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The Impact of Bariatric Surgery on Nonalcoholic Steatohepatitis

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Abstract and Introduction

Abstract

Nonalcoholic steatohepatitis (NASH) is a stage of nonalcoholic fatty liver disease (NAFLD), and in most patients, is associated with obesity and the metabolic syndrome. The current best treatment of NAFLD and NASH is weight reduction with the current options being life style modifications, with or without pharmaceuticals, and bariatric surgery. Bariatric surgery is an effective treatment option for individuals who are severely obese (body mass index ≥ 35 kg/m^2), and provides for long-term weight loss and resolution of obesity-associated diseases in most patients. Regression and/or histologic improvement of NASH have been documented after bariatric surgery. We review the available literature reporting on the impact of the various bariatric surgery techniques on NASH.

Introduction

Nonalcoholic steatohepatitis (NASH) is an advanced stage of nonalcoholic fatty liver disease (NAFLD) characterized by the presence on liver biopsy of steatosis and of necroinflammation with variable amounts of fibrosis.[1–3] NASH may progress to cirrhosis in ~20% of patients, and NASH-related cirrhosis is considered a major cause of cryptogenic cirrhosis and liver related death.[4–9]

The prevalence of NAFLD and NASH in class III or severely obese persons (body mass index [BMI] ≥ 35 kg/m^2) is ~70% and 30%, respectively.[10–12]In addition, obese individuals (BMI ≥ 30 kg/m^2) are at particularly high risk for NASH if other features of the metabolic syndrome, such as insulin resistance, type 2 diabetes, hypertension, and dyslipidemia, as well as many other features, are present. These obesity-associated diseases are all components of the metabolic syndrome and a reflection of a chronic inflammatory state caused by accumulation of white adipose tissue in the visceral fat. White adipose tissue is considered to be an endocrine organ that secretes adipocytokines and cytokines responsible for the inflammatory environment associated with central obesity and its complications, including NAFLD and NASH.[13–15]A pertinent issue in the morbidly obese is that despite the high prevalence of NASH when a liver biopsy is obtained, most patients have no symptoms directly attributable to NASH. Thus, few clinical scoring systems, which are based mostly on patient characteristics and biochemical blood tests, have been proposed to differentiate individuals at higher risk for NASH. These scoring systems can guide decisions regarding liver biopsy to detect more patients with NASH who are currently going undiagnosed, therefore assisting both the clinician and the patient in choosing and tailoring treatment for morbid obesity and its associated complications.[16–18]

The current best treatment of NAFLD and NASH is weight reduction. Current options for weight loss are life-style modifications through appropriate nutrition and increased physical activity, with or without pharmaceuticals; however, we know of no randomized controlled trials comparing different treatment options, thus supporting any treatment modality and proving to change the natural history of NAFLD.[19–21] Long-term results of the many case series are still under scrutiny.[22,23] The pathogenesis, diagnosis, and medical treatment of NAFLD and NASH is covered in detail elsewhere in this issue of the *Seminars in Liver Disease*.

For the past 30 years, most of the Western and part of the Eastern world has been rattled by exponential and alarming obesity rates and the deleterious consequences, including type 2 diabetes mellitus (T2DM), hyperlipidemia, and NAFLD, among many others. As a result of this increasing prevalence of obesity, the poor outcomes with dietary interventions and drug therapy alone in obese subjects with BMI ≥ 35 kg/m^2, and obese individuals with metabolic syndrome, bariatric surgery has become one of the most common surgical procedures performed in the United States,[24] with ~205,000 bariatric procedures performed last year.[25] Bariatric surgery, when performed in high volume centers by expert surgeons, has proven to be safe[26–28] and provides for substantial and sustained weight loss in most individuals,[26,29,30] significant improvements in

quality of life,[31,32] significant reduction or remission of most obesity-associated diseases and features of the metabolic syndrome,[30,33,34] and increased longevity.[35–37]

Unfortunately, no randomized controlled trials or case-controlled studies have examined the effect of bariatric surgery on NAFLD and NASH.[21] Consequently, the studies reviewed and summarized in this article are retrospective and prospective observational cohort studies.[38–57]

Indications, Techniques, Safety, and Outcomes for Bariatric Surgery

Currently, bariatric surgery is accepted as a treatment for obesity based on a combination of BMI levels and the presence of features of the metabolic syndrome.[58] All techniques for performing bariatric surgery may be used in subjects with BMI ≥ 35 kg/m^2 and any feature of the metabolic syndrome, or in subjects with BMI ≥ 40 kg/m^2 independent of the presence of associated diseases. Recently, the U.S. Food and Drug Administration (FDA) approved the use of laparoscopic adjustable gastric banding for use in individuals with a BMI ≥ 30 kg/m^2 and a feature of the metabolic syndrome.[59] Nevertheless, bariatric surgery is not an option for every severely obese individual. Appropriate candidates are those who are willing to make significant changes in eating habits and lifestyle, and adhere to long-term follow-up care.[60]

A few different bariatric surgery techniques are available and the choice of technique is currently based mainly on patient and surgeon preference, while taking into account the available evidence regarding the risks and benefits of each procedure.[61] All techniques can be done using the laparoscopic approach. One of the most common and standard techniques available is adjustable gastric banding (AGB) (Fig. 1), in which an inflatable and adjustable silicone band is placed around the upper stomach, close to the gastroesophageal junction, to create a 30-mL proximal gastric pouch. The band is connected to a subcutaneous access port through a narrow tube. After surgery, a series of stepwise adjustments to constrict the band stoma are made in the outpatient office. The gold standard technique in bariatric surgery is Roux-en-Y gastric bypass (RYGB) (Fig. 2).This is a proximal gastric bypass (using a 100- to 150-cm Roux-en-Y or alimentary limb is the norm in the United States). A small 30- to 50-mL proximal gastric pouch is created by dividing it from the larger stomach using staplers. The gastric pouch is then connected to the proximal jejunum (gastrojejunal anastomosis) in a Roux-en-Y fashion, using a variety of equally effective laparoscopic anastomotic techniques. Then, the biliopancreatic limb is reconnected to the jejunum (jejunojejunal anastomosis) ~100 to 150 cm from the gastrojejunostomy. Another technique is sleeve gastrectomy (SG) (Fig. 3) in which a left lateral portion of the gastric antrum (~5 cm from the pylorus), body, and fundus is separated from the medial portion using sequential stapler firings over a 36- to 46-Fr bougie. The "larger excess stomach" is removed from the abdominal cavity, leaving the smaller, left curvature-based, narrow stomach, preserving the pylorus and usual connection with the duodenum. Still another technique is biliopancreatic diversion without (BPD) or with duodenal-switch (BPD-DS) ([Fig. 4]). With this technique, a partial gastrectomy (BPD) or sleeve gastrectomy (BPD-DS) is created, and the small bowel is divided in two sections of similar length (alimentary and biliopancreatic limb).The alimentary limb is connected to the first portion of the duodenum (BPD-DS) or the stomach (BPD). The biliopancreatic limb is anastomosed to the distal small intestine ~50 to 100 cm proximal the ileocecal. Vertical banded gastroplasty (VBG) is an older technique that combines stomach stapling and gastric banding, which is not adjustable, to create a small gastric pouch. After an incision into the stomach is made, the sides of the incision are stapled, creating a hole in the stomach for the band to loop through. Above the created hole, the stomach is stapled.

