Hepatology Snapshot

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Bariatric surgery for curing NASH in the morbidly obese?

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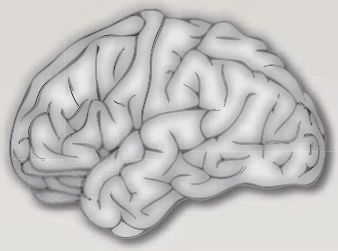
Key facts

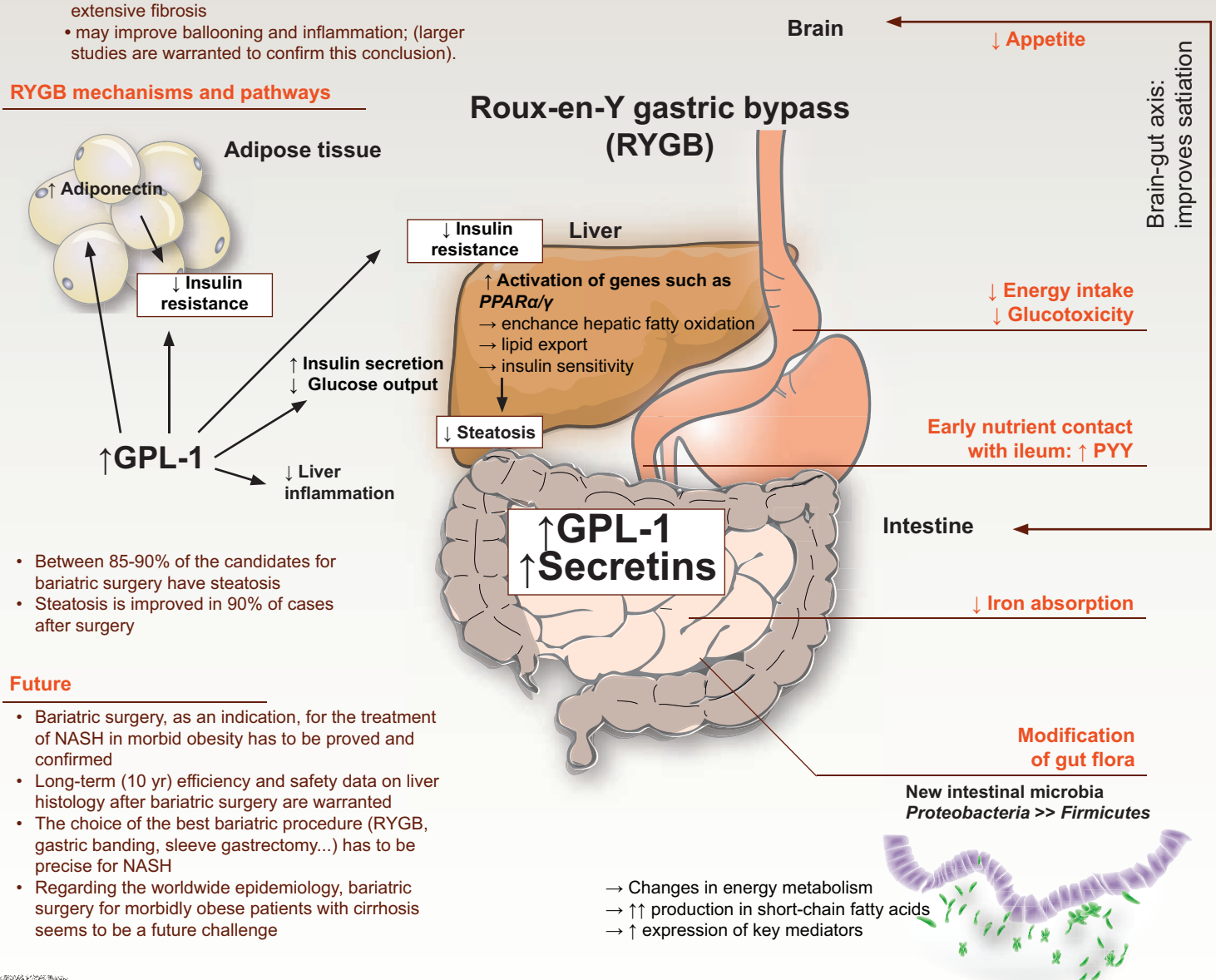
- Obesity increases the risk of NAFLD
- Batriatric surgery should be considered for patients:
  - with a body mass index >40
  - who wish to lose weight
- Bariatric surgery
  - induces long-term weight loss
  - decreases morbidity
  - decreases the incidence of cancer
  - decreases mortality
  - shows a sustained decrease in steatosis
  - do not appear to be associated with development of extensive fibrosis
  - may improve ballooning and inflammation; (larger studies are warranted to confirm this conclusion).



