# Association between non-alcoholic fatty liver disease and liver function/injury markers with metabolic syndrome components in class III obese individuals

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## Summary

**Objective:** To investigate the association between non-alcoholic fatty liver disease (NAFLD) and liver function/injury markers with components of metabolic syndrome (MS) in class III obese individuals. **Methods:** The study population consisted of 144 patients with class III obesity (body mass index [BMI] ≥ 40 kg/ m²). MS was diagnosed according to the National Cholesterol Education Program – Adult Treatment Panel III (NCEP ATP III) criteria, by determining the lipid profile, blood glucose, and basal insulin. Liver function/injury markers were also quantified. Insulin resistance (IR) was measured by HOMA-IR and NAFLD diagnosis was established by magnetic resonance imaging (MRI). Statistical calculations were performed by SPSS version 13.0. The association was assessed by the Mann-Whitney and Chi-square tests, with a level of significance set at 5%. **Results:** There was a significant association between the diagnosis of MS and NAFLD ($\chi^2 = 6.84$, $p = 0.01$). As for the diagnostic components of MS, there was a positive and significant association between HDL-C ($p = 0.05$), waist circumference ($p < 0.05$), and hypertension ($\chi^2 = 4.195$, $p = 0.041$) with NAFLD. HOMA-IR ($p < 0.001$) also showed a positive association with liver disease. **Conclusion:** A positive and significant association between NAFLD and components of metabolic syndrome in class III obese individuals was observed, suggesting the need and importance of monitoring these components in NAFLD screening.

**Keywords:** Fatty liver; metabolic syndrome X; obesity.



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## Introduction

The non-alcoholic fatty liver disease (NAFLD) is characterized by accumulation of fat in the liver when it exceeds 5-10% of its weight[1]. In addition to leading to major histopathological alterations, it may be associated with elevated liver enzymes and abnormal liver function, ranging from steatosis to steatohepatitis, fibrosis, and cirrhosis[2].

Although diagnosed worldwide, there are variations in prevalence, reaching about 20-30% in western countries[3]. In the United States, where 25% of the adult population is obese, the disease occurs in more than two-thirds of these individuals and in more than 90% of class III obese individuals[4]. It is estimated that 2% to 3% of the population has nonalcoholic steatohepatitis (NASH)[3].

Approximately 74% to 90% of patients who undergo liver biopsy show alterations due to triacylglycerol accumulation[2,5]. The disease is highly prevalent (88.7%) in obese patients undergoing bariatric surgery[6], and the likelihood of developing steatohepatitis is increased in class III obesity, with 15% to 20% of these patients diagnosed with NASH[7].

Recent studies have shown increased prevalence and higher incidence of cardiovascular disease (CVD) in individuals with NAFLD. These studies have shown hepatic steatosis as an independent risk factor for the development of this disease[8,9].

Metabolic syndrome (MS), which involves the combination of risk factors for CVD such as insulin resistance (IR), abdominal fat, dyslipidemia, glucose intolerance, and hypertension, has often been associated with more severe liver abnormalities[10].

## Objective

To investigate the association between NAFLD and liver function/injury markers with the components of MS in individuals with class III obesity treated at a private clinic in the city of Rio de Janeiro, Brazil.

## Methods

The study included 144 individuals with class III obesity, of both genders, with a mean age of 36.5 (11.7) years, from a private clinic in the city of Rio de Janeiro in the period from January to December 2006, representing approximately 60% of the total annual attendance. Pregnant women, nursing mothers, individuals with liver disease other than NAFLD (positive serology for hepatitis B and C), with daily intake of more than 20 grams of ethanol, and those using hepatotoxic drugs were excluded from the study. NAFLD diagnosis was achieved by magnetic resonance imaging assessment.

The class III obesity classification was based on the World Health Organization (WHO) criteria (1998)[11], defined by body mass index (BMI) ≥ 40 kg/m² for the diagnosis of this class of obesity. BMI calculation was performed using the anthropometric measurements weight (kg) and height (m²)[12]. Blood pressure (BP) and waist circumference (WC) were also measured. WC was measured with the patient standing with the abdomen relaxed, arms at the sides of the body and feet side by side, using an inextensible tape. The tape surrounded the individual's largest abdominal sagittal diameter, as individuals with class III obesity have what is called an abdominal "apron"[13].