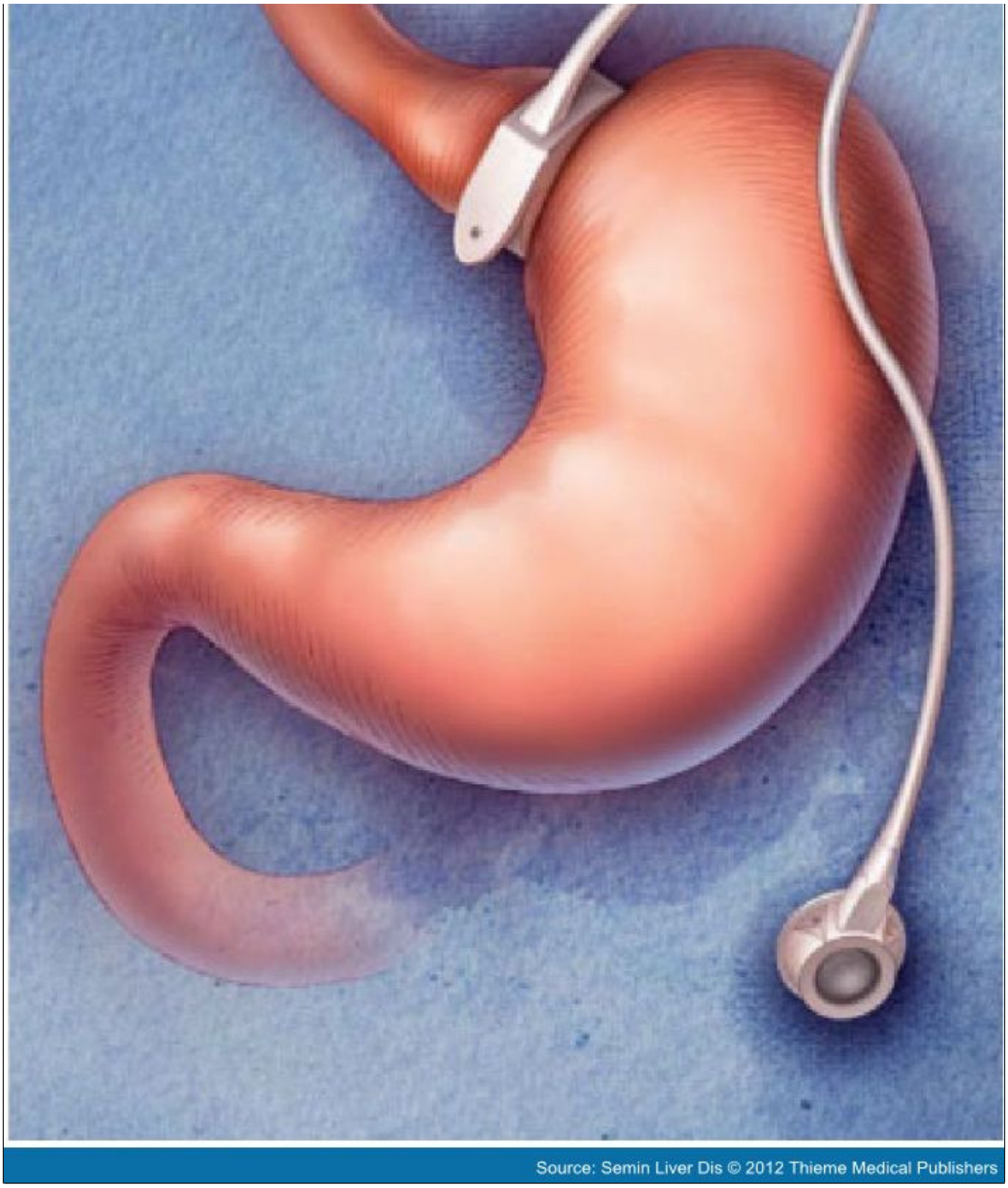

Figure 1. Adjustable gastric banding. Copyright © 2009 Covidien. All rights reserved. Used with the Permission of Covidien.

