ORIGINAL ARTICLE

Lactic acidosis in patients with diabetes

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KEY WORDS

alcohol, lactic acidosis, metformin

ABSTRACT

INTRODUCTION Lactic acidosis is a relatively rare complication diagnosed in patients with diabetes.

OBJECTIVES The aim of this study was to identify causes of lactic acidosis in patients with diabetes and to measure the extent of metabolic disturbances based on the available laboratory test results.

PATIENTS AND METHODS A total of 29 diabetic patients aged 20–87 years were admitted to the Intensive Diabetes Care Unit of the Warsaw Medical University in the years 2007–2012 with the diagnosis of lactic acidosis (lactate level >5 mmol/l). A detailed medical history was taken from all patients or their caregivers. Lactate levels, glycemia, acetonuria, and gasometry were measured on admission.

RESULTS Eight patients with type 1 diabetes, 18 patients with type 2 diabetes, and 3 patients with other types of diabetes were hospitalized with the diagnosis of lactic acidosis. Lactic acidosis (lactate levels, 5.2–27 mmol/l) was associated with increased glycemia (13.3–91.7 mmol/l) and low pH (6.73–7.28). Alcohol abuse was reported in 12 subjects based on medical history. In 3 women, acute diabetic complication was caused by psychogenic eating disorders. There were 5 fatal cases including 3 cases of metformin treatment.

CONCLUSIONS Alcohol abuse and its effects on health seem to be the main cause of lactic acidosis in diabetic patients. Metformin-treated patients, especially elderly ones, are at a risk of sudden deterioration of renal function, which in turn may increase the risk of lactic acidosis.

INTRODUCTION Lactic acidosis is defined as metabolic acidosis with a large anion gap, low pH of arterial blood, substantial reduction of bicarbonate (HCO_3^-) levels, and increased lactic acid levels. The normal range for serum lactic acid is from 0.4 to 1.2 mmol/l. An increase in the lactic acid level to 2–5 mmol/l usually does not cause any signs and symptoms of acidosis. The symptoms may occur when lactic acid levels exceed 5 mmol/l. In most publications, lactic acidosis is diagnosed when the lactate level exceeds 5 mmol/l.[1,2] However, the diagnostic criteria of lactic acidosis are not uniform. The diagnosis is made based on pH lower than 7.37 and serum lactate higher than 4 mmol/l[3]; or based on pH lower than 7.35 and lactate higher than 5 mmol/l, but one may use other criteria, that is, the anion gap larger than 16 mmol/l and HCO_3^- lower than 10 mmol/l if lactate measurements are unavailable.[4] This diagnosis could also be or based on pH lower than 7.35 and lactate between 5 and 6 mmol/l[5]; or based on lactate higher than 7 mmol/l.[6]

Lactate is a product of anerobic glucose metabolism. In anerobic conditions, pyruvate is reduced to lactate by lactate dehydrogenase, while pyruvate having access to oxygen is converted to water and carbon dioxide in the process of gluconeogenesis in the mitochondria. Normally, there is a balance between pyruvate and lactate levels but, in particular circumstances, the overproduction of lactate is possible. Lactic acid is used mostly in the liver and kidneys (10%–20%) and, to a small extent, in the skeletal muscles.[7] In 1976, Cohen and Woods in their report „Clinical and Biochemical Aspects of Lactic Acidosis"[8] identified and described 2 categories of lactic acidosis. Type A lactic acidosis occurs with decreased tissue adenosine-5'-triphosphate as a result of poor tissue perfusion or oxygenation. Type B lactic acidosis is characterized by no evidence of decreased tissue perfusion or hypoxia. However, also in type B decreased tissue blood perfusion or hypoxia have been reported in many cases.

