

Hepatic Involvement with Elevated Liver Enzymes in Type 2 Diabetes Mellitus

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ABSTRACT

26 **Background:** Diabetes mellitus (DM) is characterized by a broad disturbance in metabolism.
27 Since the liver plays a vital role in the regulation of metabolism, there is evidence of liver
28 dysfunction in DM. There is a high prevalence of non-alcoholic fatty liver disease among
29 diabetic patients in western countries. However, there is a paucity of data showing of such
30 association in Nepalese patients with DM. Therefore, the present study was carried out for a
31 better understanding of alteration of liver function in patients with type 2 DM (T2DM).

32 **Methods:** A total of 105 patients (age between 30-74 years, male/female ratio=0.6),
33 newlydiagnosed as T2DM, without the history of liver disease and other chronic diseases,
34 were recruited from out-patient department of Nepal Medical College Teaching Hospital
35 along with 58 age and sex matched healthy controls(age between 30-71 years, male/female
36 ratio=0.7). After basic anthropometric measurements, fasting venous blood was collected and
37 subjected to analysis for liver enzymes.

38 **Results:** We observed marginal, yet statistically significant increase of serum alanine
39 transferase(26.6 ± 0.84 (diabetic) vs 20.0 ± 0.69 (control), $p=0.003$) and γ -
40 glutamyltransferase(40.4 ± 1.51 (diabetic) vs 21.2 ± 1.1 (control), $p<0.001$) in the diabetic
41 patients compared to healthy controls.

42 **Conclusion:** The liver enzymes were marginally elevated in T2DM compared to controls. This
43 increment may be associated with early pathological changes in the liver. Hence, regular
44 monitoring of liver function is highly beneficial to prevent advance liver injury in T2DM.

45 **Keywords:** diabetes mellitus, liver enzymes, non-alcoholic fatty liver disease, transaminases.

46

47 **1.INTRODUCTION**

48 Diabetes mellitus (DM) is a leading cause of mortality of people across the globe causing
49 various secondary complications such as coronary heart disease (CHD), chronic kidney
50 disease (CKD), neuropathy and various ocular disorders(1). The prevalence of type 2 DM
51 (T2DM) is increasing alarmingly worldwide due to increased life expectancy, change in
52 lifestyle, and increased prevalence of obesity. Around two million people in Nepal are
53 estimated to be affected with DM. The prevalence of T2DM and impaired fasting glucose
54 (IFG) is estimated to be 9.5% and 19.2%, respectively in the semi-urban population of Nepal.
55 Prevalence of T2DM was found to be higher in men (11.8%) than in women (7.9%).
56 Similarly, IFG was noted higher in men (25%) than in women (15.4%)(2).Several studies
57 from Nepal have shown that patients with DM are at higher risk for impaired renal function
58 (3, 4), dyslipidemia (5, 6) and associated elevated cardiac risk factors (7, 8).

59 Interestingly, DM is associated with Non-alcoholic fatty liver disease (NAFLD)
60 including its severe form, non-alcoholic steatohepatitis. In the recent years, NAFLD has
61 drawn much attention to itself as a pathogenic factor of insulin resistance and T2DM. Among
62 patients with DM, the risk of chronic liver disease is doubled, independent of alcoholic liver
63 disease or viral hepatitis(9).This evidence is supported by several cross-sectional studies,
64 showing an association between NAFLD and prevalence of T2DM as well as features of
65 metabolic syndrome, including dyslipidemia and abdominal obesity, which highlights insulin
66 resistance as an important feature of NAFLD. Type 2 diabetic patients have a higher
67 incidence of liver function test abnormalities in comparison to non- diabetic individuals (10).
68 Circulating liver enzymes, namely alanine aminotransferase(ALT), aspartate
69 aminotransferase(AST) and γ -glutamyltransferase(GGT) are commonly elevated in
70 asymptomatic patients with NAFLD, and widely acceptable serum markers of liver diseases.
71 Even a minor elevation of ALT is a good predictor of mortality from liver disease(11).

