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Gastric Bypass and Influence on Improvement of NAFLD

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Abstract
Purpose of Review Obesity is recognized as a chronic and recurring disease, often accompanied by other weight-related comorbid conditions such as obstructive sleep apnea, hypertension, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD). This chapter will seek to focus on the effect of weight loss surgery (WLS), in particular Roux-en-Y gastric bypass (RYGB), on NAFLD.
Recent Findings Among several modalities available to treat NAFLD, the one most likely to achieve rapid, significant, and sustained improvement of liver disease is WLS.
Summary The most commonly studied WLS procedure at this time is RYGB, and there is significant evidence that this is a safe and effective procedure both for weight loss and to bring about improvement of multiple associated comorbid conditions, including NAFLD. Further research focusing on non-surgical approaches that might mimic the effect of WLS on liver pathology is needed.

Keywords Liver steatosis · Gastric bypass · Liver disease · Bariatric surgery · Weight loss surgery · Weight loss · Fatty liver

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Background

Compared to lean individuals, the incidence of non-alcoholic fatty liver disease (NAFLD) in patients with obesity is significantly higher, affecting 80–90% of obese patients. Diabetes and hyperlipidemia similarly increase the risk for development of NAFLD, with incidences of 30–50% and 90%, respectively, in patients with these conditions [1]. NAFLD alone confers a significant treatment burden on patients and physicians, but this issue is further complicated by the fact that NAFLD constitutes an increasing proportion of all chronic liver disease (>75% as of 2008) [2]. Current estimates place NAFLD as the second leading indication for liver transplantation in the USA [3]. In the current setting of the obesity epidemic, these facts have profound public health implications. Patients with hepatocellular carcinoma or decompensated liver failure as a result of NAFLD may qualify for liver transplantation. At the same time, fatty liver disease has decreased the supply of suitable donor livers, due to concern over delayed graft function and primary graft failure in steatotic grafts. This association raises significant concern about a potential increase in the need for liver transplantations in the face of a paucity of suitable donor organs [4–7].

The pathogenesis and progression of NAFLD are linked to the metabolic syndrome and obesity, generally through insulin resistance [8–11]. However, despite the coincident pathologies, progression of NAFLD may be independent of insulin resistance or the metabolic syndrome in some patient populations, with one study demonstrating that 73% of subjects with severe obesity but without the metabolic syndrome had biopsy-proven NAFLD (59/77–76.6% had FL, 18/77–23.4% had NASH) [12]. In effect, obesity is the overwhelmingly significant contributor to NAFLD in the USA and other developed nations, and treatment of both is necessary and appropriate.

Improvements in NAFLD are seen with diet and lifestyle modifications, particularly those that result in significant weight loss. Histologic changes in liver parenchyma can be seen following weight loss of as little as 3–5% with improvement in steatotic burden. Histologic improvement in non-alcoholic steatohepatitis (NASH) can be seen at 7% total body weight loss, and decreased fibrosis is seen with weight loss of ≥10% [13, 14]. Despite the benefits of weight loss in improvement of NAFLD, dietary modification and caloric deficit do not appear to be the major determinants of this improvement. Van Wissen et al. performed a systematic review of dietary modification on liver volumes, demonstrating the length of the diet, more so than composition of the diet and total caloric content, determined improvement in liver volume (as a surrogate for steatotic burden). Extrapolating from these data, it appears that changes in liver steatosis respond to biochemical signals and dietary or digestive composition more so than to simple calorie deprivation. Interestingly, reduction of carbohydrate and saturated fat intake has not been shown to affect the degree of NAFLD [7].