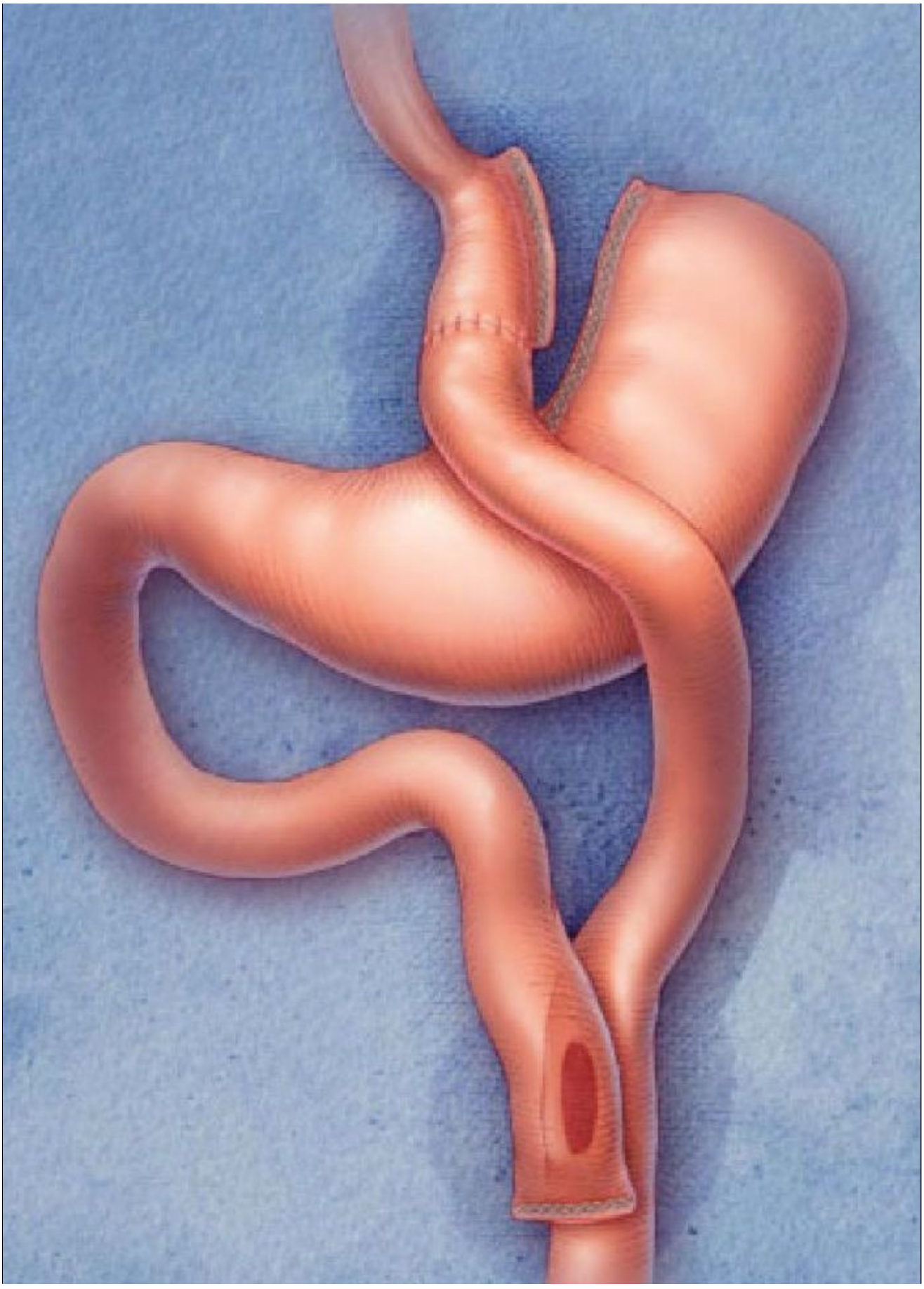

Figure 2. Roux-en-Y gastric bypass. Copyright © 2009 Covidien. All rights reserved. Used with the Permission of Covidien.

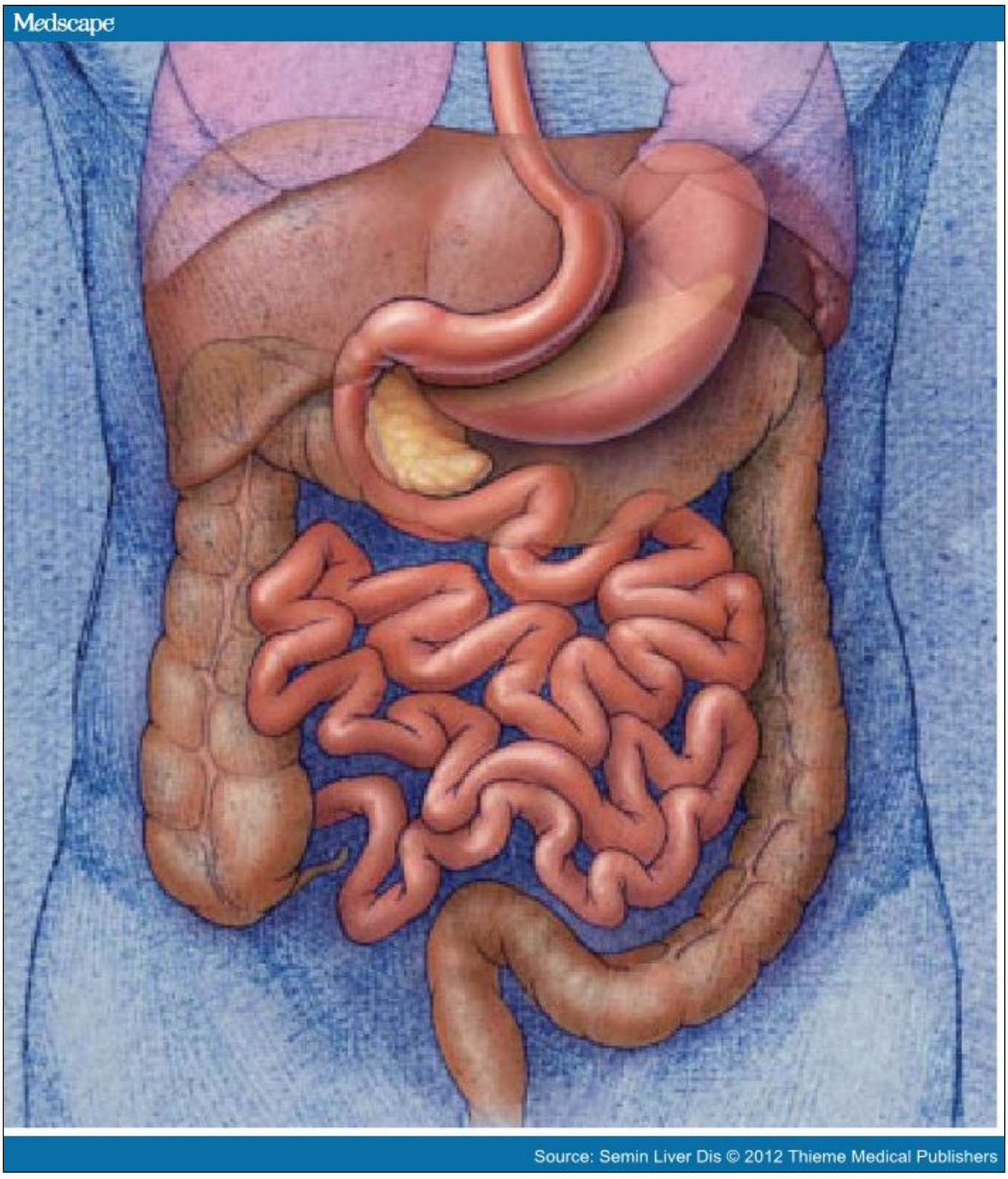

Figure 3. Sleeve gastrectomy. Copyright © 2009 Covidien. All rights reserved. Used with the Permission of Covidien.

