## **Original Research Article**

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# Alterations of liver enzymes in T2DM: a case control study

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#### **ABSTRACT**

**Background:** Liver plays an important role in regulation of blood glucose in fed state as well as in fasting. Diabetes mellitus can result as a consequence of liver disorder and vice versa. Objective of the present study is to compare the liver enzymes in type 2 diabetic patients as compared to non-diabetic patients.

**Methods:** A case- control study was conducted in Clinical Biochemistry Laboratory, Adarsha Super speciality Hospital, Udupi from April 2018 to August 2018. The data of 174 diabetic patients and 118 healthy people as controls was collected. Fasting blood glucose, aspartate aminotransferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) were estimated in the study subjects.

**Results:** It was found that AST levels (47.55±4.69U/L) in diabetics extremely significantly high as compared to controls (33.51±2.33U/L). ALT levels were insignificantly high in diabetics compared to controls. ALP was significantly elevated (p=0.0002) in diabetics. Correlation study showed a weak positive correlation between AST, ALT and blood glucose. Odds ratio showed a higher risk of liver enzyme elevation in diabetics. Risk of elevation of AST was found to be 1.65 times high and ALT was 1.25 times high in diabetics compared to non-diabetics.

**Conclusions:** Diabetics had high liver enzymes as compared to non-diabetics. An association was found between type 2 diabetes mellitus and liver enzymes. For better characterization of cause and effect, further studies need to be done on alterations in liver function tests along with the histopathological analysis of liver biopsy samples.

Keywords: Diabetes mellitus, Hepatic enzymes, Risk of liver disorders

#### INTRODUCTION

Liver disease is an important cause of death in type 2 diabetes mellitus. A population-based diabetes study by De Marco et al, reported that cirrhosis was the fourth leading cause of death and accounted for 4.4% of diabetes related deaths. In another prospective cohort study Balkau B et al, suggests that cirrhosis accounted for 12.5% of deaths in patients with diabetes. Virtually the entire spectrum of liver disease is seen in patients with type 2 diabetes. This includes abnormal liver enzymes, nonalcoholic fatty liver disease (NAFLD), cirrhosis,

hepatocellular carcinoma, and acute liver failure. In addition, there is an unexplained association of diabetes with hepatitis C. The prevalence of cirrhotic patients developing diabetes is 12.3%-57%. Thus, patients with diabetes have a high prevalence of liver disease and patients with liver disease have a high prevalence of diabetes. Elevation of serum alanine aminotransferase (ALT), while uncommon in apparently normal subjects is common in patients with type 2 diabetes. 3.

A clinical trial report suggests that 2-24% of screened type 2 DM patients had liver enzyme tests above the upper limit of normal.<sup>4</sup> In this study, investigators noted

that 5% of the patients had concomitant liver disease at baseline. Another report involving multiple clinical trials with type 2 diabetes suggests that diabetics had higher levels of serum alanine amino transferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase than the normal limits.<sup>5</sup>

Liver has an important role in the carbohydrate metabolism and regulation of blood glucose. It is the major site for glycogenesis and gluconeogenesis. This function of liver makes it susceptible in diabetes mellitus.<sup>6</sup> Increased activity of the liver enzymes is associated with Insulin resistance.<sup>7</sup> The cause and effect relationship between diabetes mellitus and liver diseases are well documented. But less explored area in the field of research in present settings.

The aim of present study was to compare the liver enzymes in type 2 diabetic patients as compared to non-diabetic healthy volunteers. Author also would like to find out the association between type 2 diabetes and liver enzyme levels.

#### **METHODS**

A case- control study was conducted in Clinical Biochemistry Laboratory, Adarsha Super Speciality Hospital, Udupi from April 2018 to August 2018. The data of diabetic patients and healthy people as controls was collected. Institutional ethics committee approval has been sought before starting the study.

- Group I: 174 type 2 diabetic patients irrespective of their treatment
- Group II: 118 non- diabetic, healthy volunteers.

The data of patients in group I and controls in group II. Sample size is calculated by using suitable formula. Diabetes mellitus (DM) is diagnosed as per American Diabetic Association guidelines 2016.8

#### Inclusion criteria for patients

Type 2 diabetic patients with a mean age of  $52.3\pm1.7$ .

#### Exclusion criteria for patients

• Type 1 diabetics, alcoholics, smokers, hypertensives, those with liver disorders

 Patients on hepatotoxic drugs and those with any other systemic illnesses.

#### Inclusion criteria for controls

- Healthy volunteers, non-diabetic, nonalcoholic individuals
- Group I subjects had a mean age of 52.3±1.7years, 64% of them being males and 36% being females.
- Group II had a mean age of 47.8±2.1 years, 72% being men and 28% women.

Data of age, gender, liver enzymes and fasting blood sugar of patients were collected from author's clinical biochemistry laboratory. Investigations were done by collecting 2ml of venous blood sample in plain tubes by puncturing antecubital vein with aseptic precautions. Samples were centrifuged at 3000rpm for 15minutes. Plasma was analyzed for liver enzymes, AST, ALT and Alkaline phosphatase with commercially available kits in fully automated chemistry analyzer, EM-200.<sup>9-11</sup>

## Statistical analysis

Data was analyzed by using the software SPSS 16. Mann-Whitney U test was used to compare the data between the groups. P <0.05 is taken as significant. Spearmann's correlation coefficient, r (between -1 and +1) is calculated to find the correlation of each parameter with blood glucose. Odds ratio was calculated to find out the relative risk.

