Regulatory Mechanisms in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.

Effect of long-term statin therapy on liver enzymes in diabetic patients

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Article info

Received 21.12.2025
Received in revised form 12.01.2026
Accepted 06.02.2026

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Qasim, Q. A., Hillfy, A. S., Kadhim, K. A., & Al-Hussaniy, H. A. (2026). Effect of long-term statin therapy on liver enzymes in diabetic patients. Regulatory Mechanisms in Biosystems, 17(2), e26033. doi:10.15421/0226033

Statins are regularly prescribed to patients with type 2 diabetes mellitus (T2DM) to lower the risk of cardiovascular outcomes, although the risk of hepatotoxicity remains an issue. Our objective was to assess the impact of statin-based long-term therapy in Iraqi adults with T2DM on liver enzymes and the factors that are related to elevated liver enzymes. Our research involved 280 adults with T2DM who received statins over 12 months, between January 2021 and December 2025. Liver enzyme abnormalities were defined in terms of local upper normal limits. Logistic regression was employed in order to determine independent predictors of enzyme elevation. A subgroup of 96 patients had matched pre- and on statin liver tests. The mean ALT, AST and ALP, GGT and bilirubin values were or near the reference range. The occurrence rate of any liver enzyme elevation was 25.0% of all patients with only a few clinically significant elevations per parameter (less than 3%), while the incidence of acute liver failure or liver-related hospitalisation was nil. Data in multivariable analysis showed that NAFLD, obesity (BMI 30 kg/m2), HbA1c 9%, and high-intensity statin therapy were independently related to enzyme elevation and NAFLD had the most significant effect. In the matched group, the significant increase in ALT and AST observed after initiation of statins was not significant. Long-term statin therapy in Iraqi patients with T2DM is generally hepatically safe. Liver enzyme abnormalities are driven mainly by underlying metabolic liver disease rather than statin exposure, supporting guideline-directed statin use with targeted follow-up liver function testing.

Keywords: type 2 diabetes mellitus; statins; liver enzymes; hepatotoxicity.

Introduction

Diabetes mellitus is a long-term metabolic illness that is manifested by chronic hyperglycaemia caused by insulin secretion defects, insulin action defects, or both (Popoviciu et al., 2023; Zhao et al., 2023). Against a background of obesity, sedentary lifestyle, and genetic predisposition, type 2 diabetes mellitus (T2DM) represents over 90% of diabtetes cases and typically occurs due to both insulin resistance of peripheral tissues and a progressive loss of b-cell functionality (Mohajan & Mohajan, 2023a; Ojo et al., 2023; Lu et al., 2024). Recent ideas define T2DM as a subset of a wider metabolic dysfunction syndrome (where hyperglycaemia is comorbid with dyslipidaemia, hypertension, visceral adiposity, and chronic low-grade inflammation) (Mohajan & Mohajan, 2023b). The available estimates of prevalence worldwide show that diabetes already reaches pandemic levels, and there are predictions of a further increase over the next decades, especially in the low- and middle-income countries (Młynarska et al., 2025). The causes of this transition in epidemiology are to a large extent, population ageing, urbanization, unhealthy food habits, and lack of exercise (Galicia-Garcia et al., 2020). Chronic hyperglycaemic and other metabolic disturbances cause microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular disease which significantly affect the quality of life and survival (Lu et al., 2024). T2DM is closely associated with non-alcohol liver fatty disease (NAFLD), currently often referred to as metabolic dysfunction-associated steatotic liver disease (MASLD), which is both its outcome and a cause of general metabolic dysfunction (Vlacho et al., 2024). Two-thirds of T2DM patients can also have a comorbid steatotic liver disease that is usually asymptomatic but exposes them to higher risks of cirrhosis, hepatocellular carcinoma, and cardiovascular disease (Ciardullo et al., 2023).

It is believed that statins are safe and well tolerated with an excellent benefit to risk profile in the general population and in high-risk groups (Russo et al., 2009). Non-obvious, mild, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) rises (usually less than three times the norm) are common (1–3%) in statin-treated patients, and are benign, without giving grounds for stopping the drug (Stoll et al., 2009). Liver damage and acute liver failure induced by drugs have been severe and are extremely uncommon, occurrence rates being about 19 cases per 100,000 statin users in extensive surveillance studies (Zeng et al., 2025). Recent observational cohorts and meta-analyses have even hinted at possible hepatoprotective efficacy of statins, such as reduced incidence of liver disease, hepatocellular carcinoma and hepatolith mortality in regular users compared to non-users (Vell et al., 2023).

