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Prevalence and Risk Factors of Nonalcoholic Fatty Liver Disease in Type 2 Diabetes Mellitus in a Tertiary Care Centre In Western India

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Abstract:
AIMS : *To determine the prevalence and risk factors of Nonalcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus and to determine its association with metabolic syndrome.*
PATIENTS AND METHODS : *All the patients attending the diabetic clinic at tertiary care hospital were evaluated for the eligibility to be enrolled into the study. Descriptive data like name, age, sex, religion, occupation, personal history like diet, addiction were obtained by interviewing the patients. They underwent thorough physical examination which included weight, height, waist circumference and hip circumference. BMI and waist/hip ratio was also calculated. All patients were subjected to various investigations at the time of inclusion into the study. NAFLD was diagnosed on utrasonography.*
RESULTS : *Out of 120 type 2 diabetes patients, the prevalence of nonalcoholic fatty liver disease was 64.2% with higher prevalence in females with M:F ratio: 1:1.85 which was statistically not significant. Mean age of NAFLD was 57.64±10.47. Mean BMI was 27.28 ± 3.71 in NAFLD and 24.15±4.03 in non- NAFLD. Age, duration of diabetes, hypertension had no significant association with NAFLD. Mixed diet, Muslim religion, Increased BMI, Abdominal obesity, dyslipidemia had significant association with NAFLD. Majority were asymptomatic. (59/77 patients) had metabolic syndrome.*
CONCLUSION : *Considering the increased risk of morbidity and mortality, NAFLD should be actively sought out in patients with diabetes having above mentioned risk factors.*

I. Introduction

The term NAFLD is used to describe a wide array of fatty liver changes from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC), in the absence of excessive alcohol intake.[1] Both hepatocellular carcinoma and intrahepatic cholangiocarcinoma have been reported to occur in NAFLD without cirrhosis suggesting that NAFLD per se maybe a pre-malignant condition.[2]

The highly accelerated incidence of type 2 diabetes has been fuelled by a tremendous increase in obesity worldwide, resulting from excess calorie intake and lack of physical exercise. Such a highly anabolic state of the body results in an accumulation of fat in both normal adipose tissue and abnormal locations as the liver, visceral fat deposits and muscle, also named 'ectopic fat accumulation'. To separate this form of ectopic lipid accumulation from alcohol induced lipid accumulation, the term Nonalcoholic fatty liver disease (NAFLD) is used. [3] Metabolic syndrome and associated co-morbidities like type 2 diabetes (T2DM), obesity and dyslipidemia are predisposing factors of NAFLD; and prevalence of NAFLD has increased parallel to these epidemics.[1]

Diagnosing NAFLD requires demonstration of increased liver fat in the absence of hazardous levels of alcohol consumption and other causes of liver fat accumulation should also be excluded. Thus, establishing the diagnosis of NAFLD does not require invasive testing, it can be accomplished by history and physical examination, liver imaging(ultrasound is an acceptable 1st line test) and blood tests to exclude other liver diseases. Because there is no one specific blood test for NAFLD, confidence in diagnosis is increased by identification of NAFLD risk factors. The latter includes Body mass index, insulin resistance/ type 2 diabetes mellitus and other parameters indicative of the metabolic syndrome.[2]

The overall prevalence of NAFLD in western countries varies from 15-40% and in Asian countries from 9-40%. In India too, NAFLD is emerging as an important cause of liver disease.[1] The prevalence of NAFLD in T2DM patients in India is reported to be in range of 12.5-87.5%.[4-6]

We conducted our study in a tertiary care centre in western India having a mixed type of population to estimate and characterize the prevalence and risk factors for NAFLD in T2DM patients, on the basis of non-invasive tests.

II. Patients And Methods

All the patients with type 2 Diabetes Mellitus attending diabetic clinic from Dec 2013 to Nov 2015 were included in the study except patients with history of alcohol consumption., hepatitis B and C, acute or chronic liver disease of any etiology,Patients on steroids, synthetic oestrogens, heparin, calcium channel blockers, amiodarone, valproic acid ,antiviral agents and anti tuberculous agents were also excluded from study.

