



# Assessing liver function and its correlation with various anti-diabetic medications: a biomarker-driven analysis of the hepatorenal protection axis

Shaimaa Saleh Khudhur<sup>1</sup>, Noor Mohammed Abdulrahman<sup>2</sup>, Qutaiba A. Qasim<sup>3\*</sup>

<sup>1</sup>Department of Clinical Pharmacy, College of Pharmacy, Tikrit University, Tikrit 34001, Iraq

<sup>2</sup>Department of Clinical Pharmacy, College of Pharmacy, University of Basrah, Basrah, Iraq

<sup>3</sup>Clinical Laboratory Sciences Department, University of Basrah, Basrah, Iraq

## ARTICLE INFO

**Article Type:**  
Original

### Article History:

Received: 2 Mar. 2025

Revised: 4 Oct. 2025

Accepted: 22 Oct. 2025

ePublished: 4 Jan. 2026

### Keywords:

Liver function  
Liver functional tests  
Anti-diabetic medications  
Metformin  
SGLT-2 inhibitors  
DPP-4 inhibitors  
Sulfonylurea  
Chronic kidney disease  
Hepatorenal protection

## ABSTRACT

**Introduction:** Chronic renal failure and diabetes mellitus commonly coexist, with each disorder adversely affecting the other's development. Liver function had a significant role in metabolic regulation and drug metabolism, affecting both glycemic control and renal outcomes.

**Objectives:** This investigation aimed to investigate liver function and its relationship with various anti-diabetic medicines by a biomarker-driven approach to better identify hepatorenal protection.

**Patients and Methods:** This cross-sectional study, conducted from October 2024 to January 2025 in Basra Governorate, Iraq. This study analyzed 250 diabetic individuals to assess hepatic biomarker profiles through anti-diabetic regimens. Diabetic individuals were classified into five groups; those who administered metformin only, the engaged populations who exclusively used sulfonylurea and cases who were taking dipeptidyl peptidase-4 inhibitors (DPP-4i), SGLT-2i (sodium-glucose co-transporter 2 inhibitors), and combination therapy. In this study levels of alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and bilirubin were assessed.

**Results:** This study indicated that, values of the ALT, AST, ALP, and bilirubin in people on sulfonylurea were significantly higher in comparison with individuals who were under the treatments of metformin, DPP-4 inhibitors, SGLT-2 inhibitors, or mix therapies. Patients, who received metformin, DPP-4 inhibitor, SGLT-2 inhibitor, and combination therapy, in their turn, did not differ in downstream metabolites of the liver and their concentrations, as they all displayed similar values of these liver enzymes and bilirubin.

**Conclusion:** We found that the administration of sulfonylurea is highly correlated with the occurrence of a significantly high level of liver functions test (ALT, AST, ALP, and bilirubin) as compared to metformin, DPP-4 inhibitors, SGLT-2 inhibitors and combination therapies, which bore the same hepatic profile. Our results demonstrated that liver safety should be evaluated in the administration of anti-diabetic drugs and particularly in cases with preexisting liver problems or prone to liver toxicity.

### Implication for health policy/practice/research/medical education:

This cross-sectional study accentuates the importance of hepatic monitoring in diabetic individuals received sulfonylureas, since their association with elevated liver enzymes and bilirubin states a strengthened risk of subclinical hepatotoxicity compared to metformin, dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter 2 inhibitors (SGLT-2i), or combination therapies. For patients with pre-existing liver conditions, metabolic dysfunction-associated steatotic liver disease, or those requiring long-term therapy, prioritizing agents like SGLT-2 inhibitors or DPP-4i, which demonstrate comparable hepatic safety profiles, may mitigate liver-related risks.

**Please cite this paper as:** Khudhur SS, Abdulrahman NM, Qasim QA. Assessing liver function and its correlation with various anti-diabetic medications: a biomarker-driven analysis of the hepatorenal protection axis. J Nephropharmacol. 2027;16(2):e12766. DOI: 10.34172/npj.2026.12766.

## Introduction

Type 2 diabetes mellitus (T2DM) has been described as increased glucose concentration and then lack of insulin release (1). Metformin is a biguanide that has been listed on the WHO list of essential medicines with its 60 years of history being a key in T2DM management, leading to a significant reduction in T2DM incidence via diverse signaling pathway, mostly via the activation of AMPK which inhibits lipogenesis and enhances the metabolism of fatty acids in the liver and muscle (1,2). As new type of anti-diabetic drug, dipeptidyl peptidase-4 inhibitors (DPP-4i) are characterized by significant reduction in HbA1c and fasting blood sugar levels without hypoglycemia and weight gain (3,4).

Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) represent another innovative class demonstrating remarkable cardiovascular benefits, with studies showing lower risks of all-cause mortality and heart failure hospitalization (5), though they may increase the risk of genitourinary infections (6). Mixing medication therapies showed clinical significance results, with studies finding that co-administration of SGLT2 inhibitors and DPP-4 inhibitors has no additional safety concerns compared to each drug, monotherapy, despite enhancing therapeutic efficacy (3). Moreover, SGLT2 inhibitors reveal greater effectiveness in diminishing epicardial adipose tissue compared to other medications (7), emphasizing their multifold advantages beyond glycemic control.

Though, the administration of anti-diabetic medications is indispensable for glycemic control in T2DM; nevertheless, they carry some complications, principally on kidney and hepatic function, which needs careful monitoring. In this regard, metformin, though commonly prescribed as first-line therapy, has been associated with metformin-related lactic acidosis, predominantly in individuals with kidney disturbance, where impaired excretion leads to elevated serum lactate levels, across with mortality rate as high as 45% in severe cases (8,9). While earlier concerns about metformin's hepatotoxicity were disputed, case reports approved rare instances of mixed hepatocellular and cholestatic hepatic damage, often presenting with jaundice and elevated transaminases, which resolve following discontinuation (10,11). Recent studies demonstrated that renal complications of dipeptidyl peptidase 4 inhibitors remain controversial (12). Conversely, SGLT2 inhibitors present kidney protective properties in chronic renal failure cases and shortening hospitalization for heart failure by 48% (13,14). Previous studies found that, combination therapy strengthens renal failure risks; since, co-administration of metformin with SGLT2 inhibitors in progressed chronic renal failure aggravates lactic acidosis susceptibility while failing to diminish the increased risk of genitourinary infections accompanied by SGLT2 inhibitors (8,15). Additionally, liver metabolism further complicates polypharmacy, since cytochrome P450 2C19 interactions with metformin and

other medication disturb renal excretion pathways, which mediated by organic cation transporters by elevating intracellular drug accumulation (16). These findings emphasize on the importance of individualized dosing adjustments, principally in cases with kidney and liver dysfunction, where alternative therapies like insulin prove safer despite their risk profiles.

## Objectives

The objective of this study is to assess and compare hepatic function, as designated by alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and bilirubin, among diabetic individuals receiving various anti-diabetic agents. Our study also sought to detect the effect of DPP-4 inhibitors, metformin, sulfonylurea, SGLT-2 inhibitors, across with combination therapies on liver enzyme and bilirubin levels, to assess potential differences in hepatic safety profiles accompanied by these commonly prescribed therapies.

## Patients and Methods

### Study design and participants

The present study on 250 diabetic patients, characterized by a cross-sectional study design, was carried out within the geographical province of Basra Governorate, located in the Republic of Iraq. The temporal scope of this investigation spanned four months, beginning in October of the year 2024 to January of 2025.

### Inclusion and exclusion criteria

In this study, participants who older than 30 years with T2DM were eligible for inclusion, if they had a diabetic duration of at least three years, and had been receiving stable medication with one of the anti-diabetic treatments, containing metformin, DPP-4 inhibitors, SGLT-2 inhibitors, or mix therapy of these drugs for a minimum of six months. Furthermore, patients with a history of acute infection, and/ or hospitalization of the past three months were excluded from study. Participants included those who had chronic liver disease, CKD, were pregnant or lactating, or who used hepatotoxic or nephrotoxic medication were also excluded.

### Data collection

This research was based on a set of information gathered with the help of the combination of clinical records, laboratory tests, and interviews. The type of demographic variables acquired were the age, sex, body mass index (BMI), history with diabetes and hypertension as well as duration of diabetes. Data on the use of anti-diabetic drugs included in the study patients receiving monotherapies of metformin and sulfonylurea, DPP-4 inhibitors, SGLT-2 inhibitors and patients who used a combination of two or more of these types of anti-diabetic medications. Liver enzymes were assessed using ALT, AST, ALP, and bilirubin

that were also determined by lab analysis of the venous blood samples of the participants of the studies.

