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Prevalence of elevated liver enzymes and its relationship with type 2 diabetes mellitus in North Indian adults

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) also referred as metabolic as metabolic (dysfunction) associated fatty liver disease. Type 2 diabetes mellitus (T2DM) is a major cause in progression of NAFLD and non-alcoholic steatohepatitis (NASH). The aim of the present study is to assess the activity of liver enzymes in T2DM in North Indian population.

Method: This was a cross-sectional descriptive study clinic-based study in patients with T2DM. A total of 612 participants (226 healthy controls and 386 T2DM) were recruited. Body mass index (BMI), activity of liver enzymes including alanine and aspartate aminotransferase (ALT, AST) along with alkaline phosphatase (ALP) was measured. Fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) along with total protein (TP) and albumin were also measured. Quantitative variables were expressed as mean ± SD, while qualitative variables as frequencies (%). Pearson/Spearman correlation test, unpaired *t*-test, Chi-squared test was used to assess the correlation, association and significant differences between study groups respectively. A P-value of $< .05$ was set as statistically significant. The Statistical Package for Social Sciences (SPSS) ® Statistics, version 23 (IBM SPSS Statistics, Armonk, NY) was used to for analysis of data.

Results: The study was conducted on 386 T2DM patients, and out of 386 patients, 139 (36.01%) were male ($P < .000$) and 247 (63.98%) were female. The mean age of the T2DM patients was 46.4 ± 13.6 years, while healthy individuals have mean age of 39.2 ± 12.0 years ($P < .000$). It was observed that the activity of AST in T2DM is comparable with the healthy persons ($P = .060$). While the level of ALT, total bilirubin and ALP in T2DM is significantly higher compared to healthy control ($P < .000$). On average, 62.53% of T2DM subjects and 32% of participants of healthy subjects had abnormal liver enzymes activity.

Conclusion: The present study has revealed widely co-existent derangements in liver function tests (LFTs) in the diabetic population of North India. A detailed workup in such patients may be helpful in timely diagnosis and treatment. Moreover, early detection and management of abnormal liver parameters in T2DM would help minimize liver-related morbidity and mortality.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder that arises from an abnormality in insulin secretion, insulin action, or both that contributes to chronic hyperglycemia which is considered the main cause of diabetic complications with long-term failure and damage to various organ

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systems [1].

According to the International Diabetes Federation (IDF), DM is estimated to impact more than 463 million people worldwide in 2019 [2]. The widespread prevalence of the disease is escalating, and it is postulated that more than 700 million people will have diabetes by 2045 [2]. The most common form, which is accounting for 90% of all cases, is T2DM [3].

The liver plays an important role in the pathogenesis of this disorder [4]. However, T2DM affects all organs of the body, and the liver is not reprieved by this killer disease. Evidence has suggested that as high as 70% of cirrhosis patients can be diagnosed with T2DM which may cause initiation and progression of chronic liver disease [5]. In DM, the exact pathogenesis to induce abnormalities in liver biomarkers is still not known.

By this frame of reference, the present study is carried out to find the prevalence of abnormal LFT parameters in the subgroup of the diabetic population. To the best of our knowledge, limited data on the Indian population is available. Therefore, the present study has been undertaken to discover the pre-dominance of LFT abnormalities in the diabetic population and to ascertain whether there is some relationship between LFT parameters and elevated blood glucose in T2DM patients, so that, it could provide new insights to clinicians for improving the disease outcome and its prognosis.

2. Materials and methods

2.1. Study area and study population

This descriptive study was conducted between September 2019 to February 2021on 386 T2DM and 226 non-diabetic subjects (age range 16–78 years) from the regions of New Delhi and Kanpur, Uttar Pradesh. The sample size was calculated using formula $Z^2\ p\ (1-p)/d^2$, where: Z = Z score at 95% confidence interval = 1.96 with power = 0.80, p = prevalence = 50%, d = mariginal error = 5% (0.05). A total of 386 study participants were recruited in the diabetic group. The participants with T2DM were enrolled from the Out-Patients Department of Jamia Hamdard Hospital, New Delhi, and Lala Lajpat Rai Hospital, Kanpur. Non-diabetic subjects were randomly selected from the family members escorting the T2DM participants for regular physical examination.

