

Roux-en-Y Gastric Bypass Improves Liver Histology in Patients with Non-Alcoholic Fatty Liver Disease

Jeanne M. Clark,*† Amir R. A. Alkhuraishi,‡ Steven F. Solga,* Patricia Allii,§ Anna Mae Diehl,¶ and Thomas H. Magnuson||

Abstract

CLARK, JEANNE M., AMIR R. A. ALKHURAISHI, STEVEN F. SOLGA, PATRICIA ALLI, ANNA MAE DIEHL, AND THOMAS H. MAGNUSON. Roux-en-Y gastric bypass improves liver histology in patients with non-alcoholic fatty liver disease. *Obes Res.* 2005;13: 1180–1186.

Objectives: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the United States and is prevalent in morbidly obese patients. While weight loss and treatment of risk factors are recommended, the reported effects of bariatric surgery on NAFLD are mixed. **Research Methods and Procedures:** We examined liver histology at the time of Roux-en-Y gastric bypass surgery and at elective incisional hernia repair after weight loss for 16 patients at one center. Slides were read by one pathologist, blinded to clinical data, using the Brunt criteria. Clinical and laboratory data were extracted from chart review. Alcohol use was ascertained by two interviews.

Results: At baseline, the mean age was 44 years, 50% were women, 88% were white, and the mean BMI was 51 kg/m². None had significant alcohol use. On initial biopsy, all patients showed steatosis, 94% had inflammation, 88% had ballooning degeneration, 88% had perisinusoidal fibrosis, and 81% had portal fibrosis. The mean time between the two biopsies was 305 ± 131 (SD) days. The mean weight loss was 118 ± 29 lb. Steatosis improved in 15 of 16

patients, with resolution in 13. Twelve of 15 patients with inflammation at baseline showed improvement, and 12 of 14 showed less ballooning. Six of 14 patients with perisinusoidal fibrosis and 6 of 13 with portal fibrosis showed improvement. No patient had worsening of steatosis, inflammation, ballooning, or fibrosis.

Discussion: Our study shows improvement in all of the histological features of NAFLD after Roux-en-Y gastric bypass surgery—induced weight loss, despite significant histopathology at baseline and substantial weight loss.

Key words: morbid obesity, bariatric surgery, non-alcoholic fatty liver disease, liver histology

Introduction

With the explosive growth in obesity (1), non-alcoholic fatty liver disease (NAFLD)¹ is now considered to be the most common liver disease in the United States (2–4). While the prevalence of NAFLD in the general population is estimated to range from 3% to 24% depending on the definition (5,6), 85% to 95% of morbidly obese populations seem to have NAFLD, and up to 33% have non-alcoholic steatohepatitis (NASH) (7–10). This has important clinical ramifications because NAFLD can progress to cirrhosis (11–13), resulting in increased liver-related morbidity and mortality, including hepatocellular carcinoma (14,15).

Given that lifestyle modification and medication are relatively ineffective strategies for achieving significant long-term weight loss among those with morbid obesity, bariatric surgery has become an increasingly popular treatment option (16,17). This trend toward surgery has grown as a result of acceptable perioperative risks and the reported benefits of bariatric surgery on various obesity-related comorbidities

Received for review August 26, 2004.

Accepted in final form May 9, 2005.

*Department of Medicine, †Department of Epidemiology, and ‡Department of Surgery, The Johns Hopkins University, Baltimore, Maryland; ‡Division of Gastroenterology, Hepatology and Nutrition, University of Texas Medical School-Houston, Houston, Texas; §Quest Diagnostics, Baltimore, Maryland; and ¶Department of Medicine, Duke University School of Medicine, Durham, North Carolina.

Address correspondence to Jeanne M. Clark, Welch Center for Prevention, Epidemiology and Clinical Research, The Johns Hopkins University, 2024 E. Monument Street, Suite 2–600, Baltimore MD 21205.

