BIOMEDICINSKA ISTRAŽIVANJA
2025;16(2):1–6

UDK: 615.252:615.035
DOI: 10.59137/BII202502519B

Review

Metformin-associated hepatotoxicity: a literature review

Goran Bokan[1-3], Zoran Mavija[1,2]

[1]University Clinical Centre of the Republic of Srpska, Internal Medicine Clinic, Department of Gastroenterology and Hepatology, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

[2]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

[3]University of East Sarajevo, Faculty of Medicine Foča, Foča, Republic of Srpska, Bosnia and Herzegovina

Primljen – Received: 21/06/2025
Prihvaćen – Accepted: 11/09/2025

Corresponding author:
Goran Bokan, MD, PhD
12 beba bb, 78 000 Banja Luka
bokan.goran@yahoo.com

Summary

Metformin (dimethyl biguanide) is an oral antidiabetic agent and one of the most commonly prescribed medications in endocrinology. In addition to its primary use in treating type 2 diabetes, it has a broader range of indications and is generally considered to have a favorable safety profile. The most common side effects are gastrointestinal, including nausea, vomiting, diarrhea, abdominal pain, and bloating. Although rare, cases of severe liver injury attributed to metformin have been reported. This paper provides a review of the existing literature on metformin-induced hepatotoxicity.

Key words: DILI, hepatotoxicity, RUCAM, metformin

Introduction

The term hepatotoxicity is increasingly encountered in clinical practice. From a clinical perspective, particular attention is given to drug-induced liver injury (DILI) and herb-induced liver injury (HILI). DILI encompasses liver injuries not only from medications but also from dietary supplements and nutrients [1].

The global incidence of hepatotoxicity varies, with the highest rates reported in Asian countries—likely due to the widespread use of traditional medicine. In Europe, the highest incidence was recorded in Iceland, with almost 20 cases per 100,000 inhabitants [2, 3].

Hepatotoxicity can be explained by two main mechanisms: the idiosyncratic (dose-independent) type, which usually manifests with a delayed onset, and the intrinsic (dose-dependent)

type, which is predictable and typically occurs when the drug is taken in doses higher than recommended [4, 5].

To consider DILI a potential diagnosis, it is crucial to obtain a detailed medical history, including data on past and current illnesses and a precise list of all medications and dietary supplements used. Diagnosis is primarily established by excluding other possible causes using laboratory and imaging methods.

Initial laboratory testing, especially of liver enzymes, helps to differentiate three types of liver injury: hepatocellular, cholestatic, or mixed [6, 7]. The ratio (R) between ALT and ALP levels aids in this classification: if $R > 5$, the pattern is hepatocellular; if $R < 2$, it suggests cholestatic injury, and an R value between 2 and 5 indicates a mixed pattern of liver injury [8].

Following laboratory assessment, testing for hepatotropic viruses, as well as determining the titer of autoantibodies and immunoglobulin levels, is performed. Imaging techniques support the diagnosis, and if necessary, a liver biopsy with histopathological evaluation can be performed [9, 10]. After these steps, suspicion of DILI can be further refined using the Roussel Uclaf Causality Assessment Method (RUCAM), which stratifies the probability that a drug caused the liver injury. RUCAM scores range from -3 to +14 and classify causality as excluded, unlikely, possible, probable, or highly probable [11].

Metformin is a first-line therapy for insulin resistance and type 2 diabetes mellitus and is one of the most commonly used medications in endocrinology. Although gastrointestinal intolerance is common, metformin-associated hepatotoxicity is considered rare [12, 13].

Methods

Literature Search

This study was conducted as a literature review aimed at identifying documented clinical cases of metformin-associated liver injury. A comprehensive literature search was conducted using PubMed, Scopus, and Embase databases. The keywords and phrases used included: "metformin," "hepatotoxicity," "drug-induced liver injury," "metformin-induced liver injury," "DILI," "hepatitis," and "case report." The search covered all publications available up to the date of the investigation.

