Hepatic complications of bariatric surgery : the reverse side of the coin

U. Vespasiani-Gentilucci*[1], F. Vorini*[1], S. Carotti[2], A. De Vincentis[1], G. Galati[1], P. Gallo[1], N. Scopinaro[3], A. Picardi[1]

(1) Internal Medicine and Hepatology Unit ; (2) Laboratory of Microscopic and Ultrastructural Anatomy, CIR ; University Campus Bio-Medico of Rome, Italy; (3) Department of Surgery, Ospedale San Martino, University of Genoa, Italy.

Abstract

Background : **Even if the jejunoileal bypass has been definitely abandoned due to the high rate of hepatic complications, cases of liver injury after the new bariatric procedures are still reported. We aimed to review the available literature concerning liver damage associated with the older and newer types of bariatric surgeries.**

Methods : **An extensive literature search of MEDLINE was performed using different combinations of the following terms: "bariatric surgery OR biliopancreatic diversion OR jejunoileal bypass OR roux-en-y gastric bypass OR vertical banded gastroplasty OR laparoscopic adjustable gastric banding" AND "hepatic/liver damage OR hepatic/liver impairment OR hepatic/liver failure".**

Results : **Although weight loss after bariatric surgery frequently induces an improvement of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, and even the regression of hepatic fibrosis, bariatric procedures have been also associated with cases of acute liver failure or of chronic liver disease evolving until cirrhosis. After the jejunoileal bypass has been definitely abandoned, most of the recently described cases concern biliopancreatic diversion with/without duodenal switch, but liver damage has been reported after almost all types of bariatric surgeries. Protein-calorie malnutrition, bacterial overgrowth, lipotoxicity and genetic background are likely to play a central role in the physiopathology of hepatic injury.**

Conclusions : **Understanding the inner mechanisms underlying acute or chronic liver injury after bariatric surgery can help in the prevention, early recognition and treatment of these rare but concrete cases.** (Acta gastroenterol. belg., **2017,** 80, **505-513**).

Key words : Bariatric surgery, liver injury, bacterial overgrowth, protein-calorie malnutrition, lipotoxicity.

Introduction

Since the early 1960s, bariatric surgery has represented the only effective treatment against severe morbid obesity (1), allowing patients to gain a long-term effective loss of 50-70% of their excess weight (2,3). It is indicated for any adult with BMI >35 kg/m2 and severe comorbidities (life-threatening cardiopulmonary problems, severe diabetes mellitus), or BMI >40 kg/m2 (4). Moreover, bariatric surgery demonstrated clear metabolic benefits: it improves glucose tolerance in type-2 diabetic patients and rebalances glucose homeostasis (5-7) ; it reduces urate levels (8), blood pressure and LDL cholesterol levels and it increases HDL cholesterol levels (5,6,9) ; it has beneficial effects on metabolic syndrome (5,10,11) ; it seems beneficial also on obstructive sleep apnea (2).

Concerning the liver, the effects of bariatric surgery are double-sided and this issue deserves special attention. Indeed, several studies demonstrated an association between weight loss and regression of nonalcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (5,9-11), and others proved a significant rate of fibrosis – and even cirrhosis – regression after bariatric surgery (12). On the other side, from the middle '70s, several reports have focused on the high rate of hepatic complications following the first widely diffused bariatric technique, the jejunoileal bypass (JIB) (13-17), which led to its progressive abandonment, even if some opposing opinions still exist (18).

Since the issue of hepatic complications following bariatric procedures is missing, we aimed to examine the available literature concerning liver injury following bariatric surgery, and theorize the possible underlying physiopathological mechanisms.

Bariatric surgery procedures

Bariatric procedures can be schematically divided into *restrictive* and *malabsorptive*, or a combination of the two.

The first bariatric procedure is the JIB. Introduced in the '50s, it revealed as a purely malabsorptive technique, and consists on the resection of a variable-long portion of the small intestine (generally 90-95%) (19), connecting the extremity of the remainder with an end-to-end or end-to-side anastomosis (Fig. 1, Panel A). This procedure gained a remarkable success in losing excess weight and maintaining weight loss, but it is now abandoned because of the short- and long-term complications.

