Liver decompensation after bariatric surgery in the absence of cirrhosis

METHODS

Liver decompensation

- jaundice
- ascites
- leg edema

after bariatric surgery

in the absence of cirrhosis

Clinical presentation ?

Histology and evolution ?

RESULTS

Mean age 44 years

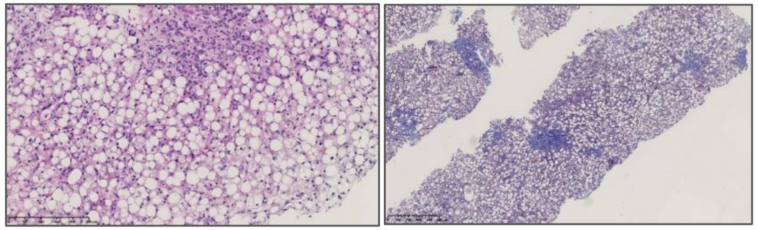
↗ AST > ALT
Cholestasis
↘ albumin

Important weight loss (-43%)

Variable delay (8 months – 17 years)

Severe steatosis

Histology



Bile duct alterations
Portal inflammation

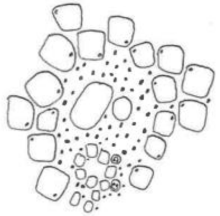
Fibrosis F1-F2

Favorable clinical course with conservative treatment and nutritional support

CONCLUSIONS

Key histological findings

Severe steatosis
Portal inflammation
Bile duct damage



Suggested mechanism

Altered liver lipid metabolism
+
inflammation

Protein depletion
Malnutrition
Muscle mass depletion

Bacterial overgrowth

Malabosrption

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Liver decompensation after bariatric surgery in the absence of cirrhosis

Shortened title: Bypass and liver decompensation

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Abstract

Purpose: Metabolic dysfunction-associated fatty liver disease related cirrhosis is possible at the time of bariatric surgery, complicated by further liver decompensation. Hepatic decompensation can also occur in the absence of cirrhosis but the presentation is less clear.

Methods: We analyze the clinical characteristics, histological findings and management of patients without cirrhosis who developed hepatic decompensation after bariatric surgery in our single tertiary-care hospital.

Results: From 2014 to 2019, 6 patients underwent a transvenous liver biopsy for liver decompensation after bariatric surgery. Mean age at diagnosis was 44 years. The time between bariatric surgery and the onset of symptoms varied widely (min. 8 months, max. 17 years). Mean % of weight loss was high at 43%. The clinical presentation was: fatigue and jaundice (5/6), leg edema (3/6) and ascites (1/6). Blood test showed increased transaminases (mean ALT 53 UI/L, mean AST 130 UI/L), bilirubin (mean 6 mg/dL) and INR (mean 1.5) with a low albumin level (mean 27 mg/dL). The hepatic venous pressure gradient was high (mean 10 mmHg). Histology revealed steatosis, hepatocyte ballooning but also portal inflammation with polymorphonuclear cells and bile duct alterations. Mean fibrosis score was 2. The clinical course was favorable with nutritional support with a mean follow-up of 36 months.

Conclusion: Liver decompensation in the absence of cirrhosis can occur after bariatric surgery with a highly variable delay. A special histological signature is present with the coexistence of steatosis, bile duct alterations and portal inflammation. Substantial clinical improvement with appropriate nutritional support seems to be effective.

Keywords: Bariatric surgery, fatty liver, liver failure, cholestasis.

Key points :

- Liver damage and decompensation can occur after bariatric surgery, even in the absence of cirrhosis.
- A special histological signature is present with the coexistence of steatosis, bile duct alterations and portal inflammation.
- Severe weight loss, protein malnutrition and bacterial overgrowth are a possible cause.
- The treatment is appropriate nutritional support.

Introduction

Obesity is on the rise and has now become one of the most prevalent source of health complications [1]. According to the latest data, in 2015 the prevalence of obesity has doubled since 1980 in more than 70 countries and has increased in most other countries worldwide. The overall prevalence of obesity among adults is 12.0% [2]. Bariatric surgery (BS) currently remains an effective treatment option of severe obesity and its complications as it can offer sustained weight loss with a rapid improvement of biological markers, diabetes, hypertension and obstructive sleep apnea [3]. Though, long term complications of BS are less known. Up to 85% of obese patients presenting for BS have different stages of steatosis, grouped under the term “metabolic dysfunction-associated fatty liver disease” (MAFLD) previously called non-alcoholic fatty liver disease (NAFLD) [4] and up to 10% of MAFLD will progress to non-alcoholic steatohepatitis (NASH) [5–7]. Preoperative liver disease, which is not always screened for, and especially if already present at the stage of decompensated cirrhosis or with portal hypertension, represents a considerable risk factor for poor outcome after BS [8,9]. Moreover alcohol disorders could be increased postoperatively in certain types of surgeries and could contribute to an increase in the number of hepatic transplants in post bypass surgery patients [10–12]. Importantly, cirrhosis can thus decompensate after BS [12,13], but liver decompensation can also occur without any underlying cirrhosis, as shown in several isolated case reports [14,15]. This complication is serious because it can lead to death, despite “rescue” transplant treatments in some cases [14–16]. However, the mode of presentation, histological results and therapeutic possibilities are poorly described. We aim to describe a case series of patients with liver decompensation after BS and no evidence of cirrhosis both at the time of BS and at the time of hepatic decompensation (histological analysis). We analyze their clinical presentation, histological features, survival and management.

