Are elevated systemic bile acids involved in the pathophysiology of sarcopenia and liver injury following gastric bypass?

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Abstract

Bariatric surgery is currently the most effective treatment for sustained weight loss in severe obesity. However, recent data describe the development of liver damage and in particular massive steatosis and cholangitis in some patients, for which certain pathophysiological mechanisms are suggested such as bacterial overgrowth, malabsorption or sarcopenia. We describe the case of a patient presenting with a new liver dysfunction 6 years after a gastric bypass. The work-up revealed sarcopenic obesity characterised by low muscle mass and low muscle function as well as elevated fasting bile acids, severe liver steatosis and cholangitis. The pathophysiology of this disease is complex and multifactorial but could include bile acid toxicity. Bile acids are increased in cases of liver steatosis, but also in cases of gastric bypass and malnutrition. In our opinion, they may contribute to the loss of muscle mass and the vicious circle observed in this situation. Treatment with enteral feeding, intravenous albumin supplementation and diuretics reversed the liver dysfunction and the patient was discharged from hospital. (Acta gastroenterol. belg., **2023,** 86, **377-381**).

Keywords: Cholestasis, biopsy, gastric bypass, malnutrition, liver failure, sarcopenia.

Introduction

Obesity is a growing health concern, where associated complications such as cardiovascular disease, type 2 diabetes mellitus and metabolic dysfunction-associated fatty liver disease (MAFLD) pose major health care challenges worldwide (1). Bariatric surgery is currently the most effective treatment for sustained weight loss, also providing improved glycemic control better than conventional weight-loss therapies. However, with the rising use of bariatric surgery, there is also greater awareness of its complications, such as the development of liver injury for a subset of patients (2-4). A large proportion of patients presenting for bariatric surgery procedures have varying stages of steatosis and MAFLD (5). The weight loss accomplished with bariatric surgery carries beneficial effects on these hepatic complications and leads to notable improvements in hepatic steatosis and fibrosis (5,6). Unfortunately, complex interactions including malnutrition, altered enterohepatic metabolism, and potential external triggers can lead to liver injury and liver decompensation in a subset of patients (2-4). Problems related to the alcohol consumption are also described (7,8). We present a case report of a patient presenting with new onset hepatic dysfunction 6 years after gastric bypass. Treatment with enteral feeding, intravenous albumin supplementation, vitamins, diuretics and alcohol cessation reversed the hepatic dysfunction and the patient was able to leave the hospital.

Case history

We received a request for a consultation regarding jaundice of unclear origin in a 43-year-old female patient. She was admitted to the emergency department in another institution for general deterioration, asthenia, jaundice and edema of the lower limbs. The patient declared a frequent alcohol consumption, up to 60 g/day. The patient had undergone gastric bypass surgery with cholecystectomy performed 6 years earlier, which resulted in the loss of 40 kg in three years (namely a weight loss percentage of 37% and an excess body weight loss percentage of 80%). The patient had a history of arterial hypertension, hypothyroidism, and a carcinoma of the left breast currently in remission. Her treatment consisted of aripiprazole, indapamide, furosemide, levothyroxine, Iron (II), tamoxifen, pantoprazole, and quetiapine. The patient declared not taking the vitamin supplements prescribed following bariatric surgery. The clinical examination revealed diffuse abdominal tenderness and bilateral edemas of the lower limbs. The patient weighted 94 kg and is 1.54 m tall, with a BMI of 39.6. Biochemical analysis revealed macrocytic anemia (Hb 11.3 g/dL, MCV 109 fl), with platelets, white blood cell counts and renal function all within normal limits. INR was 1.3 (normal 0.8-1.2). The ionogram showed hyponatremia at 131 mmol/L (normal 135-145 mmol/L) and hypokalemia at 2.3 mmol/L (normal 3.5-5 mmol/L). Inflammatory marker C-reactive protein (CRP) levels were high at 22 mg/L (normal < 5 mg/L). The liver tests showed a mixed alteration with cholestasis: total bilirubin 5.9 mg/dL (normal < 1 mg/dL), alkaline phosphatases 363 U/L (normal < 104 U/L), gamma-GT 940 U/L (normal < 32 U/L) and elevated transaminases: AST 168