The vertical banded gastroplasty (VBG) represents a purely restrictive procedure. It gained a certain popularity during the 1980s, with the decline of JIB, but it fell into disfavor because of the inadequate attitude in maintaining the weight loss (19). According to this technique, the stomach is partitioned with a 4-parallel reinforced row of staples, allowing the bolus to pass only through a small

Correspondence to : Umberto Vespasiani-Gentilucci, M.D., University Campus Bio-Medico of Rome, Via Alvaro del Portillo 200, 00128, Rome, Italy. Tel : +3906225411446 ; Fax : +39-0622541456.
E-mail : u.vespasiani@unicampus.it

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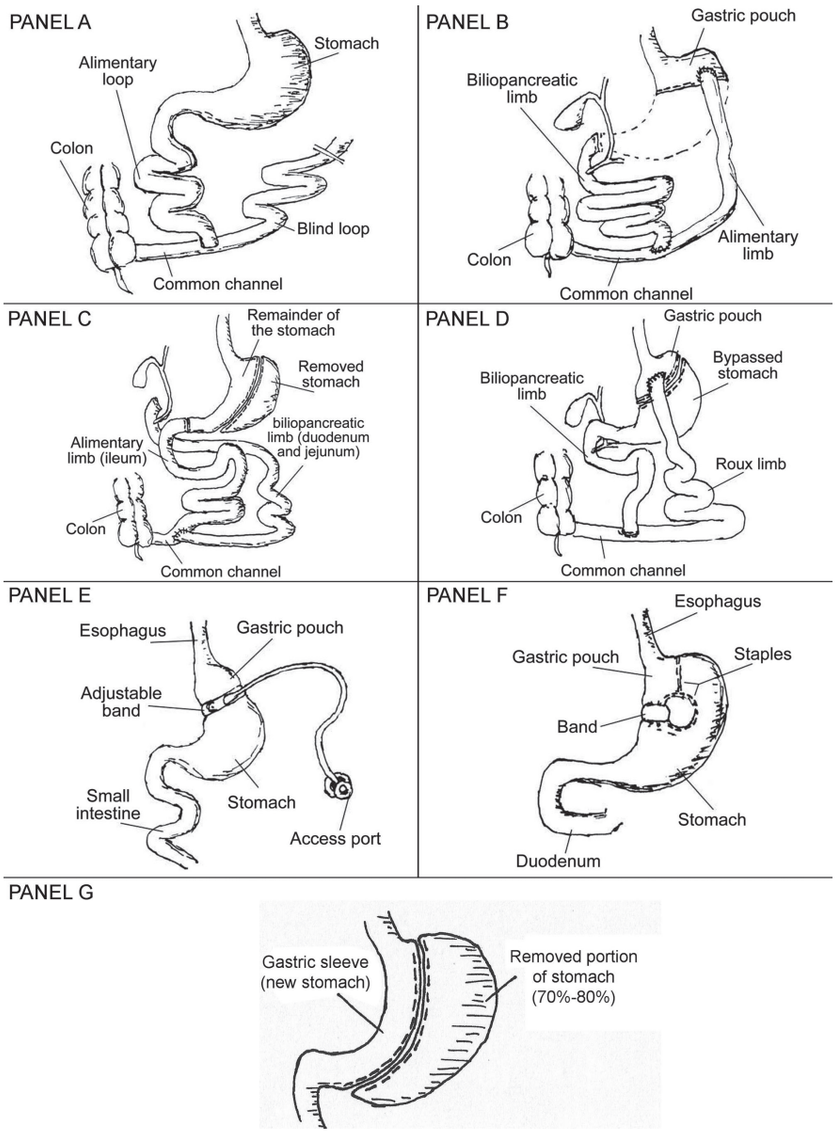

Fig. 1. — Vespasiani-Gentilucci et al. Schematic representations of the different types of bariatric surgery (See text for further details). PANEL A : Jejunoileal bypass ; PANEL B : Laparoscopic adjustable gastric banding ; PANEL C : Vertical banded gastroplasty ; PANEL D : Roux-en-y gastric bypass ; PANEL E : Biliopancreatic diversion ; PANEL F : Duodenal switch ; PANEL G : Laparoscopic Sleeve Gastrectomy.

