DOI: https://doi.org/10.53555/nnmhs.v9i7.1770 Publication URL: https://nnpub.org/index.php/MHS/article/view/1770

LACTIC ACIDOSIS IN A PATIENT WITH TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW

Devita Nur Amelia*

**Faculty of Medicine, General Achmad Yani University*

Corresponding Author:
drdevita29@gmail.com

Abstract

Background: *Lactic acidosis occurs when lactate synthesis exceeds metabolism. Multiple causes of lactic acidosis may coexist in a patient. Attending Rounds exemplifies the theme. This example shows how metformin can complicate type 2 diabetes-related lactic acidosis. Lactic acidosis treatment is controversial, because it must address the cause.*

Aim: *This article examines the link between lactic acidosis in a patient with type 2 diabetes mellitus.*

Methods: *This study showed that it met all of the requirements by looking at the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. So, the experts could make sure that the study was as current as possible. The search method used a number of electronic reference databases, such as Pubmed and SagePub, to look for papers that were published between 2000 and 2023. We didn't look at review papers, articles that had already been published, or articles that were only half done.*

Result: *In the PubMed database, the results of our search brought up 77 articles, whereas the results of our search on SagePub brought up 56 articles. The results of the search conducted for the last year of 2013 yielded a total of 17 articles for PubMed and 6 articles for SagePub. In the end, we compiled a total of 18 papers, 13 of which came from PubMed and five of which came from SagePub. We included five research that met the criteria.*

Conclusion: *Studies consistently show that blood lactate levels in patients taking metformin are increased, but are not significantly associated with the risk of developing lactic acidosis.*

Keyword: *Diabetes mellitus; Lactic acidosis; Metformin*

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Diabetic chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of various glands, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] The prevalence of DM is difficult to determine because the standard for establishing a diagnosis is different. About 10.2 million people in the United States have DM. Meanwhile, in Indonesia the prevalence of DM is 1.5-2.3% of the population aged >15 years, even in the Manado area the prevalence of DM is 6.1%. The incidence of Type 2 DM in women is higher than men.[2–4]

Type 2 diabetes mellitus consists of multiple dysfunctions characterized by hyperglycemia and resulting from a combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Uncontrolled type 2 diabetes is linked to a number of problems that can affect the microcirculation, the macrocirculation, and the nerves. When diabetes is not under control, persistently high blood sugar can lead to a number of consequences, both acute and chronic.[5]

When lactate production is greater than its metabolic rate, lactic acidosis can develop. There are a wide variety of potential causes of lactic acidosis; in any given patient, multiple reasons may be present at the same time. This example of Attending Rounds illustrates the topic perfectly.[6] The present example demonstrates how complicated metformin's part can be in the development of diabetes-related lactic acidosis in people who have type 2 diabetes. The treatment of lactic acidosis is contentious, but it is very necessary to address the underlying cause of the condition.[7,8]

The use of sodium bicarbonate as a treatment for the often worrisome metabolic derangements may be quite effective in that regard; nevertheless, the benefits of this treatment to patients are debatable. Renal replacement treatments, also known as RRTs, offer a lot of potential in this context for a variety of different reasons, but the effect that they have on clinical outcomes has not been investigated.[9] In this article, a patient with diabetes type 2 is given lactic acidosis as an example, and the article investigates the connection between the two conditions.

METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist was used as the basis for the establishment of the criteria that were used to oversee the process of carrying out this systematic review. These standards were utilised to ensure that all of the relevant information was collected and analysed. Articles on "lactic acidosis in a patient with type 2 diabetes mellitus" were the topic of this systematic review that was designed to research them. This review was designed to investigate them. These are the many aspects of the topics that were looked into during the research that is being considered right now.

The following conditions need to be fulfilled in advance in order for your work to be taken into consideration: 1) Articles have to be written in English; 2) Articles have to be able to be read online in their entirety; and 3) Articles had to have been published after 2013, but before this systematic evaluation was carried out. Under no circumstances will any of the following types of written submissions be considered for inclusion in the anthology: 1) Editorial letters, 2) submissions that do not have a DOI linked with them, and 3) article reviews and submissions that are comparable to one another.

