



Research Article

## Serum Alanine Transaminases and Lipid Profile in Type 2 Diabetes Mellitus Indian Patients

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### Abstract

**Background:** Individuals with type 2 diabetes mellitus (T2DM) have high prevalence of liver diseases due to underlying insulin resistance. Deranged lipoprotein metabolism in insulin resistant state also result in hepatic cell injury. Present study evaluated serum Alanine Transaminases (ALT) and lipid profile in diagnosed cases of T2 DM. **Methods:** Present 2 groups cross sectional study enrolled 90 patients of T2DM 90 healthy age and sex matched controls. Demographic data and anthropometric measures were recorded from all participants. After overnight fast, blood samples were collected and assayed for serum ALT, cholesterol, triglycerides, and low and high density lipoproteins. **Results:** Highly significant difference in mean value of BMI ( $27.3 \pm 3.8$  Vs  $21.7 \pm 2.4$   $p < 0.05$ ), waist circumference ( $96 \pm 7$  Vs  $82 \pm 6$   $p < 0.001$ ) and waist: hip ratio ( $1.3 \pm 0.4$  Vs  $0.7 \pm 0.3$   $p < 0.001$ ) was observed in cases compared to controls. In the cases we found significantly raised cholesterol ( $183.5 \pm 20.2$  Vs  $151.3 \pm 15.2$   $p < 0.05$ ), triglyceride ( $195.4 \pm 35.3$  Vs  $92.5 \pm 23.7$   $p < 0.001$ ), LDL ( $115.4 \pm 18.5$  Vs  $83.4 \pm 10.2$   $p < 0.001$ ), ALT ( $71.65 \pm 23.3$  Vs  $28.34 \pm 11.34$   $p < 0.001$ ) and significantly low levels of serum HDL ( $35.3 \pm 5.4$  Vs  $51.5 \pm 6.5$   $p < 0.001$ ). Serum ALT was positively correlated with BMI, waist: hip, triglycerides, LDL and negatively with HDL. **Conclusion:** DM has been proposed as a risk factor for chronic liver diseases and hepatocellular cancer. Screening of T2DM patients with simple, inexpensive, easy to measure and internationally standardized parameter serum ALT should be highly recommended. Early detection of liver abnormality and intervention will help to prevent further progression to liver cirrhosis and chronic liver disease.

**Keywords:** Alanine transaminases, type2 diabetes mellitus, liver diseases, lipid profile.

## Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder due to absolute or relative deficiency of insulin leading to derangement in carbohydrate, lipid and protein metabolism. Liver plays a central role in carbohydrate homeostasis and in maintaining blood glucose level within normal range in fasting and postprandial state. Individuals with T2DM have high prevalence of abnormal liver function tests than non-diabetics (Elizabeth 2005). Alanine transaminases (ALT) are intracellular hepatic enzyme released in circulation which is an indicator of hepatocellular injury. Mild and chronically elevated transaminases are surrogate markers of insulin resistance. (Ali Abbasi et al 2012)

T2DM is directly linked with dyslipidemia due to the lack of effect of insulin. Altered atherogenic lipoprotein pattern and elevation of some liver enzymes have been identified as independent risk factors for the development of cardiovascular disease. (Demacker et al 2000). Prevalence of liver enzymes abnormality ranges from 7.2 to 22.9% in patients of T2DM (Elizabeth 2005). As patients remain asymptomatic even if liver enzymes are elevated, liver disease progresses up to hepatic failure. Recently liver damage has been recognized as one of the major complication of T2DM, with standard mortality rates for cirrhosis greater than that for cardiovascular disease. Liver cirrhosis was the fourth leading cause of death in population based on Verona Diabetes study accounting for 4.4% diabetes related deaths (de Marco R 2000).

Patients with T2DM may suffer from entire spectrum of liver disease including elevated enzymes, non-alcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma (HCC), and acute liver failure. (Tolman et al 2007). NAFLD had been reported for the first time in 1980 as the main cause of chronic liver disease in obese women with DM. Recently numerous studies identified diabetes as an independent risk factor for

HCC (Davila et al 2005). El Serag et al (2004) studied the temporal association between DM and chronic liver diseases in a large cohort prospectively and found double risk of chronic nonalcoholic liver disease and hepatocellular carcinoma among men with DM.

There are no guidelines regarding the evaluation of liver enzymes in T2DM as a risk predictor in routine follow up of the patients in clinical practice. Present work was designed with a hypothesis of mild to moderate elevation of serum ALT with deranged lipid profile especially triglycerides in T2DM patients.

## Research Design and Methodology

This was Out Patient Department based 2 groups cross sectional study involving 90 patients of T2DM and 90 healthy age and sex matched controls. Study was conducted as per the guidelines of Institutional Ethical Committee and informed consents were obtained from all participants.

Selection criterion: Participants were enrolled by simple random sampling method.

Inclusion criterion: 90 cases of T2DM diagnosed as per standard criterion given by World Health Organization.

Exclusion criterion: Patients with previous history of liver disease, consumption of alcohol, alcoholic liver diseases, liver cirrhosis, all types of viral hepatitis, acute and chronic major illness and use of hepatotoxic and lipid lowering drugs were excluded from the study.

