

Non-Alcoholic Fatty Liver Disease in First Degree Relatives of Patients with NaflD

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Abstract

Non Alcoholic Fatty Liver Disease (NAFLD) includes a spectrum of hepatic pathology that resembles alcohol-induced liver disease but develops in individuals who deny a significant history of alcohol ingestion. NAFLD comprises a wide spectrum of liver damage, ranging from simple macrovesicular steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma. The prevalence of NAFLD has doubled during last 20 years, whereas the prevalence of other chronic liver diseases has remained stable or even decreased. Moreover with increasing incidence and prevalence, the perception of NAFLD being a benign condition of little clinical significance is rapidly changing. Obesity, metabolic syndrome, type 2 diabetes (T2DM) and dyslipidemia are predisposing factors for NAFLD. All these are directly linked with diet and lifestyle of an individual and hence preventable and modifiable. The study was conducted to identify the prevalence of NAFLD among the first degree relatives of a patient already diagnosed with NAFLD. The study demonstrated the increased prevalence of NAFLD among the family members. Further risk factor analysis in the study strengthened the role of diet and lifestyle in the etiology of NAFLD.

Keywords: NAFLD, Fatty Liver, Cirrhosis, Metabolic syndrome, Diet, Lifestyle, Obesity

Introduction

NAFLD is now a major cause of lifestyle related mortality and morbidity. The term nonalcoholic fatty liver disease (NAFLD) is used to define a spectrum of diseases related to hepatic fat deposition: hepatic steatosis (HS) when there is only fat accumulation; nonalcoholic steatohepatitis (NASH) is when besides steatosis, there is inflammation, ballooning and moderate fibrosis; and the evolution from NASH to cirrhosis and hepatocellular carcinoma (HCC). There is an epidemic of predisposing factors like diabetes, dyslipidemia, obesity, and metabolic syndrome due to changing lifestyle and dietary habits and hence there is increased prevalence of NAFLD too.

The term NAFLD was introduced in the year 1986 [1]. Its definition requires evidence of hepatic steatosis, either by imaging or by histology and absence of other causes for hepatic fat accumulation and liver disease. NAFLD is histologically further categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). The overall prevalence of NAFLD in western countries varies from 15-40% and in Asian countries from 9-40% [2, 3]. Epidemiological studies suggest the prevalence of NAFLD to be around 9-32% in general Indian population, with a higher

incidence amongst overweight/obese and diabetic/ prediabetic patients [4-7]. Insulin resistance is related to obesity and is central to the pathogenesis of NAFLD. The pathogenesis of NASH is best supported by “two-hit hypothesis”. Prolonged overnutrition leads to accumulation of free fatty acids (FFAs) and triglycerides within the liver (steatosis, first hit). The progression of NAFL to NASH is associated with other factors (second hit), such as oxidant stress, mitochondrial injury, fatty acids lipotoxicity, innate immunity and inflammatory cytokines. Hepatic iron, leptin, anti-oxidant deficiencies, and intestinal bacteria have all been suggested as potential oxidative stressors.

Male sex, dietary habits like increased intake of carbohydrates, fat and sweets, low level of physical activity are well known risk factors for NAFLD. Obesity is strongly associated with NAFLD and there is increased prevalence of NAFLD in those with diabetes mellitus and dyslipidemia [8, 9]. Ultrasonographic study of patients with T2DM showed 69% prevalence of NAFLD [10]. The prevalence of NAFLD in individuals with dyslipidemia attending lipid clinics was estimated to be 50% [11]. NAFLD is now an integral component of the metabolic syndrome in which there is a co-occurrence of metabolic risk factors for both type 2 diabetes and cardiovascular events such as abdominal obesity, hyperglycemia, dyslipidemia, and hypertension [12].