### Outcomes

The research study examines and compares the outcomes of different liver functional tests carried out on five different categories of patients undergoing treatment due to diabetes. The most significant comparison is of the concentration of the particular liver enzymes and substances, that is ALT, AST, ALP, and bilirubin. The effects of various options of medication regimens of anti-diabetic drugs on liver are assessed using these biomarkers. The five groups that will be under the investigation entail people using metformin by itself, individuals that are using the sulfonylurea drugs as a monotherapy, a group with exclusive DPP-4 inhibitors, a group with exclusive SGLT-2 inhibitors and lastly, a group of patients that is currently in progressive combination therapy where the patients are using a mixture of the above anti-diabetic drugs. It aims at ascertaining whether there are any variations in the case of liver performance, indicated by the ALT, AST, ALP, and the bilirubin, in the case of the five treatment techniques to be used in the management of diabetes.

### Data analysis

Data analysis was performed using IBM SPSS Statistics (version 27). Kolmogorov-Smirnov tests confirmed data normality. We used ANOVA to check whether liver enzyme and bilirubin levels differ among patients using different diabetes medications. Since there were several groups, we used a Scheffé post hoc test afterward to find which specific treatments caused the differences. Significance was set at  $P < 0.05$ .

### Results

In this study on 250 diabetic patients (123 men and 127 women), a range of anti-diabetic medications were administered to participants, with metformin being the most frequently used, prescribed to 60 individuals. Sulfonylureas were the next most common, taken by 50

participants, followed by SGLT-2i used by 45 participants and DPP-4i by 39 participants. Additionally, a mixed treatment regimen, involving combinations of these medications, was prescribed to 56 individuals. The statistical analysis revealed no significant differences in the distribution of key demographic and clinical characteristics, including sex, age, BMI, history of hypertension, and duration of diabetes mellitus, among diabetic patients receiving the various anti-diabetic medications (Table 1).

The analysis of the association between ALT levels and various anti-diabetic medications revealed notable differences among the treatment groups. Patients treated with sulfonylurea exhibited higher ALT levels than those receiving metformin, DPP-4 inhibitors, SGLT-2 inhibitors, or a combination of treatments, and this difference was found to be statistically significant. In contrast, ALT levels among patients using metformin, DPP-4 inhibitors, SGLT-2 inhibitors, and mixed treatment regimens were comparable, with no significant differences observed between these groups (Table 2).

The results defined that individuals who were treated with sulfonylurea demonstrated meaningfully elevated AST values compared to those on DPP-4 inhibitors, metformin, SGLT-2 inhibitors, or the combination of them. Conversely, AST serum concentration among cases receiving SGLT-2 inhibitors, metformin, DPP-4 inhibitors, and mixed therapies were quite similar, across with no substantial differences amongst these groups (Table 3).

Meanwhile, our analysis indicated that treatment by sulfonylurea was accompanied by strengthen ALP serum values than metformin, DPP-4 inhibitors and SGLT-2 inhibitors, or their combination therapy. Nonetheless, serum AST concentration, was similar among SGLT-2 inhibitor, metformin, DPP-4 inhibitor and combination regimen groups, along with no significant differences (Table 4).

The analysis of the correlation amid bilirubin levels and various anti-diabetic medications imply that individuals taking sulfonylurea had significantly higher bilirubin

**Table 1.** Demographic data distribution among different types of anti-diabetic medication users

| Demographic characteristics |                  | Anti-diabetic medications |      |                          |      |                    |      |                     |      |                           |      | P value |
|-----------------------------|------------------|---------------------------|------|--------------------------|------|--------------------|------|---------------------|------|---------------------------|------|---------|
|                             |                  | Metformin<br>(n = 60)     |      | Sulfonylurea<br>(n = 50) |      | DPP-4i<br>(n = 39) |      | SGLT-2i<br>(n = 45) |      | Mix treatment<br>(n = 56) |      |         |
|                             |                  | N                         | %    | N                        | %    | N                  | %    | N                   | %    | N                         | %    |         |
| Gender                      | Female (n = 127) | 29                        | 22.8 | 27                       | 21.3 | 21                 | 16.5 | 23                  | 18.1 | 27                        | 21.3 | 0.958*  |
|                             | Male (n = 123)   | 31                        | 25.2 | 23                       | 18.7 | 18                 | 14.6 | 22                  | 17.9 | 29                        | 23.6 |         |
| HTN                         | No (n = 108)     | 24                        | 22.2 | 27                       | 25   | 16                 | 14.8 | 22                  | 20.4 | 19                        | 17.6 | 0.262*  |
|                             | Yes (n = 142)    | 36                        | 25.3 | 23                       | 16.2 | 23                 | 16.2 | 23                  | 16.2 | 37                        | 26.1 |         |
| Variable                    |                  | Mean                      | SD   | Mean                     | SD   | Mean               | SD   | Mean                | SD   | Mean                      | SD   | P value |
| Age (year)                  |                  | 24.27                     | 8.05 | 54.46                    | 7.46 | 56.87              | 8.10 | 56.33               | 9.72 | 56.88                     | 9.32 | 0.317** |
| BMI (kg/m <sup>2</sup> )    |                  | 29.41                     | 4.17 | 28.83                    | 3.91 | 29.50              | 4.78 | 29.82               | 4.41 | 24.48                     | 4.39 | 0.533** |
| Diabetes time (year)        |                  | 9.33                      | 3.27 | 10.22                    | 3.71 | 9.54               | 3.64 | 10.38               | 3.72 | 10.45                     | 3.18 | 0.344** |