72 The excess in serum non-esterified fatty acid (NEFA) observed in the insulin
73 resistance is known to be directly toxic to hepatocyte. The insulin resistant state is also
74 characterized by an increase in pro-inflammatory cytokines such as tumor necrosis factor- α
75 (TNF- α), which may also contribute to hepatocellular injury(12).Nearly 70 to 80% of the
76 diabetic subjects have been reported to have hepatic fat accumulation referred as
77 NAFLD(13).Recently, there is renewed interest related to study of the liver enzymediabetes.
78 Many foreign studies have been conducted to find association of the liver diseases
79 withDM.Prevalence of NAFLD in T2DM is higher with the elevation of liver enzymes (14-
80 16). However, there is a paucity of data showing such association in Nepalese patients with
81 DM. The present study was therefore undertaken to investigate the compromise of Liver
82 Function in T2DM amongst Nepalese Patients.

83

84 **2. MATERIALS AND METHODS**

85 The present study is cross-sectional and prospective studyto investigate the circulating levels
86 of serum liver enzymes in T2DM. A total of 105 patients (age between 30-74 years;
87 male/female ratio: 0.6), newly diagnosed as T2DM, were recruited from outpatient
88 department of Nepal Medical College Teaching Hospital in a period of a year. DM was
89 defined as per ADA guideline(17).Exclusion criteria were apparent liver diseases,
90 alcoholism, chronic inflammatory diseases and under medication that are known to affect
91 liver functions. Individuals with prior history of any kind of liver disease were excluded from
92 the present study, as the aim of our study is to evaluate the alteration of liver enzymes due to
93 pathogenesis of diabetes mellitus.As healthy controls, 58 age and sex matched subjects(Age
94 between 30 -71, male/female ratio: 0.7) were also recruited, six out of which were later
95 excluded dueto possible liver diseases, as indicated by marked elevation of liver

enzymes. Written informed consent was taken from the participants and the study design was approved by Institutional Research Committee of Nepal Medical College, Kathmandu, Nepal.

Basic clinical examinations were performed to study subjects. Clinical history including hypertension, family history of DM, dietary habits, smoking, and alcohol drinking status were noted. Weights, heights, and waist circumferences (WC) were measured. Body mass index (BMI) was calculated by dividing weight (kg) by square of height (m). On the basis of BMI, study subjects were classified as underweight (BMI<18.5), normal (BMI of 18.5-24.9), overweight (BMI of 25.0-29.9) and obese (BMI>30.0). Systolic and diastolic blood pressure was measured using mercury sphygmomanometer. Hypertension was defined as either current use of anti-hypertensive medication or blood pressure more than 140/80 mmHg.

Fasting blood was collected and blood sugar was analyzed using hexokinase method (Vitros250, Ortho-clinical Diagnostics) within 30 min of blood collection. Remaining serum samples were stored at -20°C till used (not more than 1 month). Serum ALT, AST, and GGT were analyzed using Vitros 250 (Ortho-clinical Diagnostics, NY, USA). The normal ranges for ALT, AST and GGT are 0-50 IU/L, 0-45 IU/L and 0-55 IU/L respectively. Their intra and inter assay coefficient of variation (C.V.) were 2.6 and 3.9% for glucose, 3.1 and 4.0% for ALT, 2.6 and 3.5% for AST and 2.8 and 3.4% for GGT respectively.

Data were analyzed using SPSS 11.5 for Windows. Data were expressed as mean±SD. The comparison of the mean between different groups was done by ANOVA. All p-value were two-tailed, and those <0.05 (95% CI) were considered as statistically significant.

3. RESULTS

The average age of diabetic patients was 52±1.09 years while the average age and sex matched control was 51±1.53 years.

The mean BMI was not significantly difference among two groups (BMI: 25.9±0.49(diabetic)vs 25.6±0.66(control)); however,WC of the diabetic patients were significantly higher than healthy control (WC: 86±1.27 vs 81±1.5 cm, p<0.001) (Table 1). As many as 21 (20%) of diabetic subjects were obese and 32 (30%) were overweight. While 52% of controls have normal BMI and only 16% were obese. Our resultssupport thatthe central and abdominal obesity were associated with T2DM.