Lactic acid has 2 forms: L-lactate and D-lactate. Usually L-lactate levels are measured because L-lactate is the product of normal metabolism in humans. Its overproduction is observed in hypoxia. The other form, which is produced by bacteria,

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TABLE 1 Basic characteristics of patients with newly diagnosed diabetes or diabetes treated with insulin and diagnosed with lactic acidosis on admission

No.	Age, y	Sex	Type of diabetes	Current antidiabetic treatment	Diagnosis	Hospitalization outcome
1	23	M	1	no treatment[a]	ketoacidosis, hyperglycemic hyperosmolar state, pharyngitis	discharge
2	55	F	other	no treatment	alcoholism, chronic pancreatitis, malnutrition	discharge
3	55	F	other	no treatment[a]	alcoholism, hepatic cirrhosis, pneumonia	death
4	76	F	2	no treatment[a]	hyperglycemic hyperosmolar state, acute pancreatitis, dermatomycosis	discharge
5	20	F	1	insulin	bulimia, urinary tract infection	discharge
6	21	M	1	insulin	ketoacidosis, acute alcohol intoxication	discharge
7	27	F	1	insulin	bulimia, ketoacidosis	discharge
8	27	M	1	insulin	ketoacidosis, hepatosplenomegaly	discharge
9	34	F	1	insulin	bulimia ketoacidosis, pneumonia	discharge
10	43	M	1	insulin	alcoholism, acute pancreatitis	discharge
11	44	F	1	insulin	ketoacidosis, alcoholism, gangrenous teeth	discharge
12	50	M	2	insulin	alcoholism, chronic pancreatitis	discharge
13	50	M	other	insulin	ketoacidosis, alcoholism, pneumonia, chronic pancreatitis	discharge
14	56	M	2	?	alcoholism, past stroke, history of angioplasty, pneumonia	death
15	57	M	2	insulin	renal insufficiency, acute coronary syndrome, past stroke	discharge
16	58	F	2	insulin	ketoacidosis, past stroke, urinary tract infection	discharge
17	58	M	2	insulin	alcoholism, chronic obstructive pulmonary disease, gangrenous teeth	discharge
18	60	F	2	insulin	diabetic foot syndrome, chronic obstructive pulmonary disease, postmyocardial infarction	discharge
19	60	M	2	insulin	alcoholism, renal insufficiency, hepatic cirrhosis	discharge
20	81	F	2	insulin	urinary tract infection, renal insufficiency	discharge
21	83	F	2	insulin	pneumonia, chronic obstructive pulmonary disease	discharge

a newly diagnosed diabetes

Abbreviations: F – female, M – male

may occur in subjects with short bowel syndrome following surgical removal of the small intestine, after Roux-en-Y bypass surgery.[9]

The overall incidence of lactic acidosis of any type is difficult to assess and is usually diagnosed in patients with life-threatening conditions.[10,11]

In the past, when phenformin was used, the risk of lactic acidosis was relatively high. After metformin became the main oral antidiabetic drug in type 2 diabetes, researchers have generally become interested in the risk of lactic acidosis in the course of metformin treatment. Metformin is currently considered a safe treatment. In the COSMIC study (Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach), safety of 1-year therapy with metformin in 7227 patients was compared with safety of other antidiabetic drugs in 1505 patients and no significant differences were found. Lactic acidosis was not reported in any of the patients.[12] Salpeter et al.[13] reviewed controlled clinical trials conducted in patients who used metformin for 1 month or longer. In total, during 36,000 patient-years, no case of lactic acidosis was diagnosed. In contrast to controlled clinical trials, in postmarketing experience, the cases of lactic acidosis continue to be reported among metformin-treated patients. In the first million of patients treated with metformin in the United States, 47 cases of lactic acidosis, including 20 fatal cases, were recorded. In this group of patients, renal insufficiency was found in 43 subjects.[14] Based on the UK General Practice Research Database, Bodmer, et al.[3] estimated the incidence of lactic acidosis in metformin-treated patients as 3.3 cases per 100,000 patient-years. The question remains of how many patients who developed lactic acidosis have not been correctly diagnosed. On the other hand, it is not clear how often this serious complication results from the underlying disease with no direct association with metformin.The occurrence of lactic acidosis in the course of biguanide therapy is associated with a 50% risk of death.[15]

