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Research Article

Clinical study of non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus

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ABSTRACT

Introduction: Hepatic steatosis may range from a 'benign' indolent deposition of fat to severe lipotoxicity-induced steatohepatitis with necrosis inflammation known as nonalcoholic steatohepatitis (NASH)].NASH is an overlooked complication of Type 2 diabetes mellitus (T2DM) that if missed may carry serious long-term consequences. Aim: To study the prevalence of Nonalcoholic fatty liver disease and Nonalcoholic steatohepatitis in patients with Type 2 Diabetes Mellitus. Materials and methods: This is prospective observational study was conducted on a total of 90 patients, aged above 40yrs with type 2 diabetes mellitus. Patients were subjected to physical examination and laboratory investigations. Fatty liver by Ultrasonography & various other relevant factors were measured in all study subjects. Based on USG, patients were divided into two groups one is NAFLD group-altered echo texture of the liver parenchyma and normal liver group. Results: The prevalence of NAFLD is high (68.9%) amongst T2DM patients affecting 59.7% males and 40.3% females. Age of the patient and duration of diabetes did not have a significant difference on the incidence of NAFLD. 78% of the patients in NAFLD group had a BMI > 25 kg/m² which showed that overweight in combination with T2DM increases the prevalence of NAFLD. HbA1C, FBS and PLBS levels in the NAFLD group were significantly higher than the non NAFLD group which showed hyperglycemia increases the risk of developing NAFLD. Insulin resistance was higher among the NAFLD group (P value -0.04, P value -0.02) which indicates that it plays a crucial role in the pathogenesis of NAFLD. 96% of the patients in the NAFLD group had dyslipidemia with 41.9% of patients having hypertriglyceridemia. Serum transaminases were elevated in 58.3% of the NAFLD group with AST: ALT>1 among the 20 patients who underwent liver biopsy fatty liver was seen in 75%, NASH in 15% and fibrosis in 10%. Conclusion: The prevalence of NAFLD is high amongst T2DM patients and, considering this risk, NAFLD should be actively sought out and treated in patients with diabetes.

Key words: Non-alcoholic fatty liver disease, Type 2 diabetes

Introduction

Nonalcoholic fatty liver disease (NAFLD), which develops in the absence of alcohol abuse, has been recognized as a major health burden. The clinical implications of NAFLD are derived mostly from its common occurrence in the general population and its potential to progress to cirrhosis and liver failure [1].

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Dr. Ramanna Macherla Assistant Professor, Department of Gastroenterology, Gandhi medical college and Gandhi general hospital, Secunderabad, India Estimates suggest that about 20% to 30% of adults in developed countries have excess fat accumulation in the liver [2] 50% among people with diabetes, and about 80% in the obese and morbidly obese [3]. The high prevalence of NAFLD to the contemporary epidemics of obesity and associated metabolic complications.

Obesity, type 2 diabetes, and hyperlipidemia are recognized as risk factors for NAFLD[4].Insulin resistance is frequently detected in patients with NAFLD, as it is in those without obesity and diabetes[5].An increasing number of patients have been described with normal body mass index (BMI), although these individuals may have central adiposity and occult insulin resistance[6]. Moreover, epidemiological studies[7] indicate that this unique group of normal weight patients is characterized by an unhealthy dietary composition, as will be discussed later.

The efficacy and safety profile of pharmacotherapy in the treatment of NAFLD remains uncertain[8], and obesity is strongly associated with hepatic steatosis[9] therefore, the first line of treatment is lifestyle modification. The usual management of NAFLD includes gradual weight reduction and increased physical activity, leading to an improvement in serum liver enzymes, reduced hepatic fatty infiltration, and, in some cases, a reduced degree of hepatic inflammation and fibrosis[10]. However, most studies did not include repeated liver biopsy, and thus histological improvement could not be determined. Although research is emerging, it remains uncertain whether diets that are enriched with certain types of food or nutrients are more likely to cause fatty liver than other types of diet[11]. In light of the difficulty in reducing weight and maintaining the weight reduction in the long term[12], changing dietary composition without necessarily reducing calorific intake may offer a more realistic and feasible alternative to treat NAFLD patients. Therefore, exploring the association between specific nutrients and dietary composition and NAFLD is extremely important.

