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Hepatic Transaminases in Patients with Type-2 Diabetes Mellitus: Cross-Sectional, Analytic Study

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Abstract **Original Research Article**

The risk of chronic liver disease is higher in patient with type 2 diabetes than general population. Raised serum transaminases levels are a sensitive indicator of liver cell injury. This study was performed to estimate the prevalence of elevated serum transaminases levels in type-2 diabetic patients and to identify the associated risk factors. In this cross-sectional type of analytic study, ninety-three purposively selected type-2 diabetic patients and equal number of healthy subjects were studied. Subjects who were taking hepatotoxic drugs and known to have any liver disease were excluded. Demographic data and anthropometric measurements were recorded from all participants. Liver function tests, fasting blood sugar, fasting lipid profile and ultrasonography of the HBS were performed. Raised levels of serum ALT, AST and ALP were found in 22.6%, 14.0% and 4.3% diabetic patients and in 4.3%, 3.2% and 3.2% healthy control. Mean serum ALT, AST and ALP levels were significantly higher in cases than controls ($p < 0.05$). Significant positive correlation observed between serum ALT level with fasting blood sugar, BMI and waist circumference but significant negative correlation observed between ALT level and age of the patient and duration of the diabetes. Study results were in accordance with previously reported high prevalence rates of abnormal liver enzymes in type-2 diabetic patients. Early detection of liver enzyme abnormality and intervention will help to prevent further progression to chronic liver disease. Screening of type-2 diabetic patients with serum ALT and AST is recommended.

Keywords: Type-2 diabetes, Serum Transaminase, Hepatic Transaminases.

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorder characterized by hyperglycemia due to absolute or relative deficiency of insulin. The worldwide prevalence of DM has risen dramatically over the past two decades. It affects more than 220 million people worldwide, and it is estimated that it will affect 440 million by the year 2030 [1]. Although the prevalence of type-1 and type-2 DM is increasing, the prevalence of type-2 DM is getting up, more rapidly. The prevalence of diabetes mellitus is around 2 to 3% in Britain; however, it is 12% in the Indian subcontinent [2].

Type-2 DM is a complex condition characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism [3]. Type2 DM is often associated with other medical conditions, particularly central obesity, hypertension and dyslipidaemia [2]. Liver is the main organ of glucose metabolism; where glucose uptake, storage, synthesis, and metabolism occur [4]. Liver play a major role in glucose homeostasis. Altered insulin levels may influence hepatocyte function and integrity in diabetic patients [5]. Spectrum of liver diseases ranges from innocuous enzyme elevation to progressive chronic liver disease has been described in association with type 2 diabetes mellitus. The chronic mild elevation of the transaminases often reflects the underlying insulin resistance. It is thought that decreased insulin sensitivity, a cornerstone in the pathogenesis of type-2

diabetes, activates lipolysis leading to increased plasma levels of non-esterified fatty acids. A resultant chronic increase in fatty acid flux from the fat stores (mainly abdominal) to non-adipose tissues such as the liver, contributes to the hepatic steatosis [6, 7]. Mild chronic elevation of transaminases, especially ALT (less than 200 U/L) is a frequent finding in patients with type-2 diabetes mellitus and associated with insulin resistance, obesity, non-alcoholic fatty liver disease (NAFLD), chronic hepatitis C, chronic hepatitis B, cirrhosis, hepatocellular carcinoma, and antidiabetic drugs [8]. Raised serum ALT has also been associated with diabetes, independent of obesity [9]. The prevalence of raised serum ALT is 7.8% in type-2 diabetic patients in the United States [7]. BMI more than 25 kg/m2 and poor diabetic control is strongly associated with raised ALT in Type-2 diabetic patients [10]. The prevalence of elevated ALT and AST is10.4% & 5.4% respectively in Jordanian type 2 diabetic patients. Male gender and high waist circumference and younger diabetic patients are at increased risk of elevated ALT levels [11]. The magnitude of elevated levels of hepatic transaminases in the Bangladeshi population is currently unknown, and few studies in the Bangladesh had addressed this issue. This study was conducted to estimate the prevalence of elevated hepatic transaminases levels among patients with type 2 diabetes, compared to healthy volunteers and to determine the associated factors. Currently, Routine estimation of serum ALT & AST level in type-2 diabetic patients is not advocated. However, emerging evidence suggests that elevated serum ALT and AST level may be an early marker of metabolic syndrome and insulin resistance in type-2 diabetic patients. To reduce the cardiovascular risk and to prevent the progression to significant hepatic dysfunctions like cirrhosis and hepatocellular carcinoma in type-2 diabetic patients, it is very important to recognize the liver function abnormalities at an early stage [12].