E-mail: jmclark@jhmi.edu

Copyright © 2005 NAASO

¹ Nonstandard abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RYGB, Roux-en-Y gastric bypass surgery.

such as hypertension, diabetes, and sleep apnea (18–22). However, the effects of bariatric surgery on liver histology, particularly in individuals who have NAFLD, are less clear. In particular, since NASH was first described as a complication of jejunio-ileal bypass, there have been lingering concerns about the effects of rapid weight loss on the liver (23–26). On the other hand, some studies suggest that diet-induced weight loss improves aminotransferase levels and may improve hepatic steatosis; however, the data in this area are limited (27,28). Recent studies of bariatric surgery, particularly solely restrictive procedures, have also shown improvement in hepatic pathology (29). Because the current approach to the management of NAFLD is to treat the risk factors, namely obesity, diabetes, and hyperlipidemia, it is crucial to determine whether weight loss is helpful or harmful to the livers of obese people with NAFLD. Given that bariatric surgery is currently the most effective treatment for inducing and maintaining weight loss in the morbidly obese and is being performed more commonly, studying the effects of bariatric surgery is likely to provide useful information to clinicians caring for the morbidly obese. The purpose of this study was to use a standardized tool to evaluate changes in liver histology that accompany weight loss induced by Roux-en-Y gastric bypass surgery (RYGB).

Research Methods and Procedures

Subjects

Our patient population was selected from 225 consecutive patients undergoing open RYGB at our institution. All patients are required to meet NIH guidelines for eligibility for bariatric surgery (BMI ≥ 40 kg/m² or ≥ 35 kg/m² with comorbidities), report prior attempts of unsuccessful weight loss/maintenance, show continued motivation to lose weight and have a realistic weight loss goal postprocedure, and show an understanding of the risks and benefits associated with the procedure, the expected weight loss from the procedure, and the importance of careful postoperative follow-up.

As is our general practice in surgical patients at high risk for liver disease, all of these patients underwent an intraoperative wedge liver biopsy at the beginning of the gastric bypass procedure. The RYGB procedure itself was standardized to include a 20-mL proximal gastric pouch, 40-cm biliopancreatic limb, and 150-cm Roux-en-Y limb.

At varying times after the gastric bypass, 16 patients went on to have a second elective laparotomy for the repair of an incisional hernia. During this second operation, all of these individuals underwent a repeat wedge liver biopsy at the start of the operation. It is this cohort of 16 consecutive patients with a repeat liver biopsy after RYGB that comprise our study population.

Preoperative Evaluation of RYGB Patients

All patients at our center undergo an extensive preoperative evaluation before RYGB. This involves an evaluation by an internist, specialized nutritionist, psychologist, and the operating surgeon. The work-up includes documentation of the patient's medical history, physical examination, medications, and routine laboratory work. The same clinical investigator (A.R.A.) reviewed all patient charts and recorded patient data. In particular, alcohol use was ascertained through review of the records from the primary care doctor and from interviews with the nutritionist and psychologist. We included the highest estimate of intake as their true intake.

Liver Histology

After the biopsy, each specimen was processed and stained with hematoxylin and eosin and Masson's trichrome using standard laboratory methods. A single expert pathologist (P.A.) who was blinded to clinical information and sequence of biopsy scored each biopsy for steatosis, necroinflammation, ballooning degeneration, perisinusoidal fibrosis, and portal fibrosis using the Brunt criteria, which range from 0 (none) to 3 (marked) (30). Each component was scored individually. In addition, an overall grade was assigned to reflect the overall necroinflammatory activity, which incorporates a combination of hepatocellular ballooning and inflammation (acinar and portal). This necroinflammatory grade is scored as 0 (no necroinflammation), 1 (mild necroinflammation), 2 (moderate necroinflammation), and 3 (severe necroinflammation). Liver disease was also staged by evaluating the pattern and extent of fibrosis. A fibrosis score (i.e., stage) of 0 indicates no fibrosis, stage 1 = zone 3 perisinusoidal fibrosis only, stage 2 = zone 3 perisinusoidal fibrosis with focal/extensive portal fibrosis, stage 3 = zone 3 perisinusoidal fibrosis with focal/extensive bridging fibrosis, and stage 4 = cirrhosis.

Clinical Data

One clinical investigator reviewed all of the patient medical charts. Data retrieved from the chart included age, sex, race, height, weight, liver function tests, the presence of known liver diseases and their associated risk factors, medication use, and alcohol and tobacco consumption. The diagnoses of hypertension, diabetes, and hyperlipidemia were assigned based on self-reported history of the condition or use of specific medications for each condition.

