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Association between Metformin Use and Risk of Lactic Acidosis or Elevated Lactate Concentration in Type 2 Diabetes

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Purpose: Metformin can reduce diabetes-related complications and mortality. However, its use is limited because of potential lactic acidosis-associated adverse effects, particularly in renal impairment patients. We aimed to investigate the association of metformin use with lactic acidosis and hyperlactatemia in patients with type 2 diabetes.

Materials and Methods: This was a cross-sectional study from a tertiary university-affiliated medical center. A total of 1954 type 2 diabetes patients were recruited in 2007–2011, and stratified according to the estimated glomerular filtration rate of 60 mL/min/1.73 m^2. Lactic acidosis was defined as plasma lactate levels >5 mmol/L and arterial pH <7.35.

Results: Metformin was used in 61.4% of the patients with type 2 diabetes mellitus. Plasma lactate levels were not different in the patients with and without metformin use. There was no difference in prevalence of hyperlactatemia and lactic acidosis between the patients with and without metformin use (18.9% vs. 18.7%, p=0.905 for hyperlactatemia and 2.8% vs. 3.3%, p=0.544 for lactic acidosis). Similar results were observed in the patients with estimated glomerular filtration rate <60 mL/min/1.73 m^2. Most patients with lactic acidosis had at least one condition related to hypoxia or poor tissue perfusion. Multiple regression analysis indicated no association between metformin use and lactic acidosis, whereas tissue hypoxia was an independent risk factor for lactic acidosis [odds ratio 4.603 (95% confidence interval, 1.327–15.965)].

Conclusion: Metformin use was not associated with hyperlactatemia or lactic acidosis in patients with type 2 diabetes.

Key Words: Metformin, lactic acidosis, diabetes mellitus, lactate

INTRODUCTION

Metformin is an effective anti-hyperglycemic agent and the drug of choice in patients with type 2 diabetes.[1,2] It is well known that metformin has many beneficial effects on body weight, serum lipids, fibrinolysis, blood pressure, and endothelial function.[3-5] Furthermore, metformin can reduce diabetes-related risks up to 32%, diabetes-related death up to 42%, and all-cause mortality up to 36%.[3] However, metformin use is limited because of its potential adverse effects associated with lactic acidosis (LA), particularly in patients with reduced renal

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function.[6]

The adverse effects of biguanides associated with LA have become a concern in clinical practice with the use of the first line biguanide, phenformin. Phenformin inhibits lactate oxidation and increases lactate production.[7,8] It has been reported that the incidence of phenformin-associated LA ranges between 40 and 129 cases per 100000 patient-years.[9,10] However, despite being a biguanide, metformin does not affect anaerobic lactate production.[11] In fact, the incidence of LA is 10 to 20 times lower with the use of metformin than with that of phenformin.[12] Furthermore, several recent studies have suggested that the occurrence of LA with the use of metformin might be a coincidence rather than a consequence. Scale and Harvey[13] reported that LA was more common in patients with diabetes but was not more frequent in patients who had taken metformin. Another study has shown that the prevalence of LA is lower in patients with metformin therapy than those with sulfonylurea therapy (3.3 and 4.8 cases per 100000 patient-years, respectively).[14] Therefore, we aimed to investigate whether metformin use was associated with LA and hyperlactatemia in patients with type 2 diabetes.

MATERIALS AND METHODS

Patients and study design

This was a cross-sectional study. In the present study, patients from the diabetes registry of the Severance Diabetes Center between January 2007 and December 2011 were retrospectively evaluated. Of total 33758 diabetic patients, patients with type 1 diabetes, gestational diabetes, and patients whose lactate levels were not reported were excluded. A total of 1954 patients aged ≥20 years and with type 2 diabetes were included in this study (Fig. 1). Medical history including medication use, history of operation, and underlying diseases was collected. Hyperlactatemia was defined as plasma lactate levels above the normal upper limit of 2.2 mmol/L. LA was defined as plasma lactate levels of >5 mmol/L and arterial pH <7.35. All patients were stratified according to the use of metformin or the estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2. The metformin therapy group comprised patients who used metformin during the study period, and the non-metformin therapy group comprised subjects who did not use metformin in the year prior to data collection. This study was approved by the research ethics committee of the Severance Hospital, under protocol No. 4-2014-0420.