Materials and methods

Study population

We retrospectively collected (December 2014 to October 2019) all cases of patients with a decompensation of hepatocellular function, without cirrhosis, in a context of previous BS and that had benefited from a transvenous liver biopsy in our single tertiary-care hospital with expertise in liver pathology. Inclusion criteria for all patients were as follow: clinical or biochemical signs of hepatocellular decompensation, medical history of BS with no sign of cirrhosis at this time. Patients with known chronic liver disease except MAFLD/NASH were excluded. Self-reported alcohol consumption was recorded but did not constitute an exclusion criteria. Other causes of acute hepatitis were excluded by adequate serological and biochemical testing. A careful drug history was taken in order to exclude potential drug-induced liver injury. All patients had a liver biopsy by one investigator using the transvenous (transjugular) route. The hepatic venous pressure gradient (HVPG) was measured, and all patients had a laboratory testing including liver function tests at time of the biopsy. Baseline demographical data and clinical presentation were recorded.

Histological work-up

Liver tissue samples from all patients were fixed using 4% buffered formalin then processed and examined on standard stainings including hematoxylin-eosin, Masson trichrome and periodic acid-Schiff (PAS) + diastase. Additional immunohistochemical stainings for keratin 7 (K7), Ki67 and CD68 were also performed, as previously described [17,18]. The evaluation of histological features was based on the scoring method used for the assessment of lesions commonly observed in NASH, consisting of the SAF score, a semiquantitative evaluation of steatosis, hepatocyte ballooning, lobular inflammatory activity and fibrosis. These lesions were graded 0: absent ; 1: scarce; 2: numerous [19]. Evaluation of fibrosis was based on the Kleiner scoring [20]. Additional histological observations included portal inflammation, cholangitis, bile duct alterations, bilirubinostasis and the presence of microvesicular steatosis. Portal inflammation and microvesicular steatosis were assessed following a semiquantitative evaluation similar to the one used in the SAF score. Careful consideration was also given to the composition of the inflammatory infiltrate, in both portal tracts and lobules. Bile duct alterations were assessed as a ratio of the bile ducts that were visibly damaged on the K7 staining to the total number of bile ducts analyzed in the tissue sample and then expressed in percentages. Cholangitis and bilirubinostasis were described as either present or absent. All biopsies were assessed by the same liver pathologist (MK) and then confirmed by a second liver pathologist (PH).

Analyses

The first part of the work aimed at describing patients' baseline characteristics. The second part was a description of all histological features observed in our patients. Clinical management including standard supportive care and the requirement for nutritional intervention were analyzed. Outcomes including the reversal of the clinical picture, mortality and need for surgical reversion of the BS were monitored. Follow-up of biochemical parameters was performed from December 2014, our first patient, till 1 December 2020. Data were expressed as mean with standard deviation or range.

Results

Case presentation

From December 2014 to October 2019, 6 patients with a medical history of BS underwent a transvenous liver biopsy for liver decompensation with no cirrhosis. There were 5 females and 1 male (Table 1). Mean age at diagnosis was 44 years and mean body mass index (BMI) was 25.1 kg/m^2. Viral and auto-immune causes of acute liver decompensation were excluded in all patients by a complete blood screening (including hepatitis E…). Genetic liver diseases were also excluded (alpha1 anti-trypsin deficiency, hemochromatosis,...). The time frame between surgery and onset of liver decompensation varied widely (min. 8 months, max. 17 years). At the time of decompensation, two patients drank no alcohol, three patients consumed alcohol occasionally and only one patient had a severe chronic alcohol abuse (60 g/day). There were no other toxics reported except for one patient who took paracetamol (6 gram per day for a few days) a few weeks before the decompensation. Interestingly, four patients described limited oral intake during the days prior to the decompensation. Unfortunately, data was lacking in the two other cases. The weight loss was very important in all cases following BS. Indeed, the mean weight loss after BS at the time of liver decompensation was 54 kg (range 31-76 kg). Mean percentage of weight loss was 43% (range 26-58%). Mean percent excess body weight loss (EBWL) was high at 98% (range 64-121%). The clinical presentation, based on anamnesis and clinical appreciation of treating doctor, was as follows: recent fatigue and jaundice in 5 patients, acute edema of the lower limbs in 3 patients, ascites in one patient and mildly altered coagulation in all patients. Blood tests showed an increase in transaminases (mean ALT 53 UI/L ± 25, mean AST 130 UI/L ± 92), bilirubin (mean 6 mg/dL ± 5) and INR (mean 1.5 ± 0.3) with a low albumin level (mean 27 mg/dL ± 6). All the data on the whole group is included in the table 1 and individual data are listed in the table 2.

