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Bariatric surgery for non-alcoholic steatohepatitis in obese patients (Review)

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[Intervention Review]

Bariatric surgery for non-alcoholic steatohepatitis in obese patients

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ABSTRACT

Background

Nonalcoholic fatty liver disease (NAFLD) is increasingly recognised as a condition associated with overweight or obesity that may progress to end-stage liver disease. NAFLD histology resembles alcohol-induced liver injury, but occurs in patients with no history of alcohol abuse. NAFLD has a broad spectrum of clinical and histological manifestations, ranging from simple fatty liver to hepatic steatosis with inflammation, advanced fibrosis, and cirrhosis. The inflammatory stage is known as non-alcoholic steatohepatitis (NASH). Recent reports indicate that weight loss induced by bariatric procedures could be beneficial for NASH treatment.

Objectives

To assess the benefits and harms of bariatric surgery for NASH in obese patients.

Search methods

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register*, the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE,* and *Science Citation Index Expanded* to October 2009.

Selection criteria

All randomised clinical trials evaluating any bariatric procedure versus no intervention, placebo (sham procedure), or other interventions in patients with NASH regardless of publication status, number of patients randomised, language, or blinding. Quasi-randomised clinical studies were to be considered for the review if no randomised clinical trials were identified. If included, their bias towards positive findings was to be considered.

Data collection and analysis

We extracted data in duplicate, and we planned to analyse the data by intention-to-treat.

Main results

We could not find any randomised clinical trials or quasi-randomised clinical studies that fulfilled the inclusion criteria. Our search resulted in twenty-one prospective or retrospective cohort studies, in which improvement on steatosis or inflammation scores was reported. However, four studies also described some deterioration in the degree of fibrosis.

Authors' conclusions

The lack of randomised clinical trials and quasi-randomised clinical studies precludes us to assess the benefits and harms of bariatric surgery as a therapeutic approach for patients with NASH. Limitations of all other studies with inferior design did not allow us to draw any unbiased conclusion on bariatric surgery for treatment of NASH.

PLAIN LANGUAGE SUMMARY

Bariatric surgery for non-alcoholic steatohepatitis in obese patients

Nonalcoholic fatty liver disease (NAFLD) is the liver manifestation of metabolic syndrome in which obesity and resistance to the insulin action are the hallmark. Fat accumulation in the liver produces inflammation and chronic liver damage, known as non-alcoholic steatohepatitis (NASH). Nowadays, the best strategy to treat NAFLD and NASH is weight loss. Surgical procedures to treat obesity (bariatric surgery) have shown good results to reduce fat accumulation and even improve other obesity-related conditions. However, neither the benefits nor the harms of bariatric surgery in NASH have been assessed in any systematic review or meta-analysis of randomised clinical trials. The present Cochrane review attempted to evaluate the benefits and risks of bariatric surgery for NASH in obese patients, but as no randomised clinical trials fulfilling the inclusion criteria of the review protocol were found, the review was not able to address the pre-specified in the protocol aims. Prospective and retrospective cohort studies reported on beneficial effects on steatosis and inflammation, with potential increase of liver fibrosis, but the studies were too heterogenous and with a small number of patients. Hence, the data, which the latter studies contained, are with a high risk of bias, and a reliable summary of their data cannot be achieved. Due to the absence of trials, well-designed randomised trials to assess bariatric surgery as a safe and effective treatment of NASH are required.

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is increasingly recognised as a condition that may progress to end-stage liver disease. The pathology resembles that of alcohol-induced liver injury, but it occurs in patients with no alcohol abuse (Wanless 1990). NAFLD is becoming the preferred term to refer to a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis (Wang 2003). NAFLD prevalence ranges from 10% to 24% in the general population (Garcia-Monzon 2001), being 4.6-fold higher in obese individuals (Musso 2003). Other risk factors associated with NAFLD are waist circumference (more than 102 cm in males and more than 88 cm in females) (Hotamisligil 1995), hyperinsulinaemia, hypertriglyceridaemia, and impaired glucose tolerance, or type 2 diabetes (Day 1998; Goldstein 2004).

NAFLD is the third most common diagnosis in gastroenterological referrals, accounting for 11% of patients (Byron 1996). NAFLD is expected to become one of the most important liver diseases in the near future as a result of the obesity epidemic in the Western World (Mendez-Sanchez 2005).

NAFLD has a broad spectrum of clinical and histological manifestations, ranging from simple steatosis to its inflammatory presentation known as non-alcoholic steatohepatitis (NASH) (Matteoni 1999). NASH is defined histologically by zone 3 macrovesicular steatosis, although it can also be panacinar, in combination with hepatocyte ballooning and mixed inflammatory infiltrate (Brunt 1999). It is estimated that 3% to 4% of the general population have NASH (Falck-Ytter 2001). This is relevant because inflammation and fibrosis determine the long-term prognosis. Several studies and case reports suggest NASH might be an important cause of cryptogenic cirrhosis (Tellez-Avila 2008), potentially of cirrhosis (Fassio 2004), and even hepatocellular carcinoma (Chavez-Tapia 2009).

The molecular basis of the association between obesity-insulin resistance and NAFLD and NASH remains largely unknown (Chavez-Tapia 2009a). White adipose tissue is increasingly recognised as an endocrine organ, producing numerous proteins collectively referred to as adipokines. Some of these include: adiponectin, resistin, leptin, visfatin, apelin, vaspin, and other bioactive molecules. In addition to adipokines, adipose tissue produces a number of traditional cytokines, such as tumour necrosis factor, monocyte chemoattractant protein-1, and interleukin-6, thus adding proinflammatory pressure to other peripheral tissues. These proteins possess broad physiological functions and play important autocrine roles in obesity-associated complications (Berg 2005).

Diet and exercise constitute the central strategies in NAFLD treatment (Neuschwander 2003). Considering that several pathogenic mechanisms may be involved, various therapeutic strategies for NAFLD and NASH have been proposed to control insulin resistance using diverse drugs as gemfibrozil, metformin, betaine, N-acetylcysteine, and vitamin E (Chavez-Tapia 2006). However, no consensus regarding an effective therapy for NAFLD has been reached. Recent reports indicate that weight loss induced by bariatric surgical procedures to treat obesity could have beneficial effects in NASH, but the evidence so far is limited.

We have been unable to identify meta-analyses or systematic reviews of randomised clinical trials assessing the effects of bariatric surgery on NASH obese patients.

OBJECTIVES

To assess the benefits and harms of bariatric surgery for NASH treatment in obese patients.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials evaluating any bariatric procedure versus no intervention, placebo (sham procedure), or other interventions in obese patients with NASH, regardless of publication status, number of patients randomised, language, or blinding.

Following the instructions provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) regarding the intervention potential harm, we included available non-randomised studies to analyse reported adverse events.