Disturbances in the delicate metabolic equilibrium of the liver can result in a wide range of whole body disease and vice versa. The occurrence of the metabolic disease type 2 diabetes mellitus has experienced an extremely rapid increase, affecting currently over 190 million people worldwide. The number of patients is expected to rise to 300 million in 2025)[13]. Ectopic fat accumulation in the liver can have several negative effects on the normal metabolic functions of the liver. To separate this form of ectopic lipid accumulation in the liver from alcohol induced liver lipid accumulation, the term nonalcoholic fatty liver disease (NAFLD) is used. Together with an inflammatory reaction, the fat accumulated in the liver can progress to a condition known as nonalcoholic steatohepatitis (NASH), a highly under diagnosed condition in patients with type 2 diabetes. Since NASH can progress to (irreversible) liver fibrosis, it has been predicted that nonalcoholic fatty liver disease will be the major cause of liver transplantation in 2020[14].

Taking into account the above, investigation and monitoring of the liver metabolic function and early detection of liver lipid accumulation is of great importance. Unfortunately, the liver is not easily accessible and liver biopsy is currently considered the gold-standard to assess possible liver inflammation and degree of ectopic fat accumulation. However, liver biopsy has several drawbacks.

Diabetes, Dyslipidemia, Hypertension, and Cardiovascular disease (CVD) occur more frequently in individuals with

NAFLD. NAFLD may also be associated with a greater risk of renal disease in patients with T2DM. Health care costs have been long suspected to be higher in NASH patients.Fatty liver or hepatic steatosis is characterized by diffuse accumulation of fat in hepatocytes. Fatty liver occurring in individuals without a history of significant alcohol intake is termed as non-alcoholic fatty liver disease (NAFLD). The natural history of NAFLD ranges from pure steatosis to steatohepatitis to cirrhosis and in some patients hepatocellular carcinoma. NAFLD is strongly to associated with obesity, Type-2 diabetes mellitus and hyperlipidemia. Numerous studies show that it is hepatic component of metabolic syndrome whose central features are peripheral insulin resistance, obesity, hvper insulinemia, hypertriglyceridemia and hypertension.

It has been reported that fatty liver influences the severity of hepatic insulin resistance in Type-2 diabetes mellitus. The hepatic fat content predicts the amount of daily insulin needed to maintain adequate glycemic control. NAFLD is a type of chronic liver disorder which is gaining significant importance worldwide. It is now recognized as the most common liver disorder in the United States with an estimated prevalence of 30% in the general population. The present study was subjected to study the prevalence and risk factors non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus.

Materials and methods

The study it is a prospective observational study conducted from October 2011- October 2013. The subjects for the study were selected from patients with Type 2 diabetes mellitus diagnosed by standard criteria above the age of 40 years who attended department of gastroenterology at Gandhi medical college and Gandhi general hospital, India

Inclusion criteria

Patients of age above 40 years of either sex with Type 2 diabetes mellitus on oral hypoglycemic drugs, Patients willing to give written informed consent were included.

Exclusion criteria

Patients with any quantity of alcohol consumption based on careful history, Usage of drugs known to cause steatosis is including Amiodarone, Corticosteroids, Tamoxifen, Methotrexate and high dose Estrogen, Significant co-morbidities precluding a liver biopsy (eg. Bleeding Diathesis), Positive serological markers of viral or auto immune hepatitis, History of jejunoileal bypass or extensive small bowel resection, Findings in favour of metabolic liver diseases , including Wilson's disease , hemochromatosis and positive alpha-1 antitrypsin, Patients with Type 2 diabetes mellitus on insulin therapy.

Patients satisfying the inclusive criteria will be enrolled in this study, after providing written informed consent, a thorough medical history and physical examination will be performed for each individual.

Preliminary data based on age/name/sex address was entered. Evaluation of each patient included a proper history, detailed general and systemic examination and evaluation through necessary investigations. The history included symptoms suggestive of NAFLD – fatigue, malaise, fullness of abdomen, right upper quadrant pain. No forthcoming history or assymptomatics were noted.

In addition to above symptoms details to try and find out possible risk factors was undertaken .the history of associated illnesses and drug intake was noted, with emphasis on drugs associated with NAFLD. A relevant history of duration of diabetes and the drugs was also noted. A family history of cryptogenic cirrhosis was enquired about in other members of the family.

In general examination, in addition to the vital parameters, icterus/clubbing/pallor was looked for.