METHODOLOGY

This was a cross-sectional type of analytical study done in the department of medicine, Mymensingh medical college hospital, during the period of March 2014 to February 2015. 93 type 2 diabetic patients and 93 ages matched healthy controls were selected, who were admitted in the Medicine wards or attend at outpatient department of Medicine, MMCH. Purposive sampling technique was used. Patients were selected by i) Age more than 40 years ii) Both sex iii) Type 2 diabetes mellitus (according to WHO diagnostic criteria); Exclusion criteria were: i) Alcohol consumption ii) Hepatotoxic drugs like- Acetaminophen, NSAIDs, Chlorpromazine, High dose Oestrogens, Co-amoxiclav, Statins, Rifampicin, Isoniazid, Busulphan, Azathioprine, Methotrexate, Sodium valproate, Pioglitazone. iii) Patients who are taking insulin. iv) Acute or chronic liver disease. v) Diabetes with co-morbidity. Data were collected by using a structured questionnaire containing all the variables of interest, with a pre-designed and pre-tested data collection sheet. Data were collected by the principal investigator himself by taking interview and performing physical examination in the Dept. of Medicine. Laboratory investigations and Ultrasonography were done in the Dept. of Clinical pathology & Dept. of Radiology & Imaging, Mymensingh medical college hospital for the purpose of data collection. Informed written consent was obtained from all the participants. Data were analysed with Statistical package for social sciences (SPSS) software package with version 20.0 and appropriate statistical tools were carried out as applicable.

RESULTS

Table I shows age distribution of the study population.

Table I: Study population by age

Group	Sex	No	Mean age in years
Case (N=93)	Male	48	53.76±8.01
	Female	45	
Control (N=93)	Male	47	52.25 ±7.86
	Female	46	

Table II & III Show the nutritional status of the study population and it was observed that more than fifty percent of the respondents were overweight.

Table II: Study population by Body Mass Index

Body mass index (kg/m^2)	Cases	Control	Total
18.5-24.9	35 (37.7)	43 (46.2)	78
25-29.9	51 (54.8)	45 (48.4)	96
30-39.9	7 (7.5)	5 (5.4)	12
Total	**93**	**93**	**186**

*Figure within parentheses indicate percentage

Table III: Study population by Waist Circumference

Waist Circumference in cm	Cases	Controls	Total
Male			
≤102	25 (52.1)	29 (61.70)	54
>102	23 (47.9)	18 (38.3)	41
Female			
≤88	7 (15.6)	11 (23.9)	18
>88	38 (84.4)	35 (76.1)	73

*Figure within parentheses indicate percentage

Regarding smoking habit, 46.2% of cases and 44.15% of control were smoker. However, all female participants were non-smoker. With regard to hypertension, it was observed that hypertension was more common in case group compared to control group (44.1% vs 14.0%). Table IV, V, VI show the results of liver function test in the studied group. It was observed that liver enzymes (ALT, AST, ALP) of the diabetic patients were significantly raised, compared to control group ($p<0.05$). But levels of S. bilirubin, S. albumin and prothrombin time were not significantly different between the case and control groups ($p>0.05$).

