Received: 6 December 2019 | Revised: 22 January 2020 | Accepted: 25 January 2020

DOI: 10.1002/edm2.116

ORIGINAL ARTICLE

Endocrinology, Diabetes & Metabolism Open Access WILEY

Prevalence of elevated liver enzymes and its association with type 2 diabetes: A cross-sectional study in Bangladeshi adults

Shiful Islam[1] | Sadaqur Rahman[1] | Tangigul Haque[1] | Abu Hasan Sumon[1] | AZ Mahbub Ahmed[2] | Nurshad Ali[1]

[1]Department of Biochemistry and Molecular Biology, Shahjalal University of Science and Technology, Sylhet, Bangladesh

[2]Sylhet Diabetic Hospital, Sylhet, Bangladesh

Correspondence
Nurshad Ali, Department of Biochemistry and Molecular Biology, Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh.
Email: nur_rubd@yahoo.com, nali-bmb@sust.edu

Abstract

Background: Type 2 diabetes (T2D) is a major public health concern affecting millions of people worldwide. The relationship between liver enzymes and T2D has been reported in limited studies; however, there is still a lack of evidence for the Bangladeshi population. This study aimed to evaluate the prevalence of elevated liver enzymes and examine its association with the prevalence of T2D in Bangladeshi adults.

Methods: A total of 270 individuals (110 diabetic and 160 nondiabetic) were enrolled in the study. Alanine and aspartate aminotransferase (ALT, AST), alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) activities were measured in blood serum collected from them. T2D was defined as fasting blood glucose (FBG) ≥126 mg/dL or self-reported recent use of insulin or antidiabetic medications. Association between liver enzymes and T2D was evaluated by multinomial logistic regression analysis.

Results: Overall, 61.2% of participants in T2D and 37.1% of participants in the nondiabetes group had at least one or more elevated liver enzymes. The mean concentrations of serum ALT, AST, ALP and GGT were significantly higher in the T2D group compared to the nondiabetes group. The prevalence of elevated liver enzymes was significantly higher in the diabetes group compared to the nondiabetes group ($P < .01$). In regression analysis, serum GGT activity showed an independent association with the prevalence of T2D.

Conclusions: A high prevalence of elevated liver enzymes was observed in subjects having diabetes. Increased serum GGT activity was independently associated with the prevalence of T2D among Bangladeshi adults. More studies of this nature should be carried out in developing countries to get proper insights into the involvement of liver enzymes in T2D.

KEYWORDS

Bangladeshi adults, liver enzymes, prevalence, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus is a public health threat and one of the leading causes of morbidity and mortality in the world.[1,2] According to the International Diabetes Federation (IDF), about 1 in 11 adults worldwide is affected by diabetes mellitus and over 90% of them have type 2 diabetes (T2D).[3] About 80% of the diabetic patients live in the low- and middle-income countries; in Asia, the South-East Asian countries are particularly affected.[2] The incidence of diabetes and associated disorders in the Bangladeshi population has increased substantially since the last decades. In Bangladesh, the number of diabetic subjects was 7.3 million in 2017, which will be increased about two times by 2045.[3]

The presence of liver disease in T2D patients has received increased attention because of their long-term health consequences and economic burden for National Health Services.[4] Individuals with T2D are highly prone to liver function test abnormalities than nondiabetic healthy individuals.[5] In epidemiological studies, T2D has found to be related to different liver diseases including nonalcoholic fatty liver disease (NAFLD), liver cirrhosis and hepatocellular carcinoma.[6-8] These liver diseases are considered as a significant contributor to death in T2D.[9]

The liver is a vital organ in metabolism that plays an important role in the regulation of glucose homeostasis.[10,11] The markers for liver dysfunction, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyltransferase (GGT), have been shown as a good indicator to measure the liver health and involved with hepatic insulin resistance [12] and risk of T2D.[6] ALT is considered a specific marker for liver injury and is found predominately in this organ,[11,13] while GGT is present in most cell surface and highly active in liver, pancreas and kidney.[14] GGT mediates glutathione uptake and thought to be linked to oxidative stress and chronic inflammation,[15-17] which are also considered the important pathways of T2D development.[11] Thus, hepatic enzymes could be underlying biological markers connecting between liver disease and T2D.

Previously, some studies have been conducted to assess the relationship between liver enzymes and T2D in Asian,[5,7,11,15,18-23] European [4,24-26] and American populations.[12,27-29] Most of the previous study examined the associations that included only two or three liver enzymes, and there are a limited number of studies that examined maximum number (four) of liver enzymes to evaluate the relationship with T2D. Moreover, their findings were inconsistent. The epidemiological data concerning the association between elevated liver enzymes and T2D in Bangladeshi adults are not available so far. To address these issues, we conducted a cross-sectional study to measure the prevalence of elevated liver enzymes (ALT, AST, ALP and GGT) in nondiabetic and diabetic subjects in Bangladesh and evaluate the association of increased liver enzymes with T2D.

