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ORIGINAL ARTICLE

Evaluating Risk Factors for Development of Non-Alcoholic Steatohepatitis in Type-II Diabetes Mellitus

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Background and Aims: **Non-alcoholic steatohepatitis (NASH) is reported to be present in 49-86% of patients with type-II diabetes mellitus (DM). Risk factors for the development of NASH in DM are not clear. This prospective analysis was planned to define the chronological relation between DM and NASH as well as to define risk factors for the development of NASH in DM.**

Methods: **In a 3-year study, all consecutive NASH patients (n=100, age= 42.8±4.6 years, M: F=4.2:1) were evaluated for the presence of DM, at baseline and during three monthly follow-up. In NASH patient with DM (group A, n=27, age=39.3±5.2 years, M: F=4.4:1), risk factors such as obesity, central obesity, dyslipidemia and family history of chronic liver disease were evaluated for comparative analysis. Similar number of consecutive patients of DM without evidence of liver disease (group B, n=27, age=45.9±5.6 years, M: F=3:1) were analyzed for similar parameters.**

Results: **Among 100 patients with NASH, 27 (27%) patients had DM of whom, DM was preexisting in 13 (48.1%), was diagnosed at baseline in 11 (40.7%) and was diagnosed during follow-up in 3 (11.1%) patient. On statistical analysis (group A vs. group B), none of the risk factors were found to be statically significant: obesity (77.7% vs. 70.3%), central obesity (88.8% vs. 92.5%), dyslipidemia (51.8% vs. 44.4%), hypolipoproteinemia (7.4% vs. 3.7%), family history of chronic liver disease (7.4% vs. 0%), family history of DM (62.9% vs. 66.6%), hypertension (18.5% vs. 14.8%), ischemic heart disease (7.4% vs. 11.1%), cerebrovascular disease (3.7% vs. 0%) and hyperuricemia (11.1% vs. 14.8%).**

Conclusions: **DM does not always precede NASH, but may follow NASH in some patients. Risk factors like obesity, central obesity, dyslipidemia and family history do not predict the development of NASH in diabetic patients.**

Keywords: **Type-II Diabetes Mellitus, Non-Alcoholic Steatohepatitis, Chronic Liver Disease**

Introduction

Type-2 diabetes mellitus (DM) is present in 21-45% of the patients with non-alcoholic steatohepatitis (NASH). NASH is the commonest cause of chronic liver disease (CLD) in patients with DM [1]. Previous studies have shown high prevalence of insulin resistance (IR) and various components of metabolic syndrome (MS) in patients with NASH [2, 3]. Despite many studies supporting non-alcoholic fatty liver disease (NAFLD) being a part of the MS, the chronological relationships of NAFLD, IR, MS and DM are not clearly described. It is not clear if one of these conditions causes the others, or if all are consequences of another process [3].

NASH is prevalent in 49-86% of patients with DM [4], but why NASH develops only in some patients and does not develop in others is not known. NASH is a risk factor for progressive CLD, cirrhosis and hepatocellular carcinoma [5, 6]. We have previously tried to explore predictors of fibrosis in NASH with DM; but non-invasive markers were not of much help [4, 5, 7]. It is pertinent to know the subset of diabetics predisposed to the development of NASH. In India, incidence of DM is increasing

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in an epidemic proportion [8]. In Indian patients, this is the first study to clarify chronological relationship of NASH and DM as well as to know predisposing factors for NASH in DM.

Materials and Methods

This 3-year prospective case-control study was divided into two parts, of which first part was an observational study of non-cirrhotic patients with histological diagnosis of NASH; second part being a comparative analysis of DM patients with NASH vs. DM without NASH. The study was approved by the Ethical Review Board of the Institution.

In the first part of the study, 100 consecutive non-cirrhotic patients with histological diagnosis of NASH (age=42.8±4.6 years, M: F=4.2:1, ethnicity: Asian Indian, alcohol consumption=0%, other liver disease=0%) were included. Fasting blood glucose and 2-hour post-glucose/post-prandial glucose level were measured to diagnose DM (ADA criteria) at baseline and at every 3-mothly follow-up during the study period. In the second part of the study, 27 patients with NASH (group A, age=39.3±5.2 years, M: F=4.4:1, ethnicity: Asian Indian), who were identified having diabetes during the first part of the study, were compared to other 27 consecutive non-alcoholic patients of diabetes with no liver disease (group B, age=45.9±5.6 years, M: F=3:1, ethnicity: Asian Indian). In these patients, liver disease was excluded by performing liver function tests and imaging studies. In all patients of group A and group B, following parameters were evaluated: age, sex, family history (DM or chronic liver disease [CLD]), presence of vascular disease (hypertension, ischemic heart disease and cerebrovascular disease, peripheral vascular disease), presence of obesity, presence of central obesity (waist circumference, waist: hip ratio), dyslipidemia (total cholesterol [ULN 200 mg/dl], HDL cholesterol [ULN 60 mg/dl], LDL cholesterol [ULN 100 mg/dl], triglyceride [ULN 150 mg/dl], Apo-A1 lipoprotein [normal range: 120-176 mg/dl], Apo-B lipoprotein [normal range: 63-114 mg/dl], Lipoprotein-a [normal range: up to 30 mg/dl]), hyperuricemia (uric acid level [ULN 7.2 mg/dl]).