Collection of data:

- Descriptive data like name, age, sex, religion, occupation, personal history like diet, addiction were obtained by interviewing the patients. Weight, height, waist circumference, hip circumference was taken.BMI and waist/hip ratio were calculated. A detailed history was elicited from all patients with emphasis on duration of diabetes, hypertension. Fasting and post prandial blood sugar, lipid profile(total cholesterol, triglycerides, HDL), HBsAg, antiHCV and liver function test (Sr bilirubin, SGOT, SGPT, Alkaline phosphate) was performed in all patients at the time of inclusion into the study.

In order to reduce possible bias, we have defined the variables as follows.

Overweight was defined as body mass index (BMI) between 25-29.9 and obesity above 30 kg/m2 .Patients were considered centrally obese if the waist circumference was greater than 80 cm in females and 90 cm in males.[8]Patients with one of the criteria: Total cholesterol >200 mg/dl, Triglycerides>150 mg/dl or HDL < 40 mg/dl in males and <50 mg/dl in females were considered to have dyslipidemia.[8]

All the subjects underwent abdominal ultrasonography by the radiologist for evidence of fatty liver and its grading was done as per the standard criteria. The standard criteria accepted by the American gastroenterology association is an increase in hepatic echogenicity as a reference, the presence of enhancement and lack of differentiation in the periportal intensity and the vascular wall due to great hyperechogenicity in the parenchyma.[9]

Grade 1: Slight diffuse increase in the fine echoes. Liver appears bright as compared to the cortex of the kidney. Normal visualisation of diaphragm and intrahepatic vessel borders.

Grade 2: Moderate diffuse increase in the fine echoes. Slightly impaired visualisation of the intrahepatic vessels and diaphragm.

Grade 3: Marked increase in the fine echoes. Poor or no visualisation of intrahepatic vessel borders, diaphragm and the vessels.[25]

Statistical analysis:

SPSS 20.0 was used to code data & analyze the data. The level of significance was set at $p< 0.05$.

III. Results

The present study was conducted in a diabetic clinic of a tertiary care center from December 2013 to November 2015. 120 Diabetics were eligible for the study. Of 120 patients enrolled, 43 patients (35.8%) had normal liver on ultrasonography and 77 patients (64.2%) had NAFLD. Thus, the prevalence of NAFLD in the present study was 64.2%.Grade 1 NAFLD was seen in 40 patients (33.4%), Grade 2 NAFLD in 28 (23.3%) and Grade 3 NAFLD was seen in 9 patients (7.5%), as shown in graph no 1.

Of 120 patients, maximum no. of patients were in 51-60 years of age group (33.3%). Mean age of the patients having NAFLD was 57.64±10.47 and the mean age of non-NAFLD was 57.16 ±11.82 which was statistically not significant. Majority (n=77, 64.2%) of the study population observed were females. The prevalence of NAFLD was more in females (50/77) which was statistically not significant (table -1). Majority of the study population belonged to muslim community (n=65, 54.2%) which showed higher prevalence of NAFLD (47/77) and was highly statistically significant(table -2). 97 patients (80.8%) enrolled in the study were on mixed diet (graph -2). it has been observed (69/77) patients of NAFLD gave history of consumption of non-vegeterian food including chicken and beef more than three times per week which was also statistically significant (table-3).

According to the present study there was a very highly significant association of BMI with NAFLD. Mean BMI in NAFLD was 27.28 ± 3.71 and in non–NAFLD was 24.15±4.03. Thus, Increased BMI contributes to the development of NAFLD (graph-3). The present study also showed highly significant association between NAFLD and waist circumference. Mean waist circumference was 96.84± 8.54 in NAFLD group and 90.16± 13.50 in non- NAFLD group. Waist to hip ratio data had significant association with NAFLD too. Mean ratio found in NAFLD group was 1.04±0.08 and in non-NAFLD group was 0.99±0.07 (graph-4).Thus concluding central obesity as a risk factor of NAFLD.

