

# Metformin-induced mixed hepatocellular and cholestatic hepatic injury: case report and literature review

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**Introduction:** Metformin is a first-line drug choice for the treatment of type 2 diabetes mellitus (DM-2). Metformin-induced hepatotoxicity has rarely been reported. We report on a case of metformin-induced mixed hepatocellular and cholestatic liver injury in an elderly patient with DM-2 as well as review and summarize case reports of metformin hepatotoxicity available in English on the PubMed database.

**Case:** After receiving metformin 850 mg/day for 2 weeks, a 78-year-old male presented with a 10-day history of abdominal pain, vomiting, diarrhea, and jaundice. Laboratory analysis showed severe hepatocellular and cholestatic hepatic injury. Other causes for acute liver injury were ruled out. Discontinuation of metformin treatment led to significant subjective improvement after 1 week, and all hepatic abnormalities resolved by 2 months.

**Conclusion:** Metformin is an important drug for the treatment of DM-2, which is also used for treatment of patients with fatty liver. It can, however, induce hepatocellular and cholestatic hepatic injury; both physicians and patients should be aware of this potential side effect.

**Keywords:** metformin, hepatocellular liver injury, cholestasis, hepatotoxicity

## Introduction

Metformin is the current biguanide of choice for the treatment of type 2 diabetes mellitus (DM-2).<sup>1</sup> Studies have shown that metformin ameliorates hyperglycemia without stimulating insulin secretion, weight gain, or hypoglycemia.<sup>2</sup> A large-scale study found that metformin reduced all-cause mortality in obese patients with DM-2.<sup>3</sup>

Metformin has a multifactorial mechanism of action, but acts primarily by improving insulin sensitivity, with a concomitant decrease in hepatic glucose production and an increase in glucose transport across the skeletal muscle membrane.<sup>4,5</sup> Despite its clinical efficacy, metformin has been associated with several adverse effects. These are primarily gastrointestinal in nature (diarrhea, nausea, vomiting, bloating, and flatulence), and with long-term use, reductions in serum folic acid and vitamin B12 levels have been reported.<sup>4</sup> Because of its interference with mitochondrial oxidative processes, its most significant, although rare, side effect is lactic acidosis in the context of significantly chronically decreased renal function.<sup>6</sup> Other oral antidiabetic agents, such as acarbose,<sup>7</sup> gliclazide,<sup>8</sup> and some of the thiazolidinediones (mainly troglitazone), have been implicated in liver toxicity.<sup>9</sup> In the case of metformin, hepatotoxicity has been only rarely reported.<sup>10,11</sup>

We report a case of acute hepatocellular and cholestatic jaundice due to metformin therapy and review the literature.

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## Case report

A 78-year-old Jewish male patient was hospitalized in our department with a 10-day history of fatigue, nausea, vomiting, diarrhea, anorexia, and abdominal pain. He had also had pruritus and jaundice for 8 days. DM-2 had been recently diagnosed and metformin 850 mg/day had been initiated 2 weeks before presentation to the hospital. The patient reported no alcohol use, smoking, previous liver disease, family history of liver diseases, blood transfusion, exposure to toxins, or cholelithiasis. One month before initiation of metformin treatment, the patient had been given a 13-day amoxicillin-clavulanate (Augmentin) treatment for acute parotitis. His past medical history was significant for hypertension, gout, hyperlipidemia, and diverticulosis. His other medications included aspirin (75 mg/day), pravastatin (20 mg/day), amlodipine (5 mg/day), atenolol (100 mg/day), candesartan (16 mg/day), and hydrochlorothiazide (12.5 mg/day).

On physical examination, the patient was alert, with prominent jaundice. No stigmata of chronic liver disease were present. There was no pedal edema or ascites. His weight was 82 kg, his height 172 cm, and his body mass index 27.7 kg/m<sup>2</sup>. The laboratory findings are summarized in Table 1. The level of lactic acid was normal. Creatinine, urea, and electrolytes were normal. The levels of glucose during hospitalization were between 120–180 mg/dL. Results of serologic tests were negative for the following: hepatitis B surface antigen; anti-hepatitis B core Immunoglobulin M (IgM); anti-hepatitis A virus IgM; anti-hepatitis C virus antibody; anti-Cytomegalovirus IgM; anti-Epstein–Barr virus IgM; anti-nuclear antibodies; anti-smooth-muscle antibodies; anti-mitochondrial antibodies; and anti-neutrophil cytoplasmic antibodies. Serum ferritin and ceruloplasmin levels were also normal. C-reactive protein level was 9.97 mg/L (normal range: 0–5 mg/L). Complete blood count was normal. An ultrasound and a computerized tomography (CT) scan of the abdomen revealed no abnormalities.

**Table 1** Laboratory test results

Test	Result	Normal values
Total bilirubin (mg/dL)	22.2	0.2–1
Direct bilirubin (mg/dL)	15.2	0–0.4
Alanine transaminase (U/L)	1050	<40
Aspartate aminotransferase (U/L)	496	<40
Alkaline phosphatase (U/L)	1001	30–350
γ-glutamyl transpeptidase (U/L)	1264	5–60
Lactate dehydrogenase (U/L)	377	60–255
Albumin (g/dL)	4.2	3.5–5
INR	0.98	0.8–1.2

**Abbreviation:** INR, international normalized ratio.

On admission, metformin and pravastatin were discontinued immediately. After 1 week, the patient described significant subjective improvement and the level of bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALKP), and γ-glutamyl transpeptidase (GGT) began to decline gradually. After 9 days of hospitalization, the patient's laboratory results were as follows: total bilirubin, 16.9 mg/dL; direct bilirubin, 12.4 mg/dL; ALT, 308 U/L; AST, 77 U/L; ALKP, 809 U/L; and GGT, 876 U/L. The patient was discharged for outpatient follow-up. Two months following discharge, all hepatobiliary laboratory abnormalities resolved. Thereafter, pravastatin therapy was readministered, and no changes in bilirubin, ALT, AST, ALKP, or GGT levels were observed.

