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Original article:

Incidence of Non-Alcoholic fatty liver disease in diabetic patients

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a growing concern as a cause of chronic liver disease in the world. In India the prevalence of NAFLD is estimated to be around 9-32%, with a higher incidence rate amongst obese and diabetic patients[1].

Methods: We studied 50 patients with type 2 diabetes, to determine the incidence of NAFLD in them and to detect the risk of hepatic fibrosis using Fibrosis-4 (FIB-4) score. We also studied the risk factors for developing non-alcoholic fatty liver disease in diabetic patients.

Observations: The average age of the patients was around 54 years, with a male:female ratio of 1:1. Most of the patients(62%) had diabetes of a shorter duration of 1 to 5 years, while 8 % of patients had long standing diabetes of more than 10 years.

Results: The mean fasting blood sugar was 156.94±47.92 with a range of 80-375.The mean post prandial blood sugar was 249± 68.92 ,with a range of 150-450.The mean SGOT was 44.54 ±38.94, with a range of 10-235.The mean SGPT was 34.86 ± 34.68, with a range of 6-183.All the patients had the total bilirubin and direct and indirect bilirubin within the normal range. Among our patients ,52% had a FIB-4 score of less than 1.45 with less likelihood of cirrhosis. FIB 4 score of > 3.25 with high likelihood of cirrhosis was seen in 8% patients.

Conclusions: We conclude that FIB- 4 score is a non-invasive bedside test to evaluate for fibrosis in NAFLD patients and easy to use.

Keywords: Non-alcoholic fatty liver disease,FIB-4 score, type 2 diabetes

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the macrovascular accumulation of fat in more than 5% of the hepatocytes in the absence of hazardous level of alcohol consumption[2]. NAFLD is often asymptomatic and may be detected incidentally only by abnormal liver function or imaging. Persistent elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and fatty change on ultrasonography (US) or computed tomography (CT), without alcohol intake or positive hepatitis virus markers or autoantibodies, can point towards a diagnosis of NAFLD. Normal ALT levels do not exclude the possibility of NASH with advanced fibrosis. Liver function testing with fibrosis markers and/or imaging modalities are required for the diagnosis of NASH[3]. The majority of patients with NAFLD have isolated fatty liver, which is defined as hepatic steatosis in absence of significant necroinflammation or fibrosis[2]. NAFLD is a non-communicable disease ranging from non-alcoholic fatty liver (NAFL), marked by hepatic fat accumulation without inflammation, to non-alcoholic steatohepatitis (NASH), characterized by hepatic fat deposition with inflammation, fibrosis, and liver cirrhosis. NASH-related cirrhosis causes chronic liver disease and hepatocellular cancer[4].

NAFLD, affects 2.8-24% of the general population in the world. It is the commonest cause of abnormal liver function tests and also causes cryptogenic cirrhosis of liver. It affects middle aged and old age patients. NAFLD is associated with the development of cardiovascular disease. It is also associated with diabetes, impaired glucose tolerance and metabolic syndrome. Hence, early diagnosis and management of NAFLD is important. Dietary modification and exercise constitute the mainstay of treatment[5].

Histopathology of biopsy specimens remains the gold standard for diagnosing NAFLD/NASH. Steatosis, lobular inflammation, and hepatocellular ballooning are all necessary components for the diagnosis of NASH; fibrosis is also typically observed[6].

Following the diagnosis of NAFLD, the next step is to find out the fibrotic stage of the disease. Because the extent of fibrosis has been shown to correlate with clinical outcomes. Staging the extent of liver fibrosis noninvasively is gaining importance. The NAFLD fibrosis score (NFS), comprises data on the age, body mass index, platelet count, and aspartate transaminase and alanine transaminase levels. Other non-invasive tools used to detect the presence of advanced fibrosis in NAFLD patients include the fibrosis-4 (FIB-4) score, aspartate-aminotransferase-to-platelet ratio (APRI), enhanced liver fibrosis panel, Fibrometer, FibroTest, and Hepascore[4].