2 | MATERIALS AND METHODS

2.1 | Study area and study population

This descriptive cross-sectional study was conducted between November 2017 and July 2018 on 110 diabetic and 160 nondiabetic participants (age range 18-85 years) from the Sylhet region, a north-east part of Bangladesh. The participants with T2D were enrolled from Sylhet diabetic hospital, who went there for their regular physical examinations. More than 150 patients living with diabetes were invited, among them 110 subjects participated in this study. The subjects having diabetes were confirmed by participants' self-reported history of using of antidiabetic medications and revised criteria of the American Diabetic Association.[30] Nondiabetic participants were selected randomly from general adults of Sylhet city region, university students, and academic and nonacademic staff members of the university. The participants with a history of hepatotoxic drug intake, alcohol intake and clinical evidence of hepatic diseases were not included in the study. All participants were informed about the study, and written consent was obtained from them before inclusion in the study. The study protocol was approved by the Internal Review Committee at the Department of Biochemistry and Molecular Biology of Shahjalal University of Science and Technology and Institutional review board of Sylhet Diabetic Hospital. All steps in Methods section were carried out following the relevant guidelines and regulations.

2.2 | Anthropometric data

Trained medical personnel and graduate-level students performed the anthropometric measurements according to the standard procedure described elsewhere.[31-35] Individual's body weight and height were measured to calculate the body mass index (BMI), which was calculated as weight in kilogram divided by height in metres squared. Physical activity was categorized as low, medium and adequate based on participation in any activities such as jogging, bicycling, swimming or daily sports. The questionnaire also asked about the smoking habits of the participants (yes or no). Brief information on individual food habits and lifestyle was also recorded in the questionnaire form.

2.3 | Specimen collection and laboratory measurements

The participants enrolled in the study were at least 10 hours of overnight fast before providing the blood sample. About 5 mL of the venous blood was collected in a plain dry vacutainer tube using disposable syringes. The serum sample was separated and stored at −80°C until analysis. Serum levels of glucose, triglycerides (TG),

total cholesterol (TC) and albumin were measured by colorimetric methods. The enzyme activity (ALT, AST, ALP and GGT) was determined by kinetic methods. All measurements were performed using commercially available diagnostic kits (Human Diagnostic, Germany, except GGT from Vitro Scient, Egypt) with a biochemistry analyser (Humalyzer 3000, USA).

2.4 | Definition of elevated levels of liver enzyme

Elevated liver enzymes were defined as one or more measurement of: ALT > 45 U/L in men/ >34 U/L in women, AST > 35 U/L in men/ >31 U/L in women, GGT > 55 U/L in men/ >38 U/L in women [36] and ALP > 129 U/L in men/ >104 U/L in women.[37] Type 2 diabetes was defined according to American Diabetes Association as a fasting plasma glucose ≥ 126 mg/dL,[30] or self-reported recent use of insulin or antidiabetic medications.

2.5 | Statistical analysis

Quantitative variables are expressed as mean ± SD, whereas qualitative variables are expressed by frequencies (%). Pearson's correlation coefficient test was done to assess the correlation between hepatic markers and baseline variables. Differences for the anthropometric and baseline characteristics in the gender and case-control groups were performed by independent sample *t* test. Associations between liver enzymes and T2D were evaluated by multinomial logistic regression analysis. We used four models in the regression analysis. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, BMI, albumin and total protein. Model 3 was adjusted for variables used in model 1 and 2 and smoking status and physical activity. Model 4 was further adjusted for variables used in model 1 to 3 and TG and TC. A *P*-value of <.05 was set as statistically significant. IBM SPSS software, version 23, was used for statistical data analysis.

3 | RESULTS

3.1 | Baseline characteristics of study subjects

The baseline characteristics of the study subjects are presented in Table 1. Out of 270, 160 were nondiabetic (124 male and 36 female) and 110 were T2D participants (68 male and 42 female). The mean age for nondiabetic subjects was 36.4 ± 17.0 years and 47.2 ± 12.2 years for T2D subjects. The participants in the T2D group had a higher mean BMI (25.1 ± 3.8 kg/m^2) than the participants in the nondiabetes group (24.0 ± 3.8 kg/m^2). The average concentrations of ALT, AST, ALP and GGT were significantly higher in the diabetes group compared to the nondiabetes group (*P*-value < .05 for all significant cases). Male participants in the nondiabetes group had higher concentrations of all liver enzymes than in the female participants, but a variation was observed in the T2D group (Figure 1). Male participants in the diabetes group had significantly higher mean level of ALP ($P < .01$) and GGT ($P < .001$) than males in the nondiabetes group. On the other hand, female participants in the diabetes group had higher mean levels of ALT ($P < .01$), AST ($P < .01$) and GGT ($P < .05$) than females in nondiabetes group (Figure 1). Serum levels of TC and TG were also significantly higher in the diabetes group ($P < .001$). In both groups, no significant differences were observed at the level of serum albumin, total protein, smoking status and physical activity.