2.2. Exclusion and inclusion criteria for participant's recruitment

Study participants with confirmed diagnosis of diabetes mellitus or newly diagnosed diabetes using American Diabetes Association (ADA) screening criteria with fasting venous plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L) were included into the study [6]. Patients with history of liver disease, alcohol intake, using hepatotoxic drugs, clinical presentation of acute hepatitis, participants with presentation of virus infection like hepatitis B and C and also with history of subclinical hypothyroidism were excluded from the present study.

2.3. Human ethics

The present study was approved by the Ethics Committee, GSVM Medical College Kanpur (EC/BMHR/2021/35). All study participants were informed about the study, and written consent was obtained from them.

2.4. Anthropometric characteristics

Anthropometric measurements were performed by the trained Paramedical staff according to the standard procedure explained to them under the guidance of expert physicians. Body mass index (BMI) was calculated for each participant using their body weight (kilogram) and height (in meters squared).

Table 1
Baseline characteristics of the healthy control and diabetic participants.

Variables	Healthy Control	T2DM	P value
N	226	386	–
Gender [n (%)]			
Male	154 (68.14)	139 (36.01)	.000
Female	72 (31.85)	247 (63.98)	
Age (Yrs)	39.2 ± 12.0	46.4 ± 13.6	.000
SBP (mm of Hg)	122.8 ± 12.4	125.2 ± 16.8	.062
DBP (mm of Hg)	71.8 ± 8.2	70.6 ± 9.4	.111
BMI (Kg/m^2)	24.0 ± 3.80	25.1 ± 3.10	.000
Fasting Glucose (mg/dL)	98.61 ± 11.26	201.26 ± 24.62	.000
HbA1c (%)	5.9 ± 0.18	8.1 ± 0.33	.000
AST (U/L)	29.16 ± 10.16	31.39 ± 16.00	.060
ALT (U/L)	31.02 ± 13.9	38.7 ± 12.80	.000
ALP (U/L)	92.4 ± 26.78	108.14 ± 28.64	.000
Albumin (mg/dL)	45.64 ± 19.62	43.17 ± 18.42	.118
TP (mg/dL)	64.18 ± 21.62	66.85 ± 28.41	.222
Total Bilirubin	0.59 ± 0.05	0.68 ± 0.08	.000

Note: Data are presented as mean ± SD. P-values are obtained from independent sample *t*-test in comparison between healthy control and diabetes group.

2.5. Specimen collection and laboratory

The venous blood (5 mL) was collected in a plain dry vacutainer tube using sterilize disposable syringes from the enrolled participants. Post collection of whole blood, it was left undisturbed at room temperature for 15–30 min followed by centrifugation at 2000×*g* for 10 min under refrigerated conditions for the separation of serum and plasma. Extracted serum and plasma were stored at −80 °C until analysis. Serum levels of total bilirubin, AST, ALT, ALP, Albumin, TP, and FPG were measured using an automated biochemistry analyzer (Beckman Coulter AU480) and HbA1c by Biorad D10, California, United States respectively.

2.6. Reference range of liver enzymes level

The reference ranges used for this study were as following: TB: 0.3–1 mg/dL, ALT >45 U/L in men/>34 U/L in women, AST >35 U/L in men/>31 U/L in women, ALP >129 U/L in men/>104 U/L in women [7]. Diagnosis of T2DM was performed according to the American Diabetes Association screening criteria of fasting glucose ≥126 mg/dL.

2.7. Statistical analysis

Quantitative variables in the resent study were expressed as mean ± SD, whereas the qualitative variables are denoted with frequencies (%). To establish the correlation between liver enzymes and baseline variables, Pearson's correlation coefficient was used. Anthropometric differences among variables were performed by independent sample *t*-test. Gender-wise prevalence was calculated by using the chi-squared test. A P-value of < .05 was set as statistically significant. IBM SPSS software, version 23, was used for statistical data analysis.

