Fasting Plasma Lactate Concentrations in Ambulatory Elderly Patients With Type 2 Diabetes Receiving Metformin Therapy: A Retrospective Cross-sectional Study

Yi-Chun Lin[1,2], Liang-Yu Lin[1,3], Huei-Fang Wang[4], Hong-Da Lin[1,2]*

[1]Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, National Yang-Ming University [2]School of Medicine, and [3]Department and Institute of Pharmacology, Taipei, and [4]Division of Endocrinology and Metabolism, Department of Medicine, Saint Mary's Hospital, Luodong, Yilan, Taiwan, R.O.C.

Background: Metformin is a worldwide accepted biguanide antidiabetic agent, and its effectiveness and benefit have already been well established. Among the side effects of metformin, lactate acidosis is the most problematic because of a high mortality rate, which impedes its use in clinical practice, especially in elderly patients with type 2 diabetes. Aging is associated with a decreased renal function and increasing comorbidities, but few data are available regarding plasma lactate levels in this unique population. In this study, we assessed fasting plasma lactate levels in ambulatory, elderly Taiwanese patients with type 2 diabetes, who were taking the drug, metformin, to identify independent risk factors for hyperlactemia in this group.

Methods: Sixty-six ambulatory type 2 diabetic patients, >80 years of age (mean, 83.6 years; range, 80–90 years), receiving metformin therapy, were enrolled, from January 2005 to September 2009, in the Diabetes Case Management Program. A further 79 younger patients (also type 2 diabetics on metformin) served as controls (mean age, 59.9 years; range, 37–79 years). Fasting serum electrolytes, creatinine, bicarbonate, glycated hemoglobin, plasma glucose and lactate levels were determined.

Results: Lactate levels did not differ between the elderly and control groups (13.2 ± 5.2 mg/dL and 13.5 ± 4.8 mg/dL, respectively). None of the patients fulfilled the lactic acidosis criteria. Patients in the elderly group had a significantly lower daily metformin dose, higher creatinine levels, and lower estimated creatinine clearance, compared with the control group (all $p < 0.05$). Estimated creatinine clearance was negatively associated with lactate levels in the elderly group ($p < 0.05$, $r = -0.27$), but not in the control group. Patients with fasting plasma glucose levels >130 mg/dL had a 2.8-fold increased risk of developing hyperlactemia.

Conclusion: Plasma lactate levels in ambulatory elderly patients with type 2 diabetes receiving metformin therapy did not differ from those in a younger age group. Patients with fasting plasma glucose levels >130 mg/dL had a 2.8-fold risk of developing hyperlactemia, but none of them developed lactate acidosis. [*J Chin Med Assoc* 2010;73(12):617–622]

Key Words: elderly, lactate, metformin, type 2 diabetes

Introduction

Metformin, a biguanide, has gained increasing acceptance worldwide as an antidiabetic agent since its introduction in 1957. Metformin predominantly lowers glucose levels by reducing hepatic glucose output, while also increasing peripheral insulin sensitivity, to some extent.[1] In addition, metformin treatment is known to decrease macrovascular complications of diabetes mellitus, as has previously been reported in the well-known UK Prospective Diabetes Study.[2]

*Correspondence to: Dr Hong-Da Lin, Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C. E-mail: hdlin@vghtpe.gov.tw • Received: April 29, 2010 • Accepted: July 30, 2010

Gastrointestinal tract discomfort is the most common adverse effect of metformin treatment, a phenomenon which occurs in 5–30% of patients.[3] Lactic acidosis is a rare, but serious, metabolic consequence of metformin therapy, and it has been found to be associated with a mortality rate close to 50%.[4] The incidence of lactic acidosis has been reported to be 0.01–0.08 per 1,000 patient-years, which equates to a 1-in-10 to 1-in-20 risk of phenformin-induced lactate acidosis.[5,6]

Risk factors for the development of lactic acidosis associated with metformin use, such as preexisting cardiac disease, renal insufficiency, chronic pulmonary disease with hypoxia, and congestive heart failure, are typically considered to be contraindications for metformin therapy itself. Aging can be associated with decreased renal function and increasing comorbidities. There are little data available concerning the safety of metformin in the treatment of elderly type 2 diabetic patients. Misbin et al[7] reported that 8 of 47 patients (17%) with a confirmed diagnosis of lactic acidosis were >80 years of age 1 year after the Food and Drug Administration approved metformin. The revised label stated that metformin treatment should not be initiated in patients ≥80 years of age.