NAFLD has to be suspected in all those with history of weight gain, or in those who are overweight or obese and in any one with metabolic syndrome/diabetes or dyslipidemia. Most patients with NAFLD are asymptomatic; some patients with NASH show fatigue, malaise, and vague right upper quadrant discomfort. Hepatomegaly is detected if carefully looked for in those with NAFLD. These days patients are diagnosed incidentally by abnormal liver function tests or routine imaging. Mild to moderate elevation of serum aminotransferases (ALT and AST) is the most common lab abnormality. Ultrasound examination is the usual screening test for fatty liver [13]. NAFLD is usually a diagnosis of exclusion. We have to exclude alcoholic liver disease; drug induced liver disease, chronic viral hepatitis, autoimmune hepatitis, and metabolic liver disease like Wilson's disease depending on the clinical context. Even though liver biopsy is an accurate method for the diagnosis of NASH and to assess severity of liver damage, the risks of biopsy argue against it [14].

The management of patients with NAFLD consists of managing the associated metabolic co-morbidities such as obesity, hyperlipidemia, insulin resistance and T2DM and interventions promoting weight loss. Weight loss of 3-5% of baseline weight is necessary to improve steatosis, but a more substantial loss (>10%) may be necessary when necroinflammation is present [15]. It is speculated that DASH diet may be beneficial for subjects with NAFLD by directly acting on the risk factors, with special emphasis for HTN, dyslipidemia, and IR. A meta-analysis evaluating randomized trials concluded that DASH diet may enhance insulin sensitivity regardless of weight loss, mainly when prescribed for more than 16 weeks [16]. A moderate exercise program three to four times a week should be encouraged to achieve a heart rate of 60-75% of the age-based maximum. The efficacy of dietary and exercise measures should be assessed after a 6-month period; if they have been ineffective, additional therapeutic options such as pharmacologic therapy may then be considered. Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH. Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. Omega-3 fatty acids may be considered as the first line agents to treat hypertriglyceridemia in patients with NAFLD. Statins, can be used to treat dyslipidemia in patients with NAFLD and NASH. *Weight loss by any method is beneficial for patients with morbid obesity; but this should be considered early, as the benefits will be absent in those who are already cirrhotic.*

The genesis of NAFLD is dependent on a complex interplay between host susceptibility factors (which could be genetic or acquired like the diet and lifestyle habits) and environmental insults. The role of diet and lifestyle are identified better than genetic factors in the development of NAFLD even in a genetically predisposed individual. It's always observed that the dietary habits and lifestyle are almost the same among all the members of a given family or a community who stay and work together or even in a society. Therefore it can greatly influence the increased prevalence of NAFLD among first-degree relatives in a family. Also these factors are the ones, which can be modified and thus could alter the natural progression of the disease. A search of literature did not give any such study from India, which assesses the prevalence of NAFLD in first-degree relatives of patients with NAFLD, hence, the study.

Aims and Objectives

The study was conducted to determine the prevalence of NAFLD in first degree relatives of patients with NAFLD and to study the common etiological associations of NAFLD.

Materials and Methods

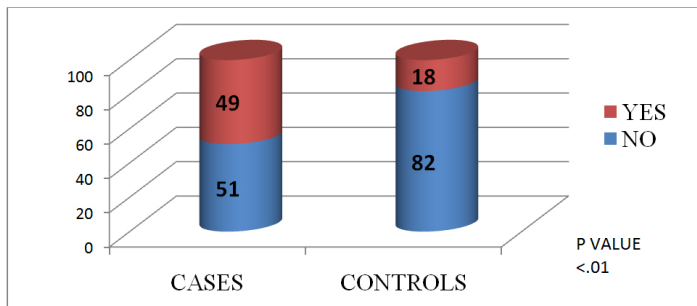
This was a cross-sectional comparative study done from January 2014 till December 2014 at Department of Internal Medicine, Government Medical College Kozhikode. 100 study subjects and 100 controls were selected. All the first-degree relatives of patients with NAFLD, above 18 yrs of age, were selected consecutively, till the sample size was completed. The controls were age and gender matched, they were all first-degree relatives of a healthy person without NAFLD. The Institutional Ethics Committee of Govt Medical College, Kozhikode, approved the study. Informed consent was taken from all study subjects. Relevant details including medical, personal, family and socioeconomic history was taken from all subjects and dietary information were assessed using a semi quantitative food frequency questionnaire derived from IDSP non communicable disease survey questionnaire. Physical activity was assessed using GPPAQ (General Practice Physical Activity Questionnaire) forms. Anthropometric measurements and clinical examination were carried out in all subjects in fasting state. Laboratory investigations including fasting blood glucose, fasting lipid profile, liver function tests, and HbA1C were done for all subjects. NAFLD was diagnosed in the subjects if they had any two of the three findings: 1) Hepatomegaly on clinical examination. 2) Elevated serum transaminases. 3) Fatty liver in USG and no other cause for the hepatomegaly and elevated liver enzymes. An earnest attempt was made to rule out all secondary causes. Statistical analysis was carried out using SPSS package. Statistical tests like chi square test and independent sample t tests were used for analysis. A p value < 0.05 was considered statistically significant.