TABLE 1 Baseline characteristics of the nondiabetic and diabetic participants

Variables	Nondiabetes	Diabetes	*P*-value
N	160	110	-
Gender [n (%)]			
Male	124 (64.6)	68 (35.4)	.000
Female	36 (46.2)	42 (53.8)	
Age (yrs)	36.4 ± 17.0	47.2 ± 12.2	.000
BMI (kg/m^2)	24.0 ± 3.8	25.1 ± 3.8	.048
Glucose (mg/dL)	101.1 ± 13.5	212.1 ± 62.9	.000
ALT (U/L)	28.0 ± 12.7	32.4 ± 14.6	.028
AST (U/L)	27.9 ± 9.9	34.1 ± 15.7	.001
ALP (U/L)	89.3 ± 30.2	109.2 ± 50.7	.001
GGT (U/L)	25.6 ± 14.8	43.5 ± 38.2	.000
TG (mg/dL)	151.2 ± 87.2	233.1 ± 149.9	.000
TC (mg/dL)	191.0 ± 59.4	281.1 ± 119.9	.000
Albumin (mg/dL)	48.8 ± 12.1	46.1 ± 15.9	.194
Total protein (mg/dL)	78.3 ± 25.6	78.3 ± 30.5	.983
Smoking status (%)			
Yes	20.6	20.4	.979
No	79.4	79.6	
Physical activity (%)			
Low	18.7	23.5	.257
Medium	72.9	71.4	
High	8.4	5.1	

Note: Data are presented as mean ± SD. *P*-values are obtained from independent sample *t* test in comparison between nondiabetes and diabetes group. χ^2-test was applied for categorical variables.

3.2 | Prevalence of elevated liver enzymes

The prevalence of elevated liver enzymes in both groups is presented in Table 2. Overall, 61.2% of participants in T2D and 37.1% of participants in the nondiabetes group had at least one or more elevated liver enzymes. The prevalence rate was significantly higher in the T2D group (ALT 19% vs 13.3%, $P < .01$; AST 34.1% vs 21.9%, $P < .01$; ALP 36.8% vs 11.9%, $P < .001$; and GGT 27.2% vs 5.7%, $P < .001$) compared to the healthy group (Table 2 and Figure 2). The prevalence of increased liver enzymes was varied in males and females in

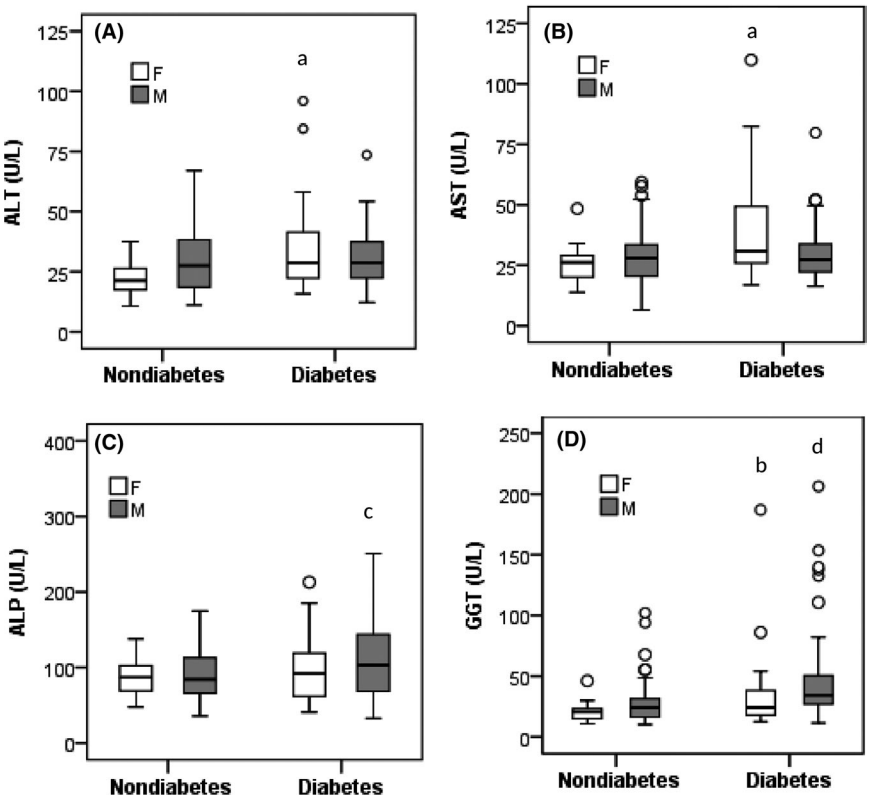

FIGURE 1 Levels of ALT (A), AST (B), ALP (C) and GGT (D) in nondiabetes and diabetes group by gender. The scale in the *y*-axis is not similar for all liver enzymes. [a]$P < .01$ when comparing mean levels of ALT and AST in females with diabetes vs. females without diabetes. [b]$P < .05$ when comparing mean level of GGT in females with diabetes vs. females without diabetes. [c]$P < .01$ when comparing mean level of ALP in males with diabetes vs. males without diabetes and [d]$P < .001$ when comparing mean level of GGT in males with diabetes vs. males without diabetes

