

Box 1 | Recommendations of the Baveno IV consensus¹² for the prophylaxis of variceal rebleeding

- Patients with cirrhosis who have not received primary prophylaxis for variceal rebleeding should be treated with nonselective β -blockers, EBL or both
- Combination therapy with nonselective β -blockers and EBL is probably the best prophylactic treatment for variceal rebleeding but more trials are needed
- EBL should be added to treatment in patients with cirrhosis who experience rebleeding while on nonselective β -blockers
- EBL is the treatment of choice for patients with cirrhosis who have contraindications or intolerance to nonselective β -blockers
- Assessment of hepatic venous pressure gradient in patients on pharmacotherapy provides prognostic information about risk of rebleeding
- If endoscopic and pharmacologic treatments fail, TIPS or surgical shunts are effective for patients with Child-Pugh class A or B cirrhosis
- TIPS placement is the only option for patients who are not suitable for surgery
- Liver transplantation provides good long-term outcomes in patients with Child-Pugh class B or C cirrhosis
- TIPS placement may be used as a bridge to liver transplantation

dual pharmacotherapy; 87% and 74% for combined therapy). The number of patients with adverse events was significantly higher in the combined treatment group (61%) than in the dual pharmacotherapy group (32%). However, given the increased risk of variceal rebleeding associated with pharmacotherapy, a more aggressive combined therapy with a greater number of adverse effects is justifiable in this setting.

Kumar and colleagues investigated EBL combined with nonselective β -blockers plus 5-ISMN versus EBL alone to determine whether combined therapy reduces the incidence of variceal rebleeding in patients with a history of variceal bleeding. The conclusion of this study was that EBL alone is sufficient to prevent variceal rebleeding and the addition of drugs does not further reduce the incidence of recurrence.¹¹

After analyzing the results of these studies it is difficult to decide how best to prevent variceal rebleeding in patients with cirrhosis. There is clearly no simple answer. I propose that until new randomized, controlled trials are published and/or new consensus statements or guidelines are issued, clinicians should adhere to the recommendations of the Baveno IV consensus meeting (Box 1).¹² In this meeting, the combination of nonselective β -blockers and EBL was accepted to probably be the best treatment for the prophylaxis of variceal rebleeding. In addition, this recommendation was supported by a survey that demonstrated that this combination therapy is used in clinical practice by 82% of experts who were questioned. Furthermore, prophylaxis of rebleeding should be started as soon as possible after the initial episode of acute variceal hemorrhage, with pharmacologic treatment given as soon

as the patient becomes hemodynamically stable. EBL should be performed 1–2 weeks after initial endoscopy for the acute bleeding episode and repeated until complete variceal eradication.

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Competing interests

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LIVER

Does bariatric surgery reduce the severity of NAFLD?

Helma P. Cotrim and Carla Daltro

A long-term follow-up study used sequential liver biopsy specimens to evaluate fibrosis and signs of steatohepatitis in a large number of severely obese patients undergoing bariatric surgery, and found that bariatric surgery reduces steatosis in most patients. There are some important lessons to be learnt from the findings of this study and some unanswered questions for further investigation.

Nonalcoholic fatty liver disease (NAFLD) ranges from simple steatosis to steatohepatitis (NASH) and has become an

important health issue in obese people. This disease is considered to be the hepatic manifestation of metabolic syndrome, and

lifestyle modifications, mitigation of risk factors and some drugs have been recommended for treatment of NAFLD. However, all these therapeutic modalities are still under investigation. In severely obese patients (body mass index [BMI] ≥ 35 kg/m²) the prevalence of NAFLD is estimated to be between 84 and 96%.¹ As there is no effective treatment for this disease, weight loss has been promoted as the standard treatment. Bariatric surgery induces weight loss, reduces the number of risk factors for NAFLD and reduces the severity of features of metabolic syndrome.

Surgical therapy for obesity has become popular in the past decade and surgical techniques have improved markedly from the early malabsorptive surgical approaches such as jejunoileal bypass, which was abandoned due to poor postoperative outcomes. New surgical techniques, such as adjustable gastric banding and Roux en-Y gastric bypass, are better tolerated overall than the earlier approaches and have been shown to improve symptoms of metabolic syndrome, insulin resistance and features of NAFLD, such as steatosis and inflammation.^{2,3} However, further studies investigating the use of bariatric surgery to treat NAFLD are needed in which the indication is clearly defined, follow-up biopsy samples are taken and histological end points are clear.

Mathurin *et al.*³ have published the results of the first 5-year prospective study to use sequential liver biopsy specimens for the evaluation of fibrosis and signs of NASH (that is, steatosis, ballooning and inflammation) in severely obese patients (BMI >35 kg/m²) undergoing bariatric surgery. This study differs from others examining the effect of bariatric surgery on NAFLD that have been published previously in that it was a long-term follow-up study with histological controls and included a large number of patients.