There was marginal, yet statistically significant increase in serum ALT (26.6±0.84 vs 20.0±0.69 IU/L, P<0.05) and GGT (40.4±1.51 vs 21.2±1.1 IU/L, P=0.001) in the diabetic subjects compared to control. However, elevation of serum AST (30.0±1.00 in T2DM vs 28.0±0.79 IU/L in control, P=0.270) is statistically insignificant. We classified the liver enzymes level into four groups as <20 IU/L, 20-40 IU/L, 40-60 IU/L and > 60 IU/L. The percentage of diabetic people vs control having ALT level of <20 IU/L, 20-40 IU/L, 40-60 IU/L and > 60 IU/L were 18.1 vs 46.2%, 76.2 vs 51.9%, 5.0 vs 2.0% and 1.0 vs 0.0 % respectively. Similarly, the percentage of diabetic subjects vs healthy controls having AST level of <20IU/L, 20-40 IU/L, 40-60 IU/L and > 60 IU/L were 11.4 vs 7.7%, 79.0 vs 90.4%, 8.6 vs 1.9% and 1.0 vs 0.0%. In the same way, the percentage of diabetic subjects vs healthy controls having GGT level of <20 IU/L, 20-40 IU/L, 40-60 IU/L and > 60 IU/L were 5.2 vs 51.9%, 45.7 vs 44.2%, 41.9 vs 3.8% and 6.7 vs 0.0%. This distribution elucidates that subjects with T2DM are more likely to be associated with increase in the serum liver enzymes compared to non-DM controls.

Another interesting findings of our study include that the WC is significantly associated with GGT level in female diabetic patients but not in male (r=0.26, p<0.05) i.e. GGTlevel was elevated in female diabetic subjects with high WC. However, we didn't observe such significant relation of WC with ALTand AST. Blood pressure of female diabetic patient is also significantly associated with serum GGT level (Table.3.). In addition,

there was no statistically significant association between BMI and all the liver enzymes. Our study showed that more patients with marginal elevation of liver enzymes were with abdominal obesity.

4. DISCUSSION

Although the difference of serum ALT and GGT level were statistically significant between diabetic patients and healthy controls, the means of ALT and GGT were within normal range. There was also increased mean AST level in diabetic patients than in healthy controls but the difference was not statistically significant. Our results support the finding of a study done by Tohidi *et al*(2008)among the general population in Tehran. In their result, AST was not raised or decreased significantly in T2DMbut ALT and GGT were significantly elevatedwith ORs of 3.07 and 2.91, respectively(18). Significant elevation of ALT but not AST may be due to the reason that ALT is more specific serum liver marker. AST is relatively not specific to liver and may also be elevated in other tissue damage such as skeletal muscle, cardiac muscle(11).

Our results also support the study done by Salmela *et al*(1984), where 57% of the diabetic outpatients (100 subjects) had, at least, one abnormal LFT; 27% (48 subjects) had, at least, two abnormal tests. T2DM patients more frequently had elevated ALT (22.9 vs. 5.3%) and GGT (23.7 vs. 10.5%) levels than those with type 1 DM(19). West *et al*(2006) studied the status of ALT only in T2DM patients, which also showed the elevated level of ALT in diabetic patients compared with non-diabetic subjects. The prevalence of elevated ALT in type 1 (9.5%) and type 2 (12.1%) diabetic patients were considerably higher than 2.7% expected in the general population and higher than 5.6% reported at baseline in clinical trials(20).

In a larger study, Erbey *et al*(2000) analyzed 18,825 patients, of which, 4.1% had elevated ALT, and 6.7% have T2DM. Of those with T2DM, the prevalence of elevated ALT was 7.8%, compared to 3.8% prevalence in those without diabetes. There was 10.6% prevalence of elevated ALT in obese diabetic versus 6.6% prevalence in obese non-diabetic patients(21). In contrast to this study; our finding suggested that there was no significant association between BMI and liver enzymes. However, WC was significantly associated with GGT, but not with aminotransferases. It is true that more patients with marginal elevation of liver enzymes were with central obesity. According to International Diabetes Federation, the cut-off value of WC for south Asianis ≥ 90 cm for male and ≥ 80 cm for female (22).

