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Association of aspartate and alanine transaminases with dyslipidemia in newly diagnosed and long duration of type 2 diabetes mellitus subjects.

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ABSTRACT… Objective: Association between alanine transaminase (ALT) and aspartate transaminase (AST) with newly diagnosed and known type 2 diabetes mellitus (DM) and to estimate association of liver enzymes with lipid profile in type 2 DM subjects. **Study Design:** Prospective Clinical study. **Setting:** Karachi University with Collaboration of Baqai Institute of Diabetology and Endocrinology. **Period:** November 2018 to May 2019. **Material & Methods:** Total 100 people were divided into four groups; Group I: 25 healthy controls with normal glucose tolerance, Group II: 25 newly diagnosed DM, Group III: 25 known DM type 2 with <5years duration and Group IV: 25 known DM type 2 between 5-10 years duration. Baseline data was collected on predesigned questionnaire. Blood samples for biochemical parameters were analyzed using standardized laboratory techniques. **Results:** Group I mean age (years) was 50.78±2.34, group II 50.56±1.96, group III 50.37±1.46 and group IV 56±1.36. In Group I, ALT and AST were significantly correlated to each other's. In group II, ALT was significantly correlated with AST, triglycerides and HDL-C, while AST correlated with ALT and HDL-C. In group III, ALT was significantly correlated with AST, while AST correlated to ALT, triglycerides and HbA1c. However, in group IV, ALT was significantly correlated with AST, LDL-C and HDL-C, and, AST with ALT, total cholesterol, LDL-C and HDL-C. **Conclusion:** Elevated ALT and AST- the salient markers for disease of non-alcoholic fatty liver with deranged dyslipidemia were found in known type 2 DM as well as in newly diagnosed type 2 DM subjects.

Key words: ALT, AST, Dyslipidemia, Duration, Type 2 DM.

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INTRODUCTION

The International Diabetes Federation has estimated the increasing prevalence of type 2 diabetes mellitus (DM) to be 463 million in 2019 and projected to reach 578 million by 2030, and 700 million by 2045, worldwide.[1] The recent second National Diabetes Survey of Pakistan (2016-2017) has estimated the current prevalence of type 2 DM as high as 26.3% including newly diagnosed type 2 DM 7.1%.[2]

Many studies have been reported that type 2 DM is associated with a number of liver abnormalities, such as abnormal glycogen deposition, non-alcoholic fatty liver disease (NAFLD), fibrosis, cirrhosis, hepatocellular carcinomas, abnormal elevated hepatic enzymes, acute liver disease, viral hepatitis and related metabolic syndrome.[3,4] Abnormal levels of liver enzymes, particularly aminotransferases are commonly used in clinical setting to diagnose liver dysfunctions. Elevated alanine trans aminase (ALT) to aspartate trans aminase (AST) ratio are two important prognostic features of NAFLD and metabolic disorders such as insulin resistance in type 2 DM subjects.[5,6] Although, the pathogenesis is unclear, hyperinsulinemia as a result of insulin resistance is thought to play an important role in pancreatic enzyme dysfunction in type 2 DM along with hepatic triglyceride accumulation and defective lipid metabolism.[7] Altered lipoprotein metabolism and derangement liver enzymes may be predisposing and have been identified as an independent risk factors for progression of cardiovascular disease and kidney disease in type 2 DM.[8,9] Moreover, a study in a white and African-

American population found that ALT ≥26 IU/L increases the diabetes prediction substantially.[10]

To our knowledge, limited studies have demonstrated the relationship of ALT and AST with diabetes in Pakistan. Thus, this study is designed to examine the association between ALT and AST with newly diagnosed diabetes (NDD) and known type 2 DM and to estimate association of liver enzymes with lipid profile in type 2 DM subjects.

MATERIAL & METHODS

This prospective clinical study was planned at Department of Biochemistry, University of Karachi-Pakistan with collaboration of Baqai Institute of Diabetology and Endocrinology (BIDE), Baqai Medical University, Karachi-Pakistan. Subjects visiting the outpatient department of BIDE were recruited between November 2018 to May 2019. Total 100 subjects were included, categorized into four groups; Group I: includes 25 control subjects with normal glucose tolerance, Group II: 25 subjects with NDD, Group III: 25 subjects with <5 years duration of known type 2 DM and Group IV: 25 subjects between 5-10 years duration of type 2 DM. Ethical approval was obtained from Institutional Review Board of BIDE (IRB no.: BIDE/IRB/NWARIS/10/26/18/0206).