The effect of bariatric surgery on liver function tests and histological abnormalities have been evaluated in some important studies, which are worth examining before discussing the results of Mathurin *et al.* in detail.

A systematic review and meta-analysis to analyze the effects of bariatric surgery on NAFLD was published by Mummadi *et al.* in 2008.⁴ Data were extracted from 15 studies (766 paired liver biopsy specimens). Improvement or resolution of steatosis was observed in 92% of patients, improvement or resolution of steatohepatitis in 81% of patients and improvement or resolution

of fibrosis in 65% of patients. Complete resolution of NASH was observed in 70% of patients and the authors of the study concluded that histological liver injury seemed to improve or become completely resolved in most patients after weight loss induced by bariatric surgery. Although this was a useful study, the heterogeneity of the studies included, including use of different histological scores for NAFLD, could have influenced the analysis.

“...bariatric surgery improves the clinical and histological parameters in severely obese patients who have NAFLD”

Also in 2008, Andrade *et al.*⁵ published the findings of a study in which they evaluated the influence of bariatric surgery on the clinical and biochemical parameters of NAFLD in 40 severely obese patients (BMI ≥ 35 kg/m²). HAIR (hypertension, alanine aminotransferases [ALTs] and insulin resistance) and BAAT (BMI, ALT, age and triglycerides) scores and the fatty liver index (FLI) were used to compare the patients at the time of surgery and for 12–30 months following weight loss. In addition to weight loss, a significant improvement was observed in all the parameters analyzed.

Portal chronic inflammation can be predominant in children with NAFLD. Although portal chronic inflammation is absent in most adult patients, it has been suggested as a histological marker of advanced NAFLD. Dixon *et al.*⁶ evaluated the effect of weight loss (34.0 ± 17.0 kg) on 36 patients with NAFLD who had undergone bariatric surgery. In paired liver biopsy specimens, taken at the time of surgery and after weight loss, they observed that despite improvements in lobular steatosis and necroinflammatory activity, portal abnormalities remained unchanged. Brunt *et al.*⁷ from the Nonalcoholic Steatohepatitis Clinical Research Network (NASH-CRN) examined liver biopsy specimens taken from 728 adults and 205 children with NAFLD. They found that increased portal chronic inflammation was associated with clinical and pathological features of progressive NAFLD in both adults and children and suggested that portal chronic inflammation is a histological marker of advanced NAFLD in these patients. Nevertheless, further studies are necessary to confirm these findings.

Mathurin *et al.*³ evaluated 381 severely obese patients who had bariatric surgery. Clinical and biological data and liver biopsy specimens were collected before surgery and at 1 and 5 years after surgery. Analysis of the histological data after 5 years of follow-up showed that severe steatosis persisted in only 8.8% of patients, whereas it was observed in 32.8% of patients before surgery. Ballooning decreased after bariatric surgery to 5 years although the levels of inflammation did not significantly change during the follow-up period. Insulin resistance was associated with poor outcomes and patients with worsening fibrosis had a trend towards being more insulin resistant. 5 years after surgery, the levels of fibrosis had increased significantly compared with the levels of fibrosis seen before surgery, but nevertheless 95.7% of the patients maintained a fibrosis score $\leq F1$. The patients who had worsening fibrosis were those who had a higher BMI (40.5 ± 8.3) than those whose fibrosis regressed or remained at the same stage at 5 years (BMI 36.9 ± 7.1).

Mathurin *et al.* did not evaluate the association between portal chronic inflammation and the severity of NAFLD, but such an analysis in this large group of severely obese patients would be of value to confirm the importance of portal chronic inflammation as a marker of advanced NAFLD.

There are some important lessons to take away from the study by Mathurin *et al.* First, all the improvements in NAFLD observed in the study occurred within the first year of follow-up and persisted for up to 5 years. This finding suggests that it might not be necessary to follow patients up for more than 1 year to evaluate the effects of bariatric surgery on NAFLD. Second, insulin resistance was associated with poor outcomes, so perhaps clinicians could use this simple parameter to evaluate their patients after bariatric surgery. Third, worsening of fibrosis was associated with higher BMIs and NAFLD scores at 5 years, with patients tending to be more insulin resistant, which suggests that a more severe natural history of NAFLD and lower benefits of bariatric surgery, rather than exacerbation by the procedure itself, might account for the worsening of fibrosis.

In conclusion, bariatric surgery improves the clinical and histological parameters in severely obese patients who have NAFLD. Although this procedure has been associated with complications, such as pulmonary embolism and some postoperative deaths,⁸ the benefit is increased long-term survival

in patients who maintain weight control for more than 10 years.^{9,10} Reductions in the occurrence of comorbidities, such as all components of metabolic syndrome and cardiovascular risk, have also been observed. However, further studies are warranted to determine whether improvement in insulin resistance and histological alterations is correlated with low morbidity and mortality in patients with advanced NAFLD.

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