3. Results

The variable characteristics of the present study participants are depicted in Table 1. Out of 612, 226 were healthy control (154 male and 72 female) and 386 were diagnosed withT2DM (139 male and 247 female). The mean age of T2DM subjects was 46.4 ± 13.6 years and 39.2 ± 12.0 years for healthy control. The SBP and DBP of both groups did not show significant differences while the BMI of T2DM had a higher value of 25.1 ± 3.10(Kg/m^2) compared to healthy controls 24.0 ± 3.80(Kg/m^2). Similarly, the value of fasting blood glucose and HbA1c of T2DM participants were found significantly higher compared to healthy persons (P < .000). The activity of AST in T2DM is comparable with that of healthy persons. While the level of ALT and ALP in T2DM is significantly

Table 2
Gender wise prevalence of abnormal liver enzymes in the healthy control and T2DM. The p values are tabulated using Chi-squared test.

	Healthy Control		T2DM	
	Male (%)	Female (%)	Male (%)	Female (%)
AST				
Normal	73.26	78.11	72.00 (.809)	51.10 (.000)
Abnormal	26.74	21.89	28.00 (.809)	48.90 (.000)
ALT				
Normal	86.90	92.11	84.22 (.514)	67.72 (.000)
Abnormal	13.10	7.89	15.78 (.514)	32.28 (.000)
ALP				
Normal	93.52	80.10	68.00 (.000)	69.35 (.075)
Abnormal	6.48	19.90	32.00 (.000)	30.65 (.075)

higher compared to healthy control ($P < .000$). Similarly total bilirubin is found significantly higher in T2DM compared to healthy participants ($P < .000$).

The prevalence of abnormal liver enzymes including AST, ALT and ALP were compared in both groups and presented in Table 2. On average, 62.53% of T2DM subjects and 32% of participants of healthy subjects had abnormal liver enzymes activity as shown in Table 2. In T2DM the females showed the most common abnormalities in liver enzyme activity compared to male participants.

Table 3 represents the correlation between liver enzymes and clinical characteristics of the study participants that plays important role in diabetes mellitus pathogenesis. All liver enzymes showed a negative correlation with the HbA1c. ALT and AST also showed a negative correlation with the fasting blood glucose except for ALP had a positive correlation with the FBG. Similarly, all liver enzymes showed a positive correlation with the total bilirubin level.

4. Discussion

The present study has been undertaken to throw some light on hepatic dysfunctions in diabetics as the present study shows that patients having abnormalities in LFT in Type 2 DM patients. Previously published study also demonstrated the association of liver enzymes with T2DM in Ethiopian population and found significant association with elevated expression in T2DM patients as observed in our study [8]. In another similar study, the authors have examined liver enzyme activity and observed high prevalence of NAFLD in T2DM patients [9]. The results of our study are in complete agreement with the results obtained from previously published study, in which the authors used elevated AST enzyme as marker for in diabetes risk assessment [10]. The first possible explanation of this abnormality is the deposition of fat in the liver leading to nonalcoholic fatty liver disease (NAFLD). In another recently published comparative cross-sectional study, it was found that there is prevalence of abnormal LFTs in T2DM compared to healthy persons [11]. The other possible assumption is the susceptibility to inflammation of the liver which alters the function of the liver and induces a change in liver biomarkers [12]. Furthermore, fatty acid accumulation causes cell membrane disruption at high concentrations, causes activation and inhibition of key steps in the regulation of various metabolism and mitochondrial dysfunction, [13].

In India a high prevalence of deranged LFTs of about 71.2% and 70% respectively in individuals with T2DM [13]. Our study also showed abnormal liver parameters with a relatively lower rate of 53% as compared to the above study. Moreover, the frequency of deranged LFTs reported, in the case of Indian diabetes is 50–70% [14–17].

