

Non-alcoholic fatty liver in patients candidates for bariatric surgery: description and evaluation of serum fibrosis markers.

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Summary:

Obesity has become a global epidemic, closely related to the increase in the prevalence of non-alcoholic fatty liver (NAFLD).

It defines a spectrum of histological abnormalities ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH) in a non-alcohol-consuming person. Insulin resistance is the main factor related to NAFLD.

Obesity is considered a state of chronic inflammation, since adipose tissue is an important source of inflammatory mediators and adipokines.

In this article, we describe the prevalence and risk factors of NAFLD in patients with morbid obesity in our series, evaluating, on the one hand, the relationship between the systemic inflammatory state of morbidly obese patients according to inflammatory markers in the white series and its association with NASH. and on the other hand, the concordance of the non-invasive serum fibrosis markers (NAFLD, FIB4, APRI score) with the definitive AP.

According to our results, the Neutrophil-Lymphocyte index could be an easy way to assess the inflammatory state of these patients, and the NAFLD score is not a good marker of fibrosis in patients with morbid obesity.

Keywords:

- Waiting Lists
- Obesity
- Bariatric Surgery
- Health Management

Introduction

According to the 2016 WHO data, more than 1.9 billion adults were overweight and, of these, 650 million were obese, obesity tripling in the last 45 years.

Furthermore, the increased incidence and severity of obesity leads to the development of metabolic syndrome and comorbidities, including, among others, type 2 diabetes mellitus (DM), non-alcoholic fatty liver (NAFLD), arterial hypertension (HTN).), dyslipidemia (DLP), etc. ... leading globally to an increase in mortality in the obese population².

NAFLD is defined as the presence of excessive fat in the liver, demonstrated by imaging techniques such as abdominal ultrasound, computed tomography, or magnetic resonance, with pathological anatomy being the definitive diagnostic method. It is a diagnosis of exclusion, previously ruling out other liver disorders such as hepatitis B or C virus (HCV), autoimmune diseases, metabolic liver diseases, absence of alcohol or drug abuse, or genetic abnormalities.

NASH defines a spectrum of histological abnormalities ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH) in a non-alcohol-consuming person. NAFLD has the potential to progress to cirrhosis, hepatocarcinoma, and end-stage liver disease³.

In fact, NAFLD is the most frequent cause of liver disease in the western world⁴ and the third most frequent cause of liver transplantation⁵. Insulin resistance is the main factor related to the development of NAFLD⁶, although obesity

has been shown to be a factor associated with NAFLD, independently of other metabolic factors. Obesity involves a state of chronic inflammation. This is because adipose tissue acts as a highly active endocrine tissue⁷, an important source of inflammatory mediators and adipokines. Adipokines are balanced in healthy individuals of normal weight, but this balance is altered in patients with obesity⁸, since the adipokines secreted by fat tissue have a more steatogenic, inflammatory and fibrogenic profile. In addition, immune cells (macrophages, B lymphocytes, T lymphocytes, and neutrophils), which are infiltrating adipose tissue (and which increase as it expands) also produce classic cytokines (IL-1, IL-6, tumor necrosis factor). [TNF] - α ...), which interact with the adipokines themselves.

Fibrosis is a prognostic factor for progression from NAFLD to NASH. There are several markers that can be used to measure the inflammatory status of these patients, including cytokines, however these are expensive and difficult to determine in daily clinical practice. For this reason, it would be very useful to find other non-invasive fibrosis markers that are more accessible on a daily basis. The objectives of our work are:

- 1) Describe the prevalence and risk factors of NAFLD in our series of patients with morbid obesity who are candidates for bariatric surgery.
- 2) Assess whether there is a relationship between the systemic inflammatory state of morbidly obese patients according to the inflammatory markers of the white series and its association with NASH.

3) To evaluate the non-invasive serum fibrosis markers (NAFLD, FIB4, APRI score) in this population and their agreement according to the pathological anatomy (PA).

Material and methods

This is a prospective cross-sectional study carried out in a single center (Hospital Universitario MútuaTerrassa). A consecutive inclusion of 111 morbidly obese patients undergoing bariatric surgery was performed.

Patients who met the criteria for bariatric surgery established by SECO9 (BMI ≥ 40 kg / m²) +/- (were selected one or more comorbidities) and who had been approved by the multidisciplinary committee of bariatric surgery of our center. Age: between 18-65, and selected cases > 65 years old.

The inclusion period ran between October 2017 and March 2019. The following exclusion criteria were used: the presence of hepatopathy or el excessive consumption of alcohol (> 30 g/d men, > 20 g/d women.)

Data collection:

The following were used as clinical data: age, gender, IMC, ethnicity, smoking and pathological background. Analytical data: metabolic, nutritional, and hepatic data were collected. There was also an MRI previous to the surgery on order to assess hepatic alterations and cholelithiasis. Indexes of the white series were estimated: Neutrophil / lymphocyte index (INL). Platelet / lymphocyte Index (IPL) and the non-invasive fibrosis markers (APRI, FIB-4 and NAFLD score). An intraoperative hepatic biopsy was performed for the anatomopathological analysis.