"stoma", strengthened with a band of prosthetic material (Fig. 1, Panel F).

Similarly, the laparoscopic adjustable gastric banding (LAGB) is a purely restrictive procedure. It is performed through the positioning of a band 1-2 cm below the gastro-oesophageal junction, creating a small pouch (~30 mL); the degree of constriction is adjustable thanks to the injection of an amount of saline contained in a subcutaneous port, connected to the band (Fig. 1, Panel E). It is effective at producing weight loss gradually and presents the lowest rate of post-operative mortality and complications among bariatric surgery procedures, but its usage was progressively limited by the risk of band migration and by weight loss failure on the long-term (20).

Considering the combined procedures, the Roux-en-Y gastric bypass (RYGB) is a both restrictive and malabsorptive procedure. It consists of a partitioning of the upper stomach, creating a small gastric pouch, which is connected to an extremity of the transected small intestine; this portion takes the name of Roux Limb, and extends from the gastrojejunostomy to the jejunojejunostomy, with an end-to-side or end-to-end anastomosis. A biliopancreatic limb, extending from the Treitz to the jejunojejunostomy, drains biliary and pancreatic juices to the common limb, the remainder of the small intestine (Fig. 1, Panel D).

The biliopancreatic diversion (BPD) is also a combined restrictive and malabsorptive procedure, generated with the purpose of avoiding the stasis associated with intestinal

bypass and ensuring the flow of bile and pancreatic juices through the biliopancreatic limb. The common channel has variable length (50-125 cm), according to the desired amount of malabsorption. The procedure includes a subtotal gastrectomy and eventually a cholecystectomy (Fig. 1, Panel B). The Duodenal Switch variation (BPD/DS) admits the preservation of the pylorus, with the construction of an ileoduodenostomy distal to the pylorus, the removal of the greater curve portion of the stomach and the creation of a longer common channel (Fig. 1, Panel C).

Finally, the laparoscopic sleeve gastrectomy (LSG) is a recently-introduced restrictive procedure which has rapidly gained an increasing popularity, due to its technical simplicity, its good results and its low post-operative mortality rates (21), becoming - to date - the second most performed bariatric procedure worldwide (22). The LSG consists of a partial, longitudinal gastrectomy, removing the entire great gastric curvature and leaving a gastric sleeve of approximately 100 mL; no anastomoses are performed (23) (Fig. 1, Panel G).

Methods

We performed a literature search of MEDLINE using different combinations of the following terms: "bariatric surgery OR biliopancreatic diversion OR jejunoileal bypass OR roux-en-y gastric bypass OR vertical banded gastroplasty OR laparoscopic adjustable gastric banding" AND "hepatic/liver damage OR hepatic/liver impairment OR hepatic/liver failure" AND "liver damage OR liver impairment OR liver failure". Only English-language studies were considered. To identify additional studies, manual searching of bibliographies from gathered articles and reviews was also performed. Case reports, letters to editor and commentaries were also considered when adding relevant information. From the 208 articles identified by the search strategy, 175 articles were excluded, mainly because dealing with aspects of bariatric surgery different from hepatic complications; 33 were then reviewed and other 46 were added from their bibliographies; finally, 14 articles were included to support the discussion on the possible mechanisms responsible for liver injury. Thus, a total of 93 articles were included in this review.

Reports of liver damage after bariatric procedures

All the studies addressing liver complications of bariatric procedures are reported in Table 1), together with their main findings.

In 1973, Weismann *et al*. firstly described 1 death due to liver failure in a series of 123 patients undergoing JIB (24). In the following years, reports about liver complications after JIB came in succession, with variable rates between different Authors in the incidence of both acute liver failure and progressive liver disease (13,15,17,25-46). Finally, because of the high risk of developing other severe complications further than hepatic damage, such as renal failure (37%), diarrhea and electrolytic impairment (29%), nephrolithiasis (29%) and death, this surgical technique was definitively abandoned (16).