DPP-4i: Dipeptidyl Peptidase-4 inhibitor; SGLT-2i: Sodium-glucose cotransporter-2 inhibitor; HTN: Hypertension; SD: Standard deviation; BMI: Body mass index.

\*Chi-square, \*\*One-way ANOVA.

**Table 2.** The association of ALT level with anti-diabetic medications

| Anti-diabetic medications |               | ALT (IU/L)      |            | P value*  |
|---------------------------|---------------|-----------------|------------|-----------|
|                           |               | Mean            | SD         |           |
| Metformin (n = 60)        |               | 29.90           | 3.47       | 0.001     |
| Sulfonylurea (n = 50)     |               | 45.66           | 7.49       |           |
| DPP-4i (n = 39)           |               | 30.23           | 5.03       |           |
| SGLT-2i (n = 45)          |               | 30.25           | 4.33       |           |
| Mix treatment (n = 56)    |               | 30.41           | 4.71       |           |
| Anti-diabetic medications |               | Mean difference | Std. error | P value** |
| Metformin                 | Sulfonylurea  | 15.76           | 0.98       | <0.001    |
|                           | DPP-4i        | 0.32            | 1.05       | 0.999     |
|                           | SGLT-2i       | 0.34            | 1.01       | 0.998     |
|                           | Mix treatment | 0.50            | 0.95       | 0.991     |
| Sulfonylurea              | DPP-4i        | 15.43           | 1.09       | <0.001    |
|                           | SGLT-2i       | 14.41           | 1.00       | <0.001    |
|                           | Mix treatment | 15.25           | 1.08       | <0.001    |
| DPP-4i                    | SGLT-2i       | 0.01            | 1.12       | 0.999     |
|                           | Mix treatment | 0.17            | 1.07       | 0.999     |
| SGLT-2i                   | Mix treatment | 0.16            | 1.02       | 0.999     |

ALT: Alanine aminotransferase; DPP-4i: Dipeptidyl peptidase-4 inhibitor; SGLT-2i: Sodium-glucose cotransporter-2 inhibitor; SD: Standard deviation. \*One-way ANOVA, \*\*Post hoc Scheffe test.

**Table 3.** The association of AST level with anti-diabetic medications

| Anti-diabetic medications |               | AST (IU/L)      |            | P value*  |
|---------------------------|---------------|-----------------|------------|-----------|
|                           |               | Mean            | SD         |           |
| Metformin (n = 60)        |               | 28.55           | 4.31       | <0.001    |
| Sulfonylurea (n = 50)     |               | 43.32           | 5.58       |           |
| DPP-4i (n = 39)           |               | 27.76           | 4.45       |           |
| SGLT-2i (n = 45)          |               | 27.98           | 6.28       |           |
| Mix treatment (n = 56)    |               | 28.24           | 4.91       |           |
| Anti-diabetic medications |               | Mean difference | Std. error | P value** |
| Metformin                 | Sulfonylurea  | 14.76           | 0.98       | <0.001    |
|                           | DPP-4i        | 0.79            | 1.05       | 0.967     |
|                           | SGLT-2i       | 0.57            | 1.01       | 0.988     |
|                           | Mix treatment | 0.31            | 0.95       | 0.999     |
| Sulfonylurea              | DPP-4i        | 15.56           | 1.09       | <0.001    |
|                           | SGLT-2i       | 15.34           | 1.05       | <0.001    |
|                           | Mix treatment | 15.08           | 0.99       | <0.001    |
| DPP-4i                    | SGLT-2i       | 0.21            | 1.07       | 1.00      |
|                           | Mix treatment | 0.47            | 1.04       | 0.995     |
| SGLT-2i                   | Mix treatment | 0.26            | 1.02       | 0.999     |

AST: Aspartate transaminase; DPP-4i: Dipeptidyl peptidase-4 inhibitor; SGLT-2i: Sodium-glucose cotransporter-2 inhibitor; SD: Standard deviation. \*One-way ANOVA, \*\*Post hoc Scheffe test.

levels than those receiving SGLT-2 inhibitors, metformin, DPP-4 inhibitors, or combination therapies. Inversely, bilirubin level was comparable among cases treated with SGLT-2 inhibitors, metformin, DPP-4 inhibitors and mixed regimens, with no noteworthy differences distinguished among the groups (Table 5).

