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Original Article

Biochemistry Section

Altered Liver Function Test in Type 2 Diabetes Mellitus Subjects and its Association with Dyslipidaemia and Fasting Blood Sugar: A Cross-sectional Study

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ABSTRACT

Introduction: Multiple organ systems are affected due to the metabolic dysregulation associated with Diabetes Mellitus (DM). Altered lipoprotein metabolism and liver enzymes have been identified as independent risk factors for the development of Cardiovascular Disease (CVD). Routine screening of liver function and ultrasound imaging of the liver should be done at the time of diagnosis of type 2 DM and thereafter at regular intervals.

Aim: To determine the association between liver function parameters and glycemic status in type 2 diabetics. Additionally, the study aimed to correlate liver enzymes and lipid profiles in Type 2 DM patients.

Materials and Methods: A cross-sectional study was conducted from August 23rd, 2021 to October 23rd, 2021 on 100 Type 2 diabetic patients attending the diabetic Outpatient Department of Biochemistry, at Annapoorana Medical College and Hospital, Salem, Tamil Nadu, India. Fasting glucose, total cholesterol, triglyceride, and High-Density Lipoprotein Cholesterol (HDL) were measured using the direct enzymatic method, while Low-Density Lipoprotein Cholesterol (LDL) was calculated using Friedewald's formula. Total bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), total protein, and albumin were analysed using the ERBA EM-200 auto analyser based-on the wet chemistry principle. Pearson's correlation analysis was performed to examine the relationship between variables.

Results: Among the total of 100 type 2 diabetic patients who participated in present study, 59 were males and 41 were females. The mean±SD age of diabetic patients was 51.23±10.810 years, ranging between 35 and 76 years. The frequency of altered liver enzymes in the study sample was found to be 33, with 25 being males and 8 being females. The mean fasting blood sugar levels with normal liver function and abnormal liver function were observed to be 128.37±13.16 mg/dL and 133.79±15.68 mg/dL, respectively, but the difference was not statistically significant. The mean values of total cholesterol, triglyceride, and low-density lipoprotein with normal liver function were observed to be 137.18±34.44 mg/dL, 175.12±65.19 mg/dL, and 75.55±9.78 mg/dL, respectively, while with abnormal liver function, they were observed to be 196.05±52.67 mg/dL, 143.28±47.63 mg/dL, and 138.83±38.11 mg/dL, respectively, showing statistical significance.

Conclusion: The present study found a strong association between deranged liver enzymes with fasting blood sugar and dyslipidaemia.

Keywords: Cardiovascular disease, Lipid profile, Metabolism

INTRODUCTION

Type 2 DM is one of the most common health problems facing mankind, representing approximately 98% of global diabetes diagnosis, although this proportion varies widely among countries [1]. Diabetes is estimated to affect 537 million adults worldwide, with a global prevalence of 10.5% among adults aged 20 to 79 years [2]. The liver plays a pivotal role in glucose homeostasis by extracting glucose from the blood to use as fuel and storing it as glycogen, as well as synthesising glucose from non carbohydrate sources. Despite its crucial role in regulating blood glucose levels, the evaluation of liver function in clinical workups by physicians is not frequently done. Studies have shown that individuals with T2DM have a higher incidence of abnormalities in liver function tests than those without DM [3,4]. These studies suggest that elevated liver enzyme levels indicate decreased insulin sensitivity, increased insulin resistance, and the development of Type 2 DM [5,6].

The insulin resistant state is also characterised by an increase in pro-inflammatory cytokines, such as Tumour Necrosis Factor (TNF), which contribute to hepatocellular injury [7]. Studies suggest that liver function is involved in the development of diabetes, but no study has determined which of these enzymes is the best marker for the development of DM [8]. Elevated serum aminotransferase levels, including AST, ALT, and γ-Glutamyltransferase (GGT), are commonly observed in diabetes. A recent report shows a significant association between increased ALT and AST levels and insulin resistance, T2DM, and metabolic syndrome [9]. Fasting plasma glucose is the most commonly used index to monitor the occurrence of early Type 2 DM, which is of great significance in the prevention of diabetes. Studies have also noted a positive correlation between elevated liver enzymes and fasting and postprandial glucose levels with the duration of DM [10]. If, elevated liver enzyme levels are significantly associated with an increase in fasting plasma glucose levels, there might be implications in considering liver enzymes as effective molecular markers for the early detection of high-risk individuals for diabetes [11].

