Open Access Review

Journal of Renal Endocrinology

J Ren Endocrinol 2023;9:e25083.
https://www.jrenendo.com
doi: 10.34172/jre.2023.25083

Nickan Research Institute

Risk of lactic acidosis following injection of iodinated contrast medium for individuals with type 2 diabetes receiving metformin during angiography

Mehrdad Rahmanian[1], Samira Moradi[2], Maryam Raziee Fijani[3], Ayda Hasanpour Dehkordi[4], Sara Dehghan[5], Erfan Ghanbarzadeh[6], Elahe Zaremoghadam[7], Hossein Mardanparvar[5], Zohreh Mohagheghi[8*]

Abstract

Lactic acidosis (LA) due to metformin prescription is a rare condition; however, this circumstance is accompanied by a very high rate of death (≥50%). Accumulation of metformin alone is hardly a cause of LA, and more than 90% of patients with metformin-associated LA had a hypoxic condition that could prompt hazards of LA. LA related to this drug occurs after iodinated contrast material (ICM) exposure when other contraindications to metformin use, particularly renal insufficiency neglected and leading to high plasma metformin accumulation. One of the most common questions for radiologists is when and at what level of kidney function this agent should be discontinued in cases receiving ICM and restarted again. In this study, we assess the requirement of metformin discontinuation in diabetic patients with chronic kidney disease (CKD) who are candidates for ICM. Therefore, we evaluate the step and withholding time of metformin discontinuation in CKD patients programmed for angiography with an intravenous contrast agent. Results demonstrated that for patients with uncertain renal function and individuals with normal estimated glomerular filtration rate and other diseases, the assessment to discontinue metformin (Before or at the time of the procedure) and when to reinitiate this drug should be made the decision, based on the individual's circumstances.

Keywords: Contrast-induced acute kidney injury, Acute renal injury, Chronic kidney disease, Metformin, Lactic acidosis, Contrast-induced nephropathy

Citation: Rahmanian M, Moradi S, Raziee Fijani M, Hasanpour Dehkordi A, Dehghan S, Ghanbarzadeh E, Zaremoghadam E, Mardanparvar H, Mohagheghi Z. Risk of lactic acidosis following injection of iodinated contrast medium for individuals with type 2 diabetes receiving metformin during angiography. J Ren Endocrinol. 2023;9:e25083. doi: 10.34172/jre.2023.25083.

Introduction

Lactic acidosis (LA) is a condition that shows insufficient cellular perfusion and oxygen provided. Inadequate oxygen release induces anaerobic glucose metabolism with the final transformation of pyruvate to lactate instead of the citric acid cycle of aerobic metabolism (1). LA is a rare condition accompanied by a very high rate of death (≥50%) (2).

Large-scale statistical data from clinical investigations and meta-analysis have proved that when metformin is selected correctly is a safe drug. Accumulation of metformin alone rarely causes LA, and most metformin-consumed patients (>90%) with developed metformin-associated LA had hypoxic conditions that made prompted the risk of LA (3,4). LA related to this drug should be regarded as an avoidable adverse effect for most outpatient patients if it is inhibited or discontinued its consumption in the presence of alcohol use, heart failure, liver failure, severe hypoxia, kidney failure, and surgery (shock) (5).

Metformin accumulation is the possible reason for LA in any subject who has most or all of these conditions; metformin as usual treatment or overdose, a noticeable raised lactate level (>5 mmol/L) with a big anion gap (≥20 mmol/L× valence of the ion), severe acidemia with a pH <7.4, an exact low-serum bicarbonate level (bicarbonate <22 mmol/L) (6).

The contribution of subjects where the LA may be directly promoted by the very high levels of accumulation

Received: 12 February 2023, Accepted: 10 April 2023, ePublished: 15 April 2023

[1]Independent Researcher, 2400 Rue Benny-Crescent, Montreal, Quebec, H4B2P7, Canada. [2]Department of General Medicine, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. [3]Student Committee Research, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [4]Department of Psychiatric, Faculty of Medical Sciences, Islamic Azad University of Khomein, Khomein, Iran. [5]Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. [6]Student Research Committee, Guilan University of Medical Sciences, Rasht, Guilan, Iran . [7]Department of Internal Medicine, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran. [8]Department of General Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
***Corresponding Author:** Zohreh Mohagheghi, Email: zohreh_mohagheghi@yahoo.com