## Discussion

The findings of our investigation showed a prominent association amid the prescription of sulfonylurea to individuals diagnosed with type 2 diabetes mellitus and elevations in some liver enzymes and bilirubin. We also found that the administration of sulfonylurea drugs in this

group was associated with an observable increase in the concentration of ALT, AST, ALP, and bilirubin within their systems. These results indicted sulfonylurea-associated elevations in ALT, AST, ALP, and bilirubin across with previous case reports. Though a previous study by Susilawati et al suggested that sulfonylureas generally lack hepatotoxicity risks compared to other anti-diabetics (17), a case report study by Kamal et al revealed idiosyncratic liver injury patterns by glipizide induced ALT/AST elevations >3×ULN within weeks (18). Similarly, the study by Liu et al found that glibenclamide increased bilirubin (1.5–2.0 mg/dL) alongside transaminase spikes in animal models (19). Mechanistically, sulfonylureas

**Table 4.** The association of ALP level with anti-diabetic medications

| Anti-diabetic medications |               | ALP (IU/L)      |            | P value*  |
|---------------------------|---------------|-----------------|------------|-----------|
|                           |               | Mean            | SD         |           |
| Metformin (n = 60)        |               | 85.52           | 12.06      | <0.001    |
| Sulfonylurea (n = 50)     |               | 101.95          | 13.43      |           |
| DPP-4i (n = 39)           |               | 80.23           | 9.67       |           |
| SGLT-2i (n = 45)          |               | 78.55           | 11.08      |           |
| Mix treatment (n = 56)    |               | 86.93           | 13.18      |           |
| Anti-diabetic medications |               | Mean difference | Std. error | P value** |
| Metformin                 | Sulfonylurea  | 16.42           | 2.31       | <0.001    |
|                           | DPP-4i        | 5.28            | 2.49       | 0.345     |
|                           | SGLT-2i       | 6.97            | 2.38       | 0.078     |
|                           | Mix treatment | 1.41            | 2.25       | 0.983     |
| Sulfonylurea              | DPP-4i        | 21.71           | 2.58       | <0.001    |
|                           | SGLT-2i       | 23.40           | 2.48       | <0.001    |
|                           | Mix treatment | 15.01           | 2.35       | <0.001    |
| DPP-4i                    | SGLT-2i       | 1.68            | 2.65       | 0.982     |
|                           | Mix treatment | 0.47            | 1.04       | 0.995     |
| SGLT-2i                   | Mix treatment | 0.26            | 1.02       | 0.999     |

ALP: Alkaline phosphatase; DPP-4i: Dipeptidyl peptidase-4 inhibitor; SGLT-2i: Sodium-glucose cotransporter-2 inhibitor; SD: Standard deviation. \*One-way ANOVA, \*\*Post hoc Scheffe test.

**Table 5.** The association of bilirubin level with anti-diabetic medications

| Anti-diabetic medications |               | Bilirubin (mg/dL) |            | P value*  |
|---------------------------|---------------|-------------------|------------|-----------|
|                           |               | Mean              | SD         |           |
| Metformin (n = 60)        |               | 0.72              | 0.13       | <0.001    |
| Sulfonylurea (n = 50)     |               | 0.86              | 0.17       |           |
| DPP-4i (n = 39)           |               | 0.71              | 0.15       |           |
| SGLT-2i (n = 45)          |               | 0.67              | 0.11       |           |
| Mix treatment (n = 56)    |               | 0.73              | 0.16       |           |
| Anti-diabetic medications |               | Mean difference   | Std. error | P value** |
| Metformin                 | Sulfonylurea  | 0.12              | 0.028      | <0.001    |
|                           | DPP-4i        | 0.02              | 0.030      | 0.957     |
|                           | SGLT-2i       | 0.06              | 0.029      | 0.372     |
|                           | Mix treatment | 0.01              | 0.027      | 0.999     |
| Sulfonylurea              | DPP-4i        | 0.15              | 0.032      | <0.001    |
|                           | SGLT-2i       | 0.19              | 0.030      | <0.001    |
|                           | Mix treatment | 0.12              | 0.029      | 0.001     |
| DPP-4i                    | SGLT-2i       | 0.03              | 0.032      | 0.874     |
|                           | Mix treatment | 0.02              | 0.031      | 0.934     |
| SGLT-2i                   | Mix treatment | 0.06              | 0.030      | 0.333     |

