

A STUDY OF NONALCOHOLIC FATTY LIVER DISEASE AND FATTY LIVER INDEX IN TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

BACKGROUND

Nonalcoholic Fatty Liver Disease (NAFLD) is closely associated with type 2 Diabetes Mellitus (DM) and its complications. Several noninvasive diagnostic methods for NAFLD have been formulated recently. Fatty Liver Index (FLI) is one such simple method to obtain and it may help clinicians to screen type 2 DM patients for fatty liver.

AIM AND OBJECTIVES

1. To know the frequency of NAFLD by ultrasound examination in type 2 DM patients of Vinayaka Missions Kirupananda Variyar Medical College and Hospital.
2. To evaluate the type 2 DM patients for risk of NAFLD by fatty liver index.

MATERIALS AND METHODS

A cross-sectional study was conducted on 50 nonalcoholic type 2 DM patients analysing their blood sample for lipid profile, fasting blood glucose, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase levels. All the subjects had liver ultrasound examination and their anthropometric measurements noted. The Fatty Liver Index (FLI) was calculated using body mass index, waist circumference, and serum GGT.

STATISTICAL ANALYSIS

All the statistical work was performed by the SPSS software. To estimate the differences between patients with and without NAFLD, the Student's t-test was applied.

RESULTS

Out of the 50 patients, 36% (n=18) had evidence of fatty liver based on the ultrasound examination. The patients with NAFLD had significantly high BMI, cholesterol, triglycerides, GGT, and ALT levels. The variables like fasting glucose, HDL-C, LDL-C, and AST did not significantly vary between the groups. 58% (n=29) of patients had fatty liver based on FLI. The frequency of NAFLD in T2DM patients is higher when using the FLI than the ultrasound examination.

CONCLUSION

The results of the present study clearly demonstrate a high association of fatty liver disease in T2DM patients diagnosed either by ultrasound or by FLI. Initial evaluation of fatty liver in all T2DM patients is essential especially by noninvasive methods like FLI, a simple and validated method.

KEYWORDS

Type 2 Diabetes, NAFLD, Fatty Liver Index, Ultrasound.

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INTRODUCTION: Nonalcoholic Fatty Liver Disease (NAFLD) is now emerging as a predominant health burden because of its raising incidence and associated complications. NAFLD represents a wide range of liver pathology from simple steatosis to Nonalcoholic

Steatohepatitis (NASH) with typical inflammatory involvement of the liver parenchyma and potential connective tissue deposition up to liver cirrhosis complete with all its complications including hepatocellular carcinoma.¹

The term 'NASH' was first introduced by Ludwig et al. in 1980 to describe histological changes indistinguishable from alcoholic hepatitis in patients with no or insignificant (less than 20 g/day) alcohol intake.² Even in the absence of alcohol intake, patients who have one or more components of the metabolic syndrome with insulin resistance develop hepatic steatosis due to increased lipolysis and increased delivery of fatty acids from adipose tissue to liver.¹

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Also, the prevalence rate of NAFLD was indeed more than alcoholic liver disease in China.³

Only recently, liver disease has been recognised as a major complication of type 2 Diabetes Mellitus (DM) with standard mortality rates for cirrhosis greater than that for cardiovascular disease.⁴ A study has revealed that survival of patients with NASH was reduced and that these patients died significantly more often from CHD and liver-related causes.⁵ An association has been reported among NAFLD and retinopathy, neuropathy, nephropathy, and CAD in a study done in Nagpur.⁶ A south Indian study also have established an association of NAFLD as diagnosed by ultrasound with microvascular and macrovascular complications of diabetes.⁷ Hence, a strong need arises to diagnose fatty liver at the earliest since patients with NAFLD have an increased risk of not only liver-related complications, but also a higher risk of micro and macrovascular complications of diabetes.