To date, there is no evidence supporting the occurrence of liver injury following LAGB and sleeve gastrectomy. Consequently, these procedures deserve to be considered safe under this profile. There are no long-term complications associated with them, with LAGB showing a higher and more stable weight loss. To note, however, Papakonstantinou *et al.* reported a case of severe acute hepatic failure from a pool of 260 morbid obese patients undergoing VBG (47). Actually, the total absence of concordant or similar reports in the medical literature, together with the rapidity of the hepatic failure onset (the patient died fourteen days after the intervention) (47), suggest that some complication generically related to surgery, rather than to the specific type of surgery, was responsible for this case of liver failure.

Liver injury cannot even be considered amongst the complications of RYGB, which is currently the most performed bariatric surgical procedure over the world (48), due to its excellent induction of weight loss in association with a low rate of short- and long-term complications (6). However, three cases of hepatic decompensation have been reported in patients who underwent RYGB with extended Roux limb (48). In two of these cases, liver histology documented cirrhosis, while in the third one, in which a good outcome was obtained by treatment with metronidazole, lactulose and nasoenteral feeding, liver biopsy showed steatosis and mild fibrosis.

Recently, thanks to the advice of a blind loop and to a certain selectivity in malabsorption, the BPD has brought malabsorptive surgery to reconquer a primary role in the bariatric technique landscape (49). Among the variegated range of possible complications of BPD, hepatic impairment holds an uncertain role. In 2001, in an invited commentary concerning one of the first published cases of liver damage after BPD (steatohepatitis and subacute liver failure 1 year after BPD) (50), Scopinaro remarked that, from over 10.000 interventions, only two cases of liver failure had been encountered (51,52), while a third was to be considered doubtful, due to the lack of complete and corroborating clinical documentation and laboratory data (53). Nevertheless, some kind of connection between BPD and liver injury is undeniable : in 1986, in a series of 384 patients undergoing BPD, Gianetta *et al.* described that a transient post-surgical elevation of ALT and AST was common (54). In the same year, in a series of 180 patients, Hollian *et al.* reported two cases showing a progressive deterioration of the liver function consequently needing surgical reversion (55). In 1992, Grimm *et al.* presented the case of a 43-year-old woman who died from hepatic failure 21 months after BPD (52). The clinical presentation was identical to that of a liver failure occurring after JIB and the exclusion of every

Table I. — **Vespasiani-Gentilucci *et al.* Studies reporting hepatic complications of bariatric surgery, divided by the type of procedure**.