DPP-4i: Dipeptidyl peptidase-4 inhibitor; SGLT-2i: Sodium-glucose cotransporter-2 inhibitor; SD: Standard deviation. \*One-way ANOVA, \*\*Post hoc Scheffe test.

may impair hepatic mitochondrial function by ATP-sensitive potassium channel inhibition, exacerbating oxidative stress and cholestasis (19,20), though these effects appear to be dose-dependent and reversible upon discontinuation (18). However, population studies found conflicting results. A prior meta-analysis by Hu et al found no significant bilirubin changes with sulfonylurea monotherapy (21), while others reported transient ALP elevations (15–20% above baseline) without clinical

significance (17). This discrepancy may arise from genetic variability in cytochrome P450 2C9-mediated sulfonylurea metabolism (19), as slow metabolizers exhibit 40–60% higher drug accumulation (17). Notably, combination therapy strengthens risks; since, concurrent metformin-sulfonylurea administration is associated with 2.3-fold higher serum ALT elevations compared to monotherapy (17,18), possibly due to OCT1 (organic cation transporter 1) transporter competition (17). Nonetheless, most of the

liver toxicity individuals disappear post-cessation of the responsible medication (18). Hence the 45% mortality risk associated with MALA in renal impairment imply the necessity of hepatic monitoring in comorbid cases (17,18). Thus, these mixed findings reminded that sulfonylurea hepatotoxicity remains a rare but clinically significant phenomenon necessitating personalized risk stratification.

The analysis of our data also reminded that cases on treatment by a variety of common diabetes medications, comprising SGLT-2 inhibitors, metformin, DPP-4 inhibitors, or the in cases receiving mixed regimens, the liver enzyme levels are comparable with healthy persons. Furthermore, our results showed that bilirubin concentrations were also within the normal range for all treatment groups studied. Critically, statistical analysis showed that there were no statistically significant differences in the liver enzymes or bilirubin levels among the metformin-treated group, the DPP-4 inhibitor-treated group, the SGLT-2 inhibitor-treated group, and the group receiving mixed treatment regimens. Our observation that different diabetes medications demonstrate comparable effects on liver enzymes without statistical differences between treatment groups is consistent with several prior investigations. A systematic review by Zhang et al of sitagliptin, a DPP-4 inhibitor, revealed minimal impact on serum ALT and AST levels while showing improvement in gamma-glutamyl transpeptidase (GGT) levels in non-alcoholic fatty liver disease (NAFLD) patients (22). Similarly, our finding that DPP-4 inhibitor treatment resulted in normal range liver enzymes complements earlier work by Klitsunova et al who reported well-tolerated hepatic safety profiles with sitagliptin treatment in type 2 diabetes patients inadequately controlled on metformin monotherapy (23). Regarding SGLT-2 inhibitors, our results showed normal liver enzyme levels in treated patients, which both supports and contrasts with previous findings. In a previous study, Zhang et al found that empagliflozin can significantly reduce AST levels and improve metabolic parameters in NAFLD patients (24). However, this contrasts with a meta-analysis by Tang et al suggesting empagliflozin treatment may not significantly improve ALT or AST levels in non-alcoholic fatty liver disease (25). For metformin, our finding is generally consistent with prior research. The recent investigation by Jaszczka et al, who examined the effects of metformin in Zucker diabetic fatty rats, found only a tendency toward diminution in liver enzymes rather than statistically significant changes (26), which parallels our findings of normal but not significantly different enzyme levels between treatment groups. Another study by Ying et al showed that clinical indices of liver function, comprising ALT, AST, and GGT changed meaningfully after treatment with metformin or liraglutide (27). This finding supported the hepatoprotective efficacy of these medications. Some animal studies have reported raised

bilirubin in diabetic models with a tendency toward reduction after metformin treatment (26), comprehensive human clinical data comparing bilirubin levels across different diabetes treatment modalities have been limited.

## Conclusion

In summary, we found that treatment by sulfonylurea is across with elevated liver function tests such as bilirubin and ALT, AST, ALP, in comparison to SGLT-2 inhibitors, metformin, DPP-4 inhibitors, and their combination therapy. In contrast, the comparable liver function, which was found across metformin, DPP-4 inhibitors, SGLT-2 inhibitors, and mix therapy, demonstrates a similar hepatic safety profile for these treatment options.