Data Analyses

Means \pm SD and medians (range) were calculated and are reported for baseline data and for weight loss after surgery. Changes in clinical parameters were assessed using paired Student's *t* tests or χ^2 tests. Changes in liver enzymes were compared using the paired sign test, and changes in

Table 1. Clinical characteristics of 16 patients at the time of RYGB and at re-biopsy

Characteristics	At RYGB (mean \pm SD, %)	At hernia repair (mean \pm SD, %)
Age (years)	43.9 \pm 8.1	
Female (%)	50	
White race (%)	88	
Weight (lb)	334.4 \pm 48.3	216.4 \pm 43.4
BMI (kg/m ²)	51.1 \pm 6.1	32.9 \pm 5.1
Hypertension (%)	50	19
Diabetes (%)	19	6
Dyslipidemia (%)	31	6
Obstructive sleep apnea (%)	50	13
AST (U/l)*	31.9 \pm 27.5	21.8 \pm 9.7
ALT (U/l)*	33.6 \pm 18.9	23.5 \pm 16.3
ALP (U/l)*	88.3 \pm 31.7	88.8 \pm 32.5

* $N = 15$.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

histology were compared using the Wilcoxon paired sign-rank test. Data analyses were performed using Stata 7.0 (College Station, TX).

The study was approved by the Johns Hopkins Institutional Review Board for clinical studies.

Results

Baseline Characteristics and Results of RYGB Surgery

The clinical characteristics of the patients at the time of RYGB and hernia repair are given in Table 1. The mean values of liver tests were within normal limits, and no patient had any known diagnosis of other liver diseases.

The mean time elapsed between the two biopsies was 305 \pm 131 (SD) days. During this time, the mean weight loss was 118.1 \pm 29.5 lb, the mean percent weight loss was 35.4 \pm 7.9%, and the mean BMI fell from 51.1 \pm 6.1 to 32.9 \pm 5.1 kg/m². After surgery, the mean values of aspartate aminotransferase and alanine aminotransferase decreased somewhat, but this was not statistically significant ($p > 0.10$).

Liver Histology

The histological findings at the time of RYGB and hernia repair are given in Tables 2 and 3. None of the study patients reported any consumption of alcohol or use of toxic medication that could account for the pathological changes seen on liver biopsy at either time-point. At the time of RYGB, all patients showed some degree of steatosis, and 10 patients (62.5%) had moderate or severe steatosis (>33% of hepatocytes involved). Overall, the extent of steatosis was

markedly reduced after RYGB ($p < 0.001$). At re-biopsy, 13 of 16 patients (81%) showed no steatosis, and 3 (19%) had a score of 1 (<33% of hepatocytes involved). No patient had an increase in steatosis.

There was also a significant reduction in inflammation and ballooning after RYGB ($p < 0.001$ for both). Of the 15 patients with inflammation on biopsy at the time of RYGB, 12 showed a reduction in the degree of inflammation at the time of re-biopsy, and 3 patients stayed the same. No patient had an increase in inflammation after RYGB. Of the 14 patients with ballooning at RYGB, 12 showed less ballooning at the time of the hernia repair, and 2 showed no change. No patient developed or showed an increase in ballooning after RYGB.

Fourteen patients showed some degree of perisinusoidal fibrosis at the time of RYGB. Of these, six showed improvement in the fibrosis score by one point and eight had no change on the second biopsy. Similarly, of the 13 patients with portal fibrosis initially, 6 had improvement in their fibrosis score by one point, whereas the remaining 7 had no change. None of the patients showed development or progression of either type of fibrosis after RYGB. Because stage is based entirely on degree of fibrosis, there was a corresponding decrease in NAFLD stage after RYGB. The changes in perisinusoidal and portal fibrosis and in stage were all statistically significant ($p = 0.01, 0.01, \text{ and } 0.003$, respectively).