Table IV: Results of liver function tests in studied group

Parameters	Cases (Mean±SD)	Controls (Mean±SD)	p. value
ALT(U/L)	38.85±15.47	26.55±6.10	<0.001*
AST (U/L)	31.95±12.47	22.96±4.67	<0.001**
ALP (U/L)	97.95±9.55	94.87±8.29	<0.01***
Serum Bilirubin (mg/dL)	0.60±0.09	0.59±0.09	>0.05
Serum Albumin (g/dL)	4.10±0.35	4.16±0.39	>0.05
Prothrombin time (sec)	13.30±1.02	13.20±1.02	>0.05

*$t_{92} = 7.899$; $p < 0.001$, **$t_{92} = 6.503$; $p < 0.001$, ***$t_{92} = 3.321$; $p < 0.01$

Table V: Study population by Serum ALT level

ALT in U/L	Case (n=93)	Control (n=93)
0-40	72 (77.4%)	89 (95.7%)
41-80	21 (22.6%)	4 (4.3%)

* Figure within parentheses indicate percentage

Table VI: Study population by Serum AST level

AST in U/L	Case (n=93)	Control (n=93)
0-35	80 (86.0%)	90 (96.8%)
36-70	13 (14.0%)	3 (3.2%)

* Figure within parentheses indicate percentage

Table VII shows the fasting lipid profiles of the study population. It was observed that case group had significantly higher level of S. cholesterol, S. triglyceride and S. LDL levels but S. HDL levels were significantly lower in case group compared to control group.

Table VII: Study population by Fasting Lipid profile

Lipids (mg/dL)	Case (n-93)	Control (n-93)
Serum Cholesterol		
100-199	74 (79.6)	88 (94.6)
200-249	19 (20.4)	5 (5.4)
Serum Triglycerides		
100-149	45 (48.4)	83 (89.3)
150-199	48 (51.6)	10 (10.7)
LDL		
50-99	11 (11.8)	54 (58.1)
100-149	82 (88.2)	39 (41.9)
HDL		
30-39	27 (29.1)	16 (17.2)
40-49	66 (70.9)	77 (82.8)

* Figure within parentheses indicate percentage

Table VIII: Risk factors by ALT Status

Parameters	Serum ALT level	
	ALT>40IU/L	ALT <40IU/L
Age in Years	49.57±5.84	55.00±8.40
BMI (Kg/m^2)	27.01±1.56	25.35±1.90
Waist Circumference in cm	105.71±3.02	97.50±5.24
Fasting Blood Glucose (mmol/L)	8.39±1.11	7.02±1.05
Duration of Diabetes in Years	5.48±2.09	8.29±3.45
Serum Cholesterol (mg/dL)	191.95±12.62	186.88±15.65
Serum Triglycerides (mg/dL)	151.62±6.27	149.63±16.35
LDL (mg/dL)	118.33±16.73	114.58±15.35
HDL (mg/dL)	41.86±5.28	42.24±4.11

Table IX: Risk factors by AST Status

Parameters	Serum AST level	
	AST> 35 IU/L	AST < 35 IU/L
Age in Years	60.31±9.29	52.71±7.55
BMI (Kg/m^2)	25.59±1.85	25.75±1.98
Waist Circumference in cm	100.54±5.68	99.16±5.98
Fasting Blood Glucose (mg/dL)	7.14±1.32	7.09±0.99
Duration of Diabetes in Years	9.23±3.40	7.40±3.34
Serum Cholesterol (mg/dL)	190.85±14.95	187.56±14.53
Serum Triglycerides (mg/dL)	150.77±13.42	149.96±14.95
LDL (mg/dL)	116.77±19.63	115.21±14.61
HDL (mg/dL)	41.69±4.40	42.23±4.39

It was observed that mean BMI and waist circumference were significantly higher in patient with raised ALT level compared to normal ALT level. Regarding age, it was observed that patients with raised ALT level were younger than patients having normal ALT level (49.57±5.84 vs 55.00±8.40, P< 0.05). Whereas patient with raised AST level were older than patient with normal AST level (60.31±9.29vs52.71±7.55, P < 0.05). It was also observed that mean duration of diabetes was less in patients with raised ALT level, compared to patients with normal ALT level. There was no significant difference in fasting blood sugar level in patients with raised ALT and AST level compared to normal ALT and AST level.

