RESEARCH LETTER

NASH in High Risk Group of Patients With Type-2 DM, Obesity & Dyslipidemia

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Nonalcoholic steatohepatitis [NASH] is a form of chronic hepatitis with histological features of alcohol induced liver disease that occurs in persons who do not consume a significant amount of alcohol. NASH has gained more clinical importance recently because it was suggested to be a major cause of unexplained raised transaminases. The highest prevalence of NASH is described in obese, diabetics; who denied alcohol use. Both population based and hospital based studies from west describe that around 10%-24% of general population, and 57%-74% of obese individuals may have NAFLD. Corrosponding figure for NASH are 3-4% and 15%-20%.It is also estimated that around 50% of all diabetics have NAFLD (1,2). Similar data is lacking from India. India is also facing the epidemics of type -2 diabetes mellitus. Already, 4.3%-13.9% of urban and 2.7-3.7% of the rural Indian population is diabetic (3-5).Further asian Indians more commonly have dyslipidemia. All these factors combined together make a very fertile ground in Indians for having the metabolic syndrome or insulin resistance and its variable manifestations including NAFLD and NASH (6). The high prevalence of NAFLD but the lack of information about its natural history has generated controversy about the wisdom of recommending diagnostic tests or attempting to develop specific therapies for patients with this disease. Efforts to prevent or improve NAFLD also have been limited by our poor understanding of its pathogenesis. Careful epidemiologic studies and basic investigations are needed to provide new data to guide the management of patients with NAFLD. This study is an initiative to collect hospital based data regarding NAFLD and NASH.

The study was conducted in the Department of Medicine, Lady Hardinge Medical College and associated hospital with investigative assistance from Department of Pathology, G.B. Pant Hospital during the year 2006-2007. A total number of 108 High risk patients were included in the study. Diagnosis of NASH was made on the basis of symptoms and signs, supplemented with analysis of liver enzymes, ultrasonography and wherever possible on liver biopsy. An information leaflet was offered to each patient and informed consent was taken. Inclusion criterias were (1). Any Patient diagnosed as having Type-2 DM.(2). All over weight patients (BMI>25) (3). Patients with Documented hyperlipidemia (S. TGS>150 mg/dl) (4)Any patient with fatty liver (discovered incidentally because of Ultrasonography findings). A patient with any of the above criteria was eligible for inclusion. Exclusion criterias were (1). Person consuming alcohol > 10g/day for any duration (2) Patients with positive viral markers (3) Clinical possibility of other types of liver disease in the patients,(Confirmed by appropriate investigations). The routine chemistries were analyzed on Synchron CX9 and Synchron CX4 Clinical Chemistry Autoanalyser (Beckman) using standard reagents/kits from Randox (U.K.). Radiological investigation like Ultrasonography was done on each patient to look for fatty liver to make the diagnosis of NAFLD. Further investigations like Viral markers, tests for Antinuclear antiboby (ANA) were carried out as required in patients to rule out other causes of elevated liver enzymes. Wherever possible liver biopsy was done for histopathological diagnosis of NASH in patients of presumptive NASH (on basis of ultrasonography and elevated liver enzymes).Using standard statistical technique, relationship between various parameters was analyzed.A total of 108 high risk groups of Patients were included in the study. 8(eight) of them were excluded due to positive HBs- Ag , anti HCV antibody or ANA. The sample thus comprised of 100 patients. In the study group comprising 100 patients, ultrasonography revealed presence of fatty liver in 70(70%) patients. Out of these 70 patients only 22(31.42%) had raised serum aminotransaminases level. Thus in 100 high risk group of patients, 70% (70/100) had evidence of fatty liver (NAFLD) while 22% (22/100) had raised serum aminotransaminases level (NASH).Distribution of patients according to high risk factors and Presence of NAFLD and/or NASH in different high risk group has been shown in *table -1*. From the above table it is clear that most of the patients had more than one high risk factor and presence of NAFLD and/or NASH were higher in patients with more

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than one risk factor than patients with single risk factor as presence of NAFLD and NASH were between 38.5%-50% and 0%-12.5% respectively in patients with single risk factor in comparison to 68%-100% and16%-45% respectively in patients who had multiple risk factors. Patients with all three risk factors in inclusion criteria i.e. DM type -2, Hyperlipidemia and Overweight, had the highest prevalence of NAFLD (100%) and NASH (45%).