PATIENTS AND METHODS About 250 patients are hospitalized annually in the Intensive Diabetes Care Unit of the Department of Gastroenterology and Metabolic Disorders of Warsaw

TABLE 2 Basic characteristics of diabetic patients treated with metformin and diagnosed with lactic acidosis on admission to hospital

No.	Age	Sex	Type of diabetes	Current antidiabetic treatment	Diagnosis	Hospitalization outcome
1	49	M	2	sulfonylurea + metformin	alcoholism, acute pancreatitis, toxic hepatitis	discharge
2	55	F	2	metformin	purulent bronchitis, pulmonary emphysema, cachexia	death
3	55	M	2	sulfonylurea + metformin	myocardial infarction, acute kidney injury	discharge
4	58	M	2	sulfonylurea + metformin	alcoholism, gangrenous teeth	discharge
5	60	F	2	metformin	atherosclerosis, massive decubitus ulcers, cachexia	death
6	71	M	2	sulfonylurea + metformin	acute coronary syndrome, chronic obstructive pulmonary disease	discharge
7	74	F	2	metformin	pneumonia, anemia, decubitus ulcer	death
8	87	F	2	metformin	pneumonia, acute kidney injury	discharge

TABLE 3 Laboratory test results of diabetic patients treated with insulin and diagnosed with lactic acidosis on admission to hospital

No.	Type of diabetes	Duration of diabetes, y	Values on admission					
			lactate, mmol/l	acetone	pH	HCO_3, mmol/l	glycemia, mmol/l	creatinine, µmol/l
1	1	0	6.0	+++	7.12	7.0	50.2	283.8
2	other	5	5.2	–	7.2	23.8	31.3	36.2
3	other	0	23.0	+	7.06	5.7	21.6	203.3
4	2	0	10.1	–	7.0	7.7	91.7	251.9
5	1	4	7.0	–	6.77	3.2	50.4	109.6
6	1	10	7.4	+++	6.92	3.4	52.8	181.2
7	1	7	6.5	+++	7.18	15	21.2	63.6
8	1	4	5.9	+++	6.78	4.1	44.1	194.5
9	1	2	14.2	+++	6.87	3.8	49.6	50.4
10	1	10	8.0	++	6.82	3.5	26.7	159.1
11	1	6	6.1	+++	6.8	2.6	51.7	113.2
12	2	8	22.0	–	7.03	4.0	30.8	229
13	other	5	6.0	+++	6.91	2.8	60.6	228.9
14	2	?	19	NA	6.73	4.0	40.1	323.5
15	2	12	9.1	+	7.18	7.7	66	334.2
16	2	33	7.5	++	7.16	7.5	56.4	401.4
17	2	12	7.3	+	7.09	14.1	65.4	287.3
18	2	10	5.5	–	7.2	12.7	27.4	174.1
19	2	14	7.2	–	7.19	14.6	14.3	265.2
20	2	22	8.2	++	6.98	5.6	55.2	164.4
21	2	38	12.2	–	7.2	23.0	51.6	121.1

Abbreviations: NA – not available

Medical University. Most of them are admitted to the hospital because of ketoacidosis, hyperglycemic hyperosmolar state, acute pancreatitis in diabetes, and so called difficult diabetes. During 4 years (2007–2012), 29 patients with diabetes (15 women and 14 men, aged 20–87 years) were hospitalized with the diagnosis of lactic acidosis (TABLES 1 and 2). The diagnosis was based on low pH (<7.35) and the lactate level higher than 5 mmol/l. The lactate level was measured along with a blood gas analysis. A detailed medical history was taken from all patients or their caregivers. Lactate levels, glycemia, gasometry, and acetonuria were measured on admission (TABLES 3 and 4). In most patients, glycated hemoglobin level was also assessed. All patients received oxygen therapy, intravenous insulin, fluids, and potassium infusion. Most patients received low doses of sodium bicarbonate. Following the initial administration of isotonic sodium chloride solution, even in significant hyperglycemia, patients received intravenous glucose infusions. Intensive treatment was continued from 1 to 6 days, depending on the patient's general condition.