However, in practice, safety indicators of statin-associated hepatotoxicity are still revealed by real-world data of spontaneous reporting systems, in particular, with a high dose of statin and with some lipophilic statins like atorvastatin and fluvastatin. These conflicting pieces of evidence lead to the continued confusion and careful prescribing in everyday practice (Zacharia et al., 2024). This is of particular relevance to T2DM, in which the steatotic liver disease is very common (Bhavya & Sanjay, 2022). Recent meta-analyses and extensive epidemiological research show that NAFLD/ MASLD occurs in 60–70% of patients with T2DM, and that a significant percentage of them have non-alcoholic steatohepatitis (NASH/ MASH) or severe fibrosis (En Li Cho et al., 2023). T2DM and NAFLD coexistence are linked to increased risks of cirrhosis, hepatocellular carcinoma, liver-associated and cardiovascular mortality (Kumar et al., 2023).

The current study aimed to evaluate the effect of long-term statin therapy on liver enzymes ALT, AST, alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), and total bilirubin in patients with type 2 diabetes mellitus, and explore associations between liver enzyme abnormalities and clinical or treatment-related factors, including statin type and dose, duration of statin use, glycaemic control, body mass index, and the presence of NAFLD/MASLD or other comorbidities.

Material and methods

The study protocol was reviewed and approved by the Institutional Review Board of the College of Pharmacy-University of Basra (ethical reference number EC/05). In addition, the Iraqi Medical Research Center ethical approval number is 239/2021. Written informed consent was obtained from all participants or their guardians in the case of minors, and the study was conducted in accordance with the Declaration of Helsinki.

The study was a retrospective cohort study that was carried out in a real-life clinical environment. Medical records of adult patients with type 2 diabetes mellitus (T2DM) who had already been receiving statins for 12 months were examined. The study was structured upon the retrospective cohort design as statins had been prescribed long enough in the study setting, and quality clinical and laboratory data were recorded routinely in both the paper medical records and electronic medical records. This study design enables the determination of liver enzyme levels and their association with statin exposure under the real-life setting of routine care conditions, without the need to expose a high-cardiovascular-risk group to the ethical and logistical dilemmas of statin deprivation.

The research was been carried out at Al-Karama governmental hospital in Baghdad, Iraq, where specialized outpatient services for diabetic, dyslipidemic, and cardiovascular disease patients are provided. The hospital is a referral centre for the urban and peri-urban populations and has integrated medical records and lab services. The medical records of T2DM patients who presented to the endocrinology and diabetes outpatient clinics and other affiliated cardiometabolic clinics were searched to retrieve data. The observation was conducted between 2021 and 2025. Eligible patients were all those who had at least one liver function test recorded during continuous statin therapy during this period.

Patients were eligible for inclusion if they met all of the following criteria: ≥18 years at the time of the index liver function test, confirmed diagnosis of type 2 diabetes mellitus, documented in the medical record by the treating physician based on standard diagnostic criteria, continuous use of any statin (e.g. atorvastatin, simvastatin, rosuvastatin, pravastatin) for a minimum duration of 12 months prior to the index liver function test (long-term use), continuous use was verified through clinic prescriptions and pharmacy refill records, allowing interruptions of ≤30 days over the preceding year, and availability of complete data on liver enzymes (ALT, AST, ALP, with or without GGT and bilirubin) and essential clinical variables (age, sex, body mass index [BMI], duration of diabetes, and HbA1c).

Patients were excluded if one or more of the following conditions was present: known chronic liver disease that was reported prior to beginning statins such as chronic hepatitis B or C, autoimmune hepatitis, cirrhosis of any etiology, Wilson disease or haemochromatosis, marked alcohol use, which is considered to be reported alcohol intake greater than 20 g/day in women and greater than 30 g/day in men or a clinical diagnosis of alcohol use disorder, use of other potentially hepatotoxic drugs within the past 6 months (high dose of methotrexate, amiodarone, isoniazid or chronic oral ketoconazole), active disease or reported systemic infection during the index liver function test, pregnancy or breastfeeding, and missing or incomplete important data (e.g. no value for liver enzyme or vague history of statin exposure) after checking both the paper and electronic records.