For biochemical evaluation, a blood sample was obtained by venipuncture, after a 12-hour fast. The lipid profile, blood glucose, and basal insulin levels were evaluated. Basal insulin was quantified by reversed phase high performance liquid chromatography (RP-HPLC). Additionally, the following markers of liver function (albumin, total bilirubin [TB] and activated prothrombin time [APT] – the latter described in seconds above the control) and liver injury (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma glutamyl transpeptidase [GGT]) were evaluated.

IR was identified by HOMA-IR[14], obtained by the formula: HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5. The receiver operating characteristic curve (ROC) was used for the identification of IR. To determine the gold standard for implementing the ROC curve, with subsequent identification of the value of highest IR sensitivity and specificity in this sample, reference values in the literature for healthy adult subjects were used[15-18], thus obtaining a value > 4.0 as cutoff point.

The diagnosis of MS was performed according to the National Cholesterol Education Program – Adult Treatment Panel III[19] (NCEP - ATP III), which defines MS by the presence of at least three of the following components: WC ≥ 102 cm in men and ≥ 88 cm in women, HDL-c ≤ 40 mg/dL in men and ≤ 50 mg / dL in women, triglycerides ≥ 150 mg/dL, fasting glucose ≥ 110 mg / dL, and blood pressure ≥ 130/85 mmHg.

Statistical calculations were carried out using SPSS, release 13.0. The comparison of numerical and continuous variables (age, WC, lipid profile, blood glucose, insulin, and liver function/injury tests) between groups with and without NAFLD was performed by the Mann-Whitney test. Associations between categorical variables (presence or absence of hypertension (SAH), NAFLD, IR and MS) were performed using the chi-square ($\chi^2$) test. The coefficient of the proportion was performed to measure the degree of association between the categorical variables NAFLD and metabolic syndrome. The ROC curve was used to identify the most accurate value of HOMA-IR to diagnose IR. The significance level was set at 5%.

This study was approved by the Ethics Committee in Research of the Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro.

## Results

The sample consisted of 144 subjects, of which 43 (29.4%) were males and 101 (70.6%) were females. The mean age of subjects was 36.5 (11.7) years, ranging from 19 to 64 years.

There was no significant difference between the mean age (p = 0.08) and BMI (p = 0.16) according to gender. The prevalence of NAFLD in the study group was 71% with a positive diagnosis in 75.0% and 69.3% of men and women, respectively.

Of the 144 class III obese patients studied 49% had metabolic syndrome, and 81.4% of those with NAFLD also had the diagnosis of MS, showing a significant association between MS and NAFLD (p = 0.01) (Table 1). Table 2 shows a comparative analysis between the groups with and without a diagnosis of NAFLD. The mean HDL-c was significantly lower in patients with NAFLD. Regarding the anthropometric component of MS, the mean WC was significantly higher in subjects diagnosed with NAFLD. The means of AST and ALT levels were significantly higher, and the APT means were significantly lower in this group. Considering the markers of liver function and injury in individuals with or without a diagnosis of MS, significantly higher means of liver injury markers, ALT and GGT, were observed in subjects who had MS (Table 3).

When association tests for categorical variables were applied, the only component of the lipid profile that was associated with NAFLD was HDL-c, which was below the amount considered adequate by the NCEP-ATP III in 83.0% of patients with liver disease (p = 0.047, $\chi^2 = 4.13$).

When analyzing the HOMA-IR, it was observed that 75.5% of subjects had insulin resistance according to this parameter, with only 15% of individuals not presenting the disease (p < 0.001, $\chi^2 = 5.641$). Furthermore, patients with NAFLD had a significantly higher mean of this index.

Finally, systemic arterial hypertension (SAH) was also associated with the presence of NAFLD (p = 0.041, $\chi^2 = 4.195$), with 57% of individuals who had a diagnosis of liver disease also having SAH.

**Table 1 –** Association between the presence of NAFLD and diagnosis of MS

| | Presence of MS | | Absence of MS | | p-value | $\chi^2$ | Coefficient of contingency |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | |
| Presence of NAFLD | 57 | 81.4 | 45 | 61.6 | 0.01 | 6.84 | 0.21 |
| Absence of NAFLD | 13 | 18.6 | 29 | 38.4 | | | |

NAFLD, non-alcoholic fatty liver disease; MS, metabolic syndrome.