Types of participants

Participants of any age, sex, or ethnic origin with overweight or obesity (defined as body mass index (BMI) more than 25 kg/m^2) and NASH diagnosed by liver histology according to the following criteria:

Liver steatosis and two of the following three histological features:

- necroinflammatory foci with mononuclear cells and/or neutrophils;
- ballooning degeneration of hepatocytes with or without Mallory bodies; and
- pericellular fibrosis, persistent elevation of aminotransferases to 1.5 times normal for more than six months, and exclusion of other liver diseases (eg, alcoholic, autoimmune, cholestatic, viral, or metabolic liver diseases).

Types of interventions

Bariatric procedures including: Roux-en-Y gastric bypass, gastric banding, vertical banded gastroplasty, duodenal switch, biliopancreatic diversion, isolated intestinal bypass, and gastrectomy versus no intervention, placebo (sham procedure), or other interventions. Co-interventions were to be allowed only if equally received in the intervention groups.

Types of outcome measures

Primary outcome measures

- All-cause mortality: number of deaths irrespective of cause at maximal follow-up.
- Surgical-related mortality.
- Surgical-related morbidity.
- Hepatic-related mortality.
- Hepatic-related morbidity.
- Cardiovascular-related mortality.
- Cardiovascular-related morbidity.

- Histological response (number of patients without histological improvement in the degree of fatty liver infiltration, inflammation, and fibrosis) based on any score systems or their modifications.

Secondary outcome measures

- Changes in body weight (assessed as BMI, fat mass, fat-free mass).
- Biochemical response (serum activity of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatases, gamma glutamyl-transpeptidase, serum total bilirubin, and ferritin).
- Metabolic response (according to the number of elements of metabolic syndrome).
- Cytokine response (serum levels of leptin, adiponectin, resistin, tumour necrosis factor alpha, interleukin 6, interleukin 1, transforming growth factor beta, monocyte chemoattractant protein, free fatty acids, vascular endothelial growth factor, plasminogen activator inhibitor, etc).

Adverse events (Long-term sequel of bariatric surgery)

- Adverse events defined as any untoward medical occurrence not necessarily having a causal relationship with the treatment (ICH-GCP 1996).
- Long-term nutrient deficiencies secondary to bariatric surgery as described in the trials (eg, iron, vitamin B12, vitamin D, calcium, protein and fat-soluble vitamin, and thiamine deficiency).

Search methods for identification of studies

Electronic searches

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2009)(October 2009), the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (Issue 4, 2009), *MEDLINE* (1950 to October 2009), *EMBASE* (1980 to October 2009), and *Science Citation Index Expanded* (1945 to October 2009) (Royle 2003). The search strategies published within the protocol underwent changes at the review stage in order to increase the number of retrieved citations of possible relevance to this review (Appendix 1).

Handsearching

Manual searches were conducted in the abstract books of the *Digestive Disease Week of the American Gastroenterological Association* (1999 to 2008), the *American Association for the Study of Liver Diseases Meetings* (2003 to 2008), and the reference lists included in retrieved publications.

Data collection and analysis

Selection of studies

Three investigators (NCT, FT, and TBG) independently reviewed titles and abstracts of all the citations identified. After all studies were abstracted, face-to-face data comparisons between investigators were conducted to ensure completeness and reliability. The inclusion criteria to all identified studies were independently applied by NCT, FT, and TBG. Minor discrepancies were recorded and resolved by referring to the original paper.

Since no randomised clinical trials were identified, evaluation of methodological quality, and statistical analyses could not be performed. Hence, the following part of the protocol could not be followed. For this reason, we kept the text in future tense, and we will change the tense accordingly whenever randomised trials fulfilling the inclusion criteria are identified.

Data extraction and management

When a trial fulfils the inclusion criteria, data concerning participant characteristics, interventions, and outcome measures will independently be extracted using a standard form and entered in Review Manager 5 (RevMan 2008). If the information to be abstracted is not presented in the published reports, we will attempt to contact the corresponding authors of the trial.

Assessment of bias risk

We will assess the bias risk of the trials independently, without masking the authors of the studies. Authors will follow the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2009). Due to the risk of overestimation of intervention effects in randomised trials with inadequate methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008), we will look at the influence of methodological quality - hence risk of bias - over results by evaluating the methodological components described below. If information is not available in the published trial, we will contact the authors.

Generation of the allocation sequence

- Adequate, sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.
- Unclear, the trial is described as randomised but the method of sequence generation was not specified.
- Inadequate, the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for risks.

Allocation concealment

- Adequate, allocation was controlled by a central and independent randomisation unit, sequentially numbered, opaque and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
- Unclear, the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for harms.

Blinding

- Yes, adequate, the trial was described as double blind and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
- Unclear, the trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trail.
- No, not performed, the trial was not double blind, so that the allocation was known during the trail.

Incomplete outcome data

- Adequate, the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

- Adequate, pre-defined, or clinically relevant and reasonably expected outcomes are reported.
- Unclear, not all pre-defined, or clinically relevant and reasonably expected outcomes are reported or are not fully reported, or it is unclear whether data on these outcomes were recorded or not.
- Inadequate, one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Any other bias

- Adequate, the trial appears to be free of other components that could put it at risk of bias.
- Unclear, the trial may or may not be free of other components that could put it at risk of bias.
- Inadequate, there are other factors in the trial that could put it at risk of bias, eg, no sample size calculation made, early stopping, industry involvement, or an extreme baseline imbalance.

Trials with adequate generation of allocation sequence, adequate allocation concealment, adequate blinding, adequate handling of incomplete outcome data, no selective outcome reporting and without other bias risks will be considered trials with low risk of bias. Trials with one or more unclear or inadequate quality component will be considered trials with high risk of bias. However, we are aware that in a large number of reviews, such optimal division of trials may not be possible.

Statistical methods

We will perform the meta-analysis according to the recommendations of The Cochrane Collaboration (Higgins 2008) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2009). We will use the software package RevMan 5 (RevMan 2008). For dichotomous variables, we will calculate the relative risk (RR) with 95% confidence interval. For continuous variables, we will calculate the mean difference (MD) with 95% confidence interval. Both a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987) will be used. In case of discrepancy between the two models we will report both results; otherwise we will report only the results from the fixed-effect model. Heterogeneity will be measured by I^2 (Higgins 2002) and explored by chi-squared test with significance set at 0.10. If statistical heterogeneity is found, sensitivity analyses will be conducted omitting trials with high risk of bias.

We will adopt the 'available-case analysis' (Higgins 2008). The analyses will be performed on an intention-to-treat basis (Schulz 1995). In case we find 'zero-event' trials in statistically significant outcomes, we will perform a sensitivity analysis with and without empirical continuity correction factors as suggested by Sweeting et al (Sweeting 2004). We will also report the risk difference.

Bias exploration

We will use funnel plots to explore bias (Egger 1997). Asymmetry in funnel plot of trial size against treatment effect will be used to detect bias. We will perform linear regression as described by Egger et al to determine the funnel plot asymmetry (Egger 1997).