In one study done in Sudan by Idris et al., 22% had at least one abnormal liver function test [18]. Harris et al. showed that ALT increases up to 9.5% in the diabetic population that is up to 4 times in comparison to the general population [19]. The present study was supported by a study in the UK of 959 diabetic patients; ALT was raised in 15.7% diabetics, alkaline phosphatase in 10.4% patients whereas only 3.9% had hyperbilirubinaemia [20]. In another study in Iran on diabetic population, a rise of ALT and AST in 10.4% and 3.3% in study subjects respectively were seen [21]. Increased level of ALT (57%) and AST (46%) was also seen in another study on DM and it was found to be statistically compared to non-diabetic controls [22].

One study conducted by Ni H et al. from Malaysia showed a relatively lower frequency for LFTs; 18%, 12%, and 5% for ALT, AST and ALP respectively in the diabetic population [23]. In our study, it was seen that LFT was deranged more in female subjects as compared to males. However, our findings on gender distribution could not be compared with other studies as some of the studies showed an overall prevalence of abnormal LFTs was significantly higher in males than in females [24]. Also, our results showed that in both females and males, ALP was the most commonly affected parameter followed by ALT.

5. Limitations of the study

The study is associated with few limitations as present study design is cross sectional, therefore it is not possible to know whether the diabetes preceded abnormal liver function, also we did not investigate the chronic or transient abnormality in LFTs. The present study did not use any imaging technique to investigate association between abnormal LFTs with NAFLD. In the present study, liver enzyme: γGT was not assessed, which is another major limitation of the present study.

6. Conclusion

The present study mainly focuses on the importance of monitoring the liver function of patients with T2DM. It has revealed widely coexistent derangements in LFTs in the Type 2 diabetics in a subgroup of the population. A detailed workup in such patients may be helpful in timely diagnosis and treatment. Moreover, early detection and management of abnormal liver parameters in diabetes mellitus would help minimize liver-related morbidity and mortality in the diabetic population. Future studies are required to find out the causes of hepatic dysfunction in diabetics and to explore the impact of abnormalities of the liver on the glycemic status. The need of the hour is to request LFTs in the diabetic population because of the high prevalence of LFT abnormalities in these patients as they may harbor co-morbid illnesses.

Table 3
Correlation between liver enzymes and clinical characteristics of the study participants.

	AST		ALT		ALP	
	Correlation (r)	P value	Correlation (r)	P value	Correlation (r)	P value
Age	−0.025	.730	−0.019	.743	0.008	.880
BMI	−0.069	.584	−0.077	.542	0.075	.552
HbA1c	−0.038	.763	−0.003	.981	−0.144	.252
Fasting Glucose	−0.048	.408	−0.041	.480	0.122	.034
Total Bilirubin	0.018	.750	0.004	.942	0.004	.945

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

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None.

Conflict of interest disclosure

The authors declare that there are no conflicts of interest.

CRediT authorship contribution statement

Sana Alam: Conceptualization, Methodology, Software, Writing – original draft. **Alok Raghav:** Conceptualization, Methodology, Software, Writing – original draft. **Alisha Reyaz:** Data curation. **Akif Ahsan:** Data curation. **Ashok Kumar Ahirwar:** Data curation. **Vineet Jain:** Visualization, Investigation. **Saurabh Agarwal:** Visualization, Investigation, Writing – review & editing. **Prashant Tripathi:** Visualization, Investigation, Supervision, Software, Validation.