The search for papers to be included in the systematic review began on July 17th, 2022 using the PubMed and SagePub databases with the search terms on "lactic acidosis" and "type 2 diabetes mellitus" Where *(("acidosis, lactic"[MeSH Terms] OR ("acidosis"[All Fields] AND "lactic"[All Fields]) OR "lactic acidosis"[All Fields] OR ("lactic"[All Fields] AND "acidosis"[All Fields])) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter]))* is used as search keywords.

After conducting a literature analysis and looking at the titles and abstracts of previously published studies, the author of the study revised the criteria for what should be included in the study and what should not be included in the study. These changes were made after the author considered what should not be included in the study. During the process of developing the systematic review that we carried out, we gave any and all consideration to only those research studies that were able to satisfy each and every one of our standards. Each study's title, author, publication date, study origin location, research study design, and research variables are all bits of information that can be gathered during the collection process.

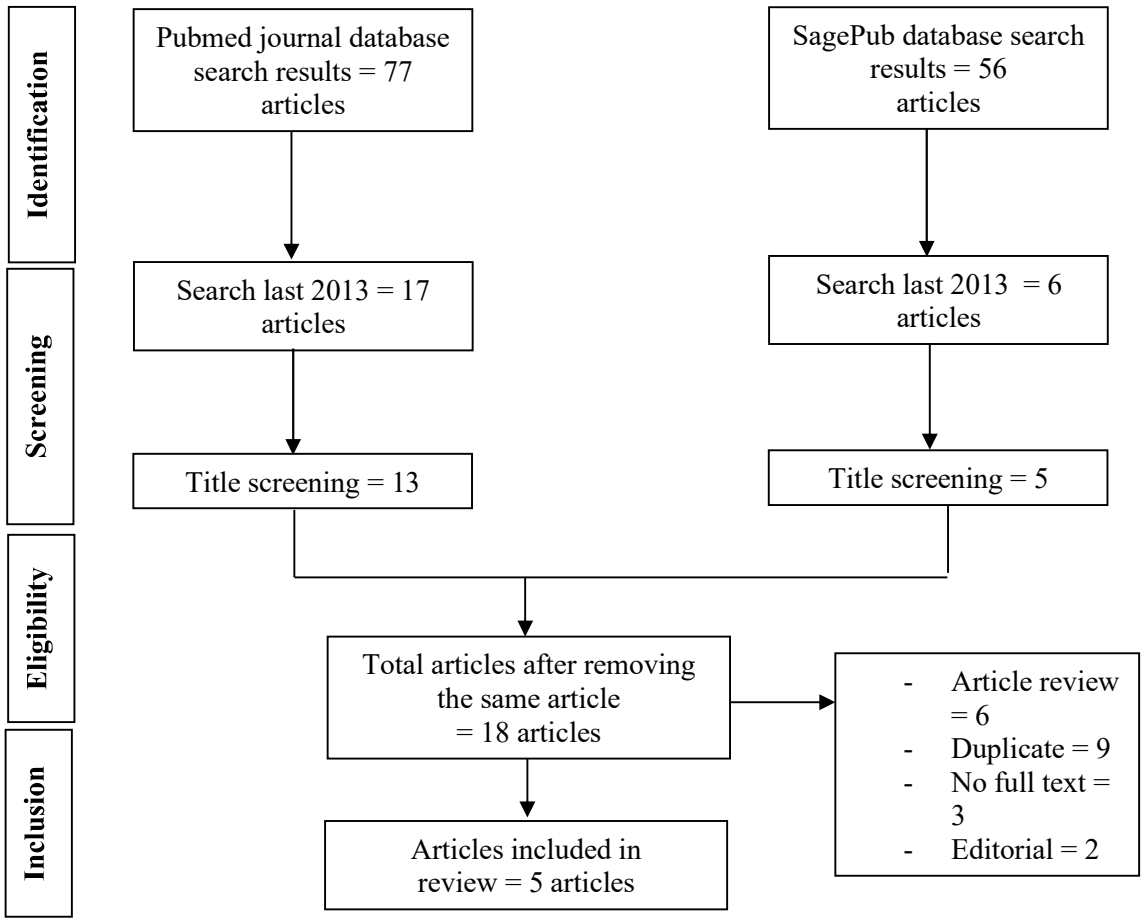

Figure 1. Article search flowchart

The writers did their own independent evaluations on a selection of the research that was given in the titles and abstracts of the publications in order to determine which studies ought to be taken into consideration. This allowed them to choose which studies ought to be taken into consideration. They were able to identify, as a result of this, which studies should be taken into consideration. The next thing that needs to be done is a study of the full texts of the studies that can be included in the systematic review since they fulfil the requirements. The objective of this analysis is to ascertain whether or not certain pieces of research may be pertinent to the goals of the review. This will be done so that the evaluation is as comprehensive as it possibly can be. This is the goal.

