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Original Article

The Biochemical Pattern of Liver Function Tests in Adult Patients of Diabetes and the Association with Hypoglycemic Medications

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ABSTRACT

Objective: To study the biochemical pattern of liver function tests in adult patients of diabetes and the association with hypoglycemic medications.

Study Design: Cross-sectional study.

Place and Duration of Study: Creek General Hospital, Karachi Pakistan, from Jun 2021 to Sep 2021.

Methodology: Two sixty patients were enrolled through consecutive non-probability sampling. Adult patients with diagnosed Type 2 diabetes mellitus were included in the study. While Type 1 diabetes patients, pregnant subjects, and people with diabetes with any other systemic disease or on any other non-diabetic medications or any history of drug abuse were excluded from the study.

Results: Raised Alanine transaminase levels were seen in 193 (74%) patients, a high Alkaline Phosphatase in 208 (80%) and a high Aspartate Aminotransferase in 202 (77%) patients. Liver markers were higher in the middle age group, females, hypertensive, and with abdominal obesity. There was no association between glycemic control and the duration of diabetes. The number of subjects having raised ALT and ALP was higher in those taking oral hypoglycemic and lower in those with insulin.

Conclusion: The liver markers are raised in patients with diabetes and can be the predictors of future hepatotoxicity.

Keywords: Diabetes, Hepatotoxicity, Liver enzymes.

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INTRODUCTION

Diabetes is linked with liver function abnormalities ranging from asymptomatic raised liver enzymes to cirrhosis.[1] Diabetic patient has an increased risk of non-alcoholic steato-hepatitis and, consequently, a fibrotic and cirrhotic liver. Liver function tests (LFTs) are regular baseline investigations for hepatic function screening, diagnosis, progress monitoring, or for the effect of medication. Derangements in LFT markers are common in diabetics.[1] Oral hypoglycemic medications (OHA) can contribute to hepatotoxicity. There is a consistent association between non-alcoholic fatty liver disease and diabetes due to insulin resistance causing hepatic parenchyma toxicity and disturbed glucose homeostasis in the liver. The resulting glycation causes accumulation of free fatty acids, cell membrane disturbance, mitochondrial dysfunction and toxin formation. This oxidative stress releases pro-inflammatory cytokines in the hepatic parenchyma.[2] The cellular damage causes alterations of liver enzymes and their abnormal release/elevation in the circulation.[3] In 2021, it was estimated that 537 million people have diabetes, projected to reach 643 million by 2030.[4] Prospective studies suggest derangement in LFTs as an indicator for future diabetes, linking elevated liver enzymes with hyperglycemia and/or insulin resistance.[5] Early diagnosis and management of disturbed liver values can reduce hepatic morbidity.[6,7]

This study aims to detect co-existent derangements in the liver function markers in Type 2 diabetes who do not have any previously diagnosed liver disease. This study will remind clinicians to perform a regular check-up of the liver status in a diabetic patient.

METHODOLOGY

The cross-sectional study was conducted at the Creek General Hospital, Karachi Pakistan, from June to September 2021, after approval from the IRB/REC committee (Reference#: UMDC/Ethics/IRB/2021/28/09/291). Two hundred sixty patients were enrolled through consecutive sampling technique. The sample size was calculated by the Raososft calculator taking reference parameters from a previous study,[8] where the raised ALT percentage was 20%, margin of error at 5%, and confidence interval at 95%.

Inclusion Criteria: Adults with diagnosed diabetes mellitus type 2 who were on Metformin, Sulphony-

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lurea, and Insulin or on combination drugs were included in the study.

Exclusion Criteria: Patients of type 1 diabetes, pregnant ladies, patients with diabetes a history of alcohol, recreational or hepatotoxic drugs, liver disease, diagnosed non-alcoholic fatty liver disease or cirrhosis, had acute hepatitis, were seropositive for Hepatitis B and C, HIV infection or had an autoimmune disease, cor pulmonale, cardiac failure were exclude from the study.