Mean duration of diabetes in NAFLD was 10.58±5.41 and non NAFLD was 9.37±6.74 had no significant association. Mean FBS value was found to be higher in NAFLD i. e 150.70±51.15 as compared to non NAFLD i.e 131.79±45.05. The difference was truly significant (table-4). Out of 77 patients of NAFLD,

32(41.6%) were asymptomatic, 26(33.8%) had abdominal pain, 19(24.7%) had fatigue ,the data was highly significant.

Mean cholesterol in NAFLD was 160.29±87.85 which was statistically not significant. Only 22 patients (18.3%) in the study had serum triglyceride level more than 150 mg/dl. But, mean triglyceride in NAFLD was 127.31±34.16 and in non-NAFLD was 111.05±30.69. The difference was found statistically significant. Mean HDL in NAFLD group was observed to be 43.14± 8.14 and in non NAFLD group was 53.05± 6.85. The difference was very highly significant. Thus concluding dyslipidemia as a risk factor of NAFLD (table-4).

Mean SGOT in NAFLD group was 39.06±34.22 and in non NAFLD group was 24.88±12.85. Mean SGPT in NAFLD group was 38.48 ±14.05 and in non NAFLD group was 27.09±12.54. Mean alkaline phosphate levels in NAFLD group was 153.83±72.03 which was higher than non NAFLD group 90.86±49.9. In our study, patients had liver enzymes within normal range but the mean values were higher making it statistically significant. But, the mean SGOT/SGPT ratio was 0.99±0.49 in NAFLD and 1.00±0.49 in non NAFLD group which was not significant (table-4)

There was a highly significant association between NAFLD and metabolic syndrome. Out of 77 patients of NAFLD, metabolic syndrome was seen in 59(76.6%) patients. Thus, the prevalence of metabolic syndrome was 76.6% in NAFLD (table-5)

IV. Discussion

The prevalence of Nonalcoholic fatty liver disease in type 2 Diabetes Mellitus was found to be 64.2**%** in our study**.** Similary in 2014, Ashutosh et al[10] observed the prevalence of 56.6% of NAFLD in type 2 diabetes mellitus. In our study, Grade 1 NAFLD was seen in 40 patients (33.4%), Grade 2 NAFLD in 28 patients (23.3%) and Grade 3 NAFLD in 9 patients (7.5%). Similarly, patients with NAFLD were further subcategorized, according to USG grading of NAFLD, into 3 grades - grade 1 to grade 3 by AK Agrawal et al[11]. It was observed, out of 77 cases of NAFLD, 50 (64.9%) were females. Thus the prevalence was higher in females.(M:F ratio: 1:1.85) which was not significant. Similar study conducted by S merat et al[12] showed the prevalence of NAFLD was higher among women(60.1%) than men (44.8%) (22/49) which was not statistically significant (p=0.069). Mean age of the patients having NAFLD was 57.64±10.47 statistically not significant. According M Prashanth et al[8] too mean age of the patients and the duration of diabetes were not significantly different. In the present study it has been observed 69 (89.6%) patients of NAFLD had mixed diet . Nicole et al[13] focused on reporting on the effect of macro and micronutrients on development and progression of NAFLD. They stated saturated fat and fructose seem to stimulate hepatic lipid accumulation and progression into NASH. Majority of the patients of the NAFLD belonged to muslim community in our study. The most plausible explanation for increased prevalence of NAFLD in muslim population in this part of world may be the habitual consumption of high quantity of animal fat along with animal protein. There was a very highly significant association of BMI with NAFLD in our study. 30 to 100% of patients diagnosed with NAFLD have been shown to be obese by Angulo P et al[14,] The present study showed highly significant association between NAFLD and waist circumference and waist hip ratio. Waist hip ratio reflects abdominal fat distribution and it has been shown by Kral JG et al[15]that there is a significant correlation between waist/hip ratio and degree of hepatic steatosis even in patients with normal BMI. In our study majority NAFLD were asymptomatic with similar findings observed by Rakesh Gaharwar et al[9] .In our study, there was no association between duration of diabetes mellitus and hypertension with NAFLD.

