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Frequency of undiagnosed Diabetes Mellitus in patients of Non-Alcoholic Fatty Liver Disease: An observational cross-sectional study

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Abstract

Background: Insulin resistance is common in people with NAFLD, although not always overt glucose intolerance. Present study was done to describe the frequency of undiagnosed diabetes mellitus in patients of non alcoholic fatty liver disease at a tertiary care centre.

Material & Methods: This was a hospital based observational cross-sectional study conducted in the Department of Medicine, Surgery and Biochemistry at Dr. Vithalrao Vikhe Patil Foundation's Medical College. Patients fulfilling the inclusion criteria were selected. A detailed informed consent was taken from all the participants. Demographic profile recorded and detailed history with examination was done in all the patients as per the proforma attached. Analysis of symptoms was done along with underlying co- morbid conditions and drugs used. Anthropometric data, such as body mass index (BMI) and blood pressure were measured.

Results: Mean age of the cases was 53.62±10.69 years. Mean age in males was 55.33±10.19 years while in female it was 51.04±10.92 years. Maximum number of patients was in 5th and 6th decades. Out of 120 total patients, total males were 29 and females were 91. Out of 18 total diabetic patients, 12 were females and 6 were males. Impaired fasting glucose were found in 55(45.83%) of patients. Increased serum Cholesterol level were seen in 56(46.66%) patients. Increased serum triglyceride level was seen in 68(56.67%) patients. Low serum HDL level was seen in 78(65%) patients. Increased serum LDL levels were 37(30.83%) of patients. ALT and AST levels were elevated in 63(52.5%) and 61(50.83%) of patients. Total of 120 cases, 64(53.33%), 52(43.33%) and 4(3.33%) of cases had grade I, II, and III fatty liver respectively.

Conclusion: The prevalence of several components of metabolic syndrome is higher in NAFLD patients, according to our findings.

Key words: Diabetes Mellitus ,Non Alcoholic Fatty Liver Disease, cross sectional study

Introduction

NAFLD is defined by fatty infiltration of the liver, primarily in the form of triglycerides, that surpasses 5% of the weight of the liver. NAFLD is histologically similar to alcoholic liver disease, however it occurs in the absence of heavy alcohol consumption and is not caused by other fatty liver causes such hepatitis C or certain drugs. [1]

NAFLD represents a spectrum of clinical–pathological features ranging from simple steatosis, which is characterized by fatty infiltration only, to non-alcoholic steatohepatitis (NASH), which is characterized by inflammation and hepatocellular injury with or without fibrosis and cirrhosis.[1,2] Most people with NAFLD have an increase in liver fat content alone, which is apparently benign; others develop NASH that can progress to cirrhosis. The diagnosis of NAFLD is typically suspected in asymptomatic patients who are found to have elevated aminotransferase levels and/or ultrasonic evidence of fatty liver.[3]

Diabetes mellitus is one of the most common metabolic disorders and leading cause of death and disability in the world. There is a strong relationship between hepatic triglyceride content and insulin resistance.[4] NAFLD is associated with insulin resistance.[5,6] It appears to be both a cause and a consequence of insulin resistance. A mechanism by which hepatic steatosis causes insulin resistance involves an inhibition of insulin signaling at the level of the insulin receptor.[7]

Insulin resistance impairs the suppression of lipolysis, and this leads to an increased release of free fatty acids from adipose tissue so that more are delivered to and taken up by the liver.[8,9]This excess amount of free fatty acids can overload the hepatic mitochondrial beta oxidation system, the major pathway of fatty acid oxidation in the liver, leading to the accumulation of fatty acids in the liver.[10] In the majority of patients, simple steatosis-the accumulation of fat in the liver-follows a relatively benign course.[11] It can be present for decades without leading to more serious liver damage.[12]However, it may evolve into NASH, which is a more aggressive liver disease that tends to be progressive and may lead to cirrhosis. [3,11]

Aims and objectives

To describe the frequency of undiagnosed diabetes mellitus in patients of non alcoholic fatty liver disease at a tertiary care centre of Hyderabad.

Materials and Methods

This is a hospital based observational and cross-sectional study was conducted in the Department of Medicine, Surgery and Biochemistry at Dr. Vithalrao Vikhe Patil Foundation's Medical College, Ahmednagar, Maharashtra.

Inclusion Criteria:

1) Who consented to be part of study.

2) Age more than 18 years.