This study aimed to assess fasting plasma lactate levels in ambulatory elderly (≥80 years old) Taiwanese patients with type 2 diabetes mellitus receiving various doses of metformin, and to identify independent risk factors associated with hyperlactemia in these patients.

Methods

Subjects

From January 2005 to September 2009, 66 elderly (≥80 years old) metformin-treated patients with type 2 diabetes, in the Diabetes Case Management Program of Taipei Veterans General Hospital, were enrolled in the study. In addition, 79 younger (<80 years old) metformin-treated patients with type 2 diabetes were recruited to serve as the control group. The research project was approved by the medical ethics committee of Taipei Veterans General Hospital.

Demographics and blood sampling

Baseline information of body weight, body height, body mass index (BMI) and medication was collected. Overnight fasting blood samples were obtained from all participants during scheduled diabetic outpatient clinic visits for measurement of sodium, potassium, chloride, creatinine, plasma glucose, glycated hemoglobin (HbA1c), bicarbonate, and lactate levels.

Laboratory tests

The anion gap was determined using the equation [sodium]-[chloride]-[bicarbonate] (mmol/L), while estimated creatinine clearance rate (eCCr) was calculated using the Cockcroft and Gault equation.[8] HbA1c levels were measured by cation-exchange high-performance liquid chromatography (Tosoh HLC-723 G7; Tosoh Corp., Tokyo, Japan). Sodium, potassium, chloride, and lactate levels were determined using a Hitachi 7180 autoanalyzer (Hitachi High-Technologies Corp., Tokyo, Japan). The reference range for fasting venous plasma lactate levels was 5.0–15.0 mg/dL.

Statistical analyses

Data are presented as mean ± standard deviation. Categorical data were compared using the χ^2 test, and continuous data were compared using the Mann-Whitney rank sum test. The associations between variables and plasma lactate level were determined by Pearson's correlation test. Fasting plasma lactate levels between patients in the 3 metformin dose groups (≤1,000, 1,001–2,000 and >2,000 mg/day) were compared using the Kruskal-Wallis test. Univariate predictors for hyperlactemia with a potential significance ($p<0.2$ in univariate analysis) were included in the multivariate analysis. The odds ratio for hyperlactemia was calculated by multivariate logistic regression analysis. All statistical analyses were performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA) for Windows. Differences were considered statistically significant when $p<0.05$.

Results

The basic characteristics of the 2 patient groups are summarized in Table 1. Male patients outnumbered female patients in both groups. Patients in the elderly group had significantly lower daily metformin doses, BMI and eCCr, and significantly higher creatinine levels, compared with the control group (all $p<0.05$). Significantly more patients in the elderly group had stage 3 or 4 chronic kidney disease than those in the control group ($p<0.01$). There were no between-group differences in fasting plasma glucose, HbA1c, bicarbonate, sodium, potassium, and chloride levels, or anion gap. Furthermore, there was no between-group difference in plasma lactate levels. There was no relationship between lactate levels and metformin dose (Figure 1).

The distribution of fasting plasma lactate levels for all patients is shown in Figure 2. Twenty patients in

Table 1. Basic characteristics of the elderly and control groups*

	Elderly group ($n=66$)	Control group ($n=79$)	p
Age (yr)	83.6±2.8	59.6±9.6	
Sex (male/female)	56/23	52/14	0.37
Body mass index (kg/m^2)	24.4±3.2	26.3±4.4	<0.05
Fasting plasma glucose (mg/dL)	132.9±29.7	139.4±26.5	0.116
HbA1c (%)	6.9±0.9	7.2±1.2	0.108
eCCr (mL/min)	48.9±12.9	80.3±30.1	<0.01
Metformin dose (mg/d)	1,408.3±501.9	1,618.9±522.8	<0.05
Plasma lactate (mg/dL)	13.2±5.2	13.5±4.8	0.888
Bicarbonate (mmol/L)	27.63±2.7	28.09±3.2	0.237
Sodium (mmol/L)	140.7±2.8	140.6±2.3	0.724
Potassium (mmol/L)	4.4±0.3	4.4±0.5	0.749
Chloride (mmol/L)	104.1±2.8	103.3±2.7	0.114
Anion gap (mmol/L)	8.8±3.1	9.2±3.1	0.615

