

# REVIEWS

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## Perioperative use of metformin in cardiac surgery

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**Key words:** metformin; lactic acidosis; diabetes mellitus; heart surgery.

**Summary.** Metformin is an oral antidiabetic agent, used to reduce blood glucose concentration in patients with non–insulin–dependent diabetes mellitus. Metformin was approved in Europe in 1957, and it is used for the treatment of non–insulin–dependent diabetes mellitus for more than 50 years. One of the most serious complications of the treatment with this drug is metformin-induced lactic acidosis. It is a rare but dangerous metabolic complication with a mortality rate of up to 50% that can result from the accumulation of lactates. Lactic acidosis is also associated with conditions such as diabetes mellitus, significant tissue hypoperfusion, and hypoxemia caused by lactic acid overproduction or underutilization. It is characterized by an increased serum lactate level ( $>5$  mmol/L or  $>45$  mg/dL), decreased blood pH ( $<7.35$ ), and electrolyte imbalance with an increased anion gap. The rate of lactic acidosis in patients receiving metformin is not precisely known. The estimated incidence of this syndrome is 2–9 cases per 100 000 patients. However, in the majority of cases, lactic acidosis is diagnosed in patients with severe acute renal failure, which itself can cause lactic acidosis.

Currently, there are no standardized guidelines for metformin administration during the perioperative period, and published data remain controversial. According to some investigators, metformin should be withdrawn before major surgery. Concerns have been raised for the use of metformin in patients with cardiovascular, renal, hepatic, and respiratory failure. The aim of the article is to overview the frequency of metformin-caused lactic acidosis and the latest recommendations for the use of metformin in the perioperative period proposed in recent years.

### Introduction

The number of patients with type 2 diabetes mellitus (DB) is dramatically increasing all over the world. This disease can be called “the pandemic diabetes”: it is estimated that by the year 2030, more than 360 million people will be affected by the disease compared to 170 million who had this disease in 2000 (Fig. 1). There are several causes of this significant increase in morbidity. Obesity, caused by improving living conditions, physical inactivity, sedentary lifestyle, and aging society are the most relevant of them. In the developed countries, the majority of diabetic patients are older than 65 years; meanwhile, in the developing countries, the majority of patients with diabetes are aged 45–64 years (2). Likewise, socioeconomic status appears to influence the development of diabetes, but the relationship is different in developed and developing countries. However, in the developed countries, people of lower socioeconomic groups have a higher risk of obesity and type 2 diabetes. The prevalence of diabetes is similar among male and female pa-

tients; however, the disease is more frequent in men younger than 60 years. In patients older than 60 years, the prevalence of diabetes is higher in female population due to their longer life expectancy. With increasing numbers of patients diagnosed with diabetes, the number of patients with diabetes referred to cardiac surgery is increasing. A considerable number of these patients use metformin to control their blood glucose levels.

### The role of normoglycemia during perioperative period

Lazar et al. investigated the impact of normoglycemia on outcomes of patients undergoing coronary artery bypass grafting (CABG) surgery. In one group, patients were treated with continuous infusion of insulin, which was started before anesthesia and continued during surgery and 12 hours after it. In another group, patients were treated with standard subcutaneous insulin injections. Blood glucose levels were lower in patients who were treated with

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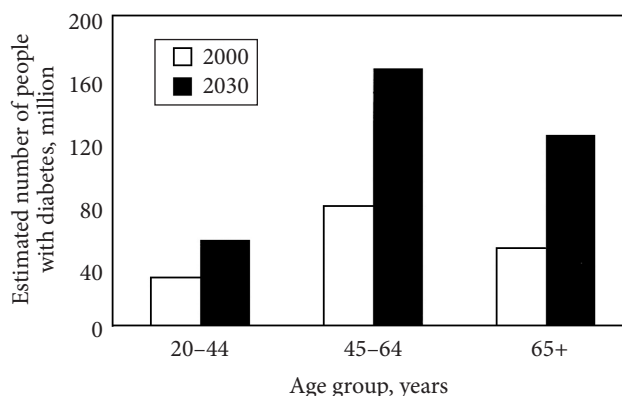


