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ORIGINAL CONTRIBUTIONS

Bariatric Surgery and Non-Alcoholic Fatty Liver Disease: a Systematic Review of Liver Biochemistry and Histology

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Abstract
Background Non-alcoholic fatty liver disease (NAFLD) is becoming a leading cause of global liver disease that is associated with the rising prevalence of obesity worldwide. There is now increasing clinical and mechanistic evidence reporting on the metabolic and weight loss effects of bariatric surgery on improving NAFLD in obese patients.
Objectives The aim of this paper was to quantify the effects of bariatric surgery on NAFLD by appraising the modulation between pre- and post-operative liver enzyme levels (as markers of liver injury) and liver histology.
Methods A systematic review of studies reporting pre-operative and post-operative liver enzymes or liver histology was done in obese patients with NAFLD undergoing bariatric surgery. Data were meta-analysed using random-effects modelling. Subgroup analysis, quality scoring and risk of bias were assessed.
Results Bariatric surgery is associated with a significant reduction in the weighted incidence of a number of histological features of NAFLD including steatosis (50.2 and 95 %CI of 35.5–65.0), fibrosis (11.9 and 95 %CI of 7.4–16.3 %), hepatocyte ballooning (67.7 and 95 %CI 56.9–78.5) and lobular inflammation (50.7 and 95 %CI 26.6–74.8 %). Surgery is also associated with a reduction in liver enzyme levels, with statistically significant reductions in ALT (11.36 u/l, 95 %CI 8.36–14.39), AST (3.91 u/l, 95 %CI 2.23–5.59), ALP (10.55 u/l, 95 %CI 4.40–16.70) and gamma-GT (18.39 u/l, 95 %CI 12.62–24.16). Heterogeneity in results was high.
Conclusions Bariatric surgery is associated with a significant improvement in both histological and biochemical markers of NAFLD. Future studies must focus on higher levels of evidence to better identify the benefits of bariatric surgery on liver disease in order to enhance future treatment strategies in the management of NAFLD.

Keywords Non-alcoholic fatty liver disease · NAFLD · Bariatric surgery · Metabolic surgery · Body mass index · Intervention · Surgery · Weight loss

Introduction

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are becoming the leading causes of liver disease in the developed world. The prevalence of NAFLD is estimated to have doubled in the last 20 years [1], with rates at between 2–44 % in the general European population (including obese children) and between 42.6–69.5 % in patients with type 2 diabetes mellitus [2]. In the USA, there are approximately 6 million individuals with NASH and 600,000 individuals with NASH-related cirrhosis [1]. There is evidence that that the global epidemic of obesity is the core contributing factor behind the increasing prevalence of NAFLD [3–5]. Obesity rates have almost doubled over the past two decades, with an estimated prevalence of 500 million obese adults worldwide in 2008 and a further 1.4 billion overweight people [6]. The number of obese people is set to continue to increase, reaching an estimated 1 billion by 2030 [7].

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NAFLD is a spectrum of chronic liver disease, ranging from simple steatosis to NASH and hepatic fibrosis, and is increasingly acknowledged as the hepatic manifestation of the metabolic syndrome. Weight loss and medication to reduce insulin resistance are the main management strategies of NAFLD. Lifestyle interventions to reduce weight have been shown to improve liver histology in steatosis and NASH [8] and may stop progression of hepatic fibrosis [9]. However, sustained weight loss through lifestyle measures and pharmacotherapy has proven difficult [10] and liver fibrosis is likely to progress in up to one third of patients with NAFLD within 4 years [11].