RESULT

In the PubMed database, the results of our search brought up 77 articles, whereas the results of our search on SagePub brought up 56 articles. The results of the search conducted for the last year of 2013 yielded a total of 17 articles for PubMed and 6 articles for SagePub. In the end, we compiled a total of 18 papers, 13 of which came from PubMed and five of which came from SagePub. We included five research that met the criteria.

Aharaz, et al (2019)[10] conducted a study with10,652 patients who were diagnosed with type 2 diabetes mellitus. The median age of these patients was 74 years old, and 51.5% of them were male. During the course of the study, there were a total of 163 patients hospitalised due to lactic acidosis; this number is equivalent to an incidence rate of 391/100,000 person years. In this study, the use of metformin was not linked to lactic acidosis; the adjusted odds ratio (OR) was 0.79 (95% confidence interval [CI] = 0.54–1.17).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Aharaz, 2019[10]	Denmark	Case-control study	10,652 patients with type 2 diabetes mellitus	Patients diagnosed with type 2 diabetes mellitus had an incidence rate of 391/100,000 person years for acute hospitalisation due to lactic acidosis. There was no correlation between taking metformin and an increased risk of lactic acidosis. However, the presence of many conditions appears to be a significant risk factor.
Lee, 2017	Republic of Korea	Cross-sectional study	1,954 type 2 diabetes patients	Patients diagnosed with type 2 diabetes who used metformin did not have an increased risk of developing lactic acidosis or hyperlactatemia.
Lepelley, 2016[11]	France	Case-control study	302 cases and 604 controls	In individuals with type 2 diabetes, the use of metformin did not appear to be related with lactic

				acidosis when compared to acute medical problems; nevertheless, in the event of AKI, the use of metformin may be associated with lactic acidosis.
Eppenga, 2014[12]	Netheland	Prospective cohort study	223,968 metformin users and 34,571 diabetic patients	This study is in line with the existing recommendations that the renal function of metformin users should be adequately monitored and that the dose of metformin should be modified, if necessary, if renal function falls below 60 mL/min/1.73 m(2).
Guelho, 2014[13]	Portugal	Prospective cohort study	138 type 2 diabetics, 66 treated with metformin, and 83 non-diabetic patients	Patients diagnosed with type 2 diabetes ran a higher chance of developing hyperlactacidemia, and this was especially true for those who were using metformin. Creatinine in the serum was the only component that could be considered an independent associated factor of lactate concentration. There was a correlation between the existence of hyperlactacidemia and a worse prognosis.

Lepelley, et al (2016)[11] used a total of 604 controls and 302 patients; the mean age was 69.5 years with an 11.93 standard deviation. It was shown that LA had a strong association with concurrent illnesses. The incidence of LA was only marginally affected by chronic medical problems, with the exception of hepatic dysfunction. In patients who had acute kidney injury (AKI), using metformin was substantially related with a higher likelihood of developing LA (odds ratio = 1.79; p value = 0.020), but this was not the case in those who did not have AKI.

Eppenga, et al (2014)[12] showed metformin users had an average rate of 7.4 per 100,000 person-years of lactic acidosis or high lactate levels, while non-users had a rate of 2.2 per 100,000 person-years. Metformin users with a kidney function of less than 60 mL/min/1.73 m(2) were more likely to have lactic acidosis or high lactate levels than people who didn't take the drug (adjusted hazzard risk [HR] = 6.37; 95% CI = 1.48-27.5). Patients who took more than 730 g of metformin in the year before the study (adjusted HR = 11.8 [95% CI = 2.27-61.5]) or a high daily amount (>2 g) of metformin (adjusted HR = 13.0 [95% CI = 2.36-72.0]) were at an even higher risk.

