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ORIGINAL PAPER

A clinical study of non-alcoholic Fatty Liver disease in Type 2 Diabetes Mellitus

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ABSTRACT

***Background**: Non-alcoholic fatty liver disease (NAFLD) is no longer considered a benign condition and has been identified as a common cause of chronic liver disease globally. **Methods**: This study was done on 199 cases of Type 2 Diabetes Mellitus with proper history, thorough clinical examination, including exact height, weight with relevant investigations. **Results:** The prevalence was 65.8%. Evidence of NAFLD was noted in 59.15% of male and 82.45% of female. Most of the cases were asymptomatic and hepatomegaly was the only commonest physical sign. 83.47% participants with high BMI were found to have NAFLD. The mean of fasting, post-prandial glucose levels and that of HbA_1C in NAFLD, were significantly higher as compared to that with normal liver. The mean AST, ALT and ALKP levels were significantly higher as compared to the normal liver group. The ratio between AST and ALT was found to be 0.96. The mean of the total cholesterol, triglycerides and LDL were found significantly higher in the group with NAFLD, while difference in the mean value of HDL in both the groups were insignificant. **Conclusion:** NAFLD is more frequently encountered in poorly controlled Diabetes Mellitus, more so in presence of obesity and/or dyslipidaemia.*

***Keywords**: Non-alcoholic fatty liver disease, hepatic steatosis, transaminases, Hyperlipidamia*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a disease practically unheard of 3 decades ago, is now considered as one of the most common causes of chronic liver disease in industrialized world.[1] The definition of NAFLD requires that a) there is evidence of hepatic steatosis either by imaging or histology, and b) there are no causes for secondary hepatic fat accumulation such as alcohol consumption, use of steatogenic medication, infection and hereditary disorders. In the majority of patients, NAFLD is associated with metabolic risk facors such as obesity, diabetes mellitus and dyslipidaemia.

The prevalence of NAFLD in the section of the people having Type 2 Diabetes Mellitus is found to be higher than that in the general population with a maximum of 87% of the Type 2 Diabetics reported to have NAFLD.[2] It is also interesting to note that female subjects with Type 2 Diabetes Mellitus are more prone to develop NAFLD than their male counterparts although the overall prevalence of Type 2 Diabetes Mellitus in males are far more as compared to the females.[3] Middle aged people, from 4^{th} to 6^{th} decades of life are seen to be affected by NAFLD, with a mean age of around 50-55 years.[4] Most of the patients of NAFLD are asymptomatic while some may present with generalized weakness or right upper quadrant discomfort/ pain of abdomen.[4,5]

Hepatomegaly is the most common finding on clinical examination as well as ultrasonography of the abdomen, in initial presentation.[4,5,6] Body Mass Index (BMI) is directly related to the development of NAFLD, so much so that it has been identified as an independent risk factor for development of NAFLD.[4,5]

Higher values of plasma glucose levels and Glycosylated haemoglobin (HbA_1C) in patients of Type 2 Diabetes Mellitus are associated with increased incidence of NAFLD as compared to the lower values of the same.[3,5]

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Asymptomatic mild elevation of serum transaminases, with the ratio of AST: ALT being usually less than 1, is sometimes seen though there is no concrete correlation between elevation of serum transaminases and development of NAFLD.[7] Hyperlipidaemia (hypertriglyceridaemia, hypercholesterolaemia or both) is another common abnormality noted in patients with NAFLD.[8,9]

Objectives: To study the prevalence and clinical presentations of NAFLD in persons with Type 2 Diabetes Mellitus and to assess its relationship to the Body Mass Index of the patient with correlation of the results of Liver Function Tests and Fasting Lipid Profile with ultrasonographic evidence of Fatty liver in these subjects.

METHODS

This observational descriptive study was conducted in Gauhati Medical College and Hospital, Guwahati from 1st August, 2014 to 31st July, 2015 with 199 participants of Type 2 Diabetes Mellitus with investigation of Complete Blood Count, Blood Sugar estimation (Random, Fasting and Post-prandial), Glycosylated Haemoglobin (HbA_1C), Creatinine and Blood Urea, Liver Function Tests, Urine R/E, Fasting Lipid Profile, HBsAg, Anti HCV, Anti HAV IgM, Anti HEV IgM, ultrasonography of whole abdomen, etc.

