

Elevated liver enzymes and its association with uncontrolled type 2 diabetes mellitus: A study from South India



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ABSTRACT

Background: Diabetes mellitus is one of the most common chronic diseases has been related to various liver illnesses such as liver enzyme derangements, non-alcoholic fatty liver disease, hepatocellular carcinoma, and cirrhosis. There has been increased interest on the contribution of liver enzymes to prediction of diabetes and glycemic control. **Aims and Objectives:** The aim is study was to correlate liver enzymes with Hemoglobin A1c (HbA1C) in type 2 diabetes mellitus (T2DM) with uncontrolled sugars. **Materials and Methods:** Diabetic patients seen on Outpatient Department basis or admitted as inpatients are included in this study. Information is collected and detailed history is taken using pre-formed proforma at the time of admission. Liver function tests are measured to all participants, and HbA1C value is measured. Liver enzymes are correlated with HbA1C values. **Results:** Among 119 patients, the mean age was 56.65 years. Eighty-three patients (69.7%) were males and 36 (30.3%) were females. The mean duration of diabetes is 8.84 ± 5.81 , mean HbA1c is 8.89 ± 2.62 . Mean fasting blood sugar and post-prandial blood sugar were 179.4 ± 96.3 and 252 ± 136.5 , respectively. There is negative correlation is seen among Aspartate transferase (AST), gamma-glutamyl transferase (GGT) and AST/Platelet (PLT) ratio, but not alanine aminotransferase (ALT). However, there is negative Pearson correlation between HbA1C and liver enzymes as mentioned above which are statistically not significant except AST/PLT ratio. **Conclusion:** The importance of monitoring the liver function tests in uncontrolled T2DM patients was studied, which showed association among AST, GGT, and AST: ALT ratio with HbA1C. All were negatively correlated with HbA1C, but statistically significant correlation is seen only with AST: PLT ratio.

Key words: Uncontrolled sugars; Type 2 diabetes mellitus; Liver enzymes; Hemoglobin A1c; aspartate transferase: Platelet ratio

INTRODUCTION

Diabetes mellitus is a group of metabolic disorder that shares phenotype hyperglycemia. Diabetes mellitus is one of the most common chronic diseases causing morbidity and mortality.^{1,2} The IDF provides the latest figures, information and projections on diabetes worldwide. In 2021, approximately 537 million adults (20–79 years) are

living with diabetes. The total number of people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045.3 in 4 adults with diabetes live in low- and middle-income countries. Almost 1 in 2 (240 million) adults living with diabetes are undiagnosed.^{3,4} Diabetes has been related to various liver illnesses such as non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and cirrhosis.⁵⁻⁷

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The liver has an important role in the maintenance of glucose homeostasis.⁸ Serum liver enzymes indicate the liver injury, these include gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), Alkaline phosphatase (ALP), and alanine aminotransferase (ALT), these are also measures for NAFLD which has been associated with insulin resistance⁹ and the risk of diabetes mellitus. In NAFLD, the altered liver enzyme levels which are biological markers linking liver disease and diabetes.^{10,11}

As recommended by ADA 2023 adults with type 2 diabetes or prediabetes, particularly those with obesity should be screened/risk stratified for NAFLD with clinically significant fibrosis (moderate fibrosis to cirrhosis) using a calculated fibrosis-4 index (derived from age, ALT, AST, and platelets [PLTs]). Clinicians underestimate its prevalence and do not consistently implement appropriate screening strategies, thus missing the diagnosis of the potentially progressive form of NAFLD in high-risk groups, such as those having obesity or type 2 diabetes mellitus (T2DM). The under diagnosis is compounded by sparse referral and inadequate prescription of medications with proven efficacy in NASH.^{12,13}

There has been increased interest on the contribution of liver enzymes to prediction of diabetes. In this regard, although many studies have shown a relation between diabetes and elevated liver enzymes, the results remain inconsistent and less studies on this topic.¹⁴

Many studies have showed a significant relationship between high levels of serum liver enzymes including AST, ALT, GGT, and diabetes mellitus.^{14,15} Even a significant increase was observed for GGT, ALT and ALP levels but not AST in some studies.¹¹ Some studies showed that significant increases in ALT and AST are associated with diabetes mellitus.¹⁶⁻¹⁸ On the other hand, in some studies, only an increase in GGT was associated with diabetes mellitus.¹⁸

Aims and objectives

The aim is study the correlation of the level of liver enzymes with Hemoglobin A1c (HbA1C) level in patients with T2DM.

