



## Impact of Glycemic Control Variability on liver Enzymes in Type 2 Diabetes Mellitus- A Cross-Sectional Study

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### KEYWORDS

Gamma-Glutamyl transferase, Alkaline Phosphatase, Aspartate transaminase, Alanine transaminase, HbA1c protein, human

### ABSTRACT:

**Background:** Elevations in liver enzyme levels represent another facet of metabolic syndrome in diabetes mellitus. Non-alcoholic fatty liver disease might even precede type 2 diabetes. However the significance of HbA1c values in predicting the course of chronic liver disease in diabetics through varying ranges of glycemic control needs to be accessed for the sake of early and better prognostication.

**Aims:** The aim of this study was to estimate the HbA1c levels and Liver enzymes in Diabetic patients and to find their association.

**Materials and methods:** This Cross sectional study was conducted in Sri Siddhartha Institute of medical sciences and research centre from March 2024 to February 2025. A total of 398 patients diagnosed to have type 2 diabetes mellitus were assessed. They were divided into four groups based upon HbA1c levels: Group 1 normal (<5.8%); group 2, HbA1c (5.9-6.4%), and group 3, group 4 (HbA1c 6.5 to 7% and HbA1c >7% respectively). Liver enzymes (ALT, AST, GGT) were assessed by fully automated analyser and HbA1c estimated by HPLC method. One-way analysis of variance (ANOVA) and Chi-square/ Fisher Exact test were performed on the data to access association and determine statistical significance. Also Pearson's coefficient value of  $\leq 0.05$  was considered significant.

**Results:** The Liver enzymes namely GGT, AST and ALP were elevated in diabetic patients and showed positive correlation with HbA1c (p value- <0.001).

**Conclusion:** The outcomes of this study were, the elevated GGT, AST, ALP levels signify prognostic utility of HbA1c with respect to chronic liver disease in type 2 diabetes. This is reflected by positive correlation of liver enzyme values with glycated hemoglobin levels, as compared to control population.

### INTRODUCTION

Liver function tests (LFTs) are extensively used parameters to screen for liver diseases, monitor the progression of known systemic or hepatic disorders and for predicting potential hepatotoxic effects of certain drugs. Diabetes is known to be associated with NAFLD, a party to various abnormalities in metabolic syndrome. Anti-oxidant property of glutathione explains, elevated levels of GGT in diabetic state with  $\beta$ -cell dysfunction. GGT plays a major role in glutathione homeostasis. Whenever there is an underlying Insulin resistance, a chronic elevation of liver transaminase levels in mild to moderate ranges can be expected.

Type 2 diabetes (T2DM) patients are more likely to demonstrate liver function test abnormalities than non-diabetics, but their association with glycaemic control is unclear. Numerous confounding factors make the assessment further ambivalent like alcoholism, lack of exercise, unhealthy food habits along with sociocultural, racial and ethnic attributes among other determinants driving altered lipid profiles.<sup>1</sup> Numerous studies have shown mild to moderate increase in liver enzymes especially ALT in diabetics with dyslipidaemia as compared to the normal population and suggested positive correlation of elevated liver function to various parameters like age, sex, body mass index, modifiable



lifestyle factors like alcoholism and abnormal lipid profile.<sup>2,3,4</sup> Some studies also suggest liver dysfunction to precede development of type 2 diabetes.<sup>5</sup>

Although there are many studies about liver enzymes derangement and diabetes, there are limited studies correlating the level of enzymes with the level of HbA<sub>1c</sub>. It is hence worth investigating if rise in different liver enzymes help predict progression of disease and the extent to which worsening liver function correlates with glycaemic indices. Therefore, in our study we are looking into the association of the spectrum of HbA<sub>1c</sub> levels with specific hepatic enzymes in diabetic patients. This would serve as a prognostic indicator and guide in prevention and early diagnosis of chronic liver disease in a patient with poor glycaemic control, irrespective of time of disease onset.

