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Renal manifestations of metformin-associated lactic acidosis; new findings

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ABSTRACT

Risk factors for metformin-associated lactic acidosis (MALA) include impaired renal function, liver disease, heart failure, sepsis, and alcohol abuse. Patients with these risk factors should be closely monitored while on metformin therapy, and the dose should be adjusted accordingly. It is also important to screen patients for these risk factors before starting metformin therapy. In addition, patients should be educated on the symptoms of lactic acidosis, such as abdominal pain, nausea, vomiting, and muscle weakness, and advised to seek medical attention immediately if they experience any of these symptoms. Overall, early recognition and appropriate management of MALA can improve patient outcomes and prevent mortality.

Keywords: Metformin, Renal function, Metformin-associated lactic acidosis, Acidosis, End-stage renal disease, Glomerular filtration rate, Acute kidney injury, Type 2 diabetes, Chronic kidney disease

Epidemiology and Prevention

Implication for health policy/practice/research/medical education:
Metformin-associated lactic acidosis (MALA) is a rare but serious side effect of metformin, and the prognosis for patients with normal renal function who develop this condition depends on several factors, including the severity of the acidosis, the presence of comorbidities, and the promptness of treatment.

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Introduction

Metformin-associated lactic acidosis (MALA) is a rare but potentially serious side effect of metformin therapy (1). Metformin is a commonly prescribed medication for the management of type 2 diabetes. It is generally well-tolerated, but in rare cases, it can lead to lactate accumulation in the blood, resulting in lactic acidosis (2). MALA is more likely to occur in individuals with certain predisposing factors, such as impaired kidney function (3). The kidneys play a crucial role in eliminating metformin from the body. In patients with impaired kidney function, metformin clearance is reduced, leading to higher drug levels in the blood. Elevated metformin levels can increase the risk of lactic acidosis (4). Several studies have investigated the relationship between metformin, lactic acidosis, and kidney function. Previous studies have shown that patients with pre-existing kidney disease, renal impairment, or acute kidney injury have an increased risk of developing MALA (5,6). These individuals often require dose adjustments or discontinuation of metformin to prevent lactic acidosis. It is important to note that metformin is generally safe when used within the recommended dosage guidelines, even in patients with mild to moderate kidney impairment. However, caution should be exercised in patients with severe renal impairment or end-stage renal disease, as metformin use may be contraindicated in these cases (7-9). Therefore, regular monitoring of kidney function is crucial in individuals receiving metformin therapy. Metformin discontinuation is recommended due to the increased risk of lactic acidosis when eGFR falls below a certain threshold (usually less than 30 mL/min/1.73 m^2) (10,11). This letter aims to provide an overview of the relationship between metformin and kidney function and the risk factors, pathophysiology, clinical presentation, and management of MALA.

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Metformin-associated lactic acidosis

Metformin-associated lactic acidosis is caused by the accumulation of lactate in the blood. One mechanism is the inhibition of gluconeogenesis by blocking pyruvate carboxylase, which is the first step of gluconeogenesis (12). Another mechanism is the inhibition of mitochondrial respiration in tissues such as the liver and muscle, increasing plasma lactate levels. Metformin overdose induces two distinct metabolic derangements—hyperlactatemia and metabolic acidosis—primarily through the inhibition of mitochondrial respiration. In most cases, lactic acidosis cannot be directly attributed to metformin use but rather depends on concomitant low cardiac output, anemia, hypoxemia, or liver failure (13,14).

Risk factors of MALA

Several risk factors have been identified that can increase the likelihood of developing MALA. Patients with impaired renal function, such as those with chronic kidney disease, are at a higher risk of developing MALA (3,7). Patients with liver disease, especially severe liver disease, are more likely to develop lactic acidosis when taking metformin. Alcoholism is a risk factor for MALA. Dehydration can increase the risk of lactic acidosis in patients taking metformin (15,16). Sepsis, a severe infection that affects the whole body, is also a risk factor for MALA. Taking high doses of metformin can increase the risk of lactic acidosis. Advanced age has been identified as a risk factor for MALA (16,17).

Diagnostic criteria for MALA in patients with normal renal function

Elevated lactate levels are a hallmark of lactic acidosis and should be measured in patients suspected of having MALA. Patients with normal renal function who develop lactic acidosis while taking metformin should be evaluated for MALA. Other causes of lactic acidosis, such as sepsis or liver disease, should be ruled out before diagnosing MALA (3,12).

Metformin-associated lactic acidosis and kidneys

Metformin-associated lactic acidosis primarily affects the renal system, leading to various manifestations. Acute kidney injury is the most common renal manifestation observed in MALA. Other renal manifestations include tubular dysfunction, such as Fanconi syndrome or proximal tubular acidosis. The pathophysiology of MALA involves impaired lactate clearance due to mitochondrial dysfunction and inhibition of gluconeogenesis. Metformin accumulates in the renal tubules, increasing lactate production and subsequent metabolic acidosis (18,19).

