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Original Research Article

TO STUDY THE PREVELANCE OF NAFLD IN TYPE 2 DIABETES MELLITUS & ITS COORELATION WITH HBA1C, IN INDEX MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, INDORE (M.P.)

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ABSTRACT

BACKGROUND: Diabetics are more prone to have liver fibrosis and hence the study was conducted to find any linear correlation between Diabetes Mellitus and liver fibrosis.

MATERIALS AND METHODS: A observational study with 100 diabetic patients was done. Detailed history was taken and examination done, patients were then subjected to various blood investigation and USG abdomen, after clearance from institutional scientific committee and after taking informed consent during the period of May 2022 to December 2022, in the Department of General Medicine, Index Medical College Hospital & Research Centre, Indore.

AIMS & OBJECTIVES: To establish the correlation of HBA1C with NAFLD in Type 2 DM.

RESULTS: Mean age group was 45 years, range 25 to 70 years. Out of 100 diabetic patients, 54% patients were positive for NAFLD. Out of 36% (65.5%) patients had higher HBA1c levels >8.5%. Thus, NAFLD leads to poor glycaemic controls and vice versa. In the study 62.9% had grade 1 fatty liver., suggesting slow progressive nature of disease. Most of the NAFLD patients (40%) were asymptomatic followed by dyspepsia. Elevated liver enzymes were found in stage 3 and 4 only.

CONCLUSION: The present study concludes that prevalence of NAFLD in DM is 54% being more in males than females with most common age of presentation is 45 to 55. NAFLD is now considered as liver manifestation of metabolic syndrome while NAFLD is associated with and responsible for poor glycaemic control (higher HBA1c levels) in diabetic patients The findings of fatty liver, even in a asymptomatic patients should prompt a thorough research for components of metabolic syndrome, and patients should advised regarding CVD risks, weight loss, smoking cessation, dietary modification, exercises and pharmacological therapies.

KEYWORDS: NASH (Non-Alcoholic Steatohepatitis), NAFLD (Non-Alcoholic Fatty Liver Disease), Diabetes Mellitus (DM), Haemoglobin (Hb), HBA1c (Haemoglobin A1c)

1. INTRODUCTION

NAFLD is a spectrum of progressive liver disease that encompasses simple steatosis, NASH (non-alcoholic steatosis hepatitis), fibrosis and ultimately cirrhosis and liver failure. Most patients with NAFLD have no symptoms or signs of liver disease at the time of diagnosis. In this, patients' abnormal liver function tests are often discovered incidentally[1&2]. NAFLD is becoming a major public health problem due to rising prevalence of obesity and DMT2. Prevalence is around 30% in western world and 10% in Asian countries[3].

In NAFLD, excess amount of fat accumulates or builds up in liver. This fat is not a result of excessive alcohol consumption. The exact causes responsible for development of NAFLD have not been established yet[4]. It appears to be linked directly to the growing epidemic of obesity in adults and children. Some researchers consider that cluster of disorders that increases the risk of developing heart disease, diabetes and stroke may be the factor behind the development of NAFLD[5].

There is no good non-invasive marker that separates steatosis from steatohepatitis, and hence liver biopsy still remains gold standard for prognostication of NAFLD[6].

The under estimated prevalence in Asia Pacific countries including India is due following problems:

- Usually asymptomatic individuals
- Lack of awareness of disease
- Slowly progressive nature
- Considered a disease of affluence

There is no definitive laboratory test for diagnosis. To identify NAFLD, ultrasound is more commonly used as it is economical and often easily available. On USG, fatty liver is seen as bright liver with echogenicity of liver more than the right kidney[7&8]. Overall, USG has the sensitivity of 60-94% and specificity of 84-95% for detecting fat, but combined fat and fibrosis can show the hyperechoic liver in up to 98.7% of the patients, known as "fatty fibrotic pattern"

FIBROSIS STAGING
STAGE 1-Pericellular fibrosis, perivenular areas, focal or extensive.
STAGE 2; As above, plus focal or extensive periportal fibrosis
STAGE 3- Bridging fibrosis, focal or extensive
STAGE 4- Cirrhosis

Fibroscan also provide important information, but availability and cost limit its use.