Sterling RK et al, studied patients with HIV/hepatitis C virus (HCV) coinfection, a multivariate logistic regression analysis revealed that platelet count (PLT), age, AST and INR were significantly associated with fibrosis. PLT, age, AST, and ALT was also found to be another optional model. Based on this, a simple index (FIB-4) was developed: age ([yr] x AST [U/L]) / ((PLT [10(9)/L]) x (ALT [U/L])(1/2)). At a cut-off of <1.45 in the validation set, the negative predictive value to exclude advanced fibrosis (stage 4-6) was 90% with a sensitivity of 70%. A cut-off of >3.25 had a positive predictive value of 65% and a specificity of 97%. FIB-4 score helps to avoid liver biopsy by predicting hepatic fibrosis[7]..

Fibrosis is predominantly peri-sinusoidal and pericellular (“Chicken-Wire” Fibrosis), mostly seen in acinar zone 3[8]. Changes in the FIB-4 score can help to monitor fibrosis[9]. Steatosis increases the long-chain fatty acids damaging the hepatocytes. Insulin resistance and hyperinsulinemia are the main cause of steatosis[10].

Aims & Objectives: The aim of our study was to study the incidence of NAFLD in diabetic patients and to detect the risk of hepatic fibrosis using FIB-4 score. The objective of our study is to study the risk factors of non-alcoholic fatty liver disease in diabetic patients.

MATERIAL AND METHODS:

This is a hospital based cross sectional descriptive study.

The study was conducted at **a tertiary care hospital in**, Sangli. The study duration was of 6 months and was conducted from July 2020 to December 2020 in the medical wards and ICU.

The study population comprised of all patients admitted in the general medicine ward. The study subjects were all the patients, diagnosed with diabetes and admitted in general medicine ward.

All the patients in the age group above 16 years of age, non-alcoholic with diabetes were included in our study. Patients with a history of alcohol consumption was excluded from our study.

FIB-4 Score

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

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FIB-4 Interpretation

Points<1.45 : Cirrhosis less likely.

Points≥1.45 and ≤3.25 : Intermediate.

Points > 3.25 : Cirrhosis more likely.

Observations &Results

Based on the study selection criteria, we included a total of 50 patients in our study. The baseline characteristics of our study population is summarized in **Table 1**.

Table 1: Baseline characteristics of study population

Parameter	Values
Age (in years), mean ± SD	54.08 ± 13.16
Gender, n (%)	
Males	25 (50)
Females	25 (50)
Past history, n (%)	
Hypertension	16 (32)
Chronic kidney disease	3 (6)
Others	4 (8)
Duration of diabetes, n (%)	
1-5 years	31 (62)
6-10 years	15 (30)
>10 years	4 (8)
Antidiabetic treatment, n (%)	
Oral hypoglycemic agents	39 (78)
Insulin	12 (24)

The average age of the patients in our study was around 54 years with a male: female ratio of 1:1. Associated past history of hypertension was seen in 32% of the patients ,chronic kidney disease was seen in 6% of the patients and some patients(8%) had some other illnesses in the past.

Most of the patients(62%) had diabetes of a shorter duration of 1 to 5 years .Patients with a duration of diabetes of 6 to 10 years was 30%.Approximately 8 % of patients had long standing diabetes of more than 10 years .Oral hypoglycemic agents was ongoing in 78% of the diabetic patients. The remaining 24% of the patients were on insulin.