Fig. 1. Morbidity of adults with diabetes mellitus in the world in 2000 and prognosis for 2030 (1)

continuous insulin infusion ( $7.6 \pm 0.2$  mmol/L vs.  $14 \pm 0.3$  mmol/L;  $P < 0.0001$ ). Patients with lower serum glucose levels had a lower incidence of cardiac arrhythmias (16.6% vs. 42%;  $P = 0.0017$ ) and shorter hospitalization time ( $6.5 \pm 0.1$  vs.  $9.2 \pm 0.3$  days;  $P = 0.003$ ). In this group of patients, a lower rate of postoperative wound infections (1% vs. 10%;  $P = 0.03$ ) was found, and two-year survival was higher (3).

Recent studies have showed that a considerable number of patients with acute myocardial infarction have unidentified diabetes or the treatment of diabetes is inappropriate (4, 5). Norhammar et al. analyzed patients with unstable angina or myocardial infarction older than 45 years. None of them had diagnosed diabetes before the onset of heart disease, and blood glucose level was below 11.1 mmol/L. Three months after the onset of the disease, a standard glucose tolerance test with 75 g of glucose was performed. The mean age of the patients was 63.5 years; 40% of the patients had impaired glucose tolerance and 25% diabetes mellitus (4). Conaway et al. in a prospective trial analyzed 10911 patients with acute coronary syndrome. Impaired glucose tolerance was found in 57% of the patients (5). In the same year Kosiborod et al. published data of 141 680 patients who were hospitalized with acute myocardial infarction during 1994–1996. A quarter of them had unrecognized diabetes; they had markedly elevated blood glucose levels of 13.3 mmol/L and even higher. The mortality rate of these patients was higher comparing with the patients who had blood glucose levels in the range of 6.11 mmol/L and 7.78 mmol/L (6). During hospitalization, patients with unrecognized diabetes were less likely to be treated with insulin than diabetic patients even having the same blood glucose concentration (6).

A prospective randomized multicenter clinical diabetes trial, performed in 15 centers in the United Kingdom and including 4075 patients, showed that

treatment with metformin or insulin was very effective for glycemic control and had a positive impact on the rate of vascular complications. Moreover, in obese patients, metformin significantly reduced mortality from cardiac causes; no episodes of hypoglycemia and weight gain were documented in these patients. Metformin-treated patients had a 36% lower all-cause mortality rate comparing with patients treated with diet only ( $P = 0.011$ ). This study showed a 32% decrease in diabetes-related morbidity ( $P = 0.0023$ ), a 42% reduction in diabetes-related mortality ( $P = 0.017$ ), and a 39% reduction in myocardial infarction rate ( $P = 0.01$ ) in these patients. Based on the results of this study, the authors have concluded that metformin is the only oral hypoglycemic drug, which has an impact on reduced mortality from cardiovascular causes, and is the first-line drug for the treatment of obese patients with type 2 diabetes (7).

Hypoglycemic drugs, such as insulin, sulfonylurea, and thiazolidinediones, have numerous dangerous side effects. Biguanides, oral hypoglycemic drugs, are attractive as they do not have an impact on weight gain. Metformin is similar in chemical structure to phenformin, a drug that was removed from the US market because of unacceptably high incidence of life-threatening lactic acidosis (8). Contrary to phenformin, which increases lactate turnover and suppresses lactate oxygenation, metformin does not suppress elimination of lactates, and lactates that cannot be metabolized via gluconeogenesis can still be eliminated by a compensatory increase in lactate oxidation (9). Due to this action, the risk of lactic acidosis is very low (10). However, due to historical experience with its predecessor – phenformin – and despite different effects of metformin and phenformin on lactate metabolism, treatment with metformin is thought to be associated with increased risk of life-threatening lactic acidosis.