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U/L (normal < 31 U/L), ALT 100 U/L (normal < 31 U/L). Lipasemia was normal. Albumin level was low at 23 g/L (normal 35-52 g/L) and ethanol level was less than 0.1 g/L. Urine analysis showed no urinary tract infection. During the hospitalization, the biological evolution was marked by a progressive rise in bilirubin reaching values up to 14 mg/dL at week 3 of follow-up. Abdominal ultrasound and abdominal magnetic resonance imaging showed hepatomegaly with hepatic steatosis without lithiasis or dilatation of the intra- and extra-hepatic bile ducts. The spleen was normal in size. An abdominal computed tomography (CT) scan performed after injection of contrast medium confirmed these findings as well as the presence of a small amount of ascites in the pelvis. Numerous examinations were then carried out in the absence of any explanation for the clinico-biological picture presented by the patient (coproculture, gastroscopy, ileocolonoscopy, thoracic radiography, bone scan and positron emission tomography (PET) scan) that did not reveal any anomaly. In view of this significant jaundice, the patient's case was reported to us to ask for a consultation and the possible indication of a transvenous liver biopsy.

In view of this jaundice associated with oedema of the lower limbs in a patient who had undergone a gastric bypass operation and was at risk of malnutrition, we suggested the diagnosis of massive steatosis and liver insufficiency secondary to the bypass, following the occurrence of similar cases (2). The patient was transferred to our institution for a transvenous biopsy. We completed the clinical examination by measuring handgrip strength, blood test by measuring fasting bile acids and measured the muscle area using CT scan. The values obtained in the handgrip test were very low: 12 kilos (right arm, normal 31.9 kilos) and 9 kilos (left arm, normal 28.3 kilos). Fasting bile acids were increased to 288 µmol/L (normal < 10 µmol/L). Measured on a previously performed CT-scan section on the third lumbar level (Fig. 1A), the muscle area was calculated (Fig. 1B). Skeletal muscle index was 33.6 cm^2/m^2 which corresponds to low muscle mass (cut-off < 41 cm^2/m^2) (9) (Fig. 1B). To confirm the diagnosis, to rule out alcoholic steatohepatitis and establish the degree of fibrosis with certainty, a liver biopsy by transvenous route was performed. The hepatic venous pressure gradient was high at 16 mmHg (normal < 4 mmHg). The biopsy measured 6 centimeters and included 9 portal tracts. Pathological analysis showed hepatocyte ballooning associated with severe macrovacuolar steatosis and a discrete lobular inflammatory infiltrate, without lobular neutrophil infiltration or satellitosis (Fig. 2A-B). No Mallory Denk body has been identified. In the portal tracts, there was a discrete inflammatory infiltrate that locally invaded the epithelium of the bile ducts (Figure 2B). The degree of fibrosis was F3 (Fig. 2C). Immunohistochemical staining for cytokeratin 7 (CK7) shows biliary duct proliferation (Fig. 2E) and some biliary damage (Fig. 2F). This histological picture was compatible with steatohepatitis and active cholangitis. Treatment with enteral feeding, intravenous albumin supplementation, vitamins, and diuretics was recommended and initiated as well as instructions of complete long-term alcohol cessation. The evolution after one week of treatment was marked by a regression of bilirubin to 11 mg/dL. Alkaline phosphatases were rapidly normalized (90 U/L) as well as ALT (34 U/L). The patient was able to leave the hospital. Six weeks later, the biochemical evolution was still favorable: bilirubin at 3.7 mg/dL with regression in other liver tests.

