

# Liver Function in Type-2 Diabetes Mellitus Patients

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## Abstract

**Background:** Diabetes mellitus (DM) is a syndrome of disordered metabolism with abnormally high blood glucose levels (hyperglycemia). In Type-2 DM (T2DM), the loss of direct effect of insulin to suppress hepatic glucose production and glycogenolysis in the liver causes an increase in hepatic glucose production. Hence, this study was intended to determine the status of parameters related to liver function in T2DM patients and compare it with that of controls.

**Objectives:** To study the activity of serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum alkaline phosphatase (ALP) in T2DM patients and compare it with that of normal healthy controls.

**Materials and Methods:** A total of 30 patients of both sexes suffering from T2DM and 30 age and sex matched normal individuals were selected for the study. The patients with fasting plasma glucose  $\geq 126$  mg/dl on 2 occasion were included in the study. Patients with any concomitant diseases which can alter liver function and patient with hepatitis, alcoholic were excluded from the study.

**Results:** The mean activity of serum ALT ( $47.86 \pm 33.66$  U/L), serum AST, ( $49.7 \pm 30.76$  IU/L), and serum ALP ( $115.9 \pm 42.65$  IU/L) of diabetic patients shows significant difference from that of the normal subjects.

**Conclusion:** The outcomes of the present study suggest that the liver enzymes (ALT, AST, and ALP) have shown higher activity with T2DM patients than individuals who do not have DM. The most common abnormality seen among these liver enzymes is elevated AST activity.

**Key words:** Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase

## INTRODUCTION

Diabetes mellitus (DM) is often simply considered as diabetes, a syndrome of disordered metabolism with abnormally high blood glucose levels (hyperglycemia). The two most common forms of DM are Type-1 diabetes and Type-2 diabetes (T2DM) both leading to hyperglycemia, excessive urine production, compensatory thirst, increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism.

T2DM is a complex heterogeneous group of metabolic conditions characterized by increased levels of blood

glucose due to impairment in insulin action and/or insulin secretion. Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells, including skeletal muscle cells and adipocytes.<sup>1</sup> The liver plays a major role in the regulation of carbohydrate metabolism, as it uses glucose as a fuel, it has the capability to store glucose as glycogen and also synthesize glucose from non-carbohydrate sources. This type of role makes the liver more susceptible to diseases in subjects having a metabolic disorder, especially for DM.<sup>2</sup>

In T2DM, the loss of a direct effect of insulin to suppress hepatic glucose production and glycogenolysis in the liver causes an increase in hepatic glucose production.<sup>3</sup> In T2DM, hyperinsulinemia in combination with a high free fatty acid (FFA) flux and hyperglycemia are known to up-regulate lipogenic transcription factors. Moreover, pathways that decrease the hepatic FFA pool, i.e., both FFA oxidation and efflux of lipids from the liver are impaired. The increased availability of FFA, glucose, and insulin contribute to the increase of malonyl-CoA by

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stimulating CoA carboxylase that converts acetyl-CoA to malonyl-CoA.<sup>4</sup>

The fatty acids overload the hepatic mitochondrial-oxidation system, leading to accumulation of fatty acids in the liver.<sup>5</sup> These mechanisms finally lead to non-alcoholic fatty liver disease (NAFLD) in T2DM patients. In addition, several studies have also shown an association between NAFLD and features of the metabolic syndrome, including dyslipidemia and DM, stressing the association with insulin resistance as an important feature of NAFLD.

Some authors have considered that NAFLD may be the hepatic component of the T2DM as metabolic syndrome.<sup>6,7</sup> In the majority of cases, NAFLD causes asymptomatic abnormality of liver enzyme levels (including alanine aminotransferase [ALT], aspartate aminotransferase (AST), and alkaline phosphatase (ALP)).<sup>8</sup> Of these liver enzymes, ALT is most closely related to liver fat accumulation<sup>9</sup> and consequently ALT has been used as a marker of NAFLD. Serum aminotransferase such as ALT and AST indicate the concentration of hepatic intracellular enzyme that has leaked into the circulation. These are the markers for hepatocellular injury and are used as primary markers.<sup>10</sup>