Inclusion Criteria: The patients included in this study were all diagnosed to have Type 2 Diabetes Mellitus (as per WHO criteria) belonging to both sexes and who were more than 18 years of age, presenting to the Out Patient Departments, with due consent.

Exclusion Criteria: Patients with history of alcohol consumption, jaundice, ascites or with history of suspected drug induced liver injury (DILI), major abdominal surgery, Chronic Renal Failure or severe ischaemic Heart disease and positive cases of Hepatitis B, Hepatitis C, Hepatitis A and Hepatitis E serology were excluded.

RESULTS

131 (65.83%) were detected to have hepatic steatosis or fatty liver on ultrasonography and were labeled as the '**NAFLD Group**' while 68 persons (34.17%) were found to have no hepatic steatosis and hence labeled as '**Normal Liver Group**'. Males out-numbered females in this study, but it was interesting to note that out of female Type 2 diabetics, the percentage of patients detected to be having NAFLD (82.46%) is much higher than that in males (59.15%) which is statistically significant (**Table 1**).

Table 1 Sex-wise distribution of prevalence of NAFLD

Group	Males (Total-142)	Females (Total-57)	Total Cases
NAFLD	84 (59.15%)	47 (82.46%)	131 (65.83%)
Normal liver	58 (17.55%)	10 (17.54%)	68 (34.17%)

The age of the participants of this study group varied from 26 to 90 years, the mean age being 54.37 ± 13 years.The age of more than half of the patients of the present study group, having NAFLD, ranged between 46 to 65 years (**Table 2**).

Table 2 Age-wise prevalence of NAFLD in Type 2 Diabetes Mellitus

Age group	Total Cases (199)	NAFLD (131)	Normal Liver (68)
26-35 years	16	6 (4.58%)	10 (14.70%)
36-45 years	41	33 (25.19%)	8 (11.76%)
46-55 years	51	36 (27.48%)	15 (22.06%)
56-65 years	54	40 (30.53%)	14 (20.59%)
>65 years	37	16 (12.21%)	21 (30.89%)

Of the patients diagnosed to have fatty liver, more than 50 percent (69 out of 131) were asymptomatic while about a quarter of patients (29.77%) had complaints of general weakness and malaise and while only 17.55% of subjects complained of abdominal discomfort or pain.

Signs of NAFLD in Type 2 Diabetes Mellitus are shown in **Table 3**.

Table 3 Presenting signs of NAFLD in Type 2 Diabetes Mellitus

Parameters (Total Cases 199)	NAFLD (131 Cases)	Normal Liver (68 Cases)
Hepatomegaly (≤ 15 cm)	92 (70.23 %)	7 (10.29 %)
Normal Size (d" 15 cm)	39 (29.77%)	61 (89.71%)
Mean Liver size	17.12± 3.53 cm	12.19± 1.94 cm

The Body Mass Index (BMI) varied from 17.4 to 30.1 kg/m^2 with a mean of 25.18 kg/m^2. The mean BMI of the patients in NAFLD group was calculated to be 26 ±1.67 kg/m^2 and in the normal group, it was found to be 23.58± 2.48 kg/m^2. A BMI of 25kg/m^2 was taken as the cut off between overweight and normal weight and 121 persons of the study group were found to be above while 78 were below the cutoff mark. Out of 121 patients in the overweight group, 101 (77.1%) had ultrasonographically detectable fatty liver, while a statistically significant number of only 30 patients (22.9%) had evidence of fatty liver in the normal weight group (**Table 4**).

Table 4 Comparison of BMI of patients with or without NAFLD

BMI group (Kg/m2)	NAFLD group (131 Cases)	Normal Liver group (68 Cases)
Normal weight (<25)	30 (22.9%)	48 (70.59%)
Overweight (≥25)	101 (77.1 %)	20 (29.41 %)
Mean BMI	26± 1.67 kg/m2	23.58 ± 2.48 kg/m2

The glycaemic status of the participants in the study group was evaluated in terms of fasting and post-prandial blood sugars alongwith estimation of glycosylated haemoglobin (HbA_1C) levels and statistically significant difference ($p<0.05$) was observed in the mean values of the parameters in both the groups of diabetic patients with or without NAFLD.