Laboratory measurements

Fasting and postprandial plasma glucose levels were measured using the glucose oxidase method on a Hitachi 747 automatic analyzer (Hitachi Instruments Service, Tokyo, Japan). Glycated hemoglobin (HbA1c) levels were measured using high-performance liquid chromatography and a Variant II Turbo hemoglobin testing system (Bio-Rad Laboratories, Hercules, CA, USA). Plasma lactate levels were measured using the amperimetric electrode method. Arterial blood pH was analyzed in patients with increased lactate levels. Serum creatinine levels were measured using the Jaffe method on a Hitachi 7600 analyzer. The eGFR was calculated using the 4-variable Modification of Diet in Renal Disease study equation: eGFR=186.3×(creatinine)$^{-1.154}$×age$^{-0.203}$×0.742 (for women).[15] Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured using the Internal Federation of Clinical Chemistry standardization without pyridoxal phosphate using a Hitachi 7600 analyzer. Among participants, we measured metformin concentration in those taking metformin and with reduced renal function (creatinine ≥1.5 mg/dL for men and ≥1.4 mg/dL for women) (n=31). None of them had severe illness such as liver cirrhosis, acute coronary syndrome, malignancy, acute infectious disease, and acute or severe renal failure (renal failure occurred within 7 days or serum creatinine ≥3 mg/dL). Metformin concentration was measured by high-performance liquid chromatography-tandem mass spectrometry using a 1200 Series HPLC system (Agilent Technologies, Santa Clara, CA, USA) and API 4000™ mass spectrometer (AB Sciex, Framingham, MA, USA). The coefficient of variance ranged between 4.7% and 7.7%.

Statistical analysis

All continuous variables are shown as mean±standard deviation or median (interquartile range) for data not normally distributed. Data were analyzed after stratification considering a threshold eGFR value of 60 mL/min/1.73 m^2. Variable comparison between two groups was performed using Student's t-test or chi-square test, as appropriate. The Mann-Whitney U test

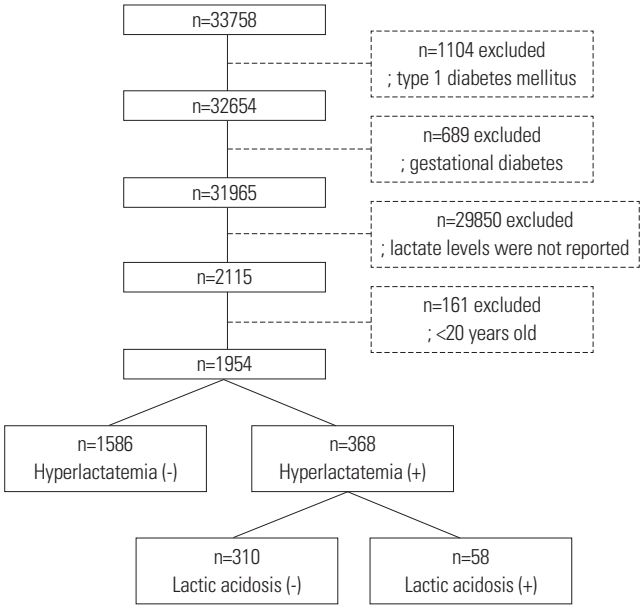

Fig. 1. Flow diagram of the study population.

Table 1. Baseline Characteristics of Subjects According to the Metformin Use and Renal Function

