Study for Prevalence of Non Alcoholic Steatohepatitis in High Risk Group

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ABSTRACT

BACKGROUND: Nonalcoholic fatty liver disease is an increasingly recognized condition that may progress to end-stage liver disease. These patients are at higher risk of developing cirrhosis, terminal liver failure and hepatocellular carcinoma.

OBJECTIVES: To study the presence of NASH in high risk group of patients and their correlation with NASH.

METHODS: 200 high risk non-alcoholic patients were selected from indoor patients and out patient department of Medicine, Guru Nanak Dev Hospital attached to Government Medical College, Amritsar during the year 2011-12. A diagnosis of NASH was made on the basis of symptoms and signs, supplemented with analysis of liver enzymes, ultrasonography abdomen. Liver biopsy was not done because all patients refused to give consent for it. Fatty liver on USG with raised AST and ALT were labelled as having NASH. FBS and lipid profile estimation, hepatitis B surface antigen and antibodies to hepatitis C virus were done in all of them.

RESULTS: The prevalence of NASH was found to be 22% (44 out of 200 patients) by ultrasonography with raised AST and ALT levels. It was significantly higher in patients with diabetes mellitus, dyslipidemia, central obesity, hypertension, females and in age group 46 - 60 years with their additive effect to each other.

CONCLUSION: The present study identifies the people at higher risk of developing NASH and offer future perspective to develop preventive strategy in them. JMS 2012;15(2):157-61

Key words: Fatty liver disease, NASH, NAFLD, lipid profile, HBSAg, metabolic syndrome

Nonalcoholic fatty liver disease is an increasingly recognized condition that may progress to end-stage liver disease. The pathological picture resembles that of alcohol-induced liver injury but it occurs in patients who do not use alcohol.¹

A variety of terms have been used to describe this entity, including fatty-liver hepatitis, non-alcoholic Laennec's disease,

diabetes hepatitis, alcohol-like liver disease and non-alcoholic steatohepatitis. Non-alcoholic fatty liver disease (NAFLD) is becoming the preferred term and it refers to a wide spectrum of liver damage ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis.²

The clinical implications of non-alcoholic fatty liver disease are derived mostly from its common occurrence in the general population and its potential to progress to cirrhosis and liver failure.²

NAFLD encompasses a broad spectrum of clinico-pathologic diseases ranging from hepatic steatosis without inflammation to nonalcoholic steatohepatitis (NASH) with

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lobular inflammation, Mallory hyaline and hepatocyte ballooning on liver biopsy. By definition, other causes of hepatic steatosis and steatohepatitis including alcohol, medications, genetic disorders or viral infections must be excluded. The pathogenesis of the inflammatory injury and fibrosis leading to NAFLD is poorly defined. NAFLD may start with hepatic steatosis and proceed to NASH and may ultimately progress to cirrhosis and end-stage liver disease.³ The estimated prevalence of NAFLD in the general adult population is 15% to 39% while the prevalence of NASH is estimated to be 2% to 3%.^{4,5} Although only 20 to 25% of subjects with NASH appear to develop progressive cirrhosis and end stage liver disease, there is concern that with the increase in obesity and type 2 diabetes mellitus, an increase in the prevalence and severity of NASH may occur.^{6,7}

Previous studies in adults with NASH have identified predictive risk factors including obesity, older age, hypertension and the insulin resistance syndrome.⁸

However, effects of race, gender, and timing of puberty, degree and duration of obesity, body composition and diet are unclear, since large scale population-based studies are lacking. In order to understand the pathophysiology and risk factors for NAFLD and NASH at younger ages, it is important to initiate population-based studies in this demographic group.⁹

The present study was undertaken to evaluate, 1) the prevalence of non-alcoholic steatohepatitis disease in high risk group, and 2) to correlate NASH with age, gender, obesity, diabetes mellitus, hyperlipidemia and metabolic syndrome.