Bariatric surgery has an important role in managing obesity with approximately 113,000 bariatric procedures performed in the USA each year [12]. It can achieve significant weight loss, normalisation of insulin tolerance (offering disease resolution of type 2 diabetes [13]), and reduce cardiovascular risk and long-term mortality [14, 15]. Some reports suggest that 87–94 % of bariatric patients demonstrate abnormal non-alcoholic liver pathology [16, 17], and a number of studies have identified the benefits of bariatric surgery on NAFLD. These have focused on liver histology and liver biochemistry (as enzymatic biomarkers of hepatic injury) before and after surgery, however, their overall combined effects on these NAFLD outcomes have not been quantified. Our aim was to do a comprehensive systematic review and meta-analysis of all bariatric studies reporting on these parameters in order to quantify the effects of bariatric surgery on changes in NAFLD liver histology and biochemistry.

Methods

Literature Search

A literature search was performed using PubMed, Embase, Ovid and Cochrane databases using combinations of the terms 'bariatric surgery' or 'metabolic surgery' or 'weight loss surgery' and 'liver biopsy' or 'liver enzymes' or 'liver histology' or 'NAFLD' or 'steatosis' or 'steatohepatitis' or 'fibrosis'. The last date for this search was 15 December 2014. Figure 1 outlines our search strategy. All studies are listed in Table 1.

Inclusion and Exclusion Criteria

All studies reporting pre-operative and post-operative liver biochemistry or liver histology (or both) were included. Studies were excluded for data inconsistency or overlapping data from other studies (for example, four studies used data from the Lille bariatric cohort [18, 25, 27, 37]).

Meta-analysis was performed in line with recommendations form the Cochrane Collaboration and in accordance with preferred reporting items for systematic reviews and meta-Analyses (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE) guidelines [53, 54]. Analyses were performed using Stata version 12 (StataCorp LP, College Station, TX).

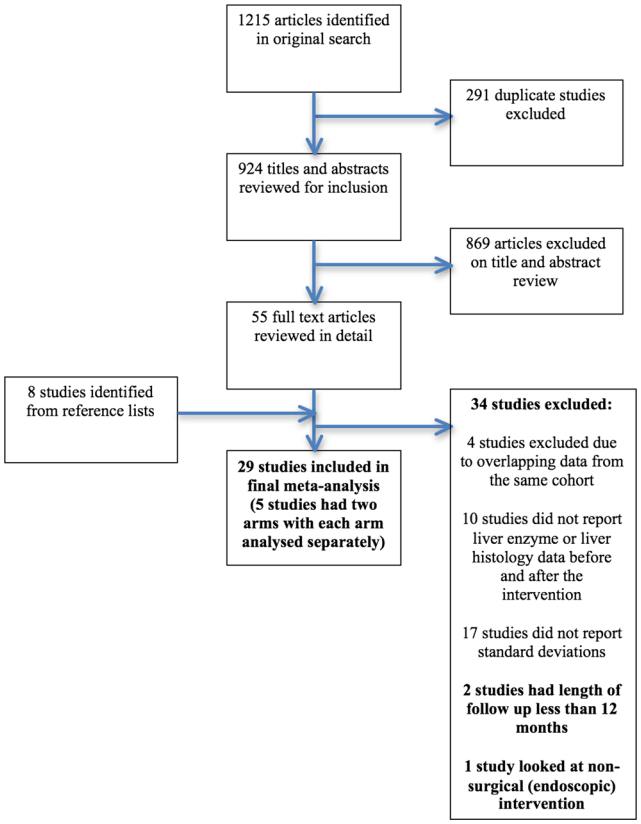

Fig. 1 Search strategy

Continuous data were investigated using weighted mean difference (WMD) as the summary statistic, and proportion difference between histological outcomes was calculated and pooled through DerSimonian and Laird random-effects modelling. Quality assessment of each study was performed using a modification of the Newcastle-Ottawa scale [53].

Results

Our review of the literature found 29 studies suitable for the final meta-analysis, out of 1215 articles identified in the original search (Fig. 1).

Liver Histology

There was a consistent decrease in all six histopathological markers of liver injury assessed after bariatric surgery. There was high heterogeneity across all studies.