Patients presented with multiple complaints. Out of 22 NASH patients, maximum number of patients complained of Malaise and fatigue, and these were present in 12(54.5%) patients. The other prominent symptom was of Upper abdominal discomfort and was present in 11(50%) patients. Most common sign on examination was hepatomegaly present in 9(40.9%) of total 22 NASH patients.

Table1. Presence of NAFLD and NASH in Different High Risk Groups

Risk Factors	Total Number	NAFLD	NASH
DM type-2 only	4	2(50%)	0(0%)
Overweight only	16	7(43.7%)	2(12.5%)
Hyperlipidemia only	13	5(38.5%)	1(7.7%)
DM +Overweight only	10	9(90%)	3(30%)
DM + Hyperlipidemia only	12	10(83.3%)	3(25%)
Overweight+ Hyperlipidemia only	25	17(68%)	4(16%)
DM +Overweight+ Hyperlipidemia	20	20(100%)	9(45%)
TOTAL	100	70(70%)	22(22%)

Liver Function Test- Out of the 70 NAFLD patients, 22(31.42%) had raised serum aminotransaminases level (NASH). Thus in 100 high risk group of patients, 22% (22/100) had raised serum aminotransaminases level (NASH). The remaining 48 patients had only NAFLD but not NASH as Liver function tests were within normal limits.*Liver Biopsy*-Out of 22 patients of NASH liver biopsy was done in only 1(one) patient because other patients refused to give consent for biopsy but the histopathological specimen of this patient did not show any evidence of fatty change or steatohepatitis.

NAFLD and NASH are increasingly common conditions particularly in association with type-2 Diabetes mellitus, Obesity or Hyperlipidemia and are higher in patients with more than one risk factor. In the high risk population presence of NAFLD is more common than that of NASH. Mean age of presentation of NASH in our study was 44.59 years with the maximum number of patients in age groups of 40 to 49 years. However Western studies by Ludwig *et al* (8) reported as average age of presentation of NASH as 54 years and Matteoni *et al* (9) reported as average age of presentation of NASH as 53 years in their study. This study and another Indian study shows a comparatively early age of presentation of NASH in our population (7). Complaints of Malaise, fatigue & Upper abdominal discomfort are common and present in one-third to half of both NAFLD and NASH patients. Patients with mild form of liver disease such as hepatomegaly are common but presentation with advanced form of liver disease is not seen in spectrum of patients of NAFLD. According to our study the presence of NAFLD and NASH in Indian obese (according to Asia pacific criteria) patients is similar to the prevalence in western obese patients, however the presence of NAFLD and NASH in patients of Diabetes is higher in our study in comparison to patients of Diabetes in the west. This high presence of NAFLD and NASH in Diabetics in our study may be attributable to the fact that most patients had more than one high risk factor (8, 9). In our study it was observed that the majority of patients with NASH had mild elevation of Serum ALT and AST level within two times of normal, however determining its presence with histopathological findings is difficult because majority of patients refuse liver biopsy. Further our study revealed that a BMI >25 kg/m2, FPG>100 mg/dl and TGS level >150mg/dl(Hyperlipidemia) while FPG>100 mg/dl and TGS >150mg/dl(Hyperlipidemia) were statistically significant risk factors for NAFLD & NASH respectively. Whether NAFLD and NASH in Indian patients are overall mild or different from other parts of world requires analysis of full spectrum of patients by further studies.

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