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Effect of Bariatric Surgery on Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis

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See Patton HM et al on page 1961 for companion article in the December 2008 issue of *Gastroenterology*.

Background & Aims: **Weight loss in overweight or obese individuals results in marked improvement or resolution of hypertension, diabetes mellitus, and hyperlipidemia. However, the overall effect of weight loss on nonalcoholic fatty liver disease (NAFLD) remains unclear. This systematic review and meta-analysis is an effort to explore the effect of weight loss after bariatric surgical procedures on NAFLD.** ***Methods:*** **We performed an electronic literature search of published articles on bariatric surgery and liver histology since inception to September of 2007. Primary outcome measures were improvement and/or resolution in the 3 components of NAFLD (steatosis, steatohepatitis, and fibrosis) after bariatric surgery–induced weight loss. A pooled proportion of patients with improvement or resolution was calculated for steatosis, steatohepatitis, and fibrosis using a random effects model. Heterogeneity among the studies was assessed using the I^2 (inconsistency) statistic and subgroup analyses.** ***Results:*** **A total of 15 studies (766 paired liver biopsies) were selected for final data extraction. The percentage reduction in mean body mass index after bariatric surgeries ranged from 19.11 to 41.76. The pooled proportion of patients with improvement or resolution in steatosis was 91.6% (95% confidence interval [CI], 82.4%–97.6%), in steatohepatitis was 81.3% (95% CI, 61.9%–94.9%), in fibrosis was 65.5% (95% CI, 38.2%–88.1%), and for complete resolution of nonalcoholic steatohepatitis was 69.5 (95% CI, 42.4%–90.8%).** ***Conclusions:*** **Steatosis, steatohepatitis, and fibrosis appear to improve or completely resolve in the majority of patients after bariatric surgery–induced weight loss.**

Obesity (body mass index [BMI] ≥30 kg/m^2) is a growing epidemic in the United States, with a significant increase in prevalence from 15% in 1980 to 32.9% in 2004.[1] The health implications of being obese or overweight are manifold—type 2 diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, stroke, and even cancer. Nonalcoholic fatty liver disease (NAFLD) is also an emerging problem related to the obesity epidemic. The spectrum of NAFLD ranges from hepatic steatosis (fat accumulation in the liver cells) to the more severe nonalcoholic steatohepatitis (NASH) and fibrosis that can progress to cirrhosis, end-stage liver disease, and hepatocellular carcinoma.[2] The prevalence of NAFLD is estimated to be around 70% in obese individuals and 85% to 95% in patients with morbid obesity.[3] The prevalence of NASH is as high as 18.5% in obese individuals and 33% in those who are morbidly obese.[3,4] The pathophysiologic mechanisms of NAFLD have not been elucidated clearly as yet, but obesity and insulin resistance are considered to be the main causative factors.[5] The initial event in the pathogenesis of NAFLD is increased accumulation of free fatty acids in the liver. Abnormal lipid accumulation in hepatocytes results in increased production of reactive oxygen species as a result of increased mitochondrial fatty acid β oxidation. As a result of this increased metabolic demand and oxidative stress, mitochondrial dysfunction and membrane damage occurs along with increased endoplasmic reticulum stress, and activation of the endoplasmic reticulum stress pathway.[6] This initiates a cascade of events that lead to progressive hepatocellular injury, steatohepatitis, and fibrogenesis. Adipocytes also create and maintain a state of constant inflammation in the hepatic tissue. The resulting macrophage infiltration of hepatic adipose tissue releases a variety of inflammatory mediators that are implicated in the pathogenesis of NAFLD including tumor necrosis factor-α, transforming growth factor-β, interleukin-1, interleukin-6, leptin, vascular endothelial growth factor, angiotensinogen, and angiotensin II. The end result of these complex mechanisms is a deranged homeostasis between the proinflammatory and anti-inflammatory, apoptotic and necrotic processes in the liver leading to injury to hepatocytes, fibrogenesis, and eventual progression to cirrhosis.[5,7,8]

