STUDY OF RAISED ALANINE AMINOTRANSFERASE IN PATIENTS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objective: The aim of the study was to determine frequency of fatty liver, hepatitis C and hepatitis B in type 2 diabetes with raised ALT in our population.

Study Design: This was a descriptive study.

Place and Duration: Study has been carried out at medical out patient clinic in CMH Malir, over a span of one year (2005-2006).

Patients and Methods: We studied patients of type 2 diabetes who had persistently raised serum ALT (alanine aminotransferases) for more than eight weeks. In medical out-patient clinic, 101 patients of type 2 diabetes with raised serum ALT were studied. Age, sex, BMI (body mass index) and duration of diabetes were recorded and blood was tested for plasma fasting glucose, triglycerides, cholesterol, anti HCV antibodies and HBsAg. Ultrasonography of upper abdomen was done in all patients to look for liver size, fatty liver or any evidence of chronic liver disease.

Results: Results showed positive association of raised ALT in type 2 diabetic patients with high body mass index, recent onset diabetes, fatty liver, raised triglycerides and poorly controlled diabetes. About 22% of the studied patients were positive for hepatitis C.

Conclusion: Mild to moderate elevation in serum ALT is commonly encountered in patients of type 2 diabetes mellitus. Most of these individuals are overweight and/or have fatty liver on ultrasonography.

Keywords: Alanine aminotransferase, type 2 diabetes mellitus, body mass index, fatty liver, hepatitis C

INTRODUCTION

Mild chronic elevations of aminotransferases especially ALT, less than 250units/l, is a frequent finding in patients of type 2 diabetes mellitus [1]. This abnormal elevation of transaminases in patients of type 2 diabetes has been found to be associated with insulin resistance, obesity, non alcoholic fatty liver disease (NAFLD), chronic hepatitis 'C', chronic hepatitis 'B', drugs, and rare conditions like haemochromatosis [1]. Raised serum ALT has also been associated with diabetes independent of obesity [2]. Hepatitis C has also been found to be more common in diabetic population [3]. Considering all these associations, we identified patients of type 2 diabetes in our medical out patient clinic, who were showing persistent mild elevation of serum ALT for more than eight weeks. We studied the relationship of raised serum ALT in this particular group, with variables like age, sex, duration of diabetes, obesity, fatty liver, hepatitis B and C, serum cholesterol and triglycerides. The aim of our study was to determine the frequency of fatty liver, hepatitis C and hepatitis B in type 2 diabetics with raised ALT, in our population. Secondly

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we examined the association of this raised ALT in type 2 diabetics with age, sex, BMI, serum cholesterol and triglycerides level and compared our results with other studies from different geographical areas.

PATIENTS AND METHODS

This is a descriptive study, which was conducted in general medicine out-patient clinic of combined military hospital, Malir, over a span of about one year (2005-06). Hundred and one (101) subjects of type 2 diabetes mellitus, showing persistent elevation of serum ALT, < 250 units/l for more than eight weeks, irrespective of their age, sex, weight or BMI and duration of diabetes were enrolled. Patients of type 1 diabetes, and type 2 diabetics, who were suffering from acute viral hepatitis or known to have chronic liver disease or impaired renal functions were excluded from the study. Patients using drugs that are generally known to cause elevation of serum ALT, like statins, thiazolidinediones or anti-tuberculosis drugs, were also excluded from the study. All these subjects were clinically examined, weight and BMI were recorded. Fasting blood sample was taken for plasma glucose, serum cholesterol and triglycerides. Serum was also tested for anti HCV antibodies and HBsAg by ELISA. Ultrasound examination of upper abdomen was performed by the same radiologist in all patients, to look for size of the liver, echogenecity of liver parenchyma, any evidence of chronic liver disease like coarse echotexture of liver, dilated portal vein and/or splenomegaly. The diagnosis of fatty liver was based on a diffuse hyperechoic echotexture (bright liver) and increased liver echotexture compared with the kidneys [4,5].

STATISTICAL ANALYSIS

SPSS 10.0 was used to analyze the results. Data is presented in mean with minimum and maximum values and standard deviation. Statistical significance of association of raised ALT with studied variables was calculated, using independent sample t test and one way Anova when it was compared with categorical data and bivariate correlation was calculated where its association with continuous data was studied.

