Metformin Does Not Induce Hyperlactatemia in Patients Admitted to Internal Medicine Ward

Shlomit Koren MD[1,3], Shani Zilberman-Itskovich MD[1], Ronit Koren MD[1], Keren Doenyas-Barak MD[2] and Ahuva Golik MD[1]

[1]Departments of Internal Medicine A and [2]Nephrology and [3]Diabetes Unit, Assaf Harofeh Medical Center, Zerifin, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Concerns about metformin-associated lactic acidosis prohibit the use of metformin in a large subset of diabetic patients, mostly in patients with chronic kidney disease. Increasing evidence suggests that the current safety regulations may be overly restrictive.

Objectives: To examine the association between chronic metformin treatment and lactate level in acute illness on the first day of admission to an internal medicine ward.

Methods: We compared diabetic and non-diabetic hospitalized patients treated or not treated with metformin in different sets of kidney function.

Results: A total of 140 patients participated in the study, 54 diabetic patients on chronic metformin treatment, 33 diabetic patients without metformin and 53 patients with no diabetes. Most participants were admitted for conditions that prohibit metformin use, such as heart failure, hypoxia and sepsis. Average lactate level was significantly higher in the diabetes + metformin group compared to the diabetes non-metformin group. Metformin treatment was not associated with higher than normal lactate level (hyperlactatemia) or low pH. No patient was hospitalized for lactic acidosis as the main diagnosis.

Conclusions: Chronic metformin treatment mildly increases lactate level, but does not induce hyperlactatemia or lactic acidosis in acute illness on the first day of admission to an internal medicine ward. These data support the expansion of metformin use.

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KEY WORDS: diabetes, metformin, lactate, acidosis, renal failure

Metformin is an insulin sensitizing agent with antihyperglycemic properties that is widely used for the treatment of type 2 diabetes mellitus (T2DM). Metformin monotherapy is not usually accompanied by hypoglycemia and leads to modest weight loss in most cases. In addition, the original United Kingdom Prospective Diabetes Study (UKPDS) and post-trial monitoring study demonstrated a reduced risk for both myocardial infarction and total mortality in patients treated with metformin. As a result, metformin is widely considered to be an ideal first line agent for the treatment of T2DM [1-5].

Metformin is generally well tolerated. The most common adverse effects are gastrointestinal and occur in 20 to 30% of patients, requiring discontinuation of the drug in less than 5% of patients [6]. Despite these proven benefits, metformin remains contraindicated in a large segment of the T2DM population, mainly in patients with chronic kidney disease (CKD) due to concerns regarding the rare adverse effects of metformin-associated lactic acidosis (MALA). Lactic acidosis is an anion gap metabolic acidosis defined by plasma lactate levels higher than 5 mmol/L, and pH less than 7.35. Severe lactic acidosis can cause multi-organ failure and be life threatening. The predecessor to this drug, phenformin, was withdrawn from the market by the U.S. Food and Drug Administration because of its association with lactic acidosis [7].

There is a concern that since metformin is cleared by the kidneys, it may accumulate when renal function decreases, inducing high lactate levels and potential exposure-dependent MALA. In addition, the drug is contraindicated in various conditions, such as significant hypoxemia, alcoholism, and cirrhosis [8]. Several studies, case-control analyses and large meta-analyses have suggested that lactic acidosis is extremely rare and that the incidence does not differ in those treated with metformin vs. other agents. Furthermore, these studies found no increased risk for MALA in different stages of CKD and suggested cautious expansion of metformin use in patients with mild to moderate CKD [9-13]. As a result, the U.S. Food and Drug Administration extended prescribing guidelines to include patients with an estimated glomerular filtration rate (eGFR) as low as 45 ml/minute/1.73 m^2. Most studies designed to examine MALA were either retrospective analyses of databases looking for diagnosis of lactic acidosis and chronic metformin use or case reports. Lactate is an indicator of acute illness. The majority of patients with acute illnesses, which might induce high lactate and lactic acidosis such as acute exacerbation of congestive heart failure, cirrhosis or infection, are admitted to internal hospital wards. The aim of this study was to examine, prospectively, whether chronic metformin treatment induces high lactate level in acute illness (the first 24 hours after admission to internal hospital wards) and whether CKD plays a role in this matter.

PATIENTS AND METHODS

In this prospective non-intervention clinical trial, 140 T2DM patients were studied following hospital admission to an internal medicine ward.