Bariatric surgery data

Four patients had a Roux-en-Y gastric bypass (RYGB), one had a biliopancreatic diversion according to Scopinaro and one patient had a distal gastric bypass (Table 2). At the time of BS, the mean age was 39 years (range 31-51), all patients were severely obese (mean body mass index 45 kg/m^2 ± 6). None of the patients were diabetic at time of the surgery, 3 patients had arterial hypertension and only two patients had dyslipidemia.

There was no evidence of cirrhosis according to the FIB-4 score prior to the bariatric surgery in 4 of the 6 patients (FIB-4 score < 1.3). In 2 patients biological analyses were not available prior to the BS. Only 2 patients had a recent hepatic ultrasound done before the intervention that showed steatosis in one of them. There was no liver biopsy performed prior or during BS.

Histological findings

Hepatic venous pressure gradient (HVPG) was high (mean 10 mmHg ± 4) (Table 1). Liver specimens were obtained and deemed adequate in all patients with a mean size of 48 mm (± 21 mm) and a mean number of 29 portal tracts (± 14). This allows an accurate histological analysis. Histology revealed massive steatosis with a mean percentage of fat-loaded hepatocytes of 73% (± 17) (Table 1). Severe, predominantly macrovesicular steatosis was present in 5 patients and moderate steatosis in 1 patient (Table 3 and Figure 1a). Microvesicular steatosis was present in 4 patients (Table 3 and Figure 2a). All patients showed hepatocyte ballooning (Table 3 and Figure 2a), associated with various amounts of Mallory-Denk bodies. Both portal inflammation, with a predominance of polymorphonuclear cells (neutrophils), and lobular inflammation were present in all patients (Table 3 and Figure 1a-2a). Interestingly, histological analysis and keratin 7 staining revealed bile duct damage and a variable degree of cholestasis in all patients (Figure 1b) with a mean percentage of damaged bile ducts (on total bile ducts) of 50% (± 23) (Table 1). Active cholangitis was observed in 2 cases (Table 3 and Figure 1a-2a). All cases also featured numerous macrophages, with cluster formation, highlighted by the CD68 staining (Figure 2b). Some of the macrophages showed ceroid inclusions in their cytoplasm. PAS + diastase staining confirmed the presence of those ceroid macrophages in all patients, in various amounts (not shown). The mean hepatocyte Ki67 index was 5,7% (Table 3). Proliferation (Ki67 positivity) was also evidenced in proliferating bile duct cells (K7 positive) as well as in inflammatory cells infiltrating the portal tracts (Figure 1d). However, only the hepatocyte Ki67 positivity was taken into consideration in the count of the hepatocyte cellular proliferation rate shown in Table 3. Median fibrosis score (Kleiner classification) was 2 (Table 1) with no patient scoring F3-4 (Table 3, Figure 1c-3c). There was no other cause of acute liver injury. Histology of the patient who took high doses of paracetamol in the past did not show any evidence suggestive of paracetamol toxicity. Neither satellitosis nor other more specific features of alcoholic liver disease (ALD) were found in the patient with alcohol abuse.

Patients' management and follow-up

Due to the prominent malnutrition among the patients and the presence of a severe liver disease, nutritional treatment was started in all patients [21]. Two patients were treated with parenteral nutrition only, three patients had parenteral and enteral feeding and one patient had only oral supplements. The two patients with ancient BS (biliopancreatic diversion according to Scopinaro and distal gastric bypass) needed home parenteral nutrition for several months. All patients were supplemented with oral or intravenous vitamin B1. Three patients had diuretics and two patients had intravenous albumin supplementation. All patients are alive and none of them evolved to hepatic failure, nor needed a surgical bypass reversal, with a median follow-up of 38 months. Biochemical reversal was observed in 3 patients and improvement in 3 patients.

