

Prevalence of elevated liver enzymes and its association with type 2 diabetes: A Descriptive Cross-Sectional Study among Nepalese Adults from Biratnagar, Nepal



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ABSTRACT

Background: Diabetes mellitus (DM) is a non-communicable metabolic disease resulting from either insulin deficiency or insulin resistance. Liver enzymes (ALT and AST) are the well-known markers of hepatocellular health while GGT also shows biliary tract function. Increased activities of liver enzymes are indicators of hepatocellular injury, are associated with insulin resistance and Type 2 Diabetes Mellitus. **Aims and Objective:** To study the status of Liver Enzymes in type 2 diabetes patients residing in the eastern part of Nepal. **Materials and Methods:** This was a descriptive cross-sectional study conducted at the Department of Clinical Biochemistry, Nobel Medical College Teaching Hospital, Biratnagar, Nepal dated from 27th Dec 2019 to 27th Dec 2020. The blood sample was taken from the patients coming to the outpatient department at Diabetic and Endocrinology Clinic for a regular check-up and follow-up and those willing to participate in research. All the data collected was entered in Microsoft Excel and Statistical Package for Social Service (SPSS) version 16. $p < 0.05$ was considered to be statistically significant. **Results:** A total of 375 subjects (255 T2DM and 120 healthy) were included. The age of the T2Diabetic subjects ranges from 27-87 years with a mean of 56.91 ± 11.00 years while age of healthy subjects ranged from 31-86 years with the mean of 53.38 ± 13.28 . Among the T2DM subjects, 11.76% (30/255) had raised AST, 17.25% (44/255) had raised ALT, 12.94% (33/255) had raised ALP, and 19.60% (50/255) had raised GGT. The level of liver enzymes (AST, $p = 0.005$, ALT, $p = 0.007$, ALP, $p = 0.000$ and GGT, $p = 0.000$) were showed statistically significant. **Conclusion:** This study concludes that liver enzyme activity was higher in T2DM subjects than individuals who do not have T2DM. In addition, Liver parameters were significantly correlated with diabetes mellitus in our study population; hence, timely diagnosis and management of the abnormal liver parameters may help to minimize liver-related morbidity and mortality in the diabetic population.

Key words: Type 2 Diabetes Mellitus; Liver Enzymes; AST; ALT; GGT; Nepalese adults; Biratnagar; Nepal

INTRODUCTION

Diabetes mellitus (DM) is a non-communicable metabolic disease resulting from either insulin deficiency or insulin resistance. It is constantly increasing worldwide due to

the aging population, urbanization, and obesity.¹ WHO reported that patients with DM will cross 350 million by 2030 and become the 7th leading cause of death.² Globally, Type 2 Diabetes Mellitus (T2DM) covers about 90% of all the cases,³ and resulting from the interaction between

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genetic, environmental, and behavioral risk factors with the feature of hyperglycemia, insulin resistance, and relative insulin deficiency.⁴

The liver plays an important role in the regulation of normal glucose levels during fasting and postprandial condition. Liver enzymes are ALT, AST, ALP, and GGT which are included in liver function tests.⁵ ALT and AST are good markers of hepatocellular function while GGT shows biliary tract function.^{6,7} Various studies have reported liver disease as a major cause of mortality in patients with T2DM.^{8,9} The disturbances in liver function tests are well recognized in some diabetic patients,¹⁰ increased activities of liver enzymes are associated with insulin resistance and T2DM.^{11,12} Chronic hyperinsulinemia and relative insulin resistance cause a cascade of reactions that lead to an increase in lipogenesis and associated fatty changes. Accumulation of free fatty acid is known to be toxic to hepatocytes engendering disruption of the cell membrane, mitochondrial dysfunction, oxidative stress, and an increase in proinflammatory cytokine.¹³ Some studies reported that accumulation of intracellular glycogen in hepatocytes leads to liver injury with typical biochemical findings of mild to moderate rise in ALT, AST, and normal synthetic function with or without ALP elevation.¹⁴ There are several previous reports from various parts of the world that showed altered liver parameters among the diabetic subjects. There is lacking such study in the Nepali population. Therefore, the present study was aimed to evaluate the prevalence of elevated hepatic enzymes among Eastern Nepali patients with Type 2 Diabetes Mellitus as compared to the non-diabetic healthy subjects.

