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A CLINICAL STUDY OF NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Dr. V. Gopala Krishna	M.D., D.M., Assistant Professor of Gastroenterology, Osmania Medical College / Osmania General Hospital, Hyderabad, Telangana.
Dr. L. Sahitya*	M.D., D.M., Assistant Professor of Gastroenterology, Osmania Medical College / Osmania General Hospital, Hyderabad, Telangana. *Corresponding Author
Dr .A. Keerthi	M.D., D.M., (Gastroenterology)

ABSTRACT 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. Insulin resistance was higher among the NAFLD, which indicates that it plays a crucial role in the pathogenesis of NAFLD.

KEYWORDS : NAFLD, Type 2 DM

INTRODUCTION

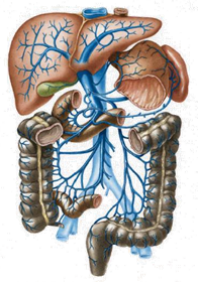
Nonalcoholic fatty liver disease (NAFLD), which develops in the absence of alcohol abuse, has been recognized as a major health burden. The clinical implications of NAFLD are derived mostly from its common occurrence in the general population and its potential to progress to cirrhosis and liver failure[1]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

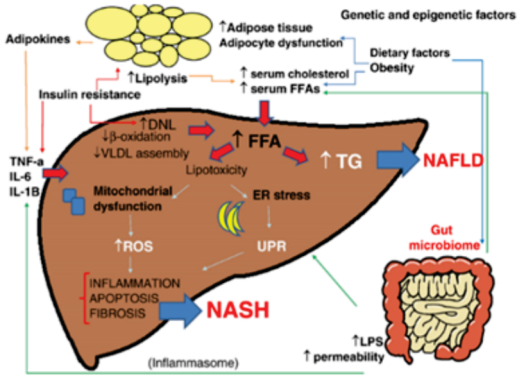
The occurrence of the metabolic disease type 2 diabetes mellitus has experienced an extremely rapid increase, affecting currently over 190 million people worldwide. The number of patients is expected to rise to 300 million in 2025.[7] Type 2 diabetes is a highly invalidating disease, especially when taking into account its severe long term complications: cardiovascular disease, blindness, kidney failure and impotence.

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.[8]

Taking into account the above, investigation and monitoring of the liver metabolic function and early detection of liver lipid accumulation, fibrosis is of great importance.



Liver anatomy and venous blood supply. The main blood supply comes from the portal vein draining nutrients and hormones from the splanchnic area directly into to liver



Multiple hithypothesisforthe development of NAFLD[9]

AIMS & OBJECTIVES

1) Main aim of the study is to know the risk factors of non-alcoholic fatty liver disease in patients with type 2 Diabetes Mellitus.
2) To determine the prevalence of Nonalcoholic fatty liver disease and fibrosis in patients with Type 2 Diabetes Mellitus.

MATERIAL & METHODS

The cases for the study were selected from patients with Type 2 diabetes mellitus diagnosed by standard criteria above the age of 40 years who attended Osmania General Hospital. This study was conducted between April 2018 -Jan 2020.

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, which included measurements of weight and height.BMI was calculated as a measure of obesity, whereas waist/hip ratio was measured as an index of splanchnic fat accumulation. After an over-night fast, serum samples were obtained from all subjects for liver function tests (as part at eamino-transferase [AST], alanine amino transferase [ALT], and alkaline phosphatase), serum lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C]), fasting blood glucose (FBS) serum insulin level and hemoglobin A1c (HbA1c).

Overweight was defined as a body mass index (BMI) between 23 and 25 kg/m2, and obesity as BMI equal or above 25 kg/ m2. Patients were considered centrally obese if the waist circumference was greater than 80 cm in females and 90 cm in males. Patients with one of the criteria: LDL-C >100 mg/dL, total cholesterol >200 mg/ dL, triglycerides >150 mg/dL, or HDL- C < 40 mg/dL in males and <50 mg/dL in females were considered to have dyslipidemia.

Homeostasis Model Assistant–Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity check Index (QUICKI) were calculated as measures of insulin resistance and sensitivity using following formula.

HOMA-IR= [fasting insulin (µU/ml) ◊fasting glucose (mmol/l)]/22.5
QUICKI=1/ [log (fasting insulin (µU/ml)) ± log (glucose (mg/dl))].

All subjects underwent abdominal ultrasonography by the radiologist for evidence of fatty liver disease. Based on ultrasonographic findings (diffuse increase in echogenicity as compared to that of the spleen or renal cortex). Those subjects of fatty liver on ultrasound subjected to fibroscan for assessment of fibrosis.

INCLUSION CRITERIA

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

EXCLUSION CRITERIA

a) Any quantity of alcohol consumption based on careful history
b) Usage of drugs known to cause steatosis is including Amiodarone, Corticosteroids, Tamoxifen, Methotrexate and high dose Estrogen.
c) Positive serological markers of viral or auto immune hepatitis (including HBsAg , HCV, HIV, ANA, anti-smooth muscle antibodies, anti-liver / kidney microsomes type 1 antibodies).
d) History of jejunoileal bypass or extensive small bowel resection
e) Findings in favour of metabolic liver diseases , including Wilson's disease, hemochromatosis and positive alpha-1 antitrypsin.
f) Patients with Type 2 diabetes mellitus on insulin therapy.