History and examination were conducted to identify hypertension or other diseases and medication intake. According to ADA guidelines good diabetic control was HbA1c <7.0% in last month or FBS <126 mg/dl, RBS <180 mg/dl in last two weeks.[9] Daily mild/moderate intensity physical activity of 20 minutes is a non-sedentary lifestyle. Body mass index (BMI) was classified as underweight (BMI: <18 kg/m2), normal (BMI:18.1-22.9 kg/m2), overweight (BMI:23 - 24.99 kg/m2) and obese (BMI: Obese I:25 - 26.99, Obese-II: 27 - 29.99, Obese III:≥ 30kg/m2).[10] Waist hip ratio (WHR) was normal if less than 0.85 for females and 0.9 for male.[11] Investigations included FBS, RBS, HbA1c, HbsAg, anti- HCV Ab, Ultrasound abdomen, and LFT markers (Total Bilirubin, ALT, Gamma GT, AST, and ALP levels) were conducted.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables were summarized as mean±SD and qualitative variables were summarized as frequency and percentages. The chi-square test was applied to find out the association. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Among the 260 adults, patients of <45 years were 34 (13%), 45-55 years were130 (50%) and >55 years were 96 (37%). The mean age was 52.87±9.89 years. There were 100 (38.5%) males and 160 (61.5%) females. There were 187 (72%) hypertensive patients. The mean BMI was 27.39±4.8, Range from 14.7 to 43.7. A raised ALT level was present in 193 (74%), a high ALP was in 208 (80%), and a high AST in 202 (77%) out of 260 subjects.

The mean total bilirubin was 0.702 mg/dl±12, ranging from 0.3 to 1.2, and the mean ALT was 31.76U/L±14.7, ranging from 10 to 93. The mean ASTU/L was 35.65±12.9, ranging from 18 to 99, mean ALP value was 232.2U/L±78.7, ranging from 76 to 491, and a mean Gamma GT level was 30.11U/L±14.615, ranging from 18 to 107. The variation of deranged serum ALT, ALP, and AST levels according to gender (*p*=<0.001) was shown in Table-I.

Table-I: The relationship of gender with raised serum Alanine Transaminase, Alkaline Phosphatase, Aspartate Aminotransferase levels (n=260)

Markers	Males (n=100)	Females (n=160)	*p*-value
High Alanine Transaminase	37 (37.0)	156 (97.5)	<0.001
High Alkaline Phosphatase	69 (69.0)	139 (87.0)	<0.001
High Aspartate Aminotransferase	23 (23.0)	35 (22.0)	0.474

The frequency of high ALT, ALP, and AST in age groups were displayed in Figure.

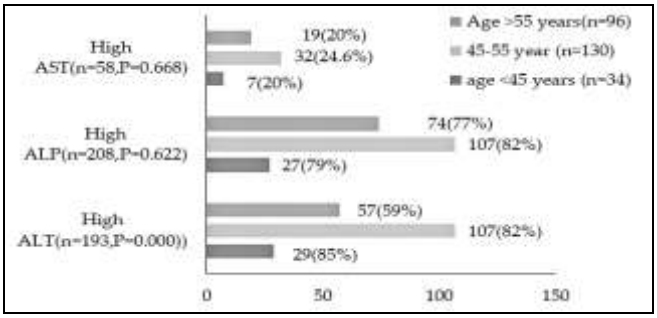

Figure: The frequency of a high Alanine Transaminase, Alkaline Phosphatase, Aspartate Aminotransferase values among the age groups (n=260)

Among the 187 hypertensive patients, high ALT activity was in 142 (76%, *p*=0.197), high ALP was found in 152 (81%, *p*=0.253) patients, and a high AST value in 41 (22%, *p*=0.456) patients. The duration of diabetes in association with liver markers was shown in Table-II. Medication of diabetes in association with liver markers was shown in Table-III.