Roux-en-Y gastric bypass

- Is one of the most efficient methods for losing weight
- RYGB achieves its physiological benefits through "**BRAVE**" effects:
  Bile flow alteration,
  Reduction in gastric size,
  Anatomical rearrangement,
  Vagal manipulation and subsequent
  Enteric gut hormone modulation
- Bariatric surgery is a powerful treatment for insulin resistance, with a remission in 42% of cases after RYGB

RYGB mechanisms and pathways



- Between 85-90% of the candidates for bariatric surgery have steatosis
- Steatosis is improved in 90% of cases after surgery

Future

- Bariatric surgery, as an indication, for the treatment of NASH in morbid obesity has to be proved and confirmed
- Long-term (10 yr) efficiency and safety data on liver histology after bariatric surgery are warranted
- The choice of the best bariatric procedure (RYGB, gastric banding, sleeve gastrectomy...) has to be precise for NASH
- Regarding the worldwide epidemiology, bariatric surgery for morbidly obese patients with cirrhosis seems to be a future challenge

Received 1 February 2012; received in revised form 24 December 2012; accepted 27 December 2012

Table 1. Evolution of histological features following bariatric surgery.

Characteristics of the studies				Results				
Studies	Sample size	Surgical procedure	Biological markers	Steatosis	Ballooning	Inflammation	NASH grade	Fibrosis
Barker KB *et al.,* Am J Gastroenterol 2006	19	RYGB	no change	improved	improved	improved		improved
Clark JM *et al.,* Obes Res 2005	16	RYGB	improved	improved	improved	improved		improved
de Almeida SR *et al.,* Obes Surg 2006	16	RYGB	not reported		improved	improved		
Dixon JB *et al.,* Hepatology 2004	36	LAGB	improved	improved	improved	improved		improved
Dixon JB *et al.,* Obes Surg 2006	60	LAGB	improved	improved	improved	improved		improved
Furuya CK *et al.,* J Gastroenterol Hepatol 2007	18	RYGB	improved	improved				improved
Jaskiewicz K *et al.,* Dig Dis Sci 2006	10	Gastroplasty	improved					
Keshishian A *et al.,* Obes Surg 2005	78	Duodenal switch	no change	improved			improved	
Klein S *et al.,* Gastroenterology 2006	7	Bypass	no change	improved				
Kral JG *et al.,* Surgery 2004	104	Biliopancreatic diversion	improved	improved				worsened
Liu X *et al.,* Obes Surg 2007	39	RYGB	improved	improved				
Luyckx FH *et al.,* Int J Obes Relat Metab Disord 1998	69	LAGB	not reported	improved		worsened		
Mathurin P *et al.,* Gastroenterology 2006	185	Bypass, LAGB	improved	improved				worsened
Mathurin P *et al.,* Gastroenterology 2009	381	Bypass, LAGB	improved	improved				worsened
Mattar SG *et al.,* Ann Surg 2005	70	RYGB, LAGB, LSG	improved	improved		improved		improved
Meinhardt NG *et al.,* Obes Surg 2006	30	Jejuno-ileal bypass	no change	improved		improved		
Mottin CC *et al.,* Obes Surg 2005	186	RYGB	not reported	improved				
Ranløv I *et al.,* Digestion 1990	15	Bypass, gastroplasty	improved	improved		no change		
Silverman EM *et al.,* Am J Clin Pathol 1995	91	RYGB	no change	improved				
Stratopoulos C *et al.,* Obes Surg 2005	216	Sleeve	improved	improved		improved	improved	improved

Obesity increases the risk of NAFLD (non-alcoholic fatty liver disease). Bariatric surgery should be considered for severely obese persons with a body mass index (BMI) higher than 40 (or 35 if co-morbidity is present) and who clearly wish to lose weight. It induces long-term weight loss and decreases morbidity, the incidence of cancer, and mortality. Compelling data consistently show a sustained decrease in steatosis, whereas an evolution in ballooning, necro-inflammatory features, and fibrosis remains subject to debate.