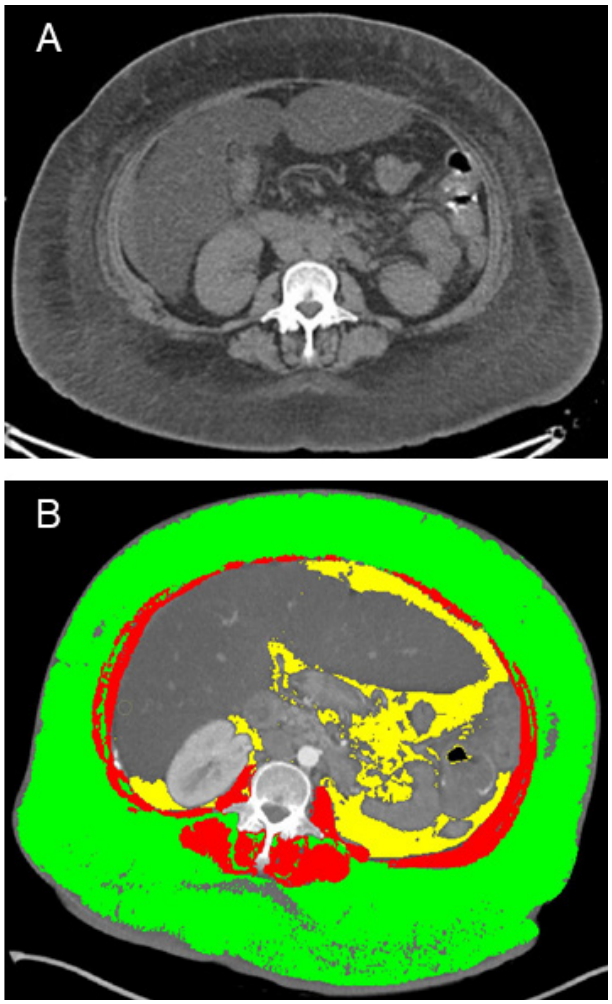

Figure 1. — Body composition evaluation using computed tomography image used for the muscularity and adiposity assessment (A). Representative picture of the subcutaneous adipose tissue and the visceral fat are evidenced in green and yellow respectively at the third lumbar level, while the muscle area appears in red (B).

Discussion

Liver decompensation after bariatric surgery without underlying cirrhosis is a poorly known entity but well described in several isolated case series for many years (10,11). A recent case report describes a recurrent steatohepatitis after liver transplantation in a patient with Roux-en-Y gastric-by-pass requiring emergency

