ORIGINAL ARTICLE

Lactic acidosis in medical ICU – the role of diabetes mellitus and metformin

Ondrej Hloch, Jiri Charvat, Jan Masopust, Jan Havlin

Intensive Care Unit of Medical department, Faculty Hospital, Prague Motol, Czech Republic

Correspondence to: Jiri Charvat, MD., PhD.
Medical department of Faculty Hospital, Prague Motol
V Úvalu 84, 150 06 Prague 5, Czech Republic.
TEL: +420224434051; FAX: +420224434020; E-MAIL: jiri.charvat@lfmotol.cuni.cz

Submitted: 2012-10-20 Accepted: 2012-11-19 Published online: 2012-12-28

Key words: **lactic acidosis; metformin; mortality; acute renal failure; diabetes mellitus; renal replacement therapy**

Neuroendocrinol Lett 2012; **33**(8):792–795 **PMID:** 23391971 NEL331112A01

Abstract

OBJECTIVES: To evaluate the significance of diabetes mellitus and metformin in patients admitted to medical ICU with lactic acidosis.
METHODS: All the patients admitted to medical ICU with serum lactic acid exceeding 5 mmol/L and pH<7.35 were enrolled into analysis. The impact of diabetes mellitus and metformin treatment on ICU presence of lactic acidosis and its mortality was evaluated. The metabolic parameters were compared with respect to the presence of diabetes mellitus and metformin application.
RESULTS: Lactic acidosis was detected in 69 (4%) out of 1 755 admitted patients, 44 were nondiabetic and 25 had diabetes mellitus, 11 of them treated with metformin. No significant impact of diabetes mellitus or metformin application on presence of lactic acidosis and its mortality was detected. In nondiabetic subjects mortality was associated with eGFR and the presence of acute renal failure while in diabetic patients with sepsis. Acute renal failure was detected in 9 out of 11 patients on metformin. Three patients died due to sepsis, however only 1 out of 6 due to another cause if renal replacement therapy was started soon after admission. The acidosis was more expressed in diabetic subjects mainly in patients taking metformin. It might be attributed to the more pronounced acute renal failure in diabetic patients.
CONCLUSION: The presence of diabetes mellitus and metformin application is not associated with the presence of lactic acidosis in medical ICU and its mortality. The prognosis of acute renal failure of patients on metformin is good if the subjects with sepsis are excluded.

INTRODUCTION

Metformin has been used for treatment of Type 2 diabetes mellitus for many years. It has the positive impact on the incidence and extent of cardiovascular complications (Nathan et al. 2009). There is no evidence from prospective comparative trials that metformin is associated with an increased risk of lactic acidosis compared to other anti-hyperglycemic treatments (Salpeter et al. 2010). COSMIC study did not identify any cases of lactic acidosis in 7 227 patients receiving metformin (Cryer et al. 2005). In patients with heart failure metformin is associated with low risk of mortality (Andersson et al. 2010). However, there are reports claiming the association of metformin with lactic acidosis – MALA (Arroyo et al. 2011; Seidowsky et al. 2009; Peters et al. 2008; Carlon et al. 2010). According to literature reports some MALA cases are associated with coronary artery disease, liver disease, cancer,

another with the development of acute renal failure (Almirall et al. 2008; Stedes et al. 2004; Biradar et al. 2010). It may be difference in risk of development lactic acidosis between stable trial patients and those who are acutely unwell for variety of reasons (Lalau 2010). Moreover the recent study claimed that diabetes rather than metformin is the major risk factor for the development of lactic acidosis in general hospital (Scale & Harvey 2011).

The main aim of the study was to evaluate the impact of metformin and diabetes mellitus on the presence of lactic acidosis and its prognosis in the patients admitted to medical intensive care unit.

METHODS

The patients evaluated in this study have been admitted in 12 beds medical ICU of Faculty hospital Prague Motol, Czech republic provided arterial or venous serum lactate on admission exceeded 5 mmol/l and pH was below 7.35 since 2008 till 2011.

Arterial blood gas measurements were available for all cases and examined on analyzer in the unit. Another laboratory tests were examined in central laboratory including venous serum lactate. Our laboratory reports venous serum lactate values below 2.2 mmol/L as normal, which is consistent with other studies relying on venous lactate values (Scale & Harvey 2011).

All the laboratory tests (including venous serum lactate) evaluated in the study were examined on admission to medical ICU.

