

## A Rare Side Effect of Metformin: Metformin-Induced Hepatotoxicity

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**Abstract:** Metformin is an oral hypoglycemic agent that is commonly used in the treatment of type 2 diabetes mellitus. While metformin-associated metabolic acidosis is a widely recognized side effect of this drug, metformin-induced hepatotoxicity has been rarely reported in the literature. We present herein the case of a 52-year-old male in whom metformin-associated lactic acidosis and metformin-induced hepatotoxicity developed.

**Key Words:** Metformin, metformin-associated lactic acidosis, hepatotoxicity, side effect

### Metforminin Nadir Yan Etkisi: Metforminin İndüklediği Hepatotoksisite

**Özet:** Metformin, tip 2 diabetes mellitus tedavisinde sık kullanılan bir oral hipoglisemik ajandır. Her ne kadar, metformin ilişkili laktik asidoz, bu ilacın iyi bilinen bir yan etkisi iken, metforminin yol açtığı hepatotoksisite literatürde nadiren bildirilmiştir. Metformin ilişkili laktik asidoz ve metforminin yol açtığı hepatotoksisite geliştiren 52 yaşındaki erkek vaka sunulmaktadır.

**Anahtar Sözcükler:** Metformin, metformin ile ilişkili laktik asidoz, hepatotoksisite, yan etki.

### Introduction

Metformin is the current biguanide of choice for the treatment of type 2 diabetes mellitus. Since metformin has an increasing spectrum of use, physicians are more likely to encounter its potential toxic effects. Here, a case of new onset metabolic acidosis and hepatic failure after initiation of metformin therapy is reported. This case report aims to emphasize the potentially increasing frequency of toxic effects of metformin.

### Case Report

A 52-year-old male was presented to the emergency department with a 10-day history of weakness, decreased exercise capacity, and fever. The day before presentation to the hospital, nausea and vomiting had developed. Diabetes mellitus and hypertension were diagnosed two weeks previously; metformin (850 mg, once a day), verapamil (240 mg, once a day), and acetylsalicylic acid (100 mg, once a day) had been initiated. Serum kidney function tests were within normal limits at this stage.

On admission, the patient had blood pressure of 124/61 mmHg, pulse 89 beats per minute, respiratory rate 32 breaths per minute, and body temperature 36.2 °C. There was no significant finding in the physical examination. Initial blood tests revealed blood urea nitrogen (BUN) 114 mg/dl, creatinine 2.84 mg/dl, sodium 132 mEq/L, potassium 6.15 mEq/L, chloride 94 mEq/L, glucose 114 mg/dl, aspartate aminotransferase 1843 IU/L, alanine aminotransferase 1469 IU/L, total bilirubin 2.76 mg/dl, direct bilirubin 1.43 mg/dl, and blood lactate 13.3 mmol/L. Blood salicylate level was within the therapeutic range. Complete blood count revealed leukocytosis (white blood cells 39,000  $\mu$ L), with a normal hematocrit and platelet count. Arterial blood gas showed metabolic acidosis with wide anion gap (pH 7.24, HCO<sub>3</sub> 8.4 mmol/L, base deficit 16.3 mmol/L, anion gap 29.4). While urinalysis was negative for ketone, leukocyte, and

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glucose, it was positive for protein (150 mg/dl). Chest X-ray displayed increased cardiothoracic ratio without infiltration.

Sixty mEq sodium bicarbonate and regular insulin with 5% dextrose was administered for acidosis and hyperkalemia. Metabolic acidosis and hyperkalemia improved with initial treatment and 3000 cc of intravenous saline administration. The patient was admitted to the intensive care unit with a diagnosis of metformin-induced hepatotoxicity, metformin-associated metabolic acidosis (MALA), and suspicion of sepsis. Metformin was discontinued; ampicillin sulbactam (1 g qid) and ciprofloxacin (500 mg bid) were initiated. Blood and urine cultures and serologic tests, including anti-hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, and anti-hepatitis C, were all negative. The symptoms and abnormal laboratory tests of the patient gradually normalized with supportive treatment. Ten days after his admission, he was discharged with a slight elevation in liver enzyme.

## Discussion

Metformin is a biguanide commonly used in type 2 diabetes and is considered to be a safe drug with minimal side effects. The antihyperglycemic effect of metformin is caused by a decrease in hepatic glucose production, a reduction in intestinal glucose absorption, an increase in insulin sensitivity and an elevation in peripheral glucose uptake and utilization. The results of the UK Prospective Diabetes Study indicated that metformin treatment was associated with a reduction in total mortality compared to other anti-hyperglycemic treatments and the recommended treatment of choice for overweight type 2 diabetic patients (1). Metformin is considered a prophylactic agent to prevent or delay development of diabetes in patients with impaired glucose tolerance (2). Furthermore, women with polycystic ovary syndrome are increasingly being treated with metformin for the purpose of reducing symptoms of hyperandrogenism and promoting fertility (3).

Lactic acidosis is a rare but well-known side effect of metformin. The estimated incidence of MALA is 0.03 per 1000 patient-years with a high (about 50%) mortality

rate (4,5). MALA occurs in patients with contraindications to the drug, such as renal dysfunction, liver diseases, alcoholism, and cardiopulmonary diseases. Clinical presentations of MALA are nonspecific and it manifests with nausea, vomiting, anorexia, epigastric pain, watery diarrhea, somnolence, lethargy, hyperpnea and thirst. Hypotension, hypothermia, myocardial infarction, cardiac dysrhythmias including ventricular fibrillation, asystole, and bradycardia, and respiratory failure have been reported as well (6,7).

Metformin-associated hepatotoxicity is very rare and few cases have been reported in the literature (8-10). These patients are presented with nausea, vomiting, weakness, jaundice with marked elevations in serum liver transaminases and intrahepatic cholestasis after initiation of metformin therapy. Pathophysiology of metformin-induced hepatotoxicity is unclear. However, it seems that acute hepatitis is caused by an idiosyncratic adverse reaction to metformin. These cases suggest that metformin can induce acute portal and parenchymal inflammation. There has been no reported specific treatment of metformin-associated hepatotoxicity. After discontinuation of metformin, the liver enzymes return to normal values within a few weeks.

Our case demonstrated the clinical and laboratory findings of metformin-induced hepatotoxicity and MALA. It is highly likely that MALA and hepatotoxicity both contributed to clinical deterioration. In our institution, the level of metformin could not be measured, but other potential causes of wide anion gap metabolic acidosis were not considered in our patient since acute onset symptoms developed immediately after initiation of metformin. Overdose of acetylsalicylic acid might have caused wide anion gap metabolic acidosis, but blood salicylate level was found within therapeutic range in our patient. Although the mechanism causing MALA is not clear, we believe that idiosyncratic hepatotoxicity triggered MALA.

In conclusion, physicians may encounter metformin-induced hepatotoxicity and MALA more frequently in the future due to increasing prescription of metformin. Metformin should be considered as a cause in patients presenting with wide anion gap metabolic acidosis and hepatic failure after initiation of metformin.

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