In India, the prevalence of NAFLD varies from 10% to 30% in the general population and increased in pre-diabetics and diabetics ranging 33-55%.⁸ Urbanisation and change of lifestyle habits and a higher tendency of diabetes inheritance maybe contributory to higher insulin resistance and its sequelae NAFLD. Unfortunately, the diagnosis of fatty liver is overlooked because of the lack of characteristic symptoms.

NAFLD is most commonly diagnosed by a combination of clinical, laboratory, and imaging studies. Even though liver biopsy is considered, the gold standard for diagnosing NAFLD, its use is limited due its expense and invasiveness. Recent studies have proposed several noninvasive panels of biomarkers for the early diagnosis of NAFLD. A fatty liver index is one such validated panel marker that uses routine measurements in clinical practice. FLI is a prediction equation first developed by Bedogni et al, which is accurate and easy to adopt.⁹ It uses simple measurements like body mass index, waist circumference, GGT, and serum triglyceride levels.⁹

Published literature on noninvasive biomarkers of NAFLD from India is sparse. Since, there is paucity of data on NAFLD and type 2 DM in this population, a study was conducted in type 2 DM patients assessing the presence of fatty liver by ultrasound examination and simple biochemical tests.

MATERIAL AND METHODS: The study protocol and all study methods were approved by the Ethics Committee of Vinayaka Missions Kirupananda Variyar Medical College and Hospital (VMKVMC and H). A cross-sectional study was conducted on 50 type 2 DM patients attending the Diabetic OPD of VMKVMC and H over a period of two months (May and June 2015). Written informed consent was obtained from all the patients after explaining the nature of the study.

Selection Criteria:

Inclusion Criteria: All the patients attending diabetic OPD were considered for the study.

Exclusion Criteria: Patients giving a history of alcohol intake, pregnancy, known hepatic diseases, hepatotoxic drug intake, and patients with type 1 diabetes mellitus were excluded. Men who consumed more than 40 g and women who consumed more than 20 g of alcohol per day were excluded from the study.

All the study subjects answered a questionnaire, which contains details of age, gender, alcohol intake, medical history, and duration of diabetes. The study subjects had to provide detailed information on the alcohol intake, height, weight, waist circumference, hip circumference, blood pressure were noted down for all the patients and recorded in a structured protocol format.

Body Mass Index (BMI) was calculated by dividing the body weight (In kilograms) by the square of height (In meters).

After a 12 hour overnight fast, about 5 ml of venous blood sample was drawn from each patient in appropriate tubes. The samples were analysed for blood glucose, lipid profile, aspartate transaminase, alanine transaminase, and Gamma-Glutamyl Transferase (GGT) levels.

All the biochemical measurements were done by using a semi-automated analyser - photometer 5010 by standard methods. LDL-C was calculated using the Friedwald's formula. Enzyme activities were measured by kinetic methods based upon the recommendations of IFCC.

Ultrasound imaging of the liver was done by a single experienced radiologist with the equipment Esaote MyLab Seven. The radiologist was unaware of the clinical and laboratory data of the participants. Hepatic steatosis was diagnosed by characteristic hyperechogenicity of liver relative to kidneys, ultrasound beam attenuation, and poor visualisation of intrahepatic structures.

The fatty liver index⁹ was calculated by using the variables - body mass index, waist circumference, triglycerides, and serum GGT. The FLI varies between 0 and 100. The score 0-29 rules out fatty liver disease and a score of greater or equal to 60 points rules in fatty liver disease. This calculation was done using an online calculator.

FLI is calculated as;

$$FLI = (e^{0.953 \cdot \log_e(\text{triglycerides})} + 0.139 \cdot BMI + 0.718 \cdot \log_e(\text{ggt}) + 0.053 \cdot \text{waist circumference} - 15.745) / (1 + e^{0.953 \cdot \log_e(\text{triglycerides})} + 0.139 \cdot BMI + 0.718 \cdot \log_e(\text{ggt}) + 0.053 \cdot \text{waist circumference} - 15.745) * 100$$

The diagnosis of NAFLD was based on the ultrasound examination. Patients who had signs of steatosis by imaging were considered as having NAFLD. Based on this finding, the study subjects were categorised into two groups, (i.e.) patients with NAFLD (Group 1) and patients without NAFLD (Group 2).