Fasting lipid profile revealed that there was no significant difference between raised ALT group and normal ALT group, regarding S. cholesterol, S. TG, S. LDL and S.HDL level.

There was also no significant difference between raised AST group and normal AST group, regarding S. cholesterol, S. TG, S. LDL and S.HDL level. Regarding gender distribution it was revealed that among the raised ALT level, 71.43% were male and 28.57% were female. Gender difference was highly significant (P<0.005).

Table-X: USG of HBS among study population

USG Findings	Cases	Controls	Total
Normal	69 (74.20)	86 (92.47)	155
Fatty change	18 (19.35)	2 (2.15)	20
Other changes (Cholelithiasis)	6 (6.45)	5 (5.38)	11
Total	**93 (100.00)**	**93 (100.00)**	**186**

* Figure within parentheses indicate percentage

Table-XI: USG findings among diabetic patients

USG Findings	Normal S. ALT group		Raised S. ALT group	
	Frequency	Percentage	Frequency	Percentage
Normal	62	86.11	7	33.33
Fatty change	6	8.33	12	57.14
Other changes (Cholelithiasis)	4	5.56	2	9.52
Total	**72**	**100**	**21**	**100**

Table XI shows, on ultrasonography of HBS 12 (57.14%) patients with raised ALT level had fatty changes in the liver whereas 6 (8.33%) patients with normal ALT level had fatty changes in the liver. The differences were statistically significant (P<0.05). None of them had cirrhosis of liver or hepatocellular carcinoma.

Table XII shows, there were significant positive correlation exists between fasting blood sugar and ALT (r=0.432, P= 0.000) and also with AST (r=0.259, P=0.012).

Table XII: Correlation of hepatic enzymes with Fasting Blood Sugar level

	ALT(IU/L)	AST (IU/L)	ALP (IU/L)
Fasting Blood Sugar	r = 0.432	r = 0.259	r = - 0.139
	p = 0.001*	p = 0.012*	p = 0.185

* Pearson's correlation coefficient significant at the 0.01 level

As shown in the table XIII, there were significant negative correlation between serum ALT and duration of DM (r = - 0.338, p=0.000), whereas there were significant but direct correlation between AST and duration of DM (r= 0.273, p=0.008). It was also observed that there was insignificant correlation between S.ALP level and duration of diabetes (r=0.122, p=0.244).

Table XIII: Correlation of hepatic enzymes with Duration of Diabetes

	ALT(IU/L)	AST (IU/L)	ALP (IU/L)
Duration of Diabetes	r = - 0.338	r = 0.273	r = - 0.122
	p = 0.001*	p = 0.008*	p = 0.244

* Pearson's correlation coefficient significant at the 0.01 level

Table XIV shows, there was significant negative correlation between ALT and age of the patients (r= - .276, p=0.007), but there was significant positive correlation of ALT with fasting blood sugar (r=0.432, P= 0.000), BMI (r=0.188, p=0.07) and waist circumference of the patient (r=0.483, p=0.000). It was also observed that serum ALT had insignificant correlation with serum lipid profile [with TC (r=0.069, p=0.509), with TG (r=0.027, p=0.798), with LDL (r=0.017, p=0.875), with HDL (r=0.044, p=0.678)].

Table XIV: Correlation of ALT value with various risk factors

Parameters	ALT U/L
Age in Years	r = - 0.276
	p = 0.007*
BMI (Kg/m^2)	r = 0.296
	p = 0.004*
Waist circumference in cm	r = 0.483
	p = 0.001*
Fasting blood sugar (mmol/L)	r = 0.432
	p = 0.001*
S. Cholesterol (mg/dL)	r = 0.069
	p = 0.509
S. Triglyceride (mg/dL)	r = 0.027
	p = 0.798
S. LDL (mg/dL)	r = 0.017
	p = 0.875
S. HDL (mg/dL)	r = 0.044
	p = 0.678