The exquisiteness of the sample was estimated to determine the prevalence of high liver enzymes among T2DM patients receiving long-term statins therapy with a satisfactory amount of accuracy. By taking the single proportion formula the minimum required sample size (n) is calculated: assuming a hypothesized prevalence (p) of elevated liver enzymes of 20, a 95% confidence level (Z = 1.96), and a margin of error (d) value of 5:

$$n = \frac{Z^2 \, p(1-p)}{d^2}$$

Substituting the values:

$$n = \frac{(1.96)^2 \times 0.20 \times 0.80}{(0.05)^2} \approx 246$$

The sample size was inflated to about 272 participants to cover a rate of 10% incomplete or ineligible records. Since the study was a retrospective study design, all consecutive patients that were eligible within the duration of time that the study was conducted were incorporated until a minimum number of at least this number was met. In practice, there were 298 charts that had satisfied the initial screening criteria. Following the use of exclusion criteria and evaluating records that lacked the key variables, 280 patients constituted the end analytic cohort. The sampling method was thus consecutive sampling of all the eligible patients who came to the diabetes and allied clinics within the given time.

The information was gathered through a structured data extraction form of the present study. Data were extracted using medical records by two trained physicians, with disagreements settled by consensus or consultation with a senior investigator. In order to be precise, 10% of charts were randomly again abstracted. Data collection forms included no patient identifiers; the subjects received unique study codes (Hosseinsabet et al., 2026).

The following parameters were recorded: continuous age (years) at the time of the index liver function test as a continuous variable and in age groups (ex: <50, 50–59, 60–69, 70 years), body mass index (BMI) = weight (kg)/height (m^2), determined by most recent measurements recorded within 3 months of index test. WHO was used to categorize patients as normal weight (BMI less than 25 kg/m^2), overweight (25–29.9 kg/m^2) and obese (30 kg/m^2), duration of diabetes, the period of time (years) that existed between the recorded date of T2DM diagnosis and the date of the liver function test index, glycaemic control measured by the glycated haemoglobin (HbA1c), 3 months after the index test. HbA1c was both a continuous variable and categorical (<7.0%, 7.0–8.9% 9.0%), comorbidities were recorded, such as hypertension, dyslipidaemia, chronic cardiovascular disease (coronary artery disease, stroke, or peripheral arterial disease), and chronic kidney disease. These were noted as positive or negative according to the physician's diagnosis, in the case of non-alcoholic fatty liver disease (NAFLD), its presence was determined by hepatic steatosis on an abdominal ultrasound report in the absence of notable alcohol intake and other particular liver ailments.Smoking (current, former, never) and alcohol use were lifestyle factors that were documented.

Statin exposure was characterized in detail to allow exploration of dose-response and agent-specific effects. The following variables were recorded: type of statin (e.g. atorvastatin, simvastatin, rosuvastatin, pravastatin, others), daily dose at the time of the index liver function test, documented in milligrams and categorized into low, moderate, or high intensity according to international guidelines (Table 1), duration of statin therapy, defined as the continuous period (months/ years) from documented initiation to the index liver function test, allowing for brief interruptions of ≤30 days, concomitant lipid-lowering therapies, including ezetimibe, fibrates, or omega-3 fatty acids, were recorded as present or absent. The history of statin discontinuation or dose reduction because of suspected adverse effects was documented when present.

Table 1

Statin types, intensity, and duration of therapy (n = 280)

Variable	n (%) or mean ± SD
Type of statin	
Atorvastatin	174 (62.1)
Rosuvastatin	67 (23.9)
Simvastatin	22 (7.9)
Pravastatin	17 (6.1)
Statin intensity	
Low	31 (11.1)
Moderate	151 (54.0)
High	98 (35.0)
Duration of statin therapy, years	4.8 ± 2.1
Duration category, n (%)	
1–2 years	68 (24.3)
3–4 years	104 (37.1)
≥5 years	108 (38.6)
Concomitant ezetimibe, n (%)	39 (13.9)
Concomitant fibrate, n (%)	26 (9.3)
History of statin dose reduction*, n (%)	19 (6.8)

Note: * due to any suspected adverse effect (myalgia, elevated liver enzymes, or other).