Methods

This was a study of 200 high risk patients, selected from indoor patients and out patient department of Medicine, Guru Nanak Dev Hospital attached to Government Medical College, Amritsar during the year 2011-12. Out of 200 patients involved, 91 cases were males and 109 cases were females. This high risk group was defined as follows, one of any four, 1) H/o T2DM (FBS $\geq$ 126 mg% or HbA1c $>$ 6.5%)¹⁰, 2) Overweight (BMI $>$ 25 Kg/m²)¹¹, 3) Hyperlipidemia (S.TG $>$ 150 mg%)¹¹, 4) Fatty liver as diagnosed on USG Abdomen.¹² Those consuming alcohol $>$ 10 gm per day for any duration and patients with positive viral markers were excluded from the study. The patients amongst the high risk group were again subdivided in subgroups for further study, as follows.

Age group distribution in the study was $<$ 30 yrs-32, 31 to 45 yrs- 63, 46 to 60 yrs-74, $>$ 60 yr-31. Obesity 11 was present in 114 patients with BMI $>$ 30 Kg/m², 86 patients had BMI $<$ 30 Kg/m². Of these 78 patients had BMI 25-29.9 Kg/m² and 8 had BMI $<$ 25 Kg/m². Central obesity was present (waist circumference $\geq$ 90cm in male, $\geq$ 80 cm in female) 11 in 155 patients. 45 patients had no obesity (waist

circumference $<$ 90cm in male, $<$ 80 cm in female). Metabolic syndrome¹¹ was present in 10 patients and absent in 91 patients. Nine patients had hypertension 13 and 91 were non hypertensives.

Radiological features of steatosis graded by ultrasonography were as follows:

Mild	Minimal diffuse increase in hepatic echogenicity: normal visualization diaphragm and intrahepatic vessels borders.
Moderate	Moderate diffuse increase in hepatic echogenicity. Slightly impaired visualization of intrahepatic vessels and diaphragm.
Severe	Marked increase in echogenicity. Poor penetration of the posterior segment of the right lobe of liver. Poor or non visualization of the hepatic vessels and diaphragm

The same might be said of computed tomography, magnetic resonance imaging, and radionucleotide techniques, all of which have findings that are characteristic of hepatic steatosis. A diagnosis of NASH was made on the basis of symptoms and signs, supplemented with analysis of liver enzymes and ultrasonography abdomen. Clinical possibility of other types of liver disease in the patients (confirmed by appropriate investigations) were also excluded from the study. Abdominal ultrasound was done in all patients.

AST, ALT, FBS and lipid profile estimation was done. Fatty liver on USG with raised AST and ALT were diagnosed to have NASH. Observed data was compiled, tabulated and statistically analysed by appropriate methods.

Results

Total prevalence of NASH in our study was found to be 22%, which was significantly higher in age group of 46-60 yrs, BMI $>$ 30 kg/m², central obesity patients (25.8%), patients with metabolic syndrome (30.27%), DM (34.94%), HTN (26.6%). Mean AST value in NASH group was 81.55 IU/L while mean ALT value was 92.43 IU/L (Table 1-5).

Stages of steatosis as defined by USG were graded as no, mild, moderate and severe. To know its relation with various biochemical markers, they were compared between NASH & Non-NASH patients. Most of the Non-NASH patients had mild steatosis on USG while most NASH patients had severe steatosis as interpreted from the table-6.

Discussion

As there is increase in the incidence of diabetes mellitus, obesity and insulin resistance in India, hence it is logical to expect increase in the incidence of NAFLD in India.

