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Prevalence and Risk Factors Associated with Elevated Liver Transaminases in Adult Type 2 Diabetes Mellitus Patients in King Abdulaziz Medical City in Riyadh, Saudi Arabia - A Cross-sectional Study

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ABSTRACT

Introduction: *Diabetes mellitus is a global health challenge associated with numerous complications, including liver function. This study aimed to investigate the prevalence and risk factors associated with elevated liver transaminases in a of 509 diabetic patients.* ***Methodology:*** *A cross-sectional observational study was conducted at King Abdulaziz Medical City Riyadh, Saudi Arabia. Diabetic patients meeting inclusion criteria were enrolled and relevant data including demographics, clinical characteristics and laboratory results were extracted from electronic medical records. Statistical analyses were performed using SPSS Pc+21.0 version, employing descriptive statistics and appropriate tests for univariate analysis.* ***Results:*** *The majority of the 509 diabetic patients were females (58%) with a mean age of 61.5 ± 12.4. Obesity was prevalent (62.9%) and more than half had complications (55%). Comorbidities, hypertension and dyslipidemia were present in 91% of patients. Notably, 44% were diagnosed with Non-Alcoholic Fatty Liver Disease (NAFLD). Elevated liver transaminases were observed in 9.3% Aspartate Aminotransferase (AST) and 4.8% alanine transaminase (ALT) of patients. 86% of patients had suboptimal glycemic control. Unexpectedly, non-insulin hypoglycemic medications did not show a significant association with elevated liver transaminases. However, patients not on insulin therapy exhibited higher ALT levels. Statin use, prevalent in over 90% of patients did not show a significant relationship with transaminitis.* ***Conclusion:*** *This study reveals a complex interplay between diabetes, liver function and associated factors. The prevalence of NAFLD and suboptimal glycemic control highlights the need for comprehensive management strategies to reduce the overall liver-related morbidity and mortality.*

Keywords: Diabetes mellitus, Elevated liver transaminases, Non-alcoholic fatty liver disease, Risk factors.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by abnormal carbohydrate metabolism leading to hyperglycemia [1]. Defects in insulin secretion, peripheral resistance to the action of insulin, or both are the main contributing factors to the pathophysiology of diabetes [1]. Diabetes stands as a leading global cause of mortality, with far-reaching consequences such as kidney failure, lower-limb amputations, and blindness [2]. The intricate interplay of hyperglycemia, low-grade inflammation, and accelerated atherogenesis renders diabetic individuals more susceptible to microvascular, macrovascular, and gastrointestinal complications [3]. Currently affecting 422 million people worldwide, the prevalence of diabetes has alarmingly doubled over the last two decades [4].

Saudi Arabia, according to the World Health Organization (WHO), ranks as the second highest in the Middle East and the seventh highest globally for diabetes prevalence [5]. A systematic review conducted by Meo SA in 2014-2015 projected an escalating prevalence of Type 2 Diabetes Mellitus (T2DM) in Saudi Arabia, foreseeing rates of 35% in 2020, 40% in 2025, and 45% in 2030 [6].

Non-Alcoholic Fatty Liver Disease (NAFLD) emerges as a prevalent chronic liver condition, affecting approximately 25% of the Saudi population [7,8]. The insidious impact of NAFLD extends beyond hepatic complications, with cardiovascular diseases and malignancies constituting major contributors to mortality [9]. Routine biomarkers such as Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and γ-Glutamyl Transferase (GGT) serve as practical indicators for hepatic injury/inflammation in epidemiological studies, circumventing the challenges posed by invasive diagnostic techniques as liver biopsy and imaging which include being time consuming, carry a higher risk of complications and are not cost effective [10–14]. Hence, aminotransferases have been described as convenient substitute indices of NAFLD for large studies [12].

Existing data establish a link between elevated liver enzymes and T2DM, with insulin resistance, NAFLD, and Non-Alcoholic Steato Hepatitis (NASH) acting as contributing factors [10,12,15–18]. However, the precise mechanisms underlying abnormal liver enzymes in T2DM remain elusive, with proposed theories centering on fatty acid deposition and inflammatory processes at the cellular level [12,18].

International studies, including those from India, Bangladesh, Ethiopia, Italy, and China, consistently reveal a higher prevalence of abnormal liver enzymes in T2DM patients compared to nondiabetics. Various risk factors such as gender, BMI, HbA1c levels, and triglyceride levels exhibit correlations with elevated liver enzymes, highlighting the multifactorial nature of this association [19–22].

In Saudi Arabia, a study in Jeddah demonstrated a noteworthy prevalence of abnormal liver enzymes in T2DM patients, although without statistically significant associations with demographic and metabolic factors. Notably, this remains the sole study in Saudi Arabia on this subject, limited by a relatively small sample size [23].