T2DM is characterised by significantly higher serum levels of triglycerides, total cholesterol, LDL, and lower levels of HDL compared to normal healthy subjects [12]. This may be due to increased lipolysis and free fatty acid flux from adipocytes, resulting from insulin resistance, leading to increased lipid synthesis in hepatocytes, which contributes to the dyslipidaemia occurring in type 2 DM [11]. A study from South Africa reported that diabetic patients with abnormal liver enzymes were significantly associated with dyslipidaemia [13]. Another study from China [14] showed a significant positive correlation between elevated ALT and Waist Circumference (WC), Body Mass Index (BMI), Total Cholesterol (TC), Triglycerides (TG), LDL Cholesterol (LDL-c), and Fasting Blood Sugar (FBS). A previous study reported an association between ALT activity and dyslipidaemia and insulin resistance in subjects with T2DM [15]. Altered lipoprotein metabolism

and liver enzymes have been identified as independent risk factors for the development of Cardiovascular Disease (CVD) [16]. Dyslipidaemia and atherogenic dyslipidaemia can lead to severe complications and increased mortality in type 2 diabetes patients, in addition to being strong potential risk factors for predicting CVDs [17].

Hence, the current study was designed to determine the association between liver function parameters and glycemic status and to compare and correlate the liver enzymes and lipid profile in T2DM patients.

MATERIALS AND METHODS

The present cross-sectional study was conducted from August 23rd, 2021, to October 23rd, 2021, at the Diabetic Outpatient Department in Annapoorana Medical College and Hospital, Salem, Tamil Nadu, India. Ethical clearance was obtained from the Institutional Ethics Committee (Approval no: AMC/IEC/Proc.No.07/2020).

Inclusion criteria: A total of 100 T2DM patients attending the diabetic clinic were enrolled in the study.

Exclusion criteria: Subjects with chronic diabetic complications (retinopathy, nephropathy, neuropathy), chronic liver disease, malignant disease, infectious disease, pregnancy and lactation, alcohol and smoking habits, and those taking statins and lipid-lowering drugs were excluded from the study.

Sample size calculation: The sample size was calculated using the formula:

$$n=Z^2(pq)/d^2$$

Where: Z=relative deviate (at 95% confidence interval) i.e., 1.96

p=prevalence of altered liver function test=80% [18]

q=100-p=100-80=20

d=acceptable margin of error 10%

$n=(1.96)^2\times0.8\times0.2/(0.08)^2$

=96.

Procedure

Data regarding socio-demographic characteristics, including age, occupation, socio-economic class according to the modified BG Prasad scale [19], and clinical data regarding the duration of DM, any past history of thyroid disorder, hypertension, CVD, cancer, and arthritis, as well as treatment history, were collected using a well-structured questionnaire. Trained laboratory technologists collected 5 mL of blood samples from each participant after an overnight fast of atleast 12 hours, using a sterile disposable syringe under aseptic conditions. The blood samples were transferred to dry clean test tubes. The collected blood specimens were kept at room temperature for 30 minutes to allow clot formation. After clot formation, the blood was centrifuged at 3,000 rpm for 10 minutes using a fixed head rotor centrifuge. The serum was analysed for liver function tests, lipid profiles, and fasting blood sugar using the fully automated clinical chemistry analyser ERBA EM-200, and kits were procured from ERBA EM-200 [Table/Fig-1]. The quality of each test was maintained by strictly following standard operating procedures. Quality control was run daily prior to each test, and the completion, accuracy, and clarity of the collected data were regularly checked.

The interpretation of test results was based-on the reference range recommended by the manufacturers' instructions [20]. For serum lipids, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) guideline were followed [21]. Anthropometric measurements (height, weight, waist circumference) were taken according to World Health Organisation (WHO) guidelines. BMI was calculated as weight divided by height squared (kg/m^2) and classified as underweight (BMI <18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2), overweight (BMI=23-24.9 kg/m^2), and obese (BMI ≥25 kg/m^2) [22]. The study subjects were categorised into normal and abnormal groups based-on the deranged liver function test parameters. The study subjects in the abnormal group exhibited an elevation in atleast one of the tested liver function test parameters.