Table 2: Haematological parameters of the study population

Parameter	Mean	Range
Haemoglobin	12.12 ± 1.80	7.5-16
WBC	8582.16 ± 3248.62	4000-17900
Platelet Count	245708 ± 89639.37	125000-572000
Blood sugar Fasting	156.94 ± 47.92	80-375
Blood sugar Post Prandial	249 ± 68.92	150-450
SGOT	44.54 ± 38.94	10-235
SGPT	34.86 ± 34.68	6-183
Total bilirubin level	0.71 ± 0.29	0.3-1.4
Direct bilirubin level	0.45 ± 0.29	0.2-2.0
Indirect bilirubin	0.29 ± 0.13	0.1-0.7

The mean Haemoglobin level of our patients was 12.12 ± 1.80, with a range of 7.5 -16.The mean fasting blood sugar was 156.94± 47.92, with a range of 80-375.The mean WBC count was 8582.16±3248.62 with a range of 400 -17900.The mean platelet count was 245708±89639.37 with a range of 125000-572000.The mean fasting blood sugar was 156.94±47.92 with a range of 80-375.The mean post prandial blood sugar was 249± 68.92 ,with a range of 150-450.The mean SGOT was 44.54 ±38.94, with a range of 10-235.The mean SGPT was 34.86 ± 34.68, with a range of 6-183.All the patients had the total bilirubin and direct and indirect bilirubin within the normal range.

Table 3:

Distribution of patients according to the FIB4 Score and ultrasound abdomen findings. Half of our study patients, i.e. 50% patients were identified to have developed NAFLD.

Table 3: FIB4 Score and ultrasound abdomen findings

Parameter	N (%)
FIB4 Score	
<1.45	26 (52)
≥1.45 and ≤3.25	20 (40)
>3.25	4 (8)
Ultrasound findings	
Fatty liver	25 (50)
NAD	25 (50)

Among our patients ,52% had a FIB score of less than 1.45 with less likelihood of cirrhosis.

FIB 4 score of ≥ 1.45 and ≤ 3.25 was seen in 40% patients. FIB 4 score of > 3.25 with high likelihood of cirrhosis was seen in 8% patients.

Ultrasonography of the abdomen done showed that 50% of the patients had fatty liver and the remaining 50% had no abnormality detected.

Table 4:

Correlation of NAFLD with various parameters calculated using Pearson's correlation. We found a statistically significant association between age above 50 years and FIB score ≥1.45 with the development of non-alcoholic fatty liver disease.

Table 4: Correlation between NAFLD and various parameters

Parameter	R	p-value
Age (≤50 years vs >50 years)	0.2884	0.0422
Duration of diabetes (<5 years vs ≥5 years)	0.1309	0.3648
FIB score (<1.45 vs ≥1.45)	0.3203	0.0234
HbA1c (≤8.5% vs >8.5%)	0.3333	0.0181
BSL fasting (<150 mg/dL vs ≥150 mg/dL)	0.0401	0.7822
OHA (none or 1 OHA vs >1 OHA)	-0.0816	0.5713
Insulin (no use vs on insulin)	-0.1873	0.1935

***Calculated using the Pearson's correlation test**

r_p = Pearson's correlation coefficient;

r_p = 1 means a perfect positive correlation, and

r_p = -1 means a perfect negative correlation

p<0.05 considered statistically significant.

Using the Pearson's correlation coefficient we found a statistically significant correlation between NAFLD and age>50 years (p=0.0422), FIB score ≥ 1.45 (p=0.0234) and HbA1c>8.5%(p=0.0181).

Discussion

In our study, there was an increased incidence of Non-Alcoholic Fatty Liver Disease in diabetic patients especially in the age group of above 50 years. Using the Pearson's correlation coefficient, we found a statistically significant correlation between NAFLD and age 50 years (p=0.0422), which is statistically significant. In a study by Sanjay Kalra et al, the prevalence of NAFLD increased between ages of 40 and 60 years.

Among the total 50 diabetic patients that we studied, 24(48%) developed non-alcoholic fatty liver disease, p-value being 0.0234, which is statistically significant[1].

In a study in Italy, they found the prevalence of NAFLD in type 2 diabetes mellitus to be 70%. Other studies have shown the prevalence of NAFLD in type 2 diabetes mellitus patients ranging between 34% - 94%. NAFLD is associated with several risk factors such as obesity, metabolic syndrome, insulin resistance and type 2 diabetes. On the other hand, the risk of developing diabetes is increased approximately 5-fold if they have NAFLD[10].Diagnosis of NAFLD is based on liver biopsy, or ultrasonography in people without alcohol or low alcohol consumption[10]. In our study HbA1c cut-off was above 8.5%, which was associated with increased risk of NAFLD, with p-value of 0.0181, which is statistically significant.