3) All patients diagnosed as NAFLD by abdominal ultrasonography.

Exclusion Criteria:

1) Patients less than 18 years.

2) Patients with history of alcohol intake more than 20 grams/day in males and more than 10 grams/day in females.

3) Known diabetic patients.

4) Patients with positive viral markers for hepatitis B and hepatitis C.

5) Patients taking drugs causing liver fat accumulation.

6) Patients not giving consent.

Methodology:

Patients fulfilling the inclusion criteria were selected. A detailed informed consent was taken from all the participants. Demographic profile recorded and detailed history with examination was done in all the patients as per the proforma attached. Analysis of symptoms was done along with underlying co- morbid conditions and drugs used. Anthropometric data, such as body mass index (BMI) and blood pressure were measured.

Serological tests for HBsAg, anti-HCV, Aspartate aminotransferase, Alanine aminotransferase, total bilirubin, lipid profile, FBG, RBG and HbA1C (by TOSOH- tm Bioscience Haemoglobin A1c Cottrol for G8 automated HPLC Analyser) were done.

Diagnosis of diabetes was made on the basis of American Diabetes Association criteria. Patients with BMI of more than 23kg/m2 were labeled as overweight and those with BMI of more than 25kg/m2 were labeled as obese (Asian standards). Diagnosis of fatty liver was made on the basis of ultrasound.

Patients diagnosed with any medical conditions other than diabetes were provided consultation from concerned departments. Ethical approval was taken from the ethical committee

Defining criteria for fatty liver (based on Diagnostic Ultrasound by Carol M. Rumack):

Mild – Minimal diffuse increase in hepatic echogenicity with normal visualization of diaphragm and intrahepatic vessel borders.

Moderate - Moderate diffuse increase in hepatic echogenicity with slightly impaired visualization of diaphragm and intrahepatic vessels.

Severe – Marked increase in echogenicity with poor penetration of posterior segment of right lobe of liver and poor or no visualization of hepatic vessels and diaphragm.

Defining criteria for diabetes mellitus (based on American Diabetes Association):

1) Symptoms of diabetes plus random blood glucose concentration =/> 200mg/dl. and/or

2) Fasting blood glucose=/>126mg/dl. Fasting defined as no caloric intake for at least 8 hours. and/or

3) HbA1C =/>6.5%. and/or

4) 2-h plasma glucose=/>200mg/dl during an oral glucose tolerance test.

Statistical Analysis

Data was entered on MS Excel spreadsheet. Results were summarized in tables and percentages. Quantitative data was summarized using means +/- & standard deviation. Cross tabulation with outcome variable of interest was done using statistical SPSS software version 22.0.

Results

Total of 120 cases, ultrasonographically diagnosed as NAFLD were included in this study. Mean age of the cases was 53.62±10.69 years. Mean age in males was 55.33±10.19 years while in female it was 51.04±10.92 years. Maximum number of patients was in 5th and 6th decades. Out of 120 total patients, total males were 29 and females were 91. Male: female ratio was almost 1:3.

On physical examination mean BMI (Kg/m2) was 26.15±3.02, mean systolic blood pressure (mm of Hg) was118.92±10.11 , mean diastolic blood pressure (mm of Hg) was 79.68±5.12. The mean fasting blood glucose (mg/dl) was 119.12±77.26, mean HbAIC was 7.65±12.34. Mean serum cholesterol (mg/dl) was 198±26.29, mean serum triglyceride (mg/dl) was 171.605±81.07, mean serum HDL (mg/dl) was 39.135±6.43 and mean serum LDL (mg/dl) was 114.45±27.93. Mean AST (u/l) was 49.343±20.38, mean ALT (u/l) were 46.675±25.76 .(Table-1)

Variables	**Mean ±SD**
SBP	118.92±10.11

DBP	79.68±5.12
BMI	26.15±3.02
FBG (mg/dl)	119.12±77.26
HbAIC (%)	7.65±12.34
Total Cholesterol	198±26.29
Serum TG	171.605±81.07
Serum HDL	39.135±6.43
Serum LDL	114.45±27.93
Asparatate amino transferase(u/L)	49.343±20.38
Alanine amino transfearse (u/L)	46.675±25.76