RESULTS

Description of studies

The electronic searches of *The Cochrane Hepato-Biliary Group Controlled Trials Register* and the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* did not produce any references. By searching *MEDLINE* and *EMBASE*, we retrieved 95 and 26 references, respectively. Of these, 100 were duplicates or clearly irrelevant references. Thus, twenty-one references of possible interest were identified and retrieved for evaluation (Ranløv 1990, Silverman 1995, Luyckx 1998, Dixon 2004, Kral 2004, Clark 2005, Keshishian 2005, Mattar 2005, Mottin 2005, Stratopoulos 2005, Barker 2006, Csendes 2006, de Almeida 2006, Dixon 2006, Jaskiewicz 2006, Klein 2006, Mathurin 2006, Meinhardt 2006, Furuya 2007, Liu 2007, Mathurin 2009). All of them were retrospective or prospective cohort studies and did not fulfil our inclusion criteria but were considered to describe adverse events. We have listed these studies in Characteristics of included studies and general information about the main outcomes can be found in Additional Table 1.

Fifteen studies were prospective cohorts, five studies were based on retrospective cohorts, and one study used a retrospective and prospective cohort. The number of the included participants ranged from 7 to 381 obese patients. Surgical techniques used in the studies were heterogeneous between and within studies. The most common procedure was Roux-en-Y gastric bypass (thirteen studies) followed by adjustable gastric band (six studies). The period of follow-up ranged from about 1 to 5 years; during this follow-up only two studies performed more than one biopsy after bariatric surgery (Stratopoulos 2005; Mathurin 2009).

Risk of bias in included studies

No randomised clinical trials were found. No quasi-randomised studies were found.

Effects of interventions

We could not find any randomised clinical trials that could fulfil the inclusion criteria of this review regarding benefits. Twenty-one observational cohort studies were identified. Improvement of liver function tests was reported in eleven studies, and in other seven studies at least one of the components of the metabolic syndrome improved; the BMI was not considered.

Regarding histological outcomes, eighteen studies reported a significant improvement in the degree of steatosis, eleven studies reported improvement in histological markers of inflammation, but only six studies showed some improvement in fibrosis scores. Furthermore, in four studies (Kral 2004, Stratopoulos 2005, Mathurin 2006, Mathurin 2009) some deterioration in the degree of fibrosis was described.

The studies included in this review did not directly report adverse-events rates after bariatric surgery. However, two trials (Stratopoulos 2005; Csendes 2006) reported histological score deterioration in a small percentage of patients: similarly, two studies reported NASH global scores deterioration (Keshishian 2005; Luyckx 1998), and four studies (Kral 2004; Stratopoulos 2005; Mathurin 2006; Mathurin 2009) reported an increase in hepatic fibrosis. All other fourteen studies did not report any adverse events.

DISCUSSION

In the current review, we tried to evaluate the efficacy and safety of bariatric surgery in NASH treatment in obese patients. Despite the comprehensive search, we were not able to find any randomised trials. This is not the first time that a Cochrane systematic review fails to find data from randomised trials in order to perform meta-analyses and conclude about an intervention (Lirussi 2007). This could be explained by the low number of randomised trials for the treatment of NASH, including medical and surgical options. In fact, only two methodologically strong studies using insulin sensitizing drugs are available nowadays (Belfort 2006; Aithal 2008).

The specific role of bariatric surgery in NASH has been assessed in a systematic review and meta-analyses based on observational studies by Mummadi 2008. It concludes that steatosis, steatohepatitis, and fibrosis are improved or completely resolved in the majority of patients after bariatric surgery induced weight loss. However, it is important to highlight that this conclusion is derived from less rigorous inclusion criteria and without addressing the potential biases. The methodological heterogeneity and high risk for bias of these studies represent serious limitations towards a systematic review that should provide scientifically sound recommendations. Even upon the lack of better studies, the inclusion of results from non-randomised studies in a systematic review could be misleading and represent a threat towards patients safety and well-being (Higgins 2008). Thus, the strength of this evidence should be considered carefully (Montori 2004; Guyatt 2008).

Designing and conducting a randomised clinical trial to test treatment strategies for NASH could be difficult. Many challenges would have to be faced, including having to obtain more than one liver biopsy to assess the effect of the therapeutic approach, dealing with drop-outs or loss to follow-up in patients subject to prolonged treatments and competing risks such as other liver co-morbidity (Adams 2005; Bedogni 2005) or cardiovascular disease (Lizardi-Cervera 2007; Bellentani 2008; Chavez-Tapia 2009b; Lizardi-Cervera 2009).

Bariatric surgery is a difficult topic for a systematic review and meta-analyses of randomised trials. In a comprehensive systematic review on obesity surgery (Colquitt 2009), for example, the authors found a positive effect related to the surgical approach when it was compared to conservative management, but a meta-analysis could not be performed as the studies included were limited and subjected to potential biases. The authors recommend developing randomised clinical trials with rigorous design for evaluation of the possible beneficial and harmful effects of this therapeutic approach.

Results reported in this review as well as studies included in the meta-analysis of Mummadi 2008 show a potential positive effect of bariatric surgery on several outcomes, among which reduction in body weight is the most important one as it is a high risk factor for NASH. Most of the studies report an improvement in liver function tests and in some components of metabolic syndrome. This finding, however, should not be considered a marker of liver improvement since improvement in liver tests is not correlated with histological findings (Angulo 2006). Some studies have found an improvement in biological markers, such as cytokines, which is a more logical finding when their role in the pathophysiology of the disease is considered. The improvement in the histologic scores is the most important finding as it has been consistent in all studies. These promising results, however, should encourage the undertaking of randomised clinical trials with low risk of bias in order to adequately assess the therapeutic effect, and not just considered blunt positive evidence. While results may be promising, the fact that some patients with NAFLD treated with bariatric surgery showed a deterioration of fibrosis scores must be considered. Researchers and clinicians should remain aware of this issue, particularly because deterioration of fibrosis was observed in larger studies with long follow-up periods and because fibrosis is one of the most important risk factors to develop advanced disease in NAFLD patients. Beyond potential benefits in the less important outcomes and the potential risk to deteriorate one of the most important outcomes, the lack of scientifically sound evidence precludes any recommendation to support or reject bariatric surgery to treat patients with NAFLD.

Most studies included in this review gave partial or no information on adverse events. Thus, any conclusion about bariatric surgery safety is potentially biased. This is a significant issue, because despite the low mortality rate associated with bariatric surgery, the adverse event rate could be important (Livingston 2006). Evidence pointing towards important histological adverse events was reported in some studies. The unexpected adverse events should be monitored carefully in future studies or trials.

Currently, there are no randomised clinical trials that compare bariatric surgery versus conservative management in patients with NASH. In several non-randomised trials, liver biopsies were obtained during bariatric surgery. Such studies can be used to explore the harmful effects of bariatric surgery on NASH, but in order to properly access the benefits and harms of the surgery, we need adequately conducted randomised clinical trials with large sample sizes and long duration of follow-up.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of randomised clinical trials to demonstrate the beneficial or harmful effects of bariatric surgery procedures for treatment of NASH could not enable us to reach any scientifically sustained conclusion. Despite positive results observed in cohort studies, due to their high risk of bias and the potential risk for worsening

in fibrosis scores, bariatric surgery needs to be assessed in randomised clinical trials.