NAFLD in our study was associated with dyslipidemia (Increased triglycerides and decreased HDL). Studies done by Angulo P et al[14] have also shown that 20-92% of patients diagnosed with NAFLD have hyperlipidemia including hypertriglyceridemia, hypercholesterolemia or both. In our study, patients had liver enzymes almost within normal range but the mean values were higher making it statistically significant.. According to **NCEP ATP III CRITERIA,** out of 77 patients of NAFLD metabolic syndrome was seen in 59 patients (76.6%) of our study and 46.5% patients had metabolic syndrome in non-NAFLD group which was very highly significant. AK Agrawal et al[11] also studied diabetic patients and found prevalence of the metabolic syndrome was significantly higher in the NAFLD subgroup, as compared to those who did not have NAFLD (61.9% vs. 13.2%).

The study had a few limitations -

1. There was restriction in the sample size in our study as
- There were more follow up patients than new patients attending the diabetic clinic.
- Most patients were excluded according to the exclusion criteria (alcoholics, viral hepatitis and on certain drugs mentioned)
- Being a government set up all the investigations which were needed (viral markers, lipid profile) were not available always. Hence, limiting the sample size.

2. Subjects did not have a liver biopsy and histological examination. Performance of this invasive procedure was not feasible as we conducted the study mostly in the patients attending the diabetic clinic. We used ultrasound to detect fatty liver in our study. USG has a sensitivity of 89% and specificity of 93% in detecting steatosis and a sensitivity and specificity of 77% and 89% respectively in detecting increased fibrosis.

V. Conclusion

The prevalence of NAFLD was very high amongst Type 2 Diabetes Mellitus patients and it was associated with metabolic syndrome, dyslipidemia, increased BMI and central obesity.

Weight loss by planned exercise, life style modification and dietary interventions along with oral hypoglycemic agents can lead to significant weight loss , reduction in liver enzyme levels and metabolic improvement hence reducing the occurance of NAFLD.[16]

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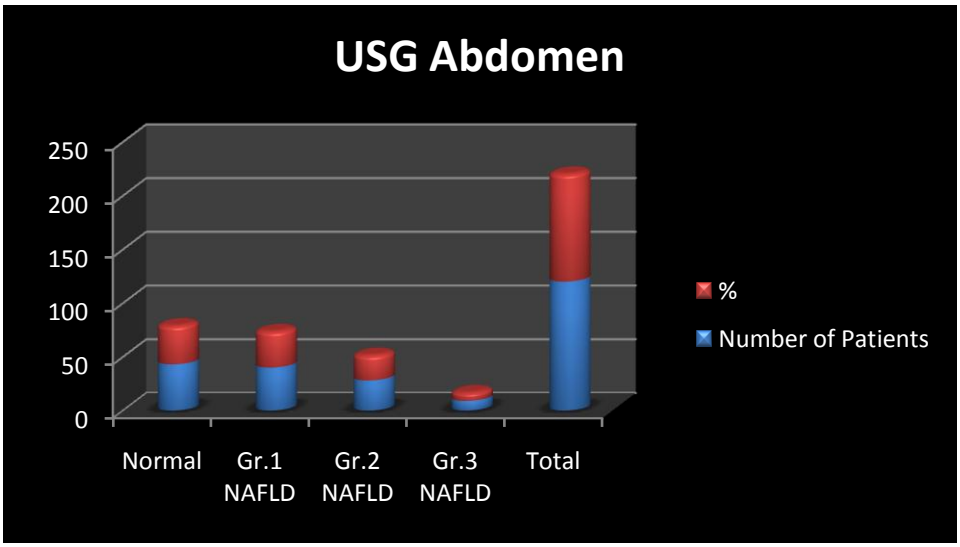