At present, interventions for NAFLD focus on weight loss and improvement in insulin resistance and associated comorbidities. Medical treatment for weight loss with drugs, diet, exercise, and other lifestyle modification measures has limited efficacy, especially in morbidly obese patients. Surgical therapy has proven to be very effective for achieving sustained weight loss, even in the morbidly obese population.[3] The number of bariatric surgical procedures being performed in the United States has increased exponentially in the past decade. Weight loss after bariatric surgery also results in significant improvement or resolution in the metabolic syndrome markers (hyperlipidemia, hypertension, and diabetes mellitus) in a vast majority of patients.[9] Because NAFLD is a component of the metabolic syndrome, it may as well be influenced by weight loss similar to other metabolic syndrome markers. The overall effect of bariatric surgery–induced weight loss on liver histology, particularly NAFLD, remains unclear as of today, with a lack of

Abbreviations used in this paper: BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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well-defined trials exploring this relationship. Older studies led to concerns that rapid weight loss from bariatric surgery could lead to worsening of liver histology and even precipitate acute liver failure.[10,11] On the contrary, several recent studies have reported significant improvement or even complete resolution of NAFLD after bariatric surgery–induced weight loss.[12–15] This systematic review and meta-analysis is an effort to explore the effect of weight loss after bariatric surgical procedures on liver histopathologic aspects of NAFLD.

Methods

Electronic databases (MEDLINE, EMBASE, ISI Web of Science, and Cochrane Controlled Trials Register) were searched (from inception to September of 2007) by 2 independent investigators (M.R. and K.S.K.) for studies that provided information on liver biopsies before and after bariatric surgical procedures. Search terms used were "bariatric surgery," "NAFLD," "liver biopsy," "weight loss surgery," "liver histology," and "obesity." Boolean logic was used to combine these search terms. Studies were included if they quantified liver histology on patients with NAFLD at the time of bariatric surgery and after achieving weight loss. A total of 131 studies were identified and reviewed. Reference lists of all the selected articles were hand-searched for any additional studies. Abstracts from national meetings (Digestive Disease Week, American Association for the Study of Liver Diseases, American College of Gastroenterology, and the European Association for the Study of the Liver annual scientific meetings) were reviewed to identify unpublished data. None of the abstracts were eligible for inclusion in the final analysis. Fifteen studies with adequate histologic follow-up evaluation were included for the final data extraction and analysis.[3,4,11–23] Data on cirrhotic patients were excluded from the meta-analysis. Studies also were excluded if jejuno-ileal bypass was the bariatric surgical procedure because of concerns for endotoxin-mediated hepatic damage. The study attrition diagram is shown (Figure 1).

Information was gathered for the following variables: (1) study: authors, year, location, and design; (2) type of weight-loss surgery; (3) number of paired liver biopsies for histologic analysis before and after bariatric surgery; (4) duration between the biopsies in months; (5) mean BMI before and after bariatric surgery; (6) mean age at the time of first biopsy in years; (7)

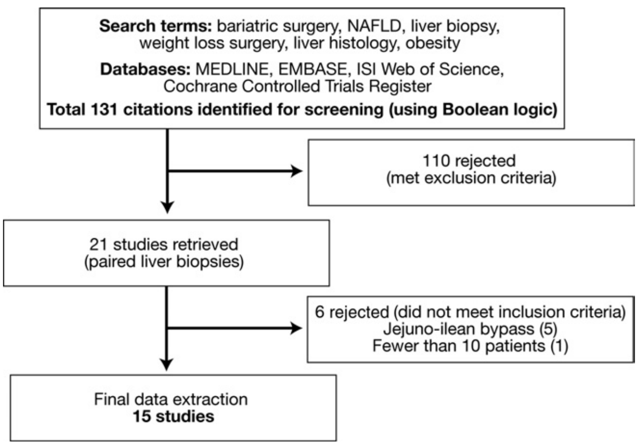

Figure 1. Study attrition diagram.

