

Prevalence of Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus

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Abstract

Objectives : Nonalcoholic fatty liver disease (NAFLD) is commonly associated with type 2 diabetes mellitus (DM) though its prevalence is not well studied. We conducted a prospective study of prevalence and risk factors of NAFLD in patients with type 2 diabetes.

Research Design and Methods : 204 type 2 DM patients attending an out-patient diabetic clinic underwent abdominal sonography. Ninety of 127 patients with fatty infiltration on ultrasound consented for liver biopsy, clinical and biochemical workup.

Results : Eighty seven percent had NAFLD on histology with 62.6% steatohepatitis and 37.3% fibrosis. Age, duration of diabetes mellitus, degree of glycemic control, body mass index, waist circumference, family history of diabetes mellitus, did not predict the presence or severity of NAFLD or fibrosis. Serum alanine aminotransferase (ALT) and alkaline phosphatase levels, though within normal limits, were significantly higher in patients with steatohepatitis. Prevalence of NASH increased with increase in the components of the metabolic syndrome. Serum AST/ALT ratio were also significantly higher ($p=0.049$) in patients with severe fibrosis. All patients with severe fibrosis had metabolic syndrome.

Conclusions : Prevalence of NAFLD and NASH in our cohort of type 2 DM patients is high and increases with multiple components of metabolic syndrome. NASH and advanced fibrosis can occur in diabetic patients without any symptoms, signs or routine laboratory test abnormalities. ©

Introduction

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of conditions characterized histologically by macrovesicular hepatic steatosis and occurs in those who do not consume alcohol in amounts generally considered to be harmful to the liver.¹ NAFLD includes both nonalcoholic fatty liver, and non-alcoholic steatohepatitis (NASH), with or without varying degrees of fibrosis and cirrhosis.¹ Cross-sectional studies in patients with NASH have shown that 30-40% of patients have advanced liver fibrosis at the time of presentation, whereas 10-15% have established cirrhosis.¹⁻³ Progression of liver fibrosis has been demonstrated in a third of patients with NASH,² with a proportion of patients progressing to end stage liver disease and hepatocellular carcinoma.^{2,4-6}

The incidence of type 2 DM is increasing throughout the world, reaching levels of a pandemic in countries like India and China.⁷ Only recently has liver disease been recognized as a major complication of type 2 DM with standard mortality rates for cirrhosis greater than that for cardiovascular disease.^{8,9} Insulin resistance (IR) plays the central pathogenetic role in both

type 2 DM and NAFLD with the latter being considered as the hepatic manifestation of the metabolic syndrome.¹⁰

Though the prevalence of liver enzyme abnormalities in patients with type 2 DM ranges from 7.8% to 22.9%,¹¹ the prevalence of NASH in these patients largely remains unknown, as it is generally an asymptomatic disorder, with liver biopsy being the only means of its detection, which would not be routinely done unless indicated. We conducted a prospective study to find out the prevalence of NAFLD and in particular NASH in patients with type 2 DM and find the risk factors predicting the same.

Material and Methods

The cohort for the study was selected from all patients with type 2 diabetes mellitus diagnosed by standard criteria between ages 20 and 70 years who attended the diabetic clinic of a tertiary referral center in India, between April 2003 and March 2005. Exclusion criteria were 1) any quantity of alcohol consumption based on careful history, 2) usage of drugs known to cause steatosis including amiodarone, corticosteroids, tamoxifen, methotrexate and high dose estrogen, 3) significant co-morbidities precluding a liver biopsy, and 4) history of jejunioileal bypass or extensive small bowel resection.

Of 1800 type 2 diabetes mellitus patients following up in the diabetic clinic, 204 randomly selected patients underwent a sonography of the liver. One hundred twenty-seven (62.25%) of these had fatty infiltration of whom 90 consented for a liver biopsy. These patients were subjected to a detailed history and physical examination with emphasis on symptoms of liver

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disease, duration of diabetes, family history of diabetes mellitus and other cause of liver disease.

Biochemical analysis

Levels of glycosylated hemoglobin (HbA1C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, serum albumin, platelet count, prothrombin time (PT), total cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides were measured using standard techniques from fasting samples of these patients. LDL cholesterol levels were calculated using the Friedewald's formula.¹² Serological markers of viral (HBsAg and HCV antibodies) and autoimmune hepatitis (antinuclear antibody, antimitochondrial antibody and anti-smooth muscle antibody) were estimated. Liver biopsy was performed with an 18G liver biopsy gun (Microvasive, Boston Scientific Corporation, MA, USA) under local anesthesia using a subcostal approach.