Graph no 1 USG Abdomen findings in study population

Association of Sex with NAFLD

Group	Sex		Total
	Male	Female	
NAFLD	27 (35.1%)	50 (64.9%)	77 (100.0)
Non- NAFLD	16 (37.2%)	27 (62.8%)	43 (100.0)
Total	**43 (**35.8%**)**	**77 (**64.2%**)**	**120 (100.0)**

Pearson χ^2 = 0. .05, df = 1, **p = 0.81 (NS)**

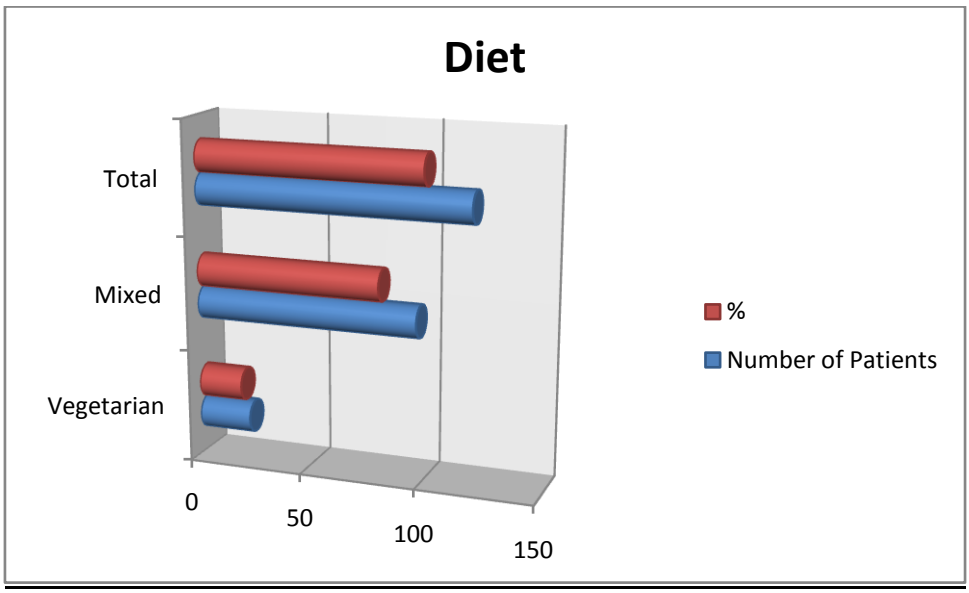
Table 1

Distribution of NAFLD IN specific communities

Group	Religion		Total
	Hindu	Muslim	
NAFLD	30 (39.0%)	47 (61.0%)	77 (100.0)
Non-NAFLD	25 (58.1%)	18 (41.9%)	43 (100.0)
Total	**55 (**45.8%**)**	**65 (**54.2%**)**	**120 (100.0)**

Pearson χ^2 = 4.08, df = 1, **p = 0.04 (Sig)**

Table 2



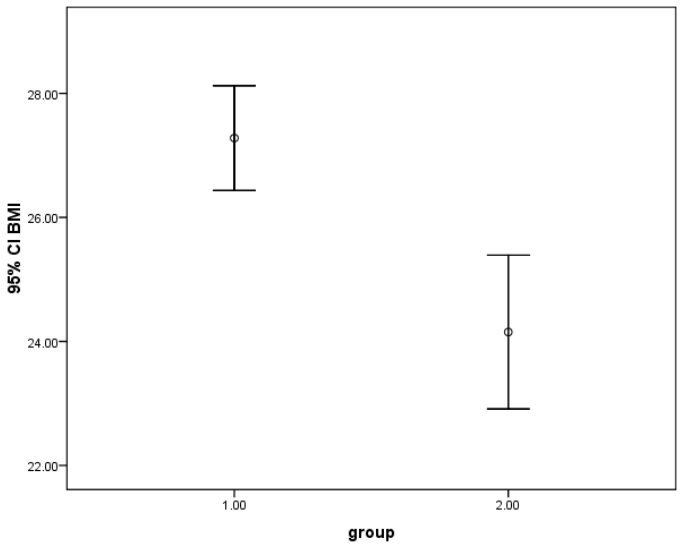
Graph no 2- Dietary pattern in study population

