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②Yokoyama Shota

③Tsuji Hideyuki, Hiraoka Sachiko, Nishihara Masayuki

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Investigation of Risk Factors Affecting Lactate Levels in Japanese Patients Treated with Metformin

Shota Yokoyama,*[,a] Hideyuki Tsuji,[b] Sachiko Hiraoka,[b] and Masayuki Nishihara[a]

[a] *Department of Pharmacy, Mazda Hospital of Mazda Motor Corporation; 2–15 Aosakiminami, Fuchu-cho, Aki-gun, Hiroshima 735–8585, Japan: and* [b] *Department of Diabetes, Mazda Hospital of Mazda Motor Corporation; 2–15 Aosakiminami, Fuchu-cho, Aki-gun, Hiroshima 735–8585, Japan.*
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Metformin is a biguanaide antidiabetic drug used worldwide, and its effectiveness and benefits have already been established. However, the safety of high doses of metformin in Japanese patients, especially in elderly patients with a decreased renal function, remains unclear. Among the side effects of metformin, lactate acidosis is the most problematic due to a high mortality rate. Therefore, we assessed plasma lactate levels in metformin-treated patients to identify independent risk factors for hyperlactemia. 290 outpatients receiving various doses of metformin at our hospital were enrolled between March and July 2014. Serum electrolytes, Cre (creatinine), BUN (blood urea nitrogen), UA (uric acid), HbA1c (hemoglobin A1c), and lactate levels were investigated. Lactate levels did not significantly differ between the elderly (≥75 years) and non-elderly (<75 years) groups. Patients in the elderly group had a significantly lower daily metformin dose and estimated glomerular filtration rate (eGFR), compared with the non-elderly group (both $p<0.005$). Between with and without hyperlactemia groups, no significant differences were observed in either Cre or age. On the other hand, patients with hyperlactemia had a significantly higher dose of metformin than those without hyperlactemia ($p<0.05$). In this study, we found that old age and mildly impaired kidney function were not associated with increased lactate levels, and that a higher dose of metformin may be an independent risk factor for elevated lactate levels in Japanese patients.

Key words biguanide; metformin; lactic acidosis; diabetes; Japan

Recently, the number of patients with type 2 diabetes mellitus has continued to increase in Japan, due in part to the westernization of lifestyles. The number of these patients in Japan was estimated to be approximately 20500000 in 2012, according to the National Health and Nutrition Survey by the Ministry on Health, Labor and Welfare in 2010. Metformin, a biguanide, is a widely used oral antidiabetic drug recommended by both the American Diabetes Association and the European Association for the Study of Diabetes, as a first-line type 2 diabetes mellitus treatment in all patients receiving a new diagnosis.[1] In contrast to other oral antidiabetic drugs, metformin is not associated with a risk of hypoglycemia.[2–4] In addition, metformin reduces the long-term incidence of macrovascular complications in type 2 diabetes mellitus, especially among overweight patients.[2,5,6]

The most serious adverse event that has been observed during metformin use is lactic acidosis, which is characterized by an elevated blood lactate concentration (>5 mmol/L), decreased blood pH (<7.35), and electrolyte disturbances.[5,7–10] Estimated rates of lactic acidosis incidence in metformin users range from 1 to 47 cases per 100000 patient-years.[11,12] Reported predisposing factors include acute kidney injury, history of lactic acidosis, hypovolemia, seizure, liver disease, alcohol abuse, acute heart failure, myocardial infarction, and shock.[13–15] Although lactic acidosis during metformin use has better prognosis than other types of severe lactic acidosis,[16] the mortality rate of lactic acidosis is reported to be as high as 25–50%.[3,5,9] A decreased glomerular filtration rate may increase the risk of lactic acidosis during metformin use, because unmetabolized metformin is eliminated by the kidneys. Therefore, one of the most important risk factors for elevated metformin concentration is the inability of efficient clearance due to renal impairment.[17]

