Original article

Incidence of Metformin-Induced Lactic Acidosis in Diabetic Patients

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ABSTRACT

Background: Metformin is a common treatment for diabetes, yet it poses a risk of lactic acidosis, especially in patients with underlying conditions such as heart failure or liver dysfunction. This study investigates the impact of metformin on lactate levels, evaluates its role as a risk factor for lactic acidosis, and examines key patient characteristics associated with elevated lactate levels.

Subjects and methods: This study was a cross sectional study at August 15, 2524 to November 15, 2024 of the occurrence of lactic acidosis in patients treated with metformin at Buriram Hospital. The study tracked outcomes from day 0 to day 90, taken with metformin Abnormal laboratory values (blood lactic acid, blood bicarbonate, blood acidity and kidney function. inclusion criteria for the study sample encompassed patients diagnosed with the following conditions: insulin-dependent diabetes mellitus with ketoacidosis and Blood oxygen level SpO_2 is lower than 95%, And study outcome involved 150 diabetic patients, whose creatinine, eGFR, and HbA1c levels were measured before and after receiving standard treatments, including metformin. Lactate levels were assessed using Enzymatic Colorimetric Assay and Biosensor techniques. Blood lactate levels above 4.4 mmol/L were used as a threshold for evaluating lactic acidosis. And analyze the results using t-test by Stata version 14 program.

Results: Patients receiving metformin, especially at doses exceeding 2,550 mg/day, exhibited significantly elevated lactate levels ($p < 0.001$). Elevated lactate was more prevalent among patients with specific conditions, including insulin-dependent diabetes mellitus with ketoacidosis, hypoglycemia, and acute renal failure. Patients treated with glipizide showed statistically significant changes in creatinine and HbA1c levels ($p < 0.05$), confirming its impact on these parameters.

Conclusion: Elevated lactate levels associated with metformin use may indicate a risk of lactic acidosis, particularly in high-risk patient groups or those receiving high doses. Lactate thresholds of 4.4 mmol/L may serve as a diagnostic criterion for lactic acidosis. Close monitoring and tailored dosing of metformin are essential for minimizing risks.

Keywords:

Lactate, Lactic acidosis, Metformin, MALA, Glycolysis, Glycogen synthesis

INTRODUCTION

Lactic acidosis is a condition where the body produces an excessive amount of lactate or has reduced lactate clearance.[1] Lactate is a substance derived from the breakdown of lactic acid and serves as a precursor in the synthesis of glucose from non-carbohydrate carbon sources in anaerobic glycolysis.[2-3] In this process, glucose is used as a carbon source and enters the Emden-Meyerhof pathway (EMP), where it is converted into pyruvate and subsequently to lactic acid.[4-5] Therefore, lactate is one of the substances formed during the breakdown of glucose, with Reduced Nicotinamide Adenine Dinucleotide (NADH) acting as a catalyst to regulate blood glucose levels, which is essential for the treatment of type 2 diabetes.[2,6]

Metformin inhibits pyruvate carboxylase, an enzyme involved in synthesizing glucose-6-phosphate from the conversion of pyruvate and lactate in the gluconeogenesis process.[7-8] This process, a reverse reaction of the glycolysis pathway, uses pyruvate or lactic acid as precursors, converting pyruvate into phosphoenolpyruvate in the liver cell mitochondria.[9-10] Initially, pyruvate is reduced to oxaloacetate by the enzyme pyruvate carboxylase, CO_2, and ATP, adding one carbon atom to form oxaloacetate.[11-12] This oxaloacetate is reduced to malate by malate dehydrogenase and NADH, after which malate is re-oxidized to oxaloacetate by malate dehydrogenase in the cytoplasm, using NAD^+ as a coenzyme.[13-14] Oxaloacetate is converted into phosphoenolpyruvate through the action of PEP carboxykinase, with GTP providing the phosphate group, releasing CO_2 in the process.[15]