NAFLD is replacing alcohol and viral hepatitis as the most common etiology of chronically elevated liver enzymes in the United States in both diabetic and non-diabetic individuals. Of those patients with NAFLD 60–95% are obese, 28–55% have T2DM, and 20–92% have hyperlipidemia(23). Lim *et al*(2007) showed the strong interaction between serum GGT and obesity on the risk of prevalent T2DM. BMI was associated with prevalent diabetes only among persons with high normal serum GGT activity (P for interaction = 0.002). BMI was not associated with T2DM when GGT was low normal, suggesting the obesity itself may not be a sufficient risk factor for T2DM. Rather, in this view, to be a risk factor for diabetes, obesity must be coupled with other factors, such as serum GGT(24). Serum ALT is more sensitive marker of fatty liver than GGT(25), however, the study by Lim JS *et al* observed no BMI and serum ALT interaction associated with prevalent diabetes(24).The association between NIDDM and GGT was independent of serum glucose and of other predictors of diabetes. In the study done by Perry *et al*(1998), mean serum GGT was significantly higher in the NIDDM patients than in the rest of the cohort (20.9 [19.3-22.6] vs. 15.3 IU/l [15.0-15.6], $p < 0.001$)(26). However, in the Tromso study, BMI was the dominant predictor of GGT levels in both men and women in multivariate analysis that included alcohol intake and major

cardiovascular disease risk factor(27).Ikai *et al*(1995) have reported significant association between hepatic steatosis and elevated GGT, insulin resistance, and hyperinsulinemia. In this Japanese study, the well-described association between serum GGT levels and blood pressure was attenuated for plasma insulin level(28).Another Japanese investigation done by Nakanishi *et al*(2003)suggested that serum GGT may be an important predictor for developing T2DM(29). Kim *et al*(2009)in South Korea have also suggested that increased serum ALT and GGT levels are risk factor for the development of T2DM(30). Lee *et al*(2004) established the significant association between GGT, obesity, and risk of T2DM. BMI appeared to be more strongly associated with T2DM in both men and women over age 50 years with GGT median or greater, compared with subjects with GGT less than median(31).

Our results support the another study done by Lee DH *et al*(2002), that have revealed that the associations between ALT or AST and diabetes were weaker than those of GGT and were mostly restricted to abnormal levels of liver enzymes(32).However, one prospective study, in Pima Indians, has reported that higher ALT, but not GGT, predictedT2DM(33).Many studies support the significant relationship between elevated serum GGT and metabolic syndrome.The higher GGT levels are accompanied by insulin resistance and greater risk of developing T2DM(34). Participants in higher GGT quartiles were older, had higher BMI and were more likely to have hypertension, and elevated lipids, fasting blood glucose, and CRP(35).Another study from Taiwan also found the important association between GGT and metabolic syndrome, the higher GGT level occurs in obese person, particularly those with high WC(36). In agreement with these studies, our result also showed elevated level of GGT in person with central obesity.Moreover, our results are in agreement with study done by Stranges *et al*(2005)in West New York, which showed the strong interaction between GGT levels and hypertension(37). Increased GGT levels are

considered as a marker of alcohol abuse; however few moderate drinkers (8% of total subjects) have been included in the study. In our study, liver enzymes get elevated in the individuals with hypertension both in diabetic and non-diabetic subjects.

In conclusion, this study suggested that serum ALT and GGT are significantly elevated in T2DM patients compared to healthy individuals. In contrast, such association was not seen with serum AST level. The study also suggested the significant association between obesity and elevation of liver enzymes. Non-alcoholic fatty liver disease is highly prevalent in patients with T2DM. Analysis of this study also revealed an interaction between central obesity and elevation of liver enzymes. Because of marginal elevation of liver enzymes within normal range in diabetic patients, estimation of liver enzymes is highly recommended for patients with T2DM for early detection of liver dysfunctions.

Limitation of study:

One limitation of this study is the small number of control compared to the T2DM. The control to case ratio in this study is 0.55. Future study with equal number of control and case can be conducted. However, we believe that our data of 58 healthy controls are still not too critically low to alter the conclusion.