Table-1: Mean and SD of various variables

According to BMI, no patient was underweight, 18(15%) were normal, 48(40%) patients were overweight and 54(45%) patients were obese (Table-2). 20(16.67%) patients were hypertensive. 18(15%) patients had diabetes mellitus. Out of 18 total diabetic patients, 12 were females and 6 were males. Impaired fasting glucose were found in 55(45.83%) of patients. Increased serum Cholesterol level were seen in 56(46.66%) patients. Increased serum triglyceride level was seen in 68(56.67%) patients. Low serum HDL level was seen in 78(65%) patients. Increased serum LDL levels were 37(30.83%) of patients. ALT and AST levels were elevated in 63(52.5%) and 61(50.83%) of patients. Total of 120 cases, 64(53.33%), 52(43.33%) and 4(3.33%) of cases had grade I, II, and III fatty liver respectively.(Table-2)

Variable	**N(%)**
Overweight (BMI 23-24.9kg/m	48(40%)
Obese (BMI>kg/m	54(45%)
Hypertension	20(16.67%)
Impaired fasting glucose	55(45.83%)
Diabetes Mellitus	18(15%)
Increased Serum cholesterol	56(46.67%)
Increased Serum triglyceride	68(56.67%)
Low Serum(HDL)	78(65%)
Increased Serum (LDL)	37(30.83%)
Aspartate Amino Transferase	63(52.5%)
Alanine Amino Transferase	61(50.83%)
Fatty liver grade 1	64(53.33%)
Fatty liver grade 11	52(43.33%)
Fatty liver grade 111	4(3.33%)

Table-2: frequency of various variables.

Percentage of diabetic patients increased as grade of fatty liver increased i.e. 10.94%,15.38 % and 75% in grade I, II, III respectively. 3(75%) of grade III fatty liver patients had increased triglyceride while 45(86.53%) of grade II and 20(31.25%) of grade I patients were having increased triglyceride levels.(Table-3)

Variable	**Grade1 N=64**	**Grade2 N=52**	**Grade3 N=4**
Diabetes Mellitus(n=18)	7(10.94%)	8(15.38%)	3(75%)
Serum TG(n=68)	20(31.25%)	45(86.53%)	3(75%)

Table-3: Diabetes and TG In relation to grade of fatty liver

In 18 patients of T2DM with NAFLD 7(38.89%), 14(77.77%), 12(66.67%), 16(88.89%) and 14(77.77%)had hypertension, hypertriglyceridemia, increased levels of LDL, increased BMI and low HDL respectively. On statistical analysis, there was positive correlation of diabetes mellitus, increased triglyceride level with grade of fatty liver. There was also positive relation between T2DM and hypertension, dyslipidemia, increased body mass index. NAFLD patients with diabetes mellitus had increased prevalence of various components of metabolic syndrome.

In patients of NAFLD with diabetes mellitus 7(38.89%) had hypertension while in patients of NAFLD patients without diabetes mellitus 6(5.88%) had hypertension and this observation was statistically significant. In patients of NAFLD with diabetes mellitus 14(77.77%) had hypertriglyceridemia while in patients of NAFLD patients without diabetes mellitus 54(52.94%) had hypertriglyceridemia and this observation was statistically significant. In patients of NAFLD with diabetes mellitus 12(66.67%) had increased levels of LDL while in patients of NAFLD patients without diabetes mellitus 27(26.47%) had increased levels of LDL and this observation was also statistically significant.

In patients of NAFLD with diabetes mellitus 16(88.89%)had increased BMI while in patients of NAFLD patients without diabetes mellitus 67(65.68%)had increased BMI and this observation was also statistically significant. 14(77.77%) of NAFLD patients with diabetes mellitus had low HDL level, while 82(80.39%) of NAFLD patients without diabetes mellitus had also low HDL. This observation was not statistically significant. (Table-4)

Variables	**NAFLD patients with DM (N=18)**	**NAFLD patients without DM(N=102)**
HTN	7(38.89%)	6(5.88%)
Serum TG	14(77.77%)	54(52.94%)
Serum LDL	12(66.67%)	27(26.47%)
BMI	16(88.89%)	67(65.68%)
Serum HDL	14(77.77%)	82(80.39%)

Table-4: Association of various variables with NAFLD.

Discussion

In our study, 18(15%) of NAFLD patients had diabetes mellitus according to American Diabetes Association criteria for diabetes mellitus. Ajay Duseja et al[13] (13%) and Kaushal Madan et al[14](10%) have had similar findings. Impaired fasting glucose was found in 45(45%) patients. Rakesh Gaharwar et al[15] (45.71%) also had similar findings. 72.4% and 28% patients had impaired fasting glucose as reported by Ajay Duseja et al[13] and Bajaj et al[16] respectively.