Table 1. Characteristics of 15 Included Studies

Study	Type of surgery	Study design	No. of paired liver biopsies	Duration between biopsies, mo	Mean age at surgery, y	M	F	Pre-BMI, mean ± SD	Post-BMI mean ± SD	% reduction in BMI
Barker et al, 2006[4]	RYGBP	P	19	13.3–31.7	48.6 (35–48)[a]	2	17	47 ± 4.4	29 ± 5.2	38.46
Clark et al, 2005[3]	RYGBP	R	16	5.8–14.5	43.9 ± 8.1	8	8	51.1 ± 6.1	32.9 ± 5.1	35.62
Csendes et al, 2006[12]	RYGBP	P	16	9–33	46.2 (21–65)[a]	1	15	44.3 (37–60)[a]	28.6 (22.5–37)[a]	35.44
Dealmeida et al, 2006[13]	RYGBP	P	16	12.8–36.6	41.5 ± 9.1	2	14	53.4 ± 8.8	31.1 ± 4.7	41.76
Dixon et al, 2004[14]	LAGB	R	36	9–51	43 ± 10.3	11	25	47 ± 10.6	34 ± 5.5	27.66
Furuya et al, 2006[16]	RYGBP	P	18	24	46.6 ± 7.3	1	17	51.7 ± 7.4	32.43 ± 6.0	37.27
Jaskiewicz et al, 2005[17]	GP	R	10	8	40.7 ± 10	N/A	N/A	46.7 ± 8.8	N/A	N/A
Liu et al, 2007[15]	RYGBP	R	39	6–41	41.4 ± 9	6	33	47.7 ± 6.2	29.5 ± 5.6	38.16
Luyckx et al, 1998[11]	GP	R	69	12–42	36 ± 11	10	59	43.9 ± 8.3	31.7 ± 4.1	27.79
Mattar et al, 2005[18]	RYGBP + LAGB + LSG	P	70	6–24	49 ± 9	22	48	56 ± 11	39 ± 10	30.36
Mathurin et al, 2006[19]	BLB + LAGB	P	121	12	40.6	N/A	N/A	47.1	38.1	19.11
Mottin et al, 2005[20]	RYGBP	P	90	12	35.6 ± 1.1	26	64	46.7 ± 0.88	N/A	N/A
Stratopoulos et al, 2005[21]	VBG	P	51	18	N/A	18	33	52.8 ± 1	N/A	N/A
Kral et al, 2003[22]	BPD	R	104	6–111	36.9 ± 9	20	84	47 ± 8.4	31 ± 7.9	34.04
Silverman et al, 1995[23]	RYGBP	R	91	2–61	39	4	87	47	33.5	28.72

RYGBP, Roux-en-Y gastric bypass; P, prospective; R, retrospective; LAGB, laparoscopic adjustable gastric banding; GP, gastroplasty; N/A, data not available; LSG, sleeve gastrectomy; BLB, bilio-intestinal bypass; VBG, vertical banded gastroplasty; BPD, biliopancreatic diversion.
[a]Range shown.

Table 2. Histopathologic Grading System, Type of Liver Biopsies, and Reasons for Follow-Up Liver Biopsy

Study	Histopathologic grading system	At the time of bariatric surgery	At follow-up evaluation	Reason for follow-up liver biopsy
Barker et al, 2006[4]	Dixon	N	N	Prospective (study protocol)
Clark et al, 2005[3]	Brunt	W	W	Elective incisional hernia repair after weight loss
Csendes et al, 2006[12]	Brunt	W	W	Incisional hernia repair
Dealmeida et al, 2006[13]	Brunt, modified	W + N	N	Prospective (study protocol)
Dixon et al, 2004[14]	Dixon	N/A	N	Second lap procedure for revision or cholecystectomy/percutaneous because of initial histology concerns
Furuya et al, 2006[16]	NAS	W	N	Prospective (study protocol)
Jaskiewicz et al, 2005[17]	Brunt	W	N/A	Prospective (study protocol)
Liu et al, 2007[15]	NAS	N	N	Prospective (study protocol)
Luyckx et al, 1998[11]	O	W	N/A	Second surgery needed for staple disruption, stenosis, pouch enlargement, slipping stomach, cholecystectomy
Mattar et al, 2005[18]	Brunt, modified	N	N	Prospective (study protocol)
Mathurin et al, 2006[19]	Brunt	N/A	N/A	Prospective (study protocol)
Mottin et al, 2005[20]	O	W + N	N	Prospective (study protocol)
Stratopoulos et al, 2005[21]	Brunt	W	N	Prospective (study protocol)
Kral et al, 2003[22]	O	W	W	Dissatisfaction with weight loss, malabsorption, diarrhea, delayed emptying, gall stones, incisional hernia
Silverman et al, 1995[23]	O	N	N	Disrupted staple line, cholecystectomy, revision, small-bowel obstruction