Variables	Total (n=1954)			eGFR ≥60 mL/min/1.73 m^2 (n=1438)			eGFR <60 mL/min/1.73 m^2 (n=516)		
	No metformin use (n=754)	Metformin use (n=1200)	*p* value	No metformin use (n=584)	Metformin use (n=854)	*p* value	No metformin use (n=170)	Metformin use (n=346)	*p* value
Age (yr)	62.3±11.7	64.6±11.0	<0.001	62.4±11.5	64.0±11.0	0.008	62.2±12.4	65.9±11.0	<0.001
Sex (women, %)	315 (41.8)	480 (40.0)	0.232	238 (40.8)	328 (38.4)	0.201	77 (45.3)	152 (43.9)	0.421
BMI (kg/m^2)	24.3±3.6	24.1±3.8	0.208	24.2±3.5	24.0±3.7	0.545	24.8±3.8	24.3±3.9	0.182
Metformin dose (mg/day)	–	1000 (500–1000)		–	1000 (500–1000)		–	1000 (500–1000)	
Lactate (mmol/L)	1.2 (0.8–1.9)	1.1 (0.8–1.9)	0.050	1.1 (0.8–1.8)	1.1 (0.8–1.8)	0.095	1.4 (0.9–2.6)	1.2 (0.8–2.5)	0.087
Cr (mg/dL)	1.3±1.6	1.2±1.1	0.531	0.8±0.2	0.8±0.2	0.508	2.9±2.8	2.3±1.7	0.009
eGFR (mL/min/1.73 m^2)	81.8±34.0	79.0±36.5	0.097	95.4±24.1	95.8±28.2	0.745	35.1±17.6	37.6±15.5	0.117
Albuminuria (mg/day)	26.3 (11.9–101.2)	14.0 (0–88.6)	<0.001	18.8 (9.8–60.8)	9.2 (0–35.0)	<0.001	71.8 (19.9–411.7)	68.3 (13.2–442.2)	0.313
CO_2 (mmol/L)	21.8±4.6	21.8±5.7	0.720	22.5±4.2	22.6±5.7	0.792	19.4±5.3	19.4±5.1	0.952
AST (IU/L)	22 (16–36)	23 (16–40)	0.186	23 (17–36)	23 (16–39)	0.437	21 (16–41)	24 (16–44)	0.243
ALT (IU/L)	20 (12–33)	19 (13–34)	0.554	20 (13–34)	19 (13–33)	0.255	17 (12–31)	19 (12–36)	0.451
FPG (mg/dL)	154.6±67.4	148.4±65.2	0.053	152.9±62.0	148.1±61.3	0.151	160.1±83.4	149.4±75.1	0.161
PPG (mg/dL)	220.7±97.4	208.7±78.0	0.041	221.7±99.3	206.0±77.3	0.022	217.3±91.3	216.1±79.7	0.913
HbA1c (%)	7.6±4.3	7.4±1.6	0.116	7.7±4.9	7.4±1.5	0.100	7.4±1.6	7.4±1.8	0.943
Total cholesterol (mg/dL)	156.0±49.9	152.9±48.7	0.196	157.4±49.2	155.6±49.7	0.510	151.1±52.2	145.6±45.2	0.234
Triglyceride (mg/dL)	126 (89–171)	118 (85–164)	0.147	126 (88–167)	118 (84–161)	0.306	127 (93–201)	119 (88–169)	0.268
HDL-cholesterol (mg/dL)	41.8±14.6	42.0±14.0	0.814	42.8±13.9	43.1±14.0	0.792	39.3±16.0	39.5±13.6	0.894
LDL-cholesterol (mg/dL)	95.5±37.1	90.3±45.8	0.081	98.3±37.8	93.6±50.1	0.207	87.9±34.2	82.1±31.2	0.161

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CO_2, bicarbonate; Cr, creatinine; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin, HDL, high density cholesterol; LDL, low density cholesterol; PPG, postprandial plasma glucose.
Data are mean±SD, median (interquartile range), or n (%).

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was used to compare two groups if variables were not normally distributed. Pearson's correlation coefficient was used to assess the association between metformin and lactate levels. Multiple logistic regression analysis was used to investigate the association between metformin use and LA after adjustment for confounding factors. Statistical analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA), and a p value<0.05 was considered significant.

RESULTS

Baseline characteristic of the study subjects

Overall, 61.4% of the patients with diabetes were treated with metformin. Metformin therapy was more common in patients with eGFR level of <60 mL/min/1.73 m^2 than in those with eGFR level ≥60 mL/min/1.73 m^2 (67.1% vs. 59.4%, p=0.002). Table 1 shows the baseline characteristics of patients with and without metformin therapy. Among total participants, patients with metformin therapy were older but had lower albuminuria and postprandial glucose levels than those without metformin therapy. There were no significant differences either in plasma lactate levels or in total bicarbonate (CO_2) levels between the patients with and without metformin therapy [1.2 (interquartile range, 0.8–1.9) mmol/L vs. 1.1 (interquartile range, 0.8–1.9) mmol/L, p=0.050 for plasma lactate; 21.8±5.7 mmol/L vs. 21.8±4.6 mmol/L, p=0.720 for total CO_2]. This was consistently observed in both eGFR subgroups. In addition, no significant correlation was found between metformin dose and plasma lactate levels (r=0.051, p=0.350) regardless of the eGFR levels.