TABLE 4 Laboratory test results of diabetic patients treated with metformin and diagnosed with lactic acidosis on admission to hospital

No.	Type of diabetes	Duration of diabetes, y	Values on admission					
			lactate, mmol/l	acetone	pH	HCO_3, mmol/l	glycemia, mmol/l	creatinine, µmol/l
1	2	10	6.5	++	7.09	13.9	27.7	62.8
2	2	4	27	NA	6.78	6.0	19.1	159.1
3	2	20	13.2	+	6.82	2.5	12.9	805.3
4	2	3	21.0	++	6.98	15.0	30,9	70.7
5	2	8	7.3	–	7.28	14.1	25	125.5
6	2	20	8.9	–	7.25	15.0	27.4	121.1
7	2	7	16.0	NA	7.28	10.7	14.4	278.5
8	2	12	21.2	–	6.9	3.4	8.0	371.9

Abbreviations: see TABLE 3

RESULTS All patients with type 1 diabetes (n = 8) were admitted in serious condition, with the signs and symptoms of massive dehydration and acidosis (pH, 6.77–7.18). In 6 cases, ketoacidosis was diagnosed in addition to lactic acidosis. In 3 women, severe acidosis (in 1 case with no ketones) was caused by psychogenic eating disorders (long-term reduction of insulin doses); in 2 men, it was caused by alcohol abuse and acute pancreatitis. In 1 male patient admitted in severe condition with the disturbance of consciousness, newly diagnosed diabetes, and acute pharyngitis, the laboratory test results revealed the lactate level of 6 mmol/l, pH of 7.12, and acetonuria (+++), while effective osmolarity was calculated at 380 mOsm/l. There were 12 patients with reported alcohol abuse (3 patients with type 1 diabetes, 6 patients with type 2 diabetes, and 3 patients with other types of diabetes). The direct cause of acute metabolic disturbances was alcohol abuse and withdrawal of insulin treatment. Within 4 to 2 days prior to hospital admission, persistent vomiting occurred in 6 patients and they refused to eat. On admission, apart from considerable hyperglycemia (26.7–65.4 mmol/l) and advanced acidosis (pH, 6.8–7.09), all patients had hyponatremia (113–135 mmol/l) and increased creatinine levels (110–287 mmol/l). One patient with numerous chronic complications of diabetes, who was admitted to the hospital in the state of alcohol intoxication in extremely serious condition (pH, 6.73; HCO_3, 4 mmol/l; lactate, 19 mmol/l; glycemia, 40.1 mmol/l), died on the first day of hospitalization. Another patient with acute alcoholic hepatitis (pH, 7.0; HCO_3, 5.3 mmol/l; lactate, 23 mmol/l) died on the 8th day of hospitalization.

Metformin was administered in 8 patients (4 of them also used sulfonylurea); 3 metformin-treated patients died. One of these patients, emaciated and with a history of alcohol abuse, was admitted to the hospital because of disseminated purulent inflammation and pulmonary emphysema. The patient died within the first few hours of hospitalization (lactate, 27 mmol/l). Death within the first 24 hours of hospitalization occurred also in a 74-year-old patient with pneumonia, decubitus ulcer, and anemia (lactate on admission, 16 mmol/l). In an unconscious, 60-year-old female patient with cachexia, massive decubitus ulcers, and cerebrovascular disease death occurred on the 5th day of hospital treatment. Two patients were successfully treated with early continuous venovenous hemodiafiltration: 1 patient treated with metformin and sulfonylurea (lactate, 13.2 mmol/l; pH, 6.82; HCO_3, 2.5 mmol/l; glycemia, 12.9 mmol/l), and 1 patient treated only with metformin admitted to hospital in a serious condition with acute kidney injury (lactate, 21.2 mmol/l; pH, 6.9; HCO_3, 3.4 mmol/l; glycemia, 8 mmol/l).