Implications for research

Randomised clinical trials with low risk of bias need to be conducted to assess the beneficial or harmful effects of bariatric surgery in NASH treatment of obese patients. Trials should follow a rigorous methodology, consider the histological confirmation of the intervention analysed, be registered in a public registry, and reported according to the CONSORT guidelines (http://www.consort-statement.org). Furthermore, such trials need to use rigorous methods to exclude hidden alcohol problems before inclusion of the patients.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barker 2006

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: presence of macrovesicular steatosis and lobular necroinflammation with or without the presence of perivenular/perisinusoidal fibrosis or Mallory's hyaline in liver biopsy Exclusion criteria: not given.
Participants	Sample size: 19 patients. Characteristics of included patients: mean age 48.6 years, female 89%, 26% with high blood pressure and/or diabetes mellitus.
Interventions	Roux-en-Y gastric bypass and second liver biopsy.
Outcomes	**Histology** Improvement in steatosis (P < 0.001), Mallory's hyaline (P = 0.008), ballooning degeneration (P < 0.001), lobular inflammation (P = 0.008), portal fibrosis (P = 0.001), and lobular fibrosis (P = 0.008). **Biochemical** AST 34 ± 21.6 vs 34 ± 16.4 U/L (P = 0.945); ALT 37 ± 32 vs 38 ± 22.7 U/L (P = 0.984); alkaline phosphatase 92 ± 38.7 vs 84 ± 17.4 U/L (P = 0.310).
Notes	Follow-up: 21.4 months.

Clark 2005

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: patients included for bariatric surgery (BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with co-morbidities). Exclusion criteria: not given.

Clark 2005 *(Continued)*

Participants	Sample size: 16 obese patients. Characteristics of included patients: mean age 43.9 ± 8.1 years, female 50%, mean BMI 51.1 ± 6.1 kg/m^2, 50% had high blood pressure, 19% diabetes, and 31% dyslipidaemia.
Interventions	Open Roux-en-Y gastric bypass and baseline liver biopsy, and second liver biopsy during second not-liver related surgery.
Outcomes	**Histology** Steatosis grade 3 (< 66%) 12.5 vs 0% (P < 0.001); inflammation grade 3, 25 vs 6.3% (P < 0.001); ballooning 0 (none) 12.5 vs 75% (P < 0.001); perisinusoidal fibrosis 0 (none) 12.5 vs 43.8% (P = 0.01), portal fibrosis 0 (none) 18.8 vs 50% (P = 0.01). **Biochemical** AST 31.9 ± 27.5 vs 21.8 ± 9.7 U/L, ALT 33.6 ± 18.9 vs 23.5 ± 16.3 U/L, alkaline phosphatase 88.3 ± 31.7 vs 88.8 ± 32.5 U/L.
Notes	Follow-up: 305 ± 131 days.

Csendes 2006

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: all patients submitted to Roux-en-Y gastric bypass with resection of the bypassed stomach due to morbid obesity. Exclusion criteria: not given.
Participants	Sample size: 16 obese patients. Characteristics of included patients: mean age 46.2 years, 15 males, BMI 44.3 kg/m^2.
Interventions	Roux-en-Y gastric bypass with resection of the bypassed stomach and second liver biopsy due to non-liver related surgery.
Outcomes	**Histology** Normalization of liver histology 10 patients (66.7%). Decrease in liver histology 2 patients (13.3%). Worsening in liver histology 1 patient (6.7%). Without change 1 patient (6.7%).
Notes	Follow-up: 22 months.

de Almeida 2006

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: patients submitted to Roux-en-Y gastric bypass due to morbid obesity. Exclusion criteria: alcohol consumption (> 40 g alcohol/day for men and > 20 g alcohol/day for women).

de Almeida 2006 *(Continued)*

Participants	Sample size: 16 obese patients. Characteristics of included patients: mean age 40.2 ± 9.5 years, mean BMI 53.4 ± 8.8 kg/m^2, high blood pressure 75% and type 2 diabetes mellitus 43.8%.
Interventions	Roux-en-Y Gastric Bypass and baseline liver biopsy, second liver biopsy, due to liver-disease in baseline biopsy.
Outcomes	**Histology** Hepatocellular ballooning 16 vs 5 patients (P < 0.005); lobular inflammation 15 vs 0 patients (P < 0.05); portal inflammation 11 vs 8 patients (P = NS); Mallory's hyaline bodies 13 vs 16 patients (P = NS). **Biochemical** Not declared.
Notes	Follow-up: 23.5 ± 8.4 months.

Dixon 2004

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: patients with a body mass index of more than 35 kg/m^2 who had significant medical, physical, or psychosocial disabilities are considered. Exclusion criteria: haemochromatosis, alpha1-antitrypsin deficiency, Wilson disease, or autoimmune liver disease if indicated on the liver biopsy. Previous history of alcoholism, consumed more than 200 g of alcohol per week, had evidence of hepatitis B or C, were taking known hepatotoxic medications, or had a history of or finding consistent with another specific liver disease.
Participants	Sample size: 36 obese patients. Characteristics of included patients: 11 male and 25 female, 43 ± 10.3 years, mean BMI 47 ± 10.6 35 kg/m^2, 39% diabetics, 50% hypertensive, 64% metabolic syndrome.
Interventions	Laparoscopic adjustable gastric banding and second liver biopsy due to non-liver related surgery (n = 19) and due to liver disease (n = 17).
Outcomes	**Histology** Absence of steatosis 1 vs 21 (P < 0.001), absence of lobular inflammation 12 vs 25 (P < 0.001), absence of fibrosis 13 vs 29 (P < 0.001), in initial vs second liver biopsy. **Biochemical** AST 27 ± 33 vs 17 ± 8 U/L (P < 0.001), ALT 43 ± 33 vs 21 ± 15 U/L (P < 0.001), AST/ALT ratio 0.77 ± 0.39 vs 0.93 ± 0.54 (P = 0.012), gamma-glutamyl transpeptidase 38 ± 36.6 vs 18 ± 9 U/L (P < 0.001), alkaline phosphatase 105.5 ± 27 vs 62 ± 25 U/L (P < 0.001). Fasting glucose 6.3 ± 2.2 vs 5.0 ± 0.8 mmol/L (P < 0.001), HbA1c 6.2 ± 2.0 vs 5.3 ± 0.9% (P < 0.001), fasting insulin 22.4 ± 16.7 vs 10.6 ± 8.3 mU/L (P < 0.001), C peptide 1.39 ± 0.50 vs 0.96 ± 0.53 pmol/mL (P < 0.001).
Notes	Follow-up: 25.6 ± 10 months.

Dixon 2006

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: BMI > 35 kg/m^2, suffering significant medical, physical or psychosocial disabilities. Exclusion criteria: alcohol consumption >200 g/week, evidence of hepatitis B or C, taking known hepatotoxic medications or a history or finding consistent with other liver diseases.
Participants	Sample size: 60 obese patients. Characteristics of included patients: mean age 43.5 ± 9.4 years, BMI 45.9 ± 7.4 kg/m^2.
Interventions	Baseline liver biopsy during laparoscopic adjustable gastric banding, and second liver biopsy related (percutaneous or non-liver related surgery).
Outcomes	**Histology** Centrilobular features of steatosis, inflammation, fibrosis and Mallory bodies all improved significantly with weight loss (P < 0.001 for all comparisons).
Notes	Follow-up: 29.5 ± 16.0 months.