In 31 patients with reduced renal function, metformin concentration was measured. Median (interquartile range) metformin concentration was 0.97 (0.30–1.90) μg/mL and it increased as metformin dose increased. However, there was no significant correlation between metformin concentration and plasma lactate levels (r=-0.018, p=0.924) or total CO_2 (r=-0.042, p=0.833) levels (Supplementary Fig. 1 and 2, only online).

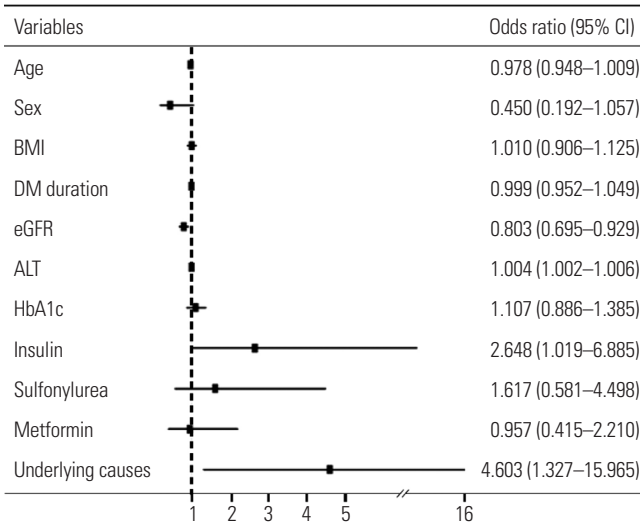

Fig. 2. Odds ratio for the development of lactic acidosis in subgroup with hyperlactatemia. The odds ratio of eGFR was expressed as an increased risk per 10 mL/min/1.73 m^2 increase of eGFR. ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

Incidence of hyperlactatemia and lactic acidosis

Among the 1954 patients with diabetes, 18.8% of them presented with hyperlactatemia and 3.0% of them with LA (Table 2). There was no significant difference in the prevalence of hyperlactatemia (18.9% vs. 18.7%, p=0.905) or LA (2.8% vs. 3.3%, p=0.544) between the patients with and without metformin therapy. Regardless of eGFR levels, there was no significant difference in the prevalence of hyperlactatemia or LA. Although not significant, the prevalence of LA in patients with metformin therapy was lower than that in patients without metformin therapy, even in the patient subgroup with eGFR <60 ml/min/1.73 m^2.

Comparison of subjects with hyperlactatemia according to the development of lactic acidosis

We further evaluated patients with hyperlactatemia according to the occurrence of LA (Table 3). LA occurred in 16.0% of the patients with hyperlactatemia. The mortality rates of patients with hyperlactatemia and LA were 15.2% and 39.0%, respectively. Compared with patients with hyperlactatemia but with-

Table 2. Prevalence of Hyperlactatemia and Lactic Acidosis in Patients with Type 2 Diabetes According to Metformin Use

Stratification by eGFR	Total, n (%)	No metformin use, n (%)	Metformin use, n (%)	p value
Total	1954	754	1200	
Hyperlactatemia	368 (18.8)	141 (18.7)	227 (18.9)	0.905
Lactic acidosis	58 (3.0)	25 (3.3)	33 (2.8)	0.544
eGFR ≥60 mL/min/1.73 m^2	1438	584	854	
Hyperlactatemia	225 (15.6)	93 (15.9)	132 (15.5)	0.810
Lactic acidosis	22 (1.5)	12 (2.1)	10 (1.2)	0.180
eGFR <60 mL/min/1.73 m^2	516	170	346	
Hyperlactatemia	143 (27.7)	48 (28.2)	95 (27.5)	0.853
Lactic acidosis	36 (7.0)	13 (7.6)	23 (6.9)	0.769

eGFR, estimated glomerular filtration rate.

