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TYPE 2 DIABETES;
NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

1. Assistant Professor, Medical Unit III, Ward-7, Jinnah Postgraduate Medical Centre Karachi
2. Professor and Head of Department Medical Unit III, Ward-7, Jinnah Postgraduate Medical Centre Karachi
3. Assistant Professor Medicine United Medical College Karachi.
4. Associate Professor, Medical Unit III, Ward-7, Jinnah Postgraduate Medical Centre Karachi
5. Assistant Professor Medicine Liaquat University of Health Sciences Jamshoro Sindh
6. Postgraduate Trainee, Medical Unit III, Ward-7, Jinnah Postgraduate Medical Centre Karachi
7. Postgraduate Trainee, Department of Nephrology, Jinnah Postgraduate Medical Centre Karachi

Correspondence Address:
Dr. Zeeshan Ali
Associate Professor,
Medical Unit III, Ward-7,
Jinnah Postgraduate Medical Centre
Karachi
dr.zeeshan.j@gmail.com

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Dr. Shabnam Naveed[1], Prof. Syed Masroor Ahmed[2], Ayesha Nageen[3], Dr. Zeeshan Ali[4], Dr. Santosh Kumar[5], Humaira Zakir[6], Lubna Ghazi[7]

ABSTRACT… Objectives: To determine the prevalence and the associated risk factors of NAFLD in Type 2 diabetic patients. **Study Design:** Cross sectional study. **Setting:** Diabetic clinic of Medical Unit 3, JPMC. **Methods:** It is a cross sectional study. 262 patients were enrolled between the ages of 18-70 years attending Diabetes Clinic of Medical Unit III, JPMC. Each consenting patient underwent a detailed medical history-taking, physical examination, laboratory assessment and abdominal ultrasonography (US). Fatty liver was diagnosed on abdominal US on the basis of two out of the three criteria: increased hepatic echogenicity, blurring of liver vasculature and deep attenuation of the ultrasonographic signal. In accordance with the guidelines, subjects diagnosed with NAFLD had to fulfill the following criteria: no history of current or past alcohol consumption, other systemic illness known to cause fatty liver disease; absence of history and clinical, biochemical and US findings consistent with cirrhosis. Body mass index (BMI) was calculated. Blood pressures of greater than 130/90 were taken as hypertensive. LFTs, FBS, HbA1c, Lipid profiles were taken. **Results:** Out of 262 diabetic patients 107 (40.8%) of them were found to be having NFALD. Prevalence was found out to be higher in age group of 41-50 years, females, obese & in Pashtoon subjects.It was also more prevalent in sedentary lifestyle patients and those on oral anti diabetics in contrast to insulin therapy. It was correlating well with US findings when the ALT cut-off value was taken as 30 IU for males and 19 IU for females compared to standard values of ALT. There was association with hypertension, metabolic syndrome and dyslipidemia. **Conclusion:** Prevalence of NAFLD was higher in our diabetic patients. Middle age, female gender and obesity were found to be statistically strong risk factors in our study.

Key words: Diabetes, Nonalcoholic Fatty Liver Disease (NAFLD), Obesity, Gender.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver disorder that describes the accumulation of lipid in hepatocytes in people who drink little or no alcohol. This disease was previously considered as benign disorder. Globally prevalence of NAFLD has been increasing for last few decades especially in Asian countries. Current estimated prevalence in Asian countries ranges from 5% to 30%.[1,2] This common disorder ranges from steatosis (simple fatty liver), to nonalcoholic steatohepatitis (NASH—fatty changes with inflammation and hepatocellular injury or fibrosis), that can finally progress to cirrhosis and hepatocellular carcinoma.[3] In fact, NASH is a leading cause of cryptogenic cirrhosis.[4]

The exact cause of NAFLD is still unknown. However, the obesity and insulin resistance play a crucial role in its pathogenesis. An association between diabetes and NAFLD is now well established and it's reported that 10-75% of NAFLD patients have T2DM and 21-72% of patients with diabetes have NAFLD.[5,6] The type 2 diabetes mellitus (T2DM) is not only a risk factor but it also increases severity of NAFLD.[4] Therefore patients with both of these diseases have poorer prognoses in terms of higher rates of cirrhosis, hepatocellular carcinoma and mortality. Other well established risk factors along with obesity are male gender, Dyslipidemia and hypertension. Among them obesity (BMI > 30 kg/m2) has the strongest association with NAFLD.[7] Regardless of the BMI, patients with truncal obesity are at the

greatest risk to develop NAFLD.