Steatosis Sixteen studies reported on the presence of steatosis before and after surgery (Fig. 2a). Pooled analysis of histological findings demonstrated the weighted mean decrease in the

Table 1 Bariatric surgical studies reporting on changes in liver histology and liver biochemistry after surgical intervention

Author	Year	Design	Quality score (0–9)	Intervention	Total participants	Follow-up (months)	Pre-op BMI (SD)	Post-op BMI (SD)	Liver biochemistry	Histology
Caiazzo G1 [18]	2014	Prospective	7	GB	165	60	46.7 (6.8)	37.3 (7.6)	AST, ALT, ALP, γ-GT	Steatosis Fibrosis
Caiazzo G2 [18]	2014	Prospective	7	RYGB	150	60	51.7 (7.4)	38.7 (8.5)	AST, ALT, ALP, γ-GT	Steatosis Fibrosis
Abdennour [19]	2014	Prospective	4	GB	243	12	47.9 (7.4)	33.2 (5.4)	AST, ALT, γ-GT	–
Coupaye G1 [20]	2014	Prospective	7	RYGB	30	12	48.5 (9.6)	36.6 (8.6)	AST, ALT, ALP, γ-GT	–
Coupaye G2 [20]	2014	Prospective	7	SG	30	12	48.6 (7.8)	35.2 (7.8)	AST, ALT, ALP, γ-GT	–
De Jonge[c] [21]	2013	Prospective	4	Endoscopic DJBL	17	12	37.0 (1.3)	34.3 (1.5)	AST, ALT, γ-GT	–
Johansson G1 [22]	2013	Prospective	4	RYGB	21	36	42.3 (5.2)	32.1 (5.3)	ALT, γ-GT	–
Johansson G2 [22]	2013	Prospective	4	BPD-DS	10	36	53.5 (3.8)	30.2 (5.0)	ALT, γ-GT	–
Vargas [22]	2012	Prospective	4	RYGB	26	16	49.3 (4.8)	30.9 (4.3)	AST, ALT, γ-GT	Steatosis Inflammation Fibrosis
Tai [23]	2012	Prospective	4	RYGB	21	12	43.8 (7.5)	28.3 (4.6)	–	Steatosis Inflammation Fibrosis
Moretto [24]	2011	Retrospective	2	GB	78		45.4 (8.1)	29.3 (5.8)	–	Fibrosis
Caiazzo[d] [25]	2010	Prospective	3	LAGB	23	60	48.3 (6.4)	–	ALT	–
Bell[d] [26]	2010	Prospective	4	RYGB/GB/SG	20	15	54 (9.0)	36.0 (9.0)	AST, ALT	–
Mathurin[d] [27]	2009	Prospective	4	RYGB/GB/BIBP	381	60	50 (7.8)	37.7 (8.4)	ALT	Fibrosis
Swierczynski[b] [28]	2009	Retrospective	3	VBG	16	6	49.0 (9.0)	36.0 (7.5)	AST, ALT	–
Frige G1 [29]	2009	Prospective	6	LAGB	24	12	48.6 (1.5)	30.1 (1.3)	AST, ALT	–
Frige G2 [29]	2009	Prospective	6	BPD-BIP	12	12	44.8 (0.7)	35.4 (0.6)	AST, ALT	–
Moschen [30]	2009	Prospective	4	LAGB	30	12	42.6 (0.7)	33.8 (0.9)	AST, ALT, ALP, γ-GT	Steatosis Inflammation Fibrosis
Kakizaki [31]	2008	Prospective	4	RYGB	84	12	43.8 (7.8)	31.0 (7.5)	AST, ALT	–
de Andrade [32]	2008	Prospective	4	Not specified	40	21	45.9 (5.7)	29.5 (23.0)	AST, ALT, γ-GT	–
Alexandrides G1 [33]	2007	Retrospective	4	RYGB	26	60	46.1 (2.9)	32.6 (5.6)	AST, ALT, γ-GT	–
Alexandrides G2 [33]	2007	Retrospective	4	BPD-RYGBP	111	26.39	59.7 (10.6)	39.9 (7.2)	AST, ALT, γ-GT	–
Furuya [34]	2007	Prospective	4	RYGB	18	24	51.0 (3.0)	31.0 (2.0)	AST, ALT, ALP, γ-GT	Steatosis Inflammation Fibrosis
Phillips[b] [35]	2007	Prospective[a]	4	LAGB	29	3	39.0 (5.0)	35.0 (4.0)	AST, ALT, ALP, γ-GT	–
Liu [36]	2007	Retrospective	4	RYGB	39	18	47.7 (6.2)	29.5 (5.6)	AST, ALT	Steatosis Inflammation
Mathurin[d] [37]	2006	Prospective	4	GB	185	12	–	–	–	Steatosis