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Phosphoenolpyruvate is then converted back into intermediates until it reaches fructose-1,6-diphosphate, reversing the glycolysis pathway.[16] Lactate is oxidized to pyruvate, or glucose-6-phosphate is hydrolyzed to glucose by the enzyme glucose-6-phosphatase (G6Pase).[17-18] This reaction occurs in the liver, kidneys, and small intestine epithelium, as the brain and muscle tissues lack the enzyme and thus cannot release free glucose into the bloodstream.[19] Consequently, pyruvate can be reconverted into glucose or glucose-6-phosphate through the mentioned reactions, as can lactate, which is oxidized into pyruvate by lactate dehydrogenase (LDH) and then converted back into glucose. The researchers recognized the importance of focusing on the mechanisms leading to the accumulation of lactic acid in the blood, which may involve the inhibition of mitochondrial respiration chain function and its impact on ATP production in cells. A deeper understanding of these mechanisms could aid in developing more effective methods for preventing and managing lactic acidosis.[20]

Therefore, the liver is essential in regulating blood glucose levels. When blood glucose rises, it is broken down for energy and synthesized into glycogen for storage. If blood glucose drops, the liver synthesizes glucose through gluconeogenesis.[21] Inhibition of pyruvate carboxylase suppresses hepatic gluconeogenesis, leading to increased lactate levels.[22] Additionally, metformin inhibits complex I of the mitochondrial electron transport chain (ETC), increasing the $NADH/NAD^+$ ratio and inhibiting pyruvate entry into the tricarboxylic acid (TCA) cycle through lactate dehydrogenase.

SUBJECTS AND METHODS

The objective of the study was to compare the effectiveness of lactate measurement methods and compare the effects of metformin use. Cross-sectional study of the occurrence of lactic acidosis in patients treated with metformin at Buriram Hospital. Causes of lactic acidosis reports from Metformin efficacy including emergency vision, clear indications/conditions, dosage and method of use Metformin Duration of metformin use Disease or cause of use of metformin List of drugs taken with metformin Abnormal laboratory values (blood lactic acid, blood bicarbonate, blood acidity and kidney function) Operational Guidelines for Ethics Committees, Buriram Provincial Health Office Number Document Approved BRO 2024-084.

This cross sectional study It is a study of a single period of time The researchers studied the time period at August 15, 2524 to November 15, 2024. measured lactate levels before and after administering metformin to analyze the risk trend of lactic acidosis and to compare the efficiency of different lactate measurement methods. Lactate levels were determined using the Enzymatic Colorimetric Assay and Biosensor methods. Blood samples were collected from fingertip pricks and residual whole blood from diagnostic services. Blood lactate levels serve as indicators of tissue hypoxia, resulting from glycolysis in the cytoplasm outside of mitochondria under anaerobic conditions, with lactate as the final product. Lactate measurement is essential in diagnosing sepsis, septic shock, and tissue hypoperfusion. In this context, lactate levels decrease rapidly (≥4 mmol/L) in septic patients (a reduction of more than 10% within two hours).

The measurement of lactate in plasma involves two primary methods. The first method uses Lactate Dehydrogenase (LDH) or Lactic Acid Dehydrogenase techniques, which are essential for diagnosing and treating lactic acidosis as well as bacterial meningitis. Blood samples are collected from the fingertip, either as fresh blood or whole blood (Heparin/EDTA), with a sample volume of 2-6 mL placed in sodium fluoride anticoagulant tubes. The plasma remaining from clinical diagnostic tests at Buriram Hospital is used for lactate analysis. These blood samples are stored in fluoride-oxalate tubes at -20°C and are immediately centrifuged to separate the plasma, which is then analyzed using an automated analyzer. The normal reference range for adult blood lactate is 0.5-2.2 mmol/L, and for cerebrospinal fluid (CSF), it is 1.1-2.4 mmol/L.

The second method applies the lactic acid oxidase technique, converting lactic acid to pyruvate. The researchers did not measure lactate sensitivity as they used standard reference values. A lactate level of 4.4 mmol/L.[2] serves as a threshold for sensitivity, specificity, and classification accuracy, making it an appropriate criterion for diagnosing lactic acidosis. Blood drawn from the fingertip is placed in a heparin tube and mixed thoroughly by inverting the tube 8-10 times. A 20 µL drop of the heparinized whole blood is then placed on a Blood Lactate Test strip, where lactate is broken down by pyruvic acid and NADH-H+. Diaphorase further processes NADH-H+, releasing NAD+ and formazan dye, with absorption measured at a wavelength of 540 nm. Using peroxidase, the reaction produces water and oxygen ions, generating an electrical current that is measured by the electrode in The EDGE Blood Lactate Analyzer. The analyzer displays results on-screen and records data in a database, with normal levels ranging from 1-5 mmol/L, elevated levels from 5-9.9 mmol/L, and critical levels above 5 mmol/L.