The disease is often asymptomatic. Mostly it is discovered incidentally through elevated liver enzyme levels or a liver ultrasonography. An elevated serum activity of alanine aminotransferase (ALT) >30 has been suggested as the hallmark of NAFLD in the general population.[8]

Diabetes and other risk factors associated with NAFLD are quite common among the Pakistani population. Despite the potentially serious outcome of both diseases, the data in Pakistan are still lacking. Therefore we designed a study to determine the prevalence of NAFLD and its risk factors among Pakistani diabetic patients.

METHODS

This is a cross sectional study. It was conducted at the Diabetes Clinic, Medical Unit III, Jinnah Post Graduate Medical Center Karachi. Patient enrollment*:* we had enrolled 262 type 2 diabetic patients, aged 18 to 70 years old using non purposive convenient sampling technique. An informed written consent was taken. Each patient underwent a detailed medical history, physical examination, laboratory assessment and abdominal ultrasonography (US). Gender, Age, Ethnicity, duration of diabetes, and history of Hypertension and medication were recorded. Patients with history of heavy alcohol intake, use of hepatotoxic drug, history of hepatitis B or C infection and other chronic liver diseases were excluded from study. Physical examination A trained examiner had measured Height, weight and waist circumference (WC). The measurement of WC was made midway between the last rib and the iliac crest at minimal inspiration. Body mass index (BMI) was calculated as weight (kg) / height (m^2). Blood pressure (BP) was obtained with a mercury sphygmomanometer, in the right arm of patients in the supine position, after 5 min of quiet rest. Laboratory assessments: Blood samples were taken from anticubitus vein after a 12 hour overnight fast for measurement of Fasting Plasma Glucose (FPG), total cholesterol (TC), triglyceride (TG), Low Density Lipoprotein cholesterol (LDL-C), High Density Lipoprotein cholesterol (HDL-C) and alanine transaminase (ALT). The measurement of HbA1c was done by A1C Now (Bayer). Hepatitis B and C serology was done by immune chromatography method (ICT) and positive cases were excluded from the study. Ultrasonographic examination: A trained sonologist had performed abdominal ultrasound to avoid inter-observer variation. Patients with presence of cirrhosis on ultrasound were excluded from the study. Ultrasonic diagnosis of Fatty liver was done in the presence of two out of three following criteria: increased hepatic echogenicity compared to the spleen or the kidneys, blurring of liver vasculature and deep attenuation of the ultrasonographic signal.[9] Statistical analyses: SPSS version 19.0 was used for statistical analysis. Data was expressed as the mean ± standard deviation or median [inter-quartile range (25%-75%)] or as percentage. Differences between groups were tested using an independent two-sample t-test for continuous variables, and the Pearson chi-square test was used to test for differences in the distribution of categorical variables. All provided *P*-values represent the results of two-sided tests. *P*-values < 0.05 were considered statistically significant.

DEFINITIONS

NAFLD

The following criteria were applied for diagnosis of NAFLD: no history of current or past alcohol consumption (based on AUDIT Screening test), not receiving or have recently received hepatotoxic drugs; the negative serology for hepatitis B and hepatitis C virus; absence of history, clinical, biochemical and US findings consistent with cirrhosis and fulfilled the criteria with fatty liver under abdominal ultrasonography.[9]

Dyslipidemia

Dyslipidemia was considered on the presence of at least one of any 3 of the following: (1) a high triglyceride level (>150 mg/dL) or drug treatment for high triglycerides; (2) a high LDL-cholesterol level (>100 mg/dL) or drug treatment for high LDL; (3) a low HDL-cholesterol level (men, <40 mg/dL; women, <50 mg/dL) or on drug treatment.[10]

Hypertension: systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg.[10]

Uncontrolled Diabetes: HbA1C > 7[10]

Obesity: Obesity was defined as Asian cut off i.e. BMI: ≥ 25 kg/ m2[11]

Serum ALT: Standard cut off > 40 IU
Modified Gender based cut off: in male > 30 IU, in female > 19 IU

RESULTS

We looked into the relationship of NAFLD and factors like age, gender, hypertension, obesity, sedentary lifestyle, waist and hip circumference, Triglycerides, LDL, HDL, serum ALT, duration and control of diabetes.