Hepatitis c was not considered an exclusion criterion for the following reasons: 1. detailed clinical history and examination of the patients did not point out towards any possibility of exposure to hepatitis virus. 2. low prevalence of hepatitis c in our region and 3. Cost factor Details of age, sex, family history of T2DM, duration of T2DM and history of medication were recorded from the standard questionnaire. Anthropometric

measures body weight (Kg.), height (cm.), waist and hip circumference (cm) were recorded. Body Mass Index (BMI) was calculated as  $\text{Weight (Kg)} / \{\text{Height (m)}\}^2$ .

For analysis of biochemical parameters, all subjects were recalled after overnight fast. Blood samples were collected from all volunteers and assayed after serum separation. Blood glucose (Glucose Oxidase Peroxidase end point method), serum ALT (UV- Kinetic method recommended by IFCC), serum total cholesterol (TC- Cholesterol Oxidase Peroxidase), serum triglycerides (TG- Lipase/Glycerokinase/Glycerophosphate oxidase) and High Density Lipoproteins (HDL- direct method-polyethylene glycolpretreated enzymes) were assayed using fully automatic analyzer from Transasia. Serum Low Density Lipoprotein

(LDL) was estimated by Friedewalds formula. Elevation in serum ALT levels was defined as values greater than 40IU/L.

Statistical analysis: The data collected in present study were recorded and analyzed statistically to determine the significance and correlation of different demographic and biochemical parameters by using SPSS package for windows version 16.0.

## Results

As we selected both study groups which were matching in relation to age, sex, demographic data and other parameters, we compared data after controlling confounding factors in the study groups. Demographic characteristics of cases and controls are represented in table 1.

**Table 1: Demographic characteristics of study population**

Variables	Cases(n=90) Mean +/- SD	Control(n=90) Mean +/- SD	pValue
Age(years)	46+/-13	43+/-9	0.07
Sex	63/27	56/34	0.06
Family history of DM	63 (70%)	23 (25.5%)	<0.05*
Smokers	23 (25.5%)	3 (3.3%)	
BMI(kg/m <sup>2</sup> )	27.3+/-3.8	21.7+/-2.4	<0.05*
Waist circumference(cm.)	96+/-7	82+/-6	<0.001**
Waist: Hip	1.3+/-0.4	0.7+/-0.3	<0.001**

\* - significant p value \*\* - highly significant

The patients of T2DM belonged to the age group of 33- 59 years (mean 46+/-13 Vs 43+/-9 p= 0.07) with no statistically significant difference compared to controls. Among them 63 were males and 27 females out of which 23 males were smokers. Highly significant difference in mean value of BMI

(27.3+/-3.8Vs21.7+/-2.4 p<0.05), waist circumference (96+/-7Vs82+/-6 p<0.001) and waist: hip ratio (1.3+/-0.4Vs0.7+/-0.3 p<0.001) was observed in cases compared to controls. Data regarding biochemical parameters assayed in cases and controls have been represented in table 2.

**Table 2: Comparison of Biochemical characteristics in study population**

Biochemical Parameters	Cases Mean +/- SD	Control Mean +/- SD	P Values
Blood glucose level mg/dL	127.5+/-32	85.5+/-11	<0.05*
Serum ALT IU/L	71.65+/-23.3	28.34+/- 11.34	<0.001**

Biochemical Parameters	Cases Mean +/- SD	Control Mean +/- SD	P Values
Serum total cholesterol mg/dL	183.5+/-20.2	151.3+/-15.2	<0.05*
Serum triglycerides mg/dL	195.4 ± 35.3	92.5+/-23.7	<0.001**
Serum LDL mg/dL	115.4+/-18.5	83.4+/-10.2	<0.001**
Serum HDL mg/dL	35.3+/-5.4	51.5+/-6.5	<0.05*

\*- statistically significant p value

Fasting blood glucose levels were significantly raised in patients of T2DM with mean 127.5+/-32 compared to controls 85.5+/-11(p<0.05). In these cases we found significantly raised values of fasting serum ALT (71.65+/-23.3 Vs 28.34+/- 11.34 p<0.001), serum cholesterol (183.5+/-20.2Vs 151.3+/-15.2p<0.05), serum triglyceride (195.4 ± 35.3Vs 92.5+/-23.7 p<0.001), LDL (115.4+/-18.5 Vs 83.4+/-10.2 p<0.001), and significantly low levels of

serum HDL (35.3+/-5.4 Vs 51.5+/-6.5 p<0.001). Data of variables of controls were within normal distribution and of cases in abnormal distribution when we checked for normality.

Pearson's correlation coefficients were calculated to study association of ALT with anthropometric and biochemical measures which are shown in table 3.

