min/1.73 m2 and in case of inter-current illness: metformin is contraindicated	Consultation	at the time of contrast exposure
How long metformin should be suspended in patients with abnormal renal function (post-exposure to contrast administration)?	No need	1.at least 48h 2.reassess metformin use	1. no need 2. 48h after contrast exposure 3. metformin is contraindicated	At least 48h	At least 48h
When renal function should be rechecked to restart metformin if renal function remains stable?	1.normal renal function with multiple comorbidities: Not mandatory but F/U should be considered 2.abnormal renal function: cautious F/U of renal function	1. normal renal function: no need 2.abnormal renal function: 48 hours after contrast exposure	1. normal renal function(eGFR≥60 mL/min/1.73 m2-IA and eGFR≥45 mL/min/1.73 m2-IV): no need 2.abnormal renal function: 48 hours after contrast exposure	Not mentioned	1. normal renal function: no need 2.abnormal renal function: 48 hours after contrast exposure

ACR, American College of Radiology; CAR, Canadian Association of Radiologists; ESUR, European Society of Urogenital Radiology; RCR, The Royal College of Radiologists; RANZCR, The Royal Australian and New Zealand College of Radiologists; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Canadian Association of Radiologists Guideline recommends that patients with normal renal function can continue taking metformin without retest renal function following administration of up to 100mL of contrast medium. In patients with eGFR < 45 ml/min/1.73 m^2, metformin should be stopped at the time of contrast administration and should not be restarted for at least 48 hours only if renal function remains stable (less than 25% increase from baseline creatinine). Patients with marked renal impairment (eGFR<30 ml/min/1.73 m^2) or acute kidney injury should stop metformin 48 hours prior to contrast administration; in addition, they should be reassessed for the indication of metformin use[29].

According to Royal Australian and New Zealand College of Radiologists, it is not necessary to stop metformin in patients with normal renal function, while a moderate

amount of contrast is used (less than 100mL). Also, there is no need to retest renal function. In patients with renal impairment, metformin should be withheld for at least 48 hours since the day of the contrast administration. Renal function should be reassessed before restarting metformin[30].

European Society of Urogenital Radiology guideline adopts a conservative approach and recommends holding metformin at the time of injection in patients with normal serum creatinine (eGFR ≥60 ml/min/1.73 m^2) and 48 hours prior to injection for elective studies in patients with abnormal renal function. Patients receiving intravenous contrast medium with eGFR ≥45 ml/min/1.73m² can continue taking metformin normally but patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73 m², should stop metformin 48 hours prior to CM administration and should only restart metformin 48 hours after exposure if renal function is stable. In patients with eGFR less than 30 ml/min/1.73 m² or with current illness causing impaired liver function or hypoxia, metformin is contraindicated and iodine-based contrast medium should be avoided. In emergency patients with unknown eGFR, metformin should be stopped from the time of exposure. After the procedure, signs of lactic acidosis should be monitored and metformin should be restarted 48 hours after contrast medium administration if serum creatinine/eGFR is stable and remains at the pre-imaging level[31].

Table 1 presents a comparison between different guidelines on CM administration in diabetic patients taking metformin. Although the recommendations vary among guidelines, most of them recommend not suspending metformin use in patients with normal renal function before the use of iodinated CM.

Discussion

Intravenous CMs are known to increase the risk of acute renal insufficiency. It is still controversial whether metformin accumulation itself is the only factor responsible for M-ALA. The only evidence which indicates that metformin use is associated with LA comes from reports of ~330 cases that have occurred in patients while on metformin treatment[3]. Taking these cases into consideration and according to expert opinion on metformin pharmacokinetics, conservative approach continues, but there are not strong academic evidences supporting current recommendations about the need to stop metformin administration and retest kidney function after intravascular CM administration; furthermore, the recommendations vary among professional international radiological organizations. However, latest guidelines are more consistent with each other than before. Although most cases of LA occurred in patients with abnormal renal function, LA seems to be rare in patients with normal baseline renal function before CM administration. In addition, intra-arterial CM injection in interventional cardiac, cerebral or peripheral CT angiography might raise the risk of contrast-induced nephropathy. Gruberg et al. showed contrast induced nephropathy developed in 37% of patients with chronic renal impairment after coronary angiography[32].

However, comparison of the risk of M-ALA after intra-arterial vs intravenous CM injection should be evaluated in patients with normal baseline renal function taking metformin

Conclusion

There appears to be a contradiction between pharmaceutical companies and clinicians regarding discontinuation of metformin in the setting of iodinated CM administration, with the former insisting upon cessation regardless of the patient's clinical situation. However, clinicians whose opinions are reflected in various guidelines tend to have a less conservative approach. Taking all the above discussion into consideration, the following appears to be a reasonable approach.

- It appears to be safe to continue metformin in patients with normal renal function (eGFR >60 *mL*/*min*/1.73 m^2) and no other comorbidity.
- In cases of renal function impairment (eGFR <30 *mL*/*min*/1.73 m^2), metformin should be discontinued and the indication to perform investigations with iodinated intravascular CM injection should be reassessed.
- In patients with equivocal renal function (30 *mL*/*min*/1.73 m^2< eGFR <60 *mL*/*min*/1.73 m^2) and those with normal renal function and other comorbidity, the decision to withhold metformin (prior to or at the time of the examination) and when to reinstate metformin should be based on the patient's clinical setting. This can only be achieved when there is clear and effective communication between the referring clinician,

radiologist and patient.

- Metformin therapy should be stopped if renal function deteriorates acutely. This deterioration is demonstrated by elevation of serum creatinine level to ≥1.5 mg/dL in men and ≥1.4 mg/dL in women 48–72 h after the procedure, or by development of CM-associated nephropathy. So, laboratory follow-up seems to be necessary in all patients.

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