STATISTICAL ANALYSIS: All the statistical work was performed by the SPSS software. The results are presented as mean $\pm$ standard deviation. The frequency of NAFLD is shown as percentages. To estimate the differences between patients with and without NAFLD, the t-test was applied. A p-value of less than 0.05 was set as significant.

RESULTS: Totally 50 type 2 DM patients were taken for the study. 40% (n=20) were men and 60% (n=30) were women out of the 50.

Out of the 50 patients, 36% (n=18) were found to be positive for NAFLD based on the ultrasound examination.

Table 1 shows the demographic and biochemical details of the study subjects. Subjects with positive NAFLD (n=18) were compared with subjects without NAFLD (n=32). The mean age of patients in both the groups was similar (53.72±12.40 vs. 54.31±12.28 yrs.). Group 1 patients had a higher BMI when compared to group 2 patients (29.53±3.57 vs. 27.04±2.34) (Table 1).

Waist circumference (101±6.13 cm vs. 100±6.13 cm) did not significantly differ between the two groups. Presence of hypertension was high in group 1 than group 2 (55% vs. 31%). Subjects in group 1 had higher total cholesterol

(197.81±51.90 vs. 155.53±42.04 mg/dL) and triglyceride levels (179.33±51.33 vs. 136.22±66.50 mg/dL) than group 2 (Table 1).

Fasting blood glucose and AST levels did not vary significantly between the groups. Serum GGT levels (26.05±5.24 vs. 20.07±4.62 IU/L) and ALT values (30.1±7.14 vs. 20.4±4.98 IU/L) were significantly higher in the patients with NAFLD than without NAFLD (Table 1).

Table 2 shows the ultrasound findings of the study subjects. Out of the 50 study subjects, 32 (64%) had normal liver study, 18 (36%) patients showed evidence of nonalcoholic fatty liver disease.

Table 3 depicts the risk of fatty liver in the study subjects using the fatty liver index. 29 (58%) patients had high risk of fatty liver disease, 17 (34%) patients had moderate risk, and 4 (8%) had low risk of fatty liver.

Variables	Patients with NAFLD n = 18	Patients without NAFLD n = 32	p-value
Age (Yrs.)	53.72 ± 12.40	54.31 ± 12.28	NS
Gender (M/F)	5/13	15/17	
Diabetes duration (Yrs.)	10.38 ± 2.56	7.67 ± 1.42	0.001
BMI (Kg/M ²)	29.53 ± 3.57	27.04 ± 2.34	0.002
Waist circumference (cm)	101 ± 6.13	100 ± 6.13	NS
Hypertension (%)	55%	31%	0.001
TC (mg/dL)	197.81 ± 51.90	155.53 ± 42.04	0.006
Triglycerides (mg/dL)	179.33 ± 51.33	136.22 ± 66.50	0.01
HDL-C (mg/dL)	45.12 ± 9.09	47.16 ± 8.98	0.41
LDL-C (mg/dL)	83.44 ± 38.27	90.03 ± 36.58	0.72
GGT (mg/dL)	26.05 ± 5.24	20.07 ± 4.62	0.001
FBG (mg/dL)	140.41 ± 48.32	134.55 ± 49.73	0.68
AST (IU/L)	20 ± 2.1	18.67 ± 2.3	0.49
ALT (IU/L)	30.1 ± 7.14	20.4 ± 4.98	0.001
Table 1: Demographic and Biochemical Details of the Study Subjects			

Ultrasound Finding	Number of Patients (%)
Normal	32(64%)
Steatosis	15(30%)
Fibrosis	2(4%)
Cirrhosis	1(2%)
Table 2: Ultrasound Findings in Study Subjects	

