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Research Article

Assessment of association between metabolic parameters and non-alcoholic fatty liver disease in type-II diabetics

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ABSTRACT

Objective: To assess the association between metabolic parameters and non-alcoholic fatty liver disease in type-II diabetics.

Methods: This cross sectional study was conducted at Department of Medicine, Lahore General Hospital, Lahore from March 2017 to September 2017 over the period of 6 months.

Results: In total, 300 cases were included in analysis. NAFLD was seen in 38.0% of the cases. Patients with fatty liver were much older than those without fatty liver ($P<0.0001$). A significant association of NAFLD was seen with all anthropometric ($P<0.05$ for each) and lipid ($p<0.05$ for each) parameters and also systolic and diastolic blood pressure measurements ($p<0.0001$ for both). There was no significant association with glycemic levels in patients with NAFLD. Other factors which had significant association with fatty liver include duration of diabetes, duration of hypertension and a known history of hypertension and dyslipidaemia ($p<0.0001$ for each).

Conclusions: NAFLD has significant association with cardio-metabolic risk factors and may be an independent risk factor for CV disease. Further prospective studies with effect of diabetes treatment and progression/regression of NAFLD and its association with CV outcomes in T2D are warranted.

Keywords: Blood pressure, BMI, Lipids, NAFLD, Type 2 Diabetes, Weight

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is found to have association with insulin resistance which is seen patients of T2D, obesity and dyslipidaemia.[1] Type 2 diabetes (T2D) is a globally evolving epidemic and there is a significant contribution to the global burden of T2D from India.[2] The prevalence of NAFLD varies from 30 to 60% and it tends to increase with increase in obesity.[3] A large nationwide cohort study from India reported NAFLD prevalence to be 56.5% in patients with T2D.[4]

Pathophysiologically, it is not only steatosis but also involves hepatic cellular injury and is associated with inflammatory changes. NAFLD is said to be representative of hepatic manifestation in metabolic syndrome (MS).3 Imbalance of adipocytokines and proinflammatory cytokines tend to increase the severity of NAFLD in T2D and further accelerate the progression to non-alcoholic steatohepatitis and cirrhosis.[5]

NAFLD is the most frequent etiology for abnormal liver function tests (LFTs) in patients

with T2D.[6]A suspicion should be raised with mild elevation of aminotransferase in T2D. Finding NAFLD is essential as it represents insulin resistance. Given its association with increasing obesity, insulin resistance and T2D, NAFLD is considered as a risk factor for cardiovascular disease (CVD). Inflammation, oxidative stress, obesity, insulin resistance, endothelial dysfunction, imbalance of adipocytokines and proinflammatory cytokines are the major linkages associating NAFLD as factor for increased CVD risk.[7] From among various modalities of screening NAFLD, ultrasonography (US) offers safe, accessible, affordable and radiation-free method of providing enough assessment details for NAFLD diagnosis and staging. With a sensitivity of 60 to 94% and specificity of 84 to 95%, US is helpful for effective screening.[8]With this background, we evaluated patients with T2D for NAFLD and studied its association with anthropometric and metabolic parameters.

MATERIAL AND METHODS

This cross sectional study was conducted at Department of Medicine, Lahore General Hospital, Lahore from March 2017 to September 2017 over the period of 6 months. An approval was taken from institutional review committee and written informed consent was taken from every patient. We included adult patients aged above 18 years, non-alcoholic patients with type 2 diabetes who had undergone abdominal ultrasound examination for any reason. Fatty liver was identified by an expert sonologist in all patients included in present study. Nonalcoholic fatty liver disease (NAFLD) defined as:on ultrasonography, hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualization of intrahepatic vessel borders and left ventricular diastolic dysfunction was diagnosed by using pulse wave Doppler on the basis of : E/A ratio of less than 1, mitral deceleration time (DT) >240 mitral and Isovolumic relaxation time (IVRT) > 90 msec. [11]Type 2 diabetes mellitus was diagnosed as per criteria of American diabetics association: 1. Fasting plasma glucose level higher than 126 mg/dl or 2. Plasma Glucose level exceeding 200 mg/dl at 2 hours in the 75 g oral glucose tolerance test or 3. Symptoms of Diabetes and Random Plasma Glucose > 200mg/dl or 4. HbA1C > 6.5%.Fatty liver was assessed as per operational definition. Findings were entered on pre-designed performa along with demographic profile of the patients. Blood samples were taken and send to laboratory for assessment of metabolic parameters.