### Metformin

Metformin is an oral antidiabetic agent, a biguanid, which has been used to reduce blood glucose concentration in patients with non-insulin-dependent diabetes mellitus in Europe since 1957 and in the United States since 1995. A beneficial effect of this drug was observed in patients with metabolic syndrome (or syndrome X), which is characterized by obesity, increased plasma glucose levels, insulin resistance, atherogenic dyslipidemia, and hypertension and decreased fibrinolytic activity (11, 12). Metformin suppresses endogenous glucose production in patients with type 2 diabetes, in particular excessive gluconeogenesis in the liver, decreases glucose absorption in the digestive tract, increases glucose uptake in the muscles and fat tissue, does not increase insulin secretion and its release from

Table 1. Contraindications for metformin treatment (1999–2005) (14–17)

Contraindications	Howlett and Bailey (14)	German Diabetes Society (15)	Package insert (16)	British National Formulary (17)
Impaired renal function	Creatinine clearance <90 mL/h	Plasma creatinine >107 $\mu$ mol/L	Creatinine clearance <60 mL/h	Plasma creatinine >133 $\mu$ mol/L
Heart failure	+	+	+	+
Respiratory failure	+	+	+	+
Severe liver disease	+	+	+	+
Tissue hypoxia	+	+	+	+
Alcohol abuse	+	+	+	–
Advanced age	–	+	–	–
Intravenous contrast media	–	+	+	+
Surgery	–	+	–	+
Hypocaloric diet	–	+	–	–
Pregnancy	+	–	+	+
Diabetic ketoacidosis, coma	+	–	+	+

the pancreas. The antihyperglycemic action of metformin is based on suppression of endogenous glucose production in patients with type 2 diabetes (9). Metformin also have beneficial effects on lipids, fibrinolysis, endothelial dysfunction, and blood pressure. At the molecular level, the activation of activated protein kinase seems to be of critical importance. In contrast to the early biguanides – phenformin and buformin – metformin is less lipophilic, does not accumulate in the liver, and is eliminated unchanged through the kidneys (9). Metformin effectively reduces patients' body weight, decreases insulin demand, and improves glycemic control without inducing hypoglycemia (13). The current absolute contraindications to the use of metformin are renal insufficiency, severe heart failure, and metabolic acidosis. Special precautions should be taken during conditions, which may lead to hypoxia and hypovolemia, and this could exactly emerge during the perioperative period. The contraindications to the use of metformin are presented in Table 1.

### Lactic acidosis

Lactic acidosis is a consequence of diseases or syndromes characterized by tissue hypoxia, associated with metabolic acidosis (pH <7.25) and elevated plasma lactate concentration (>5 mmol/L) (8). Septicemia, renal or hepatic failure, diabetes mellitus, malignant tumors, and use of salicylates are conditions that may result in lactic acidosis (17).

Lactic acidosis usually manifests in patients with impaired cardiac, renal, pulmonary, or hepatic function. The use of metformin should be restricted in these patients (18). Any condition that may predispose to lactic acidosis is a contraindication to the treatment with metformin (18). The only organs of the human body that can use lactate as a substrate are the heart and the liver, because of the specific enzyme they produce (10). However, lactates are produced in all human tissues: skin and muscles produce 50% of lactates, brain 20%, red blood cells