Finally, the overall histological activity (grade) was significantly lower at the time of re-biopsy compared with the time of RYGB ($p < 0.001$). Of the 15 patients with an initial

Table 2. Liver histopathology by the Brunt criteria of 16 morbidly obese patients at the time of RYGB and re-biopsy

Histopathology (N, %)	At RYGB	At re-biopsy	<i>p</i> *
Steatosis			<0.001
0 None	0	13 (81.3)	
1 <33%	6 (37.5)	3 (18.8)	
2 33% to 66%	8 (50.0)	0	
3 >66%	2 (12.5)	0	
Inflammation			<0.001
0 None	1 (6.3)	6 (37.5)	
1 Minimal	4 (25.0)	6 (37.5)	
2 Moderate	7 (43.8)	3 (18.8)	
3 Marked	4 (25.0)	1 (6.3)	
Ballooning			<0.001
0 None	2 (12.5)	12 (75.0)	
1 Minimal	10 (62.5)	4 (25.0)	
2 Moderate	4 (25.0)	0	
3 Marked	0	0	
Perisinusoidal fibrosis			0.01
0	2 (12.5)	7 (43.8)	
1	12 (75.0)	8 (50.0)	
2	2 (12.5)	1 (6.3)	
3	0	0	
Portal fibrosis			0.01
0	3 (18.8)	8 (50.0)	
1	10 (62.5)	6 (37.5)	
2	3 (18.8)	2 (12.5)	
3	0	0	

* *p* values reflect the results of Wilcoxon matched pairs sign-rank test for each histologic category.

score >0, all had a lower grade at re-biopsy, including 13 with complete resolution (including 4 with an initial score of two) and 2 with improvement of one point. No patient had an increase in NAFLD grade after RYGB.

Discussion

Our results show improvement in all of the characteristic morphological features of NAFLD (e.g., steatosis, ballooning, necroinflammation, and fibrosis) after significant weight reduction after RYGB surgery. Not a single patient had worsening of any of the features of NAFLD.

Although our findings are remarkably consistent, the results from previous studies on the effect of weight loss on NAFLD are conflicting. Early reports of rapid weight loss,

Table 3. Grade and stage of NAFLD in 16 morbidly obese patients at the time of RYGB and rebiopsy

Histopathology (N, %)	At RYGB	At re-biopsy	<i>p</i>
Grade			<0.001
0	1 (6.3)	14 (87.5)	
1	9 (56.3)	2 (12.5)	
2	6 (37.5)	0	
3	0	0	
Stage			0.003
0	1 (6.3)	9 (56.3)	
1	12 (75)	5 (31.3)	
2	3 (18.8)	2 (12.5)	
3	0	0	

* *p* values reflect the results of Wilcoxon matched pairs sign-rank test for each histologic category.

while showing significant resolution of both the prevalence and degree of steatosis, reported a significant increase in the degree of focal necrosis, bile stasis, portal inflammation, and/or fibrosis (31–33). However, these studies used fasting and/or very low caloric diets to reduce body weight. In contrast, a study reporting gradual weight loss by controlled caloric restriction and exercise resulted in significant reduction of steatosis with no noticeable increase in the presence or degree of fibrosis (27). Overall, the studies of the effect of diet-induced weight loss on NAFLD are inconclusive (28).

The term NASH was first coined in 1980 by Ludwig et al. (24). However, liver disease has been described in association with obesity for more than 50 years (34,35). In the 1970s, a form of fulminant liver failure was reported as a consequence of jejuno-ileal bypass surgery. Bacterial overgrowth in the dysfunctional, blind segment of bowel, along with protein/caloric malnutrition and rapid weight loss, are believed to have resulted in the progressive liver disease seen after this surgery (23,36,37). Since then, similar to our findings, the majority of studies investigating the effect of gastric bypass on liver histology have reported a beneficial effect on liver histology with improvements across the spectrum of histological features seen in NAFLD (38–42). In addition, a recent study of NAFLD after laparoscopic adjustable gastric banding showed improvement in most histological features of NAFLD (29). However, there continues to be some uncertainty since a study of gastroplasty by Luyckx et al. (26) reported a significant increase in the prevalence and degree of hepatic inflammation after gastroplasty. Another recent study by Kral et al. (25) reported an increase in the overall grade of fibrosis after biliopancreatic

diversion, despite noting a significant decrease in the prevalence and severity of steatosis. Interestingly, in the study of Kral et al., bariatric surgery seemed to have differential effects, depending on the degree of baseline fibrosis. Patients with minimal fibrosis (stage < 2) showed progressive fibrosis postoperatively, whereas those with advanced fibrosis (stage \geq 2, including cirrhosis) showed marked regression of fibrosis after surgery.