Inclusion and Exclusion Criteria

All clinical cases, case series, and review articles that clearly documented liver injury suspected to be associated with metformin use were included. Articles not published in English were excluded, as well as those in which the cause of liver injury was clearly attributable to other etiologies (e.g., viral hepatitis, alcoholism, autoimmune liver diseases, or other conditions).

Data Collection

From each included paper, the following data were extracted: patient's age and sex, type of liver injury (hepatocellular, cholestatic, or mixed), time from the start of therapy to the onset of symptoms and diagnosis, maximum laboratory values (bilirubin, AST, ALT, ALP), and the time required for complete recovery and normalization of liver enzymes.

The causality between metformin and liver injury was assessed using standardized clinical criteria. The pattern of liver injury was classified according to the RUCAM scoring system.

Results

Through a literature search, approximately 20 documented cases of hepatotoxicity directly or synergistically associated with metformin use were identified. In all cases, mild to moderate liver injury was observed. None of the reported cases required liver transplantation

Table 1. Documented cases of metformin-associated hepatotoxicity from the literature review

References number	Age, sex	Liver lesion type	Time to diagnose	Bilirubin (mg/dl)	ALT (u/l)	AST (u/l)	ALP (u/l)	Recovery
11. 1972-2011 (10 CASES)	68±10, 5 M, 5 F	5 mixed and 5 cholestatic	3.2±1.3 weeks	7.6±6.9	677±600	667±577	406±302	2.6±1.1 months
12.	67, F	hepatocellular	6 weeks	4.8	905	1152	121	4 months
13.	52, F	mixed	4 weeks	14.4	651	583	500	1 month
14.	64, M	cholestatic	5 weeks	21.3	289	214	994	3 months
15.	68, M	cholestatic	4 weeks	Unknown	Unknown	Unknown	Unknown	Unknown
16.	73, F	mixed	3 weeks	6.5	772	689	635	3 months
17.	61, M	hepatocellular	2 weeks	1.8	571	623	143	2 months
18.	61, M	mixed	6 weeks	2.9	861	290	622	2 months
19.	78, M	mixed	2 weeks	22.2	1050	496	1001	2 months

or resulted in a fatal outcome. Complete recovery and normalization of liver enzymes were noted in all patients, typically within a few weeks to several months after discontinuation of the suspected drug.

Detailed findings from the reviewed cases are summarized in Table 1. Laboratory values varied significantly.

Mallari et al. [11] conducted a literature review covering the period from 1972 to 2011 and identified 10 cases with an even sex distribution. Notably, no cases of hepatocellular-type liver injury were recorded in that cohort. On average, it took approximately one month to establish the diagnosis, while full recovery occurred within two and a half to four months after discontinuation of the suspected agent. The same authors also presented a case of potential synergistic hepatotoxicity involving metformin and statins. The patient, a 48-year-old man, exhibited a hepatocellular injury pattern. Diagnosis was made two weeks after the onset of symptoms, and complete recovery was achieved within one month after drug withdrawal.

Deutsch et al. [12] reported the case of a 67-year-old woman with hepatocellular injury. Diagnosis was established within six weeks, and full recovery occurred four months later. Babich et al. [13] described the 52-year-old patient with acute hepatitis and a mixed pattern of liver injury. Diagnosis was confirmed four weeks after symptom onset, with liver enzymes returning to normal within one month.

Desilets et al. [14] reported the case of cholestatic jaundice in the 64-year-old patient, diagnosed five weeks after symptom onset. Recovery occurred within three months. Nammour et al. [15] presented the case of the 68-year-old man with possible cholestatic hepatotoxicity; however, data on laboratory values and recovery duration were not available.

Kutoh [16] described the 73-year-old man with a mixed pattern of liver injury, diagnosed after three weeks, who achieved complete recovery after three months. Cone et al. [17] reported hepatocellular injury in the 61-year-old man, diagnosed two weeks after symptom onset, with full recovery after two months. Miralles Linares et al. [18] described the 61-year-old man with the mixed pattern of liver injury, diagnosed after six weeks, who recovered within two months. Saadi et al. [19] reported the 78-year-old patient with the mixed pattern of liver injury, diagnosed two weeks after symptom onset, who recovered after two months.