RESULTS

Out of 101, type 2 diabetes patients, selected on the basis of persistently raised ALT, 68% were female. Age of the patients varied from 27 years to 67 years with a mean of 49.09 years and median at 49 years. BMI of patients ranged between 19.8 kg/m2 to 40.9 kg/m2 with a mean value of 29.04 and median at 29 kg/m2 (table-1). In 33.7% patients the BMI was between 25 and 29.9 kg/m2, 46.5% were obese, having a BMI greater than 30 kg/m2 and 4% were extremely obese, i.e., BMI greater than 40 kg/m2. Overall about 80% of the patients were over-weight or obese (table-2). Duration from onset of diabetes varied between 1 to 20 years with a mean of 5.76 years and median at 4.0 years, suggesting relatively recent onset diabetes in majority of patients. Duration from onset of diabetes was less than 10 years in 76% of patients. Level of serum ALT ranged between 52 units/l to 220 units/l with a mean value of 76.94 and median at 64 units/l. 84% patients had serum ALT value below 100 units/l and 14% had serum ALT between 100 to 220 units/l. Serum Anti HCV antibodies were present in about 22% of the patients and HBsAg in only two patients (2%). Ultrasonography of upper abdomen suggested fatty liver in 60.4% of patients, 29.7% had unremarkable ultrasonographic appearance of the liver and rest of the upper abdomen and 9.9% of the patients showed some evidence suggestive of chronic liver disease (table-3). Majority of the patients showed a poor control of diabetes as suggested by their fasting plasma glucose values. Mean fasting plasma glucose was 8.76 mmol/l and median was at 7.90 mmol/l (table-1). Serum triglycerides value varied between 0.7 mmol/l to 2.8 mmol/l with a mean value of 1.62 and median at 1.6 mmol/l. 42% of patients had a serum triglyceride value greater than 1.7 mmol/l, which is a cut off value for inclusion criteria of metabolic syndrome. Statistical significance of relationship of raised ALT with different variables is shown in (table 4 & 5).

Table-1: Descriptive Analysis of variables studied in type 2 diabetics showing persistent elevation of serum ALT (n=101).

Parameter	Mean	Median	Standard Deviation	Minimum	Maximum
Age (years)	49.09	49.00	9.45	27	67
BMI (kg/m^2)	29.04	29.00	4.48	19.8	40.9
Duration of diabetes (years)	5.76	4.00	5.04	1.00	20.00
Cholesterol (mmol/l)	4.69	4.60	0.54	3.80	6.20
Triglycerides (mmol/l)	1.62	1.60	0.46	0.70	2.80
ALT (units/l)	76.94	64.00	35.9	52.00	220.00
Plasma fasting glucose (mmol/l)	8.76	7.90	2.95	4.9	17.00

Table-2: Frequency type 2 diabetics with elevated ALT according to body mass index (n=101)

Category	BMI (kg/m^2)	Cases with raised serum ALT
Ideal weight	< 25	20 (19.8%)
Over-weight	25 – 29.9	34 (33.7%)
Obese	30 – 35	41 (40.6%)
Moderate to severe obesity	>35	6 (5.9%)

Table-3: Abdominal Ultrasonography findings (n=101)

USG Abdomen	Number of cases
Normal study	30 (29.7%)
Fatty liver	61 (60.4%)
Chronic liver disease	10 (9.9%)

Table-4: Relationship of raised ALT with various studied variables in patients of type 2 diabetes mellitus (n=101).

variables	r-value	p-value
Age	0.17	0.07
Body mass index	0.12	0.20
Duration of diabetes	0.10	0.28
Hepatomegaly	0.14	0.15
Splenomegaly	0.08	0.42
Cholesterol	0.001	0.99
Triglycerides	0.08	0.42
Fasting plasma glucose	0.01	0.88

Table-5: Relationship of raised ALT with various categorize variables in patients of type 2 diabetes mellitus (n=101).