**Data are presented as mean±standard deviation or n. HbA1c=glycated hemoglobin; eCCr=estimated creatinine clearance rate.*

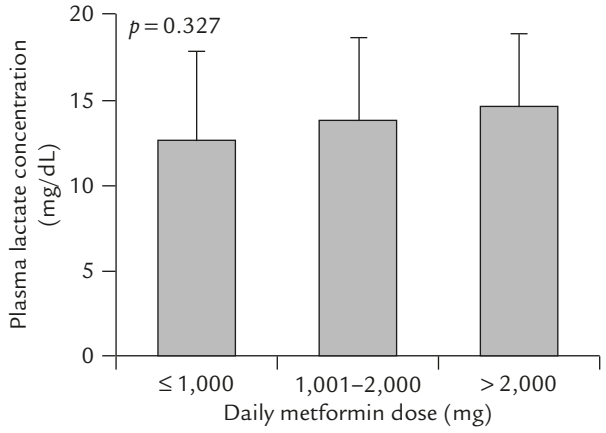

Figure 1. Mean plasma lactate level at 3 different metformin doses. There were no significant differences in fasting plasma lactate level among the 3 metformin dose groups (Kruskal-Wallis test, $p=0.327$).

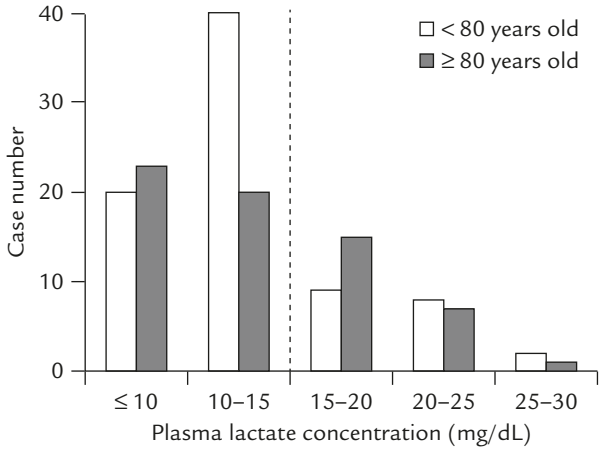

Figure 2. Distribution of fasting plasma lactate level in metformin-treated patients. The dotted line indicates the normal upper limit for plasma lactate levels.

the elderly group (33.3%) and 22 in the control group (25.8%) had plasma lactate levels that were higher than the normal upper limit of 15 mg/dL, which was not statistically significant. None of the patients fulfilled the lactic acidosis criteria indicated by anion gap acidosis with a plasma lactate >50 mg/dL.[9]

eCCr was negatively associated with plasma lactate levels in elderly patients (Figure 3A, $p<0.05$), but no such association was found in the control group (data not shown). When the data from all 145 patients were combined, plasma glucose levels were positively correlated with fasting plasma lactate levels (Figure 3B, $p<0.01$).

Table 2 summarizes the characteristics of patients with respect to those who did and those who did not have hyperlactemia. Fasting plasma glucose levels were significantly higher in hyperlactemic patients ($p=0.01$).

Multivariate logistic regression analysis revealed that patients with a fasting plasma glucose level >130 mg/dL had a 2.8-fold risk of becoming hyperlactemic. Age, eCCr, BMI, metformin dose, HbA1c, creatinine, sodium, and potassium levels were not risk factors for hyperlactemia.