TABLE 2 Prevalence of elevated liver enzymes in the nondiabetes and diabetes group by gender

	Nondiabetes		Diabetes	
	Male (%)	Female (%)	Male (%)	Female (%)
ALT				
Elevated	14.1	10.0	11.1	33.3
Normal	85.9	90.0	88.9	66.7
AST				
Elevated	22.1	21.1	25.0	50.0
Normal	77.9	78.9	75.0	50.0
ALP				
Elevated	9.6	22.2	36.0	38.5
Normal	90.4	77.8	64.0	61.5
GGT				
Elevated	5.9	5.0	21.2	37.9
Normal	94.1	95.0	78.8	62.1

both the nondiabetes and diabetes group. In the diabetes group, the most common liver enzyme abnormalities were found among female participants than the male participants.

3.3 | Correlation between liver enzymes and baseline variables

Table 3 presents the correlations between hepatic enzymes and baseline variables that are generally associated with diabetes. Serum AST and GGT activities showed a significant association with the age of the participants ($P < .05$). All liver enzymes showed a significant positive association with FBG concentration. Only ALP showed a significant positive association with BMI ($P < .05$). Serum ALT, AST and GGT were significantly correlated with TG and TC. The magnitude of these correlations was stronger for AST and GGT. Serum AST activity showed a significant negative correlation with albumin ($P < .05$), while ALT and GGT showed a significant positive association with total protein ($P < .05$ and $P < .01$, respectively).

3.4 | Association of liver enzymes with T2D

In multinomial logistic regression analysis, the liver enzymes showed a positive association with diabetes when covariates are adjusted in model 1 to model 3 except for AST in model 2 (Table 4). However, after adjusting lipids in model 4, only GGT activity showed a significant association with T2D (OR 1.02, 95% CI 1.00-1.04).

4 | DISCUSSION

The association between serum liver enzymes and T2D has not been evaluated previously for the Bangladeshi population. In this case, this is the first report, which adds to the information regarding the relationship of hepatic enzymes with T2D in a Bangladeshi adult cohort. In the present study, serum activity of GGT showed an independent association with T2D.

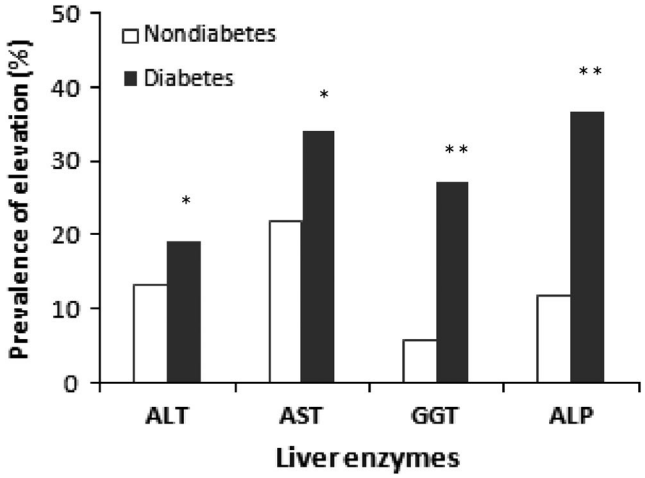

FIGURE 2 Prevalence of elevated liver enzymes (ie levels higher than the reference levels) in nondiabetes and diabetes group. *P < .01 and **P < .001 when compared to the nondiabetes group

In this study, 61.2% of participants in T2D and 37.1% of participants in the nondiabetes group had at least one or more elevated liver enzymes. The prevalence of liver enzymes (ALT, AST, ALP and GGT) above upper normal upper limit was significantly higher in subjects having diabetes. The prevalence of elevated liver enzymes in the present study (ALT 19%, AST 34.1%, ALP 36.8% and GGT 27.2%) is higher than that previously measured in a small diabetic cohort (ALT 18%, AST 3% and ALP 3%, GGT was not analysed) in Bangladesh.[38] Moreover, the association between liver enzymes and T2D was not evaluated in that previous study. In the present investigation, the prevalence of increased liver enzymes in the T2D group was higher in female than in the male participants, which are in line with a previous study.[7] The gender difference in elevated liver enzymes may be a reason for the individual's differences in body fat distribution and metabolism. The elevated levels of liver enzymes have been reported in Indian,[5,39] Thai,[40] Algerian[7] and Chinese[11,19] population. A wide variation has been observed on the prevalence of increased hepatic enzymes in these studies. Different reference values, ethnicity, age groups and demography might be considerable factors for the observed variations of these studies.