Furuya 2007

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: morbidly obese (BMI > 40 kg/m^2). Exclusion criteria: Other liver disease.
Participants	Sample size: 18 obese patients. Characteristics of included patients: mean age 46.6 ± 7.3 years, women 94.4%, and the mean preoperative BMI was 51.7 ± 7.4 kg/m^2.
Interventions	Roux-en-Y gastric bypass and baseline liver biopsy, and second liver biopsy at 2 years of follow-up.
Outcomes	**Histology** Steatosis disappeared in 89% (P < 0.05) and fibrosis disappeared in 75% (P < 0.05). **Biochemical** HOMA 7.96 ± 7.16 vs 1.27 ± 0.51 (P < 0.001); ALT 28.22 ± 21.13 vs 21.83 ± 14.54 U/L (P = 0.081), AST 25.38 ± 14.72 vs 25.16 ± 19.96 U/L (P = 0.856), alkaline phosphatase 86.94 ± 24.09 vs 83.66 ± 17.63 U/L (P = 0.420), gamma glutamyl transpeptidase 42.05 ± 26.10 vs 20.11 ± 11.17 U/L (P = 0.001).
Notes	Follow-up: 24 months.

Jaskiewicz 2006

Methods	Non-randomised study.

Jaskiewicz 2006 *(Continued)*

	Type of study: prospective cohort. Inclusion criteria: morbidly obese patients undergoing gastroplasty (restriction of storage capacity of the stomach). Exclusion criteria: not given. Characteristics of included patients: mean age 40.7 ± 10.0 years and BMI 46.7 ± 8.8 kg/m^2, all had with elevated triglycerides and/or hypercholesterolaemia; 67% of them with the metabolic syndrome.
Participants	Sample size: 10 obese patients (only those with second liver biopsy). Characteristics of included patients: mean age 40.7 ± 10.0 years and BMI 46.7 ± 8.8 kg/m^2, all had with elevated triglycerides and/or hypercholesterolaemia; 67% of them with the metabolic syndrome.
Interventions	Gastroplasty and second liver biopsy.
Outcomes	**Histology** Not reported among first and second biopsy. **Biochemical** AST 30.8 ± 13.8 vs 25.8 ± 16.2 U/L (P = 0.46), ALT 46.4 ± 21.4 vs 27.7 ± 11.7 U/L (P = 0.002).
Notes	Follow-up: 41 months.

Keshishian 2005

Methods	Non-randomised study. Type of study: retrospective cohort. Inclusion criteria: morbid obesity. Exclusion criteria: history or evidence of liver disease other than NAFLD.
Participants	Sample size: 78 obese patients. Characteristics of included patients: average age 43.5y, female 72%, mean BMI 50.5 kg/m^2.
Interventions	Duodenal switch operation and second liver biopsy during intra-abdominal operation for various indications.
Outcomes	**Histology** Significant improvement of hepatic steatosis and NASH grade. **Biochemical** No significant reduction on liver function tests.
Notes	Follow-up: 36 months

Klein 2006

Methods	Non-randomised study.

Klein 2006 *(Continued)*

	Type of study: prospective cohort. Inclusion criteria: BMI ≥ 45 kg/m^2. Exclusion criteria: history or evidence of liver disease other than NAFLD.
Participants	Sample size: 7 obese patients. Characteristics of included patients: female 85.7%, diabetics 28.5%, mean BMI 58 ± 4 kg/m^2.
Interventions	Gastric bypass surgery and baseline liver biopsy and second liver biopsy at 12 months.
Outcomes	**Histology** Significant improvement of hepatic steatosis. **Biochemical** HOMA-IR 12.9 ± 3.0 vs 2.0 ± 0.4 (P < 0.05); free fatty acids 0.55 ± 0.04 vs 0.44 ± 0.04 mmol/L (P < 0.05); ALT 32 ± 10 vs 21 ± 2 U/L (P = NS), AST 30 ± 7 vs 22 ± 2 U/L (P = NS), alkaline phosphatase 102 ± 9 vs 90 ± 13 U/L (P = NS).Significant reduction in hepatic expression of macrophage chemoattractant protein 1, interleukin 8, and transforming growth factor ß1.
Notes	Follow-up: 12 months.

Kral 2004

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: consecutive patients underwent biliopancreatic diversion for severe obesity, without liver disease. No patients with hepatotoxic medication or exposure, history of hepatitis, prior weight-loss surgery or consumption of more than 100 g of alcohol per week. Exclusion criteria: not given.
Participants	Sample size: 104 obese patients. Characteristics of included patients: female 80.8%, mean BMI 31 ± 8 kg/m^2, presence of cirrhosis at baseline 2%.
Interventions	Biliopancreatic diversion and baseline liver biopsy, and second surgery with liver biopsy.
Outcomes	**Histology** Steatosis decreased from grade 1.57 ± 0.98 to 0.52 ± 0.71 (P < 0.0001). Fibrosis increased from grade 1.36 ± 1.14 to 1.56 ± 1.17 (P = 0.053). **Biochemical** ALT 28.0 ± 24.3 vs 22.9 ± 24.4 U/L (P < 0.01); AST 20.6 ± 14.6 vs 22.7 ± 32.0 U/L (P = NS), gamma glutamyl transpeptidase 29.6 ± 33.5 vs 30.7 ± 51.4 U/L (P = NS); alkaline phosphatase 72.2 ± 30.7 vs 94.3 ± 55.2 (P = 0.001).
Notes	Follow-up: 74 ± 27 months.

Liu 2007

Methods	Non-randomised study. Type of study: retrospective cohort. Inclusion criteria: morbidly obese patients. Exclusion criteria: not given.
Participants	Sample size: 39 obese patients. Characteristics of included patients: mean age 41.4 ± 9 years, BMI 47.7 ± 6.2 kg/m^2.
Interventions	Laparoscopic Roux en-Y gastric bypass and second liver biopsy not related to liver disease.
Outcomes	**Histology** Steatosis 2.03 ± 1.1 vs 0.03 ± 0.2 (P < 0.0001). Overall centrilobular/perisinusoidal fibrosis score 0.86 ± 1.02 vs 0.33 ± 0.63 (P < 0.0001). Fibrosis 1.14 ± 1.05 vs 0.72 ± 0.97 (P = 0.002). Not improvement in portal fibrosis. **Biochemical** ALT 34.5 ± 19 vs 23.7 ± 13.2 U/L (P = 0.01); AST 30.8 ± 16.4 vs 25.6 ± 13.8 U/L (P = 0.08).
Notes	Follow-up:18 months.