The institutional ethics committee approved this study, and informed consent was obtained from patients. The study population included three groups: T2DM patients on chronic metformin treatment (diabetes + metformin), T2DM patients not on metformin (diabetes non-metformin), and those with no diabetes. Inclusion criteria were patients who were admitted to an internal medicine ward, age above 18 years, and able and willing to sign informed consent. Patients who were on metformin treatment were asked to confirm taking metformin during the month prior to hospitalization. Exclusion criteria included patients who were not able to sign an inform consent and patients who were not able to confirm 1 month of treatment with metformin. Patients' medical history was recorded and blood samples were tested for creatinine, electrolytes, pH, HCO_3 and lactate during the first 24 hours of hospital admission. eGFR was calculated using the modification of diet in renal disease (MDRD) equation. Anion gap was calculated as follows:

Anion gap = (Na+) + (K+) - (Cl) - (HCO_3-)

The primary outcomes of this study were lactate level, pH level and incidence of lactic acidosis in the different groups.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software version 21 (SPSS, Inc. Chicago, IL, USA). Categorical variables were reported as frequency and percentages, and continuous variables were reported as means (standard deviations) or medians (interquartile range, IQR). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were compared using the chi-square test or the Fisher exact test, and continuous variables by independent samples *t*-test, Mann-Whitney test, analysis of variance (Scheffee's procedure was used for posthoc multiple comparison) or Kruskal-Wallis test. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

A total of 140 patients were enrolled in this study, 54 patients in the diabetes + metformin group, 33 patients in the diabetes non-metformin group and 53 patients in the no diabetes group. Patient characteristics are presented in Table 1. The T2DM patients with or without metformin were significantly older than the no diabetes patients (72.06 ± 10.94, 72.09 ± 9.99 and 63.94 ± 17.77, respectively). The male to female ratio was higher in the no diabetes group compared to the two diabetes groups, but did not reach statistical significance. More than 50% of patients in the diabetes non-metformin group had CKD, compared to 5.6% and 15.1% in the diabetes + metformin group and the no diabetes group, respectively.

Table 1. Patient characteristics, by group

	Diabetes + metformin	Diabetes non-metformin	No diabetes	
	n=54 (%)	n=33 (%)	n=53 (%)	*P*
Age (years) SD	72.06 ± 10.94	72.09 ± 9.99	63.94 ± 17.77	0.011
Gender (male/female)	27/27 (50/50)	19/14 (57.6/32.1)	36/17 (67.9/32.1)	0.169
Smoker	15 (27.8)	3 (9.1)	18 (34)	0.034
CRF	3 (5.6)	19 (57.6)	8 (15.1)	0.0001
Hypertension	49 (90.7)	28 (84.8)	29 (54.7)	0.0001
Hyperlipidemia	41 (75.9)	19 (57.6)	19 (35.8)	0.0001
IHD	17 (31.5)	15 (45.5)	15 (28.3)	0.24
Past CVA/TIA	10 (18.5)	5 (15.2)	4 (7.5)	0.242
CHF	13 (24.1)	12 (36.4)	6 (11.3)	0.023
COPD/asthma	7 (13.1)	6 (18.2)	8 (15.1)	0.803

CRF = chronic renal failure, IHD = ischemic heart disease, CVA = cerebrovascular accident, TIA = transient ischemic accident, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, SD = standard deviation

Diabetic patients presented high prevalence of cardiovascular disease (CVD) or CVD risk factors. A significantly higher incidence of hypertension, hyperlipidemia and congestive heart failure (CHF) as well as higher ischemic heart disease, which was not statistically significant, were observed in this group.

The main reasons for hospitalization included chest pain, CVD events such as acute coronary syndrome (unstable angina, myocardial infarction), cerebrovascular accident (CVA) or transient ischemic accident (TIA). Additional illnesses included upper respiratory tract infection (URTI), pneumonia, urinary tract infection (UTI) and skin infection. Less frequent causes for hospitalization were acute renal failure (ARF), CHF exacerbation, chronic obstructive pulmonary disease (COPD) or asthma exacerbation, and syncope. There were some uncommon diagnoses including acute gastroenteritis, arrhythmias, liver cirrhosis and anemia. There was no statistically significant difference between the groups regarding the main diagnosis for hospitalization. However, more patients in the diabetes non-metformin group were admitted for CHF exacerbation compared to the other groups [Table 2].