Out of 262 diabetic patients, 107 patients had nonalcoholic fatty liver disease suggesting a prevalence of 40.8%. Prevalence was higher in the age group of 45-55yrs 58/125(46%) p=0.214 with mean age at 53.3±9.9.it was more prevalent in females 73/163(44%) compared to males 34/99(34%).p=0.062.

NAFLD was more prevalent in diabetics who were on oral anti diabetics, sulphonylureas 94/209(44.9%) p-0.005 and biguanides 102/241 (42%) compared to those patients who were on insulin in whom NAFLD was less prevalent 11/50 (22%) which is statistically significant (p=0.002).

Sedentary lifestyle leads to higher rate of NAFLD 84/203 (41%) compared to non-sedentary 23/59 (38%) p=0.431.

An important statistically significant (p=0.002) finding was correlation of ALT cut off values. When modified cut off for male 30 IU and female 19 IU were taken a higher correlation was seen for abnormal ALT values 68/150 (45%) NAFLD patients compared to being normal in 14/61 (22%) NAFLD patients. Whereas when the standard ALT values were taken as cutoff it was high only in 15/28 (53%) NAFLD patients but normal in 67/183 (36%) NAFLD patients.

The more the obesity with a higher BMI the more the NAFLD rate and it was statistically significant p-0.004. Central obesity is directly related to higher frequency of NAFLD with 97/225 (43%) being obese compared to 6/28 (21%) who were not obese. p-0.02.

Metabolic syndrome is present in 91/221 (41%) NAFLD patients compared to 6/21 (28%) NAFLD patients who did not had MetS.

DISCUSSION

The prevalence of NAFLD is much higher in diabetics as compare to general population globally. In our study prevalence found out to be 40.8%. In United Kingdom a study done in Edinburg diabetic people to check for NAFLD showed that they had a similar prevalence of 42.6%.[12] In comparison, a study that was done in South India showed that the prevalence of NAFLD was 56.5% which was higher than what it was here.[13]

It was higher in the age range of 45-55yrs which is similar to what is found in other studies as well. History of Coronary artery was seen statistically significant related to NAFLD in our study.

An important deduction from this study was that the use of oral hypoglycemic drugs was found to be related with higher frequency of NAFLD, while those patients who were on insulin therapy were less prone to NAFLD and this finding was statistically significant. This further confirms the association of NAFLD with insulin resistance which is combated better by insulin therapy. This finding was seconded by the study in Edinburgh.[12]

There have been several studies suggesting a raised ALT value to be pathognomonic of NFALD[14]. However an important finding in our study was ALT cut off values, when modified cut off for male 30 IU and female 19 IU were taken a statistically significant relation was seen with NAFLD patients for abnormal ALT values compared to normal ALT.

Category	Factors	Frequency	Percentage
Gender n 262	Male	99	37.8
	Female	163	62.9
Age N 262	<45	38	14.5
	45-55	125	47.7
	>55	99	37.8
Marital N 262	Married	253	96.6
	Unmarried	9	3.4
BMI N 257	Underweight<18	3	1.1
	Normal 18-22.9	31	11.8
	Overweight 23-24.99	43	16.4
	Obese 1 25-26.99	40	15.3
	Obese2 27-29.99	71	27.1
	Obese 3 >30	69	26.3
WHR gender wise N 256	Abd obesity	230	87.8
	No abd obesity	26	9.9
Hypertension N 258	No	71	27.1
	Yes	187	71.4
Central obesity N 253	No	28	10.7
	Yes	225	85.9
Dm contrl N 242	Good	67	25.6
	Poor	175	66.8
Dur of DM N 262	<5 yrs	51	19.5
	5-10yrs	108	41.2
	>10 yrs	103	39.3
	No	236	90.1
Ethnicity	Sindhi	15	5.7
	Punjabi	30	11.5
	Balochi	7	2.7
	Pashtun	50	19.1
	Seraiki	3	1.1
	Migrant	81	30.9
Sulphonylurea N 262	Yes	209	79.8
	No	53	20.2
Biguanides N 262	Yes	241	92.0
	No	21	8.0
Insulin therapy 262	Yes	50	19.1
	No	212	80.9
Drug gps n 262	OAD	212	80.9
	Insulin	50	19.1
Multiple drug gps	MET	5	1.9
	SU	1	.4
	INSU	20	7.6
	MET + SU	206	78.6
	MET + INSU	28	10.7
	MET + SU + INSU	2	.8
Lifestyle n 262	Sedentary	203	77.5
	Nonsedentry	59	22.5
h/o hyperlipidemia	Yes	18	6.9
	No	244	93.1
h/o liver disease n 262	Yes	21	8.0
	No	241	92.0
h/o jaundice n 262	Yes	18	6.9
	No	244	93.1
High ALT Male 30 Female 19 N 211	Normal	61	23.3
	High ALT Gender wise	150	57.3
High ALT/ SGPT n 211	Normal	183	69.8
	High ALT	28	10.7