Although the usual dose of metformin is over 2000 mg/d in Europe and the U.S.A,[18] the maximum dose allowed for clinical treatment in Japan was 750 mg/d until 2010, less than half of that in Western countries. Prospective studies, such as the Multicenter Metformin Study (MMS)[19] and the United Kingdom Prospective Diabetes Study (UKPDS),[20] reported evidence of beneficial effects, including cardiovascular protection and the safety of metformin in the treatment of type 2 diabetes mellitus, leading to an increase in the use of metformin not only in Europe and the U.S.A., but also in Japan. However, the majority of Japanese patients with type 2 diabetes mellitus are less obese than European and American patients.[21] Thus, the results of clinical trials in Western countries cannot be directly applied to Japanese patients.

Therefore, the aim of this study was to evaluate whether metformin-treatment is associated with a higher risk of lactic acidosis or elevated lactate levels in Japanese patients with normal to impaired renal function. Furthermore, the association between metformin dose and lactate levels was investigated in a large number of patients in a single hospital.

MATERIALS AND METHODS

Participants The subjects were 290 metformin-treated patients (average age was 59.3±11.3 years old), consisting of 210 men and 80 women, who visited Mazda Hospital of Mazda Motor Corporation (Hiroshima, Japan) between March and July 2014; 163 patients were treated at the department of diabetes, and 127 patients at other departments, including cardi-

* To whom correspondence should be addressed. e-mail: yokoyama.shot@mazda.co.jp

ology, gastroenterology, and respiratory. All subjects received metformin (Metgluco® 250 mg tablet, Dainippon-Sumitomo Pharma Co., Ltd., Osaka, Japan) for the treatment of diabetes mellitus. Laboratory data and patient characteristics, including age, gender, dose of metformin, and alcohol intake, were obtained from medical or pharmaceutical records. Patients with poor drug adherence were excluded before enrolling. Informed consent was obtained from all participants.

Blood Analyses Blood samples were obtained from all participants during scheduled outpatient visits for measurement of serum creatinine (Cre), blood urea nitrogen (BUN), uric acid (UA), sodium (Na), potassium (K), chloride (Cl), hemoglobin A1c (HbA1c), and lactate levels. Cre, BUN, UA, Na, K, and Cl were determined using standard methods by Arcgitect-ci16200 (TOSHIBA CORPORATION, Tokyo, Japan). HbA1c was determined by HPLC (NIPPON CHEMIHA, Tokyo, Japan). Lactate levels were determined by BioMajesty-jca-Bm12 (JEOL, Tokyo, Japan). The reference range for venous plasma lactate levels was 4.2–17.0 mg/dL (determined by BML, INC., Tokyo Japan). Estimated glomerular filtration rate (eGFR) was calculated using the formula of the Japanese Society of Nephrology: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ mL/min/1.73 m^2, further multiplied by 0.739 for female subjects.[22]

Statistical Analyses The results were calculated as the mean±standard deviation (S.D.). Comparison of the average age and dose between the department of diabetes and other departments were performed by Student's *t*-test. Comparison of the parameters between the elderly and non-elderly, and the groups with and without hyperlactemia were performed by Student's *t*-test or χ^2 test. Comparison of lactate levels between two groups (dose 1–3 tablets and 4–9 tablets) was performed by Student's *t*-test. Statistical significance was set at $p<0.05$.

Ethical Approval Our study had been approved by the Medical Ethics Committee of Mazda Hospital of Mazda Motor Corporation.

RESULTS

Clinical Characteristics of Participants A total of 290 metformin-treated patients were included in the study, consisting of 210 men and 80 women. The average age was 59.3 years.