This study, conducted at King Abdulaziz Medical City in Riyadh, aims to fill this research gap by investigating the prevalence and risk factors associated with elevated liver transaminases in adult T2DM patients. Understanding these factors is crucial for early detection and effective management, potentially mitigating liver-related morbidity and overall mortality. The emphasis on modifying metabolic risk factors, alongside glycemic control, is paramount in reducing the burden of complications. Additionally, the study may contribute valuable insights into tailored therapeutic interventions for NAFLD and NASH in the context of T2DM.

METHODS

The study was a cross-sectional observational study that was conducted at King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia. Inclusion criteria included adult individuals of both genders with Type 2 Diabetes Mellitus (T2DM). Exclusion criteria encompassed Type 1 diabetes mellitus, chronic liver diseases (cirrhosis, Hepatitis A, B, C, D, or E), alcohol consumption, and the use of medications known to cause elevated liver enzymes. The sample size was calculated using OpenEpi software freely available online (http://www.openepi.com/Menu/OE_Menu.html) based on data from a study conducted in Jeddah by Alzahrani *et al*. (2019), reporting elevated liver enzymes levels in 7% of diabetic patients. Therefore, keeping population size of 1,000,000, anticipated frequency of 7%, absolute precision of 5%, and design effect of 1 gave us the required sample size of 101. So, to account for eligibility, we aim to enroll 500 individuals for the study.

Data were collected by reviewing electronic medical records in King Abdulaziz Medical City (BestCare System). The collected data included demographics (age, gender), clinical characteristics (comorbidities, height, weight, Body Mass Index [BMI], blood pressure), and laboratory results (fasting blood glucose, HbA1c, liver enzymes (Alanine Transaminase [ALT], Aspartate transaminase [AST], Alkaline phosphatase, Gamma-glutamyl transferase [GGT]), lipid profile (Total cholesterol [Desirable: 5.18 mmol/L, Borderline: 5.18 mmol/L - 6.19 mmol/L, High: 6.22 mmol/L], Triglycerides [Optimal: <1.70 mmol/L, Near or above optimal: 1.70 - 2.25 mmol/L, High: 2.26 mmol/L - 5.64 mmol/L, Very high: 5.65 mmol/L], Low-density lipoproteins-Cholesterol [Optimal: < 2.59 mmol/L, Near or above optimal: 2.59 mmol/L - 3.34 mmol/L, High: 4.14 mmol/L - 4.90 mmol/L, Very high: 4.92 mmol/L], and High-density lipoproteins-Cholesterol levels [Major risk factor for heart disease <1.04 mmol/L, Negative risk factor for heart disease: 1.55 mmol/L]). Standard reference ranges were applied for the interpretation of laboratory results.

Data were analyzed using SPSS Pc + 21.0 version statistical software. Descriptive statistics (frequencies, percentages, mean, and standard deviation) were utilized for categorical and quantitative variables. Appropriate statistical tests were used to perform the univariate analysis. A significant level of ≤ 0.05 and 95% confidence intervals were employed to report statistical significance and precision of results.

RESULTS

A total number of 509 diabetic patients were involved in this study. Most of patients were females accounting for 58%. The mean age was 61.5 ± 12.4, 55% were above the age of 60. Only 11% of the patients were underweight or had a normal BMI while the majority (62.9%) were obese with a mean of 32.5 ± 6.9. More than half of diabetic patients were diagnosed with either microvascular or macrovascular complications (55%). Moreover, 91% of patients had a history of comorbidities either in the form of hypertension or dyslipidemia. Whereas 44% were diagnosed with NAFLD. Additionally, 82.9% of patients used non-insulin hypoglycemic medications with a higher percentage in mono or dual therapy (56%). Insulin injections were a treatment option for a total of 311 patients. More than 90% of patients were on statin therapy (Table 1).

Table 1. Demographic and clinical data

Variable	n (%)	Mean ± SD
Age		61.5 ± 12.4
≤60 years	229 (45)	
>60 years	280 (55)	
Gender		
Male	212 (41.7)	

Female	297 (58.3)	
BMI		32.5 ± 6.9
Underweight	5 (1)	
Normal	51 (10)	
Overweight	133 (26.1)	
Obese	265 (52.1)	
Morbid obese	55 (10.8)	
Complications		
No complications	229 (45)	
Complications	280 (55)	
Comorbidities		
Both HTN and DLP	466 (91.6)	
DLP	429 (84.3)	
HTN	362 (71.1)	
NAFLD	228 (44.8)	
Medications		
Non-insulin hypoglycemic	422 (82.9)	
Mono or dual therapy	287 (56.4)	
Triple or more therapy	135 (26.5)	
Insulin	311 (61.1)	
Statin use	464 (91.2)	

AST and ALT were elevated in 9.3% and 4.8%, respectively. Fasting blood sugar was not at the optimal target in 86% of patients, with a mean of 9.5 ± 4.4. In addition, elevated A1C was observed in 67.3% of the sample, on an average of 7.98 ± 1.65. Most of the patients had a normal lipid profile of which 64.1% had a normal LDL and 66.9% had a desirable triglyceride. 48.8% of patients had a low level of HDL which indicated a poor control. Only 5% of patients had a high or very high levels of LDL (Table 2).