Discussion

Lactic acidosis is the most serious side effect of biguanide therapy. Compared with phenformin, metformin does not affect lactate turnover,[10,11] accumulate in the mitochondria, inhibit the electron transport

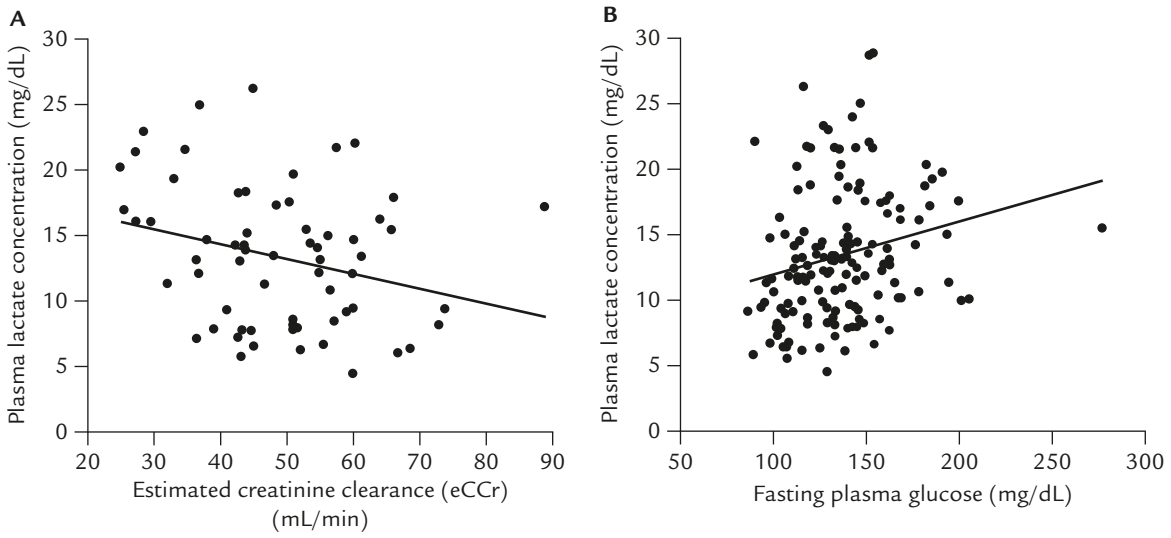

Figure 3. (A) Regression analysis demonstrating the relationship between plasma lactate levels and estimated creatinine clearance rate (eCCr) in the elderly patient group. Lactate levels were negatively correlated with eCCr ($r = -0.27$; $p = 0.029$; $n = 66$). (B) Regression analysis demonstrating the relationship between plasma lactate and fasting plasma glucose levels in all metformin-treated patients. Lactate levels were positively correlated with plasma glucose levels ($r = 0.23$; $p = 0.005$; $n = 145$).

Table 2. Characteristics of patients with and without hyperlactemia*

	Plasma lactate > 15 mg/dL ($n = 42$)	Plasma lactate ≤ 15 mg/dL ($n = 103$)	p
Age (yr)	71.5 ± 14.6 (38–90)	70.3 ± 13.6 (37–90)	0.634
Sex (male/female)	34/8	74/29	0.352
Body mass index (kg/m^2)	26.0 ± 3.5 (17.8–33.9)	25.2 ± 4.2 (17.6–36.3)	0.141
Fasting plasma glucose (mg/dL)	148.7 ± 32.1 (90–276)	131.4 ± 24.7 (90–276)	0.001
HbA1c (%)	7.3 ± 1.2 (5.3–12.2)	7.0 ± 1.1 (5.1–11.6)	0.144
Serum creatinine (mg/dL)	1.1 ± 0.4 (0.5–2.5)	1.0 ± 0.4 (0.4–2.9)	0.228
eCCr (mL/min)	64.0 ± 30.8 (24.9–129)	67.0 ± 27.8 (175–133)	0.498
CKD stages 3, 4	19 (48.7)	46 (50.0)	1
Metformin dose (mg/d)	1,590 ± 521.5 (500–2,550)	1,495.6 ± 522.7 (500–2,000)	0.262
Anion gap (mmol/L)	10.5 ± 3.4 (3.1–14.4)	8.4 ± 2.8 (1.5–12.3)	0.615

**Data are presented as mean ± standard deviation (range) or n or n (%). HbA1c = glycated hemoglobin; eCCr = estimated creatinine clearance rate; CKD = chronic kidney disease.*

chain,[10] or increase lactate oxidation.[11] Metformin is not metabolized by the liver and is excreted mainly by the kidneys. Therefore, the incidence of lactic acidosis is much lower with metformin than phenformin therapy.