Numerous studies have identified that hyperglycemia may lead to oxidative stress and glycation reactions. Over time, the initial glycation products undergo intramolecular rearrangements and oxidation reactions (glycoxidation) and ultimately transform into stable so-called advanced glycation end-products (AGEs). AGE-modification of proteins can alter or limit their functional or structural properties, which ultimately can lead to tissue damage as seen in DM. Oxidative stress may also be one of the factors which may alter liver enzymes (ALT, AST, and ALP). ALP is also used for the assessment of the liver function. It reaches extremely high levels in biliary obstruction. The altered ALP activity may reflect an increased hepatic insulin resistance or oxidative stress.<sup>11</sup>

## MATERIALS AND METHODS

A total of 30 patients of both sexes suffering from T2DM and 30 age and sex matched normal individuals were selected for the study. Patients whose fasting plasma glucose (FPG)  $\geq 126$  mg/dl on 2 occasion were included in the study. Patients with any concomitant diseases which can alter liver function and patient with hepatitis, alcoholic and taking any medicine were excluded from the study.

Estimation of fasting blood serum glucose, ALT, AST, and ALP activity were performed by glucose oxidase-peroxidase method,<sup>12</sup> IFCC kinetic assay, respectively.<sup>13-15</sup>

## Calculation

$$\text{Blood glucose (mg / dl)} = \frac{\Delta\Delta \text{ of test} \times \text{concentration of standard (100 mg/dl)}}{\Delta\Delta \text{ of standard}}$$

## Statistical Analysis

Mean  $\pm$  standard deviation was calculated for all the parameters analyzed and were compared by Student's *t*-test (2-tailed) using SPSS. *P*-value considered:

*P* < 0.005 - Significant

*P* < 0.001 - Highly significant

## RESULTS

The mean activity of serum ALT ( $47.86 \pm 33.66$  U/L), serum AST, ( $49.7 \pm 30.76$  IU/L), and serum ALP ( $115.9 \pm 42.65$  IU/L) of diabetic patients shows significant difference from that of normal subjects (Table 1 and Figures 1-3).

The prevalence of increased activity of AST was 56.1%, ALT was 19.8% and ALP was 33% in T2DM patients (Table 2 and Figure 4).

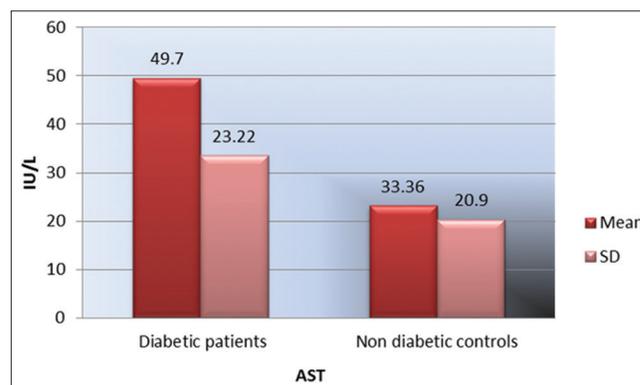


Figure 1: Comparison of serum aspartate aminotransferase activity in diabetic patients and non-diabetic controls