MATERIALS AND METHODS

Sample size

In a study done by Mojgan et al.,³¹ 11.4% of diabetic patients had elevated ALT levels with 5% absolute precision, sample required for the study is 100.

$n=4pq/d^2=100$ Sample size taken in the study is 119.

Inclusion criteria

- Patients willing to give written informed consent
- Patients with T2DM.

Exclusion criteria

- Age <18 years
- Active or chronic inflammation
- Autoimmune diseases
- Malignancy
- Acute or chronic renal/hepatic diseases or coronary artery disease
- Type 1 diabetes
- Alcohol consumption ≥ 20 g/day in the past 3 month
- Previous diagnosis of acute or chronic liver disease
- Intake of hepatotoxic drugs
- Inflammatory diseases.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPASS statistics [IBM corp. released 2011] was used to perform the statistical analysis

- Data were entered in the excel spread sheet
- Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency, and proportions for qualitative variables.

Methodology

Diabetic patients seen on Outpatient Department basis or admitted as inpatients are included in this study. Information is collected and detailed history is taken using pre-formed proforma at the time of admission. The diagnosis of T2DM was made according to the American Diabetes Association guidelines. Liver function tests are measured to all participants, and HbA1C value is measured. Liver enzymes are correlated with HbA1C values.

RESULTS

Figure 1 shows among 119 patients in the study, the mean age is 56.65. Maximum age of >75 years and minimum of age 35 years is considered. In our study, the age group distribution has 50 patients in middle age group (46–55 years), followed by 30 members in age group of 56–65 years, 24 patients in the age group of 66–75 years and 13 are in the age group of 35–45 years and 2 are elderly >75 years, respectively. In the study, 83 patients (69.7%) are male and 36(30.3%) are females.

In our study, there were many factors which were statistically significant, which include AST, GGT, and triglycerides with $P < 0.05$. AST and GGT values were statistically significant but not ALT in liver enzymes. However there was association between triglycerides and HbA1C seen. Apart

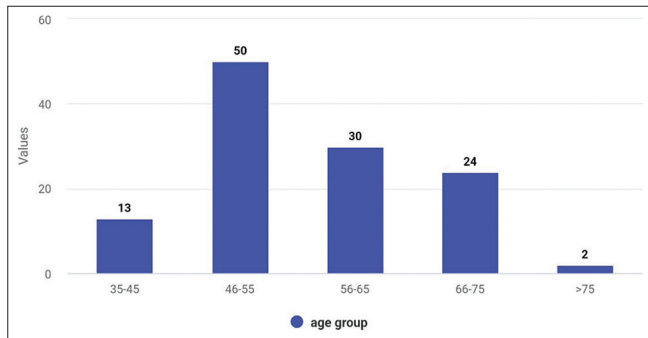


Figure 1: Demographic profile: Age and sex
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from that AST/PLT ratio is also statistically significant which was seen in our study.

The above table shows the correlation between diabetic profile and liver enzymes. There is negative correlation is seen among AST, GGT, and AST/PLT ratio, but not ALT. However, there is negative Pearson’s correlation between HbA1C and liver enzymes as mentioned above which are statistically not significant except AST/PLT ratio.

DISCUSSION

The present study has been undertaken to throw some light on derangement of liver enzymes in patients with uncontrolled type 2 diabetic patients.

In our study among 119 patients, the mean age is 56.65. Maximum age of >75 years and minimum of age 35 years. The age group distribution has 50 patients in middle age group (46–55 years), followed by 30 members in age group of 56–65 years, 24 patients in the age group of 66–75 years and 13, 2 in 35–45 years, and >5 years, respectively (Table 1). In a study done by Alam et al., the mean age of T2DM subjects was 46.4±13.6 years and 39.2±12.0 years for healthy control. The age of the diabetic subjects ranges from 27–87 years with a mean of 56.91±11.00 years while age of healthy subjects’ ranged from 31 to 86 years with the mean of 53.38±13.28 in a study done in Nepal by Jha et al. Similarly, the mean ages of the T2DM and controls participants were 55.76±10.11 and 50.93±5.41,¹⁷ respectively, in a study done in Ethiopia by Shibabaw et al.

There were 83 patients (69.7%) were male and 36 (30.3%) were female in our study (Table 3). Men constituted 121 (63%) of T2DM participants and 116 (60.4%) of the controls in a study in Ethiopia by Shibabaw et al. Similarly, 68 (68%) male and 32 (32%) female in a study done by Omer.