To examine whether metformin constitutes a risk for hyperlactatemia or lactic acidosis among metformin users in relation to renal function, we measured serum levels of lactate, pH, HCO_3, pCO_2, and creatinine. We calculated eGFR and anion gap in metformin and non-metformin users on the first day of admission to an internal hospital ward [Tables 3 and 4]. Creatinine levels were significantly increased and eGFR was significantly decreased in the diabetes non-metformin group. Mean creatinine level was 91.93 umol/L (median 76.02, interquartile interval 66.88–106.08) and 100.95 (median 76.02, interquartile interval 65.41–105.63) in the diabetes + metfor-

Table 2. Main diagnosis at hospital admission, by group

	Diabetes + metformin N (%)	Diabetes non-metformin N (%)	No diabetes N (%)	*P*
Chest pain	8 (14.81)	3 (9.09)	9 (16.98)	0.59
Acute coronary syndrome	8 (14.81)	5 (15.15)	4 (7.55)	0.41
CVA/TIA	4 (7.41)	1 (3.03)	2 (3.77)	0.69
Pneumonia /URTI	6 (11.11)	6 (18.18)	8 (15.09)	0.61
Urinary tract infection	3 (5.56)	3 (9.09)	–	0.08
Cellulitis	1 (1.85)	2 (6.06)	5 (9.43)	0.24
Acute renal failure	2 (3.7)	1 (3.03)	1 (1.89)	1
Congestive heart failure	4 (7.41)	5 (15.15)	1 (1.89)	0.054
COPD/asthma	4 (7.41)	2 (6.06)	3 (5.66)	1
Syncope	2 (3.7)	3 (9.09)	3 (5.66)	0.52
Other	12 (22.2)	2 (6.06)	17 (32.1)	0.014

CVA = cerebrovascular accident, TIA = transient ischemic accident, URTI = upper respiratory tract infection, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate

Table 3. Laboratory results at admission, by group

	Diabetes + metformin	Diabetes non-metformin	No diabetes	*P*
pH	7.37 ± 0.52	7.36 ± 0.44	7.37 ± 0.42	0.608
HCO_3 (mmol/L)	24.96 ± 4.17	24.20 ± 4.22	25.91 ± 3.03	0.117
pCO_2 (mmHg)	43.50 ± 9.95	42.0 ± 8.90	45.50 ± 7.8	0.197
Anion gap	12.72 ± 3.76	13.91 ± 4.06	11.81 ± 3.4	0.041
eGFR†	81.66 ± 34.65	47.09 ± 30.4	85.75 ± 35.6	< 0.005
Creatinine (umol/L)	91.93 (76.02, 66.88–106.08)	178.65 (135.25, 97.24–221)	100.95 (76.02, 65.41–105.63)	< 0.0001
Lactate (mmol/L)	1.67 (1.53, 1.1–1.89)	1.33 (1.31, 0.9–1.64)	1.59 (1.58,1.1–1.92)	0.028* 0.043** 0.97***

Numbers are presented as mean ± standard deviation or as mean with median and interquartile interval in brackets

Anion gap was calculated as follow: (Na+) + (K+) - (Cl-) + (HCO_3-)

†eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation

*Asymptomatic (2-tailed) significance between diabetes + metformin group and diabetes non-metformin group

**Asymptomatic (2-tailed) significance between diabetes non-metformin group and no diabetes group

***Asymptomatic (2-tailed) significance between diabetes + metformin group and no diabetes group

eGFR = estimated glomerular filtration rate

min group and the no diabetes group, respectively, compared to mean creatinine of 178.65 umol/L (median 135.25, interquartile interval 97.24–221) in the diabetes non-metformin group. Mean eGFR level was 81.66 ± 34.65 and 85.75 ± 35.6 in the diabetes + metformin group and in the no diabetes group, respectively, compared to mean eGFR of 47.09 ± 30.4 in the diabetes non-metformin group. There was no significant difference in pH, HCO_3, or pCO_2 levels. The anion gap was moderately increased in the diabetes non-metformin group. Lactate levels were significantly lower in the diabetes non-metformin group, 1.33 mmol/L, (median 1.31, interquartile interval 0.9–1.64) compared to the diabetes + metformin group, 1.67 mmol/L (median 1.53, interquartile interval 1.1–1.89) and the no diabetes group, 1.59 mmol/L (median 1.58, interquartile interval 1.1–1.92)

Table 4. Lactate levels, pH and occurrence of lactic acidosis divided by eGFR sets