The LFT markers with the BMI were shown in Table-IV. Among those with a sedentary lifestyle: 150 (77%) had a raised ALT [*p*=0.039], a raised AST was found in 43 (22%) [*p*=0.524],a raised ALP was present in 160 (82.5%) [*p*=0.065]. Those with an active life had; a raised ALT counted in 43 (65%), a raised ALP in 48 (72.7%) and 15 (22.7%) had a raised AST value. Those with abdominal obesity had raised serum ALT in 174 (75%, *p*=0.179) patients, a raised ALP in 193 (83%, *p*=< 0.001) and raised AST in 50 (21.6%, *p*= 0.304) adults. Those who did not have abdominal obesity had raised serum ALT in 19 (65%, *p*=0.179) patients, a raised ALP in 15 (51%, *p*=<0.001)) and raised AST in 8 (27%, *p*= 0.304) adults.

DISCUSSION

Our study concentrated on the hepatological facet of a diabetic patient. The frequency of patients with raised serum ALT and serum ALP values found in this study was comparable to a Malaysian study.[12] An Ethiopian and an Indian study,[13,14] recorded a higher serum AST and a lower ALT count. Han *et al.* had a comparable deranged AST count.[11] Islam *et al.* found all liver enzymes raised in diabetics and an association between increased GGT activity with the prevalence of diabetes among Bangladeshi adults.[12] Further studies also endorse this association.[15,16]

compared to controlled diabetes. Teshome *et al.*[14] mentioned an inverse relationship of duration of diabetes to abnormal LFT, which explains the early start of hepatosteatosis, which is not dependent on the diabetic control or duration. Further research needs to confirm or deny this association.

Hypertension coexisting with diabetes is an added atherosclerotic phenomenon attributed to oxidative stress, cell membrane disturbance, and mitochondrial dysfunction leading to metabolic syndrome. In contrast to our results, Kumar *et al.*[16] found raised markers in those with diabetes only compared to those

Table-II: Duration of Diabetes in Association with Liver Markers(n=260)

Duration	Serum Alanine Transaminase n (%)		*p*-value	Serum Alkaline Phosphatase n (%)		*p*-value	Serum Aspartate Aminotransferase n (%)		*p*-value
	Raised (%)	Normal (%)		Raised (%)	Normal (%)		Raised (%)	Normal (%)	
Less than 5 years	41 (74.5)	14 (25.5%)	0.795	44 (80)	11 (20)	0.916	14 (25.5)	41 (74.5)	0.086
5- 10 years	77 (76.2)	24 (24)		82 (81)	19 (19)		28 (27.7)	73 (72)	
More than 10 years	75 (72.1)	29 (28)		82 (79)	22 (21)		16 (15.4)	88 (81.6)	

Table-IV: The Liver Function Markers in Relation to the Body Mass in the patients of Diabetes(n=260)

Body Mass Index Groups	Serum Alanine Transaminase n (%)		*p*-value	Serum Alkaline Phosphatase n (%)		*p*-value	Serum Aspartate Aminotransferase n (%)		*p*-value
	Raised	Normal		Raised	Normal		Raised	Normal	
Underweight (<18)	2 (66.7)	1 (33.3)	0.061	2 (66.7)	1 (33.3)	0.221	2 (66.7)	1 (33.3)	0.315
Normal (18-22.99)	11 (26)	31 (73.8)		29 (69)	13 (31)		10 (24)	32 (76)	
Overweight (23-24.99)	17 (41)	24 (58.5)		32 (78)	9 (22)		11 (27)	30 (73)	
Obese I (25-26.99)	10 (27)	27 (73)		34 (92)	3 (14)		10 (27)	27 (73)	
Obese II (27-29.99)	14 (20)	57 (80)		57 (80%)	14 (20)		14 (20)	57 (80)	
Obese III (>=30)	13 (20)	53 (80)		54 (82)	12 (18)		11 (16.7)	55 (83)	

Bora *et al.* found elevated ALT in males and elevated ALP in females.[13] Teshom *et al.* suggested males with deranged LFT are because of fat distribution difference due to estrogen.[14] Females have limited outdoor activity/physical exercise, which, combined with a high-fat diet, contributes to disturbed fat metabolism with unbalanced liver homeostasis. Poor glycemic control plays a part in this dilemma.[17,18]