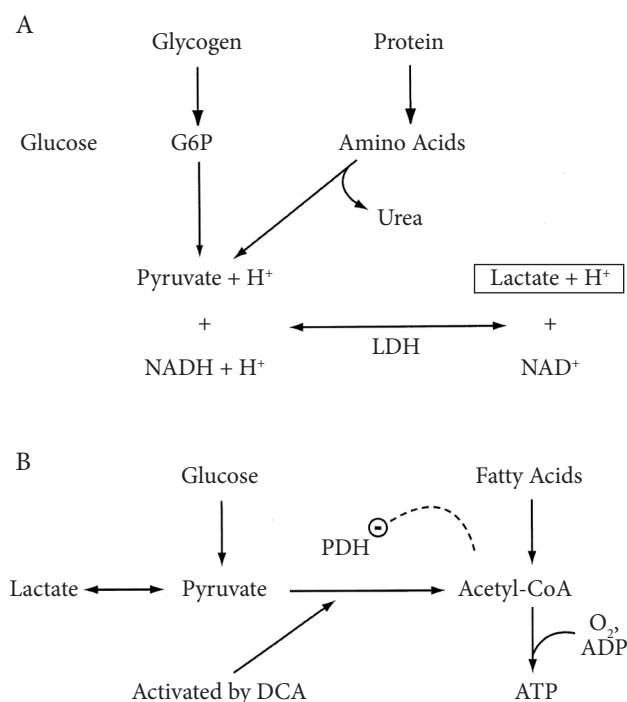


Fig. 2. Gluconeogenesis and metabolism of lactates (10)

A, lactic acid synthesis. Lactic acid accumulates if pyruvate or NADH accumulates. G6P, glucose-6-phosphate; LDH, lactate dehydrogenase. B, dichloroacetate effects. Dichloroacetate (DCA) activates pyruvate dehydrogenase (PDH), favoring lactate oxidation. Thiamine is a coenzyme for PDH.

20%, and 10% of lactates are produced in the intestine (19).

Lactates are produced from pyruvates catalyzed by lactate dehydrogenase. About 60% of all lactates produced in the body are metabolized in the liver and 30% in the kidneys. Almost half of this amount is used for gluconeogenesis and the rest of it is metabolized to H<sub>2</sub>O and CO<sub>2</sub> (Fig. 2) (10).

The classification of lactic acidosis by Cohen and Woods (20) is as follows:

A: Reduction in tissue adenosine triphosphate (ATF) predetermined by hypoxia or low oxygenation:

A1: Hyperproduction of lactates, necessitated by tissue hypoperfusion: hypovolemia, pulmonary and hematological diseases that have a negative impact on oxygen transport in the human body;

A2: Conditions that influence elimination of lactates: hepatic and biliary disorders, suppression of gluconeogenesis, vitamin B<sub>2</sub> deficiency, severe anemia, carbon monoxide (CO) poisoning, etc.

B: Normal tissue oxygenation:

B1: Systemic diseases: renal and hepatic failure, malignant tumors, intestinal ischemia, pancreatitis, pheochromocytoma, etc;

B2: Drugs and toxins: biguanides (metformin, phenformin), isoniazids, salicylates, alcohols and glycols (methanol, ethanol, propylene glycol), cyanide compounds (cyanides, sodium nitroprusside), halothane, propofol, fructose, sorbitol, xylitol,  $\beta$ -adrenergic drugs (epinephrine, terbutaline), etc.

B3: Inherited disorders of metabolism in newborns (deficit of glucose-6-phosphate, fructose-1,6 diphosphate, etc).

Therefore, lactic acidosis can be classified by its origin, i.e. hypoxic and nonhypoxic (Table 2).

Table 2. Classification of lactic acidosis according to pathophysiology

Hypoxic	Nonhypoxic
Ischemia	Increased creatinine clearance
Shock, severe anemia, clinical death	Renal or hepatic failure
Hypoxia	Dysfunction of pyruvate dehydrogenase
Carbon monoxide poisoning	Sepsis, deficit of vitamin B <sub>1</sub> , catecholamines, alcoholic or diabetic ketoacidosis
Respiratory failure	Cyanides, salicylates, methanol and ethylene glycol, antiviral agents, valproic acid, biguanides
Severe asthma, chronic obstructive pulmonary disease, asphyxia	Aerobic glycolysis
Regional hypoperfusion	Sepsis, malignant tumors
Limb or mesenteric ischemia	