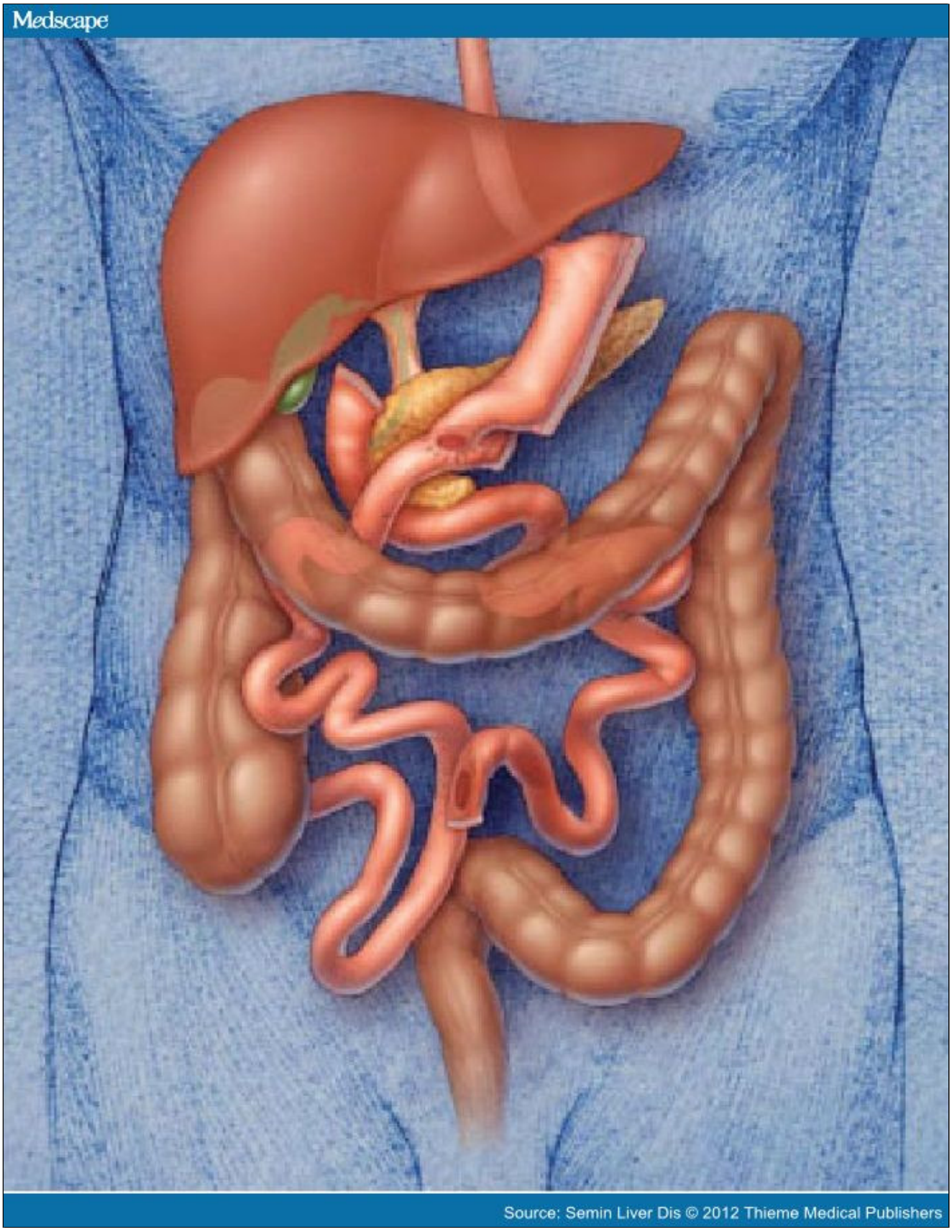

Figure 4. Biliopancreatic diversion with duodenal-switch (BPD-DS).

Many reports have been published about the safety of bariatric surgery, notably the report from the Longitudinal Assessment of Bariatric Surgery (LABS) Consortium[62] and a systematic review of 14 comparative studies of RYGB and AGB.[63] In the LABS study, where only major adverse outcomes were reported (death; venous thromboembolism; percutaneous, endoscopic, or operative re-intervention; and failure to be discharged from the hospital), the RYGB patients had higher BMI and more comorbidities than did the AGB patients. The complication and mortality rates were very low for all groups studied; it was higher for laparoscopic RYGB (4.8% and 0.2%, respectively) than for AGB (1% and 0%, respectively). In the systematic review, the rate of complications varied widely across these studies, likely also related to differences in patient baseline characteristics and in the definitions of adverse events and how they were identified.[64,65] The types of complications differ between the procedures, and while RYGB and BPD-DS are considered by most experts to be more complex, many have demonstrated that, when done on properly selected and prepared patients, by properly trained surgeons at high-volume medical centers, all offer a low complication rate that is possibly similar to that for AGB, if the long-term complications (>30 days) with AGB are accounted.[28,62,63,66–70] This is because RYGB and BPD-DS have more perioperative (<30 days) complications than AGB; however, AGB has a higher primary failure rate in providing appropriate weight loss, and more complications and reoperations after 30 days.[61] One single center study from Belgium, with more than 12 years follow-up for patients that received AGB, showed that nearly 50% of the patients required removal of the AGB (with a total reoperation rate of 60%).[71] In short, the LABS study only presented 30-day complication rates; thus, the high rates of reoperations reported by us[61] and many others[63,72] that are needed for the high failure and device-related problems rate observed after AGB are not yet accounted for. We look forward to the publication of the long-term results of the LABS Consortium. In addition, the differences in rare events such as mortality, reported by the LABS Consortium[62] and others[73] for RYGB and AGB may not be directly comparable, as there are significant differences between groups with respect to patient baseline characteristics; selection bias and confounding by severity also likely impacted these results.[64,65]

Weight loss and the expected rate of resolution or improvement of T2DM are important outcomes when a patient chooses to have bariatric surgery. One remarkable and durable effect of bariatric surgery is a remission rate of T2DM reported in patients undergoing RYGB and BPD-DS for morbid obesity.[30] Data from our studies and others demonstrate that T2DM improves or remits completely in as many as 80% of morbidly obese patients after RYGB and BPD-DS;[30,61] this effect remains for several years in ~50% of patients.[74] A recent systematic review and meta-analysis including 135,246 patients showed that excess weight loss and T2DM resolution in the first 12 months after surgery were higher for patients undergoing BPD-DS and RYGB (64% and 60% excess weight loss; 95% and 80% T2DM resolution; respectively), than for those undergoing AGB (46% excess weight loss, 57% T2DM resolution).[30] Although follow-up data was incomplete in more than 40% of patients in the studies included in the analysis was a problem, the results are similar to those from series with more complete follow-up that demonstrate better weight loss and higher rates of T2DM resolution for RYGB and BPD-DS compared with AGB.[61,62]