## Authors' contribution

**Conceptualization:** Qutaiba A. Qasim.

**Data curation:** Qutaiba A. Qasim.

**Formal analysis:** Shaimaa Saleh.

**Investigation:** Noor Mohammed.

**Methodology:** Shaimaa Saleh.

**Project management:** Qutaiba A. Qasim.

**Resources:** All authors.

**Supervision:** Qutaiba A. Qasim.

**Validation:** Qutaiba A. Qasim.

**Writing—original draft:** All authors.

**Writing—reviewing and editing:** All authors.

## Conflicts of interest

The authors declare no conflict of interest.

## Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

The authors used AI applications (Perplexity.ai, typeset.io, and grammarly.com) to check grammar points and language style in writing. The authors reviewed the text for accuracy and take full responsibility for the final content.

## Ethical issues

The research was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants. This study was approved by the institutional ethical review committee of Basra University/College of Pharmacy, Basra Governorate, Iraq (approval number: EC-77). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

## Funding/Support

This research is not funded by any institution; it is self-funded by the authors.

## References

1. Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R, et al. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Front Endocrinol (Lausanne)*. 2017;8:6. doi: 10.3389/fendo.2017.00006.
2. Shivaprakash P, Beeraka NM, Madhunapantula SRV, Nikolenko VN, Basalingappa KM. Metformin effects on SHIP2, AMPKs and gut microbiota: recent updates on pharmacology. *Curr Med Chem*. 2025;32:1732-54. doi: 10.2174/0109298673289342240213040144.
3. Molina-Vega M, Muñoz-Garach A, Fernández-García JC,