Implication for health policy/practice/research/ medical education

Lactic acidosis due to metformin administration is a rare condition, unless it is improperly prescribed in cases with various problems accompanying with enhanced generation of lactate acid or in disturbed clearance of this compound.

of metformin is very small (≤10%), mostly this rare occurrence originating from overdose or acute renal failure. When the accumulation of metformin is the only cause of LA without being accompanied by another related disease is named metformin-induced LA (7). Diabetic kidney disease (8), kidney damage (9,10), and the intravascular iodinated contrast material (ICM) diminish medullary oxygenation and causes hypoxia (11). When tissue hypoxia is detected, metformin administration should be reassessed since mortality is predicted by the degree of initial hypoxia, not by metformin or lactate concentrations (12). A recent review that analyzed using metformin therapeutically deduced no indication of a relationship between metformin and LA; though this review data cannot be involved to the overdose subjects (13).

If safety recommendations are forgotten and metformin is continued in the existence of contraindications, diabetic patients are at the hazard of advanced LA. Reduction of glomerular filtration rate and metformin clearance is the furthermost imperative risk parameter for metformin-associated LA. Other risk factors of metformin-associated LA comprise diminished tissue oxygenation (such as hypoxemia, shock, iodinated contrast media exposure, sepsis, or heart failure) and reduced lactate metabolism (such as hepatic fibrosis or alcoholism) (Table 1) (5).

Materials and Methods

In this study, we searched databases, including PubMed (Medline), Scopus, Embase, EBSCO, Web of Science, and search websites such as Google scholar by the following keywords of contrast-induced acute kidney injury, lactic acidosis, acute renal injury, chronic kidney disease, metformin, contrast-induced nephropathy, iodinated contrast media, metformin-associated lactic acidosis and glomerular filtration rate, contrast-mediated acute kidney injury.

Contrast-mediated acute renal damage

Imaging techniques such as angiography by computed tomography due to provide evidence about blood vessels and body organs are usually used in disease diagnosis and treatment. In most of these tests, use of ICM is needed; however, these agents usually can either lead to renal diseases or cause complications in patients with kidney disease. In cases with prior kidney injury, particularly those who are diabetic, the radiographic ICM may cause contrast-induced nephropathy. Contrast-mediated acute kidney injury is defined as a raise of serum creatinine greater than 25% of the standard level within 48 hours. Iodinated contrast agents could impose their nephrotoxic effects in several ways, consisting of combined hypoxic states (hemodynamic modifications such as kidney vasoconstriction and decrease of vasodilatation, reduction of renal blood flow, glomerular filtration rate and blood pressure) and direct cytotoxic effects on renal tubular cells (11,14). The kidneys are sensitive to hypoxia because they receive approximately 20% of the heart's blood output. Decreased tissue oxygenation, particularly medullary hypoxia, is a hallmark of contrast-induced acute renal damage. Iodinated contrast agents increase the viscosity of afferent arterioles of the kidney, which is the major source of blood supply to the medulla, and influence the balance between medullary oxygen delivery and its utilization. And this process leads to oxygen deficiency in arterial blood (hypoxia). Additionally, it can severely damage the endothelial cells or increases toxicological effects on kidney cells, thus complicating endothelial dysfunction (15).

Metformin-mediated lactic acidosis following iodinated contrast-induced renal damage

Iodinated contrast agents by reduction of glomerular filtration rate increase the hazard of metformin concentration and the chance for LA. According to the possible association between iodinated contrast agents and the development of LA in cases taking metformin, the current guidelines limit the prescription of metformin in situations considered at risk for the development of LA, such as iodinated contrast agents' exposure for percutaneous coronary intervention (PCI) (16). Fortunately, the incidence of nephrotoxicity after iodinated contrast agent administration with normal baseline serum creatinine is rare (17,18). The metformin-associated LA occurs after iodinated contrast agent exposure when other contraindications to metformin administration, particularly renal insufficiency are neglected, leading to high plasma metformin accumulation (19). In a previous study in diabetic patients treated with metformin joined in a LA prevention protocol who experienced intravenous ICM administration for computed tomography scan, the incidence of contrast nephropathy in cases with and without prior kidney insufficiency was 4.7% and 0%, showing that the hazard of contrast-induced renal damage

Table 1. Reduced in each of these cases causes metformin-associated lactic acidosis and is a risk factor for it

The clearance metformin	Tissue oxygenation	Lactate metabolism
Acute kidney damage Chronic renal failure	Sepsis, surgery, hypovolemia, shock, heart failure, ICM exposure	Liver fibrosis, alcohol abuse

in diabetic patients with no renal injury is minimal (16). Thereby, instructions to discontinue metformin to prevent LA in individuals who are candidates for intravenous iodinated contrast media injection may be limited to cases with abnormal kidney function.