The inclusion criteria for the study sample encompassed patients diagnosed with the following conditions: insulin-dependent diabetes mellitus with ketoacidosis, chronic kidney disease (stage 5), infections related to infusion, transfusion, or therapeutic injection, non-insulin-dependent diabetes mellitus with

ketoacidosis, insulin-dependent diabetes mellitus without complications, insulin-dependent diabetes mellitus with coma, non-insulin-dependent diabetes mellitus with coma, non-insulin-dependent diabetes mellitus without complications, congestive heart failure, and unspecified acute renal failure. And Exclusion criteria Blood oxygen level SpO_2 is lower than 95%, Received at least one antiviral medication, including favipiravir, remdesivir, lopinavir, ritonavir, interferon (β1a), chloroquine, or hydroxychloroquine, etc, Pregnant or breastfeeding women, or those planning to have children, history of allergic reaction to Metformin, Hypertensive patients regularly take blood pressure-lowering medication., history of heart disease or rheumatic heart disease, nephritis due to previous infection with Streptococcus group A., Anticoagulants such as clopidogrel, warfarin, aspirin >81 mg/day are used.

The laboratory research instruments for measuring lactate in plasma and cerebrospinal fluid (CSF) using the Enzymatic Colorimetric Assay include various materials and equipment. These consist of a liquid, ready-to-use lactate testing reagent; anticoagulant tubes containing Na-Fluoride, K-Oxalate, or Na-Heparin plasma; reagents with an onboard stability period of 12 weeks; reagents with a linearity of up to 15.5 mmol/L or 150 mg/dL; and reagents with a lower detection limit of 0.2 mmol/L or 1.8 mg/dL.

To prevent interference and analytical errors in both testing methods, certain thresholds were set: for icterus, bilirubin levels should not exceed 30 mg/dL; for hemolysis, hemoglobin levels should remain below 500 mg/dL; and for lipemia, the acceptable level is up to 500 mg/dL.

Data analysis and statistical methods for this study involved collecting blood test results from 150 diabetic patients before and after metformin administration to enable data comparison. The study utilized descriptive research to present frequency and percentage distributions. To test the hypothesis, the effects of regular medications on creatinine, eGFR, and HbA1C levels were examined using the t-test Because the data is normally distributed. Inferential statistics were then applied to evaluate the relationship between metformin use and lactate levels through t-test. Results were considered statistically significant if the p-value was less than 0.05.

RESULTS

This cross sectional study at August 15, 2524 to November 15, 2024. measured lactate levels before and after administering metformin to analyze the risk trend of lactic acidosis and to compare the efficiency of different lactate measurement methods. Lactate levels were determined using the Enzymatic Colorimetric Assay and Biosensor methods. Blood samples were collected from fingertip pricks and residual whole blood from diagnostic services. Blood lactate levels serve as indicators of tissue hypoxia, resulting from glycolysis in the cytoplasm outside of mitochondria under anaerobic conditions, with lactate as the final product. Lactate measurement is essential in diagnosing sepsis, septic shock, and tissue hypoperfusion. In this context, lactate levels decrease rapidly (≥4 mmol/L) in septic patients (a reduction of more than 10% within two hours). The effectiveness of diabetes treatment involves stimulating insulin secretion and inhibiting glucose production in the liver. This study analyzed the use of regular medications in a sample of 150 participants by comparing creatinine, eGFR, and HbA1c levels before and after medication administration. Additionally, the distinct effects of metformin, separate from other regular medications, were examined by evaluating creatinine, eGFR, and HbA1c levels. The study tracked outcomes from day 0 to day 90, with the 150 participants receiving varied treatments. The results showed a statistically significant difference in the mean values of creatinine and HbA1C before and after using Glipizide. The mean and standard deviation Appears in Table 1. of creatinine and HbA1C before Glipizide treatment were 2.06 mmol/L and 2.32 mmol/L, respectively, compared to 2.09 mmol/L and 1.86 mmol/L after treatment. This indicates that Glipizide significantly increased creatinine levels while reducing HbA1C levels. Similarly, a statistically significant difference was observed in creatinine and HbA1C levels before and after using Glibenclamide. The mean and standard deviation of creatinine and HbA1C before Glibenclamide treatment were 2.37 mmol/L and 3.01 mmol/L, respectively, compared to 2.78 mmol/L and 3.34 mmol/L after treatment. This demonstrates that Glibenclamide also significantly increased creatinine levels while reducing HbA1C levels.