Variables	P-value
Gender	0.20
ABsAg	0.45
Ultrasonography abdomen	0.001

DISCUSSION

Because the liver plays a critical role in the maintenance of carbohydrate homeostasis, glucoregulation, and insulin degradation, it is not surprising that its functions may be affected as a result of diabetes mellitus [6]. Elevated activities of serum aminotransferases are a common sign of liver disease and are observed more frequently among diabetics than in the general population6. In this study of raised serum ALT in patients of type 2 diabetes, we have noticed that about 80% of the patients were over-weight or obese i.e., BMI greater than 25 kg/m2, out of which majority (46.5%) were obese i.e., BMI greater than 30 kg/m2. About half of the patients had onset of diabetes within the past 4 years. Both these findings are consistent with previous large scale studies by Salmela et al [7] and Erbey et al [8]. Sixty percent of our patients showed fatty liver on ultrasound. It has been established that mild to moderate elevation of serum aminotransferases is the most common laboratory abnormality in patients with non alcoholic fatty liver disease (NAFLD) [9]. NAFLD is the commonest cause of elevated aminotransferases in type 2 diabetic patients, and our study confirms that too. NAFLD is a clinicopathological condition representing a spectrum of histological findings from hepatic steatosis or fat accumulation in hepatocytes without inflammation, to hepatic steatosis with a necroinflammatory component that may or may not have fibrosis, also called non alcoholic steatohepatitis (NASH). Though we did not do liver biopsies in these patients, ultrasonographic appearance of fatty liver has a good predictive value for NAFLD [8,9]. Most of the patients with fatty livers were over-weight or obese in our study. In the United States, NAFLD is replacing alcohol and viral hepatitis as the most common aetiology of chronically elevated LFTs, in both diabetic and non diabetic individuals, and 60-95 % of them are obese [9].

Insulin resistance seems to be the most important cause of chronic mild elevation of transaminases, frequently found in type 2 diabetics, but precise mechanism is not fully understood [10]. Hyperinsulinaemia in insulin resistant state causes excess in free fatty acids, known to be directly toxic to hepatocytes. Other potential explanations for elevated transaminases in insulin-resistant states include oxidant stress from reactive lipid peroxidation, peroxisomal beta-oxidation, and recruited inflammatory cells and an increase in proinflammatory cytokines such as tumor necrosis factor (TNF) [11].

In epidemiologic studies, elevated transaminases have been shown to be positively associated with the onset of type 2 diabetes [2]. Ohlson et al [2] found elevated ALT in nondiabetic Swedish men to be a risk factor for type 2 diabetes, independent of obesity, body fat distribution, plasma glucose, lipid, AST, bilirubin concentrations, and family history of diabetes. Vozaroza et al [12] found similar results in Pima Indians. The authors concluded that higher ALT is a risk factor for type 2 diabetes and indicates a potential role of increased hepatic gluconeogenesis and/or inflammation in the pathogenesis of type 2 diabetes. In our study, half of the patients had duration of diabetes, less than four years and about 11% of patients had an onset of diabetes in the previous year, a finding that may correspond to the above mentioned observations of raised transaminases as predictor of type 2 diabetes.

We have also observed like other people that raised serum ALT is closely related to other features of metabolic syndrome in addition to type 2 diabetes [13], like obesity and serum triglycerides more than 1.7 mmol/l. 42.6% of our patients had a fasting serum triglycerides level of more than 1.7 mmol/l.

Hepatitis C virus (HCV), is a known independent predictor of type 2 diabetes, the commonest endocrine disease, even in patients without cirrhosis [3,14]. HCV is known to have a higher prevalence within diabetic patients [3]. About 22% of our patients were positive for anti HCV antibodies, and 10% showed some evidence of chronic liver disease on abdominal Ultrasonography.

Though we did not include a few patients in our study who were on a statin or a thiazolidinedione drug, but review of literature suggests that no significant abnormal elevation of transaminases was noted in large scale studies, with moderate doses of statins and thiazolidinediones [15,16]. Moreover, a decrease in LFTs has been demonstrated with rosiglitazone and pioglitazone therapy in pilot studies using thiazolidinediones to treat NASH [17,18].

CONCLUSION

The study concludes that mild to moderate elevation in serum ALT is commonly encountered in patients of type 2 diabetes mellitus. Most of these individuals are overweight and/or have fatty liver on ultrasonography. HCV infection seems to be the next important cause of raised ALT in our population.

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