The grading and staging of all biopsy specimens were determined based on the method proposed by Brunt et al¹³ by a single hepatopathologist. Institutional ethics committee permission was obtained and informed written consent was obtained from all the patients included in the study.

Overweight was defined as a body mass index (BMI) between 23 and 25 kg/m², and obesity as BMI equal or above 25 kg/m².¹⁴ Patients were considered centrally obese if the waist circumference was greater than 80 cm in females and 90 cm in males.¹⁵ Patients with one of the criteria: LDL-C \geq 100 mg/dL, total cholesterol \geq 200 mg/dL, triglycerides \geq 150 mg/dL, or HDL-C < 40 mg/dL in males and <50 mg/dL in females were considered to have dyslipidemia.¹⁶ Metabolic syndrome was defined according to guidelines of IDF.¹⁵

Histology

Of the 90 patients who underwent the liver biopsy, seven were excluded from further analysis for various reasons (inadequate biopsy specimens in three, HBsAg positivity in two, Anti HCV positivity in one and biopsy showing granulomatous hepatitis in one). Although 29 were positive for ANA and 2 for ASMA, they were included in the study as none had features of autoimmune hepatitis on liver biopsy. Amongst 83 patients [28 males (M) and 55 females (F)] included in the final analysis, the mean age was 54.30 (SD-8.68, Range-33-70) years and the mean duration of diabetes was 8.17 (SD-6.16, Range-0.4-30) years. 50 (60.2%)

patients were hypertensive and 67 (80.72%- 18M & 49F) were overweight or obese with the mean BMI being 26.42 (SD 3.70) kg/m². 84.3% (64.2 % M and 94.5% F) were centrally obese. Dyslipidemia was documented in 84 % (69 out of 82) and low HDL was the most common abnormality (47 out of 82). Seventeen percent (14 of 82) had all lipid fractions abnormal. 88% of the patients were on Metformin. 73.5% of the patients including 67.8% of males and 87.3% of females satisfied the criteria for metabolic syndrome.

Results

Liver Histology (Table 1)

Eighty seven percent (72 out of 83) of patients had NAFLD on histology with 52 (62.6%) patients having steatohepatitis and 31(37.3%) having fibrosis. Of these 4 (6%) patients had severe fibrosis (Stage 3 or 4). Two patients had fibrosis (1 with advanced fibrosis) without any features of steatohepatitis on histopathology.

Comparison of anthropometric and biochemical variables between patients with and without NASH (Table 2).

Age, duration of diabetes, presence of hypertension, family history of diabetes mellitus, body mass index, waist circumference, treatment with Metformin, and prevalence of metabolic syndrome were similar between patients with and without NASH. All six patients had ALT greater than normal had NASH. Serum ALT and alkaline phosphatase levels though within normal limits, were significantly higher ($p=0.046$ between grade 1 NASH and normal biopsy group, $p=0.029$ between grade 2 NASH and normal biopsy group for ALT and $p=0.024$ between grade 1 NASH and normal biopsy group, $p=0.020$ between grade 2 NASH and normal biopsy group for alkaline phosphatase) in patients with steatohepatitis compared to normal biopsy group (not shown in table).

Comparison of anthropometric and biochemical variables between patients with and without fibrosis (Table 3)

Serum HDL cholesterol levels were significantly lower in patients with fibrosis. All patients with severe fibrosis ($n=5$) had the metabolic syndrome. Serum AST/ALT ratio were also significantly higher ($p=0.049$) in patients with severe fibrosis. (not shown in table).

Table 1 : Histopathological Findings in Study Group

Histopathology		Male (%) N=28	Female (%) N=55	Total (%) N=83
Grade	Normal	3 (10.7%)	8 (14.5%)	11 (13.3%)
	Steatosis Grade 1	5 (17.9%)	10 (18.2%)	15 (18.1%)
	Steatosis Grade 2	0	4 (7.3%)	4 (4.8%)
	Steatosis Grade 3	0	1 (1.8%)	1 (1.2%)
	NASH Grade 1	13 (46.4%)	25 (45.5%)	38 (45.8%)
	NASH Grade 2	7 (25%)	7 (12.7%)	14 (16.9%)
	NASH Grade 3	0	0	0
Stage	Nil	16 (57.1%)	36 (65.5%)	52 (62.7%)
	Stage 1 Fibrosis	11 (39.3%)	14(25.5%)	25 (30.1%)
	Stage 2 Fibrosis	0	1 (1.8%)	1 (1.2%)
	Stage 3 Fibrosis	0	4 (7.3%)	4 (4.8%)
	Stage 4 Fibrosis	1 (3.6%)	0	1 (1.2%)