For Insulin Penfill treatment, there were statistically significant differences in the mean values of creatinine, eGFR, and HbA1C before and after administration. The mean and standard deviation of creatinine before Insulin Penfill treatment were 9.99 mmol/L and 4.12 mmol/L, eGFR was 2.74 mmol/L and 3.32 mmol/L, and HbA1C was 56.55 mmol/L and 42.05 mmol/L. After treatment, the mean and standard deviation of creatinine were 8.12 mmol/L and 4.58 mmol/L, eGFR was 56.23 mmol/L and 41.85 mmol/L, and HbA1C was 8.20 mmol/L and 4.60 mmol/L. These findings indicate that Insulin Penfill significantly increased creatinine and eGFR levels while reducing HbA1C levels, as summarized in Table 1.

The study Secondary data were collected, with Buriram Hospital being the data location where patients receiving Metformin were recorded and Blood was drawn from a vein twice before and after taking Andrographis paniculata on day 0 and day 90.

Table 1: Comparison of Creatinine, eGFR, and HbA1c levels before and after regular medication administration using the enzymatic colorimetric assay method

Medications	Before	After	SD	t	95%CI of Median	p-value
Metformin ≤2000 mg						
Creatinine	2.06	2.09	-0.02	-0.12	-0.50 ±2.43	0.90
eGFR (90ml/minute)	55.73	49.96	5.76	1.51	-1.76±13.30	0.13
HbA1c (<5.7mg %)	9.44	9.29	0.15	0.42	-0.57±0.88	0.67
Glipizide ≤2000 mg						
Creatinine	2.08	55.12	-53.03	-15.28	-59.88±46.18	0.00**
eGFR (90ml/minute)	51.27	55.12	-3.84	-0.88	-12.42±4.73	0.37
HbA1c (<5.7mg %)	9.17	2.37	6.80	19.06	6.09±7.50	0.00**
Glibenclamide ≤2000 mg						
Creatinine	2.37	2.78	-0.41	-1.05	-1.18±0.36	0.29**
eGFR (90ml/minute)	61.65	54.10	7.54	1.48	-2.47±17.56	0.13
HbA1c (<5.7mg %)	9.71	8.56	1.15	2.41	0.20±2.09	0.01**
Mixtard insulin ≤1.0 ml						
Creatinine	2.17	2.23	-0.05	-0.21	-0.58±0.46	0.83
eGFR (90ml/minute)	55.53	52.37	3.15	11.53	-5.21±11.53	0.45
HbA1c (<5.7mg %)	9.24	9.31	-0.06	-0.16	-0.89±0.75	0.86
NovoMix ≤10 ml						
Creatinine	2.22	2.10	0.12	0.49	-0.36±0.60	0.62
eGFR (90ml/minute)	54.42	59.80	-5.37	-1.17	-14.42±3.67	0.24
HbA1c (<5.7mg %)	8.51	8.52	-0.01	-0.02	-0.86±0.83	0.97
PENFILL <10 ml						
Creatinine	9.99	8.12	1.87	3.56	0.83±2.09	<0.00**
eGFR (90ml/minute)	2.74	56.23	-53.49	-14.84	-60.61±46.37	<0.00**
HbA1c (<5.7mg %)	56.55	8.20	48.34	14.55	41.78±54.91	0.00**

SD: Standard Deviation; CI: Confidence Interval

**: Significant = p <0.01 (99% certain there's a difference) *** = p <0.001 (99.99% certain there's a difference) **** = p <0.0001 (99.999% certain there's a difference)

Table 2: Proportion of lactic acidosis incidence associated with metformin use, with lactate levels measured using the enzymatic colorimetric assay method