Chronic kidney disease and metformin administration

It is very controversial between using lower doses of metformin even in patients with severe renal impairment (20) and stopping use because of the increased metformin-mediated LA risk in advanced chronic kidney disease (CKD) (21-23).

Estimated glomerular filtration rate (eGFR) in mL/min/1.73 m^2 is based on equations using serum-creatinine, weight, height, age, and gender (21) is better criteria than serum-creatinine to describe renal insufficiently. In a previous investigation with more than fifty thousand diabetic patients, the consequence of various degrees of glomerular filtration rate on the safety of metformin was assessed (22).

This study found that patients with a lower eGFR were 13 times more likely to develop LA. The hazard of LA or raised lactate values were pointedly enhanced in cases with renal failure (30≤glomerular filtration rate <60 mL/min/1.73 m^2), and this danger was strengthened by increasing metformin use duration.

In patients without CKD, metformin appears to improve glucose and lipid metabolism, promote weight loss, and delay the beginning of diabetes; however, drug-controlling organizations in different countries have suggested certain limits for metformin in CKD.

Various protocols proposed that metformin administration be reevaluated when the eGFR is ≤45 mL/min/1.73 m^2 and stopped when ≤30 mL/min/1.73 m^2 (23).

It should remember that the absolute contraindicate for metformin administration in most cases is considered eGFR below 30 mL/min/1.73 m^2; therefore, the drug should be stopped when eGFR is below 30 mL/min/1.73 m^2. This drug may be continued with GFR≤60 mL/min/1.73 m^2, but renal function should be checked approximately every 3 to 6 months. The dose of metformin should be reevaluated and reduced in those with glomerular filtration rate ≤45 mL/min per 1.73 m^2; since renal function should be checked approximately every three months. Further carefulness is required in cases at risk for the sudden decline in kidney function (e.g., nephrotoxic ICMs). A maximal daily dose of 2000 and 1000 mg was proposed for eGFR of 45–60 mL/min/1.73 m^2 and 30–45 mL/min/1.73 m^2, respectively (24).

Iodinated contrast media and metformin administration in kidney insufficiently

The results of the studies indicated that besides metformin administration, other risk factors (mostly renal insufficiency) exist for the onset of metformin-associated LA after ICM exposure. These results indicate a need to assess metformin use during ICM procedures in cases with kidney failure. Making decisions about discontinuing this agent before iodinated contrast agent injection should be directed based on the patient's risk for LA and baseline renal function (25). In cases of uncertain renal function (30 < estimated glomerular filtration rate <60 mL/min/1.73 m^2) and additionally in individuals with normal kidney function, the contrast medium injection would be decided, according to the conditions. Due to the probability of contrast-mediated acute kidney injury, laboratory assessments like serum-creatinine determination seem indispensable for all cases. This compound is not a nephrotoxic agent, and there is no identified relation between metformin and intravascular ICM. The relation between metformin, ICMs, and the danger of LA is believed to be an influencing parameter directed to kidney damage. Contrast-mediated acute kidney injury increases the probability of metformin concentration, thus, the probability of LA. The prevalence of LA is assessed to an extent from 0.1% to 13%, with previous kidney damage as a principal risk factor (26). One of the most commonly requested questions for radiologists is at what time and at what level of renal function the metformin should be discontinued in cases receiving iodinated contrast agents and when it must restart again. Table 2 presents a comparison among various guidelines on ICM injection in diabetic cases receiving metformin.