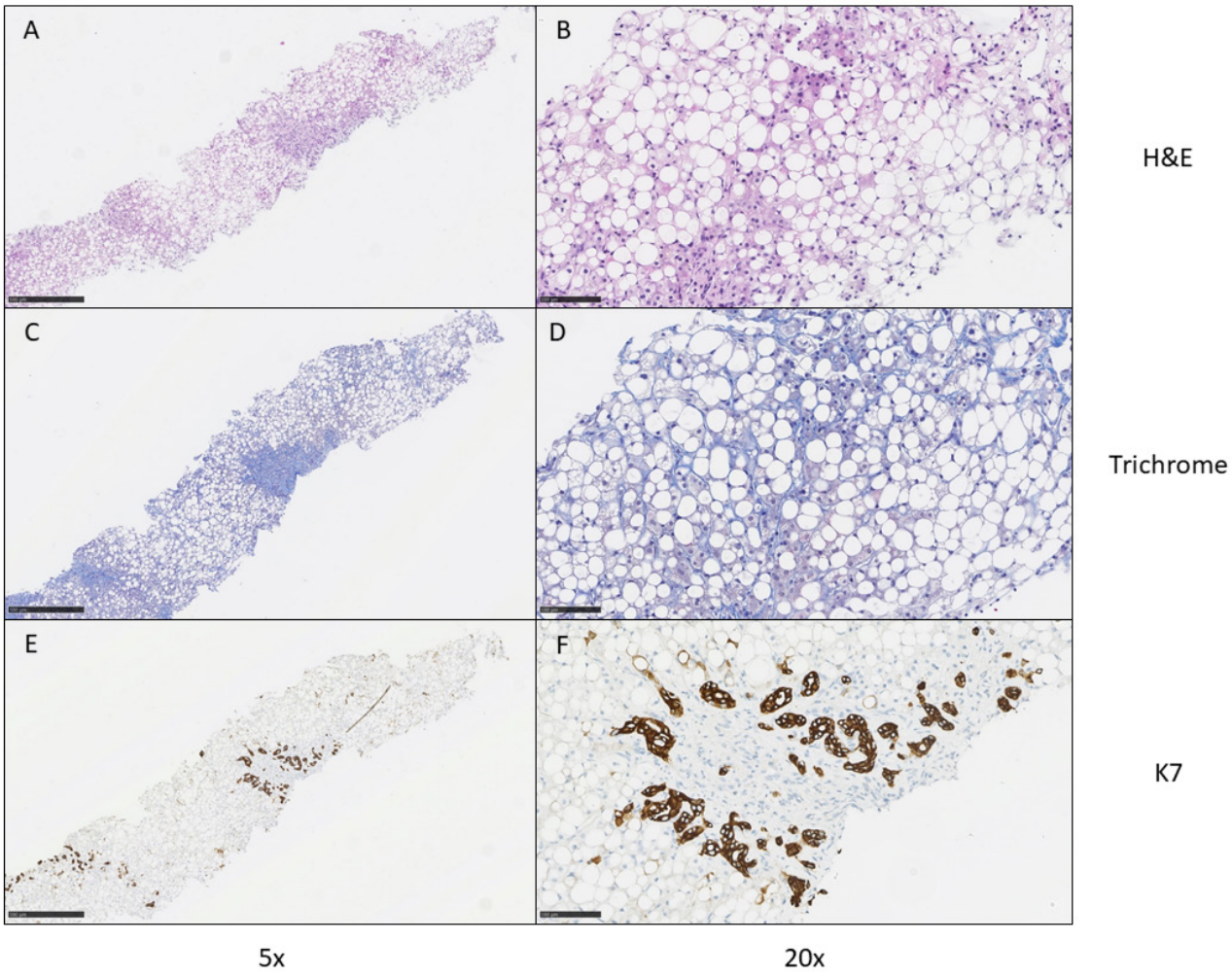

Figure 2. — Hematoxylin and eosin (H&E) staining showing macrovesicular steatosis (A) along with both discrete portal and lobular inflammation (B). Masson's trichrome staining revealing portal fibrosis with initial formation of septa (C) and pericellular fibrosis (D). Bile duct proliferation (E) and some biliary damage (F) emphasized by keratin 7 (K7) immunohistochemical staining.

bariatric surgery reversal to rescue the transplanted liver (12). Another recent publication of our group reports six similar cases of liver decompensation occurring within a very variable time frame (from 8 months to 17 years) after bariatric surgery, in patients without underlying cirrhosis (maximum F2 degree of fibrosis at biopsy) (2). The evolution of all patients was favorable after nutritional support and administration of intravenous albumin (2). Another recent case series reports three cases of acute liver injury and acute liver failure caused by bariatric surgery that required different management, including surgery reversal (in 2 cases) or liver transplantation (in one case) (3). Several mechanisms have been proposed to induce acute liver injury and acute liver failure caused in these patients following bariatric surgery, including protein-energy malnutrition, lipolysis and lipotoxicity, dysbiosis and compromised intestinal barrier function (2,13). Additional or superimposed external trigger may also play a role such as hepatotoxic medication, viral infection or alcohol, the latter being well described as a risk factor in the post-obesity surgery period (4,7,8).

In this case report, we observed the absence of vitamin intake and dietary monitoring following bariatric surgery. One of the mechanisms incriminated in the pathophysiology of this hepatic decompensation is the important rapid weight loss with protein depletion and nutritional deficiencies leading to muscle wasting resulting in sarcopenia. The latter is then responsible for metabolic disturbances with alterations in hepatic lipid metabolism. Importantly, this malnutrition occurs in people with obesity. Indeed, our patient meets the criteria of sarcopenic obesity according to the ESPEN (European Society for Clinical Nutrition and Metabolism) and EASO (European Association for the Study of Obesity) definition. In our case report, other elements may be incriminated in the occurrence of hepatic decompensation, in particular high alcohol consumption and chronic intake of tamoxifen, which is known to be involved in the occurrence of alcoholic