The data regarding laboratories were received through the central laboratory information system of the hospital. All the assays were done on automated analyzers that were standardized and calibrated following the manufacturer's recommendations. The index liver function test for each patient was taken to be the liver function test that was nearest to the end of the applied statin exposure period. Reference ranges were based on the local laboratory standards. For analytic purposes, the upper limit of normal (ULN) was defined as 40 U/L for ALT and AST, 120 U/L for ALP, and 60 U/L for GGT. Liver enzyme elevation was defined as any value above ULN, and clinically significant elevation was defined as ALT or AST ≥3× ULN, or ALP or GGT ≥2× ULN. Table 2 presents the operational definitions.

Table 2
Operational definitions and cut-off values
for liver enzyme abnormalities

Parameter	ULN (local)	Any elevation	Clinically significant elevation
ALT	40 U/L	>40 U/L	≥3 × 40 U/L (≥120 U/L)
AST	40 U/L	>40 U/L	≥3 × 40 U/L (≥120 U/L)
ALP	120 U/L	>120 U/L	≥2 × 120 U/L (≥240 U/L)
GGT	60 U/L	>60 U/L	≥2 × 60 U/L (≥120 U/L)
Bilirubin (total)	per lab reference	>ULN	≥2 × ULN or associated with symptoms

The primary outcome of interest was the status of liver enzymes among T2DM patients receiving long-term statin therapy, assessed both as: binary outcome: presence vs absence of liver enzyme elevation (ALT, AST, ALP, GGT, or bilirubin above ULN), and continuous outcome: mean and median values of individual liver enzymes. Secondary outcomes included the prevalence of clinically significant liver enzyme elevation as defined in Table 2. Associations between liver enzyme elevation (any and clinically significant), statin type (e.g. atorvastatin vs other statins), statin intensity (low, moderate, high), duration of statin use (in years, and categorized, e.g. 1–2, 3–4, ≥5 years), glycaemic control (HbA1c categories), BMI categories, and presence of NAFLD and major comorbidities were recorded. For a subset of patients with documented liver enzymes prior to statin initiation, exploratory analyses of changes in liver enzymes from baseline to the index test were planned.

Results

Two hundred and eighty (280) patients with type 2 diabetes mellitus (T2DM) under long-term statin therapy were included in the analysis and were eligible to qualify as per the inclusion criteria. The average age was 58.7 ± 9.4 years and slightly over half of the cohort were female (54.3%). Most (65%) of the patients were obese (BMI 30 kg/m^2) and the mean BMI was 31.2 ± 4.8 kg/m^2. The average duration of diabetes per patient was about 9 years and the overall control of glycaemic level was suboptimal with a mean of 8.1 ± 1.3 HbA1c; almost a third of diabetes patients had HbA1c 9%. The most common comorbidity was hypertension, which was found in 72.1% of the patients, and then cardiovascular disease was established, which was found in 35.0%. In the cohort, non-alcoholic fatty liver disease (NAFLD) was radiologically proven in 47.9%. Table 3 summarises baseline demographic and clinical characteristics.

Atorvastatin was the most prescribed statin with 62.1% of patients taking it and then rosuvastatin (23.9), simvastatin (7.9) and pravastatin (6.1). According to the categories of intensity defined by the guidelines, 54.0% of the patients were subjected to moderate-intensity therapy and 35.0% of the patients were subjected to high-intensity therapy. The average period of continuous use of statins before the index liver function test was 4.8 ± 2.1 years, and 38.6% of the patients had longer than 5 years of statin treatment. The distribution of statin types, doses, and treatment durations is presented in (Table 1).

Generally, there were no significant or excessively high liver enzyme values that were outside of or near the laboratory reference ranges. The mean of ALT and AST was 32.4 ± 14.7 and 29.8 ± 12.5 U/L, respectively. The mean ALP and GGT were 104.3 ± 31.2 and 45.7 ± 21.9 U/L and the average total bilirubin was 0.9 mg/dL. A rise in ULN above the upper limit of normal was considered significant in 25.0% of the patients (70/280) and clinically significant rises were noted in rare cases; 2.5% for ALT, 1.8% for AST, 1.1% for ALP, and 1.4% for GGT. The cohort had no cases of acute liver failure and liver-related hospitalisation. Liver enzyme values and the proportions of patients exceeding ULN are shown in (Table 4).

