

Bariatric Surgery for the Treatment of Nonalcoholic Fatty Liver Disease: Is Vertical Sleeve Gastrectomy the Best Future Option?

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ABSTRACT

There has been a worldwide rise in the prevalence of overweight and obese individuals. Due to this increase, there has been a related rise in the number of individuals with non-alcoholic fatty liver disease or NAFLD, a condition that is becoming a more common cause for cirrhosis leading to liver transplantation. Diet and activity program provide modest weight loss and are poor treatments for maintenance of weight loss. Multiple studies have shown that Roux-en-Y gastric bypass surgery can lead to histological improvement in both non-alcoholic fatty liver disease as well as in the subset of individuals who also have steatohepatitis. This editorial explores the potential for the newer bariatric surgery, vertical sleeve gastrectomy, to function as a surgical option for the treatment of non-alcoholic fatty liver disease and steatohepatitis.

Key words: Obesity; Non-Alcoholic Fatty Liver Disease; Gastric Bypass; Bariatric Surgery

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EDITORIAL

Obesity is a major health problem with increasing prevalence both in the United States as well as worldwide. One definition of obesity is based upon the use of an individual's height and weight to calculate a body mass index or BMI with units of kg/m^2 (see Table 1). The prevalence of obesity in the United States doubled from 15% to more than 30% between the years of 1976 to 2000^[1]. By 2012, 34.9% of adults age 20 years or older in the United States were obese^[2]. There has been a similar rise in the worldwide prevalence of overweight and obese individuals^[3]. Worldwide through 2013, a recent study reported that the prevalence of adults with a body mass index of $25 \text{ kg}/\text{m}^2$ or greater now includes 36.9% of men and 38.0% of women.

The term nonalcoholic steatohepatitis or NASH was first suggested by Ludwig and colleagues in 1980^[4]. In this original description, it was noted that most of the reported individuals were obese and that many patients included in this report were women. Many individuals in the original Ludwig study had obesity-related conditions including diabetes mellitus and cholelithiasis^[4].

Nonalcoholic fatty liver disease (NAFLD) is a condition that is defined by evidence for hepatic steatosis on imaging or histology with no known secondary causes for hepatic fat accumulation, such as alcohol dependence or protein malnutrition (kwashiorkor). Based on histology, NAFLD includes two different clinical entities, nonalcoholic fatty liver (NAFL) and NASH. NAFL is the presence of hepatic

steatosis without evidence of hepatocellular injury, while NASH is defined as hepatic steatosis and inflammation with hepatocyte injury with or without fibrosis^[5,6]. NAFL is a relatively benign disease with less common progression to liver fibrosis and cirrhosis, while NASH more frequently progresses to liver failure, cirrhosis, and hepatocellular carcinoma (HCC)^[7]. NAFLD is often associated with obesity, dyslipidemia, diabetes mellitus, age, and metabolic syndrome, which are all established risk factors for cardiovascular disease^[8-10].

NAFLD is a rapidly becoming more common both in the United States as well as throughout the world. NAFLD is currently the most common cause of chronic liver disease in the United States; the worldwide prevalence of NAFLD is thought to be 6.3% to 33% in the general population^[11,12]. This condition causes significant morbidity, mortality, and economical impact, and NAFLD is now the third most common indication for liver transplantation in the United States^[13]. The rate of transplant procedures continue to rise as studies have shown the percentage of patients undergoing a liver transplant for NASH increased from 1.2% in 2001 to 9.7% by 2009^[13].

The precise mechanism of progression from NAFL to NASH, fibrosis, cirrhosis, and hepatocellular carcinoma has not been fully delineated. It has been well established that NAFLD-associated diseases, including obesity and diabetes mellitus, increase the risk of HCC independent of the presence of NAFLD^[14-16]. NASH itself has also been reported to be associated with an increased risk of HCC^[7,17] even in the absence of established cirrhosis. The pathophysiology by which these three disease entities contribute to the risk of developing HCC appears to involve promotion of chronic inflammation through dysfunction of hormones and cytokines related to obesity, diabetes, and NAFLD. Insulin resistance and hyperinsulinemia have been suggested to induce increased lipolysis and delivery of free fatty acids to the liver which in turn promote fatty acid oxidation and oxidative stress of hepatocytes. This oxidative stress related to production of and release of reactive oxygen species may promote hepatocellular injury, chronic inflammation, cytokine and adipocytokine release, stellate cell activation, fibrosis, and cell proliferation^[17-20]. In addition, insulin resistance and compensatory hyperinsulinemia stimulate the insulin-like growth factor axis, which has been implicated in the pathogenesis of HCC^[21,22].