### Lactic acidosis induced by metformin

Metformin-induced lactic acidosis is a rare condition with a rate of 1 to 5 cases per 100 000 patients (21). From 1987 to 1991, 2.4 cases were diagnosed per 100 000 metformin-treated patients in Sweden. Other investigators reported the prevalence of this condition ranging from 1 to 15 cases per 100 000 patients (21, 22). Metformin was introduced in the United States in 1995, and since then lactic acidosis has been reported in 66 patients treated with metformin. In 47 patients, the diagnosis was confirmed based on the values of circulating lactate

(>5 mmol/L). Forty-three patients had several risk factors for developing lactic acidosis; 30 (64%) had preexisting cardiac disease, and 28% had preexisting renal insufficiency, requiring renal replacement therapy. Three patients had chronic pulmonary disease; 8 patients were older than 80 years. Only 4 patients survived, who did not have contraindications to the treatment with metformin (23).

In clinical practice, indications for the administration of metformin are often neglected. Analysis of the data reveals that almost every second patient has contraindications for therapy with metformin (24).

Emslie-Smith et al. reported that 24.5% of the patients treated with metformin had no indications for the treatment with this drug. These patients had acute myocardial infarction, congestive heart failure, or chronic renal insufficiency, requiring renal replacement therapy. However, of the 4600 patients, only one case of lactic acidosis was documented in a 72-year-old patient with acute myocardial infarction and renal failure (25).

Holstein et al. investigated a group of 308 patients who were treated with metformin from 1995 to 1998 and reported that 73% of them had at least one contraindication for the administration of this drug. Half of the patients (51%) had several contraindications, and all of them were of advanced age; heart failure, chronic renal failure, respiratory insufficiency, and hepatic failure were present in 25%, 19%, 6.5%, and 1.3% of patients, respectively. Alcohol abuse was reported in 3.3% of patients. However, no case of lactic acidosis was registered (26). Authors did not find any correlation between administration of metformin and concentration of lactic acid in patients who were diagnosed with lactic acidosis. Outcomes and prognosis were associated with clinically relevant hypoxia caused by a severe concomitant disease. The authors made a conclusion that advanced age, mild renal failure, and compensated congestive heart failure should not be assumed as contraindications to the treatment with metformin (9).

Lalau et al. analyzed data of 49 patients who were treated with metformin and had laboratory-confirmed lactic acidosis in blood plasma. The overall mortality of these patients was 45%. There was no difference in the concentration of lactic acid comparing the patients who survived and who did not (14.3 mmol/L vs. 13 mmol/L). Moreover, plasma concentration of metformin was three-fold higher (20.6 mg/L) in survivors than nonsurvivors (6.3 mg/L). There was no prognostic association between mortality and concentration of lactic acid or metformin. The authors hypothesized that mortality of these patients was associated with concomitant clinical diseases and worsening of health status (27).

Cusi et al. in their study showed that metformin did not increase the concentration of lactic acid in blood plasma (28). The authors examined 20 patients, diagnosed with type 2 diabetes, who were treated with insulin. During the study period, there was a significant decrease in concentration of blood glucose ( $196 \pm 18$  vs.  $152 \pm 12$  mg/dL;  $P < 0.01$ ), glycated hemoglobin (HbA1c) ( $12.5\% \pm 0.6\%$  vs.  $9.2\% \pm 0.3\%$ ;  $P < 0.01$ ), and concentration of plasma triglycerides and low-density lipoprotein cholesterol. Moreover, there was no significant increase of lactic acid concentration in patients treated with metformin as compared with the placebo group.

Salpenter et al. have conducted a meta-analysis of clinical studies published in 1959–2005. The authors evaluated metformin therapy, alone or in combination with other antidiabetic drugs. A total of 206 studies were analyzed. No cases of lactic acidosis were documented in 47 846 patients treated with metformin and 38 221 patients in the placebo group. After employing Poisson statistics with 95% confidence intervals, the upper limits for the true incidence of lactic acidosis were 6.3 and 7.8 cases per 100 000 patient-years in the metformin and placebo groups, respectively. Moreover, there were no differences in the concentration of lactic acid in both the groups. After the analysis of prospective study data, the authors reported no evidence that metformin increased the concentration of lactic acid comparing with other oral antidiabetic medications. There were 330 reported cases of lactic acidosis in patients treated with metformin (29). However, lactic acidosis was also diagnosed in patients who were not treated with metformin, but had concomitant diseases causing hypoperfusion and hypoxia (30).