Table 1 (continued)

Author	Year	Design	Quality score (0–9)	Intervention	Total participants	Follow-up (months)	Pre-op BMI (SD)	Post-op BMI (SD)	Liver biochemistry	Histology
Dixon [38]	2006	Prospective	4	GB	60	29.5	45.9 (7.4)	34.0 (5.5)	–	Steatosis Inflammation Fibrosis
Klein [39]	2006	Prospective	4	GB	7	12	48.0 (4.0)	41.0 (5.0)	AST, ALT, ALP	–
Meinhardt [40]	2006	Retrospective	4	GB	31	70	52.8 (7.5)	35.7 (35.7)	AST, ALT, γ-GT	Steatosis Inflammation Fibrosis
Csendes [41]	2006	Prospective	3	GB	16	22	44.3 (–)	28.6 (–)	–	Steatosis
de Almeida [42]	2006	Prospective	4	RYGB	16	23.5	53.4 (8.8)	31.4 (4.7)	–	Inflammation Fibrosis
Barker [43]	2006	Retrospective	4	RYGB	19	21	47.0 (4.4)	29 (5.2)	AST, ALT, ALP	–
Clark [44]	2005	Prospective	3	RYGB	16	10.89	51.1 (6.1)	32.9 (5.1)	AST, ALT, ALP	Steatosis Inflammation
Jaskiewicz [45]	2006	Prospective	3	VBG	10	41	46.7 (8.8)	–	AST, ALT	–
Mottin [46]	2005	Retrospective	3	RYGB	90	12	–	46.7 (0.9)	–	Steatosis
Keshishian [47]	2005	Retrospective	3	BPD-DS	697	48	50.5 (–)	28.5 (–)	AST, ALT	–
Mattar [48]	2005	Prospective	4	BPD-RYGBP	70	15	56.0 (11.0)	39.0 (10.0)	AST, ALT	Steatosis
Stratopoulos [49]	2005	Prospective[a]	4	VBG	51	18	52.8 (1.0)	–	AST, ALT, ALP, γ-GT	Steatosis Inflammation Fibrosis
Kral [50]	2004	Retrospective	4	BPD-DS	104	74	–	–	AST, ALT, ALP, γ-GT	–
Dixon [51]	2004	Prospective	4	GB	36	25	47.0 (10.6)	34.0 (5.5)	AST, ALT, ALP, γ-GT	Steatosis Inflammation Fibrosis
Luyckx [52]	1998	Retrospective	3	VBG	69	27	44.9 (7.1)	–	–	Steatosis Inflammation Fibrosis

[a] Design not clear

[b] Not included in analysis as length of follow-up <12 months

[c] Not included in analysis as non-surgical procedure

[d] Not included in analysis as data overlapping with other studies

GB gastric banding, *RYGB* Roux-en-Y gastric bypass, *BPD-BIP* bilio-pancreatic diversion and bilio-intestinal bypass, *SG* sleeve gastrectomy, *VBG* vertical banded gastroplasty, *LAGB* laparoscopic adjustable gastric band, *DJBL* duodenal-jejunal bypass liner, *BPD-DS* bilio-pancreatic diversion and duodenal switch, *BPD-RYGBP* bilio-pancreatic diversion with Roux-en-Y gastric bypass