In many studies, the authors used elevated AST enzyme as marker for in diabetes risk assessment.²¹ In another recently published comparative cross-sectional study, it

Table 1: Basic characteristics

Variables	Values
Sample size	119
Age, mean (SD)	56.65 (9.67)
Gender	Female-36, Male-83
Duration of diabetes (years), mean (SD)	8.84 (5.81)
HbA1C, mean (SD)	8.89 (2.65)
FBS, mean (SD)	179.44 (96.35)
PPBS, mean (SD)	252.07 (136.59)

In our study, mean duration of diabetes is 8.84±5.81, mean HbA1C is 8.89±2.62. Mean FBS and PPBS were 179.4±96.3 and 252±136.5 respectively. HbA1C: Hemoglobin A1c, FBS: Fasting blood sugar, PPBS: Post-prandial blood sugar

was found that there is prevalence of abnormal LFTs in T2DM compared to healthy persons.²² The other possible assumption is the susceptibility to inflammation of the liver which alters the function of the liver and induces a change in liver biomarkers.^{23,24}

In our study, mean duration of diabetes is 8.84±5.81, mean HbA1C is 8.89±2.62. Mean FBS and PPBS were 179.4±96.3 and 252±136.5 respectively. The mean fasting Glucose (mg/dL) 201.26±24.62 HbA1C (%) 8.1±0.33 in a study done by Alam et al. Mean FBS was (mg/dL) 189.80±64.45 in a study done by Shibabaw et al.

In our study, there were many factors which were statistically significant, which include AST, GGT and triglycerides with P<0.05. FBS in patients with HbA1C <7 142.77, >7 193.51 and PPBS with HbA1C <7 179.36 and 279.98 which is statistically significant. Furthermore, total cholesterol and triglycerides as a part of work up of T2DM done also showed significant statistical association (Table 2).

Indian studies show high prevalence of deranged LFTs of about 71.2% and 70%, respectively in individuals with T2DM.²⁴ Some studies also showed abnormal liver parameters with a relatively lower rate of 53%. Hence, the frequency of deranged LFTs reported, in the case of Indian diabetes, is around 50–70%.²⁵⁻²⁸

In a study done by Alam et al., all liver enzymes showed a negative correlation with the HbA1C. ALT and AST also showed a negative correlation with the fasting blood glucose except for ALP had a positive correlation with the FBG similar to our study.

In a study done by Ying Wan and Li-Zhen Yang (2022), there was association between blood glucose (FPG, PBG, and HbA1C) and elevated GGT and AKP, which suggests that GGT and AKP may be new indicators of whether the control of FPG, PBG, and HbA1C in T2DM patients is effective.²⁹

A study done by Omer has revealed that elevated HbA1C and triglyceride in T2DM with high GOT and GPT is

Table 2: Distribution and correlation of diabetic profile and HbA1C

Parameters	HbA1C	Mean	Standard deviation	P-value
Age	7	55.61	11.06	0.466
	>7	57.06	9.13	
Duration of DM (Years)	≤7	7.72	5.09	0.194
	>7	9.27	6.05	
Age of onset of diabetes	≤7	47.91	10.63	0.950
	>7	47.78	9.85	
FBS (mg/dL)	≤7	142.77	83.96	0.010
	>7	193.51	97.52	
PPBS (mg/dL)	≤7	179.36	104.40	0.000
	>7	279.98	137.69	
HB (g%)	≤7	11.34	2.43	0.135
	>7	12.13	2.63	
MCV	7	82.14	5.99	0.040
	>7	84.64	5.85	
TLC	7	7464.82	2816.11	0.077
	>7	8550.22	3031.90	
Platelet count	≤7	2.45	1.10	0.224
	>7	2.75	1.22	
Total cholesterol	≤7	149.90	50.47	0.015
	>7	177.61	56.65	
Triglycerides	≤7	110.48	49.96	0.044
	>7	213.84	289.24	
HDL cholesterol-direct	≤7	37.19	14.83	0.591
	>7	35.56	14.72	
T.B	7	0.88	1.32	0.908
	>7	0.91	1.66	
T. protein	≤7	6.39	1.77	0.073
	>7	6.84	0.94	
Albumin	≤7	3.79	1.01	0.849
	>7	3.85	1.91	
ALT	7	23.94	14.31	0.930
	>7	24.39	27.94	
AST	7	38.14	58.68	0.033
	>7	23.42	14.97	
GGT	≤7	42.73	30.14	0.010
	>7	77.56	112.16	
Blood urea	≤7	39.90	44.99	0.355
	>7	34.33	20.43	
S. creatinine	≤7	1.38	1.59	0.563
	>7	1.78	3.84	
AST/PLT ratio	≤7	28.62	47.01	0.134
	>7	16.50	35.81	
Tyg	≤7	4.73	0.38	0.0001
	>7	5.13	0.47	
AST/ALT	≤7	1.70	2.29	0.846
	>7	1.57	3.68	
AST/PLT ratio	≤7	0.22	0.20	0.006
	>7	0.56	1.06	