Stades et al. analyzed all the cases of lactic acidosis, caused by metformin, that were published during the period of 1959–1999. They found 37 publications with 80 cases of lactic acidosis, caused by metformin. Thirty-three studies were excluded from the analysis due to methodological issues (missing data about metformin concentration and arterial blood pH). The analysis of the remaining 47 cases did not reveal any association between metformin and lactic acidosis. The authors stated that the use of metformin was a coincidence in lactic acidosis and accidental (31).

Increased concentrations of lactates (lactic acid) and metformin were not associated with increased mortality. Meanwhile, acute heart failure, hepatic cirrhosis, and sepsis were related to a higher risk of mortality (9, 31). All the patients, except one case in this review, had at least one risk factor for developing lactic acidosis, independently from treatment with metformin. In the majority of the patients, the elevated lactate level was caused by progression of renal failure. There was no relationship between

creatinine concentration and increased level of lactic acid, metformin concentration, or mortality in this study (31).

Brassoe et al. published two cases of lactic acidosis in metformin-treated patients. In the first case, the deterioration of patient's condition was caused by renal failure after the dose of angiotensin-converting enzyme inhibitors was increased, which reduced blood pressure and renal perfusion. In another case, lactic acidosis developed due to profound vomiting and diarrhea in a patient with gastroenteritis (32).

Brown et al. examined more than 41 000 patients treated with metformin and identified 4 confirmed cases of lactic acidosis, 3 suspected cases, and 3 possible cases of lactic acidosis. In all of them, there was at least one comorbid disease that could have an impact on development of lactic acidosis. The author stated that these conditions could be responsible for the development of metabolic acidosis and they were not associated with the treatment with metformin (21).

There are only few data in literature concerning the impact of metformin on morbidity in surgical patients. Until 2007, there were two cases of death reported in the perioperative period, when lactic acidosis developed during 24 hours after surgery (33, 34). However, in both the cases, comorbidities (sepsis, respiratory distress syndrome, shock, multiple-organ dysfunction syndrome) had more influence on poor outcome than treatment with metformin.

Duncan et al. in a recent study retrospectively evaluated 1284 diabetic patients who received metformin within 8–24 hours before cardiac surgery. The outcomes were compared with the control group of patients where metformin was not used. There were no significant differences in overall mortality and frequency of major cardiac, renal, and neurological complications. On the contrary, the duration of postoperative mechanical ventilation and rate of infectious complications were lower in the group of metformin-treated patients. This study showed that metformin treatment before surgery might have a beneficial effect on patient outcome in cardiac surgery. There was no single case of lactic acidosis reported during early postoperative period in this patients' group (35).

Manlapaz et al. analyzed the data of 4528 diabetic patients who were operated on in a cardiac surgical clinic from 1994 to 2004. The patients received metformin within 8–24 hours before surgery. Mortality from respiratory causes and serum creatinine and cardiac enzyme levels were lower in these patients as compared with patients treated with other hypoglycemic agents (36).

McAfee et al. examined 26 931 patients treated with metformin, rosiglitazone, and sulfonylurea compounds. The outcomes of heart surgery performed

and risk of perioperative myocardial infarction did not differ from the control group patients (37).