Subjects with NDD (fasting plasma glucose (FPG) level ≥126 mg/dL or 2-hour post glucose level ≥200 mg/dL or both.) and controls with normal glucose tolerance (FPG levels below 100 mg/dL and post glucose levels below 140mg/dL) without any anti diabetic medications were diagnosed according to world health organization criteria. Subjects taking anti-diabetic medications with or without using statins were enrolled as known diabetes.[11] Exclusion criteria involved individuals who did not agree to participate, severe renal or hepatic dysfunction, excessive alcohol intake, dehydration, diarrhea or vomiting, gestational diabetes, type 1 DM and impaired type 2 DM. Subjects with NDD and healthy controls using lipid lowering agents such as statins were also excluded.

Following inclusion criteria, baseline demographic and anthropometric data was collected from each subject on predesigned questionnaire after obtaining informed consent. To confirm NDD and controls with normal glucose tolerance, blood samples were drawn before and after post glucose level at 120 minutes at specified tubes. For subjects with known diabetes, fasting and random blood samples were drawn for biochemical parameters. Blood samples for HbA1c, lipid profile, liver enzymes as ALT and AST were also obtained. Standardized techniques were used for biochemical analysis and to measure height, body weight and blood pressure.

Statistical Analysis

Data was presented as mean ± SEM (standard error of the mean) or n (%). Statistical analysis was performed using one-way ANOVA and followed by post hoc analysis (Least Significant Difference (LSD) test) to establish which means differed significantly. Z-test for two population proportion tests was used to check whether two groups differ significantly on some single categorical characteristic. All values are presented as mean ± SEM or n (%) for each group. For significance of difference, group II compared by group I is indicated by “a”; group III compared by group I and II is indicated by “a” and “b”, respectively; group IV compared by group I, II and III is indicated by “a”, “b” and “c”, respectively. Pearson’s correlation was performed to see the relationship of AST and ALT with various parameters. Significance of difference is considered by $p<0.05$. All statistical analyses were done using statistical package of social sciences version 20.

RESULTS

Mean age of group I was 50.78±2.34 years, group II was 50.56±1.96 years, group III was 50.37±1.46 years and group IV was 56±1.36 years. Details for anthropometric and various biochemical parameters are shown in Table-I. AST and ALT levels were significantly higher in known type 2 DM as well as NDD subjects compared to controls. Most of the subjects with known diabetes in group III 19(76%) and group IV 25(100%) were using statins.

Table-II categorize the dyslipidemic parameters

using their standard cutoff values in all groups. Hypercholesterolemia ≥200 was found 11(44%) in healthy control, 10(40%) in NDD, 5(20%) in <5 years duration of diabetes and 8(32%) in 5-10 years duration of diabetes similarly, hypertriglyceridemia ≥150 was observed in 9(36%), 14(56%), 18(72%) and 12(48%) subjects, respectively. LDL-C ≥130 was found in 7(28%), 10(40%), 3(12%) and 8(32%) and HDL-C <50/40 was found in 23(92%), 19(76%), 20(20%) and 19(76%) subjects in group I, II, III and IV, respectively. AST ≥35 was significantly found higher in group IV, group III and II, respectively, compared to group I. Meanwhile, ALT was also significantly higher in group IV and III, compared to group II and group I, respectively.

Table-III reveals the correlation between ALT and AST and lipid profile in group I, II, III and IV, respectively. In Group I, ALT and AST were significantly correlated to each other's. In group II, ALT was significantly correlated with AST, triglycerides and HDL-C, while AST significantly correlated with ALT and HDL-C. In group III, ALT was significantly correlated with AST, while AST significantly correlated to ALT, triglycerides and HbA1c. However, in group IV, ALT was significantly correlated with AST LDL-C and HDL-C, while, AST significantly correlated with ALT, total cholesterol, LDL-C and HDL-C.

All values are presented as mean ± SEM for each group. For significance of difference group II compared by group I is indicated by "a"; group III compared by group I and II is indicated by "a" and "b", respectively; group IV compared by group I, II and III is indicated by "a", "b" and "c", respectively. Significance of difference is considered by $p<0.05$.

All values are presented as n (%) for each group. For significance of difference group II compared by group I is indicated by "a"; group III compared by group I and II is indicated by "a" and "b", respectively; group IV compared by group I, II and III is indicated by "a", "b" and "c", respectively. Significance of difference is considered by $p<0.05$.