Impact of Bariatric Surgery on NAFLD and NASH

Several studies have reported changes in hepatic histology from liver biopsies obtained at the time of bariatric surgery and after weight loss (Table 1). Previous reviews[19,75–77] have documented that hepatic histology improves in most obese patients with NAFLD and NASH who undergo bariatric surgery using current techniques. Small degrees of worsening of either fibrosis or steatohepatitis have been documented, but were not associated with different bariatric surgery techniques; rather, they were associated with higher baseline BMI, NAFLD activity score, steatosis, ballooning, inflammation, fibrosis, and insulin resistance.[51] In addition, one patient who underwent BPD-DS was reported to progress from minimal fatty change before surgery to severe NASH and ultimate death due to liver failure.[78] One important physiologic aspect that may play a role in determining the rare progression of liver disease is the rate of weight loss - procedures that are associated with fast weight loss during the initial 6 months to 1 year after surgery may promote excessive increased lipolysis with transfer of large amounts of long-chain fatty acids from visceral adipose tissue via the portal vein to be metabolized in the liver.[76] Such changes may precipitate the rare cases of fulminant steatohepatitis or progression of liver histology reported.[43,44,51,52,56] However, fulminant steatohepatitis and also changes in liver histology can be influenced by many other factors, such as infection and concurrent use of medications.

Table 1. Weight Loss and Changes in Liver Histology after Bariatric Surgery

							Outcome Histology 2nd Liver Biopsy		
Study	**Year**	**N**	**Study Design**	**Preoperative BMI (kg/m^2)**	**Weight Loss**	**2nd Biopsy (Months)**	**Steatosis**	**Inflammation**	**Fibrosis**
RYGB									
Silverman[38]	1995	91	RC	Not reported	-36.4 kg WL	18.4	Improvement	Improvement lobular Worsening portal	Improvement
Clark[39]	2005	16	PC	51.1 ± 6.1	BMI change -18.2 kg/m^2	10.2 ± 4.4	Improvement	Improvement	Improvement
Mattar[40]*	2005	70	PC	56 ± 11	BMI change −17 kg/m^2	15 ± 9	Improvement	Improvement	Improvement
Mottin[41]	2005	90	RC	46.7 ± 0.9	81.4% EWL	12	Improvement	Not reported	Not reported
Klein[42]	2006	7	PC	58 ± 4	BMI change −17 kg/m^2	12	Improvement	No change	No change
Barker[43]	2006	19	PC	47 ± 4.4	BMI change -18 kg/m^2	21.4	Improvement	Improvement	Improvement, Worsening: 10.5%
Csendes[44]	2006	16	PC	44.3 (37–60)	BMI change -15.7 kg/m^2	17.5	Improvement	Improvement	Improvement, Worsening: 6.7%
de Almeida[45]	2006	16	PC	53.4 ± 8.8	BMI change -22 kg/m^2	23.5 ± 8.4	Improvement	Improvement	Improvement
Furuya[46]	2007	18	PC	51 ± 3	BMI change -20 kg/m^2	24	Improvement	Improvement	Improvement
Liu[47]	2007	39	RC	47.7 ± 6.2	BMI change -18.2 kg/m^2	18	Improvement	Improvement	Improvement
Weiner[48†]	2010	116	RC	55.2 ± 8.3	BMI change -24.7 kg/m^2	18.6 ± 8.3	Improvement	Improvement	Improvement

Moretto[49]	2011	78	RC	45.4 ± 8.1	BMI change -16.1 kg/m^2	Not reported	Not reported	Not reported	Improvement New Onset:11.6%
AGB									
Dixon[50]	2006	60	PC	45.9 ± 7.4	BMI change -11.9 kg/m^2	29.5 ± 16	Improvement	Improvement	Improvement
Mathurin[51‡]	2009	381	PC	50 ± 7.8	BMI change -12.3 kg/m^2	60	Improvement	No change	Worsening
BPD/DS									
Kral[52]	2004	104	PC	47 ± 8.4	BMI change -16 kg/m^2	41 ± 25	Improvement	Improvement, New Onset: 11.6%	Improvement: 26.8% Worsening: 40.4%
Keshishian[53]	2005	78	RC	50.5	Not reported	6–36	Improvement	Improvement	Not reported
VBG									
Ranløv[54]	1990	8	PC	Not reported	Not reported	12	Improvement	Improvement	No fibrosis
Luyckx[55]	1998	69	RC	43.9 ± 8.3	-32 ± 19kgWL	27 ± 15	Improvement	Worsening	Not reported
Stratopoulos[56]	2005	216	PC	52.8 ± 1	66% EWL	18 ± 9.6	Improvement	Improvement	Improvement: 47% Worsening: 12%
Jaskiewicz[57]	2006	10	PC	46.7 ± 8.8	-35 ± 15kg WL	8	Improvement	Improvement	Not reported

PC, prospective cohort study; RC, retrospective cohort study; BMI, Body mass index; WL, weight loss; RYGB, Roux-en-Y gastric bypass; AGB, adjustable gastric banding; BPD/DS, biliopancreatic diversion/duodenal switch; VBG, vertical banded gastroplasty.

*RYGB: 58.6%, sleeve gastrectomy: 32.9%, AGB: 8.6%.

†RYGB: 55.7%, AGB: 31.1%, BPD-DS: 13.1%.

‡AGB: 56.2%, biliointestinal bypass: 22.8%, RYGB: 21%.

The evidence for changes in hepatic histology for the various bariatric surgery techniques is reviewed below.

Roux-en-Y Gastric Bypass

As shown in Table 1 , reduction in steatosis, inflammation and fibrosis after RYGB are frequently reported, but four studies [38,43,44,49] described worsening of the degree of fibrosis in a few cases.

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							Outcome Histology 2nd Liver Biopsy		
Study	**Year**	**N**	**Study Design**	**Preoperative BMI (kg/m^2)**	**Weight Loss**	**2nd Biopsy (Months)**	**Steatosis**	**Inflammation**	**Fibrosis**
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Barker[43]	2006	19	PC	47 ± 4.4	BMI change -18 kg/m^2	21.4	Improvement	Improvement	Improvement, Worsening: 10.5%
Csendes[44]	2006	16	PC	44.3 (37–60)	BMI change -15.7 kg/m^2	17.5	Improvement	Improvement	Improvement, Worsening: 6.7%
de Almeida[45]	2006	16	PC	53.4 ± 8.8	BMI change -22 kg/m^2	23.5 ± 8.4	Improvement	Improvement	Improvement
Furuya[46]	2007	18	PC	51 ± 3	BMI change -20 kg/m^2	24	Improvement	Improvement	Improvement
Liu[47]	2007	39	RC	47.7 ± 6.2	BMI change -18.2 kg/m^2	18	Improvement	Improvement	Improvement
Weiner[48†]	2010	116	RC	55.2 ± 8.3	BMI change -24.7 kg/m^2	18.6 ± 8.3	Improvement	Improvement	Improvement