		Diabetes + metformin	Diabetes non-metformin	No diabetes	*P*
eGFR > 60	No. of patients	n=40 (74.1%)	n=9 (27.3%)	n=40 (75.5%)	0.0001
	Lactate (mmol/L)	1.65 ± 0.82	1.19 ± 0.37	1.67 ± 0.682	0.069
	pH	7.38 ± 0.046	7.37 ± 0.029	7.37 ± 0.039	0.295
	Lactic acidosis	1	0	0	–
eGFR 30–59	No. of patients	n=10 (18.5%)	n=13 (39.4%)	n=10 (18.9%)	0.001
	Lactate (mmol/L)	1.51 ± 0.55	1.41 ± 0.58	1.36 ± 0.62	0.817
	pH	7.38 ± 0.024	7.38 ± 0.052	7.39 ± 0.04	0.795
	Lactic acidosis	0	0	0	–
eGFR < 30	No. of patients	n=4 (7.4%)	n=11 (33.3%)	n=3 (5.7%)	0.001
	Lactate (mmol/L)	2.29 ± 1.99	1.36 ± 0.62	1.20 ± 0.76	0.443
	pH	7.31 ± 0.1	7.34 ± 0.035	7.41 ± 0.055	0.184
	Lactic acidosis	1	0	0	–

Number of patients in each group presented as percentage of the whole group in brackets.

eGFR was calculated using the modification of diet in renal disease (MDRD) equation.

Lactate and pH levels are presented as mean ± standard deviation.

Lactic acidosis is defined as lactate level above 5.0 mmol/L and pH < 7.35.

eGFR = estimated glomerular filtration rate

Table 4 presents lactate levels, pH and lactic acidosis events divided by eGFR sets. There were only 27.3% patients from the diabetes non-metformin group in the eGFR > 60 set, compared to 74.1% from the diabetes + metformin group and 75.5% from the no diabetes group. In the eGFR > 60 set average lactate levels were lower in the diabetes non-metformin group compared to the other two groups. The difference did not reach statistical significance. The pH level was comparable among the groups. There was one case of lactic acidosis. In the eGFR 30–59 set there was no difference in lactate and pH levels among the different groups. There were no cases of lactic acidosis. In the eGFR < 30 set there were significantly more patients from the diabetes non-metformin group (33.3%) compared to the diabetes + metformin group (7.4%) and the no diabetes group (5.7%). The average lactate level was higher and pH level was lower in the diabetes + metformin group (2.29 ± 1.99 mmol/L, pH 7.31 ± 0.1) compared to the diabetes non-metformin group (1.36 ± 0.62 mmol/L, pH 7.34 ± 0.035) and the no diabetes group (1.20 ± 0.76 mmol/L, pH 7.41 ± 0.055), but the difference did not reach statistical significance. There was one case of lactic acidosis in the diabetes + metformin group in the eGFR < 30 set.

Overall there were two mild cases of lactic acidosis (defined as lactate > 5 mmol/L and pH < 7.35). Both cases occurred in the diabetes + metformin group. The first patient was a 74 year old male admitted due to moderate asthma exacerbation. He was treated and discharged 4 days later. His lactate level was

5.57 mmol/L and pH was 7.249 on the day of admission; PCO_2 was 44.7 mmHg and HCO_3 was 19.1 mmol/L. Lactate level was gradually reduced to 2.73 mmol/L 2 days later. He had an eGFR > 60. The second patient was an 88 year old female. She was admitted for acute pancreatitis with vomiting and ARF. On admission she had an eGFR of 11, lactate of 5.21 mmol/L and pH of 7.191 with PCO_2 of 60.6 mmHg and HCO_3 mmol/L 22.7. She was treated and discharged 9 days later.

DISCUSSION

The study findings reveal that on the first day of admission to an internal hospital ward, chronic metformin use was not associated with hyperlactatemia (lactate level above the normal range > 2 mmol/L) or lactic acidosis.

Prescription restrictions to metformin in CKD (mean eGFR > 45 ml/min/1.73 m^2) and acute illness are due to concerns of MALA [11,14]. In addition, the drug is promptly withheld in the presence of any condition associated with hypoxemia, dehydration, sepsis, hepatic failure, renal failure, CHF or myocardial infarction. Increasing evidence suggests that the current limitations for metformin treatment may be overly restrictive.

A small series of studies involving patients hospitalized with lactic acidosis suggested association with metformin exposure [15-17]. In the last decade several studies, case-control analysis and large meta-analyses have suggested that lactic acidosis is extremely rare and that the incidence does not differ in those treated with metformin versus other agents. Furthermore, these studies did not find any increased risk for MALA in different stages of CKD and thus suggested cautious expansion of metformin use for patients with mild to moderate CKD [9-12]. Most of the studies were retrospective analyses looking for a diagnosis of MALA and treatment with metformin in a large population database. MALA is preceded by high lactate level in acute illness.