Table 2 : Anthropometric and Biochemical Variables in Patients with and without NASH

		No NASH (n=31) M ± SD or %	NASH (n=52) M ± SD or %	P Value
History and	Age (in years)	54.52 ± 7.94	54.17 ± 9.16	0.863
Anthropometry	Duration of DM (in years)	9.31 ± 5.96	7.50 ± 6.24	0.197
	Hypertension	67.7 %	55.8 %	0.281
	Family h/o DM	41.9 %	30.8 %	0.302
	BMI (Kg/m ²)	26.04 ± 3.48	26.64 ± 3.85	0.472
	Central Obesity	77.4%	88.46%	0.455
	Treatment with Metformin	83.9 %	90.4 %	0.378
	Biochemistry	HbA1c (%)	7.52 ± 1.69	7.69 ± 1.49
Albumin (g/dl)		4.02 ± 0.78	3.99 ± 0.98	0.901
AST (U/L)		25.56 ± 6.14	26.79 ± 9.56	0.535
ALT (U/L)		20.35 ± 6.89	23.72 ± 12.08	0.172
AST/ ALT		1.335 ± 0.362	1.278 ± 0.456	0.565
Alkaline Phosphates (U/L)		114.45 ± 38.60	131.88 ± 37.96	0.66
Platelet Count in lakh/cumm		2.95 ± 0.63	2.92 ± 0.90	0.894
T. Cholesterol (mg/dl)		183.97 ± 48.84	190.56 ± 44.02	0.530
Triglycerides (mg/dl)		147.37 ± 74.86	173.51 ± 68.84	0.111
HDL Cholesterol (mg/dl)		48.08 ± 8.27	46.15 ± 9.35	0.348
LDL Cholesterol (mg/dl)	106.41 ± 42.77	110.25 ± 41.56	0.690	
Metabolic Syndrome		77.4%	82.69%	0.726

Table 3 : Anthropometric and Biochemical Variables in Patients with and without fibrosis

		No Fibrosis (n=52) M ± SD or %	Fibrosis (n=31) M ± SD or %	P value
History and	Age (in years)	53.73 ± 8.59	55.26 ± 8.87	0.441
Anthropometry	Duration of DM (in years)	9.06 ± 59.4	6.69 ± 6.34	0.090
	Hypertension	59.6%	61.3%	0.880
	Family h/o DM	42.3%	22.6%	0.068
	BMI (Kg/m ²)	26.03 ± 3.86	27.07 ± 3.39	0.216
	Central Obesity	78.8%	90.32%	0.533
	Treatment with Metformin	84.6%	93.5%	0.227
	Biochemistry	HbA1c (%)	7.74 ± 1.77	7.43 ± 1.13
Albumin (g/dl)		4.08 ± 0.92	3.89 ± 0.87	0.408
AST (U/L)		25.94 ± 8.74	26.97 ± 8.10	0.596
ALT (U/L)		22.01 ± 10.49	23.27 ± 10.84	0.604
AST/ ALT		1.30 ± 0.42	1.29 ± 0.44	0.934
Alkaline Phosphates (U/L)		123.45 ± 34.85	127.09 ± 44.89	0.704
Platelet Count in lakh/cumm		2.91 ± 0.88	2.97 ± 0.67	0.714
T. Cholesterol (mg/dl)		185.50 ± 41.64	192.29 ± 52.20	0.518
Triglycerides (mg/dl)		164.39 ± 78.53	162.37 ± 60.50	0.903
HDL Cholesterol (mg/dl)		48.82 ± 9.18	43.69 ± 7.67	0.011
LDL Cholesterol (mg/dl)	103.80 ± 35.53	117.02 ± 50.02	0.16	
Metabolic Syndrome		75%	90.32%	0.254

Table 4 : Anthropometric and biochemical variables in patients with normal histology/steatosis/alone (Group 1) and those with steatosis with varying degrees of NASH with or without fibrosis (Group 2)