Collected data was entered in SPSS version 18 and analyzed. Mean and SD was calculated for numerical data and frequencies and percentages were calculated for categorical data.

RESULTS

From total of 300 cases, fatty liver on ultrasound was evident in 38.0% patients (Figure 1).Mean age of the population was 54.6 years and 24.7% of the study populations were above 65 years of age. Males (61.7%) were more frequent than females (38.3%). Nearly, one-fourth (22.3%) were current smokers. 36.7% were recently diagnosed with diabetes whereas rest were known cases with mean duration of 11.1 years. Hypertension (44.7%) and dyslipidemia (34.7%) were frequent comorbidities in present study population. Baseline characteristics of the patients are summarized in Table 1. Comparative evaluation of demographic, anthropometric and metabolic parameters in patients with and without fatty liver is presented in Table 2.

Among demographic parameters, mean age was significantly higher in patients with fatty liver than those with normal liver (60.5±9.9 Vs 50.9±10.8 respectively, $p<0.0001$). Elderly population more frequently were encountered with fatty liver (42.1% vs 14.0%, $p<0.0001$), but its occurrence did not differ among males and females ($p=0.074$).

Higher proportion of smokers were found to have fatty liver (29.8% Vs 17.7%, $p=0.015$). Compared to those without fatty liver, means of all

anthropometric parameters namely weight, BMI, waist circumference and waist: hip ratio were significantly higher in patients with fatty liver (p<0.0001 for all comparisons).

We assessed metabolic profile on three co-morbidities namely diabetic, hypertensive and lipid parameters. Mean duration of diabetes was also significantly greater in patients with fatty liver (14.3±7.2 vs 8.2±6.5, p<0.0001). However, measures of glycaemia including HbA1c (p=0.375), FBG (p=0.239) and PPBG (p=0.716) were not different in two groups (Table 2).

Compared to patients without fatty liver, significant higher values were seen for the presence of hypertension, mean duration of hypertension, mean systolic and diastolic blood pressure in patients having fatty liver (p<0.0001 for all comparisons) (Table 2).

Significantly higher proportion of patients with fatty liver had presence of dyslipidemia (54.4% Vs 22.6, p<0.0001). Mean levels of the lipid panel parameters namely total cholesterol (p<0.0001), triglycerides (p<0.0001), VLDL (p<0.0001) and LDL (p<0.0001) were significantly higher in fatty liver group whereas mean HDL was significantly lower (p=0.042) in these patients (Table 2).

Table 3 shows the association of control of metabolic parameters with presence of fatty liver. Glycemic control defined by HbA1c < 7% was not significantly different in patients with and without fatty liver (p=0.075) and majority of diabetes on treatment were not controlled (83.0%) to desired HbA1c goal. Interestingly, systolic BP to goal of <140 mmHg was observed in significantly lower proportion of fatty liver patients (39.5% Vs 65.6%, p<0.0001). Among lipid parameters, significantly higher proportion of patients with fatty liver had raised total serum cholesterol levels (28.1% Vs 9.1%, p<0.0001), raised serum TGs (45.6% Vs 17.7%, p<0.0001), raised serum LDL-C (71.1% Vs 57.5%, p=0.019).