Investigations

Complete blood count, Renal function test, Blood sugar level : fasting and post prandial, Lipid profile, Serum triglycerides, Total cholesterol, S.HDL, S.LDL, 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,USG – Abdomen, Out of the entire study population USG findings of NAFLD in 62 cases who were subjected for non invasive assessment of fibrosisfibroscan.

RESULTS

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

Duration of Diabetes

Duration of Diabetes (Yrs)	No. of Patients	Percentage
< 5	7	7.8
5-10	40	44.5
10-20	41	45.5
> 20	2	2.2
Total	**90**	**100.00**
Mean ± SD: 11.05±5.43		

Correlation of Glycemic Parameters / USG abdomen

S.No	Sugar Parameters	USG abdomen		P Value
		Non Alcoholic Fatty liver disease (n=62)	Normal Liver (n=28)	
I	FBS (mg/dl)			0.688
1	<130	7(11.3%)	4(14.3%)	
2	>130	55(88.7%)	24(85.7%)	
II	PPBS (mg/dl)			0.073
3	<180	37(59.7%)	11(39.3%)	
4	>180	25(40.3%)	17(60.7%)	
III	HbA1c			0.833
5	<6.5	10(15.6%)	5(17.9%)	
6	>6.5	52(83.9%)	23(82.1%)	

Correlation of Lipid parameters / USG abdomen

S.No	Lipid Parameters	USG abdomen	P Value	
		Non Alcoholic Fatty liver disease (n=62)	Normal Liver (n=28)	
I	Total Cholesterol			0.421
1	< 200	43 (69.4%)	17 (60.7%)	
2	> 200	19 (30.6%)	11(39.3%)	
II	Triglycerides			0.813
3	<150	36 (58.1%)	17(60.7%)	
4	>150	26 (41.9%)	11(39.3%)	
III	HDL			0.802
5	Males < 40, Females <50	48 (77.4%)	21 (75%)	
6	Males > 40, Females > 50	14 (22.6%)	7(25%)	
IV	LDL (mg/dl)			
7	< 100	43 (69.4%)	17 (60.7%)	0.421
8	> 100	19 (30.6%)	11 (39. 3%)	

Correlation of Fasting Insulin Level (µU/ml) / USG abdomen

S.No	Fasting Insulin Level (µU/ml) / USG abdomen	USG abdomen		P Value
		Non Alcoholic Fatty liver disease (n=62)	Normal Liver (n=28)	
1	< 30	50 (80.6%)	25 (89.3%)	0.309
2	> 30	12 (19.4%)	3 (10.7%)	

Correlation of Fasting Insulin Level (µU/ml) / USG abdomen

S.No	Insulin Index	USG abdomen		P Value
		Non Alcoholic Fatty liver disease (n=62)	Normal Liver (n=28)	
HOMA IR				
1	< 5.0	15 (24.2%)	7 (25%)	0.04
2	>5.0	47 (75.8%)	21 (75%)	
QUICKI				
3	< 0.3	41 (66.6%)	19 (67.9%)	0.02
4	> 0.3	21 (33.9%)	9 (32.1%)	

Results of Fibroscan

LSM – E(kpa)		No. of patients (62)	%
<6.0 kpa	NORMAL	14	22.5
6.0 – 9.0 kpa	PROBABLE FIBROSIS	20	32.2
9-12 kpa	FIBROSIS	28	45.1
>12 kpa	CIRRHOSIS	0	0

DISCUSSION

NAFLD is a silent serious disease, which is becoming epidemic, such as its association with metabolic syndrome. Its Aetiology 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).

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)

We also compared the frequency of NAFLD among different age groups which again did not show any significant differences (p=0.21).Previous studies by (Adams LA et al)[10] have shown that NAFLD can occur at any age, but since its prevalence increases with age, therefore it mostly affects people in their forties to sixties by (Akbar DH et al).

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).

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. Hyperglycemia has been reported in 20-75% of adult patients with NAFLD by (van Hoek B et al), which was consistent with our study wherein hyperglycemia was seen in 70.3% of patients in NAFLD group.

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 atleast 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 prevalences (20–80%).

Foster *et al* studied the accuracy of ultrasound in the detection of fatty liver and concluded that the sensitivity of Ultrasonography for detecting fatty liver was 90%. In a prospective study comparing ultrasound scanning with histological examination results, Saverymuttu *et al* showed that ultrasound examinations can accurately identify a steatosis with a sensitivity of 94% and a specificity of 84%. Another study by Graif *et al* concluded that for uncomplicated hepatic steatosis, the sensitivity of Ultrasonography was found to be 100% and specificity 60%. In our study NAFLD was diagnosed in 68.9% of the study population based on USG findings. 62 patients whose ultrasound imaging showed fatty liver underwent fibroscan normal in 22.5%, probable fibrosis in 32.2%, fibrosis in 45.1%.

CONCLUSION

1. The prevalence of NAFLD is high (68.9%) amongst T2DM patients affecting 59.7% males and 40.3% females.
2. Age of the patient and duration of diabetes did not have a significant difference on the incidence of NAFLD.
3. 78% of the patients in NAFLD group had a BMI > 25 kg/m^2 which showed that overweight in combination with T2DM increases the prevalence of NAFLD.
4. 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.
5. 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.
6. 96% of the patients in the NAFLD group had dyslipidemia with 41.9% of patients having hypertriglyceridemia.
7. Serum transaminases were elevated in 58.3% of the NAFLD group.
8. Among the 62 patients who underwent fibroscan normal in 22.5%, probable fibrosis in 32.2%, fibrosis in 45.1%.

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