NAFLD is recognised as the hepatic component of metabolic syndrome, as this has insulin resistance as common pathophysiological mechanism. The overall prevalence of NAFLD in people with Type 2 DM is believed to be much higher than general population.

As lifestyle has become increasingly sedentary and dietary pattern have changed, the worldwide prevalence of NAFLD and DM T2 with dyslipidaemia has increased dramatically and projected to be the principal aetiology for liver disorder[9].

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Till now there is no clear-cut evidence and cut-offs that at what levels of HBA1c the NAFLD occur and progresses. So, this study correlates the
levels of HBA1C with NAFLD in Type 2 DM patients.

Definition –
NAFLD is the spectrum of progressive liver disease that encompasses simple steatosis; NASH [Non-Alcoholic Steatosis Hepatitis], fibrosis and ultimately cirrhosis and liver failure. In NAFLD, excess amount of fat is not the result of excessive alcohol consumption.
Fatty liver: Defined as more than 5% of hepatocytes containing fat or more than 5% of liver weight due to fat.
NASH: It is major clinical consideration with deranged liver function and negative viral markers.
Hepatocellular injury: Three histologic features are recognised as representing hepatocellular injury death:

1. Ballooning degeneration
2. Acidophil bodies
3. Spotty necrosis

NAFLD associated cirrhosis:
Clinical, biochemical, imaging and endoscopic evidence of liver cirrhosis. Presence of at least two factors of metabolic syndrome. Exclusion of other known etiologies of liver cirrhosis. Alcohol consumption <20g/dl in men and <10g/dl in women[10]. Exclusion of HBV AND HCV infection. Exclusion of Wilson's and autoimmune liver disease using appropriate tools.

2. MATERIALS AND METHODS:

Inclusion Criteria:
100 patients with type 2 diabetes mellitus are included in study, both genders (male & female), Age 25 - 70 years, only non-alcoholic patients included as per history and Investigations done. HBA1c of more than 6.5, FBS >126 mg/dI, PPBS>200 is included in study AND correlated with NAFLD.

Exclusion Criteria: Type 1 DM not included in study, Alcoholics, Non-Diabetics, Patients taking statins or other lipid lowering drugs, Pregnant and lactating mothers, HIV, Hepatitis B, C, D, critically ill patients, Patients with haemoglobin <10 mg/di because this may alter their actual HBA1c levels and Patient not willing to participate in study.

Methods of collection of data:
Detailed history and exclusion of alcoholics, the diagnosis of Diabetes Mellitus based on symptoms and blood investigations findings: BS: 126 mg/al, PPBS>200 mg/di and HBA1c of 6.5 and history of duration of diabetes is recorded. All the routine investigations (liver function test, fasting lipid profile, CBC, urine routine microscopy) were done. Ultrasonography to identify fatty liver with grading.

Statistical analysis: All the data analysis was performed using a trial version of IBM SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare the tables. Microsoft excel is used for making tables, graphs and other calculations. Categorical data

was expressed as percentage. Categorical variables were compared by chi-square test. P value of <0.05 is considered as significant and results were drawn.

Etiology –
1. Obesity
2. Diabetes Mellitus
3. Metabolic syndrome
4. Hyperlipidaemia
5. Bariatric surgery
6. Drugs- Amiodarone, Tamoxifen

Pathophysiology-
There is evidence of steatosis (>5% at the minimum), usually variable combinations of macrovesicular and microvesicular type. Hepatocellular damage is usually perivenular and depending on severity leads to lobular
collapse. Hepatocytes show ballooning and Mallory's hyaline (clumps and skeins of dense eosinophilic material within hepatocyte cytoplasm). Inflammatory infiltrate consists of neutrophils and lymphocytes, with the
former usually predominating (except in children, where lymphocytes may be predominant). Neutrophils are primarily parenchymal distribution, surrounding and infiltrating damaged hepatocytes. Lymphocytes occupy parenchymal and portal compartments. A Kupffer cell prominence may be noted. Increased numbers of glycogenated nuclei may also be seen.