The middle age group showed greater hepatosteatosis with elevated liver enzymes. An unbalanced diet and lack of attention to health is a concern at this age. Another study,[9] concluded that ALT values were higher in subjects less than 60 years because hepatocyte damage begins at an early course of the disease, and with age, ALT activity declines due to steatotic progression with the inverse rise in AST level. However, Teshome *et al.* showed an LFT rise in the elderly.[14] No association was found between enzyme elevation with glycemic control and diabetes duration. This is in lieu to research by Bora *et al.*[13] and Saligram *et al,*[15] Nevertheless, Kumar *et al.*[16] and Moyad *et al.*[19] explained that enzymes were raised uncontrolled with diabetes and hypertension. Teshome *et al.*[14] suggested that the obstruction of blood flow due to fibrin deposition in the liver sinusoids is a probable cause of liver damage with raised liver markers in participants with both diseases. Another hypothesis is that hypertensives develop fatty liver due to elevated blood pressure, which activates pro-inflammatory responses such as TNF-α, interleukin, adiponectin and leptin, attributing to hepatotoxicity. The underlying biological relationship between hepatic enzymes and hypertension remains unclear.[20]

Studies claiming a raised ALT activity [9,11] with a higher BMI are consistent with our data. Han *et al.*[11] found raised AST levels in obese patients. Abdominal obesity is proportionate to liver markers rise associated with fat metabolism. Fatty liver develops with insulin resistance that activates lipolysis, accumulating non-esterified fatty acid from visceral adipose tissue, leading to hepatic steatosis and a liver enzyme increase. Researchers reported an association between elevated ALT activity, fatty liver, obesity, insulin resistance and type 2 diabetes.[5] A 500–1000 kcal energy deficit is

required to induce a weight loss of 500–1000 g/week. A Mediterranean diet with a high-protein intake which eventually reduces the liver fat on H1-MRS is recommended with physical activity.[7]

American Diabetes Association recommends metformin as the first-line medication for glucose control, insulin resistance management and weight control. There is speculation about its anabolic influence on bone metabolism, hence the rise of serum ALP activity.[9] Dango *et al*.[17] found that hypoglycemic monotherapy lowered enzyme levels compared to combined therapy. Insulin optimizes glycemic control with a profibrotic effect, causing proliferation of hepatic stellate cells and accumulation of type 1 collagen in the liver. It lowers liver enzymes and lipid profile in diabetic patients.[18]

Wang emphasized that higher levels of GGT and ALT are associated with increased diabetes risk.[21] The measurement of ALT activity is internationally standardized and may serve as a useful marker to identify individuals at high risk of type 2 diabetes in Asian populations. Elevated ALT and AST are associated with nonalcoholic fatty liver disease and can screen underlying fatty liver. A systematic hepatic workup in people with diabetes is beneficial in curtailing the prevalence of liver diseases and improving the outcome and prognosis of their disease. The goal is to improve the glycemic status and control all imminent complications. Future exploration will determine the impact of hepatic dysfunction in diabetics.

LIMITATIONS OF STUDY

A part from a low sample size, the study is limited to a certain region of the country, and a multicentric study across Pakistan would be more representative. The most commonly prescribed hypoglycemic medications were considered in this study, but it would have been more comprehensive if other oral hypoglycemics had been included and analyzed. Due to the patient's financial constraints in conducting cost-bearing investigations, certain specific hepatic investigations like CT abdomen, fibro scan, liver biopsy, etc., could not be completed, which would have been more convincing and conclusive in establishing a connection between diabetes and the underlying liver functionality.

CONCLUSION

This study reaffirms the close relationship between type 2 DM and liver dysfunction by the presence of deranged liver enzymes in people with diabetes who did not have previously diagnosed hepatic disorder.

Conflict of Interest: None.

Author's Contribution

AN: Compiling data and writing the manuscript.

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