N, needle; W, wedge; O, other; N/A, not available; NAS, NAFLD Activity Score.

number of male and female paired liver biopsies; (8) cirrhotic patients incidentally included in the studies; (9) histopathologic grading system used in individual studies; (10) method of obtaining the liver biopsy at the time of bariatric surgery and after weight loss and specific reasons for performing the follow-up liver biopsies; and (11) histologic changes of NAFLD—we extracted data on 3 variables (a) steatosis, (b) steatohepatitis (lobular inflammation, ballooning degeneration), and (c) fibrosis. Data on the number of subjects with steatosis, steatohepatitis, and fibrosis at the time of bariatric surgery, and the number of subjects with improvement and/or resolution were extracted for all the studies. Complete resolution of histopathologic changes consistent with steatohepatitis was mentioned in many studies and these were recorded separately. Any difference in data quantification was resolved by discussion among the lead authors.

The main outcome measures were improvement and/or resolution in NAFLD (steatosis, steatohepatitis, and fibrosis) after bariatric surgery–induced weight loss.

We defined 2 distinct categories of improvement: (1) complete resolution: the changes of the histopathologic component of interest have disappeared completely in the follow-up biopsy,

Table 3. Initial Number of Patients With Steatosis, Steatohepatitis, and Fibrosis

Study	No. of paired biopsies	Steatosis	Steatohepatitis/lobular inflammation/ ballooning degeneration	Fibrosis
Barker et al, 2006[4]	19	19	19	14
Clark et al, 2005[3]	16	16	15	14
Csendes et al, 2006[12]	16	14	4	N/A
Dealmeida et al, 2006[13]	16	16	15	4
Dixon et al, 2004[14]	36	35	23	23
Furuya et al, 2006[16]	18	18	18	9
Jaskiewicz et al, 2005[17]	10	8	2	N/A
Liu et al, 2007[15]	39	35	23	17
Luyckx et al, 1998[11]	69	57	10	N/A
Mattar et al, 2005[18]	70	70	65	54
Mathurin et al, 2006[19]	121	34[a]	N/A	N/A
Mottin et al, 2005[20]	90	90	N/A	N/A
Stratopoulos et al, 2005[21]	51	50	50	48
Kral et al, 2003[22]	104	104	18	N/A
Silverman et al, 1995[23]	91	71	37	13
Total	766	637	299	N/A

N/A, data not available or unclear.
[a]Information was available only for the number of patients with severe steatosis.

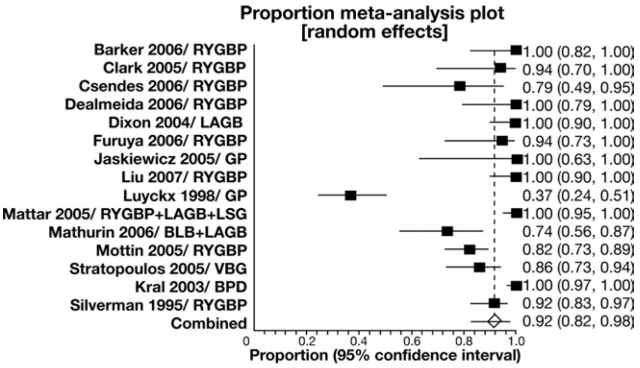

Figure 2. Forest plot showing improvement or resolution of steatosis after bariatric surgical procedures. *The left-hand column* in the Forest plot lists the names of the studies. The *squares on the right-hand column* indicate the effect measure (proportion of patients with response). The *horizontal lines* that cut through the squares indicate CIs. The size of each square is proportional to the study's weight in the meta-analysis. The *diamond* represents the meta-analyzed effect measure and the *horizontal lines* indicate the confidence interval. Available from: http://en.wikipedia.org/wiki/Forest_plot. Accessed: July 22, 2008. I^2 (inconsistency) = 91.8% (95% CI, 88.6%–93.7%). Random effects (DerSimonian-Laird): pooled proportion = 91.6% (95% CI, 82.4%–97.6%).