Parameters	Method of estimation	Cut-off range	
Total bilirubin (mg/dL)	Diazo method	0.3-1 mg/dL	
AST (U/L)	IFCC without pyridoxal phosphate	Male	>35 U/L
		Female	>31 U/L
ALT (U/L)	IFCC without pyridoxal phosphate	Male	>45 U/L
		Female	>34 U/L
ALP (U/L)	AMP method	Male	>129 U/L
		Female	>104 U/L
Total protein (g/dL)	Biuret method	6.4-8.3 g/dL	
Albumin (mg/dL)	BCG method	3.5-5.5 g/dL	
Fasting glucose	Glucose oxidase-peroxidase method	≥126 mg/dL	
Total cholesterol	Cholesterol- oxidase method	≥200 mg/dL	
Triglyceride	Glycerol phosphate oxidase-peroxidase method	≥150 mg/dL	
HDL	Direct enzymatic method	Male	≤40 mg/dL
		Female	≤50 mg/dL
LDL	Calculated by Friedewalds formula	≥100 mg/dL	

[Table/Fig-1]: Methodology and cut-off range for fasting glucose, LFT and lipid profile parameters.
IFCC: International federation of clinical chemistry; AMP: Amplification refractory mutation system polymerase chain reaction

STATISTICAL ANALYSIS

The data were recorded, cleaned, and analysed using Statistical Package for the Social Sciences (SPSS) version 20.0. Quantitative data were summarised as Mean±Standard Deviation (SD), and differences in means between the two groups were analysed using an unpaired Student's t-test. Pearson's correlation analysis was performed to examine the relationship between variables. A p-value <0.05 was considered statistically significant.

RESULTS

Among the total of 100 type 2 diabetic patients who participated in present study, 59 were males and 41 were females, respectively. The age group of study participants <50 years consisted of 57 individuals, while >50 years consisted of 43 individuals. The mean±SD age of diabetic patients was 51.23±10.810 years, ranging between 35 and 76 years [Table/Fig-2].

Characteristics		Frequency (n)
Gender	Male	59
	Female	41
Age (years)	<50	57
	≥50	43
BMI (kg/m^2)	Underweight	6
	Normal weight	20
	Overweight	64
	Obese	10
Socio-economic status	Class-I	4
	Class-II	6
	Class-III	63
	Class-IV	24
	Class-V	3
Occupation	Physical labourers	31
	Office workers	52
	Unemployed	17
Duration of DM	<5 years	68
	>5 years	32

[Table/Fig-2]: Socio-demographic and anthropometric characteristics in the study subjects.

It was observed that 67 subjects had results of LFTs within the normal reference ranges. The remaining 33 subjects had abnormalities in

the liver function parameters. These 33 subjects with deranged LFTs exhibited an elevation in atleast one of the tested liver function test parameters. Thus, the frequency of altered liver enzymes in the study sample was found to be 33%. Among these, 25 were males, and eight were females. The frequencies of abnormal LFT values observed in the study sample for total bilirubin, AST, ALT, ALP, and total protein were found to be 10%, 30%, 33%, 5%, and 2%, respectively. The most common abnormality in liver function tests was elevated values of ALT in 33 patients, whereas abnormalities in total protein in two patients were the least common abnormality observed [Table/Fig-3].

Parameters	Frequency of normal LFT	Frequency of abnormal LFT
Total bilirubin (mg/dL)	90	10
AST (U/L)	70	30
ALT (U/L)	67	33
ALP (U/L)	95	5
Total protein (g/dL)	98	2
Albumin (g/dL)	96	4

[Table/Fig-3]: Frequency of normal and abnormal liver function tests in the study sample.

The mean values of all the parameters of liver function tests in the study participants were as follows: Total Bilirubin: 0.52±0.28 (mg/dL), AST: 36.21±29.32 (mg/dL), ALT: 41.84±26.23 (mg/dL), ALP: 108.73±31.62 (mg/dL), Total protein: 7.32±0.92 (mg/dL), and Albumin: 4.59±0.61 (mg/dL) [Table/Fig-4].

Parameters	Mean±SD	
	Normal LFT	Abnormal LFT
Total bilirubin (mg/dL)	0.52±0.28	0.41±0.17
AST (U/L)	36.21±29.32	19.45±10.34
ALT (U/L)	41.84±26.23	21.12±12.56
ALP (U/L)	108.73±31.62	78.12±26.95
Total protein (g/dL)	7.32±0.92	3.25±0.13
Albumin (g/dL)	4.59±0.61	2.92±0.92

[Table/Fig-4]: Mean values of liver function tests in the study cases.

The mean age was 50±13 years in the normal LFT group and 47±9 years in the abnormal LFT group. The mean BMI was 24.07±1.67 (kg/m^2) and 26±1.89 (kg/m^2) in the normal and abnormal LFT groups, respectively, and there was no statistical significance. The fasting blood sugar level was observed to be higher in both groups, but this difference was not statistically significant. The values of total cholesterol, triglyceride, and low-density lipoprotein in both groups showed statistical significance. There was no significant difference in HDL cholesterol levels in both groups [Table/Fig-5].