ABBREVIATIONS

ALT: Alanine aminotransferase; **AST:** Aspartate aminotransferase; **BMI:** Body mass index; **CHD:** Coronary heart disease; **CKD:** Chronic kidney disease; **DBP:** Diastolic blood pressure; **GGT:** gamma-glutamyltransferase; **IFG:** Impaired fasting glucose; **LFT:** Liver function test; **NAFLD:** Non-alcoholic fatty liver disease; **SBP:** Systolic blood pressure; **T2DM:** Type 2 diabetes mellitus; **WC:** Waist circumference

Conflict of Interest: None

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Tables

Characteristics	Diabetic patients (n=105)	Controls (n=52)
Age(Years)	52 ±1.09	48±1.53
Male/female	39/66	23/29
Waist Circumference(cm)	86±1.27*	81±1.5*
BMI(kg/m ²)	25.9±0.49	25.6±0.66
SBP(mmHg)	121±2.16	120±1.08
DBP(mmHg)	86±1.06	80±1.21*
Fasting blood sugar(mg/dL)	144±5.87**	86±1.75**
Postprandial blood sugar(mg/dL)	215±0.49**	116±1.6**

Table1.Demographic and clinical characteristics of diabetic patients and controls. Data represent mean ±SE. *p<0.05 and **p<0.01. BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Liver enzymes	Study subjects	Distribution (%) of study subjects according to enzyme levels (IU/L)				P value
		<20	20-40	40-60	>60	
ALT	T2DM	18.1	76.2	4.8	1.0	0.003
	Control	46.2	51.9	1.9	0.0	
AST	T2DM	11.4	79.0	8.6	1.0	0.270
	Control	7.7	90.4	1.9	0.0	
GGT	T2DM	5.7	45.7	41.9	6.7	0.001
	Control	51.9	44.2	3.8	0.0	

Table 2. Percentage distributions of diabetic patients and control subjects according to classification of enzyme concentration (IU/L). ALT: alanine transaminase, AST: aspartate transaminase, GGT: gamma-glutamyltranspeptidase.

	Male		Female	
	r	p value	r	p value
Age vs ALT	-0.291	0.07	-0.063	0.63
Age vs AST	-0.064	0.71	0.027	0.83
Age vs GGT	-0.057	0.76	0.147	0.23
SBP vs ALT	-0.185	0.27	-0.076	0.57
SBP vs AST	-0.140	0.39	0.128	0.30
SBP vs GGT	-0.116	0.50	0.400	0.0009**
DBP vs ALT	-0.047	0.8	-0.088	0.50
DBP vs AST	-0.168	0.37	-0.002	0.90
DBP vsGGT	-0.041	0.80	0.275	0.02*
WC vs ALT	0.001	0.99	0.126	0.33
WC vs AST	0.014	0.93	0.147	0.29
WC vs GGT	-0.161	0.33	0.269	0.02*

387 Table 3. Pearson's Correlation coefficient (r) between liver enzymes and different variables
 388 among male and female diabetic patients.

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Figures legends

Fig.1. Distribution of respondent according to BMI. There were higher numbers of diabetic patients than healthy individuals who are obese.

Fig.2.Comparisons of liver enzymes activities in diabetic patients and healthy controls. The levels of ALT and ALT are significantly different, but AST activities are not significantly different between diabetic patients and healthy controls. Data represent mean $\pm$ SE. * $p<0.05$ and ** $p<0.01$.

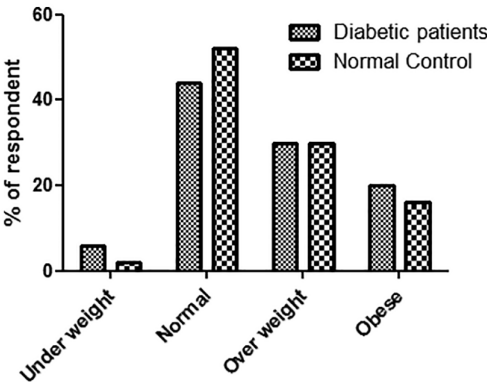


Figure 1

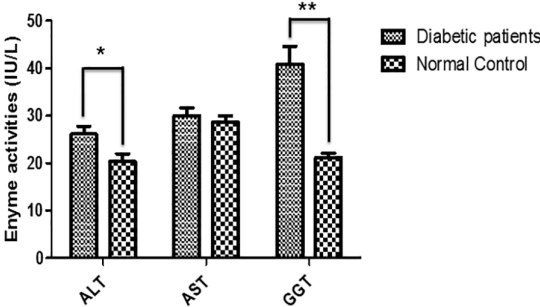


Figure 2