In a group of patients with type 2 diabetes, ketonuria was confirmed in 6 cases and in 1 female patient we also diagnosed hyperglycemic hyperosmolar state. This patient was admitted to hospital in extremely serious condition, with the signs and symptoms of extreme dehydration. On admission, her blood glucose level was 91.7 mmol/l, calculated effective osmolarity was 410 mmol/l, and the lactate level was 10.1 mmol/l.

In 18 patients, glycated hemoglobin levels were measured and the values considerably exceeded the upper limit of normal range[16] – 70–151 mmol/mol (8.6%–16%), suggesting the long-lasting lack of glucose control.

DISCUSSION All tissues can produce lactic acid and pyruvic acid. The liver and kidneys play an important role in lactate homeostasis. Lactic acidosis may occur regardless of diabetes type and may develop both in patients with a long history of diabetes and those with newly diagnosed disease. Probably the first cases of lactic acidosis were described by Doughaday et al.[17] in 1962. In 1969, more cases were presented by Watkins et al.[18] in the *British Medical Journal*. In our case reports, the most numerous group of patients admitted to the hospital with lactic acidosis consisted of patients with diabetes and alcohol dependence. In nondiabetic patients, alcohol abuse can lead to alcoholic ketoacidosis, which is quite often diagnosed in intensive care units. Acidosis manifests itself most commonly with nausea, persistent vomiting, and abdominal pain

and sometimes with consciousness disturbances. Usually alcoholic ketoacidosis occurs in chronic alcoholics who have recently been on a binge and stopped drinking alcohol and consuming food because of vomiting. There are 2 main factors that can lead to acidosis – ethyl alcohol and starvation. Alcoholic ketoacidosis occurs as a result of prolonged starvation with reduced glycogen storage, decreased insulin secretion, increased secretion of antagonistic hormones, and dehydration. Hormonal changes, particularly an increase in glucagon levels, lead to increased lipolysis, mobilization of fatty acids, and finally accumulation of ketoacids. Alcohol inhibits the conversion of lactate to pyruvate and favors the production of β-hydroksybutyrate over acetoacetate. Physical examination of patients reveals increased heart rate, hypotension, increased respiratory rate, abdominal tenderness or pain, and slightly altered mental status. Laboratory test results show large anion gap, normal or low blood glucose, normal or moderately increased creatinine, lactate levels that are not high enough to explain the degree of acidosis, undetectable or low alcohol levels, as well as ketone bodies in the urine although their absence does not preclude alcoholic acidosis.[19] Wrenn et al.[20] reported increased alcohol levels in nearly two-thirds of patients who had its levels measured. They also showed considerable electrolyte imbalance – hyponatremia, hypokalemia, hypophosphatemia, hypocalcemia, hypomagnesemia, and possibly hyperglycemia.[20] It has been widely accepted that alcoholic ketoacidosis occasionally occurs in patients with diabetes although cases with moderate hyperglycemia have been reported.[21] Prior to admission to hospital, 6 of 12 alcoholic patients experienced persistent vomiting with subsequent starvation. At the time of admission, hyperglycemia caused by insulin withdrawal was accompanied by profound acidosis (pH, 6.8–7.09), hyponatremia (sodium levels, 113–134 mmol/l), increased creatinine levels (113–287 mmol/l). It is very likely that acidosis in these cases was caused both by insulin withdrawal and persistent vomiting with starvation. Therefore, these cases of acidosis involve elements of lactic acidosis, diabetic ketoacidosis, and alcoholic ketoacidosis. In these patients, it is very difficult to identify which of the factors leading to acute, life-threatening metabolic disturbances is dominant.