Parameters	Mean±SD		p-value
	Normal LFT (67)	Abnormal LFT (33)	
Age (yrs)	50±13	47±9	0.26
BMI (kg/m^2)	24.07±1.67	26±1.89	0.34
Fasting glucose (mg/dL)	128.37±13.16	133.79±15.68	0.71
Total cholesterol (mg/dL)	137.18±34.44	196.05±52.67	≤0.001
Triglyceride (mg/dL)	175.12±65.19	143.28±47.63	≤0.001
Low density lipoprotein (mg/dL)	75.55±9.78	138.83±38.11	≤0.001
High density lipoprotein (mg/dL)	43.41±11.10	51.21±8.38	0.04
Very low density lipoprotein (mg/dL)	27.65±8.93	35.16±11.8	0.02

[Table/Fig-5]: Comparison of clinical and biochemical parameters between normal and abnormal LFT in the study sample.

It was observed that AST and ALT showed significant correlation with fasting blood sugar, total cholesterol, triglycerides, low-density lipoprotein, and were negatively correlated with high-density lipoprotein. The concentrations of ALP and total bilirubin correlated significantly with fasting glucose and triglyceride levels. Total protein and albumin showed significant negative correlation with fasting glucose, and protein showed significant negative correlation with triglyceride levels. However, the correlation was not statistically significant with the other parameters of LFT [Table/Fig-6].

DISCUSSION

With the emerging social phenomena of rapid economic development, urbanisation, an increasingly aged population, and changes in people's lifestyles, diabetes has become a major chronic disease that threatens human health. Type 2 diabetes is a heterogeneous disorder with a more complex aetiology and is far more common than type 1. Type 2 diabetes comprises more than 90% of cases of DM. The major metabolic defects that occur in type 2 diabetes are either a delayed insulin secretion relative to glucose load (impaired insulin secretion) or the peripheral tissues being unable to respond to insulin (insulin resistance). Plasma glucose homeostasis is influenced by acute and subclinical hepatocellular disturbances. Hepatocellular damage causes oxidative stress and cytokine production in the liver, leading to alterations in liver enzymes and dysregulation of blood glucose maintenance. This results in abnormal and elevated liver enzymes in circulation. Moreover, liver enzymes are not only markers of liver dysfunction but also have predictive value in assessing the severity of diabetes.

A previous study conducted in the north Indian population [23] found an association between abnormal liver function and Type 2 diabetes. The current study was conducted to assess the incidence of altered LFT in T2DM subjects. The average age of diabetic patients was 51.23±10.810 years, ranging between 35 and 76 years. Among the 100 study participants, 67 had LFT values within the normal reference ranges, and the remaining 33 had abnormalities in atleast one liver function parameter. Out of these, 25 were males and eight were females, and the likelihood of having abnormal LFTs was greater among males when compared to females. Previous studies have shown an association between male sex and abnormal LFTs, and this difference in sex may be explained by differences in body fat distribution due to the presence of oestrogen in females [24-26].

The most common abnormality observed in present study was elevated values of ALT, while abnormalities in total protein were the least common. Authors found a statistically significant association between the elevation of AST and ALT and T2DM. In a cross-sectional study conducted in Iran, ALT and AST were found to be elevated in 10.4% and 3.3% of type 2 diabetes patients, respectively. Similarly, studies conducted by Bora K et al., in India and Balogun et al., in Nigeria reported a high prevalence of deranged LFTs, with rates of about 71.2% and 70% among the diabetic population, respectively [27]. Ghimire S et al., observed increased levels of ALT (57%) and AST (46%) among patients with DM, and a significant elevation in AST and ALT was observed among patients with DM [28]. Studies conducted in Finland, Scotland [29], and England reported prevalence rates of abnormal ALT in T2DM patients of 17%, 23.1%, and 25.6%, respectively. Another study found significant increases in GGT, ALT, and ALP levels, but not in AST levels [30]. The findings of the present study are consistent with a study conducted in Iraq, which found a statistically significant association between the elevation of AST and ALT and glycemic status [31]. A comparison of the findings of previous studies with the present study is shown in [Table/Fig-7] [18,32,33].

Parameters	Total bilirubin		AST		ALT		ALP		Total protein		Albumin	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Fasting glucose (mg/dL)	0.618	≤0.001	0.768	≤0.001	0.756	≤0.001	0.772	≤0.001	-0.135	≤0.001	-0.342	≤0.001
Total cholesterol (mg/dL)	0.358	0.893	0.874	≤0.001	0.820	≤0.001	0.802	0.021	0.173	0.072	0.103	0.267

Triglyceride (mg/dL)	0.256	≤0.001	0.723	≤0.001	0.727	≤0.001	0.628	≤0.001	-0.233	≤0.001	0.271	0.036
Low density lipoprotein (mg/dL)	0.327	0.016	-0.620	≤0.001	0.835	≤0.001	0.691	0.124	0.200	0.117	0.067	0.473
High density lipoprotein (mg/dL)	0.179	0.751	0.837	≤0.001	-0.643	≤0.001	-0.618	0.007	0.197	0.119	0.438	0.134

[Table/Fig-6]: Correlation analysis between liver function tests with fasting blood glucose and lipid profile in subjects with abnormal LFT.

