

# The liver and bariatric surgery

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## ABSTRACT

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The association between obesity and chronic liver disease is well known. The path that this disorder follows has a very wide clinical spectrum, ranging from asymptomatic steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. The final stages of the disease are irreversible and aggressive, and the progression causes death. Unfortunately, there are no clearly effective treatments for these patients. One of the difficulties in identifying effective treatments is the need for long-term studies since the progression of non-alcoholic steatohepatitis to cirrhosis and its complications occurs slowly. Many different treatments have been studied, but the current mainstays of treatment aim to reduce weight and improve the metabolic disturbances associated with the metabolic syndrome, such as glucose, cholesterol and triglycerides and hypertension. Weight loss and exercise are

among the most promising treatments for nonalcoholic fatty liver disease. It does not take large amounts of weight loss to result in a decrease in liver fat. It is well known that only a minority of patients are able to accomplish this. Bariatric surgery has been shown to be superior to conservative measures with respect to weight reduction in the obese. It can lower the long-term morbidity of obesity by up to 40% and significantly decrease the incidence of illnesses associated with it. Since obesity is the main cause of nonalcoholic fatty liver disease, bariatric surgery is starting to be used as a means of treatment for the disease. Several authors concluded that nonalcoholic fatty liver disease, including steatohepatitis, improved significantly with weight loss after bariatric surgery. (REV MEX ENDOCRINOL METAB NUTR. 2014;1:29-34)

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## MATERIALS AND METHODS

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A systematic electronic literature search of published articles on bariatric surgery and liver diseases related to nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and fatty liver since January 1995 was done. In the term "bariatric surgery", restrictive procedures, such as vertical banded gastroplasty, laparoscopic adjustable gastric banding, sleeve gastrectomy, biliopancreatic diversion and biliopancreatic diversion with duodenal pouch, and Roux-en-Y gastric bypass, were included. The selection of references for the review was based on a validation of the appropriateness of the study design for the stated purpose and a relevant number of patients under study. Primary outcome measures were improvement and/or resolution in the three components of nonalcoholic fatty liver disease (steatosis, steatohepatitis, and fibrosis) after bariatric surgery-induced weight loss.

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## INTRODUCTION

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The association between obesity and chronic liver disease is well known. Fat deposition in the liver and its consequences may occur in patients with metabolic syndrome. The path that this disorder follows has a very wide clinical spectrum, ranging from asymptomatic steatosis to steatohepatitis, fibrosis, cirrhosis<sup>1</sup>, and hepatocellular carcinoma (HCC)<sup>2</sup>. At one end of the spectrum lies simple steatosis, a reversible condition in which there is an accumulation of lipids within the hepatocytes > 5% of liver weight<sup>3-5</sup>. At the other end of the spectrum is nonalcoholic steatohepatitis (NASH), which is steatosis in the presence of necroinflammatory hepatocellular changes. This subset of patients is at an increased risk of progression to fibrosis, cirrhosis, and HCC. The final stages of the disease are irreversible and aggressive, and the progression causes death. The first stages of the disease are silent, and that is the reason why patients are only diagnosed when cirrhosis or HCC are present. Fatty liver disease rarely causes symptoms until the liver disease is far advanced. At most,

there is enlargement of the liver, which may give rise to mild right upper abdominal discomfort and function liver tests (FLT) show an elevated alanine aminotransferase (ALT)<sup>6</sup>. It is very important to detect NASH in the early reversible stages of the disease, when the subjects are still candidates for treatment.

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## WHAT ARE THE DIAGNOSTIC METHODS FOR NONALCOHOLIC FATTY LIVER DISEASE?