## Discussion

This case report is a useful addition to the short list of literature describing metformin hepatotoxicity available so far. Dealing with a particular patient with diabetes and polypharmacy makes decisions regarding medication termination difficult. A few signs guided our decision to blame metformin for hepatotoxicity in this case. The patient was taking other medications, including pravastatin, for at least 1 year prior to the hepatotoxicity, without adverse sequelae. Furthermore, pravastatin was readministered following resolution of the hepatic abnormalities, without any changes in bilirubin or liver enzyme concentration. The patient's other medications included aspirin (75 mg/day), amlodipine (5 mg/day), atenolol (100 mg/day), candesartan (16 mg/day), and hydrochlorothiazide (12.5 mg/d). The patient took these medications for years without adverse sequelae. In addition, liver enzymes and bilirubin returned to normal values after metformin was stopped and despite continuation of the other medications. However, exposure to amoxicillin-clavulanate had occurred 1 month prior to the patient presenting at our hospital. Amoxicillin-clavulanate-associated liver injury has been extensively reported in the literature.<sup>12–14</sup> A recent report from England assessed the incidence of amoxicillin-clavulanate-induced liver injury at 9.91 cases to 100,000 prescriptions.<sup>14</sup> In another report, from Spain, a mixed cholestatic-hepatocellular pattern of liver injury was associated with older age; the mean time lapse between therapy initiation and jaundice onset was 16 days.<sup>13</sup> In an attempt to determine the likely cause for acute liver injury in this case – ie, metformin or amoxicillin-clavulanate – we used the Maria and Victorino scale.<sup>14</sup> This clinical scale is based on (1) the temporal relationship between treatment initiation and the onset of the clinical picture; (2) the exclusion of alternative causes for liver

**Table 2** Case reports published in English with full text on the PubMed database

Case report (reference)	Age (years), gender	Type of injury	Time to Dx (weeks) <sup>a</sup>	Bilirubin <sup>b</sup>	ALT <sup>b</sup>	AST <sup>b</sup>	ALKP <sup>b</sup>	Resolution <sup>c</sup>
6	67, F	Hepatitis	6	4.8	905	1,152	121	4 months
10	52, F	Mixed	4	14.4	651	583	500	1 month
11	64, M	Cholestasis	5	21.3	289	214	994	3 months
17	68, M	Cholestasis	4	NA	NA	NA	NA	NA
18	73, F	Mixed	3	6.5	772	689	635	3 weeks
19	61, M	Hepatitis	2	1.8	571	623	143	2 months

**Notes:** <sup>a</sup>The time from beginning metformin therapy until the diagnosis was made. <sup>b</sup>Maximal values that were reported. The values of bilirubin are in mg/dL, and those of ALT, AST, and ALKP are in U/L. <sup>c</sup>The time from stopping metformin until complete resolution of clinical and laboratory abnormalities.

**Abbreviations:** ALKP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; Dx, diagnosis; F, female; M, male; NA, not available.

injury; (3) extrahepatic manifestations; (4) re-challenging of outcomes; and (5) previous reported cases in the literature. In the present case, amoxicillin-clavulanate scored only 8 points (unlikely), while metformin scored 12 points (possible), thus implicating metformin as the cause for liver injury rather than amoxicillin-clavulanate. Moreover, using the Naranjo adverse drug reaction probability scale – which consists of ten questions that are answered with either “yes,” “no,” or “do not know,” with different point values (–1, 0, +1, or +2) assigned to each answer – the probability that the symptoms of hepatotoxicity were an adverse drug reaction of metformin was 5 (probable).<sup>15</sup> Therefore, metformin was considered to be the offending medication. Re-challenge was not performed, as it was considered to be inappropriate.

Because metformin is not metabolized in the liver, it has been considered safe from a hepatic standpoint;<sup>16</sup> however, metformin hepatotoxicity has rarely been reported. Possible mechanisms of injury are direct, idiosyncratic, or a drug–drug interaction<sup>11</sup> leading to acute hepatocellular and/or cholestatic jaundice.

We searched the PubMed database for English-language publications on metformin hepatotoxicity and found six reports (Table 2): two cases of acute hepatitis,<sup>6,19</sup> two cases of cholestasis,<sup>11,17</sup> and two cases of mixed-type (hepatocellular and cholestatic) injury.<sup>10,18</sup> In all cases, as in our case report, after discontinuation of metformin therapy, the patients' signs and symptoms resolved and the liver enzymes normalized, except for a persistently increased level of alkaline phosphatase in one case,<sup>17</sup> which was considered likely related to a prolonged cholestatic effect of metformin. No specific treatments were given to these patients. Liver biopsy was performed in three cases, and re-challenge in one case.<sup>6,10,11,17</sup>

The patient we have described represents the third case report in the literature of mixed hepatocellular and cholestatic liver injury. Discontinuation of metformin treatment led to complete resolution of the patient's signs and symptoms as well as normalization of liver enzymes and bilirubin after 2 months.

## Conclusion

Metformin can induce hepatic injury (hepatocellular and/or cholestatic), and both physicians and patients should be aware of this potential side effect.

## Disclosure

The authors report no conflicts of interest in this work.

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