Results and Observations

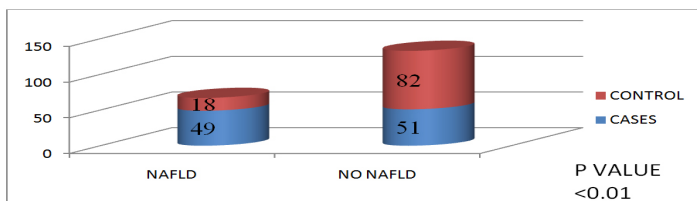
The prevalence of NAFLD among study subjects (First degree relatives of NAFLD) was 49% as compared to 18% among the controls in this study. A total of 67 NAFLD subjects (Cases) were identified from both groups and in them 58.2% were females while 41.8% were males. 85% of the NAFLD subjects belonged to 30-50 years of age. Altogether 73.1% of people with NAFLD had a positive family history of NAFLD with a significant p value. When physical activity was assessed 89.1% of NAFLD subjects were less than moderately active. There was a statistically significant difference between NAFLD group and those without NAFLD in consumption of pulses, green leafy vegetables, and fruits. The intake of junk food, fried food, and fried fish was high among NAFLD subjects than those without NAFLD. Only 41.8% of those with NAFLD were identified to have metabolic syndrome. It may be because an individual's weight gain may predispose him to NAFLD even if his BMI is low normal. In this study 28% of the NAFLD subjects had Type 2 Diabetes Mellitus also as compared to 13.5% in the non-NAFLD group. Mean HbA1C among the NAFLD group was 5.92±0.7 mg% as compared to 5.25±0.4mg% in the non-NAFLD group. Among NAFLD group 71.6% had dyslipidemia as compared to 9.7% in the non-NAFLD group with a statistically significant difference in the proportion of subjects with HDL and triglyceride levels in the metabolic syndrome cut off range. Meanwhile no significant difference was observed in other parameters like hypertension and LDL among NAFLD and non-NAFLD groups. The mean SGPT in the NAFLD

group was 43.7+/-9.09IU/ml and in the non-NAFLD group was 21.1+/-4.1 IU/ml. The result was statistically significant.

Prevalence of NAFLD among cases and controls



Positive family history of NAFLD as a risk factor of occurrence of NAFLD



Discussion

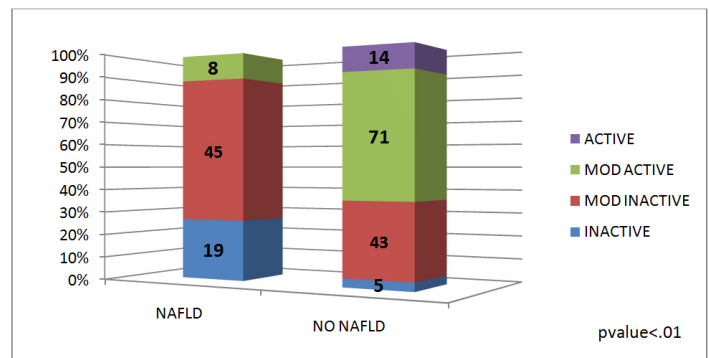
In this study there were 100 cases and 100 age and sex matched controls. The first objective of the study was to assess the prevalence of NAFLD among cases and controls. Fatty liver was assessed by USG. All the study subjects with fatty liver had only grade 1 fatty liver.