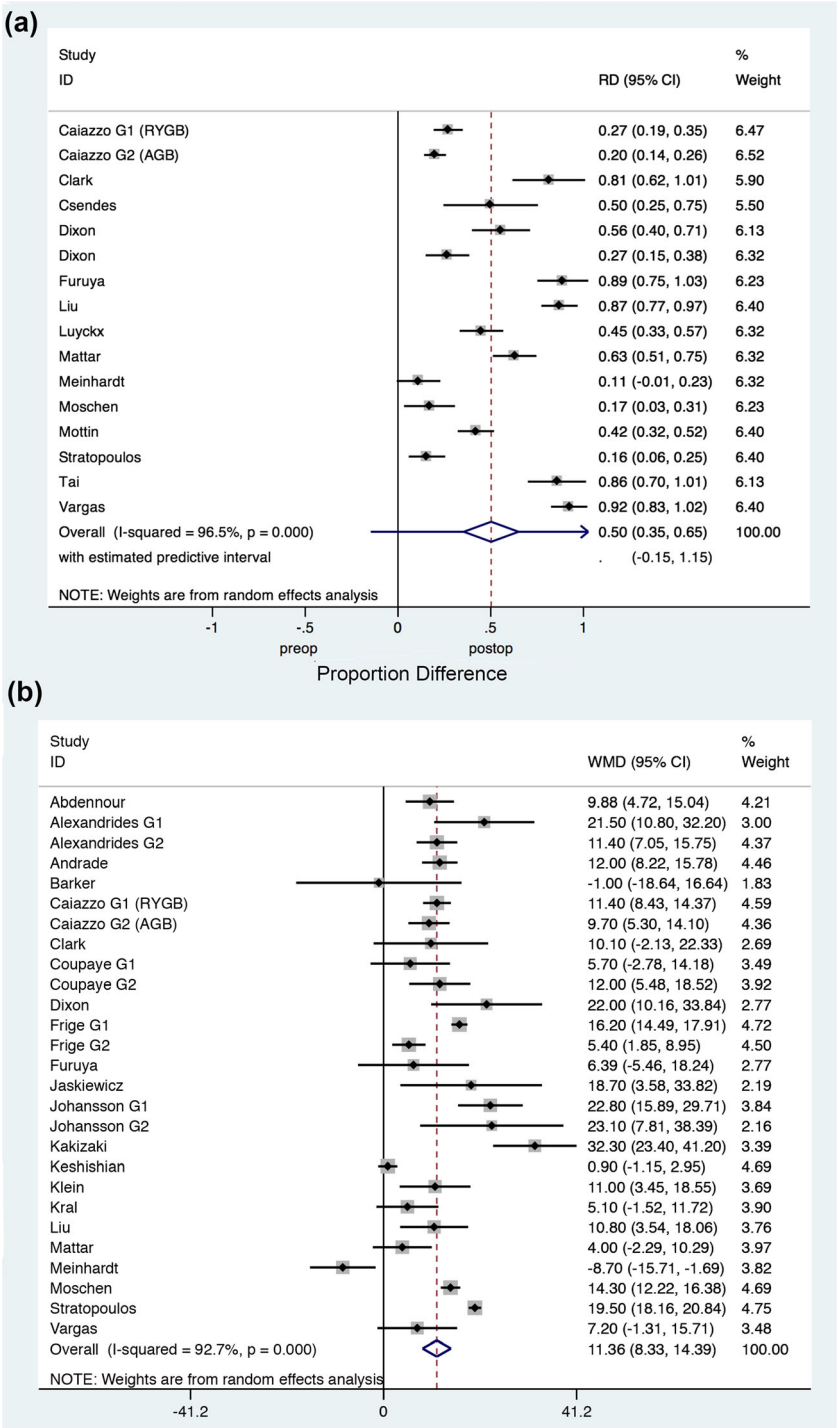

Fig. 2 Forest plots demonstrating changes in **a** liver histology for steatosis and **b** liver biochemistry for alanine aminotransferase (ALT)

incidence of steatosis was 50.2 % (95 %CI 35.5–65.0, p=<0.0001, I^2 96.5 %).