Differences in the age of patients and doses of metformin between the department of diabetes and other departments, including cardiology, gastroenterology, respiratory, are summarized in Tables 1 and 2. Table 1 shows the age range of patients receiving metformin in both groups. The average age was significantly lower in patients attending the department of diabetes, compared with other departments (56.1 and 63.4 years, respectively, $p<0.001$). Table 2 shows the dose of metformin (250 mg/tablet) in the two groups. The most often prescribed-dose of metformin in the department of diabetes was 4 tablets (36.8%), whereas 2 tablets was most common in other departments (51.2%). Additionally, 9-tablet-prescriptions, the maximum dose of metformin in Japan, were not observed in other departments. Consequently, patients in other departments received a significantly lower daily metformin dosage, compared with patients attending the department of diabetes (3.2 and 4.1 tablets, respectively, $p<0.001$).

Factors Associated with Metformin-Mediated Increased Lactate Levels The basic characteristics of the two patients groups, those over or under the age of 75, are summarized in Table 3. Male patients outnumbered female patients in both groups. Patients in the elderly group had a significantly lower

Table 1. Comparison of Age Range of Patients Receiving Metformin between the Department of Diabetes and Other Departments

Age range [years]	Department of diabetes (n=163)	Other departments (n=127)	Total (n=290)
	Number of patients (%)		
<30	2 (1.2)	0	2 (0.7)
30–40	6 (3.7)	2 (1.6)	8 (2.8)
40–50	40 (24.5)	11 (8.7)	51 (17.5)
50–60	48 (29.5)	32 (25.2)	80 (27.6)
60–70	49 (30.1)	44 (34.6)	93 (32.1)
70<	18 (11.0)	38 (29.9)	56 (19.3)
Average age [years]	***56.1±11.0	63.4±10.5	59.3±11.3

Data are presented as the mean±S.D. or *n* (%). ***$p<0.001$ *vs.* other departments.

Table 2. Comparison of Dose of Metformin between the Department of Diabetes and Other Departments

Dose [tablets](250 mg/tablet)	Department of diabetes (n=163)	Other departments (n=127)	Total (n=290)
	Number of patients (%)		
1	8 (4.9)	3 (2.4)	11 (3.8)
2	31 (19.0)	65 (51.2)	96 (33.1)
3	14 (8.6)	9 (7.1)	23 (7.9)
4	60 (36.8)	27 (21.2)	87 (30.0)
6	44 (27.0)	23 (18.1)	67 (23.1)
9	6 (3.7)	0	6 (2.1)
Average dose [tablets]	***4.1±1.8	3.2±1.6	3.7±1.8

Data are presented as the mean±S.D. or *n* (%). ***$p<0.001$ *vs.* other departments.

Table 3. Characteristics of Patients over and under 75 Years

	Age <75 (n=269)	75≤ Age (n=21)	p-Value
Gender M:F [numbers]	193:76	17:4	n.s. (p=0.36)
Age [years]	57.8±10.3	78.5±3.3	p<0.0001
Dose [tablets]	3.8±1.8	2.5±1.2	p<0.005
Lactic acid [mg/dL]	14.3±5.8	14.8±6.2	n.s. (p=0.72)
Cre [mg/dL]	0.8±0.2	0.9±0.2	p<0.05
eGFR [mL/min/1.73 m^2]	73.6±16.7	62.4±17.1	p<0.005
BUN [mg/dL]	14.6±4.4	16.6±4.2	p<0.05
UA [mg/dL]	5.6±1.4	5.2±1.0	n.s. (p=0.25)
Na [mEq/L]	140.5±2.4	140.9±2.1	n.s. (p=0.55)
K [mEq/L]	4.4±0.4	4.6±0.5	p<0.05
Cl [mEq/L]	103.3±2.7	104.9±3.1	p<0.05
HbA1c [%]	7.0±1.0	6.9±0.7	n.s. (p=0.66)

Data are presented as the mean±S.D. or n. Cre, creatinine; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; UA, uric acid; Na, sodium; K, potassium; Cl, chloride; HbA1c, hemoglobin A1c.