Most of the previous studies analysed ALT, AST and GGT in T2D individuals, and only a few studies included ALP. The increased levels of ALP found in our T2D individuals are consistent with previous studies where ALP was found to be elevated in diabetic subjects.[39,41] ALP in the liver was found to be associated with cell membrane, which adjoins the biliary canaliculus, and high serum levels of the liver isoenzyme indicate cholestasis rather than simply damage to the liver cells.[39] The correlation between baseline variables and liver enzymes was evaluated in this study

TABLE 3 Correlation between hepatic markers and baseline characteristics of the participants

	ALT		AST		ALP		GGT	
	Correlation (*r*)	*P*-value	Correlation (*r*)	*P*-value	Correlation (*r*)	*P*-value	Correlation (*r*)	*P*-value
Age	.016	.822	.150	.038	.038	.613	.143	.048
BMI	.122	.090	.144	.047	.041	.578	.108	.138
Glucose	.138	.049	.196	.007	.265	.000	.224	.001
TG	.311	.000	.278	.001	.144	.079	.465	.000
TC	.180	.028	.286	.000	.134	.103	.269	.001
Albumin	−.108	.136	−.171	.018	−.030	.694	−.081	.268
Total protein	.197	.006	.023	.751	.067	.382	.168	.020

Note: Correlation was analysed using Pearson's correlation coefficient test (two-tailed).

TABLE 4 Association of liver enzymes with diabetes

	ALT		AST		ALP		GGT	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Model 1	1.03 (1.00-1.06)	.021	1.03 (1.00-1.06)	.027	1.01 (1.00-1.02)	.003	1.04 (1.02-1.06)	.001
Model 2	1.03 (1.00-1.05)	.043	1.03 (1.00-1.06)	.060	1.01 (1.01-1.02)	.007	1.04 (1.01-1.06)	.001
Model 3	1.03 (1.00-1.05)	.048	1.03 (1.00-1.06)	.046	1.01 (1.00-1.02)	.009	1.03 (1.00-1.06)	.001
Model 4	1.01 (0.97-1.06)	.548	0.99 (0.96-1.03)	.665	1.00 (0.99-1.02)	.181	1.02 (1.00-1.04)	.039

Note: Multinomial logistic regression analysis was applied to evaluate the associations between liver enzymes and T2D.

Model 1: adjusted for age and sex.

Model 2: Model 1 plus BMI, albumin and total protein.

Model 3: Model 2 plus smoking status and physical activity.

Model 4: Model 3 plus TG and TC.

to see whether these variables have an influence on the concentration of the hepatic markers. In the present study, serum AST and GGT activities showed a significant correlation with age in Pearson's correlation analysis. In a previous study, increased age (>65 years) was found to be significantly associated with elevated levels of ALT, AST and GGT.[4] Serum AST showed a positive correlation with BMI. In the current study, all liver enzymes showed a significant positive correlation with FBG concentrations. Serum ALT, AST and GGT showed a significant correlation with TG and TC, which is consistent with the findings of previous studies that have shown a strong association between liver enzymes and several factors related to metabolic syndrome.[22,42]

Some studies have evaluated the relationship between liver enzymes and T2D. Most of these studies showed an independent association of GGT with T2D,[11,18,22,24,43-45] and our results are in agreement with these findings. A follow-up study in a Korean population also showed a strong dose-response relationship of serum GGT concentration with the incidence of T2D.[44] In some studies, both ALT and GGT were found to be significantly correlated with the risk of diabetes.[11,18,22,46] In contrast, few studies reported no significant association for ALT with diabetes when a minimum or a full range of diabetes risk factors are adjusted in the statistical models.[47,48] In the present study, ALT, ASP and ALP showed a positive association with T2D; however, the association was lost when lipid levels are adjusted in the regression models, which was consistent with the previous studies.[11,21,28,47,49,50] One possible explanation for the variability of these observations may be clarified both in terms of inadequate information of the biology of the liver enzymes and insufficient capture of their correlates and potential confounders.[22] Moreover, ethnicity could also play some roles in this regard because of a separate analysis of the Hispanic and black subjects, no significant association was found between hepatic markers and diabetes.