Parameters	(Group I)	(Group II)	(Group III)	(Group IV)
N	25	25	25	25
Age	50.78±2.34	50.56±1.96	50.37±1.46	56±1.36[abc]
Body Mass Index (kg/m^2)	27.1±0.82	29.91±1.16	26.11±0.59[b]	27.74±0.68
Systolic blood pressure (mmHg)	112.17±2.3	121.48±2.63[a]	120.65±2.27[a]	124.15±1.97[a]
Diastolic blood pressure (mmHg)	74.78±1.33	79.76±2.08[a]	77.58±1.09	78.98±0.94[a]
Fasting blood sugar (mg/dL)	91.39±1.27	149.24±2.40[a]	165.89±2.21[ab]	168.98±1.53[ab]
Random blood sugar (mg/dL)	111.45±4.32	274.88±16.87[a]	269.34±9.4[a]	275.03±4.36[a]
Cholesterol (mg/dL)	179.7±5.73	173.48±2.37	149±4.43[a]	137.42±2.58[ab]
Triglyceride (mg/dL)	154.43±4.69	183.52±5.66[a]	208.66±4.3[ab]	170.54±3.46
Low density lipoprotein (mg/dL)	111.04±4.69	109.68±5.18	92.34±3.31[a]	84.36±2.68[ab]
High density lipoprotein (mg/dL)	30.39±1.37	31.8±2.05	25.28±1.19	22.77±0.75[ab]
HbA1c (%)	5.44±0.09	7.73±0.43[a]	9.98±0.49[ab]	10.31±0.33[ab]
Aspartate trans aminase (IU/L)	27.96±1.90	34.56±3.65[a]	40.34±2.25[ab]	39.62±1.79[a]
Alanine trans aminase (IU/L)	20.43±1.12	33.56±2.67[a]	37.11±2.31[a]	33.43±1.22

Table-I. Various biochemical parameters of healthy control and diabetes groups.

Parameters	(Group I)	(Group II)	(Group III)	(Group IV)
Cholesterol (mg/dL)				
<200	14(56%)	15(60%)	20(80%)	17(68%)
≥200	11(44%)	10(40%)	5(20%)[ab]	8(32%)[ab]
Triglyceride (mg/dL)				
<150	16(64%)	11(44%)	7(28%)	13(52%)
≥150	9(36%)	14(56%)[a]	18(72%)[ab]	12(48%)
Low density lipoprotein (mg/dL)				
<130	18(72%)	15(60%)	22(88%)	17(68%)
≥130	7(28%)	10(40%)	3(12%)[ab]	8(32%)[ab]
High density lipoprotein (mg/dL)				
<50/40	2(8%)	6(24%)	5(80%)	6(24%)
≥50/40	23(92%)	19(76%)	20(20%)	19(76%)
Aspartate trans aminase (IU/L)				
<35	22(88%)	17(68%)	16(64%)	15(60%)
≥35	3(12%)	8(32%)[a]	9(36%)[a]	10(40%)[a]
Alanine trans aminase (IU/L)				
<35	21(84%)	20(80%)	15(60%)	14(56%)
≥35	4(16%)	5(20%)	10(40%)[ab]	11(44%)[a]

Table-II. Anthropometric and biochemical parameters cutoffs of healthy control and diabetes groups.

Groups	Parameters	ALT	P-Value	AST	P-Value
Group 1	Alanine trans aminase (IU/L)	1	-	0.49	0.018
	Aspartate trans aminase (IU/L)	0.49	0.018	1	-
	Cholesterol (mg/dL)	0.092	0.676	0.14	0.525
	Triglyceride (mg/dL)	0.144	0.513	0.041	0.852
	Low density lipoprotein (mg/dL)	-0.018	0.935	-0.011	0.959
	High density lipoprotein (mg/dL)	0.229	0.293	0.228	0.294
	HbA1c (%)	0.073	0.74	0.091	0.679
Group 2	Alanine trans aminase (IU/L)	1	-	0.849	<0.0001
	Aspartate trans aminase (IU/L)	0.849	<0.0001	1	-
	Cholesterol (mg/dL)	-0.149	0.476	-0.179	0.393
	Triglyceride (mg/dL)	0.418	0.037	0.353	0.083
	Low density lipoprotein (mg/dL)	-0.047	0.822	-0.209	0.317
	High density lipoprotein (mg/dL)	-0.58	0.002	-0.484	0.014
	HbA1c (%)	-0.214	0.315	-0.133	0.534
Group 3	Alanine trans aminase (IU/L)	1	-	0.755	<0.0001
	Aspartate trans aminase (IU/L)	0.755	<0.0001	1	-
	Cholesterol (mg/dL)	0.071	0.714	0.073	0.707
	Triglyceride (mg/dL)	0.258	0.177	0.242	0.020
	Low density lipoprotein (mg/dL)	0.024	0.904	-0.007	0.973
	High density lipoprotein (mg/dL)	0.042	0.827	0.069	0.722
	HbA1c (%)	-0.294	0.115	-0.348	0.059
Group 4	Alanine trans aminase (IU/L)	1	-	0.732	<0.0001
	Aspartate trans aminase (IU/L)	0.732	<0.0001	1	-
	Cholesterol (mg/dL)	-0.245	0.066	-0.323	0.014
	Triglyceride (mg/dL)	-0.083	0.538	-0.149	0.269
	Low density lipoprotein (mg/dL)	-0.292	0.025	-0.453	<0.0001
	High density lipoprotein (mg/dL)	-0.291	0.028	-0.318	0.016
	HbA1c (%)	-0.128	0.355	-0.204	0.138