Risk	Number of Patients (%)
Low (0-29)	4(8%)
Moderate (30-59)	17(34%)
High >60	29(58%)
Table 3: Risk of Fatty Liver in Study Subjects by FLI	

DISCUSSION: Nonalcoholic fatty liver disease is associated with a multitude of risk factors and more commonly T2DM. Prevalence of metabolic risk factors is rapidly increasing in India putting this population at high risk of developing NAFLD and its complications. NAFLD is present in a third of urban Asian Indians and its prevalence increases with increasing severity of glucose intolerance and in metabolic syndrome.¹⁰ NAFLD is no longer considered a benign

condition in patients with T2DM because the disease follows a more aggressive course with necroinflammation and fibrosis (NASH) in diabetes. New evidence suggests that NAFLD is associated with high risk of hepatocellular carcinoma, hypertension, cardiovascular disease, and renal disease in patients with T2DM.¹¹ With increasing incidences of NAFLD, there occurs a need to design a validated tool for the diagnosis of the disease. Also, management of patients with NAFLD may require a multidisciplinary approach involving not only the hepatologists, but also the internists, cardiologists, and endocrinologists.¹²

The overall mean age group of patients was 54.1 ± 12.40 yrs. The average age group of the patients in many Indian studies lie within the same range.^{6,13} Duvnjak et al and Targher et al have reported that the highest prevalence of NAFLD occurs in those aged 40–60 yrs.¹⁴ and that the prevalence increases with age.^{15,16} Older patients had significantly more NAFLD risk factors such as hypertension, obesity, diabetes, and hyperlipidaemia. It is important to note that older age also increases the risk of developing related problems such as severe hepatic fibrosis and hepatocellular carcinoma.¹⁷

The prevalence of fatty liver in T2DM patients in our study is 36% based on the ultrasound examination. This in accordance with other Indian studies, Suresh et al, where they have reported a prevalence of 35% among 141 diabetic patients.¹³ Mohan V et al reported a prevalence of 54.5% of NAFLD among DM patients.¹⁰ However, the prevalence of NAFLD among T2DM patients varies widely across the country ranging from 30-75%. Kalra S et al have reported a prevalence of 56.5% of NAFLD among 924 T2DM patients in a study conducted across 101 cities in India. In their study, the prevalence varies from 44.1% in Western India to 72.4% in northern states.¹⁸ The prevalence of NAFLD in T2DM patients was 57.2% in a study conducted in New Delhi by AK Agarwal et al.¹⁹ An overall prevalence of NAFLD was 9% in a first population-based study from India.¹⁶

Emerging data over recent years have shown a clear association between diabetes and nonalcoholic fatty liver disease. Studies have shown that NAFLD predicts the development of diabetes and that each condition serves as a progression factor for the other.

A number of metabolic and cellular mechanisms have been implicated in the causation of fatty liver disease in T2DM. Insulin resistance is almost universal in all NAFLD patients. It has been shown that in insulin resistant states both uptake of exogenously derived fatty acid exacerbated by decreased lipid export lead to an increase in lipid synthesis and hepatic lipid content in NAFLD.

The duration of diabetes is longer in NAFLD patients than T2DM patients without NAFLD, which goes in par with other studies like Somalwar AM et al^{6,18} and Banerjee et al where they had found that a longer duration of T2DM was significantly associated with NASH.²⁰

Our study showed a higher number of hypertensive patients in group 1 than group 2 (55% vs. 31%). Many other studies have reported a raised systolic and diastolic blood pressure in NAFLD patients.^{6,7} The prevalence of cardiometabolic risk factors was significantly high in another study by Mohan V et al in urban south Indians.¹⁰

As shown in many other studies, the BMI of patients with NAFLD was significantly higher than the patients without NAFLD. Waist circumference was slightly higher among subjects with NAFLD, but it was not statistically significant. The prevalence of obesity as shown by BMI and waist circumference is higher in NAFLD patients in many other studies. Obesity and T2DM share a "metabolic soil" that promotes hepatocyte lipotoxicity: adipose tissue insulin resistance, subclinical inflammation, hyperinsulinemia, and abnormal glucose metabolism.²¹

