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Original article

# Less liver fibrosis in metabolically healthy compared with metabolically unhealthy obese patients with non-alcoholic fatty liver disease

Y. Gutiérrez-Grobe [a,1], E. Juárez-Hernández [b,1], B.A. Sánchez-Jiménez [a], M.H. Uribe-Ramos [b], M.H. Ramos-Ostos [c], M. Uribe [a], N.C. Chávez-Tapia [a,b,*]

[a] Obesity and Digestive Diseases Unit, Medica Sur Clinic & Foundation, Mexico City 14050, Mexico
[b] Translational Research Unit, Medica Sur Clinic & Foundation, Mexico City 14050, Mexico
[c] Diagnosis and Treatment Unit, Medica Sur Clinic & Foundation, Mexico City 14050, Mexico

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ABSTRACT

*Aim.* – This cross-sectional study evaluated liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD), and compared the characteristics of metabolically healthy obese (MHO) with metabolically unhealthy obese (MUHO) patients.
*Methods.* – The study was nested within a randomized clinical trial (RCT) and included obese patients with NAFLD, as determined by liver ultrasonography. Fibrosis was assessed by transient elastography, and AST-to-platelet ratio index (APRI) and NAFLD score. Patients were compared according to obesity phenotype using various accepted criteria.
*Results.* – The RCT included 1024 patients with NAFLD, of whom 428 (41.7%) were included in the present study. The prevalence of MHO ranged from 1.2% to 63%, depending on the criteria used. According to various criteria for metabolic health, obese patients had less liver fibrosis. MHO patients, as defined by all criteria, showed a significantly lower prevalence of advanced liver fibrosis (F3–F4) than MUHO on transient elastography (16.5% *vs.* 28%, respectively; $P \leq 0.05$).
*Conclusion.* – MUHO patients are at higher risk of liver fibrosis and, therefore, the identification of obese patients with 'healthy' characteristics is imperative as their entire clinical work-ups are likely to differ.


## 1. Introduction

Obesity is a chronic disorder with an increasing worldwide prevalence due to changes in lifestyle, dietary habits, insufficient physical activity, stress and easy access to 'fast food'. In the US, the prevalence of obesity exceeds 34% while, in Mexico, the prevalence is 21% in men and 33% in women [1,2].

Obesity is a well-known key contributing factor to insulin resistance, type 2 diabetes, dyslipidemia, high blood pressure and cardiovascular disease [3]. However, previous studies have suggested that not all obese patients exhibit the same metabolic features. Sims et al. [4] proposed the presence of a phenotype in obese patients characterized by a lack of comorbidities associated with the metabolic syndrome (MetS), and a lower risk of future cardiovascular events and, therefore, lower mortality. These patients are known as the 'metabolically healthy obese' (MHO), and show near-normal insulin sensitivity, no high blood pressure, and normal lipid and hormone profiles. Some studies have suggested that nearly 30% of the obese population exhibit this phenotype of obesity [5,6].

In people with non-alcoholic fatty liver disease (NAFLD), the presence and severity of fibrosis predict their overall and liver-related mortality. The features most closely related to advanced fibrosis in these patients include advanced age, high body mass

*Abbreviations:* BMI, body mass index; MHO, metabolically healthy obese; NAFLD, non-alcoholic liver disease; MUHO, metabolically unhealthy obese; RCT, randomized clinical trial; APRI, AST-to-platelet ratio index; HOMA-IR, homoeostasis model assessment for insulin resistance; NLP3, NOD-like receptor family pyrin domain-containing 3.

* Corresponding author at: Obesity and Digestive Diseases Unit and Translational Research Unit, Medica Sur Clinic & Foundation, Puente de Piedra 150 Toriello Guerra Tlalpan, ZC 14050 Mexico City, Mexico.
*E-mail address:* khavez@gmail.com (N.C. Chávez-Tapia).
[1] These authors contributed equally.

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index (BMI) scores, and the presence of comorbidities associated with obesity and MetS.

Liver biopsy is the gold standard for the diagnosis of fibrosis; however, it is an invasive method with some limitations, including a high risk of periprocedural complications and mortality [7]. Because of these limitations, non-invasive methods for assessment of liver fibrosis have been developed, such as transient elastography, which can measure liver stiffness with good sensitivity and specificity [8].

The aim of the present study was to evaluate liver fibrosis in patients with NAFLD diagnosed by non-invasive methods and to compare the characteristics of MHO patients with metabolically unhealthy obese (MUHO) patients.

## 2. Methods

### 2.1. Patient population

The present cross-sectional study was nested within a randomized clinical trial (RCT; NCT01874249) carried out at the check-up unit of the Medica Sur Clinic & Foundation from June 2012 to September 2014. The study was approved by the Ethics Committee and conformed to the Helsinki Declaration.

The study population was selected from a series of consecutive patients diagnosed with NAFLD. All obese patients with a BMI $> 30\ kg/m^2$ were included. Patients were randomized into five intervention groups according to the protocol of the RCT. Exclusion criteria included alcohol intakes >20 g/day, known liver disease and current use of medication. The absence of any viral, genetic, autoimmune and drug-induced liver disease was confirmed in every patient by laboratory tests and by a questionnaire about medications taken at the time of the check-up.

The anthropometric parameters collected were age, gender, weight, height, blood pressure, waist circumference, hip circumference, body-fat percentage (as measured by body bioelectrical impedance analysis; Tanita Corporation, Tokyo, Japan) and BMI [calculated as weight (kg)/height ($m^2$)]. Complete blood counts, liver function tests and lipid panels were also performed.