There are several possible explanations for the apparent discrepancies between our study and those of Luyckx et al. and Kral et al.. First, the situations leading to re-biopsy differed among the studies. In our study, all patients underwent a repeat liver biopsy in the course of an elective hernia repair. In the article by Luyckx et al., the 69 patients underwent re-operation and second liver biopsy for a wide variety of reasons, ranging from staple line disruption to slipping stomach to cholecystectomy. These reasons are not further delineated, and results are not examined by indication; however, they state that a selection bias for re-biopsy cannot be ruled out. In the study by Kral et al., the 104 patients also underwent re-operation for a number of reasons ranging from dissatisfaction with weight loss (55%), to uncontrolled diarrhea (23%), to miscellaneous causes including gallstones and intestinal obstruction (22%). Conceivably, in some of these individuals, complications of bypass surgery might have caused dietary deficiencies, increased oxidative stress, and/or induced cytokines that promote hepatic damage (16,43–47). In fact, in the study of Kral et al., the increase in fibrosis was associated with diarrhea and lower albumin levels (as well as postmenopausal status and alcohol intake). Second, it is possible that the different bariatric procedures have different effects on hepatic pathology. Biliopancreatic diversion (the procedure done in the study of Kral et al.) diverts biliary and pancreatic secretions to the distal ileum, and, thus, this technique employs malabsorption as one of its antiobesity mechanisms. Because biliopancreatic diversion somewhat mimics jejuno-ileal bypass physiology, it might be expected to exert similar effects on hepatic histology (16,43). Luyckx et al. speculated that protein malnutrition might result when feeding is limited by restricting the gastric pouch and suggested that this might explain the increase in inflammation seen after simple gastroplasty (26). However, they did not report on diet composition or correlate their findings of worsening inflammation with any evidence of protein malnutrition or chemical marker (such as serum albumin). Thus, their findings remain somewhat unexplained. Finally, because of the retrospective nature of the studies, other factors that affect NAFLD progression may have differed in the studies at baseline or may have been differentially affected during the procedures.

The main limitation of our study is the non-random choice of patients for re-biopsy. Because only patients undergoing surgery for incisional hernia repair had a repeat

liver biopsy, selection bias may have influenced our results. Although there was no difference in age, initial BMI, race, or prevalence of hypertension, diabetes, or dyslipidemia compared with the rest of the RYGB patients at our center ($N = 225$; data not shown), those undergoing hernia repair were more likely to be men and more likely to have diagnosed obstructive sleep apnea. In addition, the 16 patients in this study seem to have had somewhat more severe liver disease than that in a larger cohort ($N = 189$) of our patients (48) and compared with other published series of bariatric surgery patients (8–10). However, the estimates in different studies vary widely, and the differences in our study may have been caused by chance given our small number of patients. Selection bias could also have been introduced before the initial RYGB, if patients with more severe obesity-related comorbidities were excluded from the initial surgery. It is possible that sicker patients might be more likely to develop progressive liver disease after weight loss than those healthy enough to undergo bariatric surgery. Another limitation is the small sample size. Nevertheless, the fact that in all patients histological features of NAFLD improved and none worsened suggests that the likelihood of significant harm to the liver from RYGB is low. Finally, we did not screen all patients for other causes of liver disease. Thus, although there was no known history or any histopathologic evidence of viral hepatitis or other liver disease, it is possible that we may have missed some cases of liver disease that were not NAFLD.

Our study has several strengths. First, it provides information on changes in NAFLD histology in an asymptomatic patient population. In at least some of the previous studies, the repeat liver biopsies were performed on patients with significant symptoms resulting from the initial procedure. Second, we used a standardized tool to report histological changes (30). This tool incorporates all of the morphological features of NAFLD. The majority of the prior studies were performed before the introduction of this standardized tool. Finally, our results are consistent, showing improvement in all of the different morphological features seen in NAFLD, namely steatosis, inflammation, ballooning, and fibrosis.

In conclusion, our study shows an improvement in all of the characteristic histological changes of NAFLD, namely steatosis, inflammation, and fibrosis, after RYGB-induced weight loss, adding to a growing body of literature. These beneficial changes occurred despite significant NAFLD histopathology at baseline and significant weight loss, a combination that has been shown in some studies to worsen hepatic inflammation and fibrosis. Currently there is no proven therapy for NAFLD, including weight loss achieved through lifestyle modification (28). Several medications, including insulin sensitizers, seem promising in pilot and uncontrolled studies (49–51); however, their effectiveness remains unproven, and randomized controlled trials are

ongoing (52,53). Thus, at the moment, bariatric surgery seems to be the most promising treatment.