MATERIALS AND METHODS

This was a descriptive cross-sectional study conducted at the Department of Clinical Biochemistry, Nobel Medical College Teaching Hospital, Biratnagar, Nepal dated from 27th Dec 2019 to 27th Dec 2020. Patients Diagnosed with T2Diabetes and on medication for more than 6 months were selected in this study. Before the sample collection, the informed consent form was signed by the study subjects for interviews, questionnaires, and sample collection. The blood sample was taken from the patients coming to the outpatient department at Diabetic and Endocrinology Clinic for a regular check-up and follow-up and those willing to participate in research. The ethical approval for this study was taken from the ethical committee of the Nobel Medical College Teaching Hospital (NMCTH), before the enrollment of the study subjects on 26th December 2019.

Diagnosis of DM: Defined as per the guidelines of the American Diabetes Association

Inclusion criteria

Patients with type 2 Diabetes mellitus (cases) without any previous known liver diseases. Diagnosed patients of diabetes ≥ 6 months and under oral anti-diabetic agents and/or insulin or under dietary controls.

Exclusion criteria

Diabetes subjects having confirmed Liver diseases, Type 1 DM, patients who were on medication known to modify the Liver functions e.g. Methotrexate, Digoxin, Corticosteroids, etc. Patients who were not willing to participate were not included in this study.

Data collection

The blood sample was collected from a patient coming to the outpatient department at our central sample collection center. Other data were collected using structured proforma with all relevant details. Patients meeting inclusion criteria were explained about the types of study and consent was taken from those willing to get enrolled.

Laboratory analysis

Five ml of the venous blood was collected and kept in gel tubes. Serum samples were used for the analysis of Fasting Blood sugar (FBS), HbA1c, Total Protein, Albumin, liver enzymes Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP), and Gamma Glutamyl Transferase (GGT) using (Labsystems Diagnostics) Nanolab-200 Chemistry auto analyzer. The reference range of AST employed in our laboratory was 0- 40 IU/l, ALT was 0-40 IU/L, ALP was 53-141 IU/L and GGT was 5- 50 IU/L.

Blood Glucose: Determination of blood glucose was done by the glucose oxidase method.

HbA1c: It was measured by Goldsite OPP-100 using the Nephelometry method.

Total Protein: Biuret Method, Endpoint by Meril Diagnostics

Albumin: BCG Dye Method, Endpoint Meril Diagnostics

Globulin: Total Protein - Albumin

Total and Direct Bilirubin: Modified Jendrassik and Grof's Methods using Coral Clinical Systems (Tulip Diagnostics).

Indirect Bilirubin: Total Bilirubin- Direct Bilirubin

Liver Enzymes: AST, ALT, ALP, and GGT: Modified IFCC, Kinetics by Meril Diagnostics.

Table 4: Correlation of HbA1c and FBS with liver profile parameters among T2DM subjects (N=255)

	HbA1c		FBS	
	r value	p value	r value	p value
AST/OT	0.041	0.515	0.059	0.347
ALT/PT	0.056	0.376	0.058	0.358
ALP	0.158*	0.012	0.198**	0.002
GGT	0.119	0.059	0.175**	0.005
TP	0.097	0.123	0.015	0.806
ALB	0.031	0.625	-0.050	0.428