18(15%) of our patients had diabetes, while another 55(45.83%) had impaired fasting glucose. A lower prevalence of diabetes (7%–22%) was also found in other Indian studies.[13,14] This is in contrast to western figures-38% cases of diabetes in NAFLD (UK)[17], while among Americans, diabetes was associated with half of the histologically proven patients with NAFLD[18].

In our study 20(16.67%) patients were hypertensive. In the study of Ajay Duseja et al[13] (13%) and Kaushal Madan et al[14] (10%), they had similar findings. In our study increased serum triglyceride level was seen in 60(60%) patients. In a study by Rakesh Gaharwar et al[15](67.14%), they also had similar findings.

In our study, it was observed that the percentage of diabetic patients increased as grades of fatty liver increased i.e. 10.94%,15.38 % and 75% in grade I, II, III respectively were diabetics. 3(75%) grade III fatty liver patients had increased triglyceride while 45(86.53%) of grade II and 20(31.25%) of grade I patients were having increased triglyceride levels and this observation was statistically significant.

In our study 78(65%) patients had low HDL levels (<40 mg/dl in males and <50 mg/dl in females) with a mean of 39.135±6.43 mg/dl as compared to 66.7% described by Bajaj et al. Rakesh Gaharwar et al[15] (94%) also had similar findings. In our study, it was observed that 14(77.77%) of NAFLD patients with diabetes mellitus had low HDL levels, while 82(80.39%) of NAFLD patients without diabetes mellitus had low HDL levels. This observation was not statistically significant.

In our study, the mean serum TG and mean serum Cholesterol levels were above the normal upper limit, while the mean serum HDL level was below the normal limit, signifying that most patients had dyslipidemia, which is a known risk factor for fatty liver.

In our study, the mean BMI was 26.15±3.02 while 40% and 45% of patients were overweight and obese, respectively. Similar findings were seen in most other Indian studies with a median BMI value of 26.7 kg/m2 with almost 60%–70% patients having obesity as defined by the Asia-Pacific criteria[13,14]. An exception to this was a study done in Bengal by Das K et al[19] with very low BMI (22.73±.90 kg/m2) this may be because the study was carried out in an extremely

underprivileged area; and as expected, the prevalence of NAFLD was only 8.7%. The Bengal findings cannot be applied to other populations. Our patients with NAFLD had a lower mean value of BMI as compared to the western figures (30–38 kg/m2)[20,21] Despite lower BMI, our patients had fatty liver, possibly due to characteristics of South Asian phenotype (i.e. greater propensity to IR and central obesity)[22.]

In our study, the patients of NAFLD with diabetes mellitus 7(38.89%) had hypertension while in patients of NAFLD patients without diabetes mellitus 6(5.88%) had hypertension and this observation was statistically significant. In patients of NAFLD with diabetes mellitus 14(77.77%) had hypertriglyceridemia while in patients of NAFLD patients without diabetes mellitus 54(52.94%) had hypertriglyceridemia and this observation was also statistically significant. In patients of NAFLD with diabetes mellitus 12(66.67%) had increased levels of LDL while in patients of NAFLD patients without diabetes mellitus 27(26.47%) had increased levels of LDL and this observation was statistically significant. In patients of NAFLD with diabetes mellitus 16(88.89%)had increased BMI while in patients of NAFLD patients without diabetes mellitus67(65.68%) had increased BMI and this observation was also statistically significant .

In our study, positive correlation of T2DM with hypertension, hypertriglyceridemia and elevated levels of LDL was found, and these observations were statistically significant. These findings are suggestive of strong association between NAFLD, T2DM and Metabolic syndrome.

Conclusion

In NAFLD patients, the prevalence of impaired glucose metabolism is substantially higher than in earlier research. Patients with NAFLD may benefit from early detection of Diabetes Mellitus to avoid long-term hyperglycemia problems and progression to steatohepatitis and cirrhosis.

In addition, patients with NAFLD have a higher frequency of several components of metabolic syndrome, according to our findings. When these values are seen in the clinical context, patients must be investigated for the existence of NAFLD using abdominal ultrasonography. Its early discovery may aid in the modification of the disease's course and the postponement of complications.

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