Moretto[49]	2011	78	RC	45.4 ± 8.1	BMI change -16.1 kg/m^2	Not reported	Not reported	Not reported	Improvement New Onset:11.6%
AGB									
Dixon[50]	2006	60	PC	45.9 ± 7.4	BMI change -11.9 kg/m^2	29.5 ± 16	Improvement	Improvement	Improvement
Mathurin[51‡]	2009	381	PC	50 ± 7.8	BMI change -12.3 kg/m^2	60	Improvement	No change	Worsening
BPD/DS									
Kral[52]	2004	104	PC	47 ± 8.4	BMI change -16 kg/m^2	41 ± 25	Improvement	Improvement, New Onset: 11.6%	Improvement: 26.8% Worsening: 40.4%
Keshishian[53]	2005	78	RC	50.5	Not reported	6–36	Improvement	Improvement	Not reported
VBG									
Ranløv[54]	1990	8	PC	Not reported	Not reported	12	Improvement	Improvement	No fibrosis
Luyckx[55]	1998	69	RC	43.9 ± 8.3	-32 ± 19kgWL	27 ± 15	Improvement	Worsening	Not reported
Stratopoulos[56]	2005	216	PC	52.8 ± 1	66% EWL	18 ± 9.6	Improvement	Improvement	Improvement: 47% Worsening: 12%
Jaskiewicz[57]	2006	10	PC	46.7 ± 8.8	-35 ± 15kg WL	8	Improvement	Improvement	Not reported

PC, prospective cohort study; RC, retrospective cohort study; BMI, Body mass index; WL, weight loss; RYGB, Roux-en-Y gastric bypass; AGB, adjustable gastric banding; BPD/DS, biliopancreatic diversion/duodenal switch; VBG, vertical banded gastroplasty.

*RYGB: 58.6%, sleeve gastrectomy: 32.9%, AGB: 8.6%.

†RYGB: 55.7%, AGB: 31.1%, BPD-DS: 13.1%.

‡AGB: 56.2%, biliointestinal bypass: 22.8%, RYGB: 21%.

In Furuya et al's study of 18 morbidly obese patients,[46] 67% had NASH and 33% had variable degree of steatosis. After significant weight loss, a second liver biopsy revealed resolution of steatosis in 89%, of fibrosis in 75% and of hepatocellular ballooning in 50%. Importantly, no patient had more severe steatosis or fibrosis at the follow-up biopsy. Obesity-associated comorbidities improved with weight loss. The T2DM rate decreased from 44% to 28% (*P* = ns), high blood pressure from 72% to 33% (*P* = .04) and hyperlipidemia from 61.1% to 16.7% (*P* = .01) at 2-year follow-up.

Another three studies reported improvement in steatosis, inflammation, and fibrosis in the majority of patients after weight loss without worsening in any patient and no progression to cirrhosis.[39,45,48]

Barker et al[43] found improvement in steatosis, lobular inflammation, and portal/lobular fibrosis in the majority of the 19 patients studied. In addition, histopathologic criteria for NASH were no longer found in 89.5% of patients. There was no correlation between the degree of weight-loss and histologic change, but surrogate markers of insulin resistance, including fasting glucose, HgbA1c, and lipid profiles, improved significantly, paralleling histopathologic improvement and resolution of NASH in most patients. Despite the overall improvement in this study, fibrosis worsened in two patients (10.5%), one with lobular fibrosis and the other with portal fibrosis.

Mottin et al[41] found an improvement of steatosis in 82.2% of 90 patients after weight loss at one year after surgery, and this improvement was greater among patients with a higher percentage of excess weight loss. Steatosis did not worsen in any patients, but changes in fibrosis after RYGB were not analyzed.

Moretto et al[49] reported that at the first biopsy obtained during RYGB surgery, 35 patients (44.9%) were found to have fibrosis; 31 presented with perisinusoidal and/or lobular fibrosis, four had only portal fibrosis, and seven had both lobular and portal fibrosis. The presence of fibrosis was significantly associated with T2DM and dyslipidemia. After weight loss, only 24 patients (30.8%) had fibrosis (P = .027), 19 of the 35 patients with fibrosis at the first biopsy, and five of the 43 patients without fibrosis at the first biopsy.

In Liu et al's study of 39 patients,[47] steatosis, lobular inflammation, overall inflammation score, and centrilobular/perisinusoidal fibrosis improved, as did overall stage of fibrosis, but no changes were noted in portal inflammation and portal fibrosis. No worsening of an existing fibrosis or cirrhosis occurred, but one patient (2.6%) developed fibrosis after RYGB. In this study, 58.8% patients were diagnosed with NASH at the first liver biopsy. The second biopsy after RYGB showed resolution of NASH in all patients.

Klein et al[42] reported seven extremely obese patients (BMI 58 ± 4 kg/m^2) before and one year after RYGB. After one year, patients lost 29% ± 5% of their initial body weight and hepatic steatosis decreased, but standard histologic measures of inflammation and fibrosis did not change. Nevertheless, a significant decrease was observed in hepatic factors, which are involved in regulating fibrogenesis (collagen-α1, transforming growth factor-β1, α-smooth muscle actin, tissue inhibitor of metalloproteinase 1 expression, and α-smooth muscle actin content) and inflammation (hepatic expression of chemokines, macrophage chemoattractant protein 1, and interleukin 8).

In a study of 16 patients, Csendes et al[44] reported that in 80% liver changes returned to normal appearance or improved after weight loss promoted by RYGB. However, in 13.4% of patients, liver histology was unchanged - one had mild steatosis and one had cirrhosis. In one patient (6.7%), progression from mild steatosis to pericellular fibrosis was observed.

Silverman et al[38] reported improvement of steatosis after RYGB in most of the 91 patients, but three (3.3%) showed an increased steatosis. Perisinusoidal fibrosis was eliminated or reduced in most patients, but in one patient, perisinusoidal fibrosis developed during follow-up. Portal fibrosis was unchanged while portal inflammation was worsening.

In Mattar et al's study of 70 patients after laparoscopic bariatric surgery,[40] most (58.6%) had RYGB, followed by sleeve gastrectomy (32.9%) and AGB (8.6%). Scores for liver steatosis, inflammation and fibrosis all significantly improved at the second liver biopsy and no progression of grade or stage of liver disease was observed. When RYGB was compared with the two restrictive procedures (sleeve gastrectomy, AGB), it showed a significantly greater excess weight loss at the time of the second liver biopsy (68% vs 39%, P < .001). Although there was universal weight loss and improvement in liver histology across all grades and stages, patients had significantly better results after RYGB. In the RYGB group, 93% had an improvement in grade of liver disease whereas only 66% of the patients in the restrictive group did (P = .004). The type of procedure was no longer a predictor of improvement in stage after adjustment for percent excess weight loss (P = .09). In the RYGB group, 46% showed an improvement in stage of liver disease, compared with 28% in the restrictive group.