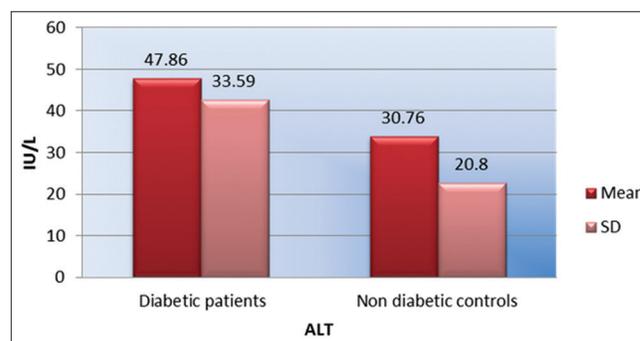
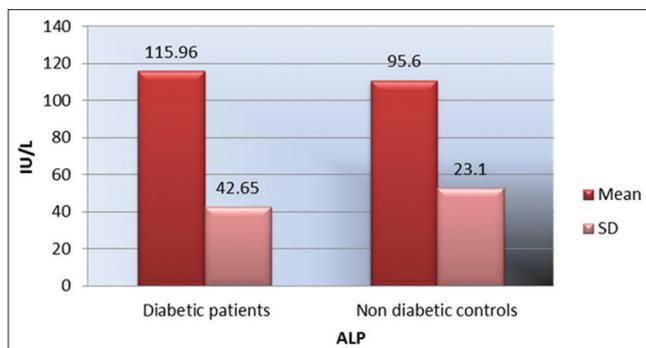
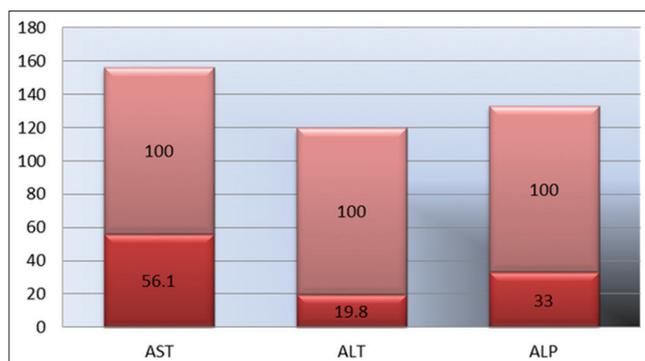


Figure 2: Comparison of serum alanine aminotransferase activity in diabetic patients and non-diabetic controls



**Figure 3: Comparison of serum alkaline phosphatase activity in diabetic patients and non-diabetic controls**



**Figure 4: Prevalence of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in diabetic patients**

**Table 1: Comparison of serum ALT, serum AST, and serum ALP activity, in non-diabetic and T2DM patients**

Parameters	Mean±SD		t value	P value
	Diabetic	Control		
AST (IU/L)	49.7±23.22	33.36±20.9	2.37	0.021
ALT (IU/L)	47.86±33.59	30.76±20.8	2.84	0.006
ALP (IU/L)	115.9±42.65	95.6±23.1	2.29	0.026

SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, T2DM: Type-2 diabetes mellitus

**Table 2: Prevalence of increased AST, ALT, and ALP activity in T2DM patients**

Parameters	AST	ALT	ALP
Increased %	56.1	19.8	33

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, T2DM: Type-2 diabetes mellitus

## DISCUSSION

DM is often simply considered as a syndrome of disordered metabolism with abnormally high blood glucose levels (hyperglycemia). Besides the microvascular and macrovascular complications in DM a compromised immune state is also a condition that increases the susceptibility of a diabetic patient to different infections.

In Harris *et al.*, studies, it was shown that individuals with T2DM have a higher incidence of liver function test abnormalities than individuals who do not suffer from DM.<sup>16</sup> Aminotransferase such as ALT and AST, activities are sensitive indicators of liver cell injury and are helpful in recognizing hepatocellular diseases. Chronic mild elevation of liver enzymes is frequently found in Type-2 diabetic patients. However, though all these reports suggest that the liver function is involved in the development of diabetes but no, study so far have been known to show which of these enzymes is the best markers for the development of DM.<sup>17</sup> This study was conducted on 30 diabetic patients and 30 healthy persons. There was no significant difference between the age and sex of the subjects from the two groups. The diabetic state of the patients was confirmed by recording their detailed medical history and finally by estimating the FPG concentration by GOD-POD method, FPG concentration > 126 mg/dl on two occasions was considered as confirmation of DM FPG recorded for diabetic patients was 257.93 ± 110.004 mg/dl. The outcomes from the present study are as follows:

### Assessment of ALT Activity

The mean level of serum ALT in Type-2 diabetic patients group was 47.86 ± 33.66 IU/L in normal controls was 30.66 ± 20.81 IU/L. The ALT in fasting serum sample in diabetic patients group was found to be significantly higher in comparison to the normal control group with P = 0.026. Raised level of ALT was noted in 19.8% diabetic patients. These findings are consistent with the results obtained from several other studies by various researchers. According to Gonem *et al.*, it was identified that the prevalence of ALT enzyme activity in diabetic patients (n = 959) was 15.7% (151).<sup>18</sup> ALT catalyzes the reversible transamination between L-alanine and α-ketoglutarate to form pyruvate and L-glutamate as such having an important role in gluconeogenesis and amino acid metabolism. The reaction is reversible, but the equilibrium of the ALT reaction favors the formation of L-alanine. ALT enzyme activity is primarily found in liver but its activity although much lower. Another explanation might be up-regulation of ALT enzyme activity. Among the amino acids, Alanine is the most effective precursor for gluconeogenesis. Gluconeogenesis is increased in subjects with T2DM due to increase substrate delivery (e.g, alanine) and an increased conversion of alanine to glucose. ALT might thus be up-regulated as a compensatory response to the impaired hepatic insulin signaling or, alternatively, may leak more easily out of the hepatocytes as a consequent of fatty infiltration and subsequent damage.<sup>19</sup>