and (2) improvement and/or resolution: data from studies that did not distinguish between complete resolution and improvement, or reported only improvement without any reference to resolution, were included in this category. Data analysis was performed using Stats Direct statistical software, (Cheshire, UK) version 2.6.5 for Windows. The pooled proportion of patients with improvement or resolution was calculated initially for steatosis, steatohepatitis, and complete resolution of inflammatory changes. A random effects model was used to generate the cumulative effect size for each outcome variable. The data on fibrosis was found to be too heterogeneous to perform a pooled analysis including all the studies. Several studies included data on fibrosis that was estimated from both needle and wedge liver biopsies. Wedge biopsies, especially if performed superficially, can overestimate the degree of fibrosis caused by artifacts such as subcapsular fibrosis, which can be a normal variation. Needle biopsy allows for deeper tissue sampling and thus provides for a more accurate estimation of hepatic fibrosis.[24] Therefore, only a subgroup analysis of the fibrosis data has been performed using the data from studies that used needle liver biopsies alone.

Heterogeneity among the studies was assessed using the I^2 (inconsistency) statistic. Further exploration of heterogeneity was performed by using subgroup analysis and the results for improvement or resolution in NAFLD were analyzed for studies with Roux-en-Y gastric bypass alone, for studies in which the follow-up liver biopsy was performed to estimate histologic changes and not for any other reason, and for studies that followed Brunt's classification.[25] Heterogeneity in fibrosis data was explored using studies with needle biopsies only because wedge biopsies overestimate the extent of fibrosis. Sensitivity analysis was performed after excluding the studies that most likely accounted for the heterogeneity. Publication bias was assessed using funnel plots.

Results

The search strategy listed in the Methods section yielded 131 relevant articles. A total of 15 studies (766 paired liver biopsies) were selected for final data extraction. The main features of the included studies are summarized (Table 1). Roux-en-Y gastric bypass was the most common bariatric surgery performed. The duration between the biopsies was wide and ranged from 2 to 111 months. The mean age of the participants at the time of weight loss surgery ranged from 35.6 to 49 years. The mean BMI at the time of weight loss surgery ranged from 43.9 to 56 kg/m^2, and the mean BMI at follow-up liver biopsies ranged from 28.6 to 39 kg/m^2. The percentage reduction in mean BMI values ranged from 19.11 to 41.76. Follow-up liver biopsies to evaluate improvement in histologic changes of NAFLD after weight loss were performed as a part of the study in 9 of 15 studies. Follow-up biopsies in the rest of the studies were obtained during a second surgery performed to revise or repair a surgical complication of the first bariatric procedure. The liver biopsy procedure and the histopathologic grading system used to quantify the liver biopsies varied among the studies. The grading and staging system of Brunt was used in 7 of 15 studies,[3,9,10,14,15,16,18] the histologic scoring system for NAFLD (NAS) from the NASH clinical research group was used by 2 studies,[12,13] and Dixon's histopathologic classification system for NAFLD was used in 2 studies[4,11] (Table 2).

Outcomes

The major outcomes of interest were improvement and/or resolution in 3 different components of NAFLD: (1) steatosis only, (2) inflammatory changes (ballooning degeneration and lobular inflammation), and (3) fibrosis.

Steatosis

Steatosis alone was present initially in 637 of 766 (83.15%) biopsies (Table 3). The pooled proportion of patients with improvement or resolution in steatosis was 91.6% (95% CI, 82.4–97.6) (Figure 2). Subgroup analyses restricted to studies that followed Brunt's classification or prospectively designed studies did not yield significantly different results from the earlier-described studies (Table 4).

Table 4. Comparison of Overall Results With Results From Analyses Restricted to Studies With Prospective Study Designs and Studies That Followed Brunt's Classification

			Pooled proportion of patients % (95% CI)	
	Number of studies	Number of paired biopsies	Steatosis	Steatohepatitis
All studies	15	766	91.6 (82.4–97.6)	81.3 (61.9–94.9)
Studies with prospective liver biopsies	9	434	93.6 (85.7–98.5)	85.4 (59.9–99)
Studies with Brunt's classification	7	300	91.1 (79.8–98.1)	81.5 (50.8–98.7)