The prevalence of NAFLD among study subjects was 49% as compared to 18% among controls in this study. Thus there was a statistically significant increased prevalence of NAFLD among the first-degree relatives of patients with NAFLD. Willner and colleagues reviewed the charts of 90 patients with a diagnosis of NASH at the University of Tennessee and the Medical University of South Carolina [17]. The investigators noted that 16 of the 90 patients came from families with 2 or more patients with NASH.

Next step in this study was that the total number of NAFLD from both the study subjects and controls were grouped together as NAFLD cases and analyzed to identify the common etiological associations of NAFLD. There were total of 67 new NAFLD cases, 49 were from among the study subjects and 18 cases from the control group. Therefore, further analysis was based on these 67 persons with NAFLD versus the 133 persons without NAFLD. Out of the total 67 NAFLD subjects identified 58.2% were females while 41.8% were males. The higher female preponderance is consistent with him National Family Health Survey (NFHS-3) India 2005-06 [18]. Out of 67 NAFLD subjects 85% belonged to 30-50 years of age consistent with various studies from India. Among 67 NAFLD patients 73.1% (49) had a positive family history of NAFLD with a significant p value. Family history of NAFLD was assessed by multinomial logistic regression and was found to have significant adjusted odd's ratio of 4.2.

When level of physical activity was analyzed in both groups it was found that 89.1% of NAFLD subjects were less than moderately active. This result directly implies that increased level of activity can decrease the occurrence of NAFLD. There are studies focused on the direct effects of exercise over NAFLD, independently of weight loss [19-21].

Comparison of level of physical activity among subjects with and without NAFLD



There was a statistically significant difference between NAFLD group and those without NAFLD in consumption of pulses, green leafy vegetables and fruits. The intake of junk food, fried food and fish was high among NAFLD subjects than those without NAFLD. These results are consistent with various studies regarding the effect of diet in occurrence of NAFLD [22, 23].

Both groups differed in terms of weight, BMI, and waist circumference. Waist circumference was subcategorized based on the IDF consensus for metabolic syndrome. According to IDF consensus, the cut off for metabolic syndrome range was WC \geq 90cm for Indian men and WC \geq 80cm for Indian women. On analysis, it was observed that, 52.2% of the NAFLD cases fell above the cut off range, meanwhile only 14.2% of the non-NAFLD group reached above the mentioned cut off range for metabolic syndrome in this study. This difference was also statistically significant with a p value of 0.01.

BMI values were also divided into those with a BMI $>$ 25kg/m² and those below this range. After analysis it was observed that, 32.8 of the NAFLD cases had a BMI above the cut off range and only 11.8% of the non-NAFLD group had a BMI above the cut off range. This difference in BMI was also statistically significant with a p value of 0.01. Out of 67 NAFLD cases 41.7% satisfied the IDF criteria for metabolic syndrome compared to 11.2% in the other group. Various studies from India have reported the presence of metabolic syndrome in 21-68% of NAFLD patients [24, 25].

The mean SGPT was found to be higher in NAFLD group (43.7+/-9.09IU/ml) than non-NAFLD group (21.1+/-4.1 IU/ml) with a significant p value. Elevation of levels of ALT and AST or both to mild and moderate levels is a very common finding in NAFLD [26]. Minor elevation of this enzyme level may be a good predictor of mortality from liver disease as suggested by some authors [27]. Thus it appears that we can predict the presence of NASH if a person is overweight or has gained weight and is having an elevated SGPT in the absence of another cause for it.

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