Vertical Banded Gastroplasty

The use of VBG to treat morbidly obese people has diminished over the past several years. A few of the studies that looked at changes in liver histology showed improvement of NAFLD and NASH, although worsening of inflammation and fibrosis has been reported.[55,56]

Small studies by Ranløv[54] and Jaskiewicz et al[57] demonstrated an improvement in steatosis and inflammation after VBG-induced weight loss at 8- or 12-month follow-up. No patient showed evidence of fibrosis.

In their study of 216 patients, Stratopoulos et al[56] showed that steatosis and steatohepatitis significantly improved after an excess weight loss of 66%. However, despite a significant overall decrease in severity of fibrosis, 41.1% of patients with fibrosis showed no change and 11.7% had an increase in fibrosis. No patient had progression in severity of steatosis or steatohepatitis and no one developed cirrhosis.

In their study of 69 patients, Luyckx et al[55] found that steatosis reduced significantly after weight loss, but the incidence of inflammatory changes increased from 14% before surgery to 26%(P < .05).

Adjustable Gastric Banding

Laparoscopic adjustable gastric banding is worldwide the second most common bariatric procedure performed. However, few centers reported improvement of NAFLD and NASH after AGB.[50,51,79]

Dixon et al[50] examined 60 morbidly obese patients who had a liver biopsy done at the time of AGB and again at 29.5 ± 16 months after surgery. At baseline, half of these patients were diagnosed with NASH. There were statistically significant improvements in lobular steatosis, inflammation, and fibrosis between baseline and second biopsy. NASH was seen at the postoperative biopsy in only 6 (10%) patients.

Mathurin et al[51] reported long-term results in 381 patients 5 years after AGB (56.2%), biliointestinal bypass (22.8%), and RYGB (21%). They observed a significant increase in fibrosis in 20% of patients, which occurred within the first year. Afterwards, there was no significant difference between 1 and 5 years. No significant difference was observed between the three different surgery techniques regarding progression of fibrosis between baseline and 5 years. The authors found higher BMI, NAFLD activity score, steatosis, ballooning, inflammation, and fibrosis in patients with worsening of fibrosis at 5 years; furthermore, there was a trend toward becoming more insulin resistant. Patients with worsening fibrosis had BMI loss similar to that of patients without worsening fibrosis (-18% ± 10.7% vs -20.7% ± 12.7%, P = .19). One patient after biliointestinal bypass progressed to cirrhosis at 5 years. Steatosis and ballooning improved significantly at 5 years, but inflammation did not change. The improvement in steatosis and ballooning occurred within the first year and no significant difference was seen between 1 and 5 years. Steatosis and ballooning was seen more frequently in patients with refractory insulin resistance profile; in multivariate analysis, the refractory insulin resistance profile independently predicted the persistence of steatosis and ballooning 5 years later.

Biliopancreatic Diversion and Biliopancreatic Diversion With Duodenal Switch

In Kral et al's study of 104 patients[52] with liver biopsies done at the time of BPD and a second biopsy performed 41 ± 25 months after surgery, steatosis grades decreased significantly and this decrease correlated with weight loss. Fibrosis increased in 40.4%, decreased in 26.8% ,and showed no change in 32.7%. The postoperative change in fibrosis was related to the degree of baseline fibrosis and was increased in patients with grade 0 or 1, and decreased in those with grades 2 to 5. Eighteen (17.3%) of the 104 patients had signs of a mild inflammation at the initial biopsy. Eleven of these patients had disappearance of inflammation, but 10 other patients developed mild inflammation. Fourteen patients were diagnosed with cirrhosis at the time of operation and 11 had at least one repeated biopsy done. Nine of the 11 patients had reversal of grade 4 and 5 fibrosis and cirrhosis. Three patients (2.9%) developed de novo cirrhosis, two of these progressed from fibrosis at baseline.

Keshishian et al[53] repeated a liver biopsy in 78 patients after duodenal switch operation ranging from 6 to 36 months and studied the course of liver function tests, hepatic steatosis, and NASH. Serum aspartate aminotransferase (AST) level showed an increase of 130% of the baseline value (P <.02) at 6 months and alanine aminotransferase (ALT) level an increase of 160% (P < .0001) at the same time. Both values returned to baseline values by 12 months and remained within the normal range. Analysis of the liver architecture showed that steatosis and inflammation improved progressively after DS. After 2 years, patients with hepatic steatosis decreased from baseline 50–70% to 20–30% and the NASH grade dropped in most patients. Interestingly, hepatic inflammation, but not steatosis, slightly worsened at 6 months after surgery, which corresponded to the elevation in liver function tests. The deterioration of inflammation was clinically not harmful to the patients and progressive improvement was observed at and after 12 months. The authors stated that this transient hepatic dysfunction may be related to early rapid weight loss, a degree of protein malnutrition, lack of hepatotrophic factors, and the effect of high levels of mobilized circulating free fatty acids.

Mechanisms for Improvements in NAFLD and NASH After Bariatric Surgery

The improvements in NAFLD and NASH that occur after bariatric surgery are due to mechanisms related to the significant weight loss and improvements in obesity-associated conditions such as T2DM, insulin resistance, hyperlipidemia, and other components of metabolic syndrome.[80,81] Although the significant and sustained weight loss obtained with bariatric surgery is one of the main factors associated with the remission rate of T2DM and the improvements in liver histology,[13,23,30,81] many other mechanisms that affect carbohydrate and lipid metabolism, some of which are independent of weight loss, have been documented after RYGB and BPD-DS, and in fewer reports after SG as well.[40,82,83] In addition to weight loss, the main mechanisms postulated as being partly responsible for T2DM remission after RYGB and BPD-DS are the altered route of delivery of food content and resultant changes in the release of a variety of gut and pancreatic hormones that affect carbohydrate and lipid metabolism and interfere with hepatic glucose output; differential decrease in quality and distribution of total and regional fat mass; changes in hepatic insulin and free fatty acid metabolism; improvement in associated diseases; and stressors with differential changes in adipocytokines and other cytokines.[42,50,51,76,77,84–87] Though a review of these other mechanisms are beyond the scope of this article, the examples below provide an idea of how, in addition to weight loss, some changes provided by RYGB or BPD-DS may alter glucose and lipid metabolism, and possibly NAFLD and NASH.