Jejunoileal Bypass (JIB)		
Authors	**Methods**	**Results**
Salmon *et al*,1971 (25)	Liver biopsy at 1, 2 and 3 years [47 patients]	Mild to severe degree of fatty infiltration in almost all patients; 1 case of jaundice 5 months after JIB
Weismann, 1973 (24)	Clinical follow-up [123 patients] Liver biopsy (10 days to 3 years) [40 patients]	1 death due to liver failure Increase of fatty infiltration (first 12 months), then progressive reduction
Baber *et al*, 1973 (26)	Clinical follow-up [86 patients] Repeated liver biopsies [12 patients]	4 cases of progressive liver disease (2 deaths) Progression of liver damage (first 12 months), then regression
Payne *et al*, 1973 (27)	Clinical follow-up [165 patients] Liver biopsy (2 to 133 months) [36 patients]	5 cases of liver failure
Brown *et al*, 1974 (28)	Clinical follow-up and liver biopsy at 1, 2 and 3 years [36 patients]	15 cases of abnormal liver function; 5 liver failures (1 death), all in the first 6 months post-operatively
Jewell *et al*, 1975 (29)	Clinical follow-up (6 months to 14-years) [52 patients]	4 cases of moderate or severe liver dysfunction
Spin and Weismann,1975 (30)	Clinical follow-up (8-12 months) [124 patients; 2 liver biopsies]	2 cases of hepatic necrosis and death
Backman and Hallberg, 1975 (31)	Clinical follow-up (5 years) [103 patients]	9 cases of liver injury (3 deaths due to liver failure)
De Wind and Payne, 1976 (32)	Clinical follow-up (1 to 14 years) [230 patients]	13 cases of liver impairment (10 deaths due to liver failure)
Campbell *et al*, 1977 (33)	Clinical follow-up (median: 5 years) [75 patients ; 4 liver biopsies]	1 death due to liver failure and 4 cases of cirrhosis
Iber and Copper, 1977 (34)	Clinical follow-up (median: 80 wks) [1139 patients]	57 cases of liver disease; estimated percentage of progressive liver disease: 3-6%
Halverson *et al*, 1978 (13)	Clinical follow-up (mean: 32 months) [101 patients]	6 cases (7% of the total) of liver failure (3 deaths)
Ravitch and Brolin, 1979 (35)	Clinical follow-up [64 patients]	9 cases of hepatocellular dysfunction (2 deaths for liver failure 8 and 6 months after JIB)
Baker *et al,* 1979 (36)	Report of 2 cases	2 women developed liver failure 4 and 12 months after JIB
Griffen *et al*, 1983 (15)	Clinical follow-up [1852 patients]	83 cases of liver disease (4.5%)
Hocking *et al*, 1983 (37)	Clinical follow-up (mean: 65.6 months, 46 to 151 months) [100 patients; 42 liver biopsies]	29% progressive hepatic structural abnormalities, 7% cirrhosis and 38% bridging or central pericellular fibrosis
Mustajoki *et al,* 1984 (38)	Clinical follow-up (mean : 4.7 years) [41 patients]	Increase in serum ALT and AST in 6 patients.
Baddeley, 1985 (39)	Liver biopsy annually till the 7th year [170 patients]	55% increasing hepatic steatosis in 1st year post-operatively; 9% micronodular cirrhosis
Gòral and Tuszewski, 1985 (40)	Clinical follow-up (2 to 10 years) [130 patients]	1 case of reversible hepatic insufficiency
Kirkpatrick *et al*, 1987 (41)	Clinical follow-up (1 to 18 years) [58 patients; 3 liver biopsies]	3 cases of hepatic failure 1 to 2 years after JIB; one of these patients died due to cirrhosis after 18 months
Vyberg *et al*, 1987 (42)	Clinical follow-up and liver biopsy (5-9 months) [34 patients]	5 cases of reversible hepatic insufficiency; histologically, most cases progressed on repeated biopsy
Rasmussen, 1989 (43)	Clinical follow-up (median: 11 years, 2 to 16) [72 patients]	1 acute liver failure and 5 cases of cirrhosis
Requarth *et al*, 1995 (17)	Clinical follow-up (mean: 12.3 years, 0 to 23) [453 patients]	10% of liver disease, with 24 cases of liver failure (7 deaths); 8% developed cirrhosis (4 deaths)
Lowell *et al*, 1997 (44)	Clinical follow-up (mean: 22.3 years) [380 patients]	4 cases of cirrhosis, requiring liver transplantation
Hocking *et al*, 1998 (45)	Clinical follow-up and liver biopsy (median: 12.6 ± 0.25 years) [43 patients]	38% of patients developed progressive hepatic fibrosis; 3 patients developed cirrhosis
Frandsen *et al*, 1998 (46)	Clinical follow-up (median: 15.9 years, 8 to 22 years) [57 patients]	1 death due to cirrhosis 5 years post-operatively (suspected alcoholism)