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References

[1] Jaganjac M, Tirosh O, Cohen G, Sasson S, Zarkovic N. Reactive aldehydes–second messengers of free radicals in diabetes mellitus. Free Radic Res 2013;47:39–48.
[2] IDF diabetes atlas. ninth ed. 2019.
[3] Amos AF, Mccarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med 1997;14: S7–85.
[4] Prabhudeva N, Pasha G, Mounika K. Hepatic dysfunction in diabetes mellitus: biochemical and ultrasonological study. J Acad Ind Res 2014;3:164–7.
[5] Hickman IJ, Macdonald GA. Impact of diabetes on the severity of liver disease. Amer. J. Med. Gastroenterol. Hepatol. 2008;4(8):568–70.
[6] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2019;42(Suppl. 1):S13–28.
[7] Kasper DI, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL. Harrison's principles of internal medicine. sixteenth ed. The United States of America: The McGraw-Hill Companies, Inc.; 2005. p. A1–7.
[8] Shibabaw T, Dessie G, Molla MD, Zerihun MF, Ayelign B. Assessment of liver marker enzymes and its association with type 2 diabetes mellitus in Northwest Ethiopia. BMC Res Notes 2019;12(1):707.
[9] Mandal A, Bhattarai B, Kafle P, Khalid M, Jonnadula SK, Lamicchane J, Kanth R, Gayam V. Elevated liver enzymes in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease. Cureus 2018;10(11):e3626.
[10] Nguyen QM, Srinivasan SR, Xu JH, Chen W, Hassig S, Rice J, Berenson GS. Elevated liver function enzymes are related to the development of prediabetes and type 2 diabetes in younger adults: the Bogalusa Heart Study. Diabetes Care 2011;34 (12):2603–7.
[11] Teshome G, Ambachew S, Fasil A, Abebe M. Prevalence of liver function test abnormality and associated factors in type 2 diabetes mellitus: a comparative cross-sectional study. EJIFCC 2019;30(3):303–16.
[12] Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'agostino RB, Haffner SM. Liver markers and development of the metabolic syndrome. J Diabetes 2005;54(11): 3140–7.
[13] Singh A, Dalal D, Malik AK, Chaudhary A. Deranged liver function tests in type 2 diabetes: a retrospective study. Int J Med Sci Publ Health 2019;4(3):27–31.
[14] Mathur S, Mehta Dk, Kapoor S, Yadav S. Liver function in type-2 diabetes mellitus patients. Int J Sci Stud 2016;3(10):43–7.
[15] Balogun WO, Adeleye JO, Akinlade KS, Adedapo KS, Kuti M. Frequent occurrence of high gamma-glutamyl transferase and alanine amino transferase among Nigerian patients with type 2 diabetes. Afr J Med Med Sci 2008;37:177–83.
[16] Prabhudeva N, Pasha G, Mounika K. Hepatic dysfunction in diabetes mellitus: biochemical and ultrasonological study. J Acad Ind Res 2014;3:164–7.
[17] Chitkara E. Alarming high levels of transaminases in non-insulin dependent diabetes mellitus. Indian J Basic Appl Med Res 2014;3:544–8.
[18] Idris AS, Mekky KFH, Abdalla BEE, Ali KA. Liver function tests in type 2 Sudanese diabetic patients. Int. J. Nutrit. Metabol. 2011;3(2):17–21.
[19] Harris EH. Elevated liver function test in type 2 diabetes mellitus. Clin Diabetol 2005;23(3):115–9.
[20] SherifGonem, Wall Alan, De Parijat. Prevalence of abnormal liver function tests in patients with diabetes mellitus. Endocr Abstr 2007;13:157.
[21] Meybodi MA, Afkhami-Ardekani M, Rashidi M. Prevalence of abnormal serum alanine aminotransferase levels in type 2 diabetic patients in Iran. Pakistan J Biol Sci 2008;11(18):2274–7.
[22] Ghimire Sumitra, Shakya Shreena, Shakya Jyotsna, Acharya Puspa, Dev Pardhe Bashu. Abnormal liver parameters among individuals with type 2 diabetes mellitus Nepalese population (Los Angel) Biochem Pharmacol 2018;7:1–5. 243.
[23] Ni H, Soe HH, Htet A. Determinants of abnormal liver function tests in diabetes patients in Myanmar. Int J Diabetes Res 2012;1:36–41.
[24] Ni Liping, Yu Dan, Wu Tianfeng, Jin Fubi. Gender-specific association between non-alcoholic fatty liver disease and type 2 diabetes mellitus among a middle-aged and elderly Chinese population. Medicine 2021;100(6):e24743.