The biological mechanism underlying the associations between hepatic enzymes and incidence of T2D remains unclear, some possible pathways can be considered. One is that elevated levels of ALT, AST and GGT reflect an excess fat deposition in the liver, a condition termed as NAFLD. This NAFLD is considered to be involved with metabolic syndrome, which refers to some cardiovascular risk factors related to insulin resistance, hypertension, central obesity, dyslipidaemia and T2D.[51-53] Moreover, NAFLD is closely linked to obesity and visceral fat accumulation, and is a common feature of insulin resistance syndrome, and visceral adiposity is considered a significant contributor to T2D.[18,51] The second possibility might be serum GGT plays an important role in intracellular antioxidant defence systems, with the basic function of regulating intracellular glutathione levels.[54] Increased oxidative stress may contribute to the development of diabetes,[55] and chronic oxidative stress results in declined responsiveness to insulin and finally leads to T2D.[56] Although the associated mechanism remains largely unknown, changes in inflammation that occur through oxidative stress are predicted to be a common step in the pathogenesis of T2D.[18] In a previous study, after adjustment of C-reactive protein, a marker of oxidative stress and inflammation, GGT showed a significant association with the risk of diabetes.[18] The significant association between GGT and T2D observed in the present study also supports that previous study findings.[18]

One of the major strengths of the present study was the adjustment of well-known diabetes risk factors including age, BMI, lipids, physical activities and other possible confounders to examine the relationships. Secondly, in most of the previous studies diabetes was diagnosed based on self-reporting evidence, whereas in the current study, diabetes was diagnosed based on both self-reporting evidence and measured FBG concentration. However, there were some limitations to the present study. Firstly, we measured the hepatic enzymes only once that may not indicate the long-term profile. Secondly, we did not measure the hepatitis B and C infection among the participants, which could result in elevated hepatic enzymes. Thirdly, the sample size of the present study was relatively small, and we did not have information on generalizability and socio-economic status variables. Moreover, data on antidiabetic medications and insulin resistance were not available in our study; however, the relationship remained significant in previous studies, after adjusting insulin resistance.[12,28]

5 | CONCLUSIONS

The liver enzymes showed higher activity in subjects having diabetes than subjects who do not have T2D. The most common abnormality of hepatic enzymes was found for AST, ALP and GGT. The prevalence of increased liver enzymes was higher in females than in the males in the diabetes group. Increased serum GGT activity was independently associated with T2D in Bangladeshi adults. More studies of this nature should be carried out in developing countries to get proper insights into the involvement of liver enzymes in T2D.

ACKNOWLEDGEMENTS

The authors wish to thank all laboratory staff members for their help in sample collection. The authors are grateful to all academic and nonacademic staff and students for their participation in this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to this manuscript.

AUTHORS' CONTRIBUTIONS

SI did the experiment, analysed the data and drafted the manuscript. SR, TH and AHS helped in sample analysis and contributed to the analysis the results. AZMH helped in sampling and contributed to revise the draft. NA played a major role in the conception and design of the study, and critical interpretation of the data, and wrote and revised the manuscript. All authors read the manuscript and approved the final version.

ETHICAL APPROVAL

All participants were informed about the study, and written consent was obtained from them before inclusion in the study. The study protocol was approved by the Internal Review Committee at the Department of Biochemistry and Molecular Biology of Shahjalal University of Science and Technology and Institutional review board of Sylhet Diabetic Hospital. All steps in Methods section were carried out following the relevant guidelines and regulations.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Nurshad Ali https://orcid.org/0000-0003-1649-0887