Table 5 Glycaemic status in patients with or without NAFLD

Parameters (Mean value)	NAFLD group	Normal Liver group
Fasting Blood Sugar	156.03±27.72 mg/dl	135.61±31.97 mg/dl
Post-prandial Blood Sugar	212.88±35.16 mg/dl	188.88±18.14 mg/dl
Glycosylated Haemoglobin (HbA_1C)	7.61±0.74 NGSP	6.73±0.34 NGSP

Liver function tests done included the Serum Transaminases, Alkaline Phophatase, Serum Total Bilirubin, Total Protein and Serum Albumin. Statistically significant difference in the mean levels of Aspartate Transaminase (AST), Alanine Transaminase (ALT), and Alkaline Phosphatase (ALKP) were noted between the group of diabetics with NAFLD and the group without it (**Table 6**).

Table 6 Mean levels of liver enzymes in patients of both groups

Liver enzyme	NAFLD group	Normal Liver group
Mean AST level (IU/L)	49.29± 11.52	28.5± 7.93
Mean ALT level (IU/L)	51.29± 10.73	33.54± 8.98
Mean ALKP level (IU/L)	151.50± 43.35	128.30± 25.73

Out of the 131 patients with NAFLD in this study group, it was observed that 85 (64.89%) had elevation of both AST and ALT levels, with approximately equal prevalence in both the sexes ; however isolated elevations in ALT were frequently noted in females (21.28%) and isolated elevations of AST were more marked in the male subjects (22.62%)(Table. 7). The AST/ALT ratio was 0.96 in this study.

Table 7 Pattern of elevation of aminotransferase in both sexes

Aminotransferase	NAFLD (131)	Male (84)	Female (47)
Isolated AST elevation	26 (19.85%)	19 (22.62%)	7 (14.89%)
Isolated ALT elevation	20 (15.27%)	10 (11.9%)	10 (21.28%)
Elevation of both AST & ALT	85 (64.89%)	55 (65.48%)	30 (63.83%)

No statistically significant difference in the mean levels of both serum total Bilirubin and serum total protein were noted in the two groups of diabetic patients, one with evidence of NAFLD and the other without it (**Table 8**).

Table 8 Mean total bilirubin and protein levels in both the groups

Parameter	NAFLD	Normal
Mean serum Total Bilirubin (mg/dl)	1.2 ± 0.23	1.0 ± 0.17
Mean serum Total Protein (gm/dl)	7.07 ± 0.31	6.97 ± 0.19

The fasting lipid profile in both the groups of patients showed statistically significant difference ($p<0.05$) in the mean levels of serum cholesterol, serum triglyceride and serum low-density lipoprotein (LDL) between the group of Type 2 Diabetics with NAFLD and that without NAFLD, while no significant difference was noted in respect of the mean levels of serum high-density lipoprotein (HDL) (**Table 9**).

Table 9 Mean levels of fasting lipid profile in both the groups

Mean levels of fasting lipids	NAFLD group (mg/dl)	Normal Liver Group (mg/dl)	p value
Cholesterol	210.52±31.51	187.08±16.87	< 0.05
Triglyceride	210.57±85.02	166.98±51.37	< 0.05
LDL	120.93±29.58	94.88±12.48	< 0.05
HDL	48.42±10.29	50.14±7.71	> 0.05

Subjects showing elevated levels of components of fasting lipid profile in both groups are shown in **Table 10**.

Table 10 Distribution of elevated values of components of fasting lipid profile in both groups

Group of patient	Total Cholesterol (>200mg/dl)	Triglyceride (>150 mg/dl	LDL (>100mg/dl)	HDL (> 50mg/dl)
NAFLD(n=131)	91 (69.47%)	77 (58.78%)	75 (57.25%)	57 (43.51%)
Normal(n=68)	26 (38.24%)	28 (41.18%)	28 (41.18%)	40 (58.82%)
Total (n= 199)	117 (58.80%)	105 (52.77%)	103 (51.76%)	97 (48.74%)

('n' indicates total number of cases in the group and percentage is calculated against "n" of each group.)

DISCUSSION

The more number of males over the female were possibly due to the fact that Type 2 Diabetes Mellitus is more common in males and that more male patients came for routine evaluation of health.The prevalence of NAFLD amongst the diabetics have been found to be 65.83 %. Similar reports of high prevalence of fatty liver in Diabetes have been reported from different parts of the world.[1,3,4,10]

In the female type 2 diabetics, the prevalence of fatty liver was higher than that in the males and the female to male ratio was 1.4:1. Female sex have been reported to have a higher predisposition to the development of fatty liver in the general population, and the same has also been found amongst the diabetics.[3,5]

The middle aged people are seen to be more affected by this entity. Maximum number of cases presented in the age range between 56 to 65 years followed by those in 46 to 55 years.[4]

As most of the patients of NAFLD present without any specific symptoms, fatty liver is detected only on clinical examination or on ultrasonographic examination. Some patients may have minor symptoms like generalized weakness, upper abdominal discomfort or pain.[4,5]As the symptoms are trivial, awareness about this entity is important not only for diabetics, but also for the general population.