Discussion

We report a case series of 6 patients with a medical history of BS that presented a liver decompensation with elevated bilirubin levels and signs of fluid retention, a picture quite comparable to decompensated cirrhosis. However, these patients had neither cirrhosis nor advanced fibrosis on histological analysis. Liver decompensation after BS can occur in patients with a known cirrhosis prior to bariatric surgery [8], with an unknown cirrhosis [16] and importantly, it can also occur in patients without cirrhosis. Cases were described after ileojejunal bypass [22],[23], biliopancreatic diversion according to Scopinaro, distal bypasses [16] ,[14] as well as after RYGB including also patients without cirrhosis [13]. As described in the literature, time to decompensation varies widely till 21 years [16] and could be influenced by alcohol consumption prior or after the surgery. King et al. in their study of 2348 patients post BS, showed a twice as high relative risk in patients using alcohol post RYGB [10]. Recently, Lefere et al. compared alcoholic liver decompensation in patients with previous BS and showed that those patients have more severe and rapid decompensations [11]. Mendoza's data are in the same direction: in a series of 17 patients, decompensation was associated with alcohol ingestion in ten patients (59%) [12]. In our series alcohol abuse was not a precipitating factor but data is lacking concerning a potential pre-existing MAFLD/NAFLD prior to surgery or the decompensation episode. Unfortunately, there was no liver biopsy performed prior or during BS. A common feature of our patients, however, is the significant weight loss observed after surgery. Typically, RYGB results in loss of 75% of excess weight [24–26] whereas in our cohort the EBWL% was higher (98%). The advantage of our case series is the number of patients for whom we describe the histological features associated with decompensation. In addition, follow-up reached at least one year after the decompensation with the longest one being 6 years.

Elementary features usually present in “classical NASH” as steatosis, lobular inflammation, hepatocellular ballooning and fibrosis [19] are present in all our patients. Microvesicular steatosis, that seems to be associated with more severe NASH [27,28] is also present in most of our samples**.** Differences with “classical NASH” are the presence of portal inflammation with predominantly polymorphonuclear cells instead of mononuclear cells [29], cholestasis and bile duct alterations. This insinuates that MAFLD does not seems to be the sole cause of the liver injury. Those bile duct alterations are also described in similar cases of liver decompensations after BS [14,15,30,31]. There are no specific feature to explain the cause or the mechanism but the resemblance with the histological abnormalities present in the case of intestinal failure associated liver disease with presence of cholestasis and biliary damage is striking [32,33].

The pathophysiology of liver injury, based on literature, biological and histological aspects, seems thus to be multifactorial (Figure 3). First, protein depletion and malnutrition (with a consequence muscle mass depletion) can still exist after malabsorptive BS and can be associated with liver decompensation. Indeed, the deleterious role of sarcopenia on liver disease (certainly at the stage of cirrhosis but probably already earlier) is clearly described [34]. Acute diminished oral intake can also promote the onset of liver decompensation as important reduced oral intake was described in most of our patients as well as two patients presented by Lammers and Mocanu [35,36] and in a recent case–series highlighting sarcopenia as a potential risk factor [12]. The pattern of transaminases abnormalities seen in our study population reinforces this hypothesis with predominant increase in AST levels compared to ALT (Table 1 and Table 2) which could represent an indirect marker of muscle damage, in addition to liver damage. As shown in experimental studies, cachexia induces major metabolic disruption, inflammation, fat and lean mass loss with impairment of hepatic lipid metabolism [37]. The rapid and massive weight loss of all our patients as well as the benefit of our intensive nutritional treatment argues in favor of this hypothesis. Secondarily, bacterial overgrowth in the blind loop also seems to play a role [16,38] as it can provoke inflammation of the mucosa and alteration of its permeability. Increased permeability can favor bacterial endotoxins passing into the portal circulation and subsequently cause liver damage. It could explain the presence of portal inflammation with polymorphonuclear neutrophils as in obstructive cholestasis. Interestingly, data from recent research indicates that gut endotoxin induces cholangiocytes to produce cytokines, which attract neutrophils [39]. Third, chronic malabsorption of micro and macro nutrients, amino acids but also vitamins and trace elements might lead to an increase in oxidative stress as well as a decreased anti-oxidative capacity via free fatty acids accumulation and peroxidation [38]. Finally, we cannot exclude the presence of an external trigger (such as infection, paracetamol toxicity, acute intake of alcoholic beverages or other toxic substances) on a fragile patient with preexisting chronic liver disease (due to MAFLD) (Figure 3). A more precise analysis of the protein synthesis pathways, the pathways leading to steatosis and oxidative stress on biopsies will be necessary to progress in the understanding of this alarming complication.

Different cases in currently available literature describe severe liver failure leading to death or the need of transplantation with various outcomes [16]. None of our patients evolved to liver failure, nor death.