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

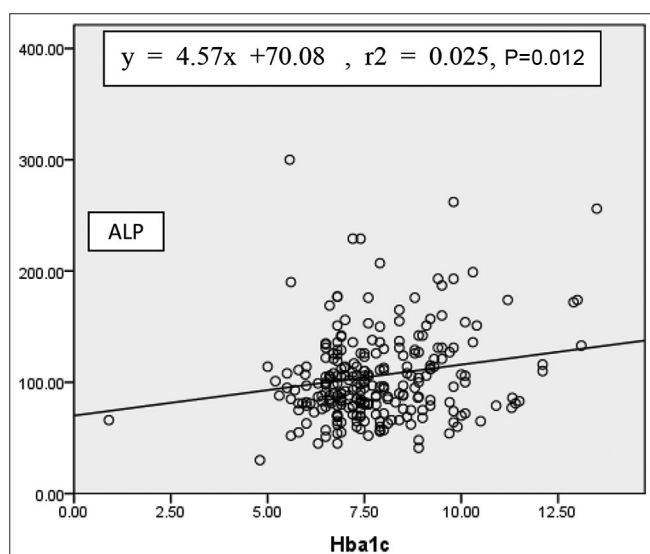


Figure 1: Linear regression curve between HbA1c and ALP

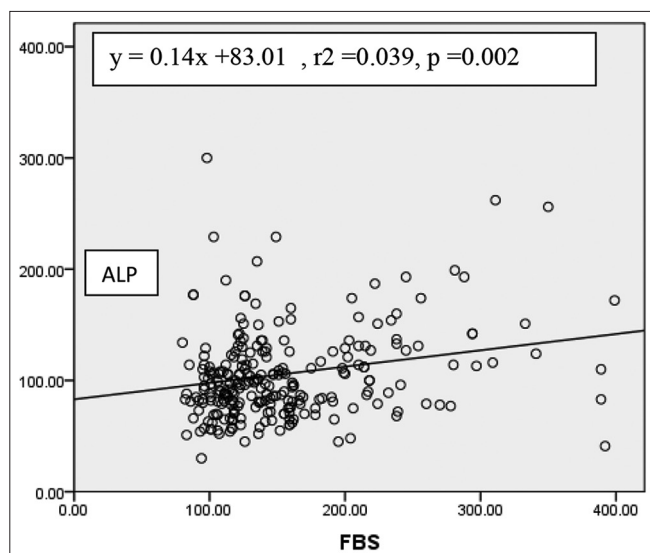


Figure 2: Linear regression curve between FBS and ALP

DISCUSSION

An increased incidence of liver function test (LFT) abnormalities has been associated with type 2 diabetes in

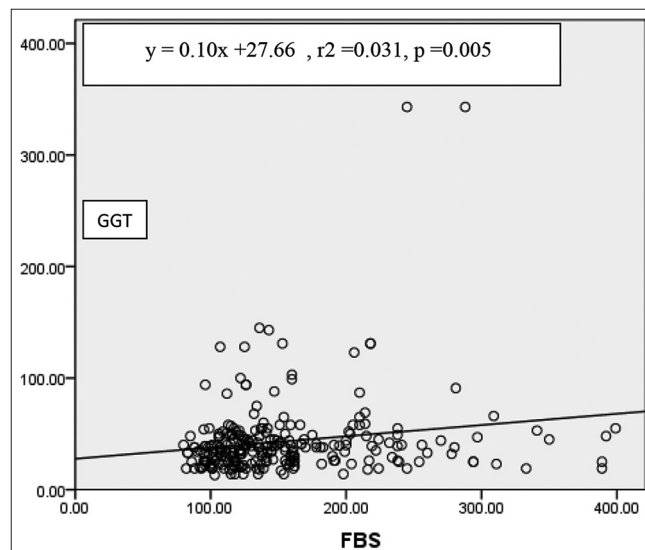


Figure 3: Linear regression curve between FBS and GGT

comparison to individuals without diabetes.¹⁵ In our study 58% of Diabetic subjects were having at least one deranged liver parameter. This finding is similar to different studies done in different countries reporting varying abnormalities in LFTs among the diabetic population. Studies conducted by Bora et al. in India reports 71.2%,¹⁶ Balogun et al., in Nigeria reports 70%,¹⁷ Ghimire et al., in Nepal reports 62.3%,¹⁸ Salman et al., in Iraq reports 46%.¹⁹ The above studies show a high prevalence of abnormal LFT in low and middle economy countries but decrease to 7.8-22.9% in developed countries like Europe and the US.¹⁵ There is no proper explanation for decreased LFT abnormalities in developed countries but may be due to a good health care system, good health awareness. Thus in context to a country like Nepal, it is good to report the scenario of LFT derangement that will help in proper treatment to the diabetic population.