out LA, patients with hyperlactatemia and LA had higher plasma lactate levels [10.4 (interquartile range, 6.4–13.3) mmol/L vs. 3.3 (interquartile range, 2.7–4.3) mmol/L, $p<0.001$], but lower arterial pH (7.2±0.1 vs. 7.4±0.1, $p<0.001$) and total CO_2 levels (14.2±5.3 mmol/L vs. 20.5±4.3 mmol/L, $p<0.001$). The eGFR level significantly decreased in patients with LA in comparison with those without LA (53.5±37.3 mL/min/1.73 m^2 vs. 71.9±32.6 mL/min/1.73 m^2, $p<0.001$). Liver enzymes significantly increased in patients with LA compared with those without LA [92 (interquartile range, 28–238) IU/L vs. 25 (interquartile range, 18–45), $p<0.001$ for AST and 49 (interquartile range, 20–137) IU/L vs. 22 (interquartile range, 15–39) IU/L, $p<0.001$ for ALT]. There was no significant difference in the number of patients with metformin therapy or in the metformin dose be-

Table 3. Biochemical Profile of Subjects with Hyperlactatemia According to the Occurrence of Lactic Acidosis

Variables	Hyperlactatemia (n=368)		*p* value
	No lactic acidosis (n=310)	Lactic acidosis (n=58)	
Age (yr)	64.5±11.2	63.5±13.2	0.556
Sex (women, %)	142 (45.8)	18 (31.0)	0.023
BMI (kg/m^2)	24.0±4.0	23.9±3.0	0.777
Duration of diabetes (yr)	2 (0–9)	3 (1–8)	0.193
Metformin dose (mg/day)	500 (0–1000)	500 (0–1000)	0.750
Lactate (mmol/L)	3.3 (2.7–4.3)	10.4 (6.4–13.3)	<0.001
Cr (mg/dL)	1.3±1.1	2.1±1.6	0.001
eGFR (mL/min/1.73 m^2)	71.9±32.6	53.5±37.3	<0.001
Albuminuria (mg/day)	17.4 (0–96.0)	33.0 (8.1–227.4)	0.065
Arterial pH	7.4±0.1	7.2±0.1	<0.001
CO_2 (mmol/L)	20.5±4.3	14.2±5.3	<0.001
AST (IU/L)	25 (18–45)	92 (28–238)	<0.001
ALT (IU/L)	22 (15–39)	49 (20–137)	<0.001
FPG (mg/dL)	168.7±95.4	171.5±76.5	0.836
PPG (mg/dL)	224.7±88.4	259.5±94.7	0.065
HbA1c (%)	7.3±1.6	7.5±1.8	0.404
Total cholesterol (mg/dL)	157.5±52.2	134.4±56.9	0.003
Triglyceride (mg/dL)	130 (94–169)	123 (62–169)	0.345
HDL-cholesterol (mg/dL)	42.0±14.4	36.0±13.3	0.026
LDL-cholesterol (mg/dL)	95.7±37.3	85.3±39.8	0.146
Insulin (n, %)	105 (33.9)	26 (44.8)	0.110
Metformin use (n, %)	194 (62.6)	33 (56.9)	0.414
Sulfonylurea (n, %)	81 (26.1)	16 (27.6)	0.817
Other OHA (n, %)	37 (11.9)	9 (15.5)	0.449

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CO_2, bicarbonate; Cr, creatinine; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin, HDL, high density lipoprotein; LDL, low density lipoprotein; OHA, oral hypoglycemic agent; PPG, postprandial plasma glucose.
Data are mean±SD, median (interquartile range), or n (%).

Table 4. Underlying Causes According to the Lactic Acidosis

Underlying causes	No lactic acidosis, n (%)	Lactic acidosis, n (%)	*p* value
Sepsis	43 (13.9)	18 (30.5)	0.002
Infection	138 (44.7)	26 (44.1)	0.933
Myocardial infarction*	6 (1.9)	2 (3.4)	0.376
Heart failure*	14 (4.5)	2 (3.4)	0.512
Hypoxia	39 (12.6)	6 (10.3)	0.598
Shock	56 (18.1)	21 (35.6)	0.003
Liver cirrhosis	15 (4.9)	12 (20.3)	<0.001
Grand mal seizure*	1 (0.3)	2 (3.4)	0.068
Bleeding	36 (11.7)	17 (28.8)	0.001

*Fisher's exact test.

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tween the patients with and without LA.