Association of Diet with NAFLD

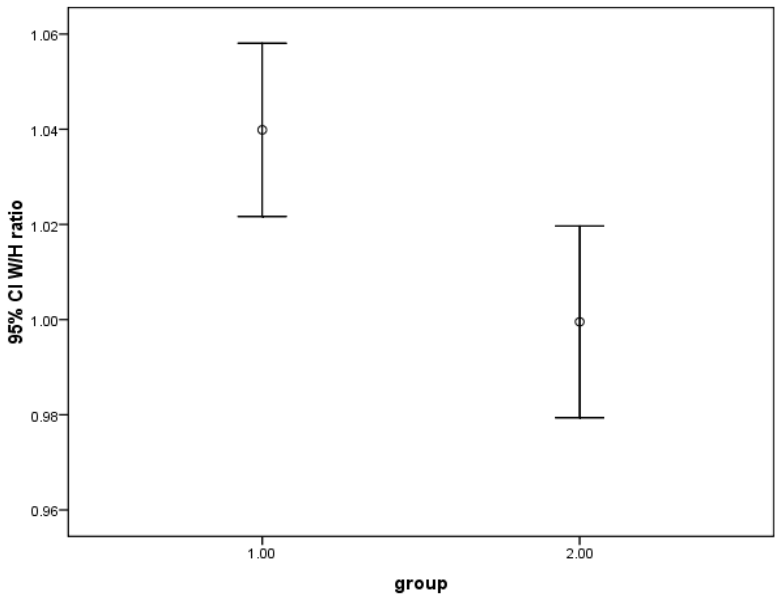
Group	Diet		Total
	Mixed	Veg	
NAFLD	69 (89.6%)	8 (10.4%)	77 (100.0)
Non-NAFLD	28 (65.1%)	15 (34.9%)	43 (100.0)
Total	**97 (**80.8%**)**	**23 (**19.2%**)**	**120 (100.0)**

Pearson χ^2 = 10.69, df = 1, **p = 0.001 (HS)**

Table 3



Graph no 3 Error bar showing Mean and SD : BMI in NAFLD and NON NAFLD groups.



Graph no 4 Error bar showing Mean and SD; Waist Hip ratio Distribution among NAFLD and NON NAFLD groups.

Comparison of variables between two groups

Variable	NAFLD (mean±SD)	Non-NAFLD (mean±SD)	p value
Age	57.64±10.47	57.16±11.82	0.81
Weight	71.51±10.39	62.98±9.76	0.000
BMI	27.28±3.71	24.15±4.03	0.000
Waist Circumference	96.84±8.54	90.16±13.50	0.001
Waist/Hip ratio	1.04±0.08	0.99±0.07	0.006
Duration of diabetes	10.58±5.41	9.37±6.74	0.284
FBS	150.70±51.15	131.79±45.05	0.045
PPBS	224±70.52	202.40±60.14	0.088
Serum Cholesterol	160.29±87.85	138.21±71.30	0.162
Serum Triglyceride	127.31±34.16	111.05±30.69	0.011
Serum HDL	43.14±8.14	53.05±6.85	0.000
SGOT	39±34.22	24.88±12.85	0.10
SGPT	38.48±14.05	27.09±12.54	0.000
SGOT/SGPT	0.99±0.49	1.00±0.49	0.860
Alkaline Phosphate	153.83±72.03	90.86±49.91	0.000

Table 4
Prevalence of metabolic syndrome in NAFLD

Group	**Metabolic syndrome**		**Total**
	Yes	**No**	
NAFLD	59 (76.6**%**)	18 (23.4%)	77 (100.0)
Non NAFLD	20 (46.5%)	23 (53.5%)	43 (100.0)
Total	**79 (**65.8%**)**	**41 (**34.2 %**)**	**120 (100.0)**

Pearson χ^2 = 11.12, df = 1**, p = 0.001 (HS)**

Table 5