* Pearson's correlation coefficient significant at the 0.01 level

DISCUSSION

This study was conducted to evaluate the hepatic transaminases (ALT and AST) levels in type 2 diabetic patients, compared to control group, among Bangladeshi population. The study revealed that serum transaminases (ALT and AST) were significantly raised in diabetic patients, compared to control group (p=<0.05). Serum ALT & AST level were raised in 22.58% & 14.0% in case group and 4.30% & 3.2% in control group respectively. The study results were consistent with the findings of Salmela *et al.,* [13] who showed that 22.9% diabetic subject had elevated ALT. Another study in Maynmar, also observed that raised ALT & AST in 18.5% & 14.8% in diabetic patients [14]. Meybodi MA *et al.,* [15] in 2005 observed that10.4% and 3.3% of diabetic population had elevated ALT and AST respectively. West *et al.,* [16] in 2006 also reported that 12.1% of their diabetic patient had elevated ALT, which were less than our study. Erbey *et al.,* [17] observed elevated ALT 7.8%, in diabetic patients & 3.8% in non-diabetic person. In present study, 4.3% of nondiabetic participants had raised ALT which was much close to their observation but prevalence of elevated ALT in type 2 diabetic patients was 22.6%, which was much higher than their observation. Current study revealed that Mean ALT and AST of the diabetic patients were 38.85±15.47 I/U and 31.95±12.47 U/L respectively. Meybodi MA *et al.,* [15] also observed that mean ALT 24.67±23 U/L and mean AST 24.57±15 U/L among the diabetic patients, which were also within normal range but significantly lower than present study. Present study revealed that 19.35% of diabetic patients had fatty changes in the liver on ultrasonography. Cusi and Kenneth *et al.,* [18] in 2009 observed that approximately 70% patients with type-2 diabetes mellitus had fatty liver. In another study conducted in 2004, Mumbai, India, observed that 49% type2 diabetic patients had fatty Liver [19]. Both of these study results had higher prevalence of fatty liver in comparison to current study. Salmela *et al.,* [20] also showed that BMI >25 kg/m2 and onset of diabetes within past 4 years had elevated ALT level. Current study had similar observation; patients with raised ALT level had more BMI but less duration of diabetes. Ahmed S *et al.,* [21] in Pakistan, showed that there were positive association of raised ALT in type 2 diabetic patients with high body mass index, recent onset of diabetes, fatty liver and poorly controlled diabetes. Present study results were consistent with their observation. The present study observed that serum cholesterol, serum triglyceride, serum LDL levels was significantly raised in diabetic subjects, compared to control group. This study finding were consistent with that of Adeniran Samuel Atiba *et al.,* [22] who analyzed liver enzymes and lipid profile in 106 T2DM patients from Nigeria and found elevated ALT and AST levels with dyslipidemia, compared to healthy subjects. Pearson's correlation coefficients were calculated to measure the association of elevated ALT and anthropometric measurement of the type2 diabetic patients and observed that there was significant positive correlation exist between elevated ALT level with high BMI and also with high waist circumference of the diabetic patients. There was also significant negative correlation observed between elevated ALT level with increased duration of diabetes and also with the increased age of the patients. The study observation was consistent with the Layla Judi *et al.,* [11] they observed younger age and high waist circumference are independent predictors of elevated transaminases levels. They also observed BMI was not associated with elevated ALT level in diabetic patients but current study observation was not in agreement with this observation. Meybodi MA *et al.,* [15] in 2005 in Iran observed that the prevalence of elevated ALT in type 2 diabetic patients is 1.6 times higher than general population and the prevalence of elevated ALT increased with increasing age, FBS and triglyceride levels, but it was not statistically significant. Current study also observed that there was insignificant correlation between elevated ALT and fasting blood sugar and lipid profile of the diabetic patients.

CONCLUSION

The prevalence of elevated hepatic transaminases is more in type 2 diabetic patients than non-diabetic population. Early detection of liver function abnormality and intervention will prevent further progression to liver cirrhosis and chronic liver disease. Estimation of hepatic transaminases in all diabetic patient is highly recommended.

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