In this prospective study we looked at lactate levels in acute illness on the first day of admission to an internal ward. Many of the participants were admitted for a diagnoses that prohibits metformin use, such as heart failure, hypoxia or sepsis. We compared diabetic and non-diabetic hospitalized patients treated or not treated with metformin. Furthermore, we examined these parameters in different sets of kidney function.

In our study the diabetic patients admitted to an internal ward were older compared to non-diabetic patients, possibly due to the fact that diabetes is more frequent in the older population [18]. Diabetic patients had higher prevalence of CVD and CVD risk factors, which is compatible with the well known two- to fourfold higher risk of CVD among diabetic patients. CVD risk factors such as hypertension and hyperlipidemia were the same as those reported in the literature for diabetic patients [19,20]. The majority of patients in the diabetes non-metformin group had chronic renal failure, probably due to the prescription policy that prohibits the use of metformin in CKD. This group of patients had more CHF exacerbation as the main reason for hospitalization, which was similar to findings showing that heart failure is highly prevalent in patients with CKD [21].

Average lactate levels were significantly higher in the diabetes + metformin group compared to the diabetes non-metformin group (even though the diabetes non-metformin group had a high prevalence of renal failure). However, average lactate levels in the diabetes + metformin group, although higher, were still in the normal range and comparable to the average lactate level of the no diabetes group.

When referring to the different kidney function sets, the difference in the average lactate level became insignificant, probably due to the small number of patients in each group. It is important to note that in the eGFR < 30 set, the average lactate levels in the diabetes + metformin group were higher compared to the diabetes non-metformin group and the no diabetes group. This can be explained by the fact that there were only four patients in this group and one of them had lactic acidosis, which might contribute to the higher average levels of lactate in this group. The lactate levels of these patients were 1.91, 0.98, 1.06 and 5.21 mmol/L.

In this study there were two mild cases of lactic acidosis. Both cases occurred in the diabetes + metformin group, one patient had normal renal function and the other had severe CKD. In both cases other factors, rather than metformin treatment alone, may have contributed to the development of lactic acidosis. Still, the only cases of lactic acidosis occurred in the metformin treated patients. In the moderate CKD set (eGFR 30–59), there was no difference in lactate and pH levels between the different groups and there were no cases of lactic acidosis.

The main study limitation is the small sample size. Particularly, the group of patients with CKD (eGFR < 30) who were on chronic metformin treatment included only four patients. Therefore, any conclusions regarding metformin treatment in advanced CKD is impossible. In this study we examined only one time point. Prospective studies are needed to follow patients with renal failure treated with metformin vs. patients with renal failure not treated with metformin.

CONCLUSIONS

In this study metformin use was associated with higher lactate levels compared to non-metformin treated diabetic patients. Metformin was not associated with hyperlactatemia or low pH on the first day of admission to internal medicine ward.

Correspondence
Dr. S. Koren
Diabetes Unit, Assaf Harofeh Medical Center, Zerifin 70300, Israel
Phone: (972-8) 977-8334
Fax: (972-8) 977-9642
email: shlomitks@gmail.com

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Capsule

Cancer and the unavoidable replicative (R) factor

Most textbooks attribute cancer-causing mutations to two major sources: inherited and environmental factors. A recent study highlighted the prominent role in cancer of replicative (R) mutations that arise from a third source: unavoidable errors associated with DNA replication. Tomasetti and colleagues developed a method for determining the proportions of cancer-causing mutations that result from inherited, environmental, and R factors (see the Perspective by Nowak and Waclaw). They found that a substantial fraction of cancer driver gene mutations are indeed due to R factors. The results are consistent with epidemiological estimates of the fraction of preventable cancers.

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Eitan Israeli

Capsule

Immune sensor maintains gut microbiome

Emerging evidence indicates that the immune system can influence microbiome composition. Chen et al. reported that patients with active ulcerative colitis have low expression of NLRP12, which is best known for its role in immune responses. The authors further showed that the function of NLRP12 in immune regulation contributes to the maintenance of the intestinal microbiome. Mice that were deficient in NLRP12 had a consistent predominance of the Erysipelotrichaceae family of bacteria, which correlates with greater colon inflammation in both humans and mice. Replenishing the colons of mice with specific "good" bacteria reduced inflammation and resulted in overall better colon function. In addition, neutralizing the inflammatory cytokines interleukin-6 and tumor necrosis factor with blocking antibodies also restored protective bacteria.

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Eitan Israeli