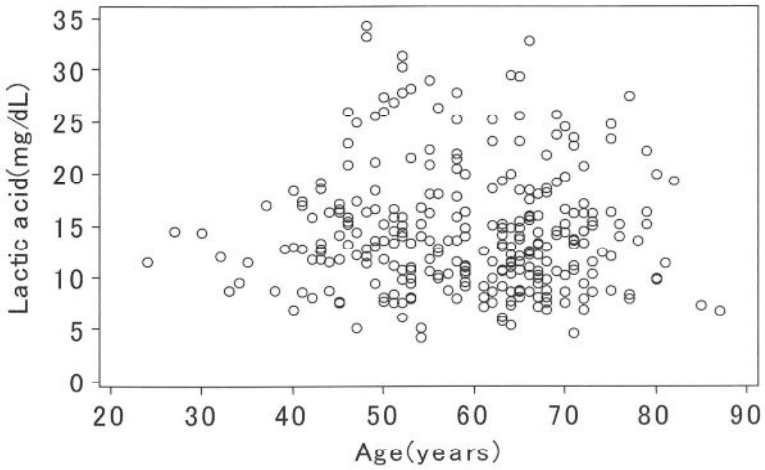

Fig. 1. Scatter Diagram of Plasma Lactate Levels with Age in All Metformin-Treated Patients

Lactate levels were not correlated with age (r=−0.0362; p=0.538; n=290).

daily metformin dose and eGFR, and significantly higher Cre levels, compared with the non-elderly group (p<0.005, p<0.005 and p<0.05, respectively). There were no difference in lactate levels between the two groups. Furthermore, Figs. 1 and 2 show no associations between plasma lactate levels and either age or Cre in all metformin-treated patients.

Table 4 summarizes the characteristics of patients with and without hyperlactemia, which was defined as those above the normal upper limit of 17 mg/dL. Male patients outnumbered female patients in both groups. The dose of metformin was significantly higher in the hyperlactemic patients (p<0.05). Age, Cre, eGFR, HbA1c, and alcohol intake were not risk factors for hyperlactemia. None of the patients fulfilled the lactic acidosis criteria, defined as a plasma lactate level of >5 mmol/L (=45.05 mg/dL) (1 mmol lactate=9 mg/dL).[23]

Figure 3 shows the comparison of lactate levels between two patient groups: Dose 1–3 tablets and 4–9 tablets. Patients treated with 4–9 tablets had significantly higher lactate levels, compared with those treated with 1–3 tablets (15.2±0.5, 13.3±0.5 mg/dL, respectively, p<0.01).

DISCUSSION

Metformin has been recommended as a first-choice drug in new-onset type 2 diabetes in a consensus algorithm from the American Diabetes Association and the European Association for the Study of Diabetes.[1] Metformin improves insulin resistance by inhibiting gluconeogenesis and enhancing peripheral glucose uptake through stimulation of AMP-activated kinase.[24] Meta-analysis has shown its effectiveness in type 2 diabetes mellitus.[25] Recent studies suggested that metformin may be effective in preventing cardiovascular events in type 2 diabetes mellitus,[26] in improving impaired glucose tolerance in patients with metabolic syndrome,[27] and limiting weight-gain induced by atypical antipsychotics.[28]

However, it has been reported that metformin-treated patients have a risk of higher plasma lactate levels than those not taking metformin.[23] Indeed, case reports of metformin-associated lactic acidosis continue to be published. Although lactic acidosis is rarely associated with metformin therapy, it has a high mortality. Lactic acidosis is defined as blood pH <7.35 and lactate concentrations >5 mmol/L (=45.05 mg/dL) (1 mmol lactate=9 mg/dL), and it has been suggested that patients with lactate concentrations >2.7 mmol/L (=24.3 mg/dL) (1 mmol lactate=9 mg/dL) should be monitored carefully.[23] In our study, 25 patients (9%) had lactate concentrations >24.3 mg/dL, and no patients had lactate concentrations >45.05 mg/dL.