Physical examination which included measurements of weight and height were recorded. BMI was calculated as a measure of obesity, whereas waist/hip ratio was measured as an index of splanchnic fat accumulation.

Systemic examination of respiratory, cardiovascular, gastrointestinal and central nervous system was carried out. Detailed per abdominal examination for palpability of liver, spleen, their size and consistency was made. Confirmation for absence of tenderness of liver and absence of free fluid was carried out.

The patients were then subjected to necessary investigations. Investigations included Complete blood

count, Renal function test, Blood sugar level (fasting and post prandial), Lipid profile (serum triglycerides, total cholesterol, S.HDL, S.LDL)

Liver function tests {SGOT (AST) & SGPT(ALT) SGOT/SGPT Ratio, S.bilirubin Total/Direct/Indirect S.alkaline phosphatases, S.proteins – Total/Albumin/Globulin, Serum GGT}, HBsAg/Anti HCV/HIV, ANA – To rule out autoimmune hepatitis, Slit lamp examination to exclude K.F ring (Wilson's Disease) HbA1C, BT/CT/PT/APTT to rule out bleeding tendencies and USG – Abdomen were done.

Out of the entire study population 20 cases with elevated serum aminases and USG findings of NAFLD who were willing were subjected to liver biopsy with informed consent. Biopsy specimens were collected in boulin's fluid or formalin. Biopsies were then processed for histopathological examination.

The Grading and Staging of all biopsies were determined based on method proposed by Brunt et al as grade I- mild, grade II- moderate and grade III- severe.

Statistical analysis

Sample size was estimated using nMaster software to access the single proportion (proportion of NAFLD and NASH among Type 2 Diabetes mellitus) where

Expected proportion - 0.44(44%) Relative proportion - 20 % Confident interval - 95% (alpha=5%)

Results

A Correlation clinical observational hospital based clinical study with 90 patients is undertaken to study the predictors of Non-alcoholic fatty Liver disease and Non-alcoholic steatohepatitis in patients with Type 2 Diabetes Mellitus.

Variable	Number of Patients	Percentage
Age In Years		
41-50	35	38.9
51-60	24	26.5
61-70	15	16.5
71-80	13	14.4
>80	3	3.3
Total	90	100
Gender		
Male	54	60
Female	36	40

Table 1: Demographic distribution of subjects

In the present study it was observed that 38.9% of cases were in the age group of 41-50 yrs with mean age group was 55.96+11.65 yrs where as 54(60%) subjects were males and 36(40%) subjects were females. (table1)

Variable	No. of Patients	Percentage	Mean \pm SD
BMI			24.90±3.52
<18.5	4	4.4	
18.6-24.9	37	40.7	
25-29.9	47	51.8	
>30	2	2.2	
Waist Circumference			96.36±6.08
<90.0	3	4.4	
90-100.0	34	37.7	
>100	53	58.9	
Duration of Diabetes			11.05 ± 5.43
<5 YRS	7	7.8	
5-10	40	44.5	
10-20	41	45.5	
>20	2	2.2	
Total	90	100	

Table 2: BMI, waist circumference and diabetes duration distribution in subjects

In the present study it was observed that the mean BMI was $24.90\pm3.52 \text{ kg/m}^2$ with 51.8 % patients being in range of 25-29.9 kg/m², mean waist circumference was 96.6cm in that 58.9% patients were with >100 cm waist circumference while mean duration of diabetes was 11.05+53 yrs with 45.5% patients were in 10-20 yrs duration.(table 2) **Table 3: Results of USG abdomen**

USG Abdomen	No.of Patients	Percentage
Normal liver	28	31.1
NAFLD	62	68.9
TOTAL	90	100

In the present study, Out of 90 patients 62 patients (68.9%) were diagnosed as NAFLD and 28 patients (31.1%) were diagnosed as normal liver. (Table 3)

Table 4: BMI, waist circumference and hip circumference in NAFLD and	l normal liver patients
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Variable	USG Abdomen		P value
	Non alcoholic fatty liver disease (n=62)	Normal liver (n=28)	
BMI (kg/m^2)			0.187
<18.5	3(4.8%)	1(3.6%)	
18.5-24.9	21(33.9%)	16(57.1%)	
25.0-29.9	36(58.1%)	11(39.3%)	
30 & above	2(3.2%)	0	
Waist Circumference(cm)			0.645
Male <90 & Female <80	3(4.8%)	2(7.1%)	
Male >90 & Female>80	59(95.2%)	26(92.9%)	
Hip Circumference (cm			
Male <100 & Female <105	54(87.1%)	25(89.3%)	1.000
Male >100 & Female>105	8(12.9%)	3(10.7%)	