The anatomic rearrangement resulting from those procedures alters both fasting levels and postprandial release of gastric, gut, and pancreatic hormones that appear to be related to the improvement in insulin sensitivity.

Glucagon-like Peptide-1

Glucagon-like peptide-1 (GLP-1), which is synthesized in the L cells in the distal portion of the small bowel, increases dramatically and reproducibly in response to feeding in patients who have undergone RYGB, BPD, or BPD-DS.[85,87,88] This is due to the early presentation of the food bolus to the small bowel.[85,88,89] GLP-1 regulates blood glucose by stimulating glucose-dependent insulin secretion, inhibiting glucagon secretion, possibly decreasing hepatic glucose production and delaying gastric emptying.[90] GLP-1 and related analogues can reduce elevated fasting and postprandial blood glucose levels in diabetic humans, generating intense interest in the use of these agents for the treatment of T2DM.[85] The effects of GLP-1 are mediated by specific binding of GLP-1 to the GLP-1 receptor (GLP-1r).This receptor belongs to the secretin family (type 2) of G-protein coupled receptors, and the downstream signaling is mediated, possibly exclusively, by an increase in intracellular cAMP.[91] Expression of GLP-1r has classically not been mapped in the liver,[92,93] but this has recently been challenged by the observation of reduced liver content of lipids in ob/ob mice[94] after 60 days of treatment with GLP-1. In addition, the presence of functional GLP-1 receptors was demonstrated using Western blots obtained from isolated hepatocytes, and GLP-1 receptor agonist was shown to induce cAMP in primary hepatocytes. Additional evidence comes from Gupta et al,[95] who demonstrated GLP-1r in cultured human hepatocytes, and from Svegliati-Baroni et al,[96] who proved GLP-1r expression in liver biopsies from patients undergoing hepatic resection for focal nodular hyperplasia or hepatic adenoma, and in liver biopsies from patients with NASH. Interestingly, the expression of GLP-1r in the biopsies from patients with NASH was generally lower than the expression in biopsies from the other patient categories. Expression of GLP-1r in liver biopsies from humans shows that GLP-1 regulates expression of transcription factors and enzymes involved in the hepatic metabolism of lipids.[96] All of this evidence challenges the classical view that the liver is not directly influenced by GLP-1.

Peptide YY

Peptide YY (PYY) is synthesized and secreted by the distal small bowel, colon, and rectum. Peripheral administration of PYY3-36, one of the circulating forms of PYY, inhibits food intake. PYY acts on the same hypothalamic neural circuits as leptin, stimulating hypothalamic receptors, decreasing neuropeptide/agouti-related protein and increasing α-melanocyte stimulating hormone levels. In addition to its anorexigenic effect, PYY inhibits gastrointestinal motility as well as pancreatic exocrine and endocrine secretion. Endogenous PYY levels are low in obese patients, suggesting that PYY deficiency may contribute to the pathogenesis. Obese subjects are not resistant to the anorectic effects of PYY.[85,97,98] Gastric bypass appears to be associated with an increase in postprandial levels of PYY.[97–99]

Ghrelin

Ghrelin is secreted primarily by oxyntic glands of the stomach fundus.[100] In addition to stimulating growth hormone secretion, ghrelin is a potent appetite stimulant,[101] and ghrelin levels have been shown to correlate with insulin levels and insulin resistance.[102,103] Although ghrelin levels increase during weight loss associated with simple caloric restriction, they

seem to decrease markedly after RYGB.[104,105] This decrease in ghrelin may contribute to the success of bypass surgery in inducing both weight loss and improvements in insulin resistance.[104,106–110]

Pancreatic and Adipocyte-derived Hormones

In addition to changes in gut peptides as mechanisms related to the significant weight loss and improvements in obesity-associated conditions, there may be a role for pancreatic and adipocyte-derived hormones.[111,112] For example, in a longitudinal study of short-term and long-term changes following RYGB, high-molecular-weight adiponectin increased 1 month after surgery, remained elevated for 12 months and were correlated with decreases in homeostatic model assessment -insulin resistance (HOMA-IR). Fasting glucagon and pancreatic polypeptide levels decreased after RYGB, and these reductions were independently associated with decreases in HOMA-IR.[112] Without a control group, however, it cannot be determined whether these changes are related uniquely to RYGB or occur in conjunction with the weight loss or negative energy balance that occurs after RYGB.

Overall, the extent to which the greater improvement in insulin sensitivity after RYGB and BPD-DS is related to greater weight loss, negative energy balance, altered release of gut and pancreatic hormones, or other factors remains a matter of speculation. The fact remains that weight loss per se is a central component in the improvements observed in all diseases related to obesity. We and others have demonstrated in controlled studies that peripheral glucose disposal; insulin resistance; reductions in leptin, resistin, and interleukin-6 levels; and increases in adiponectin levels are observed only after substantial weight loss has occurred and correlate with the magnitude of weight lost.[81,113,114] In addition, few of the studies that we reviewed documented improved liver histology changes with greater weight loss.[40,41]

The short- and long-term impact of all of these changes on glucose and lipid metabolism in the liver, adipose tissue, muscle, and pancreatic β-cell, and the interplay among metabolic processes occurring in these tissues, has not been comprehensively evaluated. These unresolved questions underscore the need to simultaneously evaluate and quantify the contribution of each of these tissues to the improvements observed after bariatric surgery.

Summary

Nonalcoholic steatohepatitis (NASH) is asymptomatic, but associated with obesity and the metabolic syndrome in most patients. Clinical scoring systems may guide the decision to perform a liver biopsy in the morbidly obese. Bariatric surgery is an effective treatment option for severely obese patients (BMI ≥ 35 kg/m^2), and provides for long-term weight loss and resolution of obesity-associated diseases in most patients. Although no prospective randomized trials are available and outcomes after long-term follow-up are still under scrutiny, regression and/or histologic improvement of NASH have been documented after weight loss after bariatric surgery using current techniques. Rare cases of fulminant steatohepatitis during the first postoperative year in patients with excessive rates of weight loss have been reported and fibrotic changes may progress. Identifying the factors associated with such outcomes and the independent roles of weight loss and other metabolic changes after bariatric surgery on improvements in obesity-associated diseases could potentially lead to a tailored and personalized approach to obesity and its consequences.

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Abbreviations

AGB, adjustable gastric banding; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BPD, biliopancreatic diversion; BPD-DS, biliopancreatic diversion with duodenal-switch; GLP-1, glucagon-like peptide-1; GLP -1r, GLP-1 receptor; HOMA-IR, homeostatic model assessment-insulin resistance; LABS, longitudinal assessment of bariatric surgery; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; T2DM, type 2 diabetes mellitus; VBG, vertical banded gastroplasty

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