Discussion

Due to the growing awareness of DILI and related concepts, hepatotoxicity has become increasingly relevant in everyday clinical practice. With the continuous expansion of the pharmaceutical market, adverse drug reactions, including hepatotoxicity, are being reported with increasing frequency.

Our analysis of documented cases of metformin-induced hepatotoxicity suggests that the majority of cases represent idiosyncratic reactions. This type of liver injury is typically unpredictable, dose-independent, and characterized by a latency period between drug initiation and symptom onset. These findings are consistent with the reviewed cases, where most diagnoses were made several weeks after therapy initiation.

Although the precise pathophysiological mechanisms remain unclear, idiosyncratic reactions are believed to involve genetic factors that influence drug metabolism or modulate the immune response, indicating a complex interaction of patient-specific characteristics.

The use of the RUCAM method is essential for objectively assessing the causal relationship between metformin and liver injury. By applying RUCAM criteria to the reviewed cases, the combination of factors—such as temporal association, improvement after drug discontinuation, and exclusion of alternative diagnoses (e.g., viral hepatitis, alcohol-related liver disease)—supports a classification of causality as "probable" to "highly probable." This formalized assessment enhances the credibility of the reported cases and provides a standardized framework for evaluating suspected DILI.

The potential for synergistic hepatotoxicity is also noteworthy. In routine clinical practice, patients receiving metformin frequently have multiple comorbidities and are often prescribed additional medications—such as statins or antihypertensives—that are also associated with hepatotoxic potential. Drug interactions and polypharmacy may contribute to liver injury in ways that are difficult to disentangle.

In our own clinical experience, we have observed mild elevations of hepatocellular and cholestatic enzymes in patients receiving metformin alongside other medications. In such cases, determining whether enzyme elevation was attributable solely to metformin or due to a synergistic interaction was often challenging. This underscores the importance of detailed medication reconciliation and vigilant monitoring in patients undergoing polypharmacy, to correctly identify the true cause of liver enzyme abnormalities.

Despite the reported cases, all available evidence suggests that metformin remains a drug with a favorable hepatic safety profile. Its hepatotoxic potential appears to be rare, mild to moderate in severity, and reversible upon drug discontinuation. No reported case required liver transplantation or resulted in a fatal outcome.

Conclusion

The available evidence confirms that metformin has a favorable hepatic safety profile. Reported cases of hepatotoxicity are rare, typically mild to moderate, and reversible upon discontinuation. Most injuries appear to be idiosyncratic, with recovery occurring within weeks to months.

Use of standardized assessment tools such as RUCAM is essential for accurate diagnosis. Clinical vigilance is advised, especially in patients on combination therapy with other potentially hepatotoxic drugs.

Funding source. The authors received no specific funding for this work.

Ethical approval. This article does not contain any studies with human participants performed by any of the authors.

Conflicts of interest. The authors declare no conflict of interest.

*The motivation for this work arose from our clinical practice, where we occasionally observed mild, transient elevations of liver enzymes in patients on metformin therapy. Although these cases did not meet the criteria for a detailed case analysis, they served as the impetus to conduct a systematic review of the available literature on metformin-associated hepatotoxicity.

***Abbreviations:** DILI (Drug-Induced Liver Injury), HILI (Herb-Induced Liver Injury), ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), ALP (Alkaline Phosphatase), RUCAM (Roussel Uclaf Causality Assessment Method).

References:

1. Bokan G, Malešević N, Licata A, Mavija Z. Drug Induced Liver Injury (DILI) and Non AlcoholicFatty Liver Disease (NAFLD). European Journal of Medical and Health Sciences 2020;2(4).
2. Fontana RJ, Bjornsson ES, Reddy R, Andrade RJ. The Evolving Profile of Idiosyncratic Drug-Induced Liver Injury. Clin Gastroenterol Hepatol 2023;21(8):2088–99.
3. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. Am J Gastroenterol 2021;116(5):878–98.
4. Hosack T, Damry D, Biswas S. Drug-induced liver injury: a comprehensive review. Therap Adv Gastroenterol 2023;16:17562848231163410.
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol 2019;70(6):1222–61.
6. Allison R, Guraka A, Shawa IT, Tripathi G, Moritz W, Kermanizadeh A. Drug induced liver injury - a 2023 update. J Toxicol Environ Health B Crit Rev 2023;26(8):442–67.
7. Clinton JW, Kiparizoska S, Aggarwal S, Woo S, Davis W, Lewis JH. Drug-Induced Liver Injury: Highlights and Controversies in the Recent Literature. Drug Saf 2021;44(11):1125–49.
8. Hayashi PH, Lucena MI, Fontana RJ, Bjornsson ES, Aithal GP, Barnhart H, et al. A revised electronic version of RUCAM for the diagnosis of DILI. Hepatology 2022;76(1):18–31.
9. Saluja M, Pareek KK, Swami YK. Study of Diversity of Metformin Related Gastrointestinal Side Effects. J Assoc Physicians India 2020;68(8):36–8.
10. Teschke R. Treatment of Drug-Induced Liver Injury. Biomedicines 2022;11(1):15.
11. Mallari A, Gorospe E, Gutman J. Metformin-Induced Hepatotoxicity: Case Report and Review of Literature. American Journal of Gastroenterology 2011;106(Suppl 2):S302.
12. Deutsch M, Kountouras D, Dourakis SP. Metformin hepatotoxicity. Ann Intern Med 2004;140(5):W25.
13. Babich MM, Pike I, Shiffman ML. Metformin-induced acute hepatitis. Am J Med 1998;104:490–2.
14. Desilets DJ, Shorr AF, Moran KA, Holtzmuller KC. Cholestatic jaundice associated with the use of metformin. Am J Gastroenterol 2001;96:2257–8.
15. Nammour FE, Fayad NF, Peikin SR. Metformin-induced cholestatic hepatitis. Endocr Pract 2003;9(4):307–9.
16. Kutoh E. Possible metformin-induced hepatotoxicity. Am J Geriatr Pharmacother 2005;3(4):270–3.
17. Cone CJ, Bachyrycz AM, Murata GH. Hepatotoxicity associated with metformin therapy in treatment of type 2 diabetes mellitus with nonalcoholic fatty liver disease. Ann Pharmacother 2010;44(10):1655–9.
18. Miralles-Linares F, Puerta-Fernandez S, Bernal-Lopez MR, Tinahones FJ, Andrade RJ, Gomez-Huelgas R. Metformin-induced hepatotoxicity. Diabetes Care 2012;35(3):e21.
19. Saadi T, Waterman M, Yassin H, Baruch Y. Metformin-induced mixed hepatocellular and cholestatic hepatic injury: case report and literature review. Int J Gen Med 2013;6:703–6.

Hepatotoksičnost povezana sa metforminom: pregled literature

Goran Bokan[1-3], Zoran Mavija[1,2]

[1]Univerzitetski klinički centar Republike Srpske, Klinika za unutrašnje bolesti,
Odjeljenje za gastroenterologiju i hepatologiju, Banja Luka, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet u Banjoj Luci, Medicinski fakultet, Banja Luka, Republika Srpska, Bosna i Hercegovina

[3]Univerzitet u Istočnom Sarajevu, Medicinski fakultet Foča, Foča, Republika Srpska,
Bosna i Hercegovina

Metformin (dimetil bigvanid) je oralni antidijabetik i jedan od najčešće prepisivanih lijekova u endokrinologiji. Pored njegove primarne upotrebe u liječenju dijabetesa tipa 2, ima širi spektar indikacija i generalno se smatra da ima povoljan bezbjednosni profil. Najčešći neželjeni efekti su gastrointestinalni i uključuju mučninu, povraćanje, dijareju, bol u stomaku i nadimanje. Iako rijetko, zabilježeni su slučajevi teškog oštećenja jetre koji se pripisuju upotrebi metformina. Ovaj rad pruža pregled postojeće literature o hepatotoksičnosti izazvanoj metforminom.

Ključne riječi: DILI, hepatotoksičnost, RUCAM, metformin