Table-III. Correlation coefficient between liver enzymes and other studied parameters of Group I, Group II, Group III and Group IV.

Values are presented in correlation coefficient (r) to see the relationship of AST and ALT with studied parameters. Significance of difference is considered by $p<0.05$.

DISCUSSION

In this study, significantly increased AST and ALT levels with deranged dyslipidemia were observed with long duration of type 2 DM subjects. Similarly, ALT and AST levels were also significantly higher in NDD subjects with hypertriglyceridemia compared to controls with normal glucose tolerance.

Significant correlation of elevated liver enzymes with deranged dyslipidemia in type 2 DM were similar to recent study.[12] Elevated ALT and AST as a significant predictor of diabetes are to some extent in agreement with earlier study.[13] Cho et al., observed increased activity of liver enzymes, markedly increase ALT was associated with two-fold increase in type 2 DM risk independently of conventional risk factors and serve as a useful marker to identify individuals at high risk of type 2 DM in Asian populations.[14] In this study, AST upper limit >35 was found higher compared to ALT opposed to recent study that showed low AST levels compared to ALT levels in type 2 DM.[15] Meanwhile, elevated ALT and AST in NDD subjects as compared to healthy subjects were also observed showing that in asymptomatic individuals with mild elevations of ALT and AST, 98% have probable risk of liver disease commonly fatty liver disease consistent with previous study.[8,16]

In our study, deranged liver enzymes were investigated with dyslipidemia in type 2 DM subjects similar to study from Nigeria.[17] In previous study, insulin resistance, hypertriglyceridemia, and hypercholesterolemia were described as a cause of NAFLD and were reported in around 40-70% diabetic subjects.[8] Hyperlipidemia in terms of hypercholesterolemia and elevated LDL-C were significantly found lower in known type 2 DM subjects compared to NDD and healthy individuals in this study. However, hypertriglyceridemia and low HDL-C were non-significantly higher in <5years duration of known DM subjects. Our results show that either known DM subjects were using lipid controlling drugs (statins), but results for hypertriglyceridemia and low HDL-C levels are consistent with the study of Han Ni et al., who reported elevated determinants of liver function tests with hyperlipidemia in type 2 DM.[18] Our results are also consistent with Saligram et al., study, who discussed the association of increased ALT levels with elevated triglycerides and low HDL-C.[19] Moreover, oral antidiabetic agents, poor glycemic control and statins are also considered as a cause of deranged liver enzymes with histological changes in liver. Deranged liver enzymes were also observed with poor glycemic status in type 2 DM subjects in this study likely to Bora et al., study.[20] Asians at lower body mass index develop type 2 DM compared to western populations. It was also suggested that liver may play a vital role in development of type 2 DM in relatively lean Asian populations.[10] We also observed non-significantly high body mass index in all groups that was comparable to study conducted in India.[21]

Liver imaging and histopathology of liver biopsy were not done are the limitations of this study. But, comparing ALT and AST with dyslipidemia in NDD and long duration of type 2 DM has unmasked some important and relevant information about the impact of DM on the liver may increase worth to literature. Routine screening of ALT and AST with dyslipidemic profile in type 2 DM subjects may assist early detection of liver abnormalities and arrest the progress of disease to chronic conditions. Further studies need to be done along with the assessment of blood coagulation and histopathology of liver biopsy.

CONCLUSION

Elevated ALT and AST- the salient markers for non-alcoholic fatty liver disease with deranged dyslipidemia were found in long duration of known type 2 DM as well as in newly diagnosed diabetes subjects.

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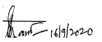
AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Nazish Waris	Concept and design, interpretation of data and wrote the manuscript.	
2	Samina Bano	Concept and design, edited and approved the final manuscript.	
3	Asher Fawwad	Concept and design, edited, reviewed and approval of the final manuscript.	
4	Abdul Basit	Reviewed and approval the final manuscript.