The diagnosis and management of NAFLD remains a complex clinical dilemma, reflective of the nature of the disorder. Despite the growing disease burden of NAFLD, current national guidelines in the United States do not recommend screening for NAFLD in high-risk individuals attending diabetes or obesity clinics^[5]. The basis for the lack of this recommendation is largely derived from uncertainties surrounding diagnostic testing, treatments, long term benefits and cost-effectiveness of screening. The complexities in diagnosing NAFLD suggest that the true prevalence of the disease may be underreported.

The present management of patients with NAFLD includes treating liver disease and its complications as well as associated metabolic diseases, such as obesity, diabetes mellitus, and dyslipidemia^[5]. Current guidelines in the United States recommend treatments limited to lifestyle interventions such as weight loss through diet and exercise, vitamin E for individuals with non-diabetic NASH^[5], and pioglitazone^[5] for NASH (although the long term safety and efficacy have not yet been established for either pharmacological intervention).

Weight loss does reduce hepatic steatosis, and loss of at least 3-5% of total body weight appears necessary to improve hepatic steatosis, but loss of up to 10% of total body weight may be necessary for improvement in NASH^[5,23,24]. Diet and activity programs alone are usually insufficient^[25-27] to result in the sustainable weight loss required to improve NASH in the morbidly obese. A recent nine year follow up

Table 1 Classification system for obesity.

Condition	BMI* (kg/m ²)	Class of Obesity
Normal	18.5 to 24.9	
Overweight	25.0 to 29.9	
Obesity	30.0 to 34.9	I
Obesity	35.0 to 39.9	II
Extreme Obesity	> 40.0	III

*BMI: Body Mass Index.

study from the United Kingdom^[25] reported that for 76,704 obese men and 99,791 obese women, the annual probability of attaining normal weight was 1 in 210 for men and 1 in 124 for women. For body mass index of > 40 kg/m², the annual likelihood of attaining normal weight was 1 in 1290 for men and 1 in 677 for women. Diet and activity programs are not sufficiently beneficial to alter these findings^[26,27]. In a meta-analysis of 19 studies of weight reduction programs based on dietary changes and physical activity^[27], the mean weight loss was only 6.4 kg.

The alternative viewpoint is that this is sufficient weight loss for the treatment of NAFLD. Indeed, it was recently reported^[28] that the use of diet and activity programs can be helpful in individuals with NASH. However, when one examines the results more closely, there were three major issues seen. First, individuals in this study had a mean body mass index of only 31.3 kg/m², and so the study results may not be applied to a population of morbidly obese individuals. Second, the weight loss program was rarely effective. In the majority (90%) of enrolled individuals, who had a mean loss of only 1.78% of their total body weight, resolution of NASH was seen in 10% of individuals. Only 10% of enrolled individuals had > 10% total body weight lost, and in that small subgroup 90% had improvement in NASH. Third, the study did not address the problem of maintenance of weight loss. It has been shown that maintenance therapy is poorly effective in individuals treated with diet and activity programs^[29].

For these reasons, bariatric surgery has become an important option for individuals with medically-complicated obesity. The "gold-standard" in bariatric surgery is performance of the Roux-en-Y gastric bypass (Figure 1). In this procedure, a proximal gastric pouch of approximately 30 ml is produced by dividing the stomach from a few cm below the gastroesophageal junction to the angle of His. The jejunum is divided 40 to 50 cm distal to the ligament of Treitz; the distal segment is used to form a gastrojejunal anastomosis with the gastric pouch; the proximal jejunum is used to form a jejuno-jejunal anastomosis 100 to 150 cm distal to the gastrojejunostomy. Studies have shown significant resolution of hypertension, dyslipidemia, and diabetes mellitus in patients after Roux-en-Y gastric bypass^[30]. Studies have also shown significant reductions in long-term mortality after gastric bypass surgery including mortality induced by cardiovascular events, diabetes, and cancer^[31,32].

It was immediately recognized in the 1970s that gastric bypass surgery could reduce fatty infiltration of the liver^[33]. However, gastric bypass surgery has never become a common therapy for NASH, perhaps due to the perception of the risk of operating on patients with advanced or fibrotic liver disease and the possibility of significant long-term risks associated with this procedure. As shown in Table 2, between 2005 and 2015, 444 patients have been reported who underwent perioperative liver biopsies with follow up postoperative liver biopsies after gastric bypass surgery^[34-40]. In these individuals with Class II and Class III obesity, resolution of steatosis and NASH ranged from 74% to 89% at periods of up to 5 years after gastric bypass surgery.