#### OBJECTIVES

- Evaluation of Aspartate transaminase, alanine transferase, Alkaline Phosphatase,  $\gamma$ - glutamyl transferase in type 2 diabetes mellitus
- Correlation of Aspartate transaminase, alanine transferase,  $\gamma$ - glutamyl transferase, Alkaline Phosphatase with HbA<sub>1c</sub>

#### MATERIALS AND METHODS

This study was conducted in Sri Siddhartha Institute of medical sciences and research centre from March 2024 to February 2025. The study was approved by Institutional ethics committee. A total of 398 patients diagnosed to have type 2 diabetes mellitus were included and their biochemical parameters assessed ad hoc, irrespective of time since diagnosis. They were divided into three groups based upon HbA<sub>1c</sub> levels as follows: Group 1 normal (HbA<sub>1c</sub> <5.8%); group 2 pre-diabetics (HbA<sub>1c</sub> 5.9-6.4%), and group 3, group 4 being diabetics (HbA<sub>1c</sub> 6.5-7 % and >7% respectively). Group 1- was taken as control population. Aspartate transaminase, alanine transferase,  $\gamma$ - glutamyl transferase, alkaline phosphatase were assessed by a fully automated analyser and HbA<sub>1c</sub> was estimated by HPLC method.

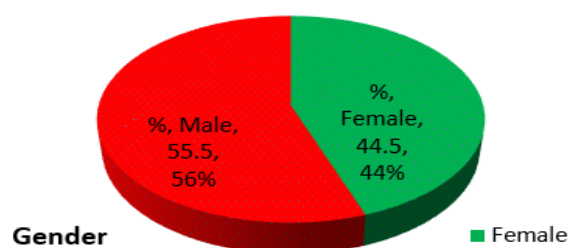
All diabetic patients with age group of 18 to 65 years were included in this cross sectional study. Patients with history of chronic alcohol consumption, liver diseases, patients on hepatotoxic drugs such as Allopurinol, Amiodarone, Anabolic steroids, Atorvastatin, Azathioprine, 6-Mercaptopurine, Busulfan, Carbamazepine, Chlorpromazine, Disulfiram- Substance abuse agent, Phenytoin, Quinidine, Pyrazinamide, Rifampin, Simvastatin, patients with diabetes complications and systemic conditions were excluded from the study.

We have performed a descriptive and inferential statistical analysis. We have presented results on continuous measurements through Mean, SD (Min-Max). Also, results on categorical measurements have been presented in Number (%). Level of significance has been fixed at 5%. On the data obtained, one-way analysis of variance i.e. ANOVA testing for determination of statistically significant differences between mean values of >3 independent (unrelated) groups and Chi-square/ Fisher Exact test for determining significance of study parameters on a categorical scale between >2 groups has been performed. For smaller samples, we used Fisher Exact test. Pearson correlation (-1 to +1) test has been used on study variables. A Pearson correlation coefficient of -1 denotes perfect negative correlation, 0 means no correlation and 1 as perfect positive correlation. The Statistical software used are SPSS 22.0 and R environment ver.3.2.2.

#### RESULTS

**Table 1: Gender- Frequency distribution of patients studied**

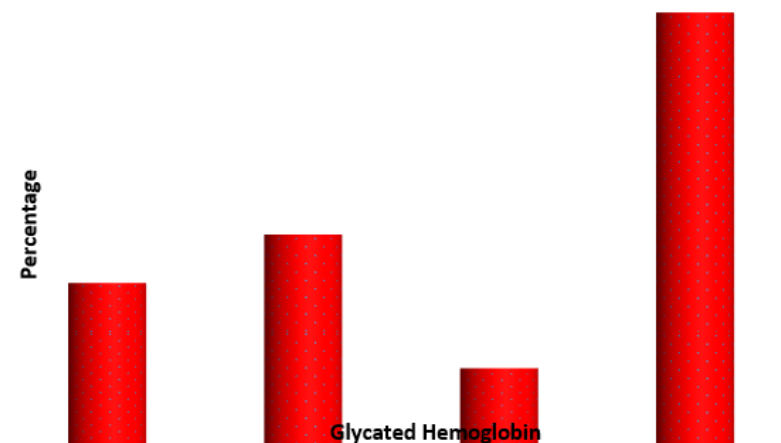
Gender	No. of Patients	%
Female	173	44.5
Male	216	55.5
Total	389	100.0