Table 3
Demographic and clinical characteristics
of the study population (n = 280)

Characteristic	Value
Age, years, mean ± SD	58.7 ± 9.4
Females, n (%)	152 (54.3)
BMI, kg/m², mean ± SD	31.2 ± 4.8
BMI category, n (%)	
– <25 kg/m²	28 (10.0)
– 25–29.9 kg/m²	70 (25.0)
– ≥30 kg/m²	182 (65.0)
Duration of diabetes, years, mean ± SD	9.3 ± 6.1
HbA1c, %, mean ± SD	8.1 ± 1.3
HbA1c category, n (%)	
– <7.0%	62 (22.1)
– 7.0–8.9%	131 (46.8)
– ≥9.0%	87 (31.1)
Hypertension, n (%)	202 (72.1)
Dyslipidaemia, n (%)	280 (100.0)
Established CVD*, n (%)	98 (35.0)
Chronic kidney disease, n (%)	61 (21.8)
NAFLD (ultrasound), n (%)	134 (47.9)
Current smoker, n (%)	64 (22.9)

Note: * CVD – coronary artery disease, stroke, or peripheral arterial disease.

Table 4
Liver enzyme profile and proportion
of patients with abnormal values (n = 280)

Parameter	Mean ± SD	Above ULN*, n (%)	Clinically significant elevation**, n (%)
ALT, U/L	32.4 ± 14.7	64 (22.9)	7 (2.5)
AST, U/L	29.8 ± 12.5	50 (17.9)	5 (1.8)
ALP, U/L	104.3 ± 31.2	42 (15.0)	3 (1.1)
GGT, U/L**	45.7 ± 21.9	59 (21.1)	4 (1.4)
Total bilirubin, mg/dL	0.9 ± 0.3	11 (3.9)	3 (1.1)

Notes: * ULN defined as ALT 40 U/L, AST 40 U/L, ALP 120 U/L, GGT 60 U/L (local laboratory ranges); ** clinically significant elevation: ALT/AST ≥3 × ULN; ALP/GGT ≥2 × ULN; bilirubin ≥2 × ULN; GGT available for 279 patients (one missing value); percentages calculated using available data.

A subset of 96 patients had liver function tests documented both prior to statin initiation and at the index visit. In this subgroup, mean ALT and AST showed no statistically significant worsening; if anything, there was a small, non-significant numerical reduction on treatment (Table 5).

Table 5
Changes in liver enzymes from pre-statin baseline
to on-treatment (subset with paired data, n = 96)

Parameter	Pre-statin, mean ± SD	On statin, mean ± SD	p-value*
ALT, U/L	33.1 ± 13.4	31.8 ± 12.7	0.18
AST, U/L	30.5 ± 11.9	29.6 ± 12.1	0.24
ALP, U/L	106.2 ± 29.7	103.9 ± 30.5	0.21

Note: * paired-samples t-test.

Patients were stratified according to whether they had any liver enzyme elevation above ULN (elevated group, n = 70) or not (normal group, n = 210). Individuals with increased liver enzymes compared with other patients with normal liver enzymes had higher mean BMI and worse glycaemic control. The percentage of obese patients (BMI 30 kg/m^2) was 78.6 in the elevated group and 60.5 in the normal group (P = 0.007). In a similar fashion, HbA1c 9% and above was more common in individuals who had high levels of enzymes (42.9% vs 27.1% P = 0.015). The elevated group also exhibited NAFLD more than the group with normal enzymes (70.0% vs 40.5%, P < 0.001). With regards to statin therapy, high-intensity regimens were more prevalent with patients with high enzymes (50.0% vs 30.0%, P = 0.002), and higher proportions of these patients had been on statins for 5 years or longer (57.1% vs 32.4% $P < 0.001$). The two groups had no major differences in terms of age or sex distribution (Table 6).