Steatohepatitis Three studies reported on rates of steatohepatitis before and after surgery. Pooled analysis of histological findings demonstrated the weighted mean decrease in the incidence of steatohepatitis was 3.8 % (95 %CI −13.4–21.0, p=0.66, I^2 90.6 %).

Portal Inflammation Four studies reported on rates of portal inflammation before and after surgery. Pooled analysis of histological findings demonstrated the weighted mean decrease in the incidence of portal inflammation was 13.1 % (95 %CI −1.7–27.9, p=0.082, I^2 72.7 %).

Lobular Inflammation Seven studies reported on rates of lobular inflammation before and after surgery. Pooled analysis

of histological findings demonstrated the weighted mean decrease in the incidence of lobular inflammation was 50.7 % (95 %CI 26.6–74.8, p=<0.0001, I^2 94.4 %).

Hepatocyte Ballooning Eight studies reported on rates of hepatocyte ballooning before and after surgery. Pooled analysis of histological findings demonstrated the weighted mean decrease in the incidence of hepatocyte ballooning was 67.7 % (95 %CI 56.9–78.5, p=<0.0001, I^2 66.6 %).

Fibrosis Twelve studies reported on rates of fibrosis before and after surgery. Pooled analysis of histological findings demonstrated the weighted mean decrease in the incidence of fibrosis was 11.9 % (95 %CI 7.4–16.3, p=<0.0001, I^2 88.9 %).

Liver Biochemistry

There was a consistent decrease in all four liver enzymes (biomarkers of liver function and injury) assessed after bariatric surgery.

ALT Twenty-six studies reported ALT levels before and after surgery (Fig. 2b). The mean ALT level pre-surgery was abnormally high in 16 of these studies. Overall, there was a weighted mean reduction of 11.63 u/l (95 %CI 8.34–14.39, p=0.0001, I^2 92.7 %).

AST Twenty-five studies reported AST levels before and after surgery. The mean AST level pre-surgery was abnormally high in four of these studies. Overall, there was a weighted mean reduction of 3.91 u/l (95 %CI 2.23–5.59, p=0.0001, I^2 90.5 %).

ALP Eleven studies reported ALP levels before and after surgery. The mean ALP level pre-surgery was abnormally high in two studies. Overall, there was a weighted mean reduction of 10.55 u/l (95 %CI 4.40–16.70, p=0.0001, I^2 92.0 %).

Gamma-GT Seventeen studies reported gamma-GT levels before and after surgery. The mean gamma-GT level pre-surgery was abnormally high in three studies. Overall, there was a weighted mean reduction of 18.39 u/l (95 %CI 12.62–24.16, p=0.0001, I^2 94.8 %).

Overall, the levels of biochemical markers used for intrahepatic damage were found to be reduced in patients following bariatric surgery. The mean pre-operative levels of AST, ALP and gamma-GT were within normal range in the majority of studies, whereas the majority of studies reported an abnormally high pre-operative mean ALT level.

Body Mass Index

Pooled data from all studies reporting pre- and post-operative BMI figures demonstrated a weighted mean reduction of 15.13 BMI points post-surgery (95 %CI 13.44–16.82, p=<0.0001, I^2 95.0 %).

Discussion

Overall, our analysis demonstrates that both the pathological histological features of NAFLD and liver enzyme levels (as biomarkers of liver function and injury) are beneficially reduced in the subjects undergoing bariatric surgery. There were statistically significant reductions in steatosis, fibrosis, hepatocyte ballooning, lobular inflammation, ALT, AST and gamma-GT. These studies also identified a reduction in steatohepatitis after bariatric surgery, although this was not significant. As expected, there was a significant reduction in the mean BMI post-operatively.