Fig. 1: Frequency of fatty liver disease

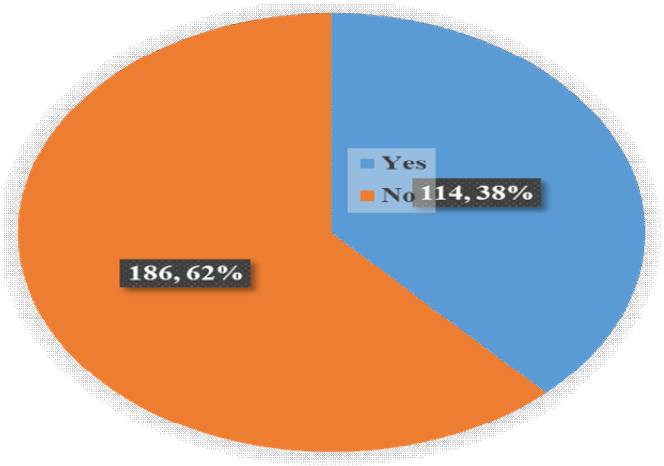

Table 1: Baseline characteristics of patient population.

Characteristics	**Observation**
Age	54.6±11.4
Age range	26 to 80
Age > 65 years	74 (24.7)
Sex	
Male	185 (61.7)
Female	115 (38.3)
Current Smoking	67 (22.3)
Diabetes status	
New (<3 months)	110 (36.7)

Old (>3 months)	190 (63.3)
Diabetes duration in old cases (years)	11.1±7.5
Known Hypertension	134 (44.7)
Hypertension Duration (years)	9.9±7.2
Known Dyslipidemia	104 (34.7)

Table 2: Demographic, anthropometric and metabolic profile in patients with and without fatty liver.

Characteristics	**Fatty Liver on USG**		**P value**
	Present (n=114)	**Absent (n=186)**	
Demographic			
Age	60.5±9.9	50.9±10.8	<0.0001
Age > 65 years	48 (42.1)	26 (14.0)	<0.0001
Male Sex	63 (55.3)	51 (44.7)	0.074
Current Smoking	34 (29.8)	33 (17.7)	0.015
Anthropometric			
Weight	68.1±13.3	57.1±10.0	<0.0001
BMI	27.0±5.2	21.5±3.5	<0.0001
Waist circumference (cm)	98.5±11.5	88.4±9.4	<0.0001
Waist: hip ratio	0.92±0.07	0.88±0.05	<0.0001
Metabolic			
Diabetic profile			
Known diabetes	90 (78.9)	100 (53.8)	<0.0001
Diabetes duration (years)	14.3±7.2	8.2±6.5	<0.0001
HbA1c (%)	8.4±1.7	8.6±1.9	0.375
Fasting blood glucose (mg/dL)	188.6±91.6	202.0±98.2	0.239
Post-meal blood glucose (mg/dL)	244.3±79.3	241.0±74.4	0.716
Hypertension Profile			
Known Hypertension	77 (67.5)	57 (30.6)	<0.0001
Hypertension Duration (years)	7.8±8.4	2.3±4.7	<0.0001
Current Systolic BP (mmHg)	140.4±29.0	127.2±23.2	<0.0001
Current Diastolic BP (mmHg)	90.8±20.8	81.8±17.3	<0.0001
Lipid Profile			
Known Dyslipidemia	62 (54.4)	42 (22.6)	<0.0001
Total cholesterol (mg/dL)	181.4±51.2	158.5±43.1	<0.0001
Triglycerides (mg/dL)	156.4±62.5	118.3±36.7	<0.0001
Very low density lipoprotein (mg/dL)	31.3±12.5	23.7±7.4	<0.0001
Low density lipoprotein (mg/dL)	120.3±27.8	106.3±25.7	<0.0001
High density lipoprotein (mg/dL)	42.4±6.4	43.9±6.5	0.042
Non-High density lipoprotein (mg/dL)	139.0±53.1	114.6±44.7	<0.0001

Table 3: Fatty liver association with control of glycaemic, blood pressure andlipid parameters

Characteristics	**Total**	**Fatty Liver disease**		**P value**
		Yes	**No**	
HbA1c (%)				
< 7	51 (17.0)	25 (21.9)	26 (14.0)	0.075