Guelho, et al (2014)[13] showed mean lactate concentration and hyperlactacidemia prevalence were significantly higher in diabetic patients (2.1 ± 0.1 mmol/L vs 1.1 ± 0.1 mmol/L, $p < 0.001$ and 39.1% vs 3.6%, $p < 0.001$, respectively) and in those under metformin compared to other diabetics (2.7 ± 0.2 mmol/L vs 1.6 ± 0.1 mmol/L, $p < 0.001$ and 56.9% vs 23.3%, $p < 0.001$, respectively). Diabetics on metformin presented a 25-fold increased risk of hyperlactacidemia (OR = 25.10, $p < 0.05$). Patients with hyperlactacidemia had 4.4 times higher odds of being hospitalized or dying (OR = 4.37, $p < 0.05$).

DISCUSSION

DM is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Diabetic chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of various glands, especially the eyes, kidneys, nerves, heart, and blood vessels.[14] The etiology of type 2 DM is a reduced response to insulin or known as insulin resistance. During this state, insulin is ineffective for glucose uptake and lowers blood glucose levels. Initially, this is offset by increased insulin production to maintain glucose homeostasis, but over time, insulin production declines, resulting in type 2 DM.[15]

Metformin makes the body more sensitive to insulin; it doesn't work without insulin. It works mostly by lowering liver gluconeogenesis, in large part by stopping mitochondrial oxidative phosphorylation and mitochondrial glycerophosphate dehydrogenase.[16] It also has some effect on the body's ability to get rid of glucose. Metformin, unlike phenformin, is not broken down in the body. Instead, the kidneys get rid of it all. It is removed from the blood by glomerular filtration and, to a greater extent, by tubular release through a number of transporters. Even though it is spread around a lot, its half-time of elimination is only about 2.7 hours.[17]

Metformin lowers hepatic gluconeogenesis, which uses lactate as a fuel source. Because it does this in part by stopping mitochondrial oxidative phosphorylation and lowering the redox state of mitochondria, it is a bit surprising that it only causes a small rise in basal and postprandial plasma lactate levels. A systematic review of 347 clinical trials found no patients with fatal or nonfatal lactic acidosis in 70,490 subject-years of metformin exposure, and a case-control study of over 50,000 patients with type 2 diabetes mellitus found about three cases of lactic acidosis for every 100,000 patient-years of metformin use, which is the same rate as for patients taking sucralose.[18]

Still, a case series of metformin-associated lactic acidosis (MALA) was described. This happened very soon after the drug was sold in the US. Since then, there have been hundreds of case reports and a dozen case stories.[19] But because people with diabetes are more likely to have hyperlactatemia and lactic acidosis, questions were raised about the role of metformin in the described lactic acidosis. Patients who took too much pure metformin make it clear that metformin can lead to lactic acidosis. This shows that, from both a mechanical and a rational point of view, metformin accumulation is a risk factor for lactic acidosis.[18]

Studies suggest that a metformin plasma level of at least 40 mg/L (10 times the therapeutic level) may be needed to cause lactic acidosis. Based on this, there are three possible relevant conditions: (1) metformin-independent lactic acidosis, in which metformin cannot be a cause, (2) metformin-induced lactic acidosis, in which there is no other possible cause of lactic acidosis, and (3) MALA, in which metformin is one of the things that could have caused lactic acidosis. Strictly speaking, these stated conditions need to measure the concentration of metformin in the plasma.[17,19]

The last two conditions can only be considered when the metformin concentration is high. The amount of metformin in the patient's plasma was not tested. Plasma metformin measurements can't be done in-house at our hospital or, I think, at most other big tertiary referral centres. Samples are sent to a reference laboratory, and it can take several days for the results to come back. So, metformin levels generally can't be used to help with acute care.[10,12] Also, there isn't much of a link between pH, plasma lactate levels, or clinical results and metformin levels. This patient's MALA diagnosis is based on speculation and circumstantial evidence, but this working diagnosis could have important effects for treatment.[20]

Some metformin-treated T2D studies employed discharge diagnosis or medical records to define LA cases. Study showed LA cases had significantly higher comorbidity rates than T2D controls.[10] Another study found. Until date, thorough study of comorbidity's impact has concentrated on specific groups such renal failure or heart failure. A Portuguese study found that renal function is an independent risk factor for increased lactate concentrations. They unexplained subgroup exhibited a similar tendency, although it was not significant.[11,21] In T2D patients with normal renal function in Michigan, elevated lactate levels were linked to increased comorbidity.[13,14]

CONCLUSION

Studies consistently show that blood lactate levels in patients taking metformin are increased, but are not significantly associated with the risk of developing lactic acidosis.