Underlying Condition Before Treatment	Lactate <4.4 mmol/L		Lactate >4.4 mmol/L		p-value
	n	%	n	%	
1. Insulin-dependent diabetes mellitus, with ketoacidosis					
Received metformin	54	36.00	16	10.66	
Not received metformin	75	50.00	5	3.33	<0.00**
2. Chronic kidney disease, stage 5					
Received metformin	78	52.00	12	8.00	
Not received metformin	54	36.00	6	4.00	0.53
3. Infections following infusion, transfusion and therapeutic injection					
Received metformin	73	48.66	1	0.66	
Not received metformin	74	49.33	2	1.33	0.57
4. Hypoglycaemia, unspecified					
Received metformin	24	16.00	72	48.00	
Not received metformin	30	20.00	24	16.00	<0.00**
5. Non-insulin-dependent diabetes mellitus, with ketoacidosis					
Received metformin	38	25.33	34	22.66	
Not received metformin	69	46.00	9	6.00	<0.00**
6. Insulin-dependent diabetes mellitus, without complications					
Received metformin	21	14.00	42	28.00	
Not received metformin	10	6.66	77	51.33	<0.00**
7. Insulin-dependent diabetes mellitus, with coma					
Received metformin	23	15.33	78	52.00	
Not received metformin	25	16.66	24	16.00	<0.00**
8. Non-insulin-dependent diabetes mellitus, with coma					
Received metformin	8	5.33	117	78.00	
Not received metformin	14	9.33	12	8.00	<0.00**
9. Non-insulin-dependent diabetes mellitus, without complications					
Received metformin	10	6.66	92	61.33	
Not received metformin	24	16.00	24	16.00	<0.00**
10. Congestive heart failure					
Received metformin	15	10.00	9	6.00	
Not received metformin	69	46.00	57	38.00	0.48
11. Acute renal failure, unspecified					
Received metformin	80	53.33	14	9.33	
Not received metformin	23	15.33	33	22.00	<0.00**

**: Significant = p < 0.01 (99% certain there's a difference) *** = p < 0.001 (99.99% certain there's a difference) **** = p < 0.0001 (99.999% certain there's a difference)

Table 3: Comparison of Lactate, eGFR, and HbA1c Levels Based on Metformin Dosage (500–2,550 mg/day vs. >2,550 mg/day) Using the Enzymatic Colorimetric Assay Method

Biochemical Parameter (mmol/L)	Mean Dosage DosageUsed (mg/day)		MD	t	95%CI of MD	p-value
	500-2,550	>2,550				
Metformin						
Lactate	2.74	10.00	-7.26	-17.57	-8.07±6.44	<0.00**
Glucose	9.18	2.38	6.80	16.86	6.00±7.60	<0.00**
HbA1c	9.46	9.18	0.28	0.68	-0.53±1.09	0.49

MD: Median; CI: Confidence Interval

**: Significant = p < 0.01 (99% certain there's a difference) *** = p < 0.001 (99.99% certain there's a difference) **** = p < 0.0001 (99.999% certain there's a difference)