According to the published data, we can conclude that;

- Some guidelines are not regarded eGFR ≤30 mL/min/1.73 m^2 as an absolute contraindication and metformin should be temporarily discontinued at the time of or before the procedure (27).
- When risk factor of ICM is added to CKD, some authors believe that it should withhold metformin at any eGFR if the patient is exposed to intravenous ICM administration (6) since some authors believe that in patients with uncertain renal function (30<eGFR<60 mL/min/1.73 m^2 particularly with

Table 2. Suggested recommendations for the administration of metformin based on the eGFR

eGFR	Recommendations
eGFR>60 (mL/min/1.73 m^2)	Continue, assess kidney function annually
45<eGFR<60 (mL/min/1.73 m^2)	Continue and kidney function assess (every 3-6 month)
30<eGFR<45 (mL/min/1.73 m^2)	Reduced dose (e.g., by 50%), renal function check (every 3 months)
eGFR<30 (mL/min/1.73 m^2)	Contraindicated for metformin or stop

attention to Table 2, in 30<eGFR<45 mL/min/1.73 m^2) and those with normal eGFR and other diseases, the assessment to discontinue of metformin before to or at the time of the injection and when to reinitiate this agent would be according to the condition (28).

- It seems safe to continue this drug in patients with normal renal function (eGFR>60 mL/min/1.73 m^2) and no other comorbidities.
- To recommend a more accurate way when assessing the hazard of contrast nephropathy, for example, the ratio between ICM dosage signified in grams of iodine (g-I) and eGFR, named I-dose/eGFR ratio. Using the I-dose/eGFR ratio may be a more appropriate way of developing risk evaluation of contrast-mediated acute kidney injury than the usual procedure of estimating ICM dose from volume alone and renal function from serum creatinine alone (23). Suitable indicator of I-dose/eGFR<1.42 is concluding the safe ICM-dose based on the pre-PCI renal function values (29).
- Other modalities like magnetic resonance imaging (MRI), iso- or low-osmolar ICM in the lowest effective dose, optimal hydration, and other ways of preventing contrast-mediated acute kidney injury should be applied when the patient is at risk.

Conclusion

Several investigations showed that metformin rarely leads to LA unless it is improperly prescribed in cases with various problems accompanied by enhanced generation of lactate acid (hypoxia) or in the disturbed clearance of this compound. It has also shown that in individuals with uncertain kidney function (30<eGFR<60 mL/min/1.73m^2, particularly 30<eGFR<45 mL/min/1.73 m^2) and cases with normal eGFR accompanied with another disease, the decision to discontinue the metformin before to or at the time of the procedure and what time it must restart would be according to the patient's situations.

Authors' contribution

Conceptualization: MR and AHD.
Methodology: SD, EGh, and EZ.
Validation: MR and HM.
Formal Analysis: ZM and EZ.
Research: AHD, MR and SM.
Resources: HM, SD and EGh.
Data Curation: SM and AH.
Writing—Original Draft Preparation: MR, MRF, HM, EZ and SD.
Writing—Reviewing and Editing: EGh, ZM, AHD and SM.
Visualization: HM and SM.
Supervision: MR.
Project Management: ZM.

Conflicts of interest

The authors declare that she has no competing interests.

Ethical issues

The authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

Funding/Support

None.