Clinical data were obtained by physician on admission including assessment for the presence of recognized precipitating factors of lactic acidosis. The patients were divided according to known history of diabetes mellitus and metformin application.

During admission in ICU the number of patients treated with artificial ventilation and renal replacement therapy was recorded. Mortality outcome refers to the admission when lactate acidosis was diagnosed.

Chronic renal insufficiency was diagnosed if the patient had previously examined glomerular filtration rate below 1 ml/s.

Acute renal injury was defined as doubling of serum creatinine during admission to ICU.

Statistical comparison is evaluated by ANOVA with Tukey's LSD test post hoc, t-test or chi-square test as appropriate. Data are given as mean ± SD (standard deviation).

RESULTS

Since 2008 till 2011 1 755 patients have been admitted to medical ICU. Their age was 67±10 years.

On admission 546 patients (31%) were known to suffer from diabetes mellitus, 305 (56%) were women and 241 men (44%). Metformin was applied to 339 (62%) and insulin to 102 (19%) of them.

Sixty-nine patients (4%) had serum lactate value on admission higher than 5 mmol/l and pH below 7.35, thirty-four men and thirty-five women. Twenty-five of them (36%) had diabetes mellitus, 11 men and 14 women. Eleven (44%) of diabetic patients with lactic acidosis have been treated with metformin before admission. The mean daily dose of metformin was 1.85 g. The rate of lactic acidosis in nondiabetic patients in our unit was 3.6%, in diabetic patients 4.6% and in patients taking metformin 3.2%. The incidence of MALA in medical ICU if taking into account all admitted patients was 0.6%.

The age of all the patients admitted with lactic acidosis was 64±11years (range from 25 to 85 years). Diabetic patients were elder but the difference did not reach statistical significance (68±10 years in diabetic and 62±11 years in nondiabetic patients, p=0.1).

No significant differences in mortality were detected among the groups despite of the higher prevalence of ischaemic heart disease in diabetic patients (Table 1). The impact of diabetes mellitus and metformin on metabolic changes is also summarized in Table 1. Hydrogen ion concentration (pH) as well as serum lactate level between nondiabetic and diabetic patients were comparable. However base excess and venous bicarbonate level significantly were lower in diabetic patients. These changes were more evident in the patients taking metformin.

In diabetic patients eGFR was significantly lower comparing nondiabetic subjects and again the drop of glomerular filtration was more evident in the patients on metformin.

In the group of nondiabetic subjects mortality was associated with eGFR and the presence of acute renal failure (Table 2). In diabetic patients mortality was associated with sepsis (Table 3).

Acute renal failure was present in 9 of 11 diabetic patients on metformin (82%). It was more frequent than in another two groups but the difference did not reach yet statistical significance (Table 1). Three diabetic patients on metformin with acute renal failure had sepsis complicated with circulatory failure – all these patients died. Contrary only one out of six diabetic patients on metformin with acute renal failure due to dehydration or application of contrast material during X-ray exam died after 48 hours due to newly developed myocardial infarction.

Renal replacements therapy (RRT) was applied in 25 (36%) patients. RRT was used more often in diabetic in comparison to nondiabetic patients (15 patients; 60% v 10 patients; 23%, p=0.001). RRT was used in 8 diabetic patients treated with metformin (73%) and 7 without metformin (50%, p=0.24).

All but one diabetic patient on metformin with acute renal failure have been treated with continuous venovenous hemofiltration (CVVH) started as soon as possible after admission.

Tab. 1. Comparison of patients with various risk factors for lactic acidosis in patients with diabetes on and not on metformin and patients without diabetes.