Appropriate nutrition (enteral or parenteral) is recommended in cases of chronic decompensated liver disease [21]. Its benefit is more questionable in cases of severe advanced cirrhosis, particularly in the context of alcoholic steatohepatitis, but it remains under study [40]. We believe that liver function can recover in patients without cirrhosis, if patients are nourished soon enough via intravenous or enteral tube supplementation. Albumin supplements given to our patients can also play a beneficial role. Indeed, we also now know that albumin, in addition to its oncotic power, also has non-oncotic properties and is able to counteract a sustained systemic inflammatory and pro-oxidant state deriving for example by an abnormal bacterial gut translocation [41].

In conclusion, liver decompensation in the absence of cirrhosis is possible after BS with a highly variable delay. We must therefore be vigilant in the face of significant weight loss, sarcopenia, hypoalbuminemia and the appearance of a disturbance in liver enzymology (relatively typical in our cases and characterized by cholestasis and an elevation of AST above ALT). Hepatic injury is characterized histologically by a unique feature of steatohepatitis with bile duct alterations and neutrophil infiltration. The precise mechanism remains unknown. Severe protein malnutrition combined with bacterial overgrowth are possible candidates. Substantial clinical improvement with nutritional support including parenteral nutrition, intravenous albumin and diuretics seems to be effective. It has been well accepted that liver function follow-up is important in high-risk groups after BS, such as patients with cirrhosis, those undergoing extended limb/distal RYGB, patients with new illnesses, those abusing alcohol, those on hepatotoxic drugs and those presenting with a surgical complication [13]. Our data clearly indicate that even in the absence of cirrhosis, liver complications can occur, but are reversible (and could probably be prevented) with appropriate nutritional management.

Conflict of interest disclosure statement: All the authors (Perrine Vande Berg, Artida Ulaj, Graziella de Broqueville, Marie de Vos, Bénédicte Delire, Philippe Hainaut, Jean-Paul Thissen, Peter Stärkel, Mina Komuta, Paulina Henry and Nicolas Lanthier) declare that they have no conflict of interest regarding this study.

Statements regarding ethics and consent:

The study was approved by the ethical committee (Commission d'éthique hospitalo-facultaire, Cliniques universitaires Saint-Luc, UCLouvain) with the following reference 2016/16MAR/129. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of retrospective study formal consent was not required.

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Tables

Table 1: Summary of results of the entire study group.

Clinical data	
Gender (n)	5 females / 1 male
Age at decompensation (years)	44 ± 10
Timing to decompensation (months after BS)	65 ± 73
Weight loss following BS (kg)	54 ± 19
Weight loss (%)	43 ± 13
Excess body weight loss (%)	98 ± 21
Biological data	
AST / ALT (IU/L)	130 ± 92 / 53 ± 25
GGT / ALP / bilirubin (IU/L, mg/dL)	258 ± 256 / 212 ± 130 / 6 ± 5
Transvenous liver biopsy data	
HVPG (mmHg)	10 ± 4
Steatosis (%)	73 ± 17
Fibrosis (score)	2 ± 1
Bile duct damage (%)	50 ± 23

Results are given as mean values with standard deviations.

Abbreviations: BS: bariatric surgery, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; HVPG: hepatic venous pressure gradient.

Table 2: Individual clinical presentation.

N°	Gender	Age	Type of surgery	Timing (months) between surgery and symptoms	Symptoms	Liver enzymes (IU/L)	Liver function tests
1	F	39	Roux-en-Y	60	Ascites, jaundice, leg edema	AST 87, ALT 31 GGT 141, ALP 131	Bilirubin 12 mg/dL INR 1.5 Albumin 23 g/L
2	F	46	Roux-en-Y	8	Scleral icterus	AST 70, ALT 40 GGT 177, ALP 259	Bilirubin 2 mg/dL INR 2.0 Albumin 36 g/L
3	F	34	Roux-en-Y	36	Jaundice	AST 243, ALT 75 GGT 772, ALP 171	Bilirubin 14 mg/dL INR 1.6 Albumin 22 g/L
4	M	57	Distal by pass	72	Leg edema	AST 75, ALT 53 GGT 207, ALP 145	Bilirubin 1.8 mg/dL INR 1.2 Albumin 31 g/L
5	F	33	Roux-en-Y	12	Jaundice	AST 51, ALT 27 GGT 74, ALP 109	Bilirubin 2.6 mg/dL INR 1.3 Albumin 22 g/L
6	F	55	Scopinaro	204	Jaundice, leg edema	AST 251, ALT 90 GGT 166, ALP 454	Bilirubin 4.9 mg/dL INR 1.3 Albumin 25 g/L

Abbreviations: AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; INR: international normalized ratio.

Table 3: Indiviudual histological evaluation.