REFERENCES

1. Akter S, Rahman MM, Abe SK, Sultana P. Prevalence of diabetes and prediabetes and their risk factors among Bangladeshi adults: a nationwide survey. *Bull World Health Organ*. 2014;92:204-213A.
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88.
3. IDF. International Diabetes Federation. IDF Diabetes Atlas — 8th Edition. Diabetes Atlas. https://diabetesatlas.org/resources/2017-atlas.html. 2017. Accessed March 2019.
4. Forlani G, Di Bonito P, Mannucci E, et al. Prevalence of elevated liver enzymes in Type 2 diabetes mellitus and its association with the metabolic syndrome. *J Endocrinol Invest*. 2008;31(2):146-152.
5. Philip R, Mathias M, Kumari SN, Gowda DK, Shetty JK. Evalation of relationship between markers of liver function and the onset of type 2 diabetes. *Nitte Univ J Health Sci*. 2014;4(2):90.
6. Ballestri S, Zona S, Targher G, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2016;31(5):936-944.
7. Belkacemi L, Belalia M. Cross-sectional pilot study about the liver enzymes profile in type 2 diabetic patients from an Algerian west region: Wilaya of Mostaganem. *Diabetes Metab Syndr Clin Res Rev*. 2016;10(1):S147-S150.
8. Marchesini G, Forlani G, Bugianesi E. Is liver disease a threat to patients with metabolic disorders? *Ann Med*. 2005;37(5):333-346.
9. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes Care*. 2007;30(3):734-743.
10. Duckworth WC, Hamel FG, Peavy DE. Hepatic metabolism of insulin. *Am J Med*. 1988;85(5):71-76.
11. Wang Y-L, Koh W-P, Yuan J-M, Pan A. Association between liver enzymes and incident type 2 diabetes in Singapore Chinese men and women. *BMJ Open Diabetes Res Care*. 2016;4(1):e000296.
12. Hanley AJ, Williams K, Festa A, et al. Elevations in markers of liver injury and risk of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes*. 2004;53(10):2623-2632.
13. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. *CMAJ*. 2005;172(3):367-379.
14. Hanigan MH, Frierson HF Jr. Immunohistochemical detection of gamma-glutamyl transpeptidase in normal human tissue. *J Histochem Cytochem*. 1996;44(10):1101-1108.
15. Kim D-J, Noh J-H, Cho N-H, et al. Serum gamma-glutamyltransferase within its normal concentration range is related to the presence of diabetes and cardiovascular risk factors. *Diabet Med J Br Diabet Assoc*. 2005;22(9):1134-1140.
16. Lee D-H, Jacobs DR. Association between serum gamma-glutamyltransferase and C-reactive protein. *Atherosclerosis*. 2005;178(2):327-330.
17. Turgut O, Tandogan I. Gamma-glutamyltransferase to determine cardiovascular risk: shifting the paradigm forward. *J Atheroscler Thromb*. 2011;18(3):177-181.
18. Ahn H-R, Shin M-H, Nam H-S, et al. The association between liver enzymes and risk of type 2 diabetes: the Namwon study. *Diabetol Metab Syndr*. 2014;6(1):14.
19. Chen S, Guo X, Chen Y, Dong S, Sun Y. Prevalence of abnormal serum liver enzymes in patients with type 2 diabetes mellitus: a cross-sectional study from China. *Postgrad Med*. 2016;128(8):770-776.
20. Doi Y, Kubo M, Yonemoto K, et al. Liver enzymes as a predictor for incident diabetes in a Japanese population: the Hisayama study. *Obes Silver Spring Md*. 2007;15(7):1841-1850.
21. Jiamjarasrangsi W, Sangwatanaroj S, Lohsoonthorn V, Lertmaharit S. Increased alanine aminotransferase level and future risk of type 2 diabetes and impaired fasting glucose among the employees in a university hospital in Thailand. *Diabetes Metab*. 2008;34(3):283-289.
22. Tohidi M, Harati H, Hadaegh F, Mehrabi Y, Azizi F. Association of liver enzymes with incident type 2 diabetes: A nested case control study in an Iranian population. *BMC Endocr Disord*. 2008;5(8):5.
23. Xu L, Jiang CQ, Schooling CM, Zhang WS, Cheng KK, Lam TH. Liver enzymes and incident diabetes in China: a prospective analysis of 10 764 participants in the Guangzhou Biobank Cohort Study. *J Epidemiol Community Health*. 2015;69(11):1040-1044.
24. André P, Balkau B, Born C, et al. Hepatic markers and development of type 2 diabetes in middle aged men and women: a three-year follow-up study. The D.E.S.I.R. Study (Data from an Epidemiological Study on the Insulin Resistance syndrome). *Diabetes Metab*. 2005;31(6):542-550.
25. Fraser A, Harris R, Sattar N, Ebrahim S, Davey Smith G, Lawlor DA. Alanine aminotransferase, gamma-glutamyltransferase, and incident diabetes: the British Women's Heart and Health Study and meta-analysis. *Diabetes Care*. 2009;32(4):741-750.
26. Monami M, Bardini G, Lamanna C, et al. Liver enzymes and risk of diabetes and cardiovascular disease: results of the Firenze Bagno a Ripoli (FIBAR) study. *Metabolism*. 2008;57(3):387-392.
27. Goessling W, Massaro JM, Vasan RS, D'Agostino RB, Ellison RC, Fox CS. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. *Gastroenterology*. 2008;135(6):1935–44, 1944.e1.
28. Vozarova B, Stefan N, Lindsay RS, et al. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes*. 2002;51(6):1889-1895.
29. Jeon CY, Roberts CK, Crespi CM, Zhang Z-F. Elevated liver enzymes in individuals with undiagnosed diabetes in the U.S. *J Diabetes Complications*. 2013;27(4):333-339.
30. American Diabetes Association 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(Suppl 1):S13-27.
31. Ali N, Rahman S, Islam S, et al. The relationship between serum uric acid and lipid profile in Bangladeshi adults. *BMC Cardiovasc Disord*. 2019;19(1):42.
32. Ali N, Perveen R, Rahman S, et al. Prevalence of hyperuricemia and the relationship between serum uric acid and obesity: A study on Bangladeshi adults. *PLoS ONE*. 2018;13(11):e0206850.
33. Ali N, Mahmood S, Islam F, et al. Relationship between serum uric acid and hypertension: a cross-sectional study in Bangladeshi adults. *Sci Rep*. 2019;9(1):9061.
34. Haque T, Rahman S, Islam S, Molla NH, Ali N. Assessment of the relationship between serum uric acid and glucose levels in