AST: Aspartate transferase, ALT: Alanine aminotransferase, PLT: Platelet, GGT: Gamma-glutamyl transferase, HDL: High-density lipoprotein, FBS: Fasting blood sugar, PPBS: Post-prandial blood sugar, TLC: Total leucocytes count, MCV: Mean corpuscular volume

Table 3: Association between gender and HbA1C

Gender	HbA1C		P-value
	≤7	>7	
Male	18 (54.5)	65 (75.6)	0.025
Female	15 (45.5)	21 (24.4)	
Total	33 (100.0)	86 (100.0)	

In the study there is correlation between gender and HbA1C. HbA1C: Hemoglobin A1c

significantly associated with FL disease. Early detection of FL in T2DM is important to prevent progression of the disease and minimize morbidity and mortality. An altered lipid profile level is a feature of diabetes mellitus.³⁰

Elevated levels of ALT, AST, GGT, and ALP are related to higher odds of diabetes. Also, increased serum levels of ALT, GGT, and ALP even within normal range were independently related with the increased odds

Table 4: Correlation of diabetic profile with liver function tests

Parameters	Ageabia	Duration of DM (years)	HbA1C	FBS (mg/dL)	PPBS (mg/dL)
AST					
Pearson correlation	0.002	-0.052	-0.169	-0.127	-0.153
Sig. (2-tailed)	0.985	0.577	0.066	0.170	0.097
ALT					
Pearson Correlation	0.072	-0.008	-0.065	-0.051	-0.074
Sig. (2-tailed)	0.433	0.928	0.484	0.584	0.424
GGT					
Pearson Correlation	0.157	0.051	-0.018	-0.134	-0.091
Sig. (2-tailed)	0.094	0.586	0.851	0.155	0.333
AST/PLT Ratio					
Pearson Correlation	-0.018	-0.119	-0.185*	-0.108	-0.120
Sig. (2-tailed)	0.844	0.198	0.044	0.244	0.194

AST: Aspartate transferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, FBS: Fasting blood sugar, PPBS: Post-prandial blood sugar, PLT: Platelet

of diabetes. These results indicated the potential of elevated liver enzymes as biomarkers for the possible presence of diabetes in a study done by Noroozi Karimabad et al.³¹

In our study, when the LFT is considered there was correlation of AST and GGT which was statistically significant, with $P=0.033$ and 0.01 . The mean and standard deviation of AST in patients with HbA1C <7 and >7 were 38.14 ± 58.68 and 23.42 ± 14.97 . Similarly for GGT with HbA1C <7 and >7 were 42.73 ± 30.14 and 77.56 ± 112.16 . However there was no statistically significant correlation was seen with ALT and total bilirubin. So, there is negative Pearson's correlation is seen among AST, GGT, and AST/PLT ratio, but not ALT with HbA1C in our study. However, statistically significant correlation was seen only with AST/PLT ratio with HbA1C (Table 4).

In a study done by Kariyawan et al., patients with HbA1C >7 liver enzymes and lipid profile were deranged. Pearson's correlation revealed a positive co-relation between HbA1C and VLDL and a negative correlation between bilirubin and HbA1C. Positive correlation between HbA1C, ALP, TG, and VLDL indicates progression of disease and probability of cardiovascular complications. The negative correlation between HbA1C and bilirubin indicates good control and may be useful in monitoring control.³²

In our study, there was significant statistical correlation was seen with AST/PLT ratio i.e APRI score, with $P=0.006$. However, the Pearson's correlation revealed a negative correlation between HbA1C with APRI score.

Similarly, a study done by Alshuweishi et al., suggested that AST/PLT ratio i.e., APRI score is inexpensive, novel markers of FBG and may serve as supportive evidence in the diagnosis and management of hyperglycemic conditions. Further studies are required for using APRI score correlating with HbA1C.³³

Limitations of the study

This is a small sample study and single centre study.

CONCLUSION

Our study mainly focuses on the importance of monitoring the liver function tests in uncontrolled T2DM patients. There were several derangements in LFTs in the Type 2 diabetic patients which include AST, GGT and AST:PLT ratio. All are negatively correlated with HbA1C, but statistically significant correlation is seen only with AST:PLT ratio. Future studies are required to find out the causes of hepatic dysfunction in diabetics and to explore the impact of abnormalities of the liver on the glycemic status.

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