Multiple regression analysis for lactic acidosis

More than 60% of the patients with hyperlactatemia and 84.7% of the patients with LA had at least one underlying disease that could cause tissue hypoxia, such as sepsis, heart failure, hypoxemia, shock, liver cirrhosis, or bleeding (Table 4). Sepsis, shock, liver cirrhosis, and bleeding were more prevalent in patients with LA compared to those without LA. Multiple logistic regression analysis indicated that metformin therapy was not associated with the development of LA (Fig. 2). In contrast, the presence of underlying disease leading to tissue hypoxia showed a significant association with LA (odds ratio, 4.603; 95% confidence interval, 1.327–15.965).

DISCUSSION

In the present study, we demonstrated that there was no significant difference in the prevalence of hyperlactatemia and LA between patients with and without metformin therapy. Despite the concerns for LA in patients with reduced renal function, the prevalence of these conditions was not increased in the metformin-treated patients with GFR <60 mL/min/1.73 m^2 or <45 mL/min/1.73 m^2 (data not shown). In consistent with our results, a recent meta-analysis from 194 prospective studies found that neither fatal nor nonfatal LA occurred in 36893 patients-years in patients with metformin therapy.[16] The estimated incidence of LA in patients with and without metformin therapy was 8.1 and 9.9 cases per 100000 patients-years, respectively. This meta-analysis also included elderly patients and those with renal impairment. Other studies involving elderly patients with renal insufficiency did not find any case of LA.[12,17,18]

There have been growing evidences that metformin does not increase plasma lactate levels. Patients with diabetes showed similar lactate turnover and lactate oxidation rates regardless of the metformin therapy.[19] Previous studies including a randomized controlled trial showed that lactate levels did not change in patients with metformin therapy or were not correlated with the use of metformin.[5,12,20-22] The switch from phenformin to metformin in patients with type 2 diabetes resulted in decreased plasma lactate levels from 28 mg/dL to 15 mg/dL (the normal range is 9–18 mg/dL).[17] Although we measured metformin concentration in a small number of participants (n=31), serum lactate levels were not correlated with plasma metformin concentration in patients with reduced renal function (mean eGFR 41.7 mL/min/1.73 m^2). Previously, few studies have measured plasma metformin concentrations. A review of case reports for LA found that there was no quantitative association between plasma metformin and lactic acid concentration (n=19).[23] Another study performed in 14 patients with LA showed similar results.[24] As far as we are aware of, only one study has directly compared plasma metformin concentration with lactate levels in patients with chronic kidney disease but without LA.[22] In accordance with our results, this study demonstrated no correlation of lactate levels with metformin concentration. In Asian population with type 2 diabetes, an observational study showed that the mean plasma lactate level was not associated with total daily dose of metformin.[25]

In the present study, most patients with LA had at least one condition that could result in tissue hypoxia. In accordance with our results, previous case series of metformin-associated LA have demonstrated that all patients except one case had clinical shock or tissue hypoxia.[24,26] In the largest study of metformin-treated patients with LA (n=49), all patients had at least one disease that could lead to tissue hypoxia, such as cardiopulmonary failure, sepsis, or hemorrhage.[20] Among the patients treated with other hypoglycemic agents except metformin, severe medical condition causing tissue hypoxia has been consistently observed in all patients with LA.[27] Taken together, previous studies suggest that underlying disease associated with tissue hypoxia rather than metformin use is linked to LA in diabetic patients. In addition to confirming the previous observation, we also found that this condition had an independent association with LA, even after adjustment for possible confounders.

It is one of strengths of our study that we measured plasma lactate and bicarbonate levels in a relatively large sample (n=1954). Previous studies with a large sample size usually used the diagnosis of acidosis or LA from the medical record. We also adjusted possible confounding factors to evaluate the association of metformin use and the presence of LA. Although a small number of participants (n=31), measurement of metformin concentration is an another strength of this study. To the best of our knowledge, this is the largest study of metformin-treated patients with LA in Asian population. However, there are several limitations. The retrospective and cross-sectional nature of the study did not allow us to accurately determine the causal relationship between metformin use and LA. Second, we could not adjust the severity of underlying diseases. Lastly, our results could not be generalized to other population.

In conclusion, we demonstrated herein that there is no association between metformin use and the risk of LA or elevated lactate concentration in type 2 diabetes, suggesting that metformin might be a bystander rather than the cause of LA. Further prospective studies are needed to elucidate the direct role of metformin on the development of LA in subjects with type 2 diabetes.

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