**Table 3: Analysis of correlation of ALT levels with different variables (r values)**

Variables	BMI	W:H	TG	LDL	Cholesterol	HDL
ALT	0.401	0.532	0.431	0.555	0.268	-0.072

## Discussion

In our cross sectional study we investigated 90 cases of T2DM for liver enzyme ALT, lipid profile and compared them with 90 non-diabetic controls. Serum ALT (71.65+/-23.3 Vs 28.34+/- 11.34 p<0.001), LDL (115.4+/-18.5 Vs 83.4+/-10.2 p<0.001) and TG levels (195.4 ± 35.3Vs 92.5+/-23.7 p<0.001) were raised significantly in cases compared to the control group. Serum cholesterol is in normal range but towards higher side in cases. Serum ALT levels were raised significantly among 36 (40%) cases of T2DM in studied group. Significant positive association of ALT was observed between BMI and W: H (r= 0.401, 0.532) and serum TG, LDL (r= 0.431, 0.555) levels. Significant negative association was observed between ALT and HDL (r=-0.072) among cases. Our findings suggest marked risk of developing liver and cardiovascular disease due to elevated ALT and atherogenic lipoprotein profile in patients with T2DM.

For assessment of liver function, we estimated serum ALT because it has been widely proved to be a surrogate marker of hepatocellular injury. As ALT is closely related to hepatic fat accumulation, it is an indirect measure of NAFLD (Andre P et al 2005). In last decade, various cross sectional and prospective studies linked association of ALT with insulin resistance, metabolic syndrome and T2DM. Han Ni (2012) studied determinants of abnormal liver function tests in DM patients in Myanmar and observed raised AST and ALT in cases with high BMI. Our study findings are in consistence with those of Adeniran Samuel Atiba et al (2013). They analyzed liver enzymes and lipid profile in 106 T2DM patients from Nigeria and found elevated ALT, AST with dyslipidemia when compared with controls. Also, our results are in agreement with Idris et al (2011), Nannipieri N et al (2005) confirming the role of insulin resistance in pathophysiology of liver diseases.

Salmella et al (1984) reported overweight, short duration, oral hypoglycemic agents,

statins and poor glycemic control as causes of elevated ALT associated with histological changes in liver. In Indian study, Jayarama and Sudha (2012) noted NAFLD in 60% cases of T2DM significantly associated with high BMI and duration of diabetes. They also observed positive correlation of ALT with fasting and postprandial blood glucose level and duration of DM. Forlani G et al (2008), in their observational point prevalence study from data of 9621 diabetic patients reported ALT levels exceeding upper limit of normal range in 16% cases. M Prashanth (2009), in their prospective study prevalence and risk factors for NAFLD in T2DM, concluded increased prevalence with multiple components of metabolic syndrome without any symptom, signs or laboratory abnormalities. Davila et al (2005) examined the association of diabetes with HCC in first population based study in the U.S. and found 43.3% of HCC patients had diabetes. They concluded diabetes as independent risk factor for HCC regardless of other major risk factor. Saligram S et al (2012) observed raised ALT as a surrogate marker of NAFLD in 25.6% newly diagnosed T2DM patients with raised triglycerides and low HDL levels.

Liver, being a central organ involved in carbohydrate and lipid metabolism gets deranged function due to insulin resistance in diabetes mellitus. Because of insulin resistance in T2DM, there is excess synthesis of free fatty acids which are directly toxic to hepatocytes due to cell membrane disruption, mitochondrial dysfunction, oxidant stress and toxin formation (Neuschwander-Tetri BA, Caldwell S 2003). Insulin resistance is a proinflammatory state contributing to liver injury. O'Brien RM and Granner DK (1991) reported suppressed gene transcription of gluconeogenic enzyme ALT by insulin rather than hepatic injury.

High prevalence of hepatitis C virus, an important leading cause of liver disease has been reported among patients of T2DM (Simo R et al 1996). This suggests screening for HCV in T2DM patients with elevated ALT. No imaging techniques were considered at this stage because we recommend ALT in T2DM as a simple, screening test which can

raise the possibility of liver involvement in DM and discriminate potential high risk individuals in a cost effective way. Rather these high risk cases can further be evaluated by precise imaging techniques as a confirmation. This may reduce the need and cost of over investigation and be beneficial for the patients.

Liver function is also deteriorated by hepatotoxic drugs like statins and oral hypoglycemic agents. Hence routine evaluation of liver function tests in these otherwise asymptomatic individuals should be recommended by clinicians. Although non-specific, we would like to emphasize the role of ALT which is a routine investigation that can be performed in simple set up as a screening tool. Also we excluded the possibilities of other diseases which can lead to rise in ALT. So we propose ALT as a simple tool for early detection of liver abnormality. Patients with abnormal liver function tests should have additional diagnostic work up with best clinical judgment.

### **Study Limitations**

Our study has the limitation of small sample size. Being cross sectional study, only single estimation of ALT can underestimate burden of liver disease. We did not carry out imaging investigations for presence of fatty liver, but positive correlation of ALT with TG and LDL suggest evidence of hepatic steatosis. Prospective population based studies investigating etiology and mechanism of elevation of ALT are required.

### **Conclusion**

To summarize, serum ALT, a surrogate marker of liver damage is elevated with dyslipidemia in the patients of T2DM. Screening of T2DM patients with simple, inexpensive, easy to measure and internationally standardized parameter serum ALT should be highly recommended. Early detection of liver abnormality and intervention will help to prevent further progression to liver cirrhosis and chronic liver disease.

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