Fibrosis is an integral component of NASH and is characteristically pericellular (Chicken-wire fibrosis). Fibrosis is brought out well with
Mason's trichrome stain.
Fibrosis may progress to cirrhosis, but this progression is most often slow. A bile ductular reaction may be present. Histologically, it may be
impossible to differentiate NASH from ASH.
The main histological changes include steatosis, hepatocellular damage, inflammation, and fibrosis.
SCORING SYSTEM FOR NASH
Necro-inflammatory grading for NASH
GRADE 1 (Mild) -Steatosis (mainly macrovascular) involving up to 66% of lobules;
occasional ballooned perivenular hepatocytes; scattered neutrophils with
or without lymphocytes; no or mild chronic portal inflammation.
GRADE 2 (Moderate)-Steatosis of any degree; obvious ballooning; intralobular neutrophils, perivenular pericellular fibrosis; mild to moderate portal and intralobular
chronic inflammation.
GRADE 3 (Severe)-Panlobular steatosis; prominent ballooning; and disarray; marked lobular inflammation, neutrophil and lymphocyte pattern similar to grade 2.

3. OBSRVATION AND RESULT:

Table1: Distribution of Fatty liver in Type 2 diabetes population

FATTY LIVER	FREQUENCY
PRESENT	54
ABSENT	46
TOTAL	100

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In the present study, out of 100 diabetic patients- fatty liver was found in 54. Thus, study was giving results as- The Prevalence of NAFLD in Type2 Diabetic Mellitus is 54%.

AGE DISTRIBUTION OF NAFLD IN PATIENTS: Mean age of the study cohort was 45 years which ranged from 25-70
wears. Majority of the patients were in the age group of 46-55 Years
48.14%) followed by 36-45 years (29.62%).

GENDER DISTRIBUTION IN PATIENTS OF NAFLD:
Male preponderance was observed in present study (63%). There were 37% female in present study cohort. Male to female ratio is found to be 1.7
CLINICAL PRESENTATION OF PATIENTS WITH NASH: Most of the diabetic patients who found to have NAFLD accidently were asymptomatic. Asymptomatic patients accounts 53% of the total. Followed by it was dyspepsia, which was further followed by anorexia, generalised weakness, recurrent constipation & functional abdominal pain of right upper quadrant discomfort.

DISTRIBUTION ACCORDING TO GRADES OF FATTY LIVER: In present study out of 54 patients, 34(62.9%) were in Grade I, 17(31.1%), in Grade Il and remaining 3(5.5%) were in Grade Ill & IV. As the disease is merely slowly progressive, maximum patients were found to be in initial grade.

TABLE 2: COMPARING HBA1c WITH NAFLD

HBA1C Range Diabetes with NAFLD	HBA1C Total without NAFLD	P Value
6.57.4 6(11.1)	20(43.4) 26	
7.58.4 12(22.2)	12(26.0) 24	
8.59.4 15(27.7)	08(17.3) 23	
>9.5 21(38.8)	06(13.4) 27	
Total 54 (100)	46(100) 100	<0.05

ELEVATION OF LIVER ENZYMES:
SGPT or ALT is released in blood stream as a result of liver cell injury due to ongoing inflammation of hepatocytes. Normal range is 7-56 UM. It is more specific for liver than SGOT or AST- which is elevated in myocardial infarction and muscle injuries. Normal range is 5-40 U/L. In the study sample it is observed that SGPT is raised more than SGOT. It was mainly found raised in Grade IlI and IV fatty liver. In Grade Ill Fatty liver the values of liver enzymes are in the higher side of normal range. While Grade I fatty liver is not associated with elevation of liver enzymes.

4. DISCUSSION:

NAFLD is becoming a major public health problem due to rising prevalence of obesity and DNIT2 worldwide? The common predisposing factors are diabetes, obesity and dyslipidaemia. As Lifestyle have become increasingly sedentary, and dietary patterns have changed, they contributed in dramatic rise of prevalence of NAFLD worldwide[11].