Diabetes was diagnosed on the basis of use of insulin and/or oral hypoglycemic drugs, fasting plasma glucose level>126 mg/dl and/or 2-hour plasma glucose level>200 mg/dl. Hyperlipidemia was diagnosed when fasting lipid values were above the 95th percentile of normal on at least 2 occasions. Hypolipoproteinemia was diagnosed when lipoprotein Apo-A1 and Apo-B levels were below 95th percentile of the normal range. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg. Obesity was defined when body mass index (BMI)>25 kg/m^2. Central obesity was defined in male as waist circumference ≥90 cm or waist-to-hip ratio>0.9 and in female as waist circumference ≥80 cm or waist-to-hip ratio>0.85. Statistical analysis was performed using chi-square test by comparing both the groups in the second part of the study. P value was considered statistically significant if it was less than 0.05 and P value more than 0.05 was considered statistically not significant.

Results

In the first part of the study (mean follow-up period: 2.1±0.3 years), of the 100 patients with NASH, diabetes was diagnosed at baseline or during follow-up in 27 patients (27%). In 13 patients (48.1%), diabetes was present before the diagnosis of NASH with mean duration of diabetes being 5.6±2.4 years. In another 11 patients (40.7%), diabetes was diagnosed at the same time of diagnosis of NASH. In another 3 patients (11.1%) with NASH, diabetes was freshly diagnosed during follow up period.

In the second part of the study, comparison of group A and group B is shown in Table 1. There was a male predominance in both groups, but there was no difference in age distribution. There was no difference in group A and group B regarding the

Table 1. Comparison of risk factors for NASH in both the groups.

Risk factors	Group A (n=27)	Group B (n= 27)	P value
Age (yrs)	39.3±5.2	45.9±5.6	NS
Sex (M:F)	4.4:1	3:1	NS
Obesity	21 (77.7%)	19 (70.3%)	NS
Central obesity	24 (88.8%)	25 (92.5%)	NS
Dyslipidemia	14 (51.8%)	12 (44.4%)	NS
Hypolipoproteinemia	2 (7.4%)	1 (3.7%)	NS
Hypertension	5 (18.5%)	4 (14.8%)	NS
Ischemic heart disease	2 (7.4%)	3 (11.1%)	NS
Cerebrovascular disease	1 (3.7%)	0 (0%)	NS
Peripheral vascular disease	0 (0%)	1 (0%)	NS
Hyperuricemia, n (%)	3 (11.1%)	4 (14.8%)	NS
Microalbuminuria	8 (28.6%)	7 (25.9%)	NS
Family history of CLD	2 (7.4%)	0 (0%)	NS
Family history of DM	17 (62.9%)	18 (66.6%)	NS

presence of risk factors for NASH or metabolic syndrome, like obesity, central obesity, hypertension and dyslipidemia. In both groups, a significant number of patients had a family history of diabetes (>60%). Complications of atherosclerosis were identically present in both groups.

Discussion

Only a few studies have examined the association of baseline liver markers with risk of type 2 diabetes, but the results have been inconsistent [9-13]. In 3 recent studies, persons with elevated ALT without any obvious cause were shown to have evidence of developing diabetes during follow-up period as compared to persons without ALT elevation [14-16]. NAFLD is the most common cause of chronic elevations of ALT [17, 18]. ALT elevation alone is not a good predictor of metabolic significance and severity of NAFLD [5, 19]. In one study, on univariate analysis but not on multiple logistic regression, FL on ultrasonography was found to be a risk factor for incident diabetes [20]. It seems logical that NAFLD may be a precursor of DM [14]. In our study, it is shown that NASH may precede the development of diabetes in some patients.

In general, MS, obesity, and IR are major risk factors in the pathogenesis of NAFLD. Prospective risk factors for the development of MS are physical inactivity, elevated waist circumference and triglyceride levels, elevated γ-glutamyltransferase, CRP and ALT [21-24]. Liver markers were significantly associated with the development of individual components of the metabolic syndrome [14]. NASH is associated with risk factors like male sex, low educational level, obesity, central obesity, diabetes, impaired glucose tolerance, dyslipidemia (hypertriglyceridemia, low HDL cholesterol and hypercholesterolemia), MS, IR, hyperinsulinemia, hypertension, elevated ALT, hyperuricemia [19, 25-28].

In few studies where risk factors for NAFLD in DM are studied, obesity, dyslipidemia and abnormal liver enzymes were associated with diabetic FL [29, 30]. In our study there was no correlation between these risk factors and the presence of NASH in DM. Other factors than features of MS might be responsible for NASH in DM. Limitation of our study is application of liver function test and imaging only to exclude NASH in group B as patients with NASH may have normal ALT and normal imaging findings [4, 5]. In recent studies, adipokines (adiponectin, resistin, leptin and TNF-α) have been implicated in the pathogenesis of DM and NASH, through their metabolic and pro-/anti-inflammatory activity [22, 27, 31-41]. Also, familial clustering of NAFLD, IR and DM is recently an issue of interest [42, 43].

Conclusions

Diabetes and NASH are linked to each other but their chronological relation is not very clear. In some patients, NASH may precede the development of diabetes. Risk factors like obesity, central obesity, dyslipidemia and family history do not predict the development of NASH in diabetic patients.

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