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

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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.

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Original

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

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

Demographic characteristics		Anti-diabetic medications										*P* value
		Metformin (n = 60)		Sulfonylurea (n = 50)		DPP-4i (n = 39)		SGLT-2i (n = 45)		Mix treatment (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^2)		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.

various anti-diabetic medications imply that individuals taking sulfonylurea had significantly higher bilirubin 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

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.

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 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 Jaszcza 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.
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Formal analysis: Shaimaa Saleh.
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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).

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