In the present study 58.1% patients with NAFLD were in 25-29.9 kg/m² BMI rate where as 57.1% patients with normal liver were in 18.5-24.9 kg/m². In most of the patients waist circumference was Male >90 & Female>80cm in both groups and hip circumference was Male <100 & Female <105cm in both groups. (Table 4)

	USG Abdomen		P Value
Variable	Non alcoholic fatty liver disease (n=62)	Normal liver (n=28)	
FBS			
<130	7(11.3%)	4(14.3%)	0.688
>130	55(88.7%)	24(85.7%)	
PPBS(mg/dl)			
<u><</u> 180	37(59.7%)	11(39.3%)	0.073+
<u>>180</u>	25(40.3%)	17(60.7%)	
HbA1c			
<6.5	10(15.6%)	5(17.9%)	0.833
>6.5	52(83.9%)	23(82.1%)	
Total cholesterol			
<200	43(69.4%)	17(60.7%)	0.421
>200	19(30.6%)	11(39.3%)	
Triglycerides (mg/dl)			
<150	36(58.1%)	17(60.7%)	0.813
>150	26(41.9%)	11(39.3%)	
HDL(mg/dl)			0.802
Males <40, Females <50	48(77.4%)	21(75%)	
Males >40, Females >50	14(22.6%)	7(25%)	
LDL (mg/dl)			0.421
<100	43(69.4%)	17(60.7%)	
>100	19(30.6%)	11(39.3%)	

Table 5: Glucose and lipid parameters in NAFLD and normal liver patients

In the present study FBS values were >130 mg/dl in NAFLD, normal liver group were 88.7%, 85.7% respectively. PPBS values in NAFLD group was <180 mg/dl in 59.7% patients whereas in normal liver group >180 in 60% patients. Most of the patients in both groups were observed with total cholesterol <200 mg/dl, triglycerides <36 mg/dl, HDL >50mg/dl and LDL <100 mg/dl values. (Table 5)

Table 6: Fasting insulin, HOMA IR and QICKI distribution in both groups

Variable	USG Abdomen		P Value
	Non alcoholic fatty liver disease (n=62)	Normal liver (n=28)	
Fasting Insulin Level (µU/ml)			0.309
<30	50(80.6%)	25(89.3%)	
>30	12(19.4%)	3(10.7%)	
HOMA IR			0.934
<5.0	15(24.2%)	7(25%)	
>5.0	47(75.8%)	21(75%)	
QUICKI			0.872
<0.3	41(66.1%)	19(67.9%)	
>0.3	21(33.9%)	9(32.1%)	

In the present study 80.6%, 89.3% patients were with $<30\mu$ U/ml fasting insulin level in NAFLD and normal liver group respectively. 75.8%, 75% patients were with >5.0 HOMA IR value and 66.1%, 67.9% patients were with <0.3 QUICKI vale in NAFLD and normal liver group respectively. (Table 6)

	USG Abdomen		P Value
Variable	Non alcoholic fatty liver disease (n=62)	Normal liver (n=28)	
Age in years	55.37±10.95	57.25±13.22	0.482
Gender			
Male	37(59.7%)	17(60.7%)	0.926
Female	25(40.3%)	11(39.3%)	
Height (cm)	5.54±0.19	5.57±0.21	0.538
Weight (kg)	72.32±11.39	69.43±10.25	0.253
$BMI(kg/m^2)$	25.30±3.62	24.03±3.19	0.116
Waist circumference(cm)	97.75±5.93	93.28±5.31	0.001**
HIP (cm)	94.98±7.27	91.23±6.60	0.022*
Waist/HIP ratio	1.03 ± 0.07	1.03 ± 0.08	0.721
Duration of DM (yrs)	10.87±4.99	11.46±6.37	0.634
Total cholesterol (mg/dl)	173.21±46.51	173.52 ± 48.63	0.977
Triglycerides (mg/dl)	157.65±98.68	138.41±91.58	0.384
HDL(mg/dl)	37.73±11.46	42.21±17.55	0.152
LDL(mg/dl)	104.67±42.17	105.90 ± 38.92	0.896
SGOT (Iu/L)	37.95±18.86	28.28±15.73	0.020*
SGPT (Iu/L)	41.50±14.62	33.46±14.05	0.017*
ALP (IU/L)	173.53±70.05	145.67±40.09	0.053+
FBS(mg/dl)	151.10±58.84	164.36±71.94	0.359
PPBS (mg/dl)	206.33±64.24	223.03±65.07	0.259
HbA1c (%)	9.39±2.47	8.72±2.26	0.225
Fasting Insulin (µU/ml)	22.69±7.66	21.21±8.36	0.412
HOMA-IR	8.39±4.27	8.64±4.91	0.815
QUICKI	0.28±0.02	0.29±0.02	0.686