Steatosis and the histological inflammatory changes of lobular inflammation and hepatocyte ballooning were significantly reduced after surgery; the latter of which is associated with hepatocyte injury and necrosis [55] and increased risk of progression to fibrosis [56]. Lobular inflammation is not as strongly associated with advanced NAFLD as portal inflammation [57] and is not sufficient for a histological diagnosis of NASH [55]. Studies reporting on portal inflammation steatohepatitis were small in number and did not reach statistical significance.

Concerns have been expressed that bariatric surgery may worsen liver disease in some patients, particularly those with fibrotic disease and cirrhosis. Our results suggest against this. One study reported that although fibrosis worsened in patients who had fibrosis at the time of operation, 95.7 % of patients maintained a fibrosis score of no higher than 1 [27], suggesting little significant disease progression post-operatively. Data on the effects of bariatric procedures on cirrhotic patients remain limited [58]. Operating on patients with advanced liver disease carries significant risk, and particularly rapid post-operative weight loss may have a role in the deterioration of liver disease [59]. A review of bariatric procedures in cirrhotics identified one peri-operative death in the 44 cases analysed [58]. A case series on 30 obese cirrhosis patients reported no peri-operative mortality or significant morbidity [60].

The majority of studies identified pre-operative values for AST, ALP and gamma-GT were within normal limits, whereas the majority of those for ALT were pre-operatively raised. High serum levels of ALT are associated with hepatocyte injury and inflammation; furthermore, increased levels of gamma-GT are also associated with increased oxidative stress within the mitochondria of hepatocytes. Together, ALT and gamma-GT are considered as reliable biomarkers of NAFLD [61]. The sensitivity and specificity for raised ALT detecting NAFLD have been estimated to be 55 and 98 %, respectively [62]. Although AST is considered less specific as a marker of liver inflammation when compared to ALT in view of its

association with other organs (such as the heart and pancreas), it has been statistically identified as an independent marker of NASH based on multivariate analysis in a bariatric patient cohort [16]. Consequently, the reduction of these liver enzymes after bariatric surgery supports the notion of hepatic biochemical and metabolic recovery from NAFLD after surgery, which may in turn contribute to improvements in patient outcomes.

Despite the beneficial live enzymatic changes after bariatric surgery, the interpretation of these serum biochemical changes in the context of NAFLD is not straightforward due to hepatic homeostatic compensatory mechanisms. In simple steatosis, liver biochemistry results are likely to be normal [61] and patients with NASH and fibrosis may also have results within the normal range [34]. There is evidence to suggest that as the disease progresses from NASH to fibrosis the reduction in inflammation is matched with falling levels of liver enzymes [61, 63]. Within our analysis, the majority of studies that assessed AST, gamma-GT, and ALP reported that mean levels of these enzymes were within normal range. Only in the case of ALT was the mean level abnormally high in the majority of studies.

Some studies report over 80 % complete regression of NAFLD histology (and a 93 % regression from necro-inflammatory activity) [17], which has been associated with the dramatic weight loss offered by bariatric operations, however, these procedures are also likely to therapeutically modulate the metabolic and systemic inflammatory component of NAFLD through their powerful metabolic activity that includes their effects in decreasing insulin resistance and resolving type 2 diabetes mellitus [13–15, 64].

In this context, NAFLD is increasingly seen as the hepatic manifestation of the metabolic syndrome, and many of the mechanisms implicated in the improvements seen in lipid metabolism and insulin tolerance following bariatric surgery are thought to play a role in ameliorating NAFLD. Obese patients, particularly those with insulin resistance, tend to have dysfunctional lipid metabolism with hepatic de novo lipogenesis and increased peripheral lipolysis. The consequent accumulation of excess lipids within hepatocytes overwhelms the usual pathways of lipid metabolism, causing increased oxidative stress, inflammation, necrosis and hepatocellular apoptosis. Prolonged hepatic inflammation secondary to steatosis and lipotoxicity (steatohepatitis) can initiate fibrotic change within the liver, leading the way to cirrhosis and may even increase the risk of hepatocellular carcinoma [65–67].