Roux-en-Y Gastric Bypass (RYGB)		
Cotler *et al*, 2004 (48)	Retrospective analysis of 332 patients who underwent surgery between 2001 and 2003	3 cases of hepatic decompensation (7, 7 and 17 months after the procedure)
Biliopancreatic Diversion (BPD)		
Hollian *et al*, 1986 (55)	Clinical follow-up [180 patients]	2 cases of progressive deterioration of liver function
Gianetta *et al*, 1986 (54)	Clinical follow-up and liver biopsy (mean: 31 months, 1 to 96 months) [384 patients]	Common transient post-operative elevation of AST and ALT; mild increase of steatosis 1-4 months post-operatively
Grimm *et al*, 1992 (52)	Case report (liver biopsy)	1 case of hepatic failure 21 months after BPD;
Antal, 1994 (56)	Clinical follow-up (mean: 4 years) [50 patients]	Persistent increase of liver enzymes in 4 cases; 1 case of jaundice
Castillo *et al*, 2001 (51)	Case report (liver biopsy)	1 case of steatohepatitis and liver failure 1 year after BPD
Papadia *et al*, 2003 (57)	Clinical follow-up (12 months) [99 patients]	Common and significant transient post-operative increase in AST and ALT values
D'Albuquerque *et al*, 2008 (59)	Case report (liver biopsy)	3 cases of subacute hepatocellular failure 7 to 24 months after BPD
Geerts *et al*, 2010 (60)	Survey of all Belgian transplant centers	9 cases of severe hepatocellular failure after an average of 5 years after BPD
Van Dongen *et al*, 2010 (61)	Case report (liver biopsy)	1 case of cirrhosis and progressive liver decompensation 14 years after BPD
Sgambato *et al*, 2013 (74)	Case report	1 case of liver failure 8 months after BIB
Lefere *et a*l, 2017 (62)	Case report	1 case of decompensated cirrhosis 5 years after BPD; subacute steatohepatitis recurring after transplantation
Biliopancreatic Diversion with Duodenal Switch (BPD/DS)		
Baltasar *et al*, 2004 (63)	Clinical follow-up (mean: 9 years) [470 patients, 2 liver biopsies]	10 cases of hepatic impairment, from transient elevation of liver enzymes to a case of severe jaundice and a death due to liver failure
Hamoui *et al*, 2007 (64)	Clinical follow-up (median: 17 months, 7 to 63) [701 patients, 2 liver biopsies]	1 case of liver failure 1 year after DS
Auclair *et al*, 2013 (65)	Case report (liver biopsy)	1 case of severe hepatic decompensation 8 months after DS
Baltasar *et al*, 2014 (66)	Case report (liver biopsy)	1 case of liver failure 20 months after DS

other possible etiology seemed to confirm the relation to the surgery. A few years later, Antal *et al.* described an increase of liver enzymes persisting beyond 6 months after surgery in 4 patients (8%) who underwent BPD (56). These first reports urged the group of Scopinaro to deepen the study of liver function after BPD (57). In a series of 99 patients, they reported a significant post-operative increase in AST and ALT values, with a peak 2 months after surgery, and a subsequent decrease in a time frame of 12 months, thus suggesting a significant transient hepatocellular necrosis. Finally, they found that, although there is no parameter able to predict the post-operative elevation of AST and ALT, body weight and pre-operative hepatic fibrosis and inflammation correlated with the degree of AST elevation (57); similar findings were reported by the group of Keshishian *et al*. after DS (58). More recently, D'Albuquerque *et al.* coped with 3 patients presenting subacute hepatocellular failure 7 to 24 months after BPD (59). Geerts *et al.* enquired all belgian transplant centers about cases of liver transplantation performed because of liver failure after BPD, and found 9 patients listed due to severe hepatocellular failure occurring after a median time of 5 years following BPD (60). Moreover, van Dongen *et al.* reported the case of a woman with cirrhosis and progressive liver decompensation 14 years after the BPD procedure (61). Finally, a very recent report by Lefere *et al.* (62) described the case of a 24-year-old woman who developed decompensated cirrhosis 5 years after BPD; thereafter, a subacute steatohepatitis associated with small intestine bacterial overgrowth recurred three times, leading to the loss of three grafts and, finally, to patient death (62).

Similar considerations can be done about the DS variant. On over 470 surgeries, Baltasar *et al.* reported 10 well-documented cases of hepatic impairment, ranging from a mild but substantial alteration of ALT and AST, to the occurrence of severe jaundice and one death from liver failure (63). All patients underwent liver biopsy, which demonstrated a variable degree of inflammation and fibrosis. The treatment with total parenteral nutrition or hypercaloric diet and proper protein supplementation led to improvement in 9 cases but one patient died from liver failure while waiting for transplantation. More recently, in a 10-year experience of DS, two cases of liver disease out of 701 patients were reported (64). Finally, two cases

of severe liver decompensation were reported 8 months after DS in a 37 years-old woman, and 20 months after DS in a 33 years-old woman, by Auclair *et al.* and by Baltasar *et al.*, respectively (65,66). Actually, it should be mentioned that several Authors raised serious concern about the BPD and DS procedures due the high rates of nutrient malabsorption - especially fat-soluble vitamins -, and the consequent malnutrition (67-71). The revision rates for excessive malabsorption for DS and BPD range from 0.5% to 4.9% and from 3% to 18.5%, respectively (72). The technical complexity and the relatively high complication and mortality rates of these procedures are the main reasons for a declining trend in their application (22).