### Assessment of AST Activity

The mean of serum AST in T2DM group was 49.7 ± 23.22 IU/L in normal control group 33.36 ± 20.9. The AST in fasting serum sample in diabetic patients was found to be

significantly higher in comparison with the normal control group with *P* value 0.021. Raised level of AST was noted in 56.1% diabetic patients. These findings are consistent with the results obtained from several other studies done by various researches. According to Goldberg *et al.*, (2007), it was identified that the prevalence of AST enzyme activity in diabetic patients was (101 patients) 15% diabetic patients.<sup>20</sup> The activity of transaminase enzymes AST is often measured; these enzymes function normally to transfer the amino group from an amino acid, Aspartate in the case of AST to a keto acid, producing pyruvate and oxaloacetate, respectively. It is located in the cytoplasm of the hepatocyte; an alternative form of AST is also located in the hepatocyte mitochondria. Although, both transaminase enzymes are widely distributed in other tissues of the body, the activities of ALT outside the liver are low and, therefore, this enzyme is considered more specific for hepatocellular damage.<sup>21</sup>

### Assessment of ALP Activity

The mean of serum ALP in T2DM group was  $115.9 \pm 42.65$  IU/L and in the normal control group was  $95.6 \pm 23.1$  IU/L. The ALP in fasting serum sample in diabetic patients was found to be significantly higher in comparison with the normal control group with *p* value 0.026. Raised level of ALP (30 patients) was noted 33% (10) diabetic patients. In a study by Han *et al.*, it was found that the level of ALP in Type-2 diabetic patients was  $10.20 \pm 22.82$  IU/L and the prevalence of ALP (*n* = 81) was 6.2% diabetic patients.<sup>22</sup> ALP is a hydrolytic enzyme serine protease acting optimally at pH 10. It has been reported in few earlier studies that many diabetics may also exhibit elevated ALP.<sup>23</sup> T2DM being a metabolic syndrome in which the fat metabolism is dysregulated, there is consequent elevation of FFA leading to subsequent fatty liver. ALP in the liver is found to be associated with cell membrane which adjoins the biliary canaliculus, and so high plasma concentration of the liver isoenzyme indicates cholestasis rather than simply damage to the liver cells. According to a study by Southampton university hospitals, 60 diabetics stabilized on insulin or oral hypoglycemic agents, routine liver function tests particularly ALP was elevated occasionally but rarely to more than twice the upper limit of normal. It can be concluded that functionally significant liver disease is uncommon amongst stabilized diabetic patients.<sup>24</sup> According to Vozarova *et al.*, it was estimated that the liver enzymes AST, ALT, and ALP were significantly higher in diabetic patients as compared to non-diabetic control.<sup>25</sup>

### CONCLUSION

The outcomes from this study suggested that the liver enzymes (ALT, AST, and ALP) have shown higher activity with T2DM patients than individuals who do not have

DM. The most common abnormality seen among these liver enzymes is elevated AST activity. The prevalence of increased activity of AST was 56.1%, ALT was 19.8% and ALP was 33%. The reason behind the elevation of these enzymes could be due to direct hepatotoxic effect of fatty acid on the liver when it is produced in excess. Mechanisms for this may include cell membrane disruption at high concentration, mitochondrial dysfunction, toxin formation, and activation and inhibition of key steps in the regulation of metabolism. Other potential explanations for elevated transaminases in insulin-resistant states include oxidative stress from reactive lipid peroxidation, peroxisomal beta-oxidation, and recruited inflammatory cells. The insulin resistant state is also characterized by an increase in pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$ , which may also contribute to hepatocellular injury.

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