Table 6
Comparison of patients with normal vs elevated liver enzymes

Variable	Normal enzymes (n = 210)	Elevated enzymes (n = 70)	P-value
Age, years, mean ± SD	58.4 ± 9.2	59.5 ± 10.0	0.42
Female sex, n (%)	111 (52.9)	41 (58.6)	0.40
BMI, kg/m², mean ± SD	30.7 ± 4.6	32.8 ± 5.0	0.001
BMI ≥30 kg/m², n (%)	127 (60.5)	55 (78.6)	0.007
Duration of diabetes, years, mean ± SD	9.1 ± 6.0	9.9 ± 6.4	0.39
HbA1c, %, mean ± SD	8.0 ± 1.2	8.4 ± 1.4	0.021
HbA1c ≥9%, n (%)	57 (27.1)	30 (42.9)	0.015
Hypertension, n (%)	148 (70.5)	54 (77.1)	0.27
Established CVD, n (%)	71 (33.8)	27 (38.6)	0.44
NAFLD, n (%)	85 (40.5)	49 (70.0)	<0.001
Atorvastatin use, n (%)	124 (59.0)	50 (71.4)	0.058
High-intensity statin, n (%)	63 (30.0)	35 (50.0)	0.002
Statin duration, years, mean ± SD	4.5 ± 2.0	5.6 ± 2.2	<0.001
Statin duration ≥5 years, n (%)	68 (32.4)	40 (57.1)	<0.001

To determine independent predictors of liver enzyme elevation, a multivariate logistic regression model was put in place. Variables that were inputted in the model were, age, sex, BMI category, HbA1c category, NAFLD status, statin intensity, and years of statin therapy (5 vs <5 years). Following the adjustment, NAFLD, obesity, and poor glycaemic control as well as high-intensity statin therapy were still significantly linked to the high liver enzymes. NAFLD was the best single predictor (adjusted odds ratio [aOR] 2.14, 95% CI 1.26–3.64; P = 0.005). Obesity (BMI > Obesity (BMI 30 kg/m^2) was related almost twice to the odds of liver enzyme elevation (aOR 1.82, 95% CI 1.02–3.25; P = 0.042). There was also an independent association between liver enzyme elevation and HbA1c 9% (aOR 1.94, 95% CI 1.06–3.56; P = 0.031). Strong intensity of statin regimens provided greater odds of high-intensity than low/moderate-intensity statin regimens (aOR 1.96, 95% CI 1.11–3.47; P = 0.020, Table 7).

Table 7
Multivariable logistic regression for predictors of any liver enzyme elevation (n = 280)

Variable	aOR	95% CI	p-value
Age (per 10-year increase)	0.89	0.70–1.14	0.36
Female sex (vs male)	1.12	0.67–1.88	0.66
BMI ≥30 kg/m² (vs <30 kg/m²)	1.82	1.02–3.25	0.042
HbA1c 7.0–8.9% (vs <7.0%)	1.24	0.67–2.30	0.49
HbA1c ≥9.0% (vs <7.0%)	1.94	1.06–3.56	0.031
NAFLD present (vs absent)	2.14	1.26–3.64	0.005
High-intensity statin (vs low/moderate)	1.96	1.11–3.47	0.020
Statin duration ≥5 years (vs <5 years)	1.57	0.95–2.61	0.078

Note: aOR – adjusted odds ratio; CI – confidence interval.

Discussion

The results of this experiment are widely in line with the global literature on statin hepatotoxicity. Significant scientific assertions and reviews have determined that severe statin-induced hepatotoxicity is exceedingly uncommon, and the rates of 0.001% (approximately 1 per 100,000 patients) or less have been established even though these drugs are heavily used (Huldani et al., 2024). In these reports, like in the current analysis, there are mild asymptomatic rises in transaminases in a minority of patients and these are typically reversible and have minimal association with significantly relevant liver injury (Gnanasekar & Veluswamy, 2024). Our information also agrees with more contemporary literature that deals with patients having NAFLD and metabolic liver disease (Alshahrani et al., 2023). The systematic review by Zhang et al. (2024) reported that patients with suspected NAFLD and a high baseline liver enzyme count did not have an increased risk of liver damage with statins as compared to those with normal baseline readings (Anjum & Raza, 2026). Recent syntheses and narrative reviews also indicate that statins can be used to enhance liver enzymes and histological markers in NAFLD/MAFLD and NASH and have cardiovascular benefit (Pastori et al., 2022). Such a randomized increase and the minimal numerical decrease in the mean of ALT and AST in our paired subset – is thus in keeping with this new hepatoprotective pattern (Eroshchenko et al., 2026). Recent recommendations on cholesterol and cardiovascular prevention have made it clear that statins are largely safe, and periodic liver functional testing is unnecessary in patients without symptoms. These recommendations are supported by our finding that clinically significant increases were infrequent, and that serious hepatic events did not happen in the presence of massive statin use (Newman et al., 2019).