**Table 2 –** Comparison between the means (SD) of biochemical and anthropometric variables between the individuals with and without NAFLD

| Variables | Presence of NAFLD (n =102) | Absence of NAFLD (n = 42) | p-value |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | |
| WC (cm) | 126.5 (15) | 121.9 (11.6) | 0.050 |
| AST (U/L) | 25.9 (10.2) | 22.4 (14.3) | 0.003 |
| ALT (U/L) | 36.5 (21.1) | 27.9 (19.1) | 0.003 |
| Bilirubin (mg/dL) | 0.56 (0.22) | 0.58 (0.22) | 0.585 |
| GGT (U/L) | 40.9 (29.8) | 45.1 (65.8) | 0.452 |
| Albumin (g/dL) | 4.4 (3.5) | 4.0 (0.4) | 0.869 |
| APT | 0.24 (0.59) | 0.31(0.39) | 0.042 |
| Total cholesterol (mg/dL) | 201.4 (41.8) | 193.7 (28.0) | 0.488 |
| Triglycerides (mg/dL) | 151.2 (76.0) | 134.3 (66.5) | 0.149 |
| HDL-c (mg/dL) | 45.9 (11.20) | 49.1 (8.8) | 0.050 |
| LDL-c (mg/dL) | 122.1 (38.5) | 113.6 (37.5) | 0.578 |
| Basal glycemia (mg/dL) | 100.3 (25.4) | 95.8 (23.9) | 0.132 |
| Basal insulin (μU/mL) | 20.59 (13.26) | 18.57 (12.27) | 0.141 |
| HOMA-IR | 4.4 (2.4) | 2.4 (0.9) | 0.000 |

SD, standard deviation; NAFLD, non-alcoholic fatty liver disease; WC, waist circumference; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; APT, seconds above the control.

**Table 3 –** Comparison between the means (SD) of the biochemical variables of liver function/injury between individuals with and without MS

| Variables | Presence of MS (n = 70) | Absence of MS (n = 74) | p-value |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | |
| AST (U/L) | 26.2 (11.1) | 23.6 (12.0) | 0.112 |
| ALT (U/L) | 37.7 (23.03) | 30.4 (18.1) | 0.022 |
| Bilirubin (mg/dL) | 0.56 (0.20) | 0.56 (0.24) | 0.579 |
| GGT (U/L) | 46.1 (33.03) | 38.5 (50.94) | 0.006 |
| Albumin (g/dL) | 4.6 (4.3) | 4.0 (0.35) | 0.242 |
| APT | 0.26 (0.44) | 0.30 (0.28) | 0.057 |

SD, standard deviation; MS, metabolic syndrome; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; APT, seconds above the control.

## Discussion

MS was diagnosed in 81.4% of individuals affected by NAFLD. This association confirms the findings by Ferreira et al.[20] and Soler et al.[21], who found a higher prevalence of MS in individuals with NAFLD. The growing recognition of the association between NAFLD and MS has been stimulating the interest in the possible role of this liver disease in the risk for the development of cardiovascular disease[22].

The diagnostic criteria of MS that were associated with NAFLD were WC, HDL-c, and blood pressure. Bitencourt et al.[6] showed a similar trend when evaluating the clinical and histological features of NAFLD in obese patients undergoing bariatric surgery, in which more than 50% of the cases had diagnostic criteria for MS.

Several studies have shown that the accumulation of body fat in the abdominal region, regardless of the individual's total body fat content, is an independent predictive factor for fat accumulation in hepatocytes and, therefore, crucial in the pathogenesis of NAFLD[23,24]. The WC is considered more sensitive to metabolic alterations and/or cardiovascular morbimortality than the simple increase in body weight measured by BMI[21].

In the present study, the mean WC was significantly higher in the group with the disease. This association is explained by the lipolytic nature of visceral fat, due to lower insulin sensitivity and higher concentration of β-receptors in this region, and its proximity to the portal system[25]. Visceral fat is drained directly into the portal system, exposing the liver to large amounts of free fatty acids, which increases the hepatic synthesis of triglycerides and may also decrease its ability to secrete them, resulting in accumulation in hepatocytes[26].

The importance of monitoring the WC in individuals with NAFLD was described in the study by Yoo[27], which suggested that this component can be used in the screening of NAFLD in Korean adults by means of specific values for the screening of the disease.