High AST n 206	Normal	171	65.3
	High AST	35	13.4
High TG >150 N 210	Normal	95	36.3
	High TG	115	43.9
High LDL>100 N 208	Normal	149	56.9
	High LDL	59	22.5
Low HDL N 207	No	66	25.2
	Yes	141	53.8
Dyslipidemia N 218	No	31	11.8
	Yes	187	71.4
NAFLD N 262	Yes	107	40.8
	No	155	59.2
Met Syn N 262	No	21	8.0
	Yes	221	84.4
	May Be	16	6.1

Table-I. Study Description/ Frequency table (n=262)

	N	Minimum	Maximum	Mean	Std. Deviation
Age (years)	262	24	80	53.03	9.905
Duration of Diabetes (years)	262	.5	30.0	10.076	6.0414
If yes, duration of hypertension(years)	150	.10	30.00	6.1737	5.47576
Ex_ BMI	257	14.71	43.70	27.6564	4.80598
WHR	256	.71	1.20	.9518	.06721
BP(systolic)	257	80	200	127.00	19.882
BP(diastolic)	257	40	120	78.44	12.496
Heart Rate (beats/min)	257	52	120	85.27	10.178
Height(cm)	257	131.00	188.00	157.0661	9.64373
Weight(kg)	257	40.00	110.00	68.1630	12.95916
Hip circumference	256	60.00	155.00	102.9629	12.22404
Waist Circumference	256	60.00	141.00	97.7285	11.43925
Hb	212	6.6	14.4	10.846	1.4335
Hct	213	24.3	44.2	35.624	3.8111
Mcv	213	62.3	104.7	83.648	7.7367
TLc	213	4.3	87.9	8.722	7.6796
Plt	213	48	587	254.28	84.571
FBS	245	64	587	177.65	70.023
T.B	211	.4	1.2	.709	.1147
D.B	211	.1	2.0	.220	.1277
I.B	206	.3	.8	.497	.0916
SGPT/ALT	211	15	193	30.87	16.669
ALPO4	211	114	675	265.91	93.199
Gamma GT	207	18	116	29.79	14.923
SGOT/AST	206	18	255	37.04	23.416
ALT/AST_ Ratio	206	.23	1.64	.8925	.25664
S. Cholestrol	210	22	354	159.08	40.660
S. Triglyceride	210	60	944	184.26	111.910
S.HDL	207	29	79	41.69	4.770
S.LDL	208	20	410	83.63	39.747
HbA1c	57	6	13	8.72	1.829
U/S Liver size	262	11.50	17.60	14.7225	1.08867

Table-II. Descriptive studies

Category	Factors	NAFLD		Total	P value
		Yes	No		
Total patients		107	155	262	
Age	<45yrs	14	24	38	0.214
	45-55yrs	58	67	125	
	>55yrs	35	64	99	
Marital Status	Married	103	150	253	0.540
	Unmarried	4	5	9	
Sulphonylureas	Yes	94	115	209	0.005
	No	13	40	53	
Biguanides	Yes	102	139	241	0.075
	No	5	16	21	
Insulin therapy	Yes	11	39	50	0.002
	No	96	116	212	
Drug groups	OAD	96	116	212	0.002
	Insulin	11	39	50	
Lifestyle	Sedentary	84	119	203	0.431
	Nonsedentary	23	36	59	
H/O hypertension	Yes	63	89	152	0.458
	No	44	66	110	
H/O hyperlipidemia	Yes	9	9	18	0.282
	No	98	146	244	
H/O cardiac problems	Yes	11	32	43	0.018
	No	96	123	219	
H/O liver diseases	Yes	7	14	21	0.313
	No	100	141	241	
H/O jaundice	Yes	7	11	18	0.535
	No	100	144	244	
Abdominal Symptoms	Yes	7	13	20	0.387
	No	100	142	242	
Gender	Male	34	65	99	0.062
	Female	73	90	163	
High ALT Male 30 Female 19	Normal	14	47	61	0.002
	High ALT Gender wise	68	82	150	
High ALT/ SGPT	Normal	67	116	183	0.067
	High	15	13	28	
High AST	Normal	63	108	171	0.079
	High	18	17	35	
High Triglyceride >150	Normal	32	63	95	0.096
	High	50	65	115	
High LDL > 100	Normal	60	89	149	0.407
	High	22	37	59	
Low HDL	No	23	43	66	0.270
	Yes	57	84	141	
Dyslipidemia	No	11	20	31	0.412
	Yes	74	113	187	
	No	35	43	78	
	inconclusive	2	11	13	
BMI Groups Asian Criteria	Underweight (<18)	0	3	3	0.004
	Normal (18 - 22.99)	7	24	31	
	Overweight (23 - 24.99	16	27	43	
	Obese 1(25-26.99)	12	28	40	
	Obese2(27-29.99)	31	40	71	
	Obese 3(>30)	40	29	69	