Metformin was administered in 8 patients (4 of them used also sulfonylurea); 3 metformin-treated patients died. *A* consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes recommends metformin as the first-line treatment in newly diagnosed type 2 diabetic patients, which should be accompanied by health behavior changes.[22] Although the risk of lactic acidosis during metformin therapy has always been emphasized,[23] today the therapy is generally regarded as safe. The reduction of metformin doses is recommended only in the case of concomitant diseases that can lead to lactic acidosis.[24] Philbrick et al.[25] indicated that increased creatinine is a risk factor for lactic acidosis, but it is not an absolute contraindication to its use. Also in patients with heart failure, metformin therapy can provide therapeutic benefits unless other risk factors of lactic acidosis are present.[26] Despite these data, new case reports of lactic acidosis occurring in metformin-treated patients continue to be published.[27,28] Lactate levels strongly correlate with the severity of the disease and the risk of death in patients with sepsis.[29] It is important to emphasize the fact that death occurred in 3 female patients with severe infection of 8 cases treated with metformin and only 2 deaths occurred in 21 patients with newly diagnosed diabetes or those treated with insulin. Although metformin is generally considered as safe, when health risks that may lead to lactic acidosis occur during the treatment, particular precautions are necessary.[30] In metformin-treated patients, especially in elderly ones, the possibility of a sudden deterioration of renal function has to be considered, which can increase the risk of lactic acidosis. The question remains as to the frequency of lactate measurement in patients treated with metformin admitted to the hospital in a serious condition.

In patients with type 1 diabetes, long-term insufficient glycemic control and malnutrition may result in a considerable increase in lactic acid and ketone bodies and the development of life-threatening acidosis. Alcohol abuse and related consequences for health seem to be the main cause of lactic acidosis in patients with diabetes.

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Kwasica mleczanowa u pacjentów z cukrzycą

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alkohol, kwasica mleczanowa, metformina

STRESZCZENIE

WPROWADZENIE Kwasica mleczanowa jest stosunkowo rzadkim powikłaniem rozpoznawanym u osób z cukrzycą.

CELE Celem pracy było ustalenie przyczyn wystąpienia kwasicy mleczanowej w grupie osób z cukrzycą oraz dokonanie oceny stopnia zaburzeń metabolicznych na podstawie wykonanych badań biochemicznych.

PACJENCI I METODY 29 pacjentów z cukrzycą w wieku 20–87 lat zostało przyjętych w latach 2007–2012 na Pododdział Intensywnej Opieki Diabetologicznej Warszawskiego Uniwersytetu Medycznego z rozpoznaniem kwasicy mleczanowej (stężenie mleczanu >5 mmol/l). U wszystkich pacjentów lub opiekunów przeprowadzono dokładny wywiad chorobowy. W chwili przyjęcia oznaczenia stężenia mleczanu, glikemii, acetonu w moczu, wykonywano badanie gazometryczne,

WYNIKI 8 osób z cukrzycą typu 1, 18 osób z cukrzycą typu 22 i 3 osoby z cukrzycą innego typu było hospitalizowanych z rozpoznaniem kwasicy mleczanowej. Wystąpieniu kwasicy mleczanowej (stężenia mleczanu: 5,2–27 mmol/l) towarzyszył wzrost glikemii (13,3–91,7 mmol/l) oraz obniżenie pH (6,73–7,28). W 12 przypadkach na podstawie wywiadu rozpoznano chorobę alkoholową. U 3 kobiet z cukrzycą typu 1 przyczyną wystąpienia ostrego powikłania cukrzycy były psychogenne zaburzenia odżywiania. U 5 osób, w tym 3 leczonych metforminą, doszło do zgonu.

WNIOSKI Nadużywanie alkoholu i wynikłe z tego faktu konsekwencje zdrowotne wydają się główną przyczyną wystąpienia kwasicy mleczowej u osób z cukrzycą. U osób leczonych metforminą, szczególnie w wieku podeszłym, należy zawsze brać pod uwagę możliwość nagłego pogorszenia czynności nerek powstałego z różnych przyczyn, które może zwiększyć ryzyko wystąpienia kwasicy mleczanowej.

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