Luyckx 1998

Methods	Non-randomised study. Type of study: retrospective and prospective cohort. Inclusion criteria: severely obese patients submitted to a vertical ring gastroplasty or adjustable gastric banding. Exclusion criteria: insufficiently motivated patients, alcohol abusers (> 20 glasses/week) or drug addicts.
Participants	Sample size: 69 obese patients. Characteristics of included patients: 10 males and 59 females, aged 36 ± 11 years, BMI 43.9 ± 8.3 kg/m^2.
Interventions	Vertical ring gastroplasty or an adjustable gastric banding and second liver biopsy due to non-liver related surgery.
Outcomes	**Histology** Normal histology 13 vs 45 % (P < 0.001), steatosis 83 vs 38% (P < 0.001), steatohepatitis 14 vs 25% (P < 0.05), fibrosis 1.5 vs 1.5%, first vs second liver biopsy respectively.
Notes	Follow-up: not declared

Mathurin 2006

Methods	Non-randomised study. Type of study: prospective cohort.

Mathurin 2006 *(Continued)*

	Inclusion criteria: (1) severe obesity (BMI ≥ 35 kg/m^2) with comorbidity/co-morbidities or morbid obesity alone (BMI ≥ 40 kg/m^2) for at least 5 years and resistance to medical treatment; (2) absence of medical or psychological contraindications for bariatric surgery; (3) absence of current excessive drinking, as defined by an average daily consumption of alcohol of < 20 g/day for women and < 30 g/day for men, no history of past excessive drinking for a period longer than 2 years at any time in the past 20 years; (4) absence of long-term consumption of hepatotoxic drugs; and (5) negative screening for chronic liver diseases, including negative testing for hepatitis B surface antigen and hepatitis C virus antibodies; negative testing for antinuclear, anti-smooth muscle actin, anti-liver-kidney microsomes, and antimitochondrial antibodies; no evidence of genetic haemochromatosis; and normal ceruloplasmin and alpha1-antitrypsin serum levels. Exclusion criteria: reported exhaustively in inclusion criteria.
Participants	Sample size: 185 obese patients. Characteristics of included patients: 185 consecutive obese patients (148 women and 37 men; mean age, 41 ± 9 years) with a mean BMI at 49 ± 8 kg/m^2.
Interventions	Biliointestinal bypass or adjustable gastric band inserted by laparoscopy with liver biopsy, and second liver biopsy.
Outcomes	**Histology** Median of steatosis 20 vs 8% (P < 0.001), severe steatosis 34 vs 9% (P = 0.001), mean fibrosis score 0.14 ± 0.39 vs 0.38 ± 0.64 (P = 0.0001). **Biochemical** ALT 19 vs 18.5 U/L (P = 0.005); gamma glutamyl transpeptidase 28 vs 23 U/L (P = 0.0002); IR index 3.13 vs 2.8 (P < 0.00011).
Notes	Follow-up: 1 year.

Mathurin 2009

Methods	Non randomised study. Type of study: prospective cohort. Inclusion criteria
Participants	Inclusion criteria: patients with BMI > 40 kg/m^2 or BMI > 35 and at least one comorbidity factor, absence of medical or psychological contraindications for bariatric surgery; absence of current excessive alcohol consumption (average daily consumption > 20 g/d for women and 30 g/d for men, and no history of past excessive drinking for a period > 2 years at any time in the past 20 years), absence of long-term consumption of hepatotoxic drugs, and negative screening for chronic liver diseases. Exclusion criteria: reported exhaustively in inclusion criteria.
Interventions	Biliointestinal bypass, gastric bypass, and gastric band surgery.
Outcomes	**Histology** Amount of steatosis 37.4 vs 16% (P < 0.001), severe steatosis 29 vs 8.5% (P < 0.001), Nonalcoholic fatty liver disease score 1.97 vs. 1 (P < 0.001), extent of fibrosis 0.27 vs 0.36 (P = 0.002). **Biochemical**

Mathurin 2009 *(Continued)*

	ALT 30 vs 22 UI/L (P < 0.001), GGT 39.9 vs 29.2 UI/L (P < 0.001), fasting glucose 1.18 vs 0.94 g/L (P < 0.001), insulin resistance index 3.2 vs 2.83 (P < 0.001).
Notes	Follow-up: 5 years

Mattar 2005

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: patients with elevated liver function tests, gross features of fatty liver as depicted by ultrasonographic interrogation or intraoperative visual assessment of the liver, or histologic evaluation of liver biopsy specimens obtained at the time of surgery. Exclusion criteria: previous history of alcoholism, consumption > 20 g alcohol per day, had evidence of autoimmune hepatitis, chronic hepatitis B or C virus, HIV, genetic haemochromatosis, alpha1 antitrypsin deficiency, Wilson disease, or were taking known hepatotoxic drugs. Other exclusion criteria included patients in whom no repeat liver biopsy was performed, or if the time interval between initial and repeat liver biopsy was less than 3 months.
Participants	Sample size: 70 obese patients. Characteristics of included patients: 48 (65%) women, mean age was 49 ± 9 years, mean BMI of 56 ± 11 kg/m^2.
Interventions	The Roux-en-Y gastric bypass, the laparoscopic adjustable gastric band, or the sleeve gastrectomy, with baseline liver biopsy, and second liver biopsy.
Outcomes	**Histology** Absence of steatosis 1.4 vs 64.3%, absence inflammation 7.1 vs 40%, grade 0 histology 7.1 vs 44.3%, stage 0 histology 20 vs 40%; P < 0.001 in all cases. **Biochemical** AST 31 ± 18 vs 24 ± 11 UI/L (P = 0.003), ALT 37 ± 19 vs 33 ± 19 (P = 0.06).
Notes	Follow-up: 15 ± 9 months.

Meinhardt 2006

Methods	Non-randomised study. Type of study: historical cohort. Inclusion criteria: all patients underwent the end-to-side jejuno-ileal bypass. Exclusion criteria: not given.
Participants	Sample size: 30 obese patients (only those with second liver biopsy). Characteristics of included patients: female 84%, mean age 37.9 ± 7.6 years.
Interventions	End-to-side jejuno-ileal bypass and baseline liver biopsy and second liver biopsy.
Outcomes	**Histology**

Meinhardt 2006 *(Continued)*

	Steatosis 87.8% vs 76.7%. Steatohepatitis 31.7% vs 23.3%. Fibrosis 39% vs 36.7%. **Biochemical** ALT 27.9 ± 12.5 vs 36.6 ± 15.5 U/L (P = 0.085), AST 16.3 ± 6.9 vs 20.0 ± 10.0 U/L (P = 0.096).
Notes	Follow-up:70.0 ± 42.8 months.

Mottin 2005

Methods	Non-randomised study. Type of study: historical cohort. Inclusion criteria: not given. Exclusion criteria: no histological alterations in intraoperative biopsy, presence of histological alteration other than steatosis, history of ethanol abuse or other possible etiology for the hepatic damage and patients with insufficient material.
Participants	Sample size: 186 obese patients, only 90 patients with a second biopsy. Characteristics of included patients: ninety patients, 71.1% women, mean age 35 years, initial BMI 46.7 kg/m^2, 10% diabetes, 52% hypertension, and 73% dyslipidaemia.
Interventions	Baseline liver biopsy, during Roux-en-Y gastric bypass by the Fobi technique, and second liver biopsy one year after surgery.
Outcomes	**Histology** Steatosis 100% vs 45.6%.
Notes	Follow-up: 12 months.