In June 1996, 1 year after metformin was approved for use

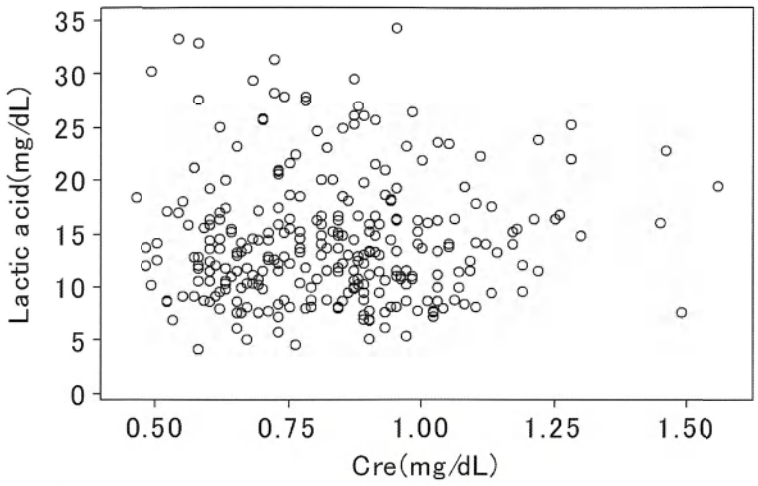

Fig. 2. Scatter Diagram of Plasma Lactate and Cre Levels in All Metformin-Treated Patients

Lactate levels were not correlated with Cre (r=0.023; p=0.695; n=290).

Table 4. Characteristics of Patients with and without Hyperlactemia

	Lactic acid ≤17 (n=222)	17< Lactic acid (n=68)	p-Value
Gender M:F [numbers]	158:64	52:16	n.s. (p=0.39)
Age [years]	59.3±11.6	59.5±10.4	n.s. (p=0.88)
Dose [tablets]	3.6±1.8	4.1±1.7	p<0.05
Lactic acid [mg/dL]	11.7±3.0	22.9±4.5	p<0.0001
Cre [mg/dL]	0.8±0.2	0.8±0.2	n.s. (p=0.63)
eGFR [mL/min/1.73 m^2]	72.4±16.6	73.9±18.2	n.s. (p=0.53)
BUN [mg/dL]	14.9±4.3	14.3±4.8	n.s. (p=0.30)
UA [mg/dL]	5.5±1.3	5.6±1.5	n.s. (p=0.62)
Na [mEq/L]	140.7±2.4	140.1±2.4	n.s. (p=0.07)
K [mEq/L]	4.4±0.4	4.4±0.4	n.s. (p=0.93)
Cl [mEq/L]	103.7±2.7	103.5±3.0	n.s. (p=0.61)
HbA1c [%]	6.9±0.9	7.1±1.0	n.s. (p=0.41)
Alcohol/d [g]	6.5±13.8	9.5±19.4	n.s. (p=0.16)

Data are presented as the mean±S.D. or n. Cre, creatinine; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; UA, uric acid; Na, sodium; K, potassium; Cl, chloride; HbA1c, hemoglobin A1c.

in the U.S.A., 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.[29] The subsequently revised instructions stated that metformin therapy should not be initiated in patients ≥80 years old. In Japan, the Japan Diabetes Society (JDS) recommends that physicians do not start to prescribe metformin to patients older than 75 years, as suggested by the JDS committee in 2012, for the proper use of meformin. Therefore, in the present study, we divided patients into elderly and non-elderly groups based on this age.

It remains controversial as to whether old age is a risk factor for metformin-associated lactic acidosis. In this study, we observed that there was no significant difference in plasma lactate levels between elderly and non-elderly patients, which was consistent with the previous study by Gregorio *et al.*[30] Importantly, mean daily metformin doses were significantly lower in the elderly patient group with lower eGFR. These observations may be partially attributed to physicians being cautious with the use of metformin, who may intentionally restrict the dose of metformin when prescribing to elderly patients with lower eGFR, to avoid potential side effects, such as lactic acidosis or gastrointestinal discomfort.