Hypertension	No	28	43	71	0.488
	Yes	76	111	187	
Central obesity	No	6	22	28	0.020
	Yes	97	128	225	
High Triglycerides	No	38	61	99	0.536
	Yes	43	68	111	
Met S	No	6	15	21	0.509
	Yes	91	130	221	
	May Be	7	9	16	
Diabetes Control	Good control	28	39	67	0.488
	Poor control	71	104	175	
Age Groups 4	<41	11	25	36	0.413
	41-50	41	52	93	
	51-60	33	48	81	
	>60	19	29	48	
	Missing	3	1	4	
Duration of Diabetes in groups	<5	18	33	51	0.131
	5-10	52	56	108	
	10-15	37	66	103	
Ethnicity	Sindhi	6	9	15	0.745
	Punjabi	13	17	30	
	Balochi	3	4	7	
	Pashtu	22	28	50	
	Saraiki	2	1	3	
	Migrant	27	54	81	
	Others	34	42	76	

Table-III. Descriptive studies - category vs. NAFLD
OAD; oral anti diabetic drugs

Whereas when the standard ALT values were taken as cutoff it was not statistically significant.[15]

The association of NAFLD remains with sedentary life style, hypertension, obesity[16], metabolic syndrome, poor control of diabetes and dyslipidemia, as have been reinforced by other studies on this topic.[12,13,17]

The diagnosis of NAFLD should be considered in all diabetic patients who present with other risk factors. Though, not all patients with risk factors will have NAFLD and not all patients with NAFLD will have standard risk factors.[18] Diabetic patients should have their disease controlled appropriately to reduce their risk for NAFLD. The impact of glycemic control and the type of anti-diabetic therapy on liver histology in patients with diabetes and NASH could not be overemphasized.[19]

CONCLUSION

The prevalence of NAFLD was high in female diabetic patients. It was higher in age group 45-55 years and in obese diabetics. Gender specific lower thresholds for ALT were found more sensitive to pick up NAFLD early in the course of the disease. Insulin therapy was having some kind of protective effect as these patients had lower prevalence of NAFLD.

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PREVIOUS RELATED STUDY

Mohammad Mohsin Rana, Muhammad Saeed Akhtar, Muhammad Badar bashir, Abaid-ur-Rehman. TYPE 2 DIABETICS COMPONENTS OF THE METABOLIC SYNDROME (Original) Prof Med Jour 13(3) 453-459 Jul, Aug, Sep, 2006.

Mohammad Mohsin Rana, Muhammad Saeed Akhtar, Badar Bashir, Abaid-ur-Rehman. TYPE 2 DIABETICS; THE RELATIONSHIP BETWEEN THE SERUM CHOLESTEROL AND TRIGLYCEROIDS (Original) Prof Med Jour 14(2) 337-343 Apr, May, Jun, 2007.

“Opportunities multiply as they are seized.”

Sun Tzu

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Shabnam Naveed	Conceptualized of study design, contributed in manuscript writing and proof reading	
2	Prof. Syed Masroor Ahmed	Organized and supervised the study, proof reading	
3	Ayesha Nageen	Reviewed the literature and contributed in discussion	
4	Dr. Zeeshan Ali	Contributed in data interpretation, Data analysis, critically reviewed the manusctipt	
5	Dr. Santosh Kumar	Contributed in analysis of data	
6	Humaira Zakir	Contributed in acquisition, analysis and interpretation of data	
7	Lubna Ghazi	Reviewed literature, Contributed in acquisition, analysis and intretation of data	