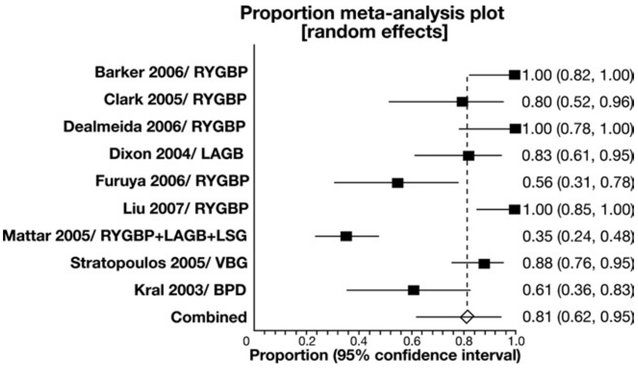

Figure 3. Forest plot showing improvement or resolution of steatohepatitis after bariatric surgical procedures: I^2 (inconsistency) = 91.6% (95% CI, 86.9%–94.1%). Random effects (DerSimonian-Laird): pooled proportion = 81.3% (95% CI, 61.9%–94.9%).

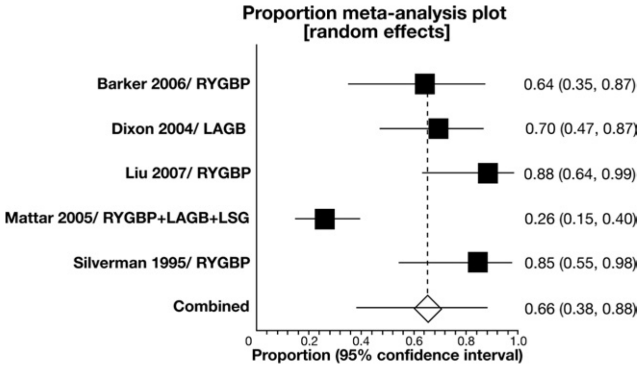

Figure 5. Forest plot showing improvement or resolution of fibrosis (subgroup analysis using studies with needle biopsies only) after bariatric surgical procedures: I^2 (inconsistency) = 88.8% (95% CI, 75%–93.5%). Random effects (DerSimonian-Laird): pooled proportion = 65.5% (95% CI, 38.2%–88.1%).

Steatohepatitis

Histopathologic changes of NASH (ballooning degeneration and lobular inflammation) were present in 299 of 555 (53.87%) biopsies (Table 3). The pooled proportion of patients with improvement or resolution of steatohepatitis was 81.3% (95% CI, 61.9%–94.9%) (Figure 3). The pooled proportion of patients with complete resolution in histopathologic changes of NASH was 69.5 (95% CI, 42.4%–90.8%) (Figure 4). Subgroup analyses restricted to studies that followed Brunt's classification or prospectively designed studies did not yield significantly different results from the overall results (Table 4).

Fibrosis

Fibrosis was mentioned to be present in 300 of 460 (65.21%) biopsies. The data on fibrosis is shown in Table 3. Only 5 studies with needle biopsies (total, 121 paired biopsies) were included for assessment of improvement or resolution of fibrosis. Studies with wedge biopsy were excluded from this analysis. The pooled proportion of patients with improvement or resolution in fibrosis was 65.5% (95% CI, 38.2%– 88.1%) (Figure 5).

Significant heterogeneity was present as assessed using the I^2 (inconsistency) statistic. Studies varied widely in design, type of surgery performed, method of obtaining the liver biopsy specimens, histopathologic grading systems, and reasons for follow-up liver biopsies. The methods used to explore the heterogeneity lowered the inconsistency statistic to some extent, but did not alter the pooled effect sizes in a statistically significant manner. Funnel plots showed that publication bias was a significant factor in the data included in our study.

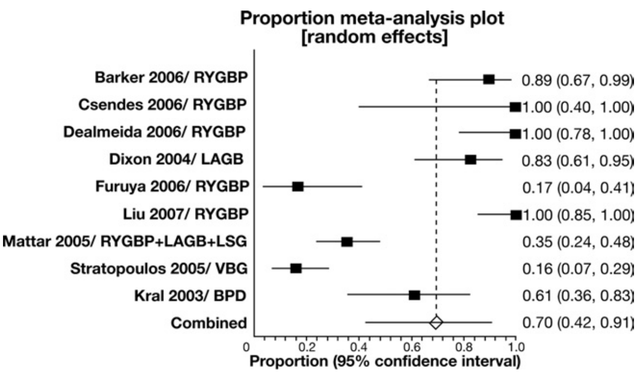

Figure 4. Forest plot showing complete resolution of steatohepatitis after bariatric surgical procedures: I^2 (inconsistency) = 94.4% (95% CI, 92%–95.9%). Random effects (DerSimonian-Laird): pooled proportion = 69.5% (95% CI, 42.4%–90.8%).