### Guidelines for preoperative assessment

Recent recommendations that have the main goal to reduce the risk of perioperative lactic acidosis are controversial. A growing body of evidence shows that metformin itself has no impact on the rate of development of lactic acidosis. Heart failure is not a contraindication for the treatment with metformin. On the contrary, recent studies show that metformin ingestion may be beneficial for patients with isolated cardiac insufficiency (35). The risk of metformin-induced lactic acidosis is insignificant in these patients, and it does not correlate with plasma metformin concentration (27, 29–31). Only other comorbidities, such as renal failure, etc, can increase the risk of lactic acidosis. Should metformin treatment be withdrawn or continued in heart failure patients, it must be determined on individual basis. Blood glucose concentration must be measured in all the patients before cardiac surgery. If it exceeds 7 mmol/L, treatment with insulin should be initiated perioperatively. In cases of blood glucose levels within reference limits, the glucose tolerance test should be performed to detect and treat unrecognized cases of diabetes (38).

Some authors suggest withdrawing metformin

treatment 48 hours before surgery (34, 39, 40); others, on the contrary, believe that metformin withdrawal can impair glycemic control during the preoperative period (41). Recent studies have showed that treatment with metformin is a good option and this drug can be used safely until surgery (36). The British National Formulary recommends withdrawing metformin ingestion 48 hours before surgery and renewing its intake only in patients without renal insufficiency, and counsels the usage of insulin for the control of hyperglycemia (16).

### Conclusions

A large body of evidence supports the opinion that treatment with metformin does not have any impact on the rate of postoperative lactic acidosis in patients without comorbidities. In every case of preoperative metformin administration, benefits and potential risks should be reevaluated. Impaired renal function, plasma lactate concentration, comorbidities, and contraindications to the treatment with metformin should be taken into account. At present, there are no clear guidelines for perioperative administration of metformin. On the other hand, there is a lack of prospective randomized trials showing that metformin is a safe drug for the use in the perioperative period, and this should be the object of further investigations.

## Metformino vartojimas širdies chirurgijoje perioperaciniu laikotarpiu

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**Raktažodžiai:** metforminas, laktatacidozė, cukrinis diabetas, širdies chirurgija.

**Santrauka.** Metformino hidrochloridas – tai geriamasis hipoglikemizuojamasis vaistas 2 tipo cukriniam diabetui gydyti. Biguanidas vartojamas Europoje nuo 1957 m., t. y. daugiau kaip 50 metų. Viena pavojingiausių komplikacijų, vartojant šį vaistą, laktatacidozė. Tai reta, tačiau potencialiai mirtina metabolinė būklė, pasireiškianti atsiradus audinių hipoksijai ir hipoperfuzijai, mirštamumas nuo jos, įvairių šaltinių duomenimis, 50 proc. Laktatacidozė apibūdinama laktatų padidėjimu serume (>5 mmol/l ar >45 mg/dl), sumažėjusiu kraujo pH (<7,35) ir elektrolitų disbalansu su padidėjusiu anijoniniu tarpu. Tikras metformino sukeltos laktatacidozės dažnis tiksliai nežinomas. Remiantis paskelbtų tyrimų duomenimis, laktatacidozės dažnis yra 2–9 atvejai iš 100 000. Tačiau dažniausiai aprašyti laktatacidozės atvejai nustatyti pacientams, sergantiems sunkia ūmine gretutine liga: inkstų funkcijos nepakankamumu, kuris ir pats savaime gali sukelti laktatacidozę. Šiuo metu nėra standartizuotų metformino vartojimo rekomendacijų, o literatūroje paskelbti duomenys yra prieštaringi. Vieni autoriai siūlo metformino nevartoti prieš numatomą didelės apimties operaciją, kiti autoriai teigia, kad metforminas kontraindikuotinas esant daugeliui lėtinių ligų: širdies ir kraujagyslių, inkstų, kepenų, kvėpavimo funkcijos nepakankamumui, nes jų metu susidaro sąlygos rasti audinių hipoksijai ir laktatacidozei. Šiame straipsnyje apžvelgiami įvairių autorių tyrimai, kuriuose nagrinėjamas metformino sąlygotos laktatacidozės dažnis perioperaciniu laikotarpiu bei tyrėjų pateikiamos rekomendacijos.

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