Table 2. Biochemical variables

Variable	n (%)	Mean ± SD
AST		21.82 ± 21.186
Normal	456 (90.7)	
High	47 (9.3)	
ALT		23.68 ± 25.514
Normal	481 (95.2)	
High	24 (4.8)	
GGT		
Normal	116 (61.7)	
High	72 (38.3)	
ALP		
Normal	467 (93.2)	
High	34 (6.8)	
FBS		9.498 ± 4.3958
Normal	65 (13.8)	
High	407 (86.2)	

A1C		7.9846 ± 1.65441
Normal	164 (32.7)	
High	337 (67.3)	
TC		
Desirable	424 (85.3)	
Borderline high	56 (11.3)	
High	17 (3.4)	
LDL		
Normal	322 (64.1)	
Borderline high	155 (30.9)	
High	15 (3)	
Very high	10 (2)	
HDL		
Poor	244 (48.8)	
Better	235 (47)	
Best	21 (4.2)	
TG		
Desirable	324 (66.9)	
Borderline high	91 (18.8)	
High	65 (13.4)	
Very high	4 (0.8)	

Younger population (<60) had a higher ALT than older population. (P-Value: 0.03). Men were more likely to have higher ALT than women. (P-Value: 0.01). AST levels were not varied in gender and age groups. No significant relation was found between either AST and the age nor gender. No specific pattern of elevated liver enzymes and the higher BMI was noted. Patients with no documented complications were found to have a significant relation with higher levels of ALT (P-value:0.03), whereas AST showed no difference. Furthermore, no association between the level of diabetic control using A1C as an indicator and the higher levels of liver transaminases. Patients with history of hypertension or dyslipidemia showed no specific relation with abnormal liver enzymes.

Non-insulin hypoglycemia medications including injectable and oral therapies were not found to be associated with any elevation of liver transaminases including AST and ALT, whether the patient's used monotherapy, dual therapy, or triple therapy. In contrast, patients who were not on insulin therapy were found to have a higher level of ALT with a P-value of (0.049). No association between elevated AST and insulin use was noted. In addition, Statin use among diabetic patients was not noted to be related to neither elevated AST nor ALT (Table 3).

Table 3. Association participants characteristic with elevated AST and ALT

Variable	Elevated AST (%)	P value	Elevated ALT (%)	P value
Age				
≤60 years	25 (11.1)	0.22	16 (7)	0.03
>60 years	22 (7.9)		8 (2.9)	
Gender				
Male	19 (9)	0.8	16 (7.6)	0.01
Female	28 (9.6)		8 (2.7)	
BMI				

Underweight	0 (0)	0.11	0 (0)	0.27
Normal	1 (2)		0 (0)	
Overweight	16 (12.2)		9 (6.8)	
Obese	28 (10)		14 (5.3)	
Morbid obese	2 (3.8)		1 (1.9)	
DM complications:				
No	23 (10.1)	0.58	16 (7.0)	0.03
Yes	24 (8.7)		8 (2.9)	
Comorbidities:				
No	5 (11.9)	0.55	4 (9.3)	0.14
Yes	42 (9.1)		20 (4.3)	
A1C				
Controlled	14 (8.6)	0.65	7 (4.3)	0.7
Uncontrolled	33 (9.9)		17 (5.1)	
Statin				
Not on statin	3 (6.8)	0.547	0 (0)	0. 116
On statin	44(9.6)		24 (5.2)	
Insulin				
Not using insulin	21 (10.8)	0.382	14 (7.1)	0.049
On insulin	26 (8.4)		10 (3.3)	
Non-insulin hypoglycemic				
Mono or dual therapy	31 (10.9)	0.384	19 (6.6)	0.065
Triple or more therapy	10 (7.5)		4 (3)	

DISCUSSION

Diabetes mellitus, a global health concern, is associated with various complications that significantly impact patient outcomes [24]. This study, involving 509 diabetic patients, aimed to explore the prevalence and potential risk factors associated with elevated liver transaminases in this population. The results reveal a nuanced picture, shedding light on demographic and clinical characteristics, medication use, and the association between liver transaminases and various parameters.