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Table no 8: Liver biopsy and severity distribution

Variable		No. of patients (20)	Percentage %
Pathology			
Fatty liver	15		75
NASH	3		15
Fibrosis	2		10
Severity			
Mild	7		35%
Moderate	11		55%
Severe	2		10%

In present study 20 patients were undergone with liver biopsy in that 15 patients were diagnosed as fatty liver, 3 patients as NASH and 2 patients as fibrosis. 7 patients graded as mild, 11 patients graded as moderate and 2 patients graded as severe.

Discussion

NAFLD is a silent serious disease, which is becoming epidemic, such as its association with metabolic syndrome. Its etiology is still unknown and further investigations are needed to better understand the pathophysiological processes, and to identify molecular targets for more selective therapies.

In our study, there were no significant sex differences for incidence of NAFLD between the two groups (p=0.92) (table 7). This pattern is also seen in a recent study by (Reid AE et al), where both sexes are afflicted equally.

The mean age of patients in both the NAFLD and non-NAFLD groups was 55.37 ± 10.95 and 57.25 ± 13.22 , respectively which was not statistically different

(p=0.482). (Table 7)We also compared the frequency of NAFLD among different age groups which again did not show any significant differences (p=0.21). Similar results were found in studies done by AK Agarwal et al[15] and Hui et al[16]. Previous studies by (Adams LA et al)[17] have shown that NAFLD can occur at any age, but since its prevalence increases with age. The mean duration of DM was significantly lower in patients with NAFLD (10.87±4.99) as compared to patients without NAFLD (11.46±6.37; p=0.634), which indicated that duration did not have a significance on NAFLD. BMI was significantly higher in patients with NAFLD (25.30±3.62) than those without NAFLD (24.03±3.19; p=0.011). (Table 7)

Most patients had abnormally high BMI's and 78% of patients had a BMI >25.0 kg/m2 (Overweight or obese according to NCEP ATPIII Guidelines). In our study particularly noteworthy is the preponderance of Central obesity in our patients with NAFLD. Thus, all but 04 patients (92%) had central obesity.

In our study, the waist/hip ratio was not significantly different between the two groups (p=0.721).

HbA1c was significantly higher with NAFLD group (83.9%) when compared to the non NAFLD group. Ak Agarwal et al[15] and Targher et al[18] also have shown in their studies that the mean HbA1C levels were higher in patients with fatty liver than those without. Many studies have shown that insulin resistance has a critical role in the pathogenesis of NAFLD. We observed similar results with significant differences in insulin resistance parameters (HOMA-IR and QUICKI) between the two groups (p=0.04 and 0.02, respectively).58 of the 62 patients (96%) fulfilled at least one criterion for Dyslipidemia as per ATP III guidelines. All of them (96%) had abnormalities that are characteristic of Insulin Resistance syndrome/ Metabolic Syndrome, High TG and/or low HDL levels. Other studies have reported similar prevalence (20-80%). 20 patients out of 62 who underwent liver biopsy, 15 patients had fatty liver, 3 had NASH and 2 patients had Fibrosis. In our study NAFLD was diagnosed in 68.9% of the study population based on USG findings.

Conclusion

Out of 90 patients that were studied 62 patients were diagnosed with NAFLD based on USG .Of the 62 patients with NAFLD there was a significant impact of BMI, hyperglycemia, hypertriglyceridemia and insulin resistance on the incidence of NAFLD. The prevalence of NAFLD is high amongst T2DM patients and NAFLD should be actively sought out and treated in patients with diabetes.

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