N°	HVPG (mmHg)	Number of portal tracts	Steatosis (S) Ballooning (Bal) Microvesicular steatosis (Mi) (grade)	Lobular inflammation (grade)	Fibrosis level (stage)	Portal inflammation (grade)	Biliary damage (%)	Hepatocyte Ki67 (%)
1	16	34	S3 Bal 2 Mi 1	1	F2	2	55	5.4
2	6	23	S3 Bal 1 Mi 0	2	F1	1	30	0.9
3	18	12	S3 Bal 1 Mi 1	1	F2	1	73	1.9
4	7	19	S2 Bal 1 Mi 0	1	F2	1	43	9.4
5	11	39	S3 Bal 2 Mi 1	2	F2	2	20	1.8
6	8	49	S3 Bal 2 Mi 1	1	F1	2	76	14.9

Abbreviations: HVPG: hepatic venous pressure gradient.

Figures legends

Figure 1: General histological findings.

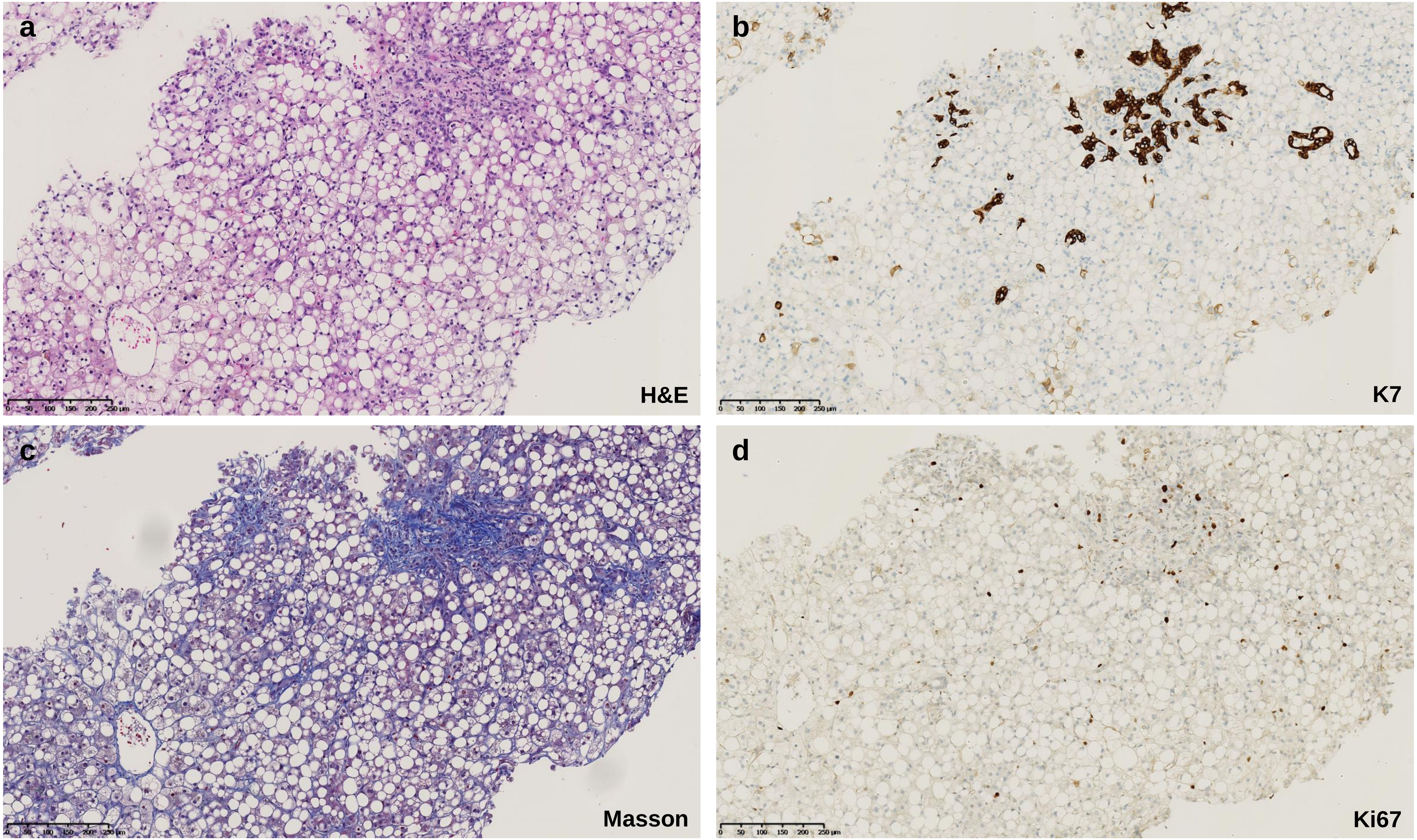
Hematoxylin and eosin (H&E) staining showing macrovesicular steatosis along with both portal and lobular inflammation (A). Bile duct damage accompanied by canalicular proliferation is emphasized by keratin 7 (K7) immunohistochemical staining (B). Masson's trichrome staining revealing no severe fibrosis, with only mild periportal and pericellular fibrosis (C). Ki67 immunostaining showing some nuclear positivity in canalicular cells, inflammatory cells and hepatocytes (D).