Discussion

Obesity continues to increase in prevalence in the United States and worldwide, and it is estimated that at the present rate about 40% of the US population will be classified as obese by the year 2025.[18] NAFLD, owing to its association with obesity, has now become one of the most common causes of liver disease in the United States.[26] Several therapeutic modalities for weight reduction among obese individuals have been tried including diet, exercise regimen, and insulin sensitizers, with varied results. Weight reduction by conservative measures is particularly difficult in morbidly obese individuals. Bariatric surgery recently has become quite popular as a rapid and permanent means of achieving significant weight loss in morbidly obese individuals.[9] It has been shown to improve or resolve the metabolic syndrome markers in a majority of patients. An overall long-term reduction in mortality from diabetes, heart disease, and cancer after weight loss surgeries has been affirmed by 2 recent studies.[27,28]

Even today, the effect of weight loss after bariatric surgery on liver histology remains unclear. In this meta-analysis, we have tried to assess and quantify this effect. The results of our meta-analysis show that bariatric surgery results in an improvement of histopathologic features of NAFLD in more than three fourths of the patients. The most encouraging finding is that a majority of patients experience complete resolution of NAFLD after bariatric surgery, and the risk of progression of inflammatory changes and fibrosis seems to be minimal as per the results of our study. The most striking improvement is noted in steatosis, followed by steatohepatitis and fibrosis. Improvement in steatosis was observed in all studies included for meta-analysis. Patients with cirrhosis were excluded from our study; therefore, the impact of bariatric surgery was evaluated only in less advanced stages of fibrosis. Moreover, a uniform assessment of change in the degree of fibrosis was limited because of the use of wedge biopsies in 9 of 15 studies and needle biopsies in the rest. Subgroup analysis performed after exclusion of studies with wedge biopsies still showed a favorable effect of bariatric surgery–related weight loss on stage of fibrosis.

Our study had several limitations. Heterogeneity was significant in our studies, and we have tried to explore it further by performing subgroup analysis with reduction in the inconsistency statistic, with an almost identical effect size. Publication bias was a significant factor (assessed using funnel plots) and sensitivity analysis performed after removing the studies that appeared as outliers in the forest plots did not have a significant impact on the results. The histopathologic grading system was different among the included studies and we have tried to overcome this by using a broad outcome measure such as improvement and/or resolution in histopathologic changes, and not basing our analyses on the grading given by the studies. The inherent limitations of a liver biopsy would account for some of the heterogeneity in our study owing to sampling and interobserver variability. The need for a uniform assessment of liver biopsy specimens cannot be overemphasized. The study designs also were different; all were observational in nature, and the reasons for performing the follow-up liver biopsies varied widely. Correlation between the percentage improvement in BMI and the proportion of patients with improvement in steatosis, steatohepatitis, and fibrosis was not statistically significant. The sample size of our study was small when compared with the actual number of bariatric surgeries that currently are being performed. The rate of weight loss in the subjects and the actual duration from surgery to the second liver biopsy would have contributed to the heterogeneity among the studies as well. Lack of individual patient data limited the analyses of these factors in our systematic review. The rationale for pooling the data from heterogeneous studies was to obtain an estimate of the effect size for the proportion of patients with improvement or complete resolution of NAFLD after bariatric surgery. Sustainability of the favorable changes in liver histology has to be assessed on a long-term basis because the follow-up periods in the individual studies that were part of our analysis varied widely.

Conclusions

Steatosis, steatohepatitis, and fibrosis appear to improve or completely resolve in the majority of patients after bariatric surgery results in significant weight loss. In view of the small sample size of individual studies, the presence of significant heterogeneity and publication bias in our meta-analysis, the generalizability of the results may require confirmation from multicenter, large-scale, well-designed trials. Our study underscores the importance of uniform histopathologic assessment of liver biopsy specimens.

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