	(Group 1) (n=29) Normal + steatosis	(Group 2) (n=54) NASH +/- fibrosis	P Value
Age (in years)	54.6 ± 8.2	54.2 ± 9	0.82
Duration of DM (in years)	9.2 ± 5.4	9.3 ± 8	0.104
Hypertension	69 %	55 %	0.235
Family h/o of DM	41.38%	33.33%	0.478
BMI (Kg/m ²)	26.03 ± 3.6	26.5 ± 3.8	0.544
Central Obesity	96.55%	92.59%	0.534
Treatment with Metformin	82.76%	90.74%	0.31
HbA1C (%)	7.22 ± 2.2	7.4 ± 2.1	0.687
Albumin (g/dl)	4.03 ± 0.80	3.99 ± 0.96	0.896
AST (U/L)	23.3 ± 8.6	26.6 ± 10.1	0.142
ALT (U/L)	18.9 ± 8.5	23.3 ± 12.2	0.095
AST/ALT	1.22 ± 0.49	1.26 ± 0.48	0.727
Alkaline phosphatase (U/L)	103.21 ± 49.9	106.68 ± 62.29	0.743
Platelet count in lakh/cmm	2.94 ± 0.65	2.93 ± 0.89	0.96
T. Cholesterol (mg/dl)	183 ± 47.15	187.04 ± 51.7	0.766
Triglycerides (mg/dl)	147.3 ± 76.4	169.4 ± 71.7	0.195
HDL Cholesterol (mg/dl)	48.4 ± 8.5	45.3 ± 11	0.18
LDL Cholesterol (mg/dl)	105.9 ± 40.9	108.4 ± 44.8	0.797
Metabolic Syndrome	69%	74%	0.62

Risk factors for NASH (Table 4)

Patients were divided into 2 groups, group 1 with normal histopathology or steatosis alone vs. group 2 with steatosis and varying degrees of steatohepatitis with or without fibrosis. Factors of significance on univariate analysis like duration of diabetes, elevated triglyceride levels, low HDL, ALT levels and presence of hypertension were further studied on multivariate analysis which showed only ALT level to be an independent significant (p<0.05) factor. It was further noted that with every increment of ALT the risk of NASH went up by 4% (OR 1.04, 95% CI of OR 1.0-1.09).

Discussion

In our study we have examined asymptomatic diabetic patients attending a diabetes outpatient clinic to find out the prevalence of NAFLD. In this study, only patients with fatty liver on ultrasound were chosen for liver biopsy. This was done to increase the yield of NASH in the cohort of patients and to

justify the need of an invasive biopsy in a cohort of asymptomatic patients. However, it is reasonable to believe that at least a small proportion of patients with sonologically normal liver may still be having NAFLD, as it is known that specificity and sensitivity of sonography in identifying fatty liver is 93% and 89% only.¹⁷ As we did not have a histological diagnosis in patients who did not have fatty liver on sonography, the estimation of prevalence is at the most conservative. Thus, even if we assume that none of the other patients who did not undergo the liver biopsy had NASH or fibrosis, the prevalence of NASH in our cohort of type 2 DM patients is around 25% (52 out of 204) and the prevalence of fibrosis is 15% (31 out of 204) with advanced fibrosis in 1.9% (5 out of 204). In a similar small group of asymptomatic type 2 DM, in which 32 patients were biopsied, 49% of patients had NAFLD on histology, of which 87.5% were found to have NASH.¹⁸

The finding of fibrosis in NAFLD suggests more advanced and severe liver injury.³ The proportion of patients with fibrosis on histology associated with NAFLD ranges from 10 to 55%¹ but in those with NAFLD and type 2 DM it ranges from 22% to 75%.¹⁸⁻²¹ As the disease progresses, histological changes considered typical to suggest diagnosis of NAFLD may regress and eventually in the cirrhotic state may be conspicuous by its absence.²² Two of our patients had advanced fibrosis with no evidence of steatohepatitis on histology.