**Figure 1**

**Table 2: Glycated Hemoglobin- Frequency distribution of patients studied**

Glycated Hemoglobin	No. of Patients	%
NORMAL	72	18.5
PRE-DIABETICS	93	23.9
DIABETICS(6.5-7.0)	35	9.0
DIABETICS(>7.0)	189	48.6
Total	389	100.0



Figure

Table 3: Comparison of mean values of clinical and study variables according to levels of HbA1C of patients studied

Variables	HBA1c				Total	P Value
	NORMAL	PRE-DIABETICS	DIABETICS(6.5-7.0)	DIABETICS(>7.0)		
Age	43.68±12.58	50.45±12.32	52.57±11.42	54.51±10.72	51.36±12.17	<0.001**
RBS	92.22±13.97	105.84±21.51	129.74±39.54	180.98±71.66	141.98±65.56	<0.001**
HbA1c	5.32±0.25	6.08±0.24	6.81±0.14	9.27±1.84	7.55±2.14	<0.001**
GGT	30.26±18.81	30.65±14.36	33.37±18.67	36.25±14.71	33.54±16.54	<0.05*
SGOT	18.7±13.65	24.3±11.52	36.13±14.57	41.89±21.18	30.22±15.24	<0.001**
SGPT	23±11.67	37.12±9.15	43.45±12.36	54.78±18.97	39.25±13.3	<0.001**
ALP	78.39±24.3	82.68±28.54	123±30.45	136.78±37.12	105.21±30.1	<0.05*

ANOVA test

**Abbreviations:** RBS- Random blood sugar, GGT-Gamma Glutamyl-transferase

Positive correlation of older age and higher RBS levels are observed with worsening glycaemic control. The mean values of biochemical parameters RBS, HbA1c, **SGOT**, **SGPT**, GGT and **ALP** were increased in diabetics compared to control. (table 3) (P value: <0.001).

Table 4: PEARSON CORRELATION

Variables	r Value	P Value
HbA1c vs. SGOT	0.011	0.825
HbA1c vs. SGPT	0.142	0.005**
HbA1c vs. GGT	0.105	0.038*
HbA1c vs. ALP	0.217	<0.001**

**Abbreviations:** SGOT- Serum Glutamyl oxaloacetate transferase, SGPT- Serum Glutamyl Pyruvate transaminase, ALP- Alkaline phosphatase, GGT: Gamma-glutamyl transferase .

Positive Pearson correlation is seen with HbA1c and SGPT, GGT, ALP. (Table 4) (P value: <0.001)

## DISCUSSION

Type 2 diabetes takes centre stage in metabolic syndrome. Diabetes is also shown to be associated with NAFLD, however the association with glycemic control is rather unclear. Few studies suggest strong association of elevated liver enzymes in diabetic patients of older age, higher BMI, male sex and dyslipidaemia suggesting liver function abnormality to be a facet of metabolic syndrome, even preceding diagnosis of diabetes mellitus.<sup>2,6</sup> Study by Ko *et al.* noted that a liver marker combination of highest ALT and GGT and lowest



AST/ALT quartiles significantly raises risks of both T2DM and impaired fasting glucose.<sup>5</sup>

Study by Bodhe *et al.* suggested that in diabetics, HbA1c served as a predictor of dyslipidaemia and atherogenicity.<sup>7</sup> Also, HbA1c levels are known to be unreliable in decompensated stage of cirrhosis of liver.<sup>8</sup> Limited studies however have ventured into studying the correlation of glycaemic indices with elevated liver enzymes in diabetics who aren't chronic alcoholics. Christman *et al.* suggested a J curve association of HbA1c <4 % with that of AST and ALT elevation in non-alcoholic non diabetic adults.<sup>9</sup> Hence studying spectrum of liver enzyme changes in diabetics at varying spectrum of glycaemic control becomes imperative for better prognostication and clinical management.