This study thus, tried the best to throw the light in the disease status in diabetic population and also tried to establish correlation with HBA1c levels. Insulin resistance is often a primary abnormality in patients with NAFLD, there is often a genetic predisposition to insulin resistance, even in the absence of frank diabetes[12]. The relationship between NAFLD and Diabetes, however is complex and bidirectional. NAFLD has been merely recognised as the hepatic manifestation of metabolic syndrome, as these condition share insulin resistance as the common pathophysiological mechanism[13]. IV has been postulated that insulin resistance is the central pathophysiologic defect in Metabolic Syndrome, Obesity is directly related to insulin (psistance and adipocytes produce numerous circulating inflammatory markers including pro- and anti-inflammatory factors, chemokines, growth factors, and proteases that induce a systematic low-grade inflammatory state and insulin resistance. Moreover, the association of NAFLD with diabetes remained statistically significant even after adjusting for age, gender and waist circumference[14]. In addition, presence of the metabolic syndrome predicts higher risk for the development of NAFLD in both men and women. it is clear that insulin resistance and visceral adiposity, the two main drivers of metabolic syndromes, plays a major role[15]. These two factors can lead to increased energy input to the liver and reduced rates of output, through inhibition of the enzymes PPAR-A, PPAR-G and SREBP1. This sets the stage for fat accumulation in the liver and subsequent chain of events.
Once NAFLD developed, DMT2 has the potential to promote the progression to NASH, cirrhosis and in some patients HCC[16]. On investigation, ultrasound should be the initial investigation of choice for detecting hepatic steatosis. Liver biopsy remains the gold standard in detecting and grading necro-inflammation and staging hepatic fibrosis. In this study after being reported the prevalence of NAFLD in diabetic population was 54%. The next we correlated NAFLD with HBA1c[17].
We have used USG in diagnosis of NAFLD other diagnostic approaches include the following:

1. Non-invasive biological markers for liver fibrosis in NAFLD. Using varying combination of indirect markers following scoring systems are made:

a. NASH test
b. Fibro Test
c. Steato Test

2. Invasive procedure - Liver biopsy -the Gold standard
3. Role of imaging- Ultrasound, Fibroscan , contrast USG, computed tomography, Magnetic resonance Imaging, MRS (MR Spectroscopy)

FIBRO TEST

Fibro test scores from 0 to 1 is a validated marker to quantitate extent of fibrosis in most common etiologies of chronic liver disease. Ratziu et al. Found encouraging results using fibro test for diagnosis of advanced fibrosis in NAFLD. In a meta-analysis it was shown that in NAFLD patients a mean standardized AUROC for advanced fibrosis was 0.84 (95% CI, 0.76-0.92). Moreover, the AUROC for the diagnosis of the intermediate adjacent stages F2 vs F1 did not differ from that of the extreme stages F3 vs F4 or F1 vs FO.

Table3: Conversion between Fibro Test Score and Fibrosis Stages Based on METAVIR Scoring System

Fibro test	Fibrosis stage estimate
0.75-1.00	F4
0.73-0.74	F3-F4

0.59-0.72	F3
0.49-0.58	F2
0.32-0.48	F1-F2
0.28-0.31	F1
0.22-0.27	F0-F1
0.00-0.21	F0

NAFLD fibrosis score- The NAFLD fibrosis score consists of six variables, namely age, BMI, AST/ALT ratio, hyperglycaemia, platelet punt, and albumin. In a multicentre trial consisting of 45O patients in the derivation cohort and 253 patients in the validation cohort, a low cut-off (<1.455) signified the absence of advanced fibrosis and a high cut-off (>0.676) indicated presence of advanced fibrosis.

5. CONCLUSION:

The present study concludes that prevalence of NAFLD in DM is 54%. NAFLD is found more in males than females with ratio of 1.7. Most common age of presentation is 45 to 55 years and mostly asymptomatic followed by dyspepsia. NAFLD is now considered as liver manifestation of metabolic syndrome. Liver is a major site of insulin resistance. NAFLD is associated with and responsible for poor glycaemic control (higher HBA1c levels) in diabetic patients The findings of fatty liver, even in a asymptomatic patients should prompt a thorough research for components of metabolic syndrome, and patients should advised regarding CVD risks, weight loss, smoking cessation, dietary modification, exercises and pharmacological therapies.

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