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Journal of Hepatology 45 (2006) 600–606

Journal of Hepatology

www.elsevier.com/locate/jhep

Special article

Hepatic histology in obese patients undergoing bariatric surgery

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***Background/Aims*: Obesity is one of the most important clinical associations with non-alcoholic steatohepatitis (NASH). Our aim was to assess the prevalence of non-alcoholic fatty liver disease (NAFLD)/NASH in morbidly obese patients and the risk factors to more aggressive liver disease in this population.**

***Methods*: Review of available studies on prevalence of NAFLD/NASH in severely obese patients submitted to bariatric surgery.**

***Results*: Twelve observational and transversal studies were included, with consecutive recruitment, and prospective evaluation of data, summing 1620 patients with severe obesity. Prevalence of steatosis and NASH was 91% (range: 85–98%) and 37% (24–98%), respectively, with unexpected cirrhosis in 1.7% (1–7%). NASH was not related with age or body mass index, but there was an association between male sex and NASH/hepatic fibrosis. Diabetes mellitus and insulin resistance were the conditions most frequently associated with NASH, and hypertension with advanced hepatic fibrosis.**

***Conclusions*: There is a very high prevalence of NAFLD in asymptomatic morbidly obese patients, more than one-third presenting histological criteria for NASH. This review underscores the large variations in prevalence of NASH between studies, calling for the need for a better agreement in the use of the histological criteria.**

***Keywords*: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Morbid obesity; Bariatric surgery**

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease that encompasses steatosis alone to non-alcoholic steatohepatitis (NASH) and can progress to cirrhosis and liver failure. NAFLD is one of the most important forms of liver disease in the developed countries, occurring in 20% to 25% of the general population [1], whereas NASH occurs in about 3% [2,3].

Obesity and insulin resistance (IR) are believed to exert the main pathophysiological role in the development of NAFLD [4–8]. The prevalence of obesity has increased tremendously in the last half century [9]. A further increase in the prevalence of NAFLD is expected in the future. However, until recently, few data were available on the prevalence of NAFLD and NASH in severely obese patients, defined as a body mass index (BMI) higher than 35 kg/m^2. Further, the risk factors for a more aggressive liver disease in this population have yet to be clearly defined.

In the last 5 years, investigators have been trying to identify the real prevalence of NAFLD and NASH in the population of severely obese patients admitted to bariatric surgery, with systematic liver biopsy at the time of surgery. Although most studies had a very similar design, still their results were quite dissimilar. Thus, we conducted an in-depth review of available studies on the prevalence and risk factors for NAFLD in

Received 15 May 2006; received in revised form 5 June 2006; accepted 7 June 2006; available online 25 July 2006

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Abbreviations: NAFLD, non- alcoholic fatty liver disesase; NASH, non-alcoholic steatohepatitis; IR, insulin resistance; BMI, body mass index; DM, diabetes mellitus; WHR, waist to hip ratio; AST, alanine aminotransferase; ALT, aspartate aminotransferase.

0168-8278/$32.00
doi:10.1016/j.jhep.2006.06.013

morbidly obese subjects, in order to summarize and evaluate the published data and to discuss discrepant findings.

2. Materials and methods

We conducted a literature search using MEDLINE and Current Contents to identify relevant articles published in any language, until December 2005. We also manually searched the references of retrieved articles to identify additional relevant published studies. Search criteria included MEDLINE medical subject heading terms for NAFLD, NASH, morbidly obesity and bariatric surgery. Studies were eligible if they reported prevalence data regarding systematic liver biopsy in morbidly obese patients submitted to bariatric surgery.

Data elements sought from each included study were protocol-specified (including histological criteria of NASH/NAFLD, and maximum alcohol consumption allowed), study location, demographical data, prevalence of steatosis, inflammation, fibrosis, cirrhosis, NAFLD and NASH, as well as, risk factors for steatosis or NASH. For calculations, we computed the actual number of subjects from each study and performed a pooled analysis of the data.

3. Results

Seventeen studies were selected [10–26], of which five [10,17,20,21,26] were excluded because of their retrospective design or other methodological issues. The remaining twelve publications were transversal, observational studies with a prospective and consecutive recruitment of patients, enrolling a total of 1620 severely obese patients. Their main characteristics are summarized in Table 1.

Inclusion criteria were similar in all studies:

- Indication for bariatric surgery, defined as BMI higher than 40 kg/m^2, or higher than 35 kg/m^2 and significant co-morbidity attributable to obesity;
- Age equal or above 18 years.

Exclusion criteria were also similar in all studies:

- Significant alcohol consumption (this criterion was the most variable among all studies, the most frequent cut-off being 30 g per week in males and 20 g per week in females). Two exceptions were the study of Marceau et al. [11], in which alcohol consumption was not an exclusion criterion, although the majority of patients were abstinent, and the study of Spaulding et al. [16], which did not allow any alcohol consumption;
- Exclusion of other causes of liver disease: hepatitis B and C viruses and metabolic (hemachromatosis, α_1-antitrypsin deficiency or Wilson's disease), autoimmune liver disease or drug-induced liver disease;
- Previous jejunoileal bypass or small bowel resection surgery.

Stratopoulos et al. [25] also excluded patients with known diabetes mellitus (DM).

The definitions of NASH were not uniform in all studies. Marceau et al. used a semi-quantitative grading of steatosis, inflammation and fibrosis [11]; seven studies [13,16,18,19,23–25] used the histopathological classification of Brunt et al. [27], although in a modified form in some cases [24] as well as her stratification model (grading necroinflammation and staging fibrosis). In that classification, NASH diagnosis requires the presence of steatosis in at least 5% to 10% of hepatocytes, as well as lobular inflammation and hepatocellular ballooning, typically in zone 3. Two studies [12,15] used the NASH diagnostic criteria proposed by Lee et al. [28], which require the presence of steatosis and two of the following three: (1) necroinflammatory foci with mononuclear cells and/or neutrophils; (2) ballooning degeneration of hepatocytes with or without Mallory bodies, and (3) pericellular fibrosis. The remaining two studies [14,22] did not clearly specify their diagnostic criteria defining NASH.

Table 1
Main characteristics of the studies

Study	Year	Study location	No. of patients	Women (%)	Age (years)	BMI (kg/m^2)	NASH (%)
Marceau et al. [11]	1999	USA, Canada	551	80	36 ± 9	47 ± 9	–
Dixon et al. [12]	2001	Australia	105	78	41 ± 11	47 ± 7	25
Sepulveda-Flores et al. [13]	2002	Mexico	35	74	33 ± 10	44 ± 8	91
Poniachik et al. [14]	2002	Chile	68	85	39 ± 12	44 ± 8	–
Beymer et al. [15]	2003	USA	48	69	42 ± 10	60 ± 12	33
Spaulding et al. [16]	2003	USA	48	83	NR	51 ± 20	56
Abrams et al. [18]	2004	USA	195	88	41 ± 9	48 ± 7	36
Shalhub et al. [19]	2004	USA	68	87	42 ± 1*	51 ± 1*	37
Ong et al. [22]	2005	USA	212	80	42 ± 10	48 ± 9	24
Boza et al. [23]	2005	Chile	127	62	40 ± 11	42 ± 6	26
Lima et al. [24]	2005	Brazil	112	74	36 ± 10	49 ± 8	57
Stratopoulos et al. [25]	2005	Greece	51	65	NR	53 ± 1*	98
Total	–	–	1620	77	39 ± 10	48 ± 8	37

BMI = body mass index, *standard average error instead of standard deviation. NR, not reported.