The only clinical sign of significance in non-alcoholic fatty liver disease is hepatomegaly, which is mostly asymptomatic and it was detected in about 70% of the subjects having evidence of NAFLD in our study. The rest had ultrasonographic evidence of hepatic steatosis without enlargement of liver. None of the patients included in our study had evidence of splenomegaly or

ascites. Statistically significant difference was noted on comparison of the mean liver size in the NAFLD group and the normal liver group.[4, 5]

The mean Body Mass Index (BMI) was found to be significantly higher in the NAFLD group than that in the normal liver group. Amongst the whole study population, 121 had a BMI of more than 25 kg/m^2 irrespective of their hepatic status, 101 (83.5%) of whom were found to have NAFLD. The relationship between high BMI and prevalence of NAFLD, as seen in many studies worldwide, has prompted the identification of obesity as an independent risk factor for the development of NAFLD.[3, 4]

It has been noted in many earlier studies that poor glycaemic control is associated with higher incidence of NAFLD.[3,5] In our study also, it was observed that the levels of the fasting and the post-prandial blood sugar and that of the glycosylated hemoglobin were significantly higher in the NAFLD group than those in the normal liver group.

Statistically significant difference between the two groups, in the quantum of elevation of AST, ALT and Alkaline Phosphatase, in terms of their mean levels and also in terms of the number of persons showing enzyme elevation, was noted in this study. In the group with NAFLD, majority of the patients had elevation of both AST and ALT while isolated elevation of ALT was frequently noted in the female subjects and isolated AST elevation was seen more often in the males. Asymptomatic mild elevation of transaminases is one of the most commonly reported and studied abnormality in NAFLD.[11] Usually the ratio between AST and ALT is reported to be less than 1 and in our study also it was found to be 0.96. In a few major studies, the levels of ALT were noted to be higher than that of AST in case of NAFLD whereas the pattern is altered in case of alcoholic hepatitis. Although values <1 suggest NAFLD, a ratio of ≥ 2 is strongly suggestive of alcoholic liver disease.[11]

There was no significant difference in the levels of total bilirubin and total protein between the two groups which were similar to the studies done elsewhere.

Fasting lipid profile estimation in the patients showed statistically significant higher values of total cholesterol, triglyceride and LDL in terms of both i) the number of patients showing elevation of the values more than the upper limit of normal and ii) and the mean values of the individual parameters, in the NAFLD group as compared to the normal liver group. Hyperlipidaemia (hypertriglyceridaemia, hypercholesterolemia or both) is a common abnormality and has been reported in 20% to 81% of patients with NAFLD.[8] Dyslipidaemia was present in 65% of cases of NAFLD at the Virginia NAFLD Clinic.[9] Hyperlipidaemia, specifically hypertriglyceridaemia, has been strongly correlated with liver fat accumulation and has been postulated as an independent risk factor for development of NAFLD.[12]

A significant proportion of patients previously thought to have 'Cryptogenic Cirrhosis' share many of the clinical and demographic features of NAFLD, suggesting that the etiology of their cirrhosis may be unrecognized NAFLD.[13] Outcomes of NAFLD are different in different groups and various studies, that looked at the outcome of people with Type 2 Diabetes with NAFLD, report a more aggressive form of disease and grave outcome.

CONCLUSION

The present study concludes that NAFLD is commonly associated with type 2 diabetes mellitus, particularly in those who are overweight, and is also associated with dyslipidaemia and poor glycaemic control, even though the patient may not have any specific signs or symptoms. Asymptomatic elevation of liver enzymes, and particularly when the ratio between AST and ALT is less than one, may be an useful non-invasive indicator of liver dysfunction in the form of NAFLD. It is, therefore, crucial that the modifiable factors such as weight, dyslipidaemia and hyperglycaemia be adequately controlled to prevent further liver dysfunction. It is of immense importance to educate the patients as well as the general public about these seemingly innocuous factors so as to ensure earlier presentation, diagnosis and management of NAFLD and to prevent its progression further.

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