healthy, prediabetic and diabetic individuals. *Diabetol Metab Syndr*. 2019;11:49.
35. Ali N, Mahmood S, Manirujjaman M, et al. Hypertension prevalence and influence of basal metabolic rate on blood pressure among adult students in Bangladesh. *BMC Public Health*. 2017;18(1):58.
36. Schumann G, Klauke R. New IFCC reference procedures for the determination of catalytic activity concentrations of five enzymes in serum: preliminary upper reference limits obtained in hospitalized subjects. *Clin Chim Acta Int J Clin Chem*. 2003;327(1–2):69-79.
37. Tietz NW, Shuey DF. Reference intervals for alkaline phosphatase activity determined by the IFCC and AACC reference methods. *Clin Chem*. 1986;32(8):1593-1594.
38. Or Rashid MH, Haque MZ, Rahman MK, et al. Study on liver dysfunction in type 2 diabetic patients in Bangladesh. *Euroasian J Hepato-Gastroenterol*. 2016;6(1):1-4.
39. Mathur S, Mehta DK, Kapoor S, Yadav S. Liver function in type-2 diabetes mellitus patients. *Int J Sci Stud*. 2016;3(10):43-47.
40. Ni H, Soe HHK, Htet A. Determinants of abnormal liver function tests in diabetes patients in Myanmar. *Int J Diabetes Res*. 2012;1(3):36-41.
41. Shaheen A, Khattak S, Khattak AM, Kamal A, Jaffari SA, Sher A. Serum alkaline phosphatase level in type - 2 diabetes mellitus and its relation with periodontitis. *KMUJ Khyber Med Univ J*. 2009;1(2):51-54.
42. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology*. 2003;37(4):917-923.
43. Lee DH, Silventoinen K, Jacobs DR Jr, Jousilahti P, Tuomileto J. γ-Glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. *J Clin Endocrinol Metab*. 2004;89(11):5410-5414.
44. Lee D-H, Ha M-H, Kim J-H, et al. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. *Diabetologia*. 2003;46(3):359-364.
45. Nakanishi N, Suzuki K, Tatara K. Serum γ-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. *Diabetes Care*. 2004;27(6):1427-1432.
46. Kim C-H, Park J-Y, Lee K-U, Kim J-H, Kim H-K. Association of serum gamma-glutamyltransferase and alanine aminotransferase activities with risk of type 2 diabetes mellitus independent of fatty liver. *Diabetes Metab Res Rev*. 2009;25(1):64-69.
47. Nannipieri M, Gonzales C, Baldi S, et al. Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City diabetes study. *Diabetes Care*. 2005;28(7):1757-1762.
48. Schindhelm RK, Dekker JM, Nijpels G, Heine RJ, Diamant M. No independent association of alanine aminotransferase with risk of future type 2 diabetes in the Hoorn study. *Diabetes Care*. 2005;28(11):2812-2812.
49. Kunutsor SK, Apekey TA, Walley J. Liver aminotransferases and risk of incident type 2 diabetes: a systematic review and meta-analysis. *Am J Epidemiol*. 2013;178(2):159-171.
50. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Hepatic enzymes, the metabolic syndrome, and the risk of type 2 diabetes in older men. *Diabetes Care*. 2005;28(12):2913-2918.
51. Finelli C, Tarantino G. What is the role of adiponectin in obesity related non-alcoholic fatty liver disease? *World J Gastroenterol WJG*. 2013;19(6):802.
52. Lebovitz HE. Insulin resistance - a common link between type 2 diabetes and cardiovascular disease. *Diabetes Obes Metab*. 2006;8(3):237-249.
53. Balkau B, Lange C, Vol S, Fumeron F, Bonnet F. Nine-year incident diabetes is predicted by fatty liver indices: the French DESIR study. *BMC Gastroenterol*. 2010;10(1):56.
54. Karp DR, Shimooku K, Lipsky PE. Expression of γ-glutamyl transpeptidase protects ramos B cells from oxidation-induced cell death. *J Biol Chem*. 2001;276(6):3798-3804.
55. Ceriello A. Oxidative stress and glycemic regulation. *Metabolism*. 2000;49(2):27-29.
56. Tarantino G. JNKs, insulin resistance and inflammation: A possible link between NAFLD and coronary artery disease. *World J Gastroenterol*. 2011;17(33):3785.

How to cite this article: Islam S, Rahman S, Haque T, Sumon AH, Ahmed AZM, Ali N. Prevalence of elevated liver enzymes and its association with type 2 diabetes: A cross-sectional study in Bangladeshi adults. *Endocrinol Diab Metab*. 2020;3:e00116. https://doi.org/10.1002/edm2.116