The BRAVE effects of metabolic surgery (bile flow alteration, restriction of stomach size, altered flow of nutrients, vagal manipulation and modulation of enteric gut hormones) offer a framework of how bariatric procedures (such as the Roux-en-Y gastric bypass) initiate many beneficial downstream metabolic changes in obese subjects [68, 69]. With regards to NAFLD, bariatric procedures seem to stimulate significant change in three metabolic domains: improved lipid metabolism, improved insulin tolerance, and a reduction in the chronic inflammation associated with obesity. Increased beta-oxidation of hepatic lipids, with reduced hepatic de novo lipogenesis and peripheral lipolysis, reduces the lipotoxic state and the inflammation and necrosis associated with it. There is a significant overlap between the pathways which initiate these changes, and the extent to which each domain contributes to improvements in NAFLD post-bariatric surgery has not yet been delineated.

Major contributors to these changes are increased secretion of glucagon-like peptide-1 (GLP-1) and adiponectin following surgery [68, 70–72], increased bile acid absorption [73] and changes in the gut microbiome [74, 75]. GLP-1, adiponectin and bile acids contribute to improvements in insulin sensitivity [65, 72] and lipid metabolism by reducing the peripheral lipolysis and hepatic de novo lipogenesis associated with insulin resistance, which in turn is associated with improved liver histology [37, 48]. Bariatric procedures may reduce systemic inflammatory activity (such as TNF-alpha levels) associated with obesity [68, 76] through GLP-1 [77, 78], whilst adiponectin may also reduce hepatic inflammation and fibrosis through its inhibitory action on hepatocyte stellate cells (a key cell in the fibrotic pathway) [79].

Strengths and Limitations

This study offers a quantifiable measure of liver biochemistry and histology after bariatric surgery. The heterogeneity of the studies however represents a significant interpretive limitation. Patient selection, follow-up time, reason for biopsy, type of biopsy, interpretation of histology and type of procedures performed all vary significantly between studies and may lead to reporting biases. Furthermore, the levels of evidence in these studies are comparably low and preclude definitive conclusions regarding outcomes.

A number of different histological classification systems have been used between studies in our analysis. Although there is some inter-study difference between scoring systems, each study employed the same histological scoring system to pre- and post-operative biopsies (i.e. there was consistency of scoring system within each study). Although this carries a limitation when deriving conclusions from our results, we feel that by applying a proportional change methodology (albeit with different scoring systems) may still offer some value in the appraising the wider scope of bariatric effects on liver histology.

Conclusion

The effect of bariatric surgery on liver histology and biochemistry suggests that these procedures are associated with a significant improvement in NAFLD status whether the disease is

in its steatotic, hepatitic or fibrotic stage. Significant heterogeneity between studies limits our interpretation of the results. Reduction in ALT, AST and gamma-GT is consistent with the reduction in chronic inflammation seen following surgery and improvements in histological features associated with liver-specific inflammation (e.g. hepatocyte ballooning). Improvements in steatosis, steatohepatitic features and fibrosis are also consistent with current mechanistic evidence for the metabolic changes stimulated by bariatric procedures. Further studies, particularly randomised controlled trials with mechanistic studies, are justified to clarify the role of surgery in obesity and NAFLD and may help elucidate advances to current interventions and novel diagnostic tools to minimise the growing clinical burden of mortality and morbidity associated with obesity-associated liver disease.

Ethical Approval For this type of study, formal consent is not required.

Conflict of Interest The authors declare that they have no conflict of interest.

Financial Disclosure None

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