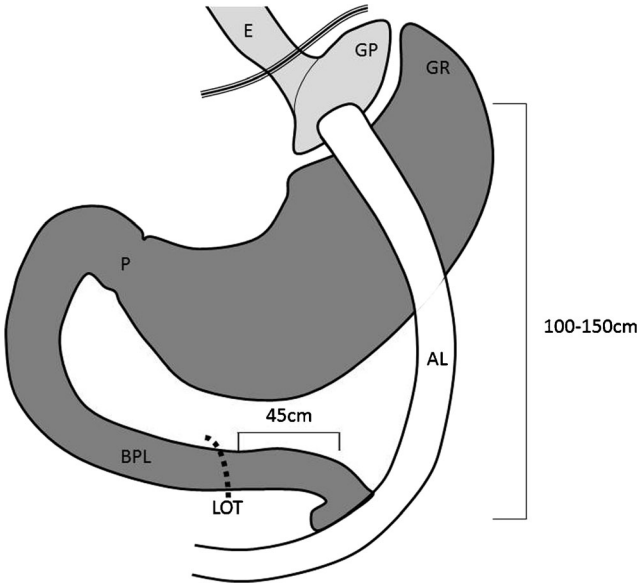

Fig. 1 Schematic representation of Roux-en-Y gastric bypass. *E* esophagus, *GP* gastric pouch, *GR* gastric remnant, *P* pylorus, *LOT* ligament of Treitz, *JJ* jejunojejunostomy with representative lengths of limbs noted: *AL* alimentary limb (100–150 cm), *BPL* biliopancreatic limb (45 cm)

Role of Gastric Bypass in Improvement of NAFLD

Roux-en-Y gastric bypass (RYGB) has been a gold standard weight loss surgery (WLS) procedure since it was first described by Mason and Ito in the 1960s [15, 16]. While it is currently the second most commonly performed WLS procedure, it continues to enjoy popularity as a safe and effective operation that confers excellent early and sustained weight loss, as well as significant and fairly rapid improvement or resolution of nearly all weight-related comorbid conditions. Figure 1 illustrates the basic reconstruction seen with the gastric bypass. The operation includes creation of a small proximal gastric pouch, generally measuring 30 mL or less in volume, that is completely divided and separated from the remainder of the distal stomach. Next, the jejunum is transected at about 45 cm from the ligament of Treitz and the distal portion is then connected to the proximal pouch. Finally, the proximal split end of jejunum is attached farther down along the length of the small bowel such that food travels 100–150 cm before finally mixing with digestive enzymes.

While restriction and malabsorption were previously felt to be the cornerstones of weight loss through RYGB, current literature indicates that hormonal effects related to the reconstruction are the driving forces behind both weight loss and comorbidity improvement. These hormonal effects derive from a "foregut hypothesis," which proposes that the lack of foodstuffs passing through the duodenum changes hormonal signaling, as well as a "hindgut hypothesis," that the rapid passage of relatively undigested food into the hindgut also alters this signaling [17, 18].

The multiple benefits of WLS, beyond loss of weight alone, are thought to be due to changes in the enteroinsulin axis, helping to realign several dysfunctional processes, including insulin resistance, glucose metabolism, and hyperlipidemia [19]. Following RYGB specifically, there are substantial alterations in incretin signaling as part of this process. Increased concentrations of glucagon-like peptide-1 (GLP-1), elevations of gastric inhibitory peptide (GIP), and changes in substances such as peptide YY and oxyntomodulin after RYGB alter enteric signaling pathways. These incretin effects are unique to RYGB and are not seen with non-surgical weight loss [20].

With the staggering increase in obesity and weight-related medical problems, WLS is becoming a far more accepted option to treat these conditions. There has been much attention paid to the data showing that RYGB can rapidly, and sometimes in the same hospitalization, improve or eliminate T2DM. Similarly, there is a significant body of literature demonstrating the beneficial effect of RYGB on NAFLD, as will be summarized in this chapter. Physicians treating patients with NAFLD should include a conversation about WLS as an effective part of the care plan. Based on substantial data, it is clear that any patient with NAFLD and a body mass index (BMI) of 35 or greater should be referred for consideration for WLS.

There are significant differences between the various WLS operations that have been offered historically and currently. For instance, RYGB brings about more significant weight loss than either adjustable gastric banding (AGB) or vertical sleeve gastrectomy (VSG) [21], with a corresponding improvement of

severity of NAFLD [22]. The immediate metabolic effects of RYGB, evidenced by rapid improvements in postoperative hyperglycemia in patients with T2DM, may play a role in biochemical mechanisms by which NAFLD improves. Conversely, the weight loss from the AGB is uniquely due to restrictive effects, while weight loss through VSG comes about primarily through combined restrictive effects and appetite suppression through a decrease in ghrelin. Therefore, improvement of weight-related comorbid conditions tends to be higher with RYGB than with these other commonly offered procedures.