The only lipid fraction and diagnostic factor of MS that was associated with the presence of the disease was HDL-c, which showed a significantly lower mean in subjects with NAFLD. Generally, hypertriglyceridemia and low HDL-c are the lipid fraction disorders most often associated with the presence of steatosis[28]. Boza et al.[29] observed significantly lower mean HDL-c levels in class III obese individuals with NAFLD, when compared with the group without the disease, which is the only lipid fraction variable that was associated with NAFLD diagnosis. In the study by Dixon et al.[30], which evaluated possible predictors of NAFLD in these individuals, no correlation was observed between any lipid fraction with more advanced stages of the disease. However, a weak negative correlation was observed between levels of HDL-c and the degree of simple steatosis, graded according to the lobular parenchyma involvement. The authors suggest that dyslipidemia may have a greater impact on the disease in class I or class II obesity and a lower influence in class III.

Marchesini et al.[31], who studied the components of MS in 304 individuals with NAFLD, found that over 90% of patients with some degree of liver disease have at least one component of this syndrome, with approximately one third of individuals having all components. Moreover, they observed a higher prevalence of disease in diabetic individuals, being associated to 20% to 75% of cases. However, this prevalence seems to be more related to the IR than to the hyperglycemia.

In the present study, a significant association between IR, as indicated by the HOMA-IR, and the presence of NAFLD was observed. Probably due to the accumulation of abdominal fat, metabolic abnormalities such as these are very prevalent in these individuals[21], which is in agreement with studies that suggest that NAFLD is a component of MS, associated with visceral adiposity and IR[23,32].

IR, both in the liver and adipose tissue, has been strongly associated with NAFLD[33,34], as IR has been shown to increase with disease severity[35]. Compared with control subjects, individuals with NAFLD have fatty acid oxidation inhibition, shown as decrease in glucose uptake and use as fuel, which suggests the possibility that IR may be an

intrinsic defect of the disease and the lower response to insulin in adipocytes stimulates tissue lipolysis, contributing to the progressive accumulation of lipids in hepatocytes through an increased flow of free fatty acids in the liver[36]. The storage of lipids can reach toxic levels and exacerbate the production of reactive oxygen species in the liver, stimulating the proliferation of macrophages and TNF-α, which also interfere with insulin sensitivity[37]. Thus, abnormal lipid peroxidation results in direct liver damage, with inflammation and even fibrosis[21].

A limitation of the present study was the method used to assess IR. The hyperinsulinemic euglycemic clamp technique is considered the gold standard for IR evaluation, as it allows the evaluation of insulin sensitivity in both liver and peripheral tissues. However, this method is not very practical and it is high-cost to be used in population-based studies or in clinical practice[38]. To date, there is no IR laboratory method that can meet all of the following criteria for universal acceptance and use: sufficiently precise measures so that IR can be compared between individuals, measures that can be obtained independently from the glucose from which it is obtained, data collection within the physiological range of insulin action and low cost and possibility of use in clinical practice.

HOMA is a simple and low cost method for the evaluation of IR but it has some limitations. In this model, IR measurement is performed for total body surface, considering that insulin sensitivity would be the same in the liver and peripheral tissues. There is some criticism regarding the specificity of the techniques used to evaluate basal insulin, which can be corrected by using specific and standardized methodologies that do not suffer influence of pro-insulin levels. The proportionality between insulinemia and the degree of IR is also debatable[39]. Despite its limitations, this has been the method most often used to assess insulin resistance in population studies.

Liver damage can be identified through liver damage markers: AST, ALT, and GGT. In the present study, the means of AST and ALT, although within the reference values, were significantly higher in those with NAFLD. Furthermore, higher mean levels of ALT and GGT were observed in individuals with MS.

The present study did not assess the severity of NAFLD, which can justify the fact that no difference was found in the means of the other liver functions and injury tests in individuals with and without MS, as well as explain the fact that the mean values of liver function tests are within the normal range in the group with the disease, as more severe alterations at liver function and injury tests are observed only in individuals with advanced liver disease. However, data published in the "Third national health and nutrition survey" showed a significant association between high concentrations of ALT and insulin resistance, diabetes mellitus type 2, and MS[40]. Moreover, Koller et al.[41] suggested that the markers of liver injury may be indicators for the screening of individuals with MS or its components. However, further studies should be performed to determine the association between MS and NAFLD severity.

## Conclusion

In the present study, the association between the diagnosis of NAFLD and MS was observed. MS components cause metabolic alterations, such as insulin resistance and oxidative stress that may contribute to the progression and worsening of liver disease. Therefore, the determination and monitoring of these components are of crucial importance for the screening of NAFLD.

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