In our study, prevalence of NASH was found to be 22%. In 200 high risk group of patients, 68% (136/200) had

TABLE 1. Clinical, biochemical and radiological features of the 2 groups

	Parameter	NASH (%)	Without NASH(%)	Chi square	p value
A. <u>Clinical features</u>					
Sex	Males	22	78%	0.03	0.86
	Females	22	78%		
Age (yrs)	<30	9.4	90.6	4.1	0.25
	31-45	25.4	74.6		
	46-60	25.7	74.3		
	>60	19.4	80.6		
BMI(kg/m ²)	25-29	15.38	84.62	4.22	0.04
	>30	28.07	71.93		
Central obesity	Present	25.8	74.2	5.25	0.04
	Absent	8.8	91.2		
B. <u>Biochemical features</u>					
Serum AST	<40	0	100	41.8	0.0001
	>40	36.9	63.1		
Serum ALT	<40	1	99	40	0.001
	>40	38	62		
C. <u>Radiological features</u>					
	Non steatosis	0	100	72	0.0001
	Mild steatosis	5.6	94.4		
	Moderate steatosis	39.2	60.3		
	Severe steatosis	0	0		

Hyperlipidemia was found to be one of the principal determinant of NASH

TABLE 2. Profile of hyperlipidemias in study group

Variable	Value (%)	Number of pts
Total cholesterol(mg)	>=200	87
	<200	113
Total LDL(mg)	>=130	71
	<130	129
Total HDL(mg)	<40	36
	>=40	164
Total TG(mg)	>=150	147
	<150	53

TABLE 3. Frequency of dyslipidemia in NASH patients (n=44)

Analyte	Abnormal	Normal
Total cholesterol frequency (%)	68.18	31.82
HDL-C frequency (%)	56.82	43.18
TG frequency (%)	72.73	27.27
LDL-C frequency (%)	65.91	34.09

evidence of NAFLD, while 22% (44/200) had NASH. These results are consistent with a study by Sanyal AJ¹⁴ *et al* and by Angulo P⁶ in which prevalence of NASH and NAFLD was found to be 15%-20% and 57%-74% respectively in high risk group patients.

This study showed that the prevalence of NASH was

TABLE 4. Mean values of lipid profile in NASH and Non-NASH patients

Variables	NASH	Non-NASH
Mean Serum total cholesterol (mg/dl)	259.27	191.03
Mean Serum triglyceride (mg/dl)	269.50	178.42
Mean Serum HDL (mg/dl)	41.98	46.62
Mean Serum LDL (mg/d)	143.0	100.4

TABLE 5. Comparison between abnormal component of lipid profile in NASH and Non-NASH

	NASH +	NASH -
Serum cholesterol >200mg%(n=87)	82	5
Serum TG >150 mg%(n=147)	137	10

Chi square 0.1; p value 0.75

TABLE 6. Ultrasonographic staging of steatosis in NASH and non-NASH patients

	NASH		Non-NASH		Total
	Mean S. AST=81.55 IU/L		Mean S. AST=37.08 IU/L		
	Mean S. ALT=92.43 IU/L		Mean S. ALT=42.93 IU/L		
	No.	%	No.	%	
No steatosis	0	0	64	100	64
Mild	3	5.6	51	94.9	54
Moderate	25	39.7	38	60.3	63
Severe	16	84.2	3	15.8	19
Total	44	22	156	78	200

X² = 80.9, df = 3, p < 0.001; HS

Summary of the study and prevalence of NASH in study population (n=200)

Parameters		Prevalence in NASH		Prevalence in Non-NASH		p value
		No.	%age	No.	%age	
Total study population		44	22%	156	78%	(p < 0.001)
Sex	Male	20	45.5%	71	46%	(p > 0.05)
	Female	24	54.5%	85	54%	
Age (yrs)	<30	3	6.8%	29	18.58%	p < 0.05
	31 - 45	16	36.36%	47	30.12%	
	46 - 60	19	43.18%	55	35.25%	
	>60	61	3.6%	25	16.02%	
BMI (kg/m ²)	25 - 29.9	12	27.28%	74	45.97%	p < 0.05
	>30	32	72.72%	87	54.03%	
Central obesity		40	25.80%	4	8.88%	p < 0.05
		(n=155)		(n=45)		
Metabolic syndrome		33	30.27%	11	12.08%	p < 0.05
H/o DM		29	34.93%	15	12.82%	p < 0.05

found to be equal in both sexes. The prevalence of NAFLD in female group was 22% and in male group 22% (p > 0.05). Our result is discordant with study done by Amarapurkar D *et*

al¹⁵ in which the prevalence of NAFLD was 24.6% in males and 13.6% in females.

