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ORIGINAL ARTICLE

Nonalcoholic fatty liver disease (NAFLD) without insulin resistance: Is it different?

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Summary
Background and aims: Nonalcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of insulin resistance [IR]. However, a significant proportion of NAFLD patients are devoid of IR. Is NAFLD sans IR a different entity? The aim of the study was to compare the anthropometric, metabolic, biochemical, ultrasonography, and histological profile of NAFLD patients with and without IR.
Methods: Retrospective analyses of 336 NAFLD patients diagnosed during the last two years was done. Patients without IR were compared with those with IR.
Results: Out of 336 patients, 153 [45.53%] were without IR. Although age, gender, BMI and transaminase levels were comparable, significantly higher proportion of patients in non-IR group were non-obese [43.14% vs. 25/14%; $P=0.0005$], and had mild fatty change on ultrasonography; [78.43% vs. 67.21%; $P=0.022$]. Higher proportion of them had elevated transaminases; [67.97% vs. 56.83%; $P=0.036$]. Serum triglyceride [178.52 ± 78.78 vs. 204.86 ± 94.72 mg/dl; $P=0.02$], FBG [85.39 ± 13.80 vs. 98.93 ± 31.56 mg/dl; $P=0.00$], PGBG [123.76 ± 36.77 vs. 148.07 ± 64.67 mg/dl; $P=0.00$], and serum insulin [6.33 ± 2.18 vs. 15.39 ± 12.56 μIU/ml; $P=0.00$] were significantly lower in patients without IR. Although there was no difference in histology, interestingly fibrosis was seen in one third of patients despite absence of IR.
Conclusion: Nearly half of our NAFLD population was without IR; one third of them had significant fibrosis. NAFLD is probably a heterogeneous disease and IR is not the sole factor responsible for NAFLD; further studies are needed to find out other possible etiological factors.

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Introduction

NAFLD is now recognized as the commonest cause of hepatic dysfunction in the general population [1]. NAFLD includes a spectrum of liver damage, ranging from simple steatosis, which is usually benign, to NASH, which can progress to cirrhosis, liver failure and liver cancer [2,3]. NAFLD is present in the general population in industrialized countries in 20 to 40% and is the most prevalent chronic liver disease [4,5]. The prevalence of fatty liver in the general population of India has been shown to be 16.6—24%, which is similar to that reported from the developed countries [5,6]. The prevalence of fatty liver in our region ranges from 14.6 to 24% [7,8]. Besides, the burden of NAFLD is expected to rise in India due to the predicted alarming growth of obesity and type 2 diabetes mellitus (DM). Almost 30—65% of adult urban Indians are either overweight/obese or have abdominal obesity [9], and there is an increasing prevalence of obesity-related comorbidities: hypertension, metabolic syndrome (MS), dyslipidemia, type 2 DM, and cardiovascular disease (CVD) [10,11]. NAFLD is in fact currently considered the hepatic manifestation of IR. However, a previous study from our region had found prevalence of IR in only 46% of NAFLD patients [12]; almost half of the NAFLD population was devoid of IR. This created the suspicion that NAFLD sans IR could be a different entity from NAFLD with IR. In the present study, we have compared the clinical including anthropometric, metabolic, biochemical and histological profile of NAFLD patients with and without IR to characterize the NAFLD sans IR phenotype, and to understand the differences between the groups.

Patients and methods

Retrospective analysis of clinical, biochemical and histological parameters was performed in 336 patients in whom fatty liver was diagnosed incidentally on ultrasonography during the period August 2010—June 2012.

Inclusion criteria

Patients with fatty liver on ultrasonography for whom complete anthropometric, metabolic and biochemical data including fasting blood glucose (FBG), serum insulin, liver function test (LFT) and lipid profile were available were included in the study.

Exclusion criteria

Patients with significant alcohol intake (> 20 gm/d), evidence of acute/chronic viral hepatitis, drug induced hepatitis, autoimmune hepatitis, other metabolic liver diseases and patients who had undergone gastrointestinal surgery, patients with malnutrition, history of recent weight gain or loss prior to diagnosis of fatty liver were excluded.

The study was approved by the Institutional Ethics Committee of Kalinga Gastroenterology Foundation, Cuttack, India.

FBG, lipid profile had been assayed by an autoanalyser (BIOLIs 24i Tokyo Boeki, Japan) using standard kit. Serum insulin level was estimated by electrochemiluminescence using standard kit (Roche-Diagnostics, USA) with autoanalyser Elecsys 2010 (Roche-Hitachi, Japan).

Diagnosis of DM was made as per ADA criteria [13]. Transaminitis was diagnosed when AST and ALT levels > 40 IU/L. The modified criteria of National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) were considered for diagnosis of MS [14]. However, patients with BMI > 23 were deemed overweight and those with a BMI of > 25 were labeled as obese (Asian standards) [15].

Since we did not have measurements of waist and hip in a significant number of patients, we replaced abdominal obesity with BMI > 25 kg/m^2 in the NCEP-ATP III-2 criteria as a surrogate criterion for MS, as done by Madan et al. [16].

IR was calculated using the homeostatic model assessment (HOMA) method using a mathematical model derived from FBG and plasma insulin. The value of HOMA was calculated by the following equation: (fasting insulin (μU/ml) $\times$ FBG (mg/dl))/405, and depicted as HOMA-IR value [17].

HOMA-IR score > 1 implies insulin sensitivity < 100% and could mean IR. Although a HOMA score of 1.0 is adequate, the study by Bonora et al. had found a mean HOMA-IR score of 2.06 ± 0.14 in the normal non-diabetic population [18]. However, study done in our population had shown that the normal value of IR as assessed by HOMA-IR is less than 2 [19,20]. For our study, HOMA-IR value above 2 was considered to indicate IR. Beta cell function (HOMA-B) was calculated using the formula 360 $\times$ fasting serum insulin μuml/FBG (mg/dl)—63 [17].

Hepatic ultrasonography had been performed following 8 hours of fasting using a 3.5 MHz probe. NAFLD cases were graded as per Gore et al.:

- Grade 1 (mild): normal visualization of diaphragm/intrahepatic vessels;
- Grade 2 (moderate): impaired visualization of diaphragm/intrahepatic vessels;
- Grade 3 (severe): poor visualization of diaphragm/intrahepatic vessels [21].

Liver biopsy had been performed in only 30 patients who consented for the procedure, using Menghini's needle or BARD liver biopsy gun [16 Fr] through the intercostal approach. Histologic grading and staging were done as per the classification proposed by Kleiner et al. [22]. Histopathology was initially evaluated by two pathologists and finally reviewed by a senior pathologist. Basing on IR and Beta cell function, the patients were categorized into 3 groups [23]. [A (Insulin Resistant): IR > 2; HOMA-B% > 50; B (normal): IR < 2; HOMA-B% > 50%; C (Impaired beta cell function): IR < 2; HOMA-B% < 50%]. After excluding the diabetic and prediabetics, the remaining 213 NAFLD patients were divided into four quartiles according to the IR values, and comparison was made between the patients in the first and fourth quartiles' extreme IR values.

Statistical analysis was done using SPSS 17.0 software; independent sample *t*-test was used to compare the variables between IR and non-IR groups. Z test was used to compare significance between two proportions. Comparison of more than two variables were made using one way