Bariatric surgery is the most efficient method for losing weight. Malabsorptive procedures (Roux-en-Y gastric bypass (RYGB) or duodenal switch) induce greater weight loss than restrictive procedures (laparoscopic gastric banding (LAGB)), with a range of around 60% of excess weight [1]. These variations may be due to differing physiological effects. LAGB and sleeve gastrectomy (SG) promote satiation via stretch mechano-receptor activation, with an additional effect after SG related to partial removal of fundus, a secretion site of ghrelin, an orexigenic hormone. Conversely, RYGB acts via several pathways, including early contact of nutrients with the ileum and increased secretion of PYY, an anorectic hormone, and incretins (GLP-1, GLP-2) involved in the enteroinsular axis. For example, GLP-1 stimulates insulin secretion and decreases hepatic glucose output and insulin resistance in the liver and adipose tissues. GLP-1 also decreases steatosis via activation of genes such as *PPARα/γ* that enhance hepatic fatty oxidation, lipid export, and insulin sensitivity. GLP-1 lowers liver inflammation via the attenuation of TNFα, IL-6, IL-1β, and MCP-1 expression [2]. More recently, GLP-1 appeared to reduce fatty-acid-related hepatocyte death through activation of macro- and chaperon-mediated autophagy that reduces endoplasmic reticulum stress and liver fatty acid accumulation responsible for apoptotic liver injuries [3]. RYGB also affects insulin resistance through an increase in adiponectin and changes in gut microbiota secondary to alterations in bile and nutrient flow. The new intestinal microbiota, with fewer *Firmicutes* and more *Proteobacteria*, change energy metabolism, directing oligosaccharide metabolism to higher production of short-chain fatty acids (propionate, acetate, etc.) that stimulate expression of key mediators of insulin sensitivity (see Figure) [4].

Between 85% and 90% of bariatric surgery candidates have steatosis, which can be severe (i.e., present in more than two-thirds of hepatocytes) in 27% of them [5,6]. Meta-analysis revealed steatosis improvement in 90% of cases after surgery [7]. The improvement occurred within the first year and persisted up to five years. Mechanisms involved in the evolution of both insulin resistance and steatosis are intimately connected. Indeed, bariatric surgery is a powerful treatment for insulin resistance, with remission of type 2 diabetes occurring in 42% of cases after RYGB [8]. Patients with insulin resistance refractory to surgery have a probability of presenting with severe steatosis that is twice as high as that of patients with improved insulin resistance [6]. Moreover, weight gain relapse occurs in 46–63% of subjects two years after bariatric procedure. As surgical success is linked to drastic changes in eating habits, weight gain may be secondary to psychological disorders, dilatation of the gastric pouch, an increase in volume intake or a sedentary lifestyle [9]. As a consequence, future prospective studies must evaluate its impact on liver injury over a follow-up of longer than 5 years.

Cochrane meta-analysis was unable to evaluate the specific impact of bariatric surgery on NASH features [7]. Indeed, most studies had insufficient sample sizes and their designs lacked sequential biopsies focusing on NASH patients. In a princeps study of 23 NASH patients treated with LAGB, necro-inflammatory activity and fibrosis improved in approximately 80% of cases [10]. Other clinical and experimental studies showed the same trend in improvement of NASH and a decrease in key inflammatory mediators such as IL8 and MCP1 (measured by RT-PCR from liver samples) [11], but their sample sizes were insufficient for obtaining valid conclusions (Table 1).

Concern about worsening of fibrosis stems from ileojejunal bypass, a no-longer-used procedure that produced up to 7–10% cirrhosis at long term (5 years), related, in part, to bacterial overgrowth and translocation [12]. Recent procedures do not appear to be associated with development of extensive fibrosis [10]. A slight increase in fibrosis in patients who were poor responders to bariatric surgery has been described. A decrease in collagen-alpha-1, TGFβ1, SMA, a tissue inhibitor of metalloproteinase 1 expression and SMA content (measured by RT-PCR from liver samples), supports the beneficial effects of current surgical procedures [11]. Nevertheless, additional studies are required to determine whether fibrosis progresses in patients treated with current surgical procedures.

Severely obese cirrhotic patients, as compared to non-cirrhotic and non-obese cirrhotic patients, have the highest risk of mortality and require a specific therapeutic strategy possibly involving bariatric surgery. However, such an approach warrants discussion. Indeed, malabsorptive procedures are less suitable for cirrhotic patients in light of their nutritional status, increased surgical complexity, and absorption of drugs, particularly immunosuppressive molecules in the case of liver transplantation. Decompensated cirrhotic patients are contraindicated

for bariatric surgery because of the 21-fold increase in postoperative mortality following bariatric procedures [13]. Moreover, the 2-fold mortality increase observed for compensated cirrhotics compared to non-cirrhotics in the national US database (but not confirmed in other series) emphasized that selection criteria for bariatric surgery candidates remain to be sharply defined [13]. For some experts, for example, portal hypertension evaluated by CT scan and endoscopy, a previous episode of hepatic decompensation or biological signs of hepatic insufficiency would exclude the possibility of bariatric surgery. All these questions warrant further study.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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