References

1. Prakash S, Mehta S. Lactic acidosis in asthma: report of two cases and review of the literature. Can Respir J. 2002;9:203-8. doi: 10.1155/2002/368695.
2. Lalau JD. Lactic acidosis induced by metformin: incidence, management and prevention. Drug Saf. 2010;33:727-40. doi: 10.2165/11536790-000000000-00000.
3. Goergen SK, Rumbold G, Compton G, Harris C. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. Radiology. 2010;254:261-9. doi: 10.1148/radiol.09090690.
4. Lalau JD, Lacroix C, Compagnon P, de Cagny B, Rigaud JP, Bleichner G, et al. Role of metformin accumulation in metformin-associated lactic acidosis. Diabetes Care. 1995;18:779-84. doi: 10.2337/diacare.18.6.779.
5. Pasquel FJ, Klein R, Adigweme A, Hinedi Z, Coralli R, Pimentel JL, et al. Metformin-associated lactic acidosis. Am J Med Sci. 2015;349:263-7. doi: 10.1097/MAJ.0b013e3182a562b7.
6. Kalantar-Zadeh K, Kovesdy CP. Should restrictions be relaxed for metformin use in chronic kidney disease? No, we should never again compromise safety! Diabetes Care. 2016;39:1281-6. doi: 10.2337/dc15-2327.
7. Ortiz-Lasa M, Gonzalez-Castro A, Peñasco Martín Y. Lactic acidosis associated (or induced by) metformin. Med Clin (Barc). 2017;149:415-6. doi: 10.1016/j.medcli.2017.07.009.
8. Heyman SN, Rosenberger C, Rosen S, Khamaisi M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? Biomed Res Int. 2013;2013:123589. doi: 10.1155/2013/123589.
9. Haase VH. Mechanisms of hypoxia responses in renal tissue. J Am Soc Nephrol. 2013;24:537-41. doi: 10.1681/asn.2012080855.
10. Takiyama Y, Haneda M. Hypoxia in diabetic kidneys. Biomed Res Int. 2014;2014:837421. doi: 10.1155/2014/837421.
11. Heyman SN, Rosen S, Rosenberger C. Renal parenchymal hypoxia, hypoxia adaptation, and the pathogenesis of radiocontrast nephropathy. Clin J Am Soc Nephrol. 2008;3:288-96. doi: 10.2215/cjn.02600607.
12. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin. BMJ. 2003;326:4-5. doi: 10.1136/bmj.326.7379.4.
13. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2003(2):CD002967. doi: 10.1002/14651858.cd002967.
14. Mamoulakis C, Tsarouhas K, Fragkiadoulaki I, Heretis I, Wilks MF, Spandidos DA, et al. Contrast-induced nephropathy: basic concepts, pathophysiological implications and prevention strategies. Pharmacol Ther. 2017;180:99-112. doi: 10.1016/j.pharmthera.2017.06.009.
15. Fähling M, Seeliger E, Patzak A, Persson PB. Understanding and preventing contrast-induced acute kidney injury. Nat Rev Nephrol. 2017;13:169-80. doi: 10.1038/nrneph.2016.196.
16. Zeller M, Labalette-Bart M, Juliard JM, Potier L, Feldman LJ, Steg PG, et al. Metformin and contrast-induced acute kidney injury in diabetic patients treated with primary percutaneous coronary intervention for ST segment elevation myocardial infarction: amulticenter study. Int J Cardiol. 2016;220:137-42. doi: 10.1016/j.ijcard.2016.06.076.
17. Kruse JA. Review: metformin does not increase risk for lactic

acidosis or increase lactate levels in type 2 diabetes. ACP J Club. 2004;141:7.
18. Sirtori CR, Pasik C. Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. Pharmacol Res. 1994;30:187-228. doi: 10.1016/1043-6618(94)80104-5.
19. Thomsen HS, Morcos SK. Contrast media and metformin: guidelines to diminish the risk of lactic acidosis in non-insulin-dependent diabetics after administration of contrast media. ESUR Contrast Media Safety Committee. Eur Radiol. 1999;9:738-40. doi: 10.1007/s003300050746.
20. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. Metabolism. 2016;65:20-9. doi: 10.1016/j.metabol.2015.10.014.
21. Nyman U, Almén T, Aspelin P, Hellström M, Kristiansson M, Sterner G. Contrast-medium-Induced nephropathy correlated to the ratio between dose in gram iodine and estimated GFR in ml/min. Acta Radiol. 2005;46:830-42. doi: 10.1080/02841850500335051.
22. Ekström N, Schiöler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open. 2012;2:e001076. doi: 10.1136/bmjopen-2012-001076.
23. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis. 2012;60:850-86. doi: 10.1053/j.ajkd.2012.07.005.
24. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014;312:2668-75. doi: 10.1001/jama.2014.15298.
25. Kim SK, Jung J, Jung JH, Kim KY, Baek JH, Hahm JR. The association between use of metformin and change in serum CO2 level after administration of contrast medium. Clin Radiol. 2016;71:532-6. doi: 10.1016/j.crad.2016.02.007.
26. Chang JB, Prasad K, Olsen ER, Sumpio BE. Textbook of Angiology. New York: Springer-Verlag; 1900.
27. ACR Manual on Contrast Media Version 10.3. ACR Committee on Drugs and Contrast Media; 2017.
28. Ohno I, Hayashi H, Aonuma K, Horio M, Kashihara N, Okada H, et al. Guidelines on the use of iodinated contrast media in patients with kidney disease 2012: digest version: JSN, JRS, and JCS Joint Working Group. Clin Exp Nephrol. 2013;17:441-79. doi: 10.1007/s10157-013-0843-3.
29. Yoon HJ, Hur SH. Determination of safe contrast media dosage to estimated glomerular filtration rate ratios to avoid contrast-induced nephropathy after elective percutaneous coronary intervention. Korean Circ J. 2011;41:265-71. doi: 10.4070/kcj.2011.41.5.265.