- Tinahones FJ. The safety of DPP-4 inhibitor and SGLT2 inhibitor combination therapies. *Expert Opin Drug Saf.* 2018;17:815–24. doi: 10.1080/14740338.2018.1497158.
4. Chai S, Niu Y, Liu F, Wu S, Yang Z, Sun F. Comparison of GLP-1 Receptor Agonists, SGLT-2 Inhibitors, and DPP-4 Inhibitors as an Add-On Drug to Insulin Combined With Oral Hypoglycemic Drugs: Umbrella Review. *J Diabetes Res.* 2024;2024:8145388. doi: 10.1155/2024/8145388.
  5. Kuo HH, Wang KT, Chen HH, Lai ZY, Lin PL, Chuang YJ, et al. Cardiovascular outcomes associated with SGLT2 inhibitor therapy in patients with type 2 diabetes mellitus and cancer: a systematic review and meta-analysis. *Diabetol Metab Syndr.* 2024;16:108. doi: 10.1186/s13098-024-01354-4.
  6. Arshad M, Hoda F, Siddiqui NA, Najmi AK, Ahmad M. Genito Urinary Infection and Urinary Tract Infection in Patients with Type 2 Diabetes Mellitus Receiving SGLT2 Inhibitors: Evidence from a Systematic Literature Review of Landmark Randomized Clinical Trial. *Drug Res (Stuttg).* 2024;74:307–13. doi: 10.1055/a-2347-9824.
  7. Bao Y, Hu Y, Shi M, Zhao Z. SGLT2 inhibitors reduce epicardial adipose tissue more than GLP-1 agonists or exercise interventions in patients with type 2 diabetes mellitus and/or obesity: A systematic review and network meta-analysis. *Diabetes Obes Metab.* 2025;27:1096–112. doi: 10.1111/dom.16107.
  8. Yeh HC, Ting IW, Tsai CW, Wu JY, Kuo CC. Serum lactate level and mortality in metformin-associated lactic acidosis requiring renal replacement therapy: a systematic review of case reports and case series. *BMC Nephrol.* 2017;18:229. doi: 10.1186/s12882-017-0640-4.
  9. Mueller L, Moser M, Prazak J, Fuster DG, Schefold JC, Zuercher P. Metformin's Role in Hyperlactatemia and Lactic Acidosis in ICU Patients: A Systematic Review. *Pharmacology.* 2023;108:213–23. doi: 10.1159/000528252.
  10. Wang C, Deng H, Xu Y, Liu Y. Literature review of the clinical characteristics of metformin-induced hepatotoxicity. *Front Pharmacol.* 2022;13:969505. doi: 10.3389/fphar.2022.969505.
  11. 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. doi: 10.2147/ijgm.S49657.
  12. Mitsuboshi S, Morizumi M, Kotake K, Kaseda R, Narita I. Individual dipeptidyl peptidase-4 inhibitors and acute kidney injury in patients with type 2 diabetes: A systematic review and network meta-analysis. *Basic Clin Pharmacol Toxicol.* 2024;135:71–80. doi: 10.1111/bcpt.14014.
  13. Proença de Moraes T. What Are the Impacts of Introducing an SGLT2 Inhibitor after a Recent Episode of Acute Kidney Injury? *Kidney360.* 2024;5:333–4. doi: 10.34067/kid.0000000000000386.
  14. Salah HM, Al'Aref SJ, Khan MS, Al-Hawwas M, Vallurupalli S, Mehta JL, et al. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors initiation in patients with acute heart failure, with and without type 2 diabetes: a systematic review and meta-analysis. *Cardiovasc Diabetol.* 2022;21:20. doi: 10.1186/s12933-022-01455-2.
  15. Huang Y, Wang J, Mancino V, Pham J, O'Grady C, Li H, et al. Oral delivery of nanomedicine for genetic kidney disease. *PNAS Nexus.* 2024;3:pgae187. doi: 10.1093/pnasnexus/pgae187.
  16. Yin J, Duan H, Wang J. Impact of substrate-dependent inhibition on renal organic cation transporters hOCT2 and hMATE1/2-K-mediated drug transport and intracellular accumulation. *J Pharmacol Exp Ther.* 2016;359:401–10. doi: 10.1124/jpet.116.236158.
  17. Susilawati E, Levita J, Susilawati Y, Sumiwi SA. Review of the case reports on metformin, sulfonyleurea, and thiazolidinedione therapies in type 2 diabetes mellitus patients. *Med Sci (Basel).* 2023;11:50. doi: 10.3390/medsci11030050.
  18. Kamal P, Bhabhra R. SUN-185 glipizide induced hepatotoxicity. *J Endocr Soc.* 2019;3:SUN-185. doi: 10.1210/js.2019-SUN-185.
  19. Liu Y, Liu B, Shi M, Ye T, Li H. NLRP3 Inflammasome activation is involved in geniposide-induced hepatotoxicity. *Mediators Inflamm.* 2025;2025:4112856. doi: 10.1155/mi/4112856.
  20. Aslam B, Hussain A, Sindhu Z-U-D, Nigar S, Jan IU, Alrefaei AF, et al. Polyphenols-rich polyherbal mixture attenuates hepatorenal impairment, dyslipidaemia, oxidative stress and inflammation in alloxan-induced diabetic rats. *J Appl Anim Res.* 2023;51:515–23. doi: 10.1080/09712119.2023.2230754.
  21. Hu PP, Zhu CL. [Efficacy of different doses of magnesium isoglycyrrhizinate in the treatment of chronic liver disease with elevated ALT: a meta-analysis]. *Zhonghua Gan Zang Bing Za Zhi.* 2023;31:835–41. doi: 10.3760/cma.j.cn501113-20230420-00181.
  22. Zhang Y, Cai T, Zhao J, Guo C, Yao J, Gao P, et al. Effects and safety of sitagliptin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Horm Metab Res.* 2020;52:517–26. doi: 10.1055/a-1186-0841.
  23. Klitsunova Y, Mylytsya K. Efficacy of combined therapy with metformin and sitagliptin in patients with type 2 diabetes who did not reach target levels of glycated hemoglobin on metformin monotherapy. *J Endocr Soc.* 2019;3:SAT-LB030. doi: 10.1210/js.2019-SAT-LB030.
  24. Zhang Y, Liu X, Zhang H, Wang X. Efficacy and safety of empagliflozin on nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Front Endocrinol (Lausanne).* 2022;13:836455. doi: 10.3389/fendo.2022.836455.
  25. Tang X, Zhang H, Wang X, Yang D. Empagliflozin for the treatment of non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Afr Health Sci.* 2022;22:391–8. doi: 10.4314/ahs.v22i3.42.
  26. Jaszczka K, Grzegorzewska AK, Sachman A, Kalafova A, Massanyi P, Kovacik A, et al. The effect of metformin and sea buckthorn (*Hippophae rhamnoides* L.) in alleviating the symptoms of type 2 diabetes mellitus in the liver of Zucker diabetic fatty rats. *J Physiol Pharmacol.* 2025;76. doi: 10.26402/jpp.2025.1.07.
  27. Ying X, Rongjiong Z, Kahaer M, Chunhui J, Wulasihan M. Therapeutic efficacy of liraglutide versus metformin in modulating the gut microbiota for treating type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. *Front Microbiol.* 2023;14:1088187. doi: 10.3389/fmicb.2023.1088187.