Different serum enzymes were studied in the diabetic population, but the data presented are often not related and controversial.^{20,21} In our study population prevalence of elevated liver enzyme levels was about 12% for AST, 17% for ALT, 13% for ALP, and 20% for GGT. Similar different studies done in different countries have shown the different prevalence of elevated liver enzymes.^{18,19,22-25} A Study conducted by Salman et al. in Iraq showed that 13% have increased AST, 15% have increased ALT, and 9% have increased ALP.¹⁹ Another Study conducted by Thambiah et al., in Malaysia showed that 27.3% increased ALT and 13% have increased ALP.²² Similar Study conducted by Ghimire et al., in Nepal reported that 46% have increased AST, 57% have increased ALT, and 7% have increased ALP respectively.¹⁸ Another Study conducted by Mandal et al., in Nepal reported that 17% have increased AST, 40% have increased ALT, and 16% have increased ALP respectively.²³

Studies conducted by Pardhe et al., in Nepal reported that 42.2% have increased AST, 58.9% have increased ALT, and 59.4% have increased GGT respectively.²⁴ Similar study conducted by Mathur et al. in India reported that 56.1% have increased AST, 19.8% have increased ALT, and 33% have increased ALP respectively.²⁵ The above different prevalence for elevated liver enzymes may be because of different methodology, reference range used for different populations, the prevalence of diabetes and its complications in the study population other associated factors, and pathophysiology.

In our study, the mean value of AST and ALT in T2DM in relation to non-diabetic healthy subjects was found to be increased significantly. Our study was similar to Salman et al., Ghimire et al., and Mathur et al., studies which have documented that mean of both these enzymes in DM in comparison to control were found to be significantly increased.^{19,18,25} These increases in liver enzymes in diabetic could be because of chronic and insulin resistance leading to an increase in fatty acid that has a toxic effect on hepatocytes.²⁶ Accumulation of excess free fatty acid disturbs cell membranes, dysfunction of mitochondria, toxin formation, oxidative stress, all these causes elevation of proinflammatory cytokines like Tissue Necrotic Factors.¹³ All these are responsible for the increase in transaminases and reduced synthetic functions of the liver.¹⁵

In our study, the mean value of ALP in T2DM in relation to non-diabetic control subjects was found to be increased significantly. There was a positive significant correlation of HbA1c and FBS with ALP in T2DM.

Our study was similar to Salman et al., Mathur et al., Shrestha et al., study which has documented that mean of ALP in DM in comparison to control was found to be significantly increased.^{19,25,27} Similar studies done by Ghimire et al., has documented that the mean of ALP in DM in comparison to control was found to be insignificantly increased.¹⁸ Most of the time there is an elevation in transaminases in all types of injury to the liver but ALP remains normal or slightly increased.¹⁵ ALP is markedly increased in liver cholestasis than liver injury. In T2DM ALP is increased due to Hepatosteatosi and insulin resistance.²⁵ All these along with few drugs may have a hepato-toxic effect on elevation of ALP.

In our study, the mean value of GGT in T2DM in relation to non-diabetic control subjects was found to be increased significantly. There was a positive significant correlation of FBS with GGT in T2DM. There are very few studies done on GGT. Our study was similar to Balogun et al. study, who has documented that mean of GGT in DM

in comparison to control was found to be significantly increased.¹⁷ GGT is the most sensitive but less specific marker of liver injury when compared to all other liver enzymes. There is an elevation in GGT level even in low-grade inflammation or liver damage that is most common in diabetic and metabolic syndrome.²⁸ GGT is also influenced by oxidative stress, hepatic steatosis, obesity, hypertension, metabolic syndrome, diabetes and is progressively involved in further pathogenesis.²⁹

CONCLUSION

This study concludes that the liver enzymes (ALT, AST, ALP, and GGT) have shown higher activity with T2DM patients than individuals who do not have T2DM. Despite clinicians considering hepatic complications as a negligible component in T2DM, the present findings may encourage more attention for screening of liver dysfunction in diabetics which will prevent further complications associated with the liver. Therefore, we believe this report would be helpful in encouraging the clinicians to give interest in monitoring this neglected diabetic hepatic complication in individuals suffering from T2DM. In addition, Liver parameters were significantly correlated with diabetes mellitus in our study population; hence, timely diagnosis and management of the abnormal liver parameters may help to minimize liver-related morbidity and mortality in the diabetic population.

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SKJ- Concept and design of the study; prepared first draft of manuscript, Statistically analysed and interpreted; **SR-** Concept, coordination, review of literature and manuscript preparation; **NKY-** Interpreted the results preparation of manuscript and revision of the manuscript.

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