≥ 7	249 (83.0)	89 (78.1)	160 (86.0)	
Systolic BP (mmHg)				
< 140	167 (55.7)	45 (39.5)	122 (65.6)	<0.0001
≥ 140	133 (44.3)	69 (60.5)	64 (34.4)	
Total cholesterol (mg/dL)				
< 200	251 (83.7)	82 (71.9)	169 (90.9)	<0.0001
≥ 200	49 (16.3)	32 (28.1)	17 (9.1)	
Triglycerides (mg/dL)				
< 150	215 (71.7)	62 (54.4)	153 (82.3)	<0.0001
≥ 150	85 (28.3)	52 (45.6)	33 (17.7)	
LDL-C (mg/dL)				
< 100	112 (37.3)	33 (28.9)	79 (42.5)	0.019
≥ 100	188 (62.7)	81 (71.1)	107 (57.5)	
HDL-C in Males (mg/dL)				
< 40	71 (38.4)	30 (47.6)	41 (33.6)	0.063
≥ 40	114 (61.6)	33 (52.4)	81 (66.4)	
HDL-C in Females (mg/dL)				
< 50	26 (22.6)	9 (17.6)	17 (26.6)	0.256
≥ 50	89 (77.4)	42 (82.4)	47 (73.4)	

DISCUSSION

Present study identifies significant association of NAFLD with anthropometric and metabolic parameters in patients with T2D. Similar findings have been reported previously in many studies.[4,9-12] These findings corroborate NAFLD as risk factor for increased CVD risk.[13] Fatty liver was evident in 38% of the diabetic patients in present study. This is lower as compared findings of Rao et al reporting prevalence of 64.2% in T2D.[12] From a rural population, Majumdar et al reported prevalence of 30.7% in adults including those with or without T2D.[10]

Risk of NAFLD is increased significantly in diabetes as suggested by a study from Mohan et al.[14] Study found significantly higher prevalence of NAFLD (54.5%) in patients with diabetes in comparison to pre-diabetes (33%), isolated impaired glucose tolerance (32.4%), isolated impaired fasting glucose (27.3%) and normal glucose tolerance (22.5%). A comparative evaluation of anthropometric and metabolic risk factors in NAFLD cases.[9,15-20] These findings suggestsignificant association of NAFLD with anthropometric measurements and metabolic parameters and cardio-metabolic risk factors. We found no association with any glycemic parameters and NAFLD. This contrasts with other studies who reported higher HbA1c or FBG levels as evident from Table 4. But some reports also have found similar results as cited in table 4. This probably suggests that NAFLD is more co related with duration of diabetes and its long-term control as well as with the degree of lipotoxicity, dyslipidaemia, insulin resistance and obesity than glycemic parameter at any single point of time.21 Further, genetic factors may also play role in development of NAFLD.[22]

There is significant association of NAFLD with hypertension (HTN). Ryoo et al identified clinical association between NAFLD and development of HTN reported increasing rates of HTN with increasing severity of NAFLD. NAFLD is an independent risk factor for development of HTN. Further, altered dipping status of blood pressure has also been reported to be associated with NAFLD and could possible because of insulinresistance in NAFLD cases.[24] NAFLD is now evolving as potential target for T2D treatment because of its association with insulin resistance. NAFLD increases risk of developing diabetes and once it is established, diabetes further contributes to the progress of NAFLD.[25] Thus,

forming a vicious cycle contributing to cardio metabolicrisk factors for micro and macrovascular complications in future. This results in deranged glycemic control with changes in lipid levels and increasing obesity. Thus, NAFLD can be considered as a target to treat in diabetics especially those with significant fibro-progression and relevant family history of metabolic complications.

CONCLUSION

NAFLD has significant association with anthropometric parameters and metabolic risk factors in type 2 diabetes. In present study presence of NAFLD is not correlated with glycemic parameters. This association suggests a possible link between NAFLD and increased risk forCVD. Given the pathophysiology and its implications in type 2 diabetes, NAFLD can be considered as a target to reduce CVD risk in future. A prospective study evaluating NAFLD as potential target for treatment and its role in determining CV outcomes in T2D is needed.

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