It has been reported that patients with type 2 diabetes taking metformin have higher plasma lactate levels than those not taking metformin.[12] Indeed, case reports of metformin-associated lactic acidosis continue to be published. In the present study, we found that a fasting plasma glucose level in excess of 130 mg/dL increased the risk of hyperlactemia 2.8-fold. The reason for this increased risk is unclear; however, several explanations have been proposed.[12–15] It may be partially explained by sympathetic overactivity related to hyperglycemia, leading to increased plasma lactate levels.[12] Alternatively, decreased expression of acetyl-CoA associated with metformin therapy may favor the formation of lactate from glucose.[15] However, it is still unclear as to whether metformin treatment, in the face of existing hyperglycemia, causes a synergistic increase in plasma lactate levels and further increases the risk of lactic acidosis.

There is controversy in the literature as to whether or not old age is a risk factor for metformin-associated lactic acidosis. In this study, we found that there was no significant difference in plasma lactate levels between elderly and comparatively younger patients. Our findings are consistent with those reported by Gregorio et al,[16] who also failed to find higher plasma lactate

levels in elderly patients with diabetes receiving metformin monotherapy or add-on sulfonylurea therapy. Mean daily metformin doses were significantly lower in our elderly patient group than in the control group. This difference may have been due to the prescribing physician being overly concerned about potential side effects, such as lactic acidosis or gastrointestinal discomfort, in older patients. Nevertheless, we found no significant differences in plasma lactate levels among patients taking different doses of metformin. Davis et al[12] and Lim et al[17] also reported that plasma lactate levels are not related to metformin dose.

In agreement with the findings from several previous clinical series,[9,18] we did not encounter any cases of lactic acidosis in elderly patients on metformin therapy. In contrast, Khan et al[19] reported 2 cases of metformin-associated hyperlactemia in patients aged 82 and 76 years. In June 1996, 1 year after metformin was approved for use in the USA, the Food and Drug Administration received reports of 47 confirmed cases of metformin-associated lactic acidosis. Among these, 8 patients (17%) were older than 80 years.[7] The subsequently revised label stated that metformin treatment should not be initiated in patients ≥80 years old. In our series, fasting plasma lactate levels in elderly metformin-treated patients with type 2 diabetes did not differ from those in younger patients, despite the finding that these patients had lower eCCr rates. However, fasting plasma lactate levels were negatively correlated with eCCr in the elderly patient group, but not in the younger control group. Rachmani et al[20] suggested that metformin is tolerable with mild renal impairment, even when the creatinine level is >1.47 mg/dL. This may not have been the case in our study, especially for the elderly group of patients. It is important to be aware that creatinine levels often overestimate renal function, particularly in the elderly. Calculation of eCCr, not just creatinine monitoring, is especially prudent in elderly patients in whom even a minor elevation in creatinine levels (even within the normal range) may be associated with accumulation of lactate in the serum. Therefore, we suggest that metformin should be cautiously prescribed for patients older than 80 years with mildly impaired renal function.

This study has several limitations. First, it was a cross-sectional, but not prospective, study, in which none of the patients developed lactic acidosis. We do not know the evolution of these patients with mild hyperlactemia. Second, the patients in this study were ambulatory elderly patients; therefore, the findings may not necessarily be applicable to the entire elderly population receiving metformin treatment for type 2 diabetes, many of whom undoubtedly have comorbidities.

In conclusion, our findings suggest that old age *per se* should not preclude prescription of metformin for treatment of type 2 diabetes. We found that fasting plasma lactate levels in elderly patients with type 2 diabetes patients were not different from those in control group patients, and none of them met the criteria for diagnosis of lactic acidosis. However, metformin should still be cautiously prescribed, especially in elderly diabetic patients with mild renal impairment, and assessment of not only serum creatinine but also eCCr is recommended in this population. Patients with a fasting plasma glucose level >130 mg/dL had a 2.8-fold risk of developing hyperlactemia. The clinical implication of this phenomenon remains uncertain. Lactate measurement to assess incipient acidosis may be helpful in such situations.

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