Possible pathophysiological mechanisms for liver damage after bariatric surgery

In 1970, Drenick et al. firstly implied bariatric surgery on liver injury by observing that significant weight loss obtained by diet or fasting was accompanied by a progressive diminution of liver steatosis, whereas comparable weight loss after JIB led to cases of massive hepatic fatty degeneration and to fibrosis progression (73).

Actually, every bariatric intervention implies rapid weight loss and lipid mobilization from peripheral deposits : the vast and rapid demolition of adipose tissue leads to massive release of FFAs that reach the liver and possibly provoke hepatotoxicity (57,63,74,75). However, the increased load of FFAs to the liver alone is not sufficient to justify fatty degeneration: indeed, fasting and semistarvation diets are associated with a paradoxical reduction in liver fat content notwithstanding comparable FFAs overload to the liver (73,76). Hence, Moxley et *al.* suggested that protein malnutrition or the deficiency of specific amino acids could contribute as co-factors in the genesis of fatty liver degeneration observed shortly after JIB (77), by analogy with the fatty liver in kwashiorkor in which the diet is protein-deficient and disproportionately high in carbohydrates (78).

A mechanism of liver injury - very specific for procedures that imply the creation of a blind loop (JIB) -is bacterial overgrowth. Bacterial overgrowth in the blind loop has been considered responsible for many of the detrimental effects associated with JIB, such as diarrhea, malabsorption, pneumatosis cystoides intestinalis and, mainly, liver damage (79). Consistently, the rarity of liver disease after BPD -compared to JIB- has been attributed to the absence of the blind loop. As a matter of facts, the intestinal tract excluded from food in BPD continue to receive biliopancreatic secretions. Definitely, any surgery producing the absence of food in an intestinal tract would result in decreased motility of that segment, permitting overgrowth of bacteria, mainly anaerobes (80). The mucosal damage consequent to bacterial overgrowth leads to increased permeability to endotoxins, which reach the liver through the portal blood. Endotoxins directly activate toll-like receptor-4 signaling on Kupffer cells, hepatocytes, cholangiocytes and even hepatic progenitor cells and trigger the expression of pro-inflammatory cytokines. The activation of the TLR4 axis in these different hepatic cells could play a pivotal role in the progression of liver damage in terms of inflammation and fibrosis, as recently demonstrated in the context of both NAFLD and chronic HCV infection (81,82).

Another possible mechanism of liver injury is represented by the alteration of bile metabolism and the reabsorption of toxic amounts of bile acids (17,54,56,57,63,73-80). Actually, increased reabsorption of bile acids is associated with almost all malabsorptive or mixed bariatric procedures, and that is because bile acids have less time to mix with food prior to their transit through the ileum (83). By the way, non-toxic bile acids have recently emerged as key metabolic signalling molecules and increased serum bile acids have been associated with many of the beneficial effects determined by bariatric surgery, i.e., satiety, improved lipid and glucose metabolism, etc. (84). Therefore, the possibility that a toxic hepatic load of bile acids could play a role in liver injury after malabsorptive bariatric procedures cannot be definitely excluded, but seems highly questionable.

It is clear that endotoxin and toxic bile acid-mediated liver injury can be implied only in surgeries that entail an intestinal loop excluded from either food or biliopancreatic flow. It is not surprising, therefore, that most of the reports of hepatic damage following bariatric surgery concern purely malabsorptive or at least mixed procedures, and that reports following purely restrictive ones are somehow anecdotal. It seems also evident that none of these mechanisms is by itself sufficient to produce