In a study by Chen Changxi et al, higher HbA1c levels was associated with increased risk of NAFLD. In a study by Ma H et al, the prevalence of NAFLD was significantly higher in subjects with increased serum HbA1c level (HbA1c ≥6.5%) than in those with normal range of serum HbA1c level (51.71% vs. 25.20%; P <0.001), and the prevalence increased along with progressively higher serum HbA1c levels (P for trend <0.001). Stepwise logistic regression analysis showed that serum HbA1c level was significantly associated with the risk for NAFLD (odds ratio: 1.547, 95% confidence interval: 1.054 – 2.270; P =0.026)[11].

In our study FIB-4 value was above 1.45 (p=0.0234) which was considered statistically significant. FIB 4 score of > 3.25 is associated with high likelihood of cirrhosis was seen in 8% patients. Among our patients ,52% had a FIB score of less than 1.45 with less likelihood of cirrhosis. FIB 4 score of ≥ 1.45 and ≤ 3.25 was seen in 40% patients. The FIB-4 was originally used to evaluate fibrosis in hepatitis C virus/human immunodeficiency virus co-infected population. The score is calculated based on available clinical data of: age, AST, ALT and platelet counts[12]. FIB-4 and APRI, utilise the biochemical test components of age, AST, ALT, glucose, BMI, platelets and albumin. These scores tend to increase in the elderly[3]. The importance of evaluating the degree of fibrosis is because it is highly predictive and liver-specific and predictive of mortality. Generally, many of the patients with NAFLD do not become cirrhotic, unlike type 2 diabetes patients who are more predisposed to risk of steatohepatitis (NASH) and liver-related mortality. NAFLD not only affects the liver, but it is also associated with cardiovascular (CVD) events, chronic kidney disease (CKD), and diabetic microvascular complications

such as nephropathy, retinopathy and sensitive-motor and autonomic neuropathy. Hence it is of utmost importance to detect liver fibrosis early and start the anti fibrotic drugs and monitor the response to treatment[12].

Shah *et al*. validated the FIB-4 for use in NAFLD, in their comparative study against other non-invasive scoring systems In their study a FIB-4 score of ≥2.67, had an 80% positive predictive value and a FIB-4 score of ≤1.30 had a 90% negative predictive value for advanced fibrosis. FIB-4 has been useful in the predicting mild to moderate fibrosis in NAFLD. Comparing several non invasive models for predicting hepatic fibrosis, a FIB-4 cut-off of 1.43 had the best AUROC (0.821; 95% CI: 0.75–0.891) to detect stage 1 fibrosis or higher[9].

As per a study by Sun W et al ,FIB-4 index with a 1.30 cut-off was more accurate than the FIB-4 index with a 3.25 cut-off, NFS and BARD score, though it has limited value for predicting NAFLD-related advanced fibrosis [13].Davyduke T et al, studied the use of FIB-4 score to reduce the need for vibration controlled transient elastography and hepatology referral[14]. In another study by Fallatah H I, FIB-4 score could be used to diagnose early stages of NAFLD where liver biopsy was not indicated[15].

Conclusions

Though liver biopsy remains the gold standard in diagnosing NAFLD, it is invasive and has safety issues. Non invasive techniques with bedside scoring systems, such as FIB-4,NFS and APRI help to accurately assess necroinflammation and fibrosis. These methods help in doing serial assessments for monitoring the disease progression in a safer manner. Bedsides, scoring systems such as FIB-4, NFS and APRI are easily calculated using commonly available parameters and are helpful tools to allow the clinician to identify patients with advanced fibrosis[16]. FIB-4 scoring provides a useful non-invasive method in assessing liver fibrosis. Though FIB-4 scoring cannot replace liver biopsy. Lifestyle modification includes low Carbohydrate and low fat diet along with exercise.

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