CLINICOPATHOLOGICAL SPECTRUM OF NON-ALCOHOLIC FATTY LIVER DISEASE AMONG PATIENTS IN KERALA

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ABSTRACT

Non-alcoholic fatty liver disease and its more aggressive form, non-alcoholic steatohepatitis are entities that are becoming more and more interesting to the medical community in general. A total of 93 Non-alcoholic fatty liver disease patients (64 male and 29 female) within the age range between 28 to 63 years were studied. All of them showed elevated alanine aminotransferase level (104.07 ± 56.04). Aspartate aminotransferase level (58.13 ± 31.96) was elevated more than its normal level in 82% cases and AST to ALT ratio was found 0.59 ± 0.26 . Predisposing factors were diabetes mellitus (37%), obesity (13%) and hyperlipidemia (41%). In addition, 32% of the subjects were overweight. 18% of the patients had elevated serum bilirubin. Our findings recommend a lower cutoff value than suggested by the World Health Organization for overweight and obesity among this racial-ethnic group.

KEY WORDS

Body mass index, Diabetes mellitus, Hyperlipidemia, Non-alcoholic fatty liver disease, Obesity, Waist-to-hip ratio.

INTRODUCTION

Non- alcoholic steatohepatitis (NASH) is a distinct hepatic disorder observed in patients without a history of significant alcohol consumption that histologically resembles alcohol-induced liver damage. It was first described in obese and diabetic women (1). NASH is considered to be part of the spectrum of non-alcoholic fatty liver disorders (NAFLD), extends from non-progressive disease, through NASH and finally to "cryptogenic" cirrhosis (2).

NASH has been associated with insulin resistance, which includes obesity, diabetes, hypertriglyceridemia and hypertension. In addition, NASH has also been associated with hyperlipoproteinemia, jejunal bypass, parenteral nutrition, drugs, α_1 -antitrypsin deficiency, bacterial overgrowth, and

environmental toxins. Exposure to chemicals is suspected to be another risk factor. There is an increasing body of evidence that some cases of cryptogenic cirrhosis, requiring liver transplantation could have been the result of NASH. Iron overload, H63D mutation of the HFE gene, and immune system anomalies are frequent in patients with non- alcoholic steatohepatitis. Recent reports have also described hepatocellular carcinoma arising in patients with NASH associated cirrhosis (3). Here we studied the clinicopathological features of NAFLD patients in Kerala.

MATERIALS AND METHODS

The study protocol was in keeping with the ethical guidelines of the 1975 Declaration of Helsinki and all the patients gave written informed consent to the study. Patients were selected from those who had visited Gastroenterology Department, Amrita Institute of Medical Sciences, Cochin. NAFLD patients were categorized on the basis of absence of history of significant alcohol intake, clinical characteristics, laboratory findings, and ultrasound/ CT scan imaging where applicable. Major clinical presentation of patients were (i) asymptomatic transaminase elevations and (ii) right upper quadrant pain. Inclusion criteria were: i. elevated liver aminotransferases, ii.

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no findings on investigations suggestive of viral, metabolic or other specific etiologies of liver diseases. Exclusion criteria were: i. recent gastrointestinal surgery, ii. older age (>65 yrs), iii. pregnancy, iv. usage of drugs known to result in steatosis, including glucocorticoids, synthetic estrogens, aspirin, tamoxifen, amiodarone, calcium channel blockers and Methotrexate or v. malignancy. A total of 93 patients (64 male and 29 female) were identified in this group. Institutional Ethics Committee approved the procedures.

Mean age, height, weight, waist circumference, hip circumference, body mass index (BMI), percent body fat and waist-to- hip ratio of patients were determined. Laboratory study included routine investigations such as blood sugar, lipid profile and liver function tests. The patients were labeled as diabetic if random glucose was > 200 mg/dl or fasting glucose >126 mg/dl on 2 occasions or having documented use of oral hypoglycemic medications or insulin. Obesity was defined as BMI > 30 kg/m² for both males and females. Hyperlipidemia was considered when fasting cholesterol and/ or triglycerides were above 95th percentile of normal on at least 2 occasions.

RESULTS AND DISCUSSION

Ludwig's pioneer report on NAFLD states that female gender is in association with fibrosis (1). Although this may still be true, the prevalence of NAFLD *per se* has been shown to be higher among males in several epidemiological studies (4), including this one. Age of these patients varied from 28 to 63 years (42.9 ± 10.24 yrs). All of them showed elevated alanine

aminotransferase level (104.07 ± 56.04 IU/L). Aspartate aminotransferase level (58.13 ± 31.96 IU/L) was elevated in 82% cases, and AST to ALT ratio was found 0.59 ± 0.26 . Predisposing factors were diabetes mellitus (37%), obesity (13%) and hyperlipidemia (41%). In addition, 32% of the subjects were overweight. 18% of the patients had elevated serum bilirubin.