In a laparoscopic adjustable gastric band surgery, an inflatable plastic band is placed approximately 4 cm below the gastroesophageal

junction and around the upper part of the stomach. The band is connected to an access port by using tubing so that the band volume can be adjusted via this port (which is attached to the abdominal musculature). In individuals who have undergone laparoscopic gastric banding, there is reportedly significantly less weight loss and, not surprisingly, at 1 year 30.4% of these individuals have persistent NASH^[40]. These results demonstrate the increased efficacy of enhanced weight loss induced for the resolution of NAFLD and NASH.

Vertical sleeve gastrectomy is a bariatric surgical procedure which involves substantial reduction of gastric capacity with subsequently large restriction (Figure 2). The surgical construction of a vertical sleeve gastrectomy involves resection of 60% to 80% of the stomach along the greater curvature by using staples to produce a lesser curvature-based stomach^[41]. A systematic review of fifteen randomized trials has reported a mean complication rate of 12.1% for individuals who underwent vertical sleeve gastrectomy compared to a mean complication rate of 20.9% for individuals who underwent Roux-en-Y gastric bypass surgery^[42]. Restrictive procedures including vertical sleeve gastrectomy have been thought to result in fewer nutritional deficiencies compared to malabsorptive bariatric surgical procedures such as gastric bypass surgery, the biliopancreatic diversion, and the duodenal switch^[41]. Worldwide, there were 468,609 individuals who underwent bariatric surgery in 2013, and the percentage of individuals undergoing vertical sleeve gastrectomy for treatment of obesity rose from essentially 0% in 2003 to 37% by 2013^[43].

Initial weight loss results achieved with the vertical sleeve gastrectomy are comparable to results achieved with the Roux-en-Y gastric bypass^[44]. In individuals with NAFLD, vertical sleeve gastrectomy is effective for normalization of hepatic laboratory values^[45]. However, there are as yet no large published studies evaluating potential long-term histologic improvement in NASH following vertical sleeve gastrectomy.

The use of non-invasive testing to assess severity of NASH following bariatric surgical procedures presents a number of potential problems. Proposed biomarkers for hepatic fibrosis^[46] require further validation in the morbidly obese. Liver stiffness measurements by transient elastography (FibroScan) will also require further validation in the morbidly obese due to the high reported failure rate in individuals with body mass index greater than 30 kg/m² ^[47]. Among the newer imaging techniques, magnetic resonance elastography appears to be useful in predicting advanced fibrosis^[48]. However, this newer imaging technique also requires further validation in morbidly obese individuals.

The proven benefits of vertical sleeve gastrectomy on weight loss, dyslipidemia, and diabetes mellitus may prove to be a potential therapeutic option which directly addresses the pathogenesis of NASH and its related co-morbidities, obesity and diabetes mellitus. By decreasing adipocytokine release through weight loss and adipocyte reduction, inflammation may potentially be inhibited. The potential for vertical sleeve gastrectomy to resolve diabetes mellitus and its hyperinsulinemia state may cause down regulation of the insulin-like growth factor axis and its potential effects on the pathogenesis of hepatocellular carcinoma. Reduction of insulin resistance could in turn decrease fatty acid oxidation and oxidative stress of hepatocytes, potentially slowing progression of steatosis, inflammation, cirrhosis formation, and ultimately hepatocellular carcinoma.

However, recent studies have suggested emerging evidence supporting the progression of NAFLD patients to hepatocellular carcinoma without evidence of cirrhosis. This would clearly reduce the potential benefit of utilizing vertical sleeve gastrectomy

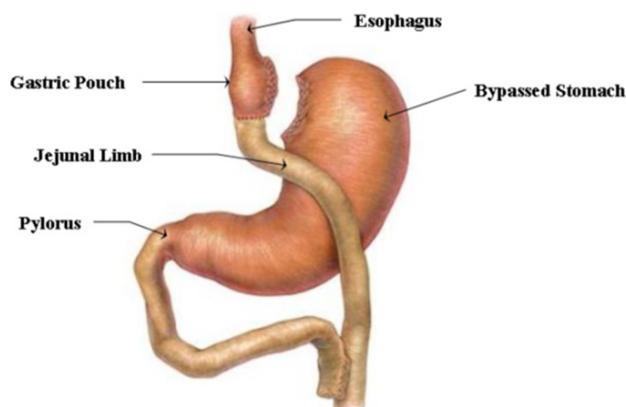


Figure 1 Roux-en-Y Gastric Bypass Surgery. Digestion and absorption occur in the jejunal limb and in the ileum distal to the jejuno-jejunal anastomosis. Bile and pancreatic secretions mix with chyme in ileum distal to the jejuno-jejunal anastomosis. The length of the pancreatico-biliary limb is the distance from the pylorus to the jejuno-jejunal anastomosis and a longer limb decreases small intestine available for the absorption of nutrients. Reproduced with permission from Elsevier B.V.: Nutrition Research 2008; 28(5): 293-298.