### 2.2. Diagnosis of NAFLD and liver fibrosis

The presence of NAFLD was identified by liver ultrasonography based on the presence of a bright liver in fasting patients. A 3.5-MHz transducer (Elegra; Siemens Healthineers, Erlangen, Germany) was used to obtain a sagittal view of the right lobe and transverse view of the lateral segment of the liver, plus any focal areas of altered echotexture. Fibrosis was diagnosed based on liver transient elastography (FibroScan™ 502 Touch, Echosens, Paris, France), using an XL probe (2.5-Hz frequency), from a single measurement performed by a single operator. For the FibroScan procedure, patients were placed in the dorsal decubitus position with the right arm extended [9], and fibrosis was classified by the Brunt score [10]. Other non-invasive methods used to assess fibrosis were the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and NAFLD fibrosis scores, both of which have been validated in Latin American populations [11]. APRI and NAFLD score were calculated using the following equations: APRI = {AST (IU/L)/[upper normal value of 41 (IU/L)]}/platelet count ($\times 10^9$/L) × 100 [12]; and NAFLD fibrosis score = 1.675 + 0.037 × age (years) + 0.094 × BMI ($kg/m^2$) + 1.13 × abnormal fasting glucose level or diabetes (yes = 1, no = 0) + 0.99 × AAR − 0.013 × number of platelets ($\times 10^9$/L) − 0.66 × albumin concentration (g/dL) [13].

The cut-off values used to define significant fibrosis were >1 for the APRI and >0.676 for the NAFLD score. With the FibroScan procedure, cut-off values for NAFLD were ≥6.0 kPa for F1–F2 stages and ≥9.0 kPa for advanced fibrosis (F3–F4). NAFLD and APRI scores were calculated for all our study patients, with FibroScan performed in 150 patients (according to the RCT protocol).

### 2.3. Determination of metabolic health

The aim of our study was to evaluate liver fibrosis in MHO and MUHO patients as classified by different accepted criteria, using the available clinical and biochemical data from the RCT, for this reason other criteria were not considered [14–16]. The characteristics used to define MHO patients (Table 1) are criteria that have been applied in cohort [5,17–21] and cross-sectional studies [22,23]. The major differences among them are the inclusion (or not) of C-reactive protein (CRP), waist circumference, triglycerides and patients with diabetes, as well as differences in cut-off values for CRP and waist circumference. These criteria have been compared to evaluate cardiovascular risk in MHO patients [24].

### 2.4. Statistical analysis

The distribution of variables was determined by the Kolmogorov–Smirnov test, while continuous variables were described using measures of central tendency and the standard deviation (SD) or interquartile range (IQR). Mean values were compared using Student's *t* test, while non-parametric data were analyzed by the Mann–Whitney U test. Categorical variables have been expressed as numbers and percentages, and compared using Fisher's exact test. A $P$ value $< 0.05$ was considered significant. All statistical analyses were performed using statistical SPSS/PC version 15.0 software (SPSS, Chicago, IL, USA).

## 3. Results

The RCT included 1024 patients with NAFLD, of whom 428 (41.7%) were obese and included in the present substudy. Fig. 1 shows the distribution of the MHO patients according to various diagnostic criteria.

Most patients were male (84.6%) with a mean age of 47.6 ± 8.7 years and a mean BMI of 33.4 ± 3.2 $kg/m^2$. Other general patients' characteristics are shown in Table 2. According to each non-invasive method, the prevalence of fibrosis in MHO and MUHO patients according to NAFLD score was 48.8% ($n$ = 209) for F0–F2 and 4.2% ($n$ = 18) for F3–F4 and, by APRI, 2.3% ($n$ = 10) and, by transient elastography, 13.1% ($n$ = 56) for any stage of fibrosis and 7% ($n$ = 30) for advanced fibrosis; however, 10.9% ($n$ = 16) of the studies were not reliable.

In patients with a positive diagnosis of MHO by all criteria, moderate-to-severe steatosis was more commonly seen (59.8% *vs.* 40.2% in MUHO; $P$ = 0.02). The prevalence of diabetes and high

**Table 1**
Criteria used to define metabolically healthy obese (MHO) subjects.

| Study | Year | Definition of MHO | |
|---|---|---|---|
| | | Body mass index | Number of MetS criteria |
| Katzmarzyk | 2005 | ≥30 $kg/m^2$ | <3 |
| Song | 2007 | ≥30 $kg/m^2$ | <3[a] |
| Voulgari[e] | 2011 | ≥30 $kg/m^2$ | <3 |
| Hosseinpanah | 2011 | ≥30 $kg/m^2$ | <3[b] |
| Hamer | 2012 | ≥30 $kg/m^2$ | <2[c] |
| Ortega | 2013 | ≥30 $kg/m^2$ | ≤1[a] |
| Irace | 2009 | >29.9 $kg/m^2$ | <3 |
| Khan | 2011 | >25 $kg/m^2$ | <3[d] |
| Consensus | 2009 | >30 $kg/m^2$ | <3 |

[a] Waist circumference (WC) excluded.
[b] WC ≥ 89 cm in women, ≥91 cm in men, blood pressure ≥140/85 mmHg.
[c] Triglycerides excluded, but including C-reactive protein (CRP) > 3.0 mg/dL, WC > 88 cm in women, >102 cm in men.
[d] WC excluded, but including CRP ≥ 3.0 mg/dL.
[e] Excluding patients with diabetes.

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