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Liver biopsy is still the gold standard for diagnosing NASH and assessing the stage of fibrosis in patients with nonalcoholic fatty liver disease (NAFLD). However, it has many limitations such as high cost, possible side effects and, rarely, death. So the actual recommendation is to do a liver biopsy when non-invasive markers suggest advanced fibrosis and, in indeterminate cases, when the suspicion of fibrosis remains<sup>7,8</sup>. Traditionally, NAFLD is characterized by a hepatocellular pattern of liver-related enzymes with mild elevations (1-2 times the upper limit of normal) in serum ALT and aspartate aminotransferase (AST)<sup>9-11</sup>. However, despite having the disease, up to 50% of NAFLD patients can have normal ALT and AST levels, so in many cases the determination of ALT and AST is not useful for the diagnosis. In this case, the diagnosis should be based in other biomarkers. Several biomarkers have been proposed to aid in the diagnosis. Some of the biomarkers that help to distinguish between simple steatosis and NASH include: serum C-reactive protein, interleukin-6, ferritin, hyaluronic acid, tumor necrosis factor alpha, leptin, adiponectin, and resistin<sup>5,6</sup>. Routine liver enzyme levels are not reliable; however, novel plasma hepatocyte cell death markers either alone or in combination with clinical risk factors are potential noninvasive diagnostic tools for the future<sup>12,13</sup>. Since apoptosis plays a key role in the pathogenesis of NASH, plasma cytokeratin 18 (CK-18) is being studied, and other biomarkers for oxidative stress have also been studied such as oxidized low-density lipoprotein, thiobarbituric acid reacting substances, superoxide dismutase, and glutathione peroxidase dismutase<sup>14,15</sup>. Two of the most promising tests for

diagnosing advanced fibrosis in NAFLD are the European liver fibrosis (ELF) panel and the NAFLD fibrosis score. The ELF score includes hyaluronic acid, tissue inhibitor of metalloproteinase 1, aminoterminal peptide of procollagen 3, and age<sup>16</sup>. Guha, et al. have reported that the ELF panel has good diagnostic accuracy in an independent validation cohort of patients<sup>17</sup>. The NAFLD fibrosis score includes age, body mass index (BMI), impaired fasting glucose/diabetes, AST, ALT, platelets, and albumin<sup>18</sup>. This scoring system consists of routinely measured and readily available clinical and laboratory data to separate NAFLD patients with and without advanced fibrosis. Several studies have validated their utility in diagnosing high-risk patients for NAFLD<sup>19,20</sup>. Ultrasound had a global accuracy of 78% to detect NAFLD. Most routine biochemical studies had poor correlation with NAFLD and ultrasound was useful but not definitive to detect NAFLD<sup>21</sup>. The diagnostic accuracy of transient elastography (FibroScan<sup>®</sup>) for the diagnosis of liver fibrosis in bariatric surgery candidates with suspected NAFLD has been recently described. The authors conclude that transient elastography allows the early diagnosis of fibrosis in severely obese patients and their results also suggest that it could identify a subgroup of NAFLD patients at high risk of progressive liver disease<sup>22</sup>. Other studies have also validated the accuracy of transient elastography to detect liver fibrosis in patients with NAFLD<sup>23,24</sup>.

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## WHAT IS THE TREATMENT FOR NONALCOHOLIC FATTY LIVER DISEASE?

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Unfortunately there are no clearly effective treatments for these patients. One of the difficulties in identifying effective treatments is the need for long-term studies since the progression of NASH to cirrhosis and its complications occurs slowly. Many different treatments have been studied, but the current mainstays of treatment aim to reduce weight<sup>25</sup> and improve the metabolic disturbances associated with the metabolic syndrome, such as glucose, cholesterol and triglycerides, and hypertension. The most widely studied drugs are thiazolidinediones, metformin,

vitamin E, and anti-obesity medications. However, no drugs are specifically licensed for the treatment of NAFLD<sup>26</sup>.

Weight loss and exercise are among the most promising treatments for NAFLD. It does not take large amounts of weight loss to result in a decrease in liver fat: a less than 10% decrease in weight may be enough. Unfortunately, only a minority of patients are able to accomplish this. Bariatric surgery has been shown to be superior to conservative measures with respect to weight reduction in the obese<sup>27</sup>. Sjöström, et al. prospectively studied a controlled group of Swedish obese subjects that included subjects who underwent gastric surgery and contemporaneously matched, conventionally treated, obese control subjects. They concluded that as compared with conventional therapy, bariatric surgery appears to be a viable option for the treatment of severe obesity, resulting in long-term weight loss, improved lifestyle, and, except for hypercholesterolemia, amelioration in risk factors such as diabetes, hypertriglyceridemia, and hyperuricemia that were elevated at baseline<sup>28</sup>. Other studies have also reported that bariatric surgery significantly decreases the incidence of illnesses associated with obesity<sup>29,30</sup>. Since obesity is the main cause of NAFLD, bariatric surgery is starting to be used as a means of treatment for this disease and the number of surgical bariatric procedures is increasing worldwide. There are several different bariatric surgeries based on their mechanism of action:

- Restrictive procedures, where the aim is to restrict the amount of food that can be eaten by surgically reducing the size of the stomach. In this group of procedures are vertical banded gastroplasty, laparoscopic adjustable gastric banding, and sleeve gastrectomy.
- Malabsorptive procedures are more technically demanding to perform and patients often develop nutritional deficiencies. In this group of procedures, biliopancreatic diversion and biliopancreatic diversion with duodenal pouch are included.
- Hybrid procedures aim to restrict food intake by creating a small gastric pouch which also limits absorption by bypassing the proximal small bowel, the Roux-en-Y gastric bypass. It avoids many of

the unwanted malabsorptive side effects such as diarrhea and nutritional deficiencies<sup>28,31</sup>.

Depending on the country, all different techniques have different frequencies. In Mexico the most frequently performed procedure is sleeve gastrectomy followed by Roux-en-Y gastric bypass<sup>32</sup>. Because of the obesity epidemics, bariatric surgery has also been reported in adolescents<sup>33,34</sup>.

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## BARIATRIC SURGERY AS TREATMENT OF NONALCOHOLIC FATTY LIVER DISEASE

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Nowadays, there is evidence that when performed by skilled surgeons, bariatric surgery is safe<sup>35</sup>, effective in reducing weight<sup>36,37</sup>, improves quality of life<sup>38</sup>, decreases obesity related disease<sup>39</sup>, and increases life expectancy. Nevertheless, there is currently a lack of randomized controlled trials examining the effects of bariatric surgery on NAFLD. Because of the weight loss and improved metabolic control achieved with bariatric operations in appropriate medically complicated obese individuals, the utility of malabsorptive and/or restrictive bariatric procedures for NASH and non-NASH NAFLD is of current interest. The techniques used are decided by the surgeons with the approval of the patients. Adjustable gastric banding is one of the most common bariatric procedures, but nowadays the gold standard technique is the Roux-en-Y gastric bypass, in which a proximal gastric pouch is separated from the remainder of the stomach; this creates a proximal bypass when it is anastomosed to the alimentary limb<sup>40</sup>.

Mummadi, et al. compared a total of 15 studies (766 paired liver biopsies) and showed that the percentage reduction in mean BMI after bariatric surgeries ranged from 19.11 to 41.76%. The pooled proportion of patients with improvement or resolution in steatosis was 91.6% (95% CI: 82.4-97.6%), in steatohepatitis it was 81.3% (95% CI: 61.9-94.9%), in fibrosis it was 65.5% (95% CI: 38.2-88.1%), and for complete resolution of NASH it was 69.5% (95% CI: 42.4-90.8%). They concluded that steatosis, steatohepatitis, and fibrosis appear to improve or completely resolve in

the majority of patients after bariatric surgery-induced weight loss<sup>41</sup>.