### **RESULTS**

The results were expressed as mean±standard error of mean (SEM) calculated for blood glucose, AST, ALT and alkaline phosphatase and are represented in the Table 1. It was found that AST levels (47.55±4.69U/L) in diabetics extremely significantly high as compared to controls (33.51±2.33U/L). ALT levels were insignificantly high in diabetics compared to controls. ALP was significantly elevated (p=0.0002) in diabetics.

Spearmann's correlation coefficients calculated to assess the correlation between blood glucose and AST as well as blood glucose and ALT were statistically insignificant. But there was a weak positive correlation between fasting blood glucose and liver enzymes.

Table 1: Laboratory parameters of diabetic patients and controls.

| Lab parameters                       | T2DM        | Non-diabetic | P value   |
|--------------------------------------|-------------|--------------|-----------|
| Fasting plasma glucose (mg/dl)       | 182.28±8.42 | 96.79±1.05   | <0.0001** |
| Post prandial plasma glucose (mg/dl) | 257.8±14.9  | 136.6±5.3    | <0.0001** |
| Aspartate amino transferase (U/L)    | 47.55±4.69  | 33.51±2.33   | 0.0256*   |
| Alanine amino transferase (U/L)      | 45.66±3.2   | 44.13±4.47   | 0.51      |
| Alkaline phosphatase (U/L)           | 103.45±7.6  | 71±2.224     | 0.0002**  |

<sup>\*</sup>significant; \*\*highly significant

Odds ratio for ALT and AST are calculated and given in Table 2 and Table 3. It is evident from Table 2 that AST levels were high in 23% of diabetics and 18% of non-diabetics. Odds ratio showed a higher risk of liver enzyme elevation in diabetics. Risk of elevation of AST was found to be 1.65 times high. Table 3 shows that ALT levels were high in 169% of diabetics and 36% of non-diabetics. Risk of elevation of ALT was 1.25 times high in diabetics compared to non-diabetics.

Table 2: Odd's ratio for aspartate amino transferase.

|                                       | No. of T2DM | No. of Non-<br>diabetics |
|---------------------------------------|-------------|--------------------------|
| Increased aspartate amino transferase | 40          | 18                       |
| Normal aspartate amino transferase    | 134         | 100                      |

Odd's Ratio = (40x100) / (134x18) = 1.65 (standard statistical formula)

Table 3: Odd's ratio for alanine amino transferase.

|                                     | No. of T2DM | No. of<br>Non-<br>diabetics |
|-------------------------------------|-------------|-----------------------------|
| Increased alanine amino transferase | 71          | 42                          |
| Normal alanine amino transferase    | 103         | 76                          |

Odd's ratio = (71x76) / (103x42) =1.25 (standard statistical formula)

#### **DISCUSSION**

A significant elevation of ALT, AST and ALP levels were observed in diabetics, AST levels were 1.4 times high in diabetes patients as compared to normal controls. ALP levels were 1.45 times high in diabetes patients. This suggests that diabetes patients have an inclined tendency towards alterations of liver enzymes.

There are several studies which report that there is an elevation in liver enzymes in diabetics. In a report involving clinical trials with type 2 diabetes patients, serum ALT, AST or alkaline phosphatase were 1-2.5 times higher than the upper normal. 5.6% had serum ALT values between 1 and 2.5 times upper normal limit.<sup>5</sup> Asymptomatic individuals with mild elevations of ALT and AST revealed that 98% had liver disease, fatty liver disease and chronic hepatitis.<sup>12</sup> The most common cause of a mild elevation of serum ALT is non-alcoholic fatty liver disease, which is the most prevalent liver disease in type 2 diabetes.<sup>13</sup>

Odds ratio (OR) for AST suggest that the risk of development of liver disease is 1.65 times in diabetics as compared to controls. Odds ratio for ALT suggest that risk of liver disease is 1.25 times in diabetics. A similar finding was noted in a previous study. 14 A study by Gupte

et al, reported that 49% patients with DM had evidence of fatty liver; of these 32% underwent liver biopsy. <sup>15</sup> In the biopsy report it was found that 66%, 13% and 9% showed mild, moderate and severe nonalcoholic steatohepatitis respectively and 22% showed fibrosis.

Since author's have not assessed the histopathology of liver biopsy specimens, we cannot specify whether there is a fatty change or to which liver disorder they are prone. But comparatively high liver enzymes suggest a probable risk of chronic liver disease in future. Present study is supported by a recent review report by Paola et al, suggests that patients with type 2 DM are at the highest risk of non-alcoholic steatohepatitis (NASH), even in the setting of normal plasma aminotransferases. <sup>16</sup>

However hepatic fat accumulation is a well-known complication of diabetes with a reported frequency of 40-70%. If fat in the hepatocytes is accompanied by lobular inflammation and steatonecrosis, it should be considered as a cause for chronically elevated liver enzymes in asymptomatic diabetic patients.<sup>17</sup> In type 2 diabetic patients with or without obesity, up to 30% have fat with inflammation, 25% have associated fibrosis, and 1-8% have cirrhosis.<sup>18-20</sup>

Limitations of present study are various confounding factors like obesity, metabolic syndrome and infection with hepatitis C, being not taken in to account.

#### **CONCLUSION**

Author conclude that diabetic patients had high liver enzymes as compared to non-diabetics. An association was found between type 2 diabetes mellitus and liver enzymes. For better characterization of cause and effect further studies need to be done along with the assessment of blood coagulation, abdominal ultrasound, histopathology of liver biopsy and other parameters of liver profile need to be done.

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Institutional Ethics Committee

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