Conclusion

Metformin-associated lactic acidosis can have severe renal manifestations, including acute kidney injury and tubular dysfunction. Prompt recognition and management are crucial for improving patient outcomes. Healthcare professionals should be aware of these potential complications when prescribing metformin and closely monitor patients for signs of renal impairment during treatment.

Authors' contribution

Conceptualization: Majid Foroutan.
Data curation: Parisa Tajdini.
Investigation: Parisa Tajdini.
Resources: Parisa Tajdini.
Supervision: Majid Foroutan.
Validation: Parisa Tajdini, Majid Foroutan.
Visualization: Parisa Tajdini.
Writing–original draft: Majid Foroutan.
Writing–review and editing: Majid Foroutan.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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References

1. Mahmood R, Maccourtney D, Vashi M, Mohamed A. A Case of Metformin-Associated Lactic Acidosis. Cureus. 2023 Apr 27;15:e38222. doi: 10.7759/cureus.38222.
2. Dyatlova N, Tobarran NV, Kannan L. Metformin-Associated Lactic Acidosis (MALA) [Updated 2023 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK580485/
3. Rahman F, Tuba S. Lactic Acidosis Associated with Metformin in Patients with Diabetic Kidney Disease. Med Arch. 2022;76:297-300. doi: 10.5455/medarh.2022.76.297-300.
4. Hsu WH, Hsiao PJ, Lin PC, Chen SC, Lee MY, Shin SJ. Effect of metformin on kidney function in patients with type 2 diabetes mellitus and moderate chronic kidney disease. Oncotarget. 2017;9:5416-5423. doi: 10.18632/oncotarget.23387.
5. 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.
6. Santoli J, Aldakkour JL, Tohidi H, Lin Y. Metformin-Associated Lactic Acidosis: A Case Report. HCA Healthc J Med. 2023;4:215-218. doi: 10.36518/2689-0216.1508.
7. Kim MJ, Han JY, Shin JY, Kim SI, Lee JM, Hong S, et al. Metformin-associated lactic acidosis: predisposing factors and outcome. Endocrinol Metab (Seoul). 2015;30:78-83. doi: 10.3803/EnM.2015.30.1.78.
8. Klachko D, Whaley-Connell A. Use of Metformin in

Patients with Kidney and Cardiovascular Diseases. Cardiorenal Med. 2011;1:87-95. doi: 10.1159/000327151.
9. Roberts DM, Ghannoum M. Expanding the evidence for managing metformin poisoning to support decision-making. Clin Toxicol (Phila). 2023;61:203-206. doi: 10.1080/15563650.2023.2196372.
10. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011;34:1431-7. doi: 10.2337/dc10-2361.
11. Chiarito M, Sanz-Sanchez J, Piccolo R, Condello F, Liccardo G, Maurina M, et al. Safety of metformin continuation in diabetic patients undergoing invasive coronary angiography: the NO-STOP single arm trial. Cardiovasc Diabetol. 2023 Feb 6;22:28. doi: 10.1186/s12933-023-01744-4.
12. Blough B, Moreland A, Mora A Jr. Metformin-induced lactic acidosis with emphasis on the anion gap. Proc (Bayl Univ Med Cent). 2015;28:31-3. doi: 10.1080/08998280.2015.11929178.
13. Rivera D, Onisko N, Cao JD, Koyfman A, Long B. High risk and low prevalence diseases: Metformin toxicities. Am J Emerg Med. 2023;72:107-112. doi: 10.1016/j.ajem.2023.07.020.
14. Foucher CD, Tubben RE. Lactic Acidosis. [Updated 2023 Mar 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470202/.
15. Tahrani AA, Varughese GI, Scarpello JH, Hanna FW. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? BMJ. 2007;335:508-12. doi: 10.1136/bmj.39255.669444.AE.
16. Rajasurya V, Anjum H, Surani S. Metformin Use and Metformin-associated Lactic Acidosis in Intensive Care Unit Patients with Diabetes. Cureus. 2019;11:e4739. doi: 10.7759/cureus.4739.
17. Hur KY, Kim MK, Ko SH, Han M, Lee DW, Kwon HS; Committee of Clinical Practice Guidelines, Korean Diabetes Association; Committee of the Cooperative Studies, Korean Society of Nephrology. Metformin Treatment for Patients with Diabetes and Chronic Kidney Disease: A Korean Diabetes Association and Korean Society of Nephrology Consensus Statement. Diabetes Metab J. 2020;44:3-10. doi: 10.4093/dmj.2020.0004.
18. Iftikhar H, Saleem M, Kaji A. Metformin-associated Severe Lactic Acidosis in the Setting of Acute Kidney Injury. Cureus. 2019;11:e3897. doi: 10.7759/cureus.3897.
19. Greco P, Regolisti G, Antoniotti R, Maccari C, Parenti E, Corrado S, et al. Acidosi lattica associata a metformina e insufficienza renale acuta [Metformin-associated lactic acidosis and acute kidney injury]. G Ital Nefrol. 2016;33:gin/33.6.12. [Italian].

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