Interestingly, initial data involving rapid weight loss from highly malabsorptive procedures, such as the jejunoileal bypass, demonstrated a counterintuitive increased incidence of NASH after surgery [23••]. This, however, was not related to the amount of weight lost but to bacterial overgrowth in a defunctionalized small bowel limb, leading to hepatic insult. Based on these findings, certain highly malabsorptive WLS operations are no longer performed. The currently accepted malabsorptive operation, the biliopancreatic diversion with duodenal switch, has the best rate of weight loss as well as improvement of weight-related conditions such as NAFLD. However, this operation accounts for less than 1% of all WLS operations performed, and as such it will not be covered here [24, 25].

In a study evaluating serial liver biopsies performed at 1 and 5 years following WLS, where the majority of patients underwent RYGB, Mathurin et al. demonstrated that the pathogenesis of steatosis was closely linked to insulin resistance. Their data showed parallel changes in insulin resistance and steatosis, with early improvement (within 1 year after surgery) predicting long-term outcome of NAFLD [26]. Mixed cohorts of post-WLS patients have been noted to have improvement in steatosis, necroinflammatory activity, and hepatic fibrosis, with complete resolution of NAFLD seen in 83% of patients [27]. Similarly, a large mixed series by Taitano et al. demonstrated 75% improvement of steatosis and 90% improvement in NASH [28••]. In a smaller, but more homogeneous study of female patients undergoing RYGB with an extended follow-up of at least 40 months, Schneck et al. showed significant and durable improvement in NAFLD, with 100% of patients experiencing improvement in steatosis, inflammatory response, and NAFLD score. Hepatocyte ballooning improved in 88% of patients and steatosis resolved completely in 55% after RYGB [29].

Extrapolating from data obtained from invasive biopsies, Cazzo et al. sought to follow improvement in NAFLD using the NAFLD fibrosis score, after benchmarking to intraoperative liver biopsy performed at the time of WLS. These scores were then recalculated 1 year post-RYGB. The sensitivity and specificity between baseline NAFLD score and biopsy in this group's population was 97 and 75.9%, respectively. Of the patients with fibrosis at baseline, 55% had complete resolution at 1 year on the basis of repeat NAFLD score [30••]. Similarly, Moretto et al. demonstrated histopathologic resolution of fibrosis in 50% of patients with serial liver biopsies following RYGB. This was associated with an average excess weight loss of >80% in their patients [31]. These findings raise the point that WLS can be offered to patients with advanced hepatic fibrosis, and even well-compensated cirrhosis, with expectation not only of survival but also of improvement of what had been thought to be irreversible liver disease.

Beyond NAFLD, recent studies have also demonstrated impaired hepatocellular function and excretion of bile in patients with obesity. After undergoing RYGB, patients have been shown to experience improvement in these NAFLD-associated impairments by radionucleotide scintography [32]. There has been at least one study showing ultrasound-confirmed improvement in liver steatosis after RYGB [33]. Similarly, two recent publications examined radiologic improvement by computed tomography (CT) of hepatic steatosis after RYGB. Winder et al. retrospectively reviewed the charts of 986 RYGB patients, looking for those who had both preoperative and postoperative abdominal CT scans. Of those with scans for comparison, 84% of patients experienced significant radiologic improvement of liver steatosis at a mean time point of 2.3 years. This was concomitant with significant weight loss—a mean loss of 19.3 body mass index (BMI) points. In a further analysis of this population [34], Schock et al. noted that there was an associated 83.3% resolution of T2DM or insulin resistance in affected patients [35]. Interestingly, there was not 1:1 overlap between those who lost weight, those whose insulin resistance improved, and those whose steatosis improved, indicating that this topic is more complex than current data can fully explain.

Conclusion

Obesity is now well recognized as a disease process, and one that is regularly accompanied by other detrimental medical issues, including NAFLD. Among several modalities available to treat NAFLD, the one most likely to achieve rapid and sustained improvement of liver disease is WLS. The most commonly studied WLS procedure at this time is RYGB, and there is significant evidence that this is a safe and effective procedure both for weight loss and to bring about improvement of multiple associated comorbid conditions, including NAFLD.

Compliance with Ethical Standards

Conflict of Interest Vamsi Alli and Ann Rogers declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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