	DM - on metformin	DM-without metformin	No DM	*p*-value
N	11	14	44	
Male (number/%)	5(45%)	6(43%)	23(52%)	0.80
Deceased (number/%)	6(55%)	10(71%)	30(68%)	0.63
Age (years)	73±6*	64±10	62±11	F=2.6, p=0.07
pH	7.15±0.11	7.18±0.11	7.18±0.10	F=0.2, p=0.79
Lactate (mmol)/L	16.4±6.8	12.5±5.7	12.6±5.1	F=1.7, p=0.18
HCO3 (mmol)/L	10.1±3.1*	11.2±3.4	14.3±4.1	F=4.2, p=0.02
BEecf(mmol)/L	−17.5±5.1*	−15.0±4.5	−12.4±5.2	F=3.2, p=0.04
eGFR (ml/s)	0.27±0.21**	0.35±0.17**	0.76±0.26	F=18.5, p<0.001
Chronic renal insuff. (number/%)	2(18%)	3(21%)	3(7%)	0.27
Acute renal failure (number/%)	9(82%)	8(57%)	21(47%)	0.11
Sepsis (number/%)	4(36%)	6(43%)	15(34%)	0.81
Ischaemic heart disease (number/%)	10(91%)	9(64%)	16(36%)	0.01
Alcoholism (number/%)	0(0%)	2(18%)	10(23%)	0.19
Hypothermia (number/%)	0(0%)	0(0%)	1(2%)	0.72
Cancer (number/%)	1(9%)	1(7%)	9(20%)	0.45
Liver disease (number/%)	1(9%)	4(29%)	18(41%)	0.25

*p< 0.05 versus nondiabetic patients; **p<0.01 versus nondiabetic patients
DM - diabetes mellitus; BE - base excess; eGFR - calculated glomerular filtration rate

Tab. 2. Number of nondiabetic patients with fatal outcome according to presence of risk factors for lactic acidosis.

	dead	alive	*p*-value
N	30	14	0.51
Male (number/%)	16(53%)	7(50%)	0.36
Age (years)	64±12	60±10	0.39
pH	7.19±0.09	7.16±0.13	0.41
Lactate (mmol/L)	12.6±5.2	12.7±4.9	0.95
eGFR (ml/s)	0.69	0.9	0.04
Chronic renal insuff. (number/%)	1(3%)	2(14%)	0.2
Acute renal failure (number/%)	18(60%)	3(21%)	0.01
Sepsis (number/%)	11(37%)	4(29%)	0.58
Ischaemic heart disease (number/%)	11(37%)	5(36%)	0.94
Alcoholism (number/%)	7(23%)	3(21%)	0.88
Cancer (number/%)	8(27%)	1(7%)	0.15
Liver disease (number/%)	13(43%)	5(36%)	0.64

eGFR - calculated glomerular filtration rate

Tab. 3. Number of diabetic patients with fatal outcome according to presence of risk factors for lactic acidosis.

	dead	alive	*p*-value
N	16	9	
Male (number/%)	8(50%)	3(33%)	0.4
Age (years)	69±8	65±11	0.39
pH	7.16±0.13	7.18±0.09	0.75
Lactate (mmol/L)	16±6.3	11.1±5.7	0.12
eGFR (ml/s)	0.39	0.18	0.02
Metformin (number/%)	6(37.5%)	5(55.5%)	0.4
Chronic renal insuff. (number/%)	3(19%)	2(22%)	0.83
Acute renal failure (number/%)	9(56%)	8(89%)	0.09
Sepsis (number/%)	9(56%)	1(11%)	0.03
Ischaemic heart disease (number/%)	12(75%)	7(78%)	0.84
Alcoholism (number/%)	1(6%)	1(11%)	0.4
Cancer (number/%)	1(6%)	1(11%)	0.64
Liver disease (number/%)	4(25%)	1((11%)	0.4

eGFR - calculated glomerular filtration rate

DISCUSSION

The incidence of the patients using metformin admitted to ICU with lactic acidosis in our study was 0.6%. This figure corresponds to previously reported data (Biradar et al. 2010; Lalau 2010). More than thirty percents of all admitted patients to medical ICU had diabetes mellitus. Metformin was given to 62% of all admitted diabetic patients while in the group of patients with LA only to 44%. These data do not support the importance of met-

formin in the development of LA in diabetic patients admitted to medical ICU.

The mortality of the patients with lactic acidosis in ICU was high – 67% have died. According to our result the presence of diabetes mellitus and metformin application have not been associated with the increased mortality.

Mortality of nondiabetic patients was associated with eGFR and the presence of acute renal failure. Contrary mortality of diabetic patients was associated with the presence of sepsis. Circulatory failure of the diabetic patients with sepsis could have the more serious consequences comparing nondiabetic subjects because of the significantly higher incidence of ischaemic heart disease.

Acute renal failure was more frequent in diabetic patients on metformin than in diabetic patients without metformin and nondiabetic subjects. Treatment with continuous venovenous hemofiltration was started as soon as possible after admission and prognosis was relatively good in these patients if patients with sepsis were excluded. There is discussion in the literature about the impact of RRT on mortality in MALA patients. According to Finkle (2009) RRT is beneficial in preventing a higher mortality rate in those who required it. Our experience supports this point of view. These diabetic patients are in the similar situation like people with severe metformin intoxication who had good prognosis if treated early (Runge et al. 2008; Wills et al. 2010).