Acknowledgments

Support for this project was obtained, in part, from the AASLD/Schering Advanced Hepatology Fellowship (S.F.S.).

References

1. **Flegal KM, Carroll MD, Ogden CL, Johnson CL.** Prevalence and trends in obesity among US adults, 1999–2000. *JAMA.* 2002;288:1723–7.
2. **Clark JM, Brancati FL, and Diehl AM.** Nonalcoholic fatty liver disease: the most common cause of abnormal liver enzymes in the U.S. population. *Gastroenterology.* 2001;120(Suppl 1):A-65.
3. **Clark JM, Brancati FL, Diehl AM.** Nonalcoholic fatty liver disease. *Gastroenterology.* 2002;122:1649–57.
4. **Clark JM, Brancati FL, Diehl AM.** The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol.* 2003;98:960–7.
5. **Ruhl CE, Everhart JE.** Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology.* 2003;124:71–9.
6. **Angulo P.** Nonalcoholic fatty liver disease. *N Engl J Med.* 2002;346:1221–31.
7. **Dixon JB, Bhathal PS, O'Brien PE.** Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology.* 2001;121:91–100.
8. **Crespo J, Fernandez-Gil P, Hernandez-Guerra M, et al.** Are there predictive factors of severe liver fibrosis in morbidly obese patients with non-alcoholic steatohepatitis? *Obes Surg.* 2001;11:254–7.
9. **Gholam PM, Kotler DP, Flancaum LJ.** Liver pathology in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. *Obes Surg.* 2002;12:49–51.
10. **Beymer C, Kowdley KV, Larson A, et al.** Prevalence and predictors of asymptomatic liver disease in patients undergoing gastric bypass surgery. *Arch Surg.* 2003;138:1240–4.
11. **Caldwell SH, Oelsner DH, Iezzoni JC, et al.** Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology.* 1999;29:664–9.
12. **Powell EE, Cooksley WG, Hanson R, et al.** The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology.* 1990;11:74–80.
13. **Matteoni CA, Younossi ZM, Gramlich T, et al.** Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology.* 1999;116:1413–9.
14. **Ratziu V, Bonyhay L, Di M, et al.** Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. *Hepatology.* 2002;35:1485–93.
15. **Nair S, Mason A, Eason J, et al.** Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? *Hepatology.* 2002;36:150–5.
16. **Mun EC, Blackburn GL, Matthews JB.** Current status of medical and surgical therapy for obesity. *Gastroenterology.* 2001;120:669–81.
17. **Sugerman HJ.** The epidemic of severe obesity: the value of surgical treatment. *Mayo Clin Proc.* 2000;75:669–72.
18. **Sugerman HJ, Kellum JM, Engle KM, et al.** Gastric bypass for treating severe obesity. *Am J Clin Nutr.* 1992;55(2 Suppl):560S–6S.
19. **MacDonald KG Jr, Long SD, Swanson MS, et al.** The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J Gastrointest Surg.* 1997;1:213–20.
20. **Balsiger BM, Kennedy FP, Abu-Lebdeh HS, et al.** Prospective evaluation of Roux-en-Y gastric bypass as primary operation for medically complicated obesity. *Mayo Clin Proc.* 2000;75:673–80.
21. **MacLean LD, Rhode BM, Forse RA.** Late results of vertical banded gastroplasty for morbid and super obesity. *Surgery.* 1990;107:20–7.
22. **MacLean LD, Rhode BM, Nohr CW.** Late outcome of isolated gastric bypass. *Ann Surg.* 2000;231:524–8.
23. **Holzbach RT.** Hepatic effects of jejunioileal bypass for morbid obesity. *Am J Clin Nutr.* 1977;30:43–52.
24. **Ludwig J, Viggiano TR, McGill DB, Ott BJ.** Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc.* 1980;55:434–8.
25. **Kral JG, Thung SN, Biron S, et al.** Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. *Surgery.* 2004;135:48–58.
26. **Luyckx FH, Desai C, Thiry A, et al.** Liver abnormalities in severely obese subjects: effect of drastic weight loss after gastroplasty. *Int J Obes Relat Metab Disord.* 1998;22:222–6.
27. **Ueno T, Sugawara H, Sujaku K, et al.** Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol.* 1997;27:103–7.
28. **Wang RT, Koretz RL, Yee HF Jr.** Is weight reduction an effective therapy for nonalcoholic fatty liver? A systematic review. *Am J Med.* 2003;115:554–9.
29. **Dixon JB, Bhathal PS, Hughes NR, O'Brien PE.** Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. *Hepatology.* 2004;39:1647–54.
30. **Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR.** Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol.* 1999;94:2467–74.
31. **Andersen T, Gluud C, Franzmann MB, Christoffersen P.** Hepatic effects of dietary weight loss in morbidly obese subjects. *J Hepatol.* 1991;12:224–9.
32. **Drenick EJ, Simmons F, Murphy JF.** Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small-bowel bypass. *N Engl J Med.* 1970;282:829–34.
33. **Rozenal P, Biava C, Spencer H, Zimmerman HJ.** Liver morphology and function tests in obesity and during total starvation. *Am J Dig Dis.* 1967;12:198–208.
34. **Zelman S.** The liver in obesity. *Arch Intern Med.* 1952;90:141–56.
35. **Macdonald RA.** Pathogenesis of nutritional cirrhosis. *Arch Intern Med.* 1962;110:424–34.
36. **Vyberg M, Ravn V, Andersen B.** Pattern of progression in liver injury following jejunioileal bypass for morbid obesity. *Liver.* 1987;7:271–6.