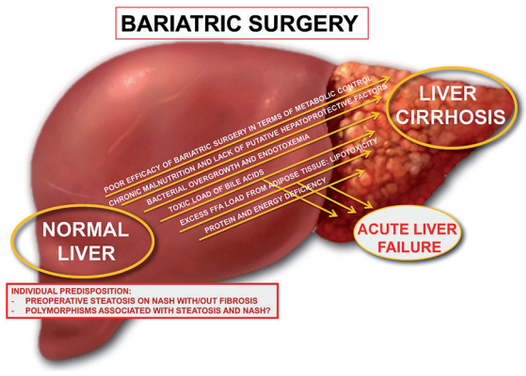

Figure 2. — Vespasiani-Gentilucci *et al.* Mechanisms contributing to liver damage after bariatric surgery. On a substrate of individual predisposition based on the degree of pre-operative steatosis and likely on genetic determinants, lipotoxicity resulting from excess of free fatty acids reaching the liver, protein/energy malnutrition and, possibly, a toxic hepatic load of bile acids due to the disturbed enterohepatic circulation, can all contribute to the onset of individual cases of acute liver failure. On the other side, these same factors, together with portal endotoxemia due to bacterial overgrowth, chronic malnutrition and even persistent non-alcoholic steatohepatitis due to the reduced success of the bariatric procedure, can favor the onset of cases in which progressive liver damage evolves until cirrhosis.

hepatic deleterious effects, while, probably in the context of a genetic predisposition, a synergic combination of multiple hits determines the occurrence of individual cases of severe liver damage (Fig. 2).

Concerning the phenotypic expression of liver damage, there are two possible clinical presentations: a rapid evolution to liver failure, usually within 24 months from surgery (48,52,59,63-66), or the development of a sneaky chronic liver disease evolving into cirrhosis (17,33,37,39,43-46,60,61). It is likely that lipotoxicity from excessive FFA load together with protein malnutrition have a prominent role in cases of acute liver failure; while, bacterial overgrowth, toxic bile acids and, malnutrition, with possible lack of some hepatotrophic factors, are more reasonably implied in cases of chronic steatohepatitis with fibrotic evolution (85,86).

Perspectives

To date, there are no codified recommendations for the management of liver injury following bariatric procedures, although starting points for intervention can be derived from the discussed physiopathological mechanisms of damage and from some successful experiences reported in literature (36,48,56,63,65,66,87-93).

As soon as signs of liver injury emerge (e.g. aminotransferase elevation), proper protein and calorie nutrition should be guaranteed by means of enteral or parenteral feeding, and by supplementation of fat-soluble vitamins and trace elements. The importance of proteins in this setting is documented by cases of improved liver function following amino acid infusions, which either allowed safer reversal of the JIB or became the basis of oral nutritional support for patients who did not have reversal (36,87-92). Supplementation of pancreatic enzymes should be considered when severe malabsorption is sustained by diversion of biliopancreatic secretions (56). Even if bacterial overgrowth and endotoxemia are recognized causes of liver toxicity when surgery determines the exclusion of an intestinal tract from food, evidence to recommend antibiotic/intestinal decontaminating therapies in this context is almost completely lacking. Actually, the most significant experience in this sense dates back to 1982, when metronidazole treatment was reported to significantly improve hepatic steatosis in the first year after JIB (93). An approach based on cyclic treatment with metronidazole as well as rifaximin or neomycin, seems reasonable mainly if liver injury is accompanied by symptoms of dysbiosis (diarroea, meteorism, etc.). Surgery reversal is mandatory in cases of liver disease progression notwithstanding the attempts made to control it. Finally, it should be kept in mind that background NASH can paradoxically progress after surgery, when it has limited success in terms of weight loss and amelioration of associated metabolic disturbances (86).

Conclusions

Bariatric surgery is acquiring a growing role in the therapeutic management of the obesity epidemic. In the majority of cases, the liver benefits from bariatric procedures in terms of reduction of fat infiltration, of the inflammatory response and of fibrosis progression.

However, liver damage - even if rare - should be still included among the possible complications of the current bariatric procedures. The possible mechanisms leading to liver injury are lipotoxicity, malnutrition with the lack of hepatotrophic factors, and bacterial overgrowth with the consequent high hepatic endotoxin load. While awaiting a better understanding of this specific entity in order to prevent, recognize and treat it in the best possible way, the available evidences suggest that a close assessment of liver enzymes and liver function is mandatory in the first post-operatory year and should be periodically re-obtained also life-long after a bariatric procedure along with a comprehensive nutritional assessment.

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Conflict of interest

Nothing to disclose.

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