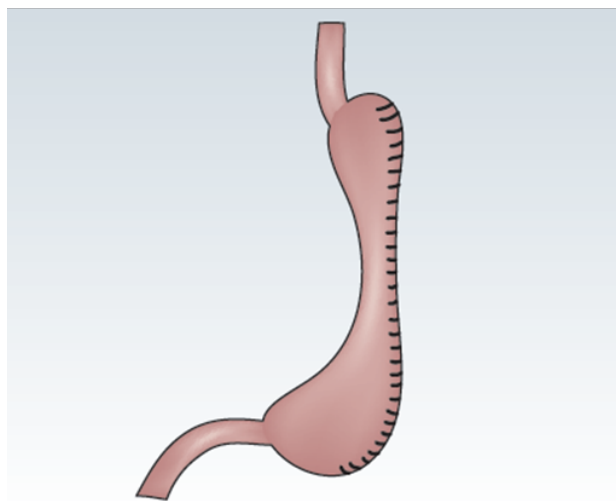


Figure 2 Vertical Sleeve Gastrectomy. This bariatric surgical procedure involves resection and removal of 60% to 80% of the stomach along the greater curvature by using staples to produce a tubular gastric pouch. Reprinted with permission from Mcmillan Publishers Ltd: Nature Reviews Endocrinology 2012; 8(9): 544-556.

Table 2 Effects of Roux-en-Y gastric bypass surgery on liver biopsy findings in obese individuals with NAFLD/NASH*.

First Author (Year)	N	Time Period	Result
Clark (2005)	16	Mean: 305 Days	Resolution of Steatosis: 81%
Barker (2006)	19	Mean: 21.4 Months	Resolution of NASH: 89%
Weiner (2010)	68	Mean: 18.6 Months	Regression of NAFLD: 83%
Moretto (2012)	78	Not Stated	Resolution of Fibrosis: 46%
Vargas (2012)	26	Mean: 16 Months	Resolution of NASH: 84%
Caiazzo (2014)	167	60 Months	Resolution of Steatosis: 74%
Lassailly (2015)	70	12 Months	Resolution of NASH: 85%
TOTAL: 444			

*Non-Alcoholic Fatty Liver Disease: NAFLD; Non-Alcoholic Steatohepatitis: NASH

for treatment of NASH. Guzman *et al*^[49] identified 50 cases of histologically confirmed hepatocellular carcinoma between 2004 and 2007 at a single center, with 3 of those cases being patients with NAFLD without cirrhosis. Alexander *et al*^[50] evaluated a large cohort of patients with hepatocellular carcinoma in non-cirrhotic livers compared to patients with intrahepatic cholangiocarcinoma occurring in non-cirrhotic livers. These authors reported^[50] that

there was significant steatosis in the nontumor liver associated with hepatocellular carcinoma in 54% (85/157) compared with 27% (32/120) of the cholangiocarcinoma patients. Studies examining evidence for non-cirrhotic hepatocellular carcinoma in NAFLD patients generally have not fulfilled all design criteria for a strong direct observational epidemiologic study. The studies either did not include well-defined exposure and outcome groups, sufficient sample size, or a longitudinal follow-up time interval^[51]. Therefore, additional studies are required to further elucidate the association between non-cirrhotic NAFLD and hepatocellular carcinoma.

To summarize, NAFLD and its associated metabolic diseases of obesity, diabetes mellitus, and dyslipidemia are an increasing public health issue both in the United States and worldwide. Current guidelines do not recommend routine screening for NAFLD in high risk groups. The suggested therapeutic options, which include diet and activity programs, provide limited benefit as lifestyle interventions with minimal evidence for long term maintenance of weight loss. By contrast, vertical sleeve gastrectomy is a bariatric surgical procedure which has proven benefits with regards to metabolic diseases including obesity, diabetes mellitus, and dyslipidemia. A recent systematic review reported a mean complication rate of 12.1% for individuals after vertical sleeve gastrectomy compared to a mean complication rate of 20.9% after Roux-en-Y gastric bypass surgery. By improving metabolic diseases and slowing or reversing NAFLD, vertical sleeve gastrectomy may prove to be a major treatment for obese individuals by altering the pathogenesis of cirrhosis and ultimately hepatocellular carcinoma in individuals with NAFLD. Since NAFLD patients without cirrhosis may progress to hepatocellular carcinoma, this alternative pathogenetic pathway could limit the benefit of vertical sleeve gastrectomy in individuals with NAFLD. Further clinical studies are required to further define the role of vertical sleeve gastrectomy in obese individuals with NAFLD.

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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