Ranløv 1990

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: biopsy-proven fatty liver Exclusion criteria: not given
Participants	Sample size: 15. Characteristics of included patients: consecutive persons aged under 50 with an overweight exceeding 75%.
Interventions	Internvention: gastric bypass or gastroplasty.
Outcomes	**Histology** Significatn reduction on steatosis grades **Biochemical**

Ranløv 1990 *(Continued)*

	Improvement on alkaline phosphatase.
Notes	Follow-up: 12 months

Silverman 1995

Methods	Non-randomised study. Type of study: retrospective cohort. Inclusion criteria: patients with at least 200% of the ideal body weight or at least 45 kg more than the ideal body weight; patients must have had no success in maintaining weight loss with conservative therapies. Exclusion criteria: not given.
Participants	Sample size: 91 obese patients.Characteristics of included patients: eighty-seven women and four men. Mean age 39 years. Six patients had diabetes mellitus.
Interventions	Baseline liver biopsy, during Roux-en-Y gastric bypass, and second liver biopsy during non-liver related surgery.
Outcomes	**Histology** Steatosis 78 vs 21%, perisinusoidal fibrosis 14 vs 3%, porta lfibrosis 10 vs 9%, portal inflammation 44 vs 48%, lobular inflammation 41 vs 30%. **Biochemical** AST 23 vs 25 U/L.
Notes	Follow-up: 18.4 months

Stratopoulos 2005

Methods	Non-randomised study. Type of study: prospective cohort. Inclusion criteria: non-diabetic, non-alcoholic, morbidly obese (BMI > 40 kg/m^2). Exclusion criteria: other liver diseases, heart failure, organic renal disease, cancer or other major disease.
Participants	Sample size: 216 obese patients. Characteristics of included patients: mean BMI 52.8 ± 1 kg/m^2, prevalence of steatosis and steatohepatitis 98%, prevalence of fibrosis 94%, prevalence of cirrhosis 0%.
Interventions	Vertical banded gastroplasty and baseline liver biopsy, second biopsy in all patients, and third biopsy in only 16 patients.
Outcomes	**Histology** Second biopsy Steatosis. Improvement 84.3%, without change 15.6%, worsening 0% ($P < 0.001$). Steatohepatitis. Improvement 86.2%, without change 13.7%, worsening 0% ($P < 0.001$). Fibrosis. Improvement 47%, without change 41.1%, worsening 11.7% ($P < 0.002$).

Stratopoulos 2005 *(Continued)*	Third biopsy Reduction of liver steatosis (P = 0.014), steatohepatitis (P = 0.011) and fibrosis (P = 0.008). **Biochemical** AST 27.7 ± 2.1 vs 19.3 ± 1.2 U/L (P = 0.001); ALT 39.8 ± 4.3 vs 20.3 ± 2.3 U/L (P < 0.001); alkaline phosphatase 79.8 ± 3.4 vs 73.2 ± 5.8 U/L (P = 0.224), fasting plasma glucose 94.8 ± 1.6 vs 86.9 ± 1.0 (P < 0.001).
Notes	Follow-up:18 ± 9.6 months after gastroplasty.

vs = versus

ADDITIONAL TABLES

Table 1. Summary of findings from non-randomised studies

Study	Type of study	Sample size	Intervention	Outcome Histology	Outcome LFT
Ranløv 1990	Prospective cohort	15	Gastric bypass or gastroplasty	Improvement: steatosis Worsening: not reported No change: inflammatory and granulomatous scores	Improved
Silverman 1995	Retrospective cohort	91	Roux-en-Y gastric bypass	Improvement: steatosis, perisinusoidal fibrosis and lobular inflammation Worsening: portal inflammation No change: portal fibrosis	No change
Luyckx 1998	Retrospective and prospective cohort	69	Vertical ring gastroplasty or adjustable gastric banding	Improvement: steatosis Worsening: steatohepatitis No change: fibrosis	Not reported
Dixon 2004	Prospective cohort	36	Laparoscopic adjustable gastric banding	Improvement: steatosis, lobular inflammation, fibrosis Worsening: not reported Unchange: not reported	Improved
Kral 2004	Prospective cohort	104	Biliopancreatic diversion	Improvement: steatosis Worsening: fibrosis Unchange: not reported	Improved
Clark 2005	Prospective cohort	16	Roux-en-Y gastric bypass	Improvement: Steatosis, inflammation, ballooning, perisinusoidal fibrosis, portal fibrosis Worsening: not reported	Improved

Table 1. Summary of findings from non-randomised studies *(Continued)*

				Unchange: not reported	
Keshishian 2005	Retrospective cohort	78	Biliopancreatic diversion	Improvement: steatosis, NASH grade Worsening: NASH grade (only at 6 months) No change: Not reported	No change
Mattar 2005	Prospective cohort	70	Roux-en-Y gastric bypass, laparoscopic adjustable gastric band, or the sleeve gastrectomy	Improvement: steatosis, absence inflammation Worsening: not reported No change: not reported	Improved
Mottin 2005	Retrospective cohort	90	Roux-en-Y gastric bypass	Improvement: steatosis Worsening: not reported No change: not reported	Not reported
Stratopoulos 2005	Prospective cohort	216	Vertical banded gastroplasty	Improvement: steatosis, steatohepatitis, fibrosis Worsening: small percentage in all histologic outcomes No change: small percentage in all histologic outcomes	Improved
Barker 2006	Prospective cohort	19	Roux-en-Y gastric bypass	Improvement: steatosis, Mallory's hyaline, ballooning degeneration, lobular inflammation, portal fibrosis, and lobular fibrosis Worsening: not reported No change: fibrosis	No change
Csendes 2006	Prospective cohort	16	Roux-en-Y gastric bypass	Improvement: 66% of the patients Worsening: 6.7% of the patients Unchange: 13.35% of the patients	Not reported
de Almeida 2006	Prospective cohort	16	Roux-en-Y gastric bypass	Improvement: ballooning, lobular inflammation Worsening: not reported No change: portal inflammation, Mallory's hyaline bodies	Not reported
Dixon 2006	Prospective cohort	60	Laparoscopic adjustable gastric banding	Improvement: steatosis, inflammation, fibrosis and Mallory's hyaline bodies Worsening: not reported No change: not reported	Not reported
Jaskiewicz 2006	Prospective cohort	10	Gastroplasty	Not reported	Improved
Klein 2006	Prospective cohort	7	Gastric bypass surgery	Improvement: steatosis Worsening: not reported	No change