37. **Styblo T, Martin S, Kaminski DL.** The effects of reversal of jejunoileal bypass operations on hepatic triglyceride content and hepatic morphology. *Surgery.* 1984;96:632–41.
38. **Griffen WO Jr, Young VL, Stevenson CC.** A prospective comparison of gastric and jejunoileal bypass procedures for morbid obesity. *Ann Surg.* 1977;186:500–9.
39. **Buckwalter JA.** Clinical trial of jejunoileal and gastric bypass for the treatment of morbid obesity: four-year progress report. *Am Surg.* 1980;46:377–81.
40. **Halverson JD, Zuckerman GR, Koehler RE, et al.** Gastric bypass for morbid obesity: a medical–surgical assessment. *Ann Surg.* 1981;194:152–60.
41. **Ranlov I, Hardt F.** Regression of liver steatosis following gastroplasty or gastric bypass for morbid obesity. *Digestion.* 1990;47:208–14.
42. **Silverman EM, Sapala JA, Appelman HD.** Regression of hepatic steatosis in morbidly obese persons after gastric bypass. *Am J Clin Pathol.* 1995;104:23–31.
43. **Scopinaro N, Gianetta E, Adami GF, et al.** Biliopancreatic diversion for obesity at eighteen years. *Surgery.* 1996;119:261–8.
44. **Diehl AM.** Cytokines and the molecular mechanisms of alcoholic liver disease. *Alcohol Clin Exp Res.* 1999;23:1419–24.
45. **Diehl AM.** Cytokine regulation of liver injury and repair. *Immunol Rev.* 2000;174:160–71.
46. **Tilg H, Diehl AM.** Mechanisms of disease: cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med.* 2000;343:1467–76.
47. **Murr MM, Balsiger BM, Kennedy FP, et al.** Malabsorptive procedures for severe obesity: comparison of pancreaticobiliary bypass and very very long limb Roux-en-Y gastric bypass. *J Gastrointest Surg.* 1999;3:607–12.
48. **Solga SF, Clark JM, Alkuraishi A, et al.** Race and comorbid factors predict NAFLD histopathology in severely obese patients. *Int J Obes Related Metab Disord.* 2005;1:6–11.
49. **Marchesini G, Brizi M, Bianchi G, et al.** Metformin in non-alcoholic steatohepatitis. *Lancet.* 2001;358:893–4.
50. **Caldwell SH, Hespeneide EE, Redick JA, et al.** A pilot study of a thiazolidinedione, troglitazone, in nonalcoholic steatohepatitis. *Am J Gastroenterol.* 2001;96:519–25.
51. **Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, et al.** Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology.* 2003;38:1008–17.
52. **Bugianesi E, Marzocchi R, Villanova N, Marchesini G.** Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH): treatment. *Best Pract Res Clin Gastroenterol.* 2004;18:1105–16.
53. **Nonalcoholic steatohepatitis clinical research network.** *Hepatology.* 2003;37:244.