Serum aminotransferase levels serve to access degree of hepatocyte injury. Insulin-resistant states show elevated free fatty acid levels which is directly hepatotoxic by disrupting cell membranes, causing mitochondrial dysfunction and interfere directly or via toxic metabolites in the regulation of metabolism by activation and inhibition of key steps. This stands as a possible explanation to higher incidence of raised transaminases in diabetics. Also high oxidant levels induce reactive lipid peroxidation and peroxisomal beta-oxidation. They further recruit inflammatory cells causing hepatocyte injury.<sup>3</sup>

ALP, GGT and bilirubin are markers of biliary function and cholestasis with GGT being frequently used to access liver function in chronic alcoholism. Serum gamma-glutamyl transferase is an ectoplasmic enzyme and an antioxidant that has a major role in glutathione homeostasis by intracellular uptake of glutathione and breakdown of extracellular glutathione synthesized in epithelial cells of intrahepatic duct. Higher levels of GGT may be linked to greater oxidative stress as seen with  $\beta$ -cell dysfunction and reduced insulin action.<sup>10</sup>

In our study, patients of a wide age group were sampled randomly, irrespective of their time of onset of diabetes on an ad-hoc basis, after exclusion of alcoholic liver diseases and an extensive list of other possible parameters known to effect the liver function tests. There was positive correlation of elevated liver enzymes with increasing age group in diabetes. However, no difference was noted among both genders with respect to level of elevations in liver enzyme. Few studies have found higher association of elevated liver enzymes in diabetic males.<sup>11,12</sup> However study by Belkacemi *et al.* found higher SGPT levels in diabetic females as compared to males.<sup>13</sup> These differences could be because of varying ethnic and socio-demographic characteristics influencing dyslipidemia in above study populations.

The worsening HbA1c profile correlated with increasing levels of Random blood sugar levels as expected. Most significantly, categorisation of patients based on worsening glycaemic control showed positive correlation with elevation of three of the liver enzymes, being maximum for ALP followed by SGPT and GGT suggesting HbA1c to be a possible prognostic indicator of chronic liver disease in diabetic patients. A study by Teshome *et al.* and Meltzer *et al.* found similar higher levels of SGPT in diabetics.<sup>4,12</sup> As in a study by Chang *et al.*, Meltzer *et al.* found that the odds ratio for diabetes as predictor of elevated SGPT was a significant 3.0, even after adjustment for confounding factors like age, sex, body mass index and alcohol consumption among others.<sup>12,15</sup>

The mean values of elevation of liver enzymes in our study was noted to be mild to moderate. This was similar to findings by other studies estimating SGPT, SGOT levels in type 2 diabetics.<sup>14,15</sup> The increase in mean of liver enzyme levels of SGPT, GGT and ALP was mild in the prediabetic category while the mean SGOT levels were fairly within the normal range. Among the diabetic categories, mild increase in all 4 liver enzymes were noted with higher mean values in diabetics with HbA1c >7.0 compared to the diabetics with a glycaemic control range of 6.5 to 7.0. Hence a statistically significant positive correlation was noted between ALP, followed by SGPT and GGT levels with that of worsening glycaemic control in pre-diabetic and diabetic population as compared to non-diabetics.

Through our study we wish to emphasise that DM is a significant risk factor for liver injury and regular assessment of LFTs correlated with glycaemic indices in diabetic patients forms integral part of screening and early clinical management of chronic liver disease.<sup>16,17</sup> Assessment for correlation of liver enzyme levels with features of the metabolic syndrome like obesity and dyslipidaemia were not performed and sole purpose of the study was to assess possible association of elevated liver enzymes with glycaemic control. In our study, we excluded chronic alcoholics, diabetics with complications, systemic disorders and patients with history of hepatotoxic drug intake and other known causes of hepatic disorders. Hence agreeing upon conclusions of other studies suggesting association of LFT abnormalities with that of dyslipidaemia, we purport to strengthen upon the understanding that a better glycaemic control allows for better managing of chronic liver disease associated with the metabolic syndrome of type 2 diabetes mellitus.



## CONCLUSIONS

The present study helped us to investigate type 2 diabetes mellitus more precisely with liver enzymes, which further can be used for its early diagnosis and management. In this study, SGPT, ALP and GGT were significantly associated with worsening glycaemic control in type 2 diabetes.

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