The hepatic transaminases are markers of liver injury and are expected to be increased in steatohepatitis. In NAFLD, ALT elevation is noted with AST/ALT >1, only in advanced stages.²⁰ In our study only 6 patients had ALT elevation above the upper limit of normal, all of whom had NASH. In the rest despite the presence of steatohepatitis, ALT levels were within the normal range. However, patients with NASH had significantly elevated ALT and alkaline phosphatase levels, though within the normal range, in comparison with those with normal histology. In a similar study, only 10 out of 32 patients with NAFLD and NASH had elevated ALT and there was no significant difference in mean ALT between patients with fatty liver and NASH.¹⁸ It is now clearly known that the whole spectrum of histological findings of fatty liver and NASH may exist without elevation of transaminases.²³

A growing body of evidence shows close relationship between NASH and components of metabolic syndrome. As insulin resistance is the central factor in NASH, the pathogenesis of NAFLD may have started long before the diagnosis of type 2 DM. The median duration of diabetes has been found to be larger in higher grades of NASH.¹⁸ Age has been found to be an independent risk factor for both NASH and fibrosis in some studies.^{20,24} In our study, mean age of the patients and the duration of diabetes were not significantly different between those with and without NASH.

Although initial studies emphasized that NASH occurred mostly in women, more recent studies have shown that NASH occurs with equal frequency in men,^{25,26} as is also seen in this study. The HbA1C levels were similar between the patients with and without NASH and those with and without fibrosis. Since NASH is a form of chronic liver disease, the effect of prolonged periods of poor glycemic control may need to be assessed, which cannot be inferred from a single HbA1C report.

Insulin sensitizers like metformin may have a protective role in prevention and progression of NASH.²⁷ As the non-metformin group was too small for comparison, the protective role of metformin in our study could not be substantiated.

Obesity and in particular central obesity has been described as one of the strongest risk factors for NAFLD and fibrosis, with NASH being prevalent in 18.5% of the obese patients.¹ In our study, the body mass index was not significantly different between patients with and without NASH or in those with and without fibrosis. The association of diabetes and obesity may pose an added risk. In a study among severely obese patients with diabetes, 100% were found to have at least mild steatosis, 15% had steatohepatitis and 19% had cirrhosis.²⁸ In our study, only 61.4% patients were obese with none having severe obesity as is commonly found in studies from the west. However 84.3% had truncal obesity that correlates with IR. 65.7% of these patients had NASH and 40% had fibrosis compared to 40% and 21.4% respectively in patients without truncal obesity.

Hypertension has also been reported frequently in patients with NAFLD^{29,30} but has not been found to be an independent risk factor as is also found in this study. Dyslipidemia has been reported in 20 to 92% of patients with NAFLD³ Elevated serum triglycerides and low HDL cholesterol are features of the metabolic syndrome.¹⁵ In our study, there was no significant difference among mean values of any lipid fraction between different severities of NASH or fibrosis except for a lower HDL levels in those patients with fibrosis. The high percentage of statin use in this cohort could have contributed to this. In the study by Gupte et al,¹⁸ the mean cholesterol was higher in patients with moderate NASH compared to those with mild NASH.

As most of the proposed risk factors of NAFLD are components of the metabolic syndrome, an attempt was made to correlate the presence and severity of NAFLD and fibrosis with the number of components of the metabolic syndrome in each patient. The prevalence of NASH increased from 54% to 83% when the components of the metabolic syndrome increased from 3 to 5 .It was also seen that severe fibrosis was present only in those who had the metabolic syndrome (3 or more components).

In different studies³⁰⁻³² of obese subjects undergoing bariatric surgery, the factors independently associated with NASH were male gender, insulin resistance, AST, and type 2 DM. On multivariate analysis only ALT was shown to be significantly associated with NASH in our group of patients with type 2 DM.

In various studies of NASH, the factors independently associated with fibrosis on histology were older age, obesity, diabetes, AST, ALT and AST: ALT ratio > 1 and presence of Mallory bodies.^{20,33,34} In our study, by logistic regression analysis, low serum HDL cholesterol was the only factor independently associated with the presence of fibrosis.

In conclusion, we found that the prevalence of NAFLD, NASH and fibrosis in our cohort of type 2 diabetes mellitus patients is high .It is evident from this study that NASH and advanced fibrosis can occur in diabetic patients without any symptoms, signs or laboratory abnormalities in their liver functions. Since advanced fibrosis is unlikely to regress spontaneously, these patients have the risk of progression to cirrhosis, hepatocellular carcinoma and liver cell failure. It is therefore important to identify type 2 diabetes patients who are at the highest risk. As is found in this study, the presence of multiple components of the metabolic syndrome, low HDL levels, AST/ALT ratio greater than 1 and ALT value greater than upper limit of normal are significant risk factors for development of fibrosis.

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ANNOUNCEMENT

The following members were awarded the
Fellowship of the Indian college of Physicians (FICP) at APICON 2009 Greater Noida.

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