The good prognosis of diabetic patients with acute renal failure but without circulatory failure explains why low eGFR was associated with decrease of mortality in diabetic group.

Recent studies point out liver disease as the important risk and prognostic factors (Seidowsky et al. 2009; Peters et al. 2008). Liver disease was diagnosed in one third of all our patients with lactic acidosis but no significant association could be seen in diabetic as well as nondiabetic patients.

The changes of acid basic balance are more pronounced in diabetic patients comparing to nondiabetic subjects. These abnormalities are the most likely due to the more significant deterioration of renal function in diabetic patients because no significant differences of serum lactate had been found between groups. These results correspond to the previous study (Scale & Harvey 2011).

CONCLUSION

Our results did not support the impact of diabetes mellitus and metformin application on the presence of lactic acidosis in medical ICU. Mortality of patients with lactic acidosis was very high but no differences could be detected between diabetic patients on or without metformin and nondiabetic subjects. In nondiabetic patients mortality was associated with acute renal failure and eGFR while in diabetic patients with sepsis. The prognosis of diabetic patients on metformin with acute renal failure but without circulatory failure was good if renal replacement therapy (CVVH) was started early.

REFERENCES

1 Almirall J, Bricullé M, Gonzales-Clemente JM (2008). Metformin-associated lactic acidosis in type 2 diabetes-mellitus: incidence and presentation in common clinical practice. Nefrol Dial Transpl. **23**(7): 2436–8.
2 Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jorgensen CH et al (2010). Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. **53**(12): 2546–53.
3 Arroyo D, Melero R, Panizo N, Goicoechea M, Rodriguez-Benitez P, Vinuesa SV et al (2011). Metformin-Associated Acute Kidney Injury and Lactic Acidosis. Int J Nefrol. 749653 EPUB 2011; Jul 18.
4 Biradar V, Moran JL, Peake SL, Peter JV (2010). Metformin-associated lactic acidosis (MALA): clinical profile and outcome in patients admitted to the intensive care unit. Crit Care Resusc.**12**(3): 191–5.
5 Carlon R, Dal Cero P, Corbanese U, Possamai C (2010). Three cases of severe metformin-realted lactic acidosis. Eur J Anaesthesiol. **27**(7): 666–7.
6 Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV (2005). Comparative Outcome Study of Metformin Intervention versus Conventional Approach: The COSMIC Approach Study. Diabetes Care. **28**: 539–43.
7 Finkle SN (2009) Should dialysis be offered in all cases of metformin-associated lactic acidosis? Crit Care. **13**(1): 110.
8 Lalau JD (2010). Lactic acidosis induced by metformin: incidence, mangement and prevention. Drug Saf. **33**(9): 727–40.
9 Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R et al. (2009). Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. **25**: 17–30.
10 Peters N, Jay N, Barraud D, Cravoisy A, Nace L, Bollaert PE, Gibot S (2008). Metformin-associated lactic acidosis in an intensive care unit. Critical Care **12**: R149.
11 Runge S, Mayerle J, Warnke C, Robinson D, Roser M, Felix SB, Friesecke S (2008). Metformin-associated lactic acidosis in patients with renal impairment solely due to drug accumulation? Diabetes Obes Metab. **10**(1): 91–3.
12 Salpeter SR, Greyber W, Pasternak GA, Salpeter EE (2010). Risk of fatal and non fatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane database of systematic Review. **4**, CD002967.
13 Scale T, Harvey JN (2011). Diabetes, metformin a lactic acidosis. Clin Endocrinol **74**: 191–6.
14 Seidowsky A, Nseir S, Houdret N, Fourrier F (2009). Metformin-associated lactic acidosis: a prognostic and therapeutic study. Critical Care Medicine **37**: 2191–6.
15 Stades AM, Heikens JT, Erkelens DW, Holleman F,Hoekstra JB (2004). Metformin and lactic acidosis: cause or coincidence? A review of case reports. Journal of Internal Medicine **255**: 179–87.
16 Wills BHJ, Bryant SM, Buckley P, Seo B (2010). Can acute overdose of metformin lead to lactic acidosis? Am J Emerg Med. **28**(8): 857–61.