The study population, predominantly female (58%), had a mean age of 61.5 ± 12.4, with 55% being above 60 years old. Obesity was prevalent, with 62.9% having a mean BMI of 32.5 ± 6.9, aligning with the literature indicating a strong association between obesity and diabetes [25–27]. More than half of the patients had microvascular or macrovascular complications (55%), emphasizing the systemic impact of diabetes on various organ systems [28]. Furthermore, 91% of patients presented with comorbidities, primarily hypertension and dyslipidemia, underscoring the common coexistence of these conditions.

The high prevalence of NAFLD (44%) in diabetic patients is consistent with existing literature [29–31], highlighting the intricate relationship between diabetes and liver diseases, especially NAFLD. Additionally, the majority of patients were on non-insulin hypoglycemic medications (82.9%), with insulin therapy chosen for 311 patients. The high utilization of statin therapy (more than 90%) aligns with established recommendations for cardiovascular risk management in diabetic patients [32].

Elevated liver transaminases, specifically AST and ALT, were observed in 9.3% and 4.8% of patients, respectively. In India, a cross-sectional study found that higher prevalence of abnormal liver enzymes were found in 62% of T2DM patients compared to 32% of healthy individuals [19]. Similar findings were concluded in a Bangladeshi study on 110 diabetic and 160 nondiabetics with 61.2% and 37.1% of derangements in liver function tests, respectively [20]. Likewise, in an Ethiopian study almost more than half of diabetic patients had abnormal liver enzymes with ALT being the most frequently raised (n=37, 23.3%) [18]. In Italian patients, Higher ALT, AST, and GGT were present in 16.0%, 8.8%, 23.1% of patients, respectively [21]. Our results are in line with a Chinese study where the prevalence of elevated ALT and AST was found to be 10.3% and 6.1%, respectively [22]. In the Middle East, a study of Jordanian population showed that elevated ALT and AST levels were found in 10.4% and 5.4%

of T2DM patients, respectively [33] and in Jeddah, the authors reported a high prevalence of abnormal liver enzymes in almost 6-7% of T2DM patients [23]. This finding emphasizes the need for vigilance regarding liver function in the diabetic population.

The study also revealed suboptimal glycemic control, with 86% of patients not meeting the optimal fasting blood sugar target. Elevated A1C levels in 67.3% of patients further underscore the challenges in glycemic management.

Interestingly, the younger population (<60) exhibited higher ALT levels than the older population, aligning with studies suggesting age-related variations in liver enzyme levels [33]. Men were also more likely to have higher ALT than women, consistent with the known gender differences in liver enzyme concentrations that had been reported in different studies [21,22,33]. However, no significant relationship was found between AST levels and age or gender which is not consistent with the results of previous studies which showed that AST also is associated with male gender [21,22]. On the other hand, a study conducted in Jeddah showed no statistically significant link between elevated levels and gender and age [23].

Contrary to expectations as reported in previous studies, no specific pattern of elevated liver enzymes was noted concerning BMI, complications, or glycemic control using A1C levels. Patients with no documented complications exhibited a significant association with higher ALT levels, emphasizing the potential impact of undiagnosed complications on liver function [36-38]. Moreover, no clear association was found between the presence of hypertension or dyslipidemia and abnormal liver enzymes.

Surprisingly, non-insulin hypoglycemic medications, both injectable and oral therapies, did not show a significant association with elevated liver transaminases. This contradicts some literature suggesting a potential link between certain antidiabetic medications and liver enzyme abnormalities [20,39,40]. Notably, patients not on insulin therapy demonstrated higher ALT levels, suggesting a potential role of insulin in liver function regulation.

Statin use, a cornerstone in managing cardiovascular risk in diabetics, did not show a significant relationship with elevated liver transaminases. This finding aligns with the established safety profile of statins, emphasizing their crucial role in diabetic patient care without significant hepatotoxic effects [39,41].

CONCLUSION

This study contributes valuable insights into the prevalence and factors associated with elevated liver transaminases in diabetic patients. The nuanced relationships observed highlight the complexity of diabetes management, urging clinicians to consider various patient-specific factors. The findings underscore the importance of regular liver function monitoring in diabetic individuals, as early detection and management of abnormal liver parameters would help minimize liver-related morbidity as well as overall mortality. Future research should delve deeper into the intricate interplay between diabetes, medications, and liver health to refine therapeutic strategies and improve patient outcomes.

Declarations

Ethics approval and consent to participate

The study was approved by KAIMRC Institutional Review Board (IRB, NRC22R/415/08)

Data collected by reviewing the electronic medical record in King Abdulaziz Medical City (Best Care System).

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Authors' contributions

- RA Contributed with writing proposal, IRB application, data collection, data analysis, manuscript writing, and manuscript revision.
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- AA Contributed with writing proposal, IRB application, data collection, data analysis, manuscript writing, and manuscript revision.
- NA Contributed with writing proposal, IRB application, data analysis, manuscript writing, and manuscript revision.

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