Table 1. Summary of findings from non-randomised studies *(Continued)*

				No change: not reported	
Mathurin 2006	Prospective cohort	185	Biliointestinal bypass or laparoscopic adjustable gastric band	Improvement: steatosis Worsening: fibrosis No change: inflammation	Improved
Meinhardt 2006	Retrospective cohort	30	End-to-side jejuno-ileal bypass	Improvement: steatosis, steatohepatitis Worsening: not reported No change: fibrosis	No change
Furuya 2007	Prospective cohort	18	Roux-en-Y gastric bypass	Improvement: steatosis, fibrosis Worsening: not reported No change: portal fibrosis	Improved
Liu 2007	Retrospective cohort	39	Roux-en-Y gastric bypass	Improvement: steatosis, inflammation, overall centrilobular/perisinusoidal fibrosis Worsening: not reported Unchange: portal fibrosis	Improved
Mathurin 2009	Prospective cohort	362	Biliointestinal bypass, gastric bypass, and gastric band surgery	Improvement: steatosis Worsening: fibrosis No change: inflammation	Improved

LFT = liver function tests

APPENDICES

Appendix 1. Search strategies

Database	Period of search	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	October 2009.	ORIGINAL SEARCH STRATEGY ("jejunoileal bypass" OR "vertical banded gastroplasty" OR "gastric bypass" OR "gastric bypass loop" OR "adjustable gastric band" OR "biliopancreatic diversion" OR "bariatric*") AND ("non*alcoholic fatty liver" OR "non alcoholic fatty liver" OR "nonalcoholic fatty liver" OR "NAFL*" OR "NASH" OR (non*alcoholic AND steato*hepatitis) OR (non alcoholic AND steato*hepatitis) OR (nonalcoholic AND steato*hepatitis)) EXPANDED SEARCH STRATEGY ('jejunoileal bypass*' OR 'vertical banded gastroplast*' OR 'gastric bypass*' OR 'adjustable gastric band*' OR 'biliopancreatic diversion*' OR bariatric*) AND (liver* OR hepat* OR steatohepat* OR NAFL* OR NASH*)
Cochrane Central Register of	Issue 4, 2009.	ORIGINAL SEARCH STRATEGY #1 MeSH descriptor Bariatric explode all trees in MeSH products

(Continued)

Controlled Trials (CENTRAL) in The Cochrane Library		#2 MeSH descriptor Obesity explode all trees in MeSH products #3 MeSH descriptor Surgery explode all trees in MeSH products #4 (#1 OR #2 OR #3) #5 (liver and (non-alcoholic or non alcoholic or nonalcoholic or fatty or disease or steato*)) or NAFL or NASH in All Fields in all products #6 (#4 AND #5) EXPANDED SEARCH STRATEGY #1 MeSH descriptor Bariatric Surgeryexplode all trees #2 jejunoileal bypass* OR vertical banded gastroplast* OR gastric bypass* OR adjustable gastric band* OR biliopancreatic diversion* OR bariatric* #3 (#1 OR #2) #4 MeSH descriptor Liverexplode all trees #5 liver* OR hepat* OR steatohepat* OR NAFL* OR NASH* #6 (#4 OR #5) #7 (#3 AND #6)
MEDLINE (Ovid SP)	1950 to October 2009.	ORIGINAL SEARCH STRATEGY ("jejunoileal bypass" OR "vertical banded gastroplasty" OR "gastric bypass" OR "gastric bypass loop" OR "adjustable gastric band" OR "biliopancreatic diversion" OR "bariatric*") AND ("non*alcoholic fatty liver" OR "non alcoholic fatty liver" OR "nonalcoholic fatty liver" OR "NAFL*" OR "NASH" OR (non*alcoholic AND steato*hepatitis) OR (non alcoholic AND steato*hepatitis) OR (nonalcoholic AND steato*hepatitis)) EXPANDED SEARCH STRATEGY #1 exp Bariatric Surgery/ #2 (jejunoileal bypass* or vertical banded gastroplast* or gastric bypass* or adjustable gastric band* or biliopancreatic diversion* or bariatric*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] #3 (#1 or #2) #4 exp Liver/ #5 (liver* or hepat* or steatohepat* or NAFL* or NASH*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] #6 (#4 or #5) #7 (#6 and #3) #8 (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] #9 (#8 and #7)
EMBASE (Ovid SP)	1980 to October 2009.	ORIGINAL SEARCH STRATEGY #1 explode "bariatric-surgery"/ all subheadings #2 jejunoileal bypass* or banded gastroplast* or gastric bypass* or gastric band* or biliopancreatic diversion* or bariatric* #3 (#1 or #2) #4 explode "nonalcoholic-fatty-liver"/ all subheadings #5 non*alcoholic fatty liver or NAFL or non*alcoholic steato*hepatitis or NASH #6 (#4 or #5) #7 (#3 and #6) #8 random* or blind* or placebo* or meta-analysis #9 (#7 and #8) EXPANDED SEARCH STRATEGY #1 exp Bariatric Surgery/ #2 (jejunoileal bypass* or vertical banded gastroplast* or gastric bypass* or adjustable gastric band* or biliopancreatic diversion* or bariatric*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

(Continued)

		#3 (#1 or #2) #4 exp liver/ #5 (liver* or hepat* or steatohepat* or NAFL* or NASH*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] #6 (#4 or #5) #7 (#6 and #3) #8. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 9 (#8 and #7)
Science Citation Index Expanded (http://apps.isi-knowledge.com)	1900 to October 2009.	ORIGINAL SEARCH STRATEGY #1 MeSH descriptor Bariatric explode all trees in MeSH products #2 MeSH descriptor Obesity explode all trees in MeSH products #3 MeSH descriptor Surgery explode all trees in MeSH products #4 (#1 OR #2 OR #3) #5 (liver and (non-alcoholic or non alcoholic or nonalcoholic or fatty or disease or steato*)) or NAFL or NASH in All Fields in all products #6 (#4 AND #5) EXPANDED SEARCH STRATEGY # 1 TS=(jejunoileal bypass* OR vertical banded gastroplast* OR gastric bypass* OR adjustable gastric band* OR biliopancreatic diversion* OR bariatric*) # 2 TS=(liver* or hepat* or steatohepat* or NAFL* or NASH*) # 3 (#2 AND #1) # 4 TS=(random* or blind* or placebo* or meta-analysis) # 5 (#4 AND #3)

WHAT'S NEW

Date	Event	Description
2 July 2009	Amended	A peer reviewers' contribution acknowledged.

CONTRIBUTIONS OF AUTHORS

Norberto C. Chavez Tapia: conceived, designed, co-ordinated, collected, analysed, interpreted data, wrote and approved the review.
Nahum Mendez-Sanchez: provided general advice on the review, read and approved the review.
Javier Lizardi-Cervera: provided general advice on the review, read and approved the review.
Felix Tellez-Avila: designed, collected, analysed, interpreted data, corrected and approved the review.
Tonatiuh Barrientos-Gutierrez: collected, analysed, interpreted data, corrected and approved the review.
Misael Uribe: provided general advice on the review, read and approved the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After discussion with the editors and authors of the review we decided to include non-randomised studies to assess the rate of adverse events.

The original search strategy was expanded to identify more reports.

NOTES

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Bariatric Surgery; Fatty Liver [etiology] [*surgery]; Obesity [complications] [*surgery]

MeSH check words

Humans