Name of the authors	Place and year of the study	Sample population and sample size	n (%) of subjects with altered LFT	n (%) of subjects with dyslipidaemia
Shahwan MJ et al., [18]	Palestine, March 2018 to January 2019	453 T2DM patients	81%	67%
Kathak RR et al., [32]	Bangladesh. December 2018 and February 2020	138 T2DM patients	33%	69%
Alfred SD et al., [33]	Chennai, August 2018 to March. 2019	100 T2DM patients	73%	47%
Present study	Salem, August 2021 to October 2021	100 T2DM patients	33%	28%

[Table/Fig-7]: Comparison of frequencies of dyslipidaemia and liver dysfunction in various studies [18,32,33].

Authors also observed an association between deranged LFTs and dyslipidaemia and fasting blood sugar. A study from South Africa [13] previously reported a significant association between abnormal liver enzymes and dyslipidaemia. Patients with one or more of the following criteria: LDL-C >100 mg/dL, total cholesterol >200 mg/dL, triglycerides >150 mg/dL, or HDL-C <40 mg/dL in males and <50 mg/dL in females were considered to have dyslipidaemia [34]. Authors found a significant correlation between AST and ALT with fasting blood sugar, total cholesterol, triglycerides, low-density lipoprotein, and a negative correlation with high-density lipoprotein. There was no significant difference in HDL cholesterol levels between the groups. According to a recent study, out of 80 type 2 diabetic patients, 39, 62, 47, and 52 patients had abnormal TC, LDL, TAG, and HDL, respectively. This indicates a high association between dyslipidaemia and type 2 diabetic patients, which is also associated with impairments in liver function. Fatty liver is associated with increased LDL, TAG, and TC, combined with low HDL levels [35].

Several studies have reported high levels of TAG, TC, and LDL-C among diabetic patients, which is consistent with the findings of the present study. However, a study conducted in Nigeria reported a different finding, with higher TAG levels observed in controls. The main cause of lipid abnormalities in patients with T2DM is impaired insulin secretion, which affects the production of liver apolipoprotein and regulates the enzymatic activity of Lipoprotein Lipase (LpL) and Cholesterol Ester Transport Protein (CETP). Insulin deficiency reduces the activity of hepatic lipase, which may alter the production of biologically active LpL in T2DM.

HDL metabolism is dysregulated in T2DM and is associated with low HDL cholesterol levels, which is an independent cardiovascular risk factor. The findings of the present study are consistent with a study by N H et al., who reported elevated liver function parameters with hyperlipidemia [36]. Adeniran SA et al., investigated the association of increased ALT and AST with dyslipidaemia in patients from Nigeria diagnosed with T2DM [37]. A comparison of the findings of previous studies with the present study is shown in [Table/Fig-8] [38-40].

Name of authors	Sample size	Place and year of the study	Correlation between liver enzymes and lipid profile parameters
Kariyawasan CC et al., [38]	201 T2DM patients	Sri Lanka, June 2019 to June 2020	ALT showed a significant positive correlation with TG and VLDL-C.
Lotfi S et al., 2021 [39]	142 T2DM patients	Yemen January to May 2020	ALT and GGT was significantly associated with the hyperglycaemic and hyperlipidemia profile.
Imran M et al., [40]	88 T2DM patients	India January 2018-June 2018)	Of the four liver enzymes, the serum levels of GGT showed an independent association with all lipid components.
Present Study	100 T2DM patients	Salem, August 2021 to October 2021	AST and ALT showed significant correlation with fasting blood sugar, total cholesterol, triglycerides, low density lipoprotein.

[Table/Fig-8]: Comparison of correlation between liver enzymes and lipid profile parameters with the past studies [38-40].

Limitation(s)

The major limitation of this study is that it included only hospital-based samples, which may not truly represent the diabetic population of this region.

CONCLUSION(S)

The results of the present study provide evidence that ALT activity is higher in T2DM patients. Additionally, a statistically significant correlation was found between altered liver function tests and lipid profile parameters, as well as fasting sugar levels. The present study highlights the importance of monitoring liver function in T2DM patients. Efficient management and early screening can be very helpful in preventing the highly morbid complications of this preventable disease.

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