Since it was first described, NAFLD has been consistently associated with obesity (60%-95%), diabetes (28%-55%), and dyslipidemia (27%-92%), and less clearly with raised arterial pressure (5). Obesity, more specifically central obesity, characterized by abdominal fat accumulation is definitely associated with NAFLD. In the general population, obesity increases the risk of steatosis (6). In severe obesity, the prevalence of liver abnormalities is nearly the rule (7). Body mass index is an independent predictor of the degree of fat infiltration of the liver (8) and the likelihood of developing NASH increases with the severity of obesity (9). Various regulatory agencies and scientific societies have proposed different criteria to define the metabolic syndrome, all including data on obesity- namely visceral obesity, glucose regulation, dyslipidemia, and blood pressure (10) (Table 1).

Persons with an increased waist circumference have been shown to be more likely to exhibit type 2 diabetes, dyslipidemia, and other components of metabolic X syndrome than persons with a normal waist circumference independent of race, BMI, age, income, socioeconomic class, or physical activity (11). It was shown that waist-to- hip ratio correlates with visceral

Table 1: Criteria for the definition of the Metabolic Syndrome According to the Most Commonly quoted Proposals

Criteria	WHO@	NCEP*	IDF#	Present Results	Range
BMI (Kg/m ²)	≥30	-	-	26.13 ± 3.55	20.98-37.8
Waist Circumference (cm)	-	>102 (M)	>94 (M)	96.43 ± 7.17 (M)	89-112
	-	>88 (F)	>80 (F)	95.07 ± 12.69 (F)	76-112
Waist to hip ratio	>0.9 (M)	-	-	1.03 ± 0.06 (M)	0.98-1.23
	>0.85 (F)	-	-	0.99 ± 0.1 (F)	0.91-1.05
Arterial pressure (mm Hg)	≥140/ 90	≥130/ 85	≥130/ 85	ns	
Triglyceride (mg%)	≥150	≥150	≥150	175.54 ± 97.32	59-580
HDL-Cholesterol (mg%)	< 35 (M)	< 40 (M)	< 40 (M)	38.3 ± 9.79	27-52
	< 39 (F)	< 50 (F)	< 50 (F)	45.6 ± 12.1	30-61
Fasting blood glucose	IGT/ Insulin resistance	≥110mg%	≥100mg%	120.27 ± 51.62	69-364
Microalbuminuria	≥20µg/min	-	-	ns	

Abbreviations: WHO, World Health Organization; NCEP, National Cholesterol Education Program; IDF, International Diabetes Foundation; M, male; F, Female; IGT, Impaired Glucose Tolerance; ns, not studied.

@ Altered glucose regulation or insulin resistance and two or more of the criteria (22); * Three or more of the criteria (23). # Abdominal obesity (i.e. waist circumference) and two or more of the remaining criteria (10).

adiposity in white women but not in African-American women, highlighting the existence of racial variability in these anthropometric parameters (12). The prevalence of NAFLD varies among different racial groups (13).

Although the World Health Organization currently defines overweight and obesity as a BMI of 25 kg/m² or more, and 30 kg/m² or more, respectively; these definitions may vary by racial-ethnic group. Based on the observation that Hong Kong Chinese have a higher percentage of body fat than whites for a given BMI, a lower cutoff value for BMI in persons of Asian race (BMI $\geq$ 23 kg/m² for overweight and BMI $\geq$ 27 kg/m² for obesity) was recently proposed (14). Our findings also support the recommendation for a lower cutoff for overweight and obesity among racial-ethnic groups. In another study, Asians were shown to have a higher amount of visceral adiposity (15) and more subcutaneous fat than whites (16), highlighting the limitations of BMI as a single surrogate marker for obesity. Accumulation of visceral fat was previously shown to be more common in males regardless of total body fat, and deep subcutaneous adipose tissue has been associated with insulin resistance in men, but not in women (17, 18). Racial-ethnic differences in the relationship between BMI, percent body fat, and body fat distributions among whites, Hispanics, and African Americans also have been reported and may contribute to the sex and ethnic variations in NAFLD prevalence (19, 20). Whether sex differences in fat distribution and insulin resistance are more or less pronounced in individuals of different races or ethnicities remains unclear, but the variability in risk factors by sex as well as race and ethnicity were highlighted (21).

The increased prevalence of diabetes, obesity, hypertension, and hypertriglyceridemia are considered to be important causes for NAFLD. Though obesity is often a dominating finding among Western as per WHO guidelines, the same is not prevalent in our subjects. Therefore, a new definition on obesity and overweight is recommended among our population.

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