Figure 2: Specific histological features.

Higher magnification on hematoxylin and eosin (H&E) staining evidencing polymorphonuclear cell (PMN) within the portal tract (PT), hepatocyte ballooning (Bal) and microvesicular steatosis (Mi) (A). Numerous macrophages, with cluster formation, highlighted by the CD68 staining (B). Masson's trichrome staining at lower magnification showing no severe fibrosis and no significant architectural alteration of the liver parenchyma (C).

Figure 3: Pictorial representation of potential causes of liver damage.

Pathophysiology seems to be multifactorial based on clinical, biological and histological data. This figure was partly created using Servier Medical Art templates, https://smart.servier.com.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H&E
0 50 100 150 200 250 µm
b
K7
0 50 100 150 200 250 µm
c
Masson
0 50 100 150 200 250 µm
d
Ki67
0 50 100 150 200 250 µm

Figure 1

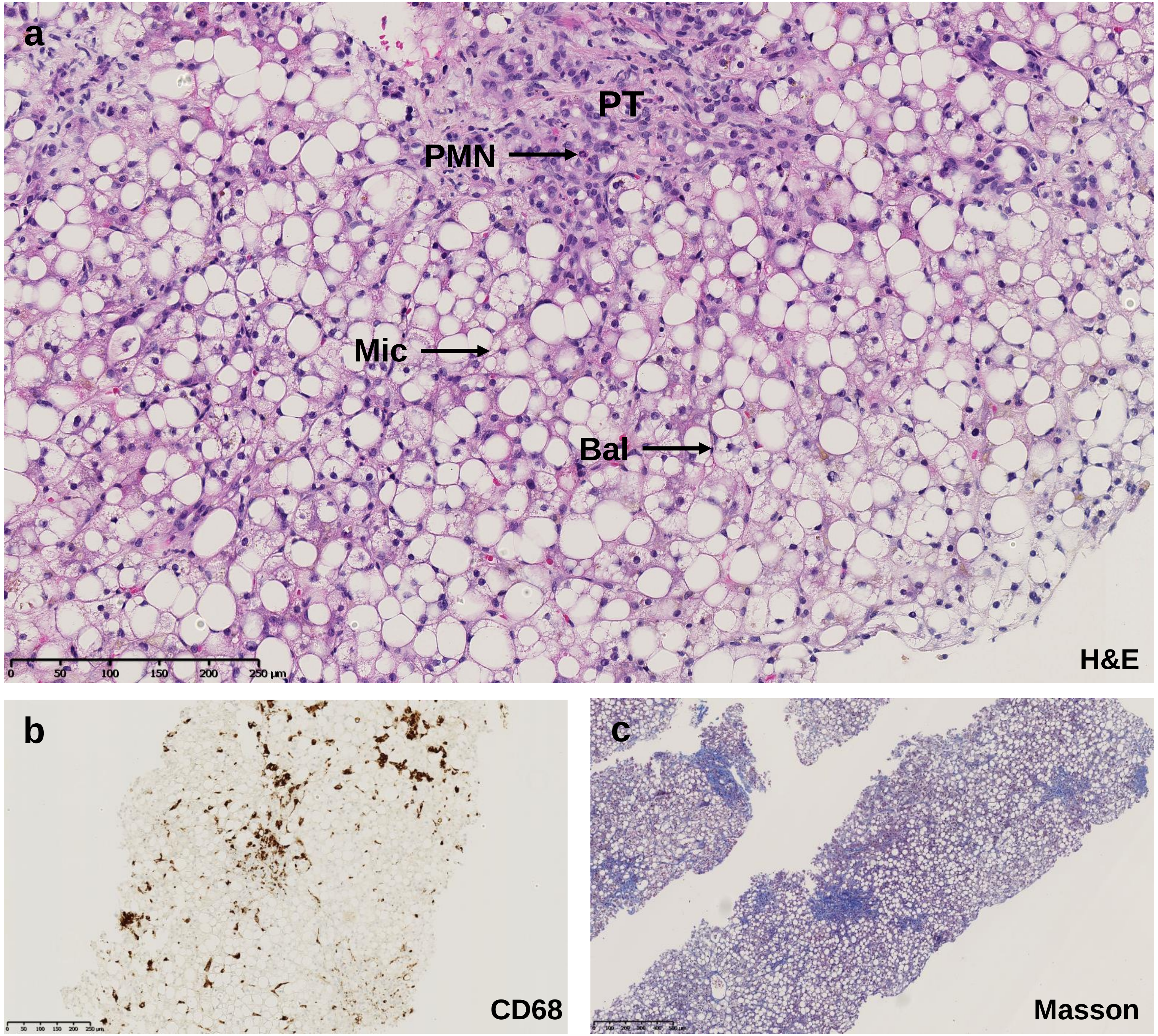
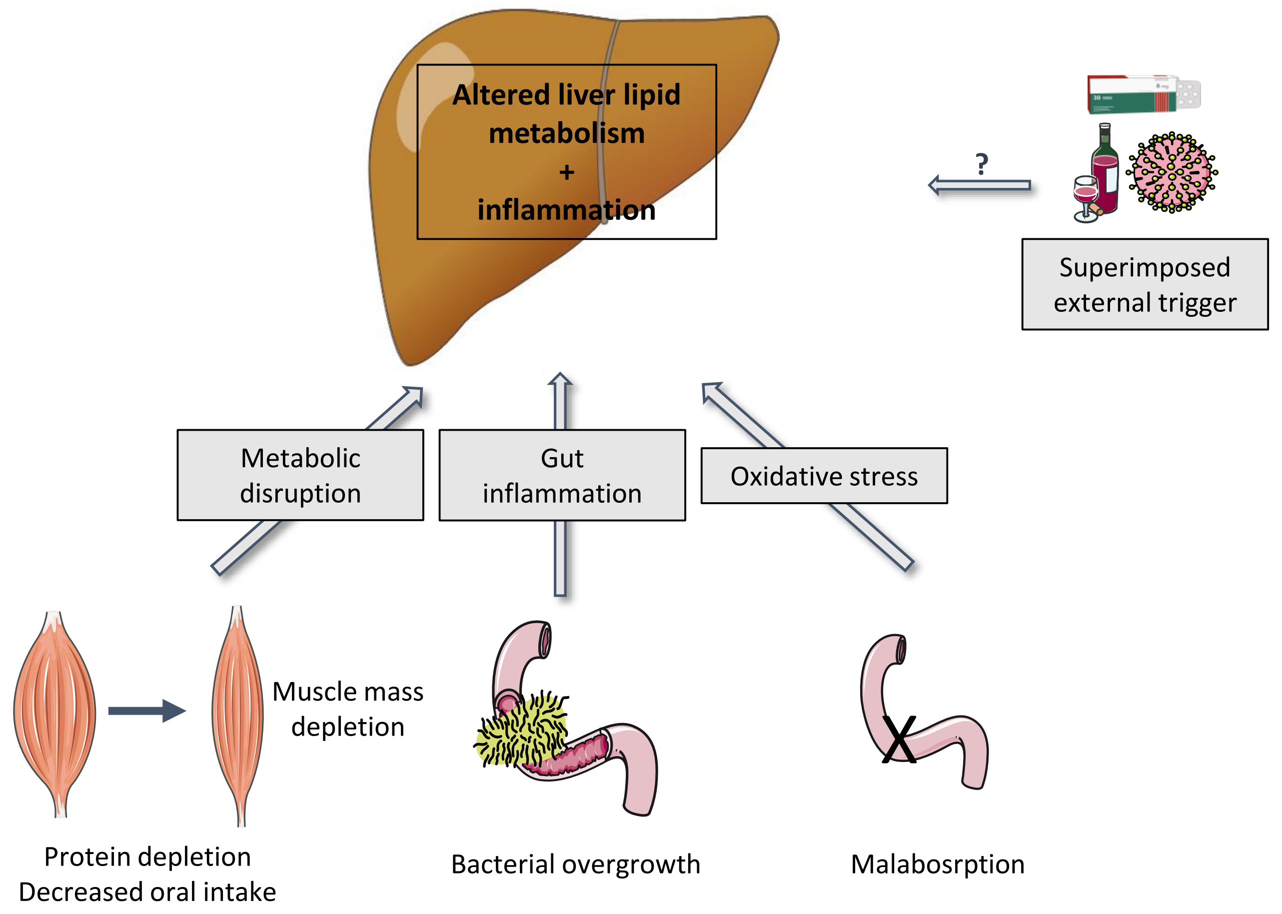


Figure 2



Altered liver lipid metabolism
+
inflammation
?
Superimposed external trigger
Metabolic disruption
Gut inflammation
Oxidative stress
Muscle mass depletion
Protein depletion
Decreased oral intake
Bacterial overgrowth
Malabosrption

Figure 3