REFERENCE

[1]. International Diabetes Federation. Diabetes. Brussels: IDF; 2017.
[2]. Evans K. Diabetic ketoacidosis: update on management. Clin Med. 2019 Sep;19(5):396–8.
[3]. Association AD. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2019. Diabetes Care [Internet]. 2018 Dec 7;42(Supplement_1):S173–81. Available from: https://doi.org/10.2337/dc19-S015
[4]. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2016;62–9.
[5]. Soelistijo SA, Lindarto D, Decroli E, et al. Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia. Jakarta: PB Perkeni; 2021.
[6]. Patoulias D, Papadopoulos C, Stavropoulos K, et al. Prognostic value of arterial stiffness measurements in cardiovascular disease, diabetes, and its complications: The potential role of sodium-glucose co-transporter-2 inhibitors. J Clin Hypertens. 2020;22(4):562–71.
[7]. Kraut JA, Madias NE. Lactic acidosis. N Engl J Med. 2014 Dec;371(24):2309–19.
[8]. Chen W, Levy DS, Abramowitz MK. Acid Base Balance and Progression of Kidney Disease. Semin Nephrol. 2019 Jul;39(4):406–17.
[9]. Kennelly PJ, Rodwell VW. Harper's: Illustrated Biochemistry. New York: McGraw-Hill Education; 2016.
[10]. Weisberg LS. Lactic Acidosis in a Patient with Type 2 Diabetes Mellitus. Clin J Am Soc Nephrol. 2015 Aug;10(8):1476–83.
[11]. Aharaz A, Pottegård A, Henriksen DP, Hallas J, Beck-Nielsen H, Lassen AT. Risk of lactic acidosis in type 2 diabetes patients using metformin: A case control study. PLoS One. 2018;13(5):e0196122.
[12]. Lepelley M, Giai J, Yahiaoui N, Chanoine S, Villier C. Lactic Acidosis in Diabetic Population: Is Metformin Implicated? Results of a Matched Case-Control Study Performed on the Type 2 Diabetes Population of Grenoble Hospital University. J Diabetes Res. 2016;2016:3545914.
[13]. Eppenga WL, Lalmohamed A, Geerts AF, Derijks HJ, Wensing M, Egberts A, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. Diabetes Care. 2014 Aug;37(8):2218–24.
[14]. Guelho D, Paiva I, Carrilho F. Relation between metformin treatment and the development of hyperlactacidemia at the emergency room. Acta Med Port. 2014;27(2):196–203.
[15]. Fauci AS, Jameson JL, Kasper D, et al. Harrison's Principles of Internal Medicine 19th Edition. New York: McGraw-Hill Education; 2018.
[16]. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med. 2002;137(1):25–33.
[17]. Lalau J-D, Arnouts P, Sharif A, De Broe ME. Metformin and other antidiabetic agents in renal failure patients. Kidney Int. 2015;87(2):308–22.
[18]. Scale T, Harvey JN. Diabetes, metformin and lactic acidosis. Clin Endocrinol (Oxf). 2011 Feb;74(2):191–6.
[19]. Madiraju AK, Erion DM, Rahimi Y, Zhang X-M, Braddock DT, Albright RA, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature. 2014 Jun;510(7506):542–6.
[20]. Vecchio S, Giampreti A, Petrolini VM, Lonati D, Protti A, Papa P, et al. Metformin accumulation: lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. Clin Toxicol. 2014;52(2):129–35.
[21]. Lee EY, Hwang S, Lee YH, Lee SH, Lee YM, Kang HP, et al. Association between Metformin Use and Risk of Lactic Acidosis or Elevated Lactate Concentration in Type 2 Diabetes. Yonsei Med J. 2017 Mar;58(2):312–8.