Our study showed a significantly higher triglyceride and total cholesterol levels in T2DM patients with NAFLD than without NAFLD. This has been reported in Western studies²² as well as in Indian studies.⁶ Karel Dvorak et al have reported an elevation only in triglycerides, but not cholesterol levels.²² Treeprasertsuk et al reported that there is no significant difference of TG and TC levels in patients of NAFLD with low and high probability of advanced liver fibrosis by NAFLD fibrosis score at baseline.²³ It has been demonstrated that insulin resistance frequently associated

with NAFLD leads to higher triglyceride synthesis and increased secretion of triglyceride from the liver. Hypertriglyceridemia have been strongly correlated with liver fat accumulation.⁶

Although, the fasting blood glucose levels were higher in the NAFLD patients, they did not significantly differ in the two groups. This finding is supported by Karel Dvorak et al. But, many other studies have reported either an elevated fasting glucose or HbA1c.^{6,7}

Enzyme activities were well within the normal range except for a few patients. Serum ALT and GGT levels were significantly higher in NAFLD patients whereas AST levels did not differ from the group without NAFLD. This is similar to Prashanth M et al where serum ALT and alkaline phosphatase levels though within normal limits were significantly higher in patients with steatohepatitis.²⁴

Fatty liver index is a simple index and it may help physicians to select subjects for liver ultrasonography and intensified lifestyle counselling and researchers to select patients for epidemiologic studies.⁹ The FLI is a continuous measure that has been validated against US for the qualitative detection of NAFLD and has never been validated vs. liver biopsy.²⁵ In our study, the mean values of fatty liver index (54.66 ± 13.66 vs. 43.45 ± 15.72) was significantly high in patients with NAFLD (Diagnosed by ultrasound) when compared with T2DM patients without NAFLD. Among the 50 T2DM patients, 29 (58%) patients had high risk of fatty liver (FLI >60), 17 (34%) patients had moderate risk, and only 4 (8%) had low risk of fatty liver (FLI <30).

58% (n=29) of patients had fatty liver based on FLI. The number is high when compared to the patients diagnosed by ultrasound. The difference observed here maybe due to the fact that FLI has only moderate agreement with ultrasonographic methods either regular AUS or HRI,²⁵ but the same study recommends further validation of FLI against liver biopsy and in different populations.

The FLI has recently been used as a surrogate marker for NAFLD in large epidemiological studies. In a large European cross-sectional population-based study, high values FLI was associated with reduced insulin sensitivity, higher Framingham risk score and increased intima-media thickness.²⁶ The predictive validity of FLI was demonstrated in two large cohorts. In the French general population, cohort FLI was an independent predictor for diabetes in a 9 year follow up²⁷ as would be expected from ultrasound diagnosed NAFLD in Korean adults.²⁸ In an Italian population cohort after 15 years follow up, FLI was independently associated with liver-related mortality.²⁹

The findings in this hospital-based study in a small population, although not exactly representative of the general population, but nevertheless can make a valuable contribution to the clinicians for evaluating the risk of fatty liver disease in T2DM patients.

CONCLUSION: The results of the present study clearly demonstrate a high association of fatty liver disease in T2DM patients diagnosed either by ultrasound or by FLI. FLI is a simple and validated method and can be used for the initial

evaluation of fatty liver in all T2DM patients. Early diagnosis of NAFLD is essential for timely implementation of lifestyle, nutritional, and therapeutic modifications. Clinicians should be aware of the possibility of fatty liver disease in asymptomatic patients and evaluation for NAFLD by noninvasive methods can be considered as a part of the routine examination of patients with T2DM.

LIMITATIONS:

1. The sample size is very small due to lack of time as this was an ICMR short-term student project.
2. This is only a hospital-based study. The study could have been extended into the general population.

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