Eppenga *et al.*[31] reported that the risk of lactic acidosis or elevated lactate levels is increased in long-term heavy metformin users. Another report concluded that the metformin-associated lactic acidosis due to metformin accumulation is possible and underestimated, thus, metformin, if prescribed in patients with renal impairment, can cause fatal lactic acidosis due to drug accumulation.[32] In our study, the dose of metformin was found to be slightly, but significantly higher in hyperlactemic patients. In addition, patients treated with 4–9 tablets had significantly higher lactate levels than those treated with 1–3 tablets. Some authors argue the relevance between high concentrations of metformin and lactic acidosis, because supratherapeutic plasma concentrations of metformin have frequently been found in patients with lactic acidosis during metformin use, and high metformin concentrations have been shown to increase plasma lactate levels in rats.[3,10,33]

However, both chronic renal insufficiency and a high dose of metformin remain controversial as risk factors for lactic acidosis. The risk of lactic acidosis or elevated lactate levels was reported to be significantly increased in patients with mild to moderate renal insufficiency.[31] On the other hand,

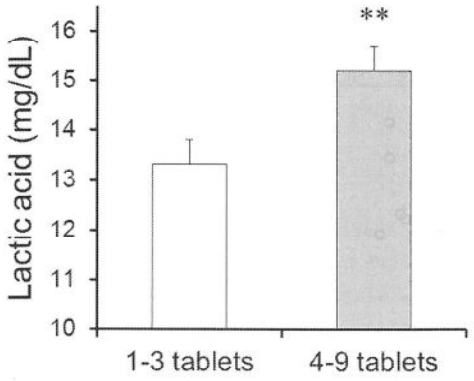

Fig. 3. Comparison of Lactate Levels between Two Patient Groups: Dose 1–3 Tablets (n=130) and 4–9 Tablets (n=160)

Patients treated with 4–9 tablets had significantly higher lactate levels, compared with those treated with 1–3 tablets (**p<0.01).

the role of chronic renal impairment in lactic acidosis during metformin use was not confirmed in large epidemiological studies.[13,34,35] In an Asian study (not including Japanese patients), there was no correlation between the total daily dose of metformin and eGFR with lactate levels in type 2 diabetic patients taking metformin.[36]

This study has several limitations. First, it was a cross-sectional study in which none of the patients developed lactic acidosis. Second, the patients in this study were ambulatory patients. Therefore, the present findings may not necessarily be applicable to the entire, especially elderly, population receiving metformin treatment for type 2 diabetes, because many of these individuals may have comorbidities. Third, the number of patients older than 75 years was small due to physician awareness of the need for caution with prescribing metformin to such patients. Forth, this study does not include body weight (b.w.) and/or body mass index (BMI) which might influence the results. In fact, in the department of diabetes, a patient's b.w. is measured on every scheduled visit, however it is not the case in other departments. Last, we did not evaluate metformin concentrations in the participants. It is reported that the oral availability of metformin is highly variable, ranging at least threefold (25–75%).[3] Furthermore, there is considerable variability in the relationship between the renal clearances of metformin and creatinine.[3,37] Thus, in light of its pharmacokinetics, monitoring metformin concentrations may be useful for further in-depth analysis.

In conclusion, among Japanese patients, we observed that the plasma lactate levels in the elderly patients did not significantly differ from those in non-elderly patients, and no patients met the criteria for diagnosis of lactic acidosis. However, it is expected that high doses of metformin will be used in Japan in the next decade with the recognition of its effectiveness. Therefore, metformin should still be cautiously prescribed because higher doses of metformin were found to increase the risk of hyperlactemia.

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Conflict of Interest The authors declare no conflict of interest.

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