These data also offer substantial reassurance about the clinical safety of long-term statin use in patients with T2DM, including those with an excessive burden of obesity and NAFLD (Abd-Alrassol et al., 2020). Statin use of about five years in this cohort of Iraqis was hardly related to the clinically significant hepatotoxicity, and there were no serious liver events (Alrassol et al., 2019). This is in line with the opinion of regulatory bodies, as well as the work of expert committees, that the cardiovascular effects of statins are well-worth the risk of severe liver effects, which is minimal (Homer et al., 2017). The issue of monitoring is also addressed in our findings (Hashim et al., 2022). In line with guideline and policy statements, the findings indicate that regular and frequent liver function testing in the entire statin-treated population is unlikely to be warranted and cost-effective, as baseline testing with regular further monitoring is a more rational practice (Odden et al., 2015). The obvious connection between NAFLD, liver enzyme increase, and obesity and poor glycaemic control suggests that those high-risk groups can be followed up more stringently by biochemical monitoring, and less stringently in patients who are not at high-risk (Al-Hussaniy & Al-Zobaidy, 2024).

According to the results of the study, these recommendations can be given to clinicians working with T2DM in Iraq and other countries: adherence to the recommendations of the international lipid management guidelines and the use of statin therapy guided by the recommendations should be recommended even in the presence of stable NAFLD or slightly increased baseline liver enzymes (Abdulhamza et al., 2024). To rule out unidentified advanced liver disease, baseline liver functioning tests should be requested, but continuous monitoring can justifiably be placed high on the priority list of an obese person with poorly controlled diabetes, with known NAFLD or undergoing high-intensity statin therapy (Hussein et al., 2023). Moving to statin therapy, a structured approach that deals with lifestyle, glycaemic control maximisation and assessment of other hepatotoxic exposures must precede any alterations in case of mild asymptomatic elevations (Rana et al., 2023).

Future research must build on this retrospective and single centre study by undertaking prospective multicentric research incorporating non-invasive fibrosis (e.g. vibration-controlled transient elastography, fibrosis scores) as well as long-term outcomes of hepatic and cardiovascular outcomes in T2DM with NAFLD. According to recent articles, the fibrosis stage, but not steatosis, facilitates liver-related and cardiovascular risks in NAFLD and MAFLD (Targher et al., 2021). The inclusion of these measures would help elucidate the effect that statins have on liver disease, whether they stabilize it or alter its course (Yu et al., 2023). Also, research on combined intervention with statins and new cardiometabolic interventions, including SGLT2 and GLP-1 receptor agonists, which both have shown potential in alleviating cardiovascular and liver morbidity, may contribute to the establishment of the truly integrated approach to improve cardiovascular and liver morbidity in this at-risk group (Lee et al., 2020).

Conclusion

Among this retrospective cohort of Iraqi adults with type 2 diabetes mellitus receiving long-term statin therapy, we discovered that liver enzyme changes were quite common but mostly mild and barely achieved a clinically significant level. ALT, AST, and ALP, GGT and bilirubin mean values were within or near reference ranges and there were no instances of acute liver failure or liver-related hospitalisation even during a mean statin exposure of almost five years. Multivariate analysis showed that liver enzyme increases were more positively correlated with underlying metabolic factors, obesity, poor glycaemic control and ultrasound-confirmed NAFLD than with statin use per se. Statin therapy on a high-intensity level demonstrated a small independent significance of abnormal enzymes, which was convincingly overcome by the impact of metabolic liver disease. Statin initiation did not deteriorate and possibly slightly increased aminotransferase levels in a subset in which paired measurements were used. Combined, these results indicate the hepatic safety of long-term statin use in patients with type 2 diabetes mellitus and indicate that fears regarding statin-induced hepatotoxicity should not exclude their use in such a high-cardiovascular-risk group. Routine intensive follow-up liver function testing or premature withdrawal of statins does not seem to be the most suitable approach, whereas baseline and targeted follow-up liver function testing, targeting NAFLD patients at risk, with obesity and poor glycaemic control, is more suitable.

We thank all medical staff at Al-Karama governmental hospital in Baghdad.

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