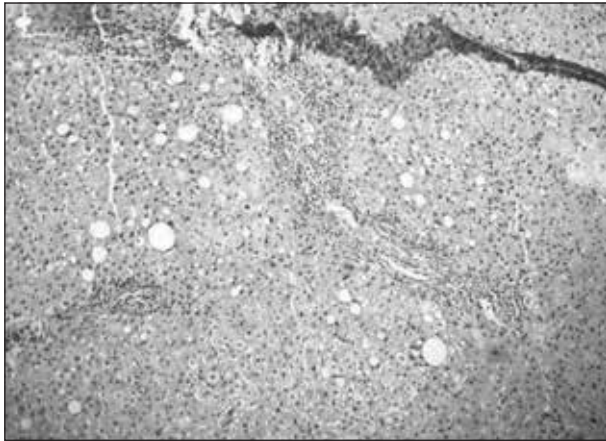
Furuya, et al. studied the impact of Roux-en-Y gastric bypass surgery on NAFLD with a follow-up of two years. Eighteen NAFLD patients (BMI > 40 kg/m) undergoing gastroplasty with Roux-en-Y were enrolled; liver biopsy was obtained at the operation and after two years. At baseline, 67% of patients had NASH and 33% had steatosis. Cirrhosis was present in 5.5% of the patients with NASH. After a mean excess weight loss of 60%, steatosis disappeared in 84% and fibrosis disappeared in 75% of the patients; hepatocellular ballooning disappeared in 50%. The authors concluded that NAFLD including steatohepatitis improved significantly with massive weight loss at two years after Roux-en-Y surgery and no patient had progression of hepatic fibrosis<sup>42</sup>. In other studies, the resolution of NASH after gastric bypass surgery has also been reported<sup>43</sup>. Liu, et al. analyzed 39 patients where 23 (58.9%) had steatohepatitis, 12 with fatty liver (30.7%), and four were normal (10.2%). Follow-up needle liver biopsies were performed at a mean interval of 18 months (range 6-41 months). The authors reported an initial prevalence of hepatic pathology as follows: steatosis (89.7%), hepatocellular ballooning (58.9%), and centrilobular/perisinusoidal fibrosis (50%); after Roux-en-Y, steatosis was (2.9%), ballooning (0%), and centrilobular fibrosis (25%). No improvements were detected in portal tract inflammation and fibrosis. Nowadays, there are no long-term studies that assess the relapse of NASH that could result from weight regain or malnutrition<sup>43</sup> (Fig. 1 and 2).

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## CONCLUSIONS

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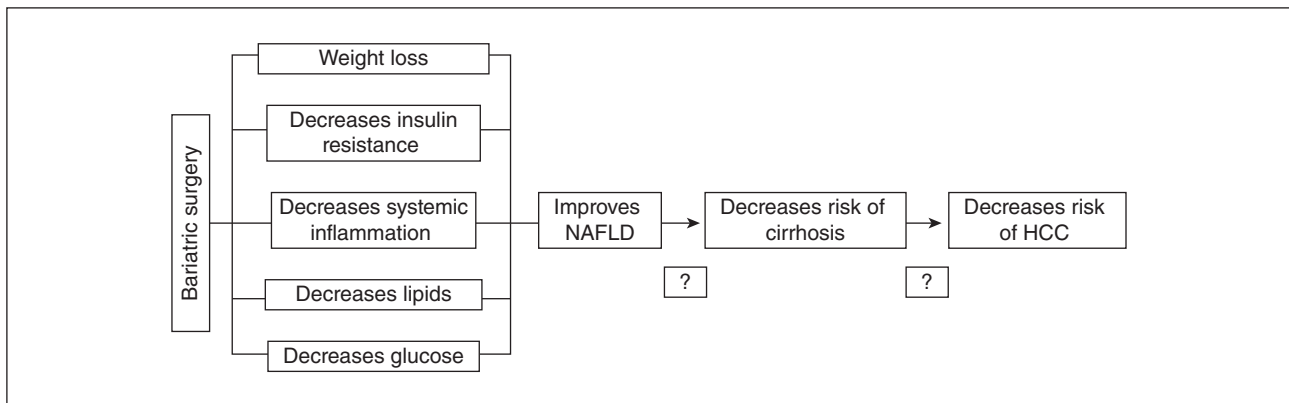
In conclusion, since bariatric surgery achieves weight loss and controls metabolic alterations, in appropriately selected patients, the utility of malabsorptive or restrictive procedures for NAFLD is gaining increasing attention for its treatment. So, the hypothesis is that if it can decrease NAFLD, it should also decrease the incidence of cirrhosis and HCC. However, randomized trials are necessary to show the real long-term effects of the bariatric procedures for treating NAFLD (Fig. 3).



**Figure 1.** Liver biopsy (4X) stained with hematoxylin and eosin in a patient pre-bariatric surgery, with 80% of micro and macro vesicular steatosis.



**Figure 2.** Liver biopsy (4X) of the same patient, one year after sleeve gastrectomy, with scant micro and macro vesicular steatosis.



**Figure 3.** The long-term hypothetical benefits of bariatric surgery on the liver caused by all the metabolic improvements. NAFLD: nonalcoholic fatty liver disease; HCC: hepatocellular carcinoma.

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