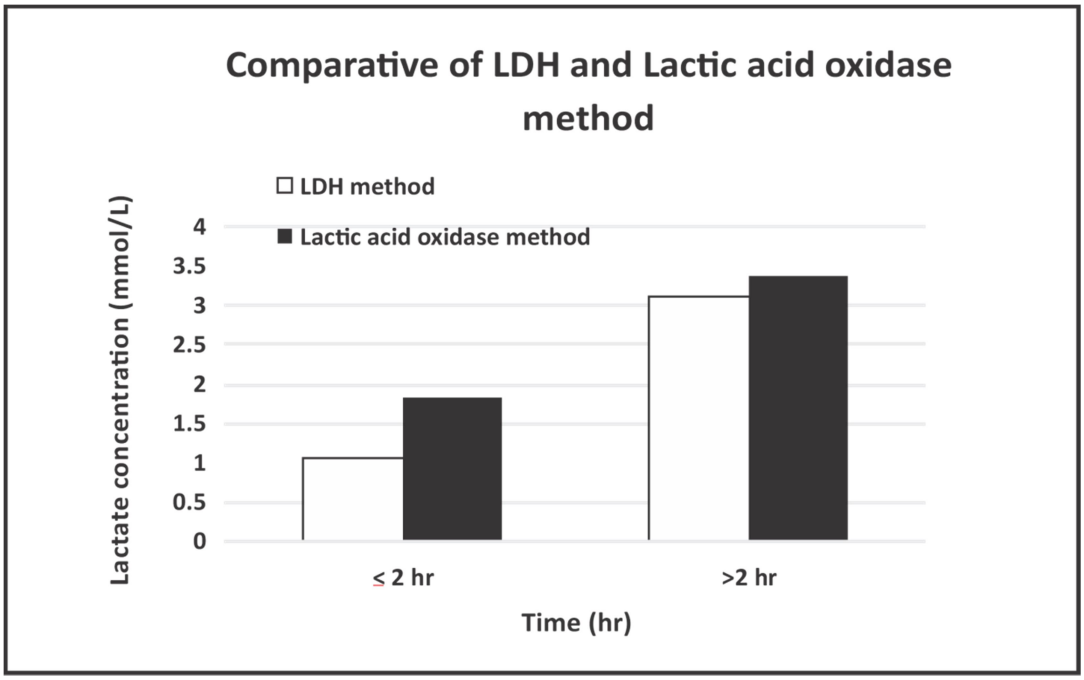

Figure 1: Comparison of plasma separation techniques between LDH method and lactic acid oxidase method

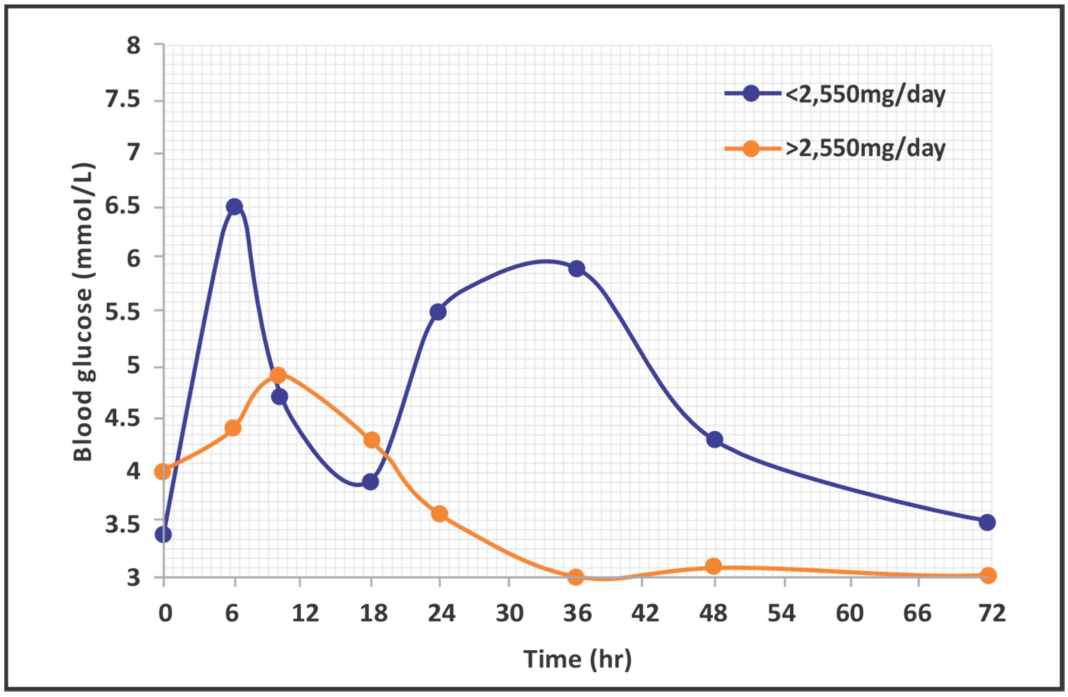

Figure 2: Changes in blood glucose levels based on metformin dosage

This step was performed by a professional nurse to prevent harm to the volunteers. Investigated the relationship between elevated lactate levels and patients with insulin-dependent diabetes mellitus (IDDM) with ketoacidosis who were treated with metformin. The objective was to determine whether metformin use increased the risk of elevated lactate levels in these patients. A total of 150 patients were included in the study, among whom diagnoses included insulin-dependent diabetes mellitus with ketoacidosis, hypoglycemia (unspecified), non-insulin-dependent diabetes mellitus (NIDDM) with ketoacidosis, insulin-dependent diabetes mellitus without complications, insulin-dependent diabetes mellitus with coma, non-insulin-dependent diabetes mellitus without complications, and acute renal failure (unspecified). All patients received metformin.