A univariant analysis was performed with the test X² or the McNemar test for the paired qualitative variables and the test of the Student t for quantitative variables. We also performed the multivariate logistic regression analysis in order to assess the risk factors of the EHNA. In order to evaluate the concordance of the fibrosis tests, the Cohen test of kappa was used.

Results

111 patients (67% female, 97% Caucasian) with a mean age and BMI of 48 ± 9.4 years and 45.8 ± 6.3 kg / m², respectively, were included. 49% (54) were hypertensive, 27% (30) diabetics, 44% (48) had insulin resistance and 32% (35) had metabolic syndrome.

The prevalence of NAFLD by ultrasound was 74% (82/111) and by histology 67% (75/111): 51% (56/111) with simple steatosis and 16% (18/111) with NASH. One patient was cirrhotic (0.9%) and 4 had some degree of fibrosis (3.6%). In the univariate analysis, the factors statistically significantly associated (p < 0.005) with NASH were diabetes, basal glycemia, triglycerides, and metabolic syndrome.

VARIABLES	NASH (n=18) vs. No NASH (n=88)	P
Diabetes mellitus 2	64,2% / 20%	0,002
Fasting blood sugar (mg/dL)	150 / 109	0,001
Triglyceride (mg/dL)	197,7 / 134,8	0,041
Metabolic syndrome	64,2% / 25,3%	0,006

Table 1, NASH: non-alcoholic steatohepatitis

When performing the multivariate analysis, we see that patients with DM have a 7-fold higher risk of developing NASH than non-diabetic patients. Regarding the white series indices, the INL was associated with NASH, while the ILM and IPL indices were not.

VARIABLE	NASH / NO NASH	P
NEUTROPHILE/LYMPHOCYTE	3,9 / 2,1	0,014
PLATELET/LYMPHOCYTE	135,5 / 125,2	0,07
LYMPHOCYTE/MONOCYTE	5,27 / 5	0,17

Table 2, NASH: non-alcoholic steatohepatitis

In the case of fibrosis scores, initially developed to evaluate patients with chronic HCV infection, APRI and FIB4 showed quite similar results since 95% of patients in one and 92% in the other were classified as absence of fibrosis, and both classified 1% of the patients as advanced fibrosis. In contrast, NAFLD erroneously classifies more than 37% of patients as advanced fibrosis. The differences between NAFLD, APRI and FIB4 were significant.

SCORE	PARAMETERS	N, %
NAFLD n= 111	Age, BMI, glucose/DM, AST, ALT, platelets, albumin	F0-F2 30 (27,3%) Indeterminate 40 (34,9%) F3-F4 41 (37,3%)
FIB4 n= 111	Age, AST, ALT, platelets	F0-F2 106 (95,4%) Indeterminate 4 (3,7%) F3-F4 1 (0,9%)
APRI n= 111	AST/platelets	F0-F2 102 (91,9%) Indeterminate 8 (7,2%) F3-F4 1 (0,9%)

(McNemar test p<0.005 NAFLD vs. FIB-4 i APRI)

Table 3

APRI and FIB-4 scores presented a moderate degree of agreement regarding histology (k = 0.48), but the NAFLD score erroneously classified 37.3% (31/83) of patients as advanced fibrosis and presented a degree of agreement very bad (k = 0.03). We believe that this could be due to the fact that the NAFLD score is the only one that includes BMI among its parameters, making the results of this score automatically high in patients with morbid obesity.

Discussion

In our work, the high rate of NAFLD in patients who are candidates for bariatric surgery is revealed, with percentages even higher than ours in the literature 10.



Regarding the factors statistically significantly associated with NASH, we found DM, basal glycemia, triglycerides, and metabolic syndrome, seeing that mainly DM significantly increases the risk of developing it, which coincides with what has been found in the literature, which describes that NAFLD is the consequence at the liver level of insulin resistance 11.

As for the white series indexes, the INL was associated with NASH. This could be very useful since fibrosis is the most important prognostic factor in the progression from NAFLD to NASH12 and even to cirrhosis, and at the moment we do not have any other marker as easy and cheap to calculate as INL.

Until now, there was no study comparing the three most widely used serum fibrosis markers (NAFLD score, FIB-4 and APRI) in morbidly obese patients and their agreement with AP.

The systematic performance of the liver biopsy has allowed us to verify that the NAFLD score does not have a good correlation with the AP results since it overestimates the risk of fibrosis. We believe that the BMI factor in this formula weighs heavily on the outcome and could bias the morbidly obese patient population. The great correlation that exists between obesity and NAFLD may be determined by metabolic factors, rather than by weight gain per se.

Conclusion

NAFLD is a very common pathology in patients who are candidates for bariatric surgery, with percentages in our series of 67% steatosis and 16% steatohepatitis.

The INL is associated with NASH and is a very simple and cheap marker to calculate. The NAFLD score, unlike APRI and FIB4, is not a good marker of fibrosis in patients with morbid obesity..

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