In this study the prevalence of NASH was found to be 25.7% (19 out of 74 patients) in the 46-60 years which is higher as compared to other age groups. In subjects less than 30 years, prevalence was only 9.4% (3 out of 32 patients), in 31-45 years it was 25.4% (16 out of 63 patients) and in >60 years, it was 19.4% (6 out of 31 patients) indicating that maximum persons having NASH were from the age group of 46-60 years. In the study done by Matteoni¹⁶ *et al*, the highest prevalence of NASH was found at average 53 years of age. In the study done by Duseja A¹⁷, the highest prevalence of NAFLD was found in age group of 40-50 years.

The prevalence of NASH was found to be 28.07% (32 out of 114 patients) in the obese patients (BMI >30 kg/m²), 15.38% (12 out of 78 patients) in the standard BMI group (25 - 29.9 kg/m²) and no case of NAFLD was found in the BMI group (<25 kg/m²). In the study done by Das K¹⁸ *et al*, prevalence of NAFLD was more in patients with BMI >25.9 kg/m². It was also observed that patients with normal BMI (18.5 - 24.9 kg/m²) were associated with a 2-fold increased risk of NAFLD than in those with a BMI <18.5 kg/m².

The prevalence of NAFLD was found to be 25.8% (40 out of 155 persons) in the centrally obese patients which is very high as compared to not centrally obese persons in this study. In a study by Ludwig¹ *et al*, prevalence of NASH was found to be 90% in patients with central obesity.

The prevalence of NASH in hypertensive patients was 26.6% (29 out of 109 patients) indicating a strong correlation of hypertension with NASH ($p < 0.001$) in this study. In the study done by Duseja A¹⁷, the prevalence of NAFLD in hypertensive patients was 10-12%.

In the present study, 34.94% diabetics (29 out of 83 patients) were found to be having NASH indicating a strong correlation of diabetes and NASH ($p < 0.001$). Our results were consistent with the study done by Powell *et al*.⁷

In the present study, the prevalence of NASH was found to be 30.27% (33 out of 109 patients) in patients with metabolic syndrome, which is less than that found in a study conducted by Duseja A.¹⁷

In the present study, the levels of AST and ALT were found significantly higher in NASH group as compared to non-NASH group. The AST levels amongst NAFLD group were mean $\pm$ S.D of 81.55 $\pm$ 10.42 IU/L while the levels of AST amongst non-NASH group were mean $\pm$ S.D. of 37.08 $\pm$ 10.64 IU/L ($p < 0.001$). The ALT levels amongst NASH group were mean $\pm$ S.D of 92.43 $\pm$ 11.81 IU/L while the levels of ALT amongst non-NASH group were mean $\pm$ S.D. of 42.93 $\pm$ 11.93 IU/L ($p < 0.001$). The difference between NASH and non-NASH was statistically highly significant ($p < 0.001$).

In the present study, it was observed that 32.35% of fatty liver patients were having raised AST and ALT levels (44 out

of 136 patients). In a study done by Angulo P⁶, it was observed that 90% patients of NAFLD had asymptomatic elevation of aminotransferase levels.

In the present study, 68.2% patients (30 out of 44 patients) had raised total cholesterol level in NASH patients. Thus the present study confirms that the patients of NASH have significantly higher ($p < 0.001$) level of total serum cholesterol as compared to non-NASH patients.

Regarding symptomatology, out of 44 NASH patients, maximum number of patients 24 (54.5%) complained of malaise and fatigue. The other prominent symptom was of upper abdominal discomfort observed in 22 (50%) patients. The most common sign detected on examination was hepatomegaly present in 18 (40.9%) of total 44 NASH patients. Liver biopsy was not done because of majority of patients refused to give consent for biopsy.

We conclude prevalence of NASH was more in age group 46 - 60 years, in patients with central obesity, diabetics and hypertensive patients and those with metabolic syndrome as well as dyslipidemia.

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