The results demonstrated that elevated lactate levels were associated with the patients' underlying conditions and metformin use. The OR values were 4.45, 3.75, 0.11, 0.25, 3.53, 17.06, 9.2, and 0.25, respectively, when compared to patients without elevated lactate levels. The 95% confidence intervals (95% CI) of the relative risks (RR) were 1.42-16.31, 1.74-8.09, 0.10-0.64, 1.59-7.79, 5.27-56.05, 3.59-24.27, and 0.10-0.58, respectively, as summarized in Table 2. The researchers wanted to study whether patients with underlying diseases who took metformin had a higher chance of developing lacticacidosis.

The increase in lactate levels can be analyzed to predict the likelihood of lactic acidosis in patients receiving doses exceeding 2,550 mg of metformin per day. A significant difference in lactate levels was observed with a p-value <0.00. Additionally, HbA1c levels serve as another predictor of lactic acidosis, with significance at p-value <0.02. A comparison of lactate levels in plasma using the LDH method and blood lactate levels using the lactic acid oxidase method was conducted to test the hypothesis that delayed plasma separation from whole blood increases lactate levels. Delayed separation allows LDH from red blood cells to leak out, artificially elevating lactate levels, as illustrated in Figure A.

The hypothesis that metformin causes mitochondrial dysfunction was also explored. Results showed that metformin stimulates glucokinase to draw glucose from the bloodstream into cells for energy production. In cases of high blood glucose concentration, glucokinase regulatory protein (GKRP) and glucokinase (GK) dissociate and translocate to the nucleus, regulating glucose metabolism and reducing blood glucose levels, as shown in Figure B. In diabetic patients treated with metformin, if blood glucose levels fall below 60 mg/dL, the liver converts glycogen into glucose and synthesizes glucose from amino acids and glycerol. Conversely, when blood glucose levels increase to 100-130 mg/dL, glucose is utilized by the body, and the liver synthesizes glycogen for storage. This process demonstrates a reduction in blood glucose levels over time, indicating that metformin improves mitochondrial function, as summarized in Table 3.

DISCUSSION

Metformin is well-known for its role in activating AMP-activated protein kinase (AMPK), which reduces hepatic gluconeogenesis. However, it has also been shown to directly affect other enzymes involved in metabolic processes. Notably, research has indicated that metformin-induced glycolysis and lactate production can lead to lactic acidosis, a potentially life-threatening side effect.[23] In this study, we demonstrate that metformin inhibits pyruvate carboxylase, a key enzyme in gluconeogenesis responsible for converting pyruvate into oxaloacetate. This step is essential for the synthesis of glucose from non-carbohydrate precursors.[24]

Several studies have described the relationship between pyruvate carboxylase, an enzyme located in mitochondria, and the anaplerotic pathway, which involves the addition of intermediates to the citric acid cycle during glucose production in diabetic patients. Pyruvate carboxylase (PC) facilitates continuous glucose production from lactate, glycerol, and other substrates. By converting pyruvate into oxaloacetate, it supports the gluconeogenic pathway in the liver and kidneys, enabling sustained glucose synthesis.[25]

Clinical investigations into the cellular respiration process following metformin administration have revealed that it stimulates AMPK, leading to a reduction in cellular ATP levels. This effect involves enzymes associated with glycolysis and gluconeogenesis, including the inhibition of pyruvate carboxylase, which reduces hepatic glucose production. This mechanism represents a significant additional action of metformin in diabetes treatment. This study suggests that the inhibition of pyruvate carboxylase by metformin may play a key role in treating hyperglycemia in patients with type 2 diabetes by suppressing glucose production at multiple points, including pyruvate carboxylase activity. Metformin effectively reduces the release of hepatic glucose into the bloodstream. However, there are potential risks associated with inhibiting pyruvate carboxylase, a key enzyme in the citric acid cycle, as this may disrupt mitochondrial metabolism and lead to metabolic complications. Clinical studies indicate that the benefits of metformin in controlling hyperglycemia outweigh these

risks, as it is generally well-tolerated and has a low incidence of side effects. Nonetheless, using metformin to inhibit pyruvate carboxylase alone is insufficient to lower elevated blood lactate levels. To address this issue, the study identified mechanisms to enhance the body's utilization of external lactic acid, which aligns with increased lactate absorption. Previous research has proposed supplementing lactic acid alongside metformin. However, lactic acid supplementation may induce resistance to other medications. Lactate has been shown to regulate gene expression via G-proteins, and its conversion to pyruvate by lactate dehydrogenase B promotes lysosomal acidification, which can interfere with glucose metabolism.[26]

In conclusion, this study demonstrates that the inhibition of pyruvate carboxylase by metformin represents a complex mechanism for regulating glucose homeostasis through adjustments to key metabolic pathways, including gluconeogenesis. Metformin effectively reduces excessive hepatic glucose production in patients with type 2 diabetes. The findings of this research highlight the impact of metformin on insulin sensitivity and other metabolic pathways, driven by specific interactions between metformin and enzymes such as pyruvate carboxylase. The study emphasizes the role of glucose metabolism in preventing elevated blood lactate levels while maintaining treatment effectiveness.

CONCLUSIONS

Energy production from glucose or amino acids relies heavily on pyruvate, a crucial intermediate that is converted into Acetyl CoA before entering the Krebs cycle to generate energy. Only a small portion of pyruvate is converted into lactate by the enzyme LDH. Under normal conditions, lactate is maintained at low levels (0.5–2.2 mmol/L in venous blood and 0.5–1.6 mmol/L in arterial blood) in the body.[23] Through the Cori cycle in the liver and kidneys, lactate can be reconverted into glucose, ensuring that blood lactate levels do not become excessively high.[24] However, when PDH (pyruvate dehydrogenase) activity is inhibited, such as by metformin, pyruvate is increasingly converted into lactate. If the liver or kidneys are unable to clear lactate effectively, blood lactate levels can rise. Levels exceeding 2.2 mmol/L warrant further investigation, while levels above 4 mmol/L, coupled with a blood pH below 7.35, indicate lactic acidosis.[25] Studies have shown that mitochondrial dysfunction, caused by toxin exposure or injury, increases intracellular calcium, leading to necrosis and apoptosis. Metformin has been implicated in mitochondrial dysfunction by inhibiting the enzyme fructose-1,6-bisphosphatase, resulting in decreased blood glucose levels. Additionally, metformin activates AMP-activated protein kinase, enhancing insulin action by accelerating phosphorylation. This improves glucose utilization through glycolysis and glycogen synthesis, highlighting the efficient functioning of mitochondria in the liver.[26]

This study found that metformin use can lead to elevated lactate levels, a diagnostic indicator of lactic acidosis. Patients with impaired kidney function are particularly at risk and should avoid metformin if creatinine levels exceed 1.4 mg/dL in women and 1.5 mg/dL in men. Patients with liver failure or heart failure are similarly at risk. Insulin synthesis, initiated by β-cells in the pancreas, involves translating insulin mRNA into Preproinsulin, which transitions into proinsulin in the endoplasmic reticulum (ER). Proinsulin, comprising the amino-terminal B chain, carboxy-terminal A chain, and connecting C peptide, undergoes enzymatic cleavage by endopeptidases, resulting in mature insulin. Both insulin and free C peptide are packaged in the Golgi apparatus, stored in the cytoplasm, and secreted when β-cells are stimulated. While insulin regulates blood glucose levels, it is also part of the insulin-like growth factors (IGF-1 and IGF-2) family, which includes Relaxin. These hormones can enhance cell proliferation and metabolism, increasing the efficiency of glucose utilization for energy production. We observed that the inhibition of pyruvate carboxylase by metformin is a mechanism that helps reduce production in the liver of patients with type 2 diabetes by decreasing gluconeogenesis. Gluconeogenesis is the process through which the liver generates glucose from non-carbohydrate precursors. Inhibiting pyruvate carboxylase, a key enzyme in this process, reduces the availability of oxaloacetate needed for glucose synthesis. As a result, glucose production from the liver decreases, helping to regulate blood sugar levels.

This discovery highlights the mechanism of metformin in regulating blood sugar balance, including its inhibition of pyruvate carboxylase in the treatment of diabetes. Although there is a risk of metabolic disturbances in certain cases, metformin remains a primary treatment option for type 2 diabetes due to its high efficacy and low incidence of side effects in most patients. Further studies on the mechanisms of metformin will deepen our understanding of the drug's function and support the development of new, highly effective treatment strategies.

Author Contributions

AA: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, final approval.

SS: Analysis and interpretation of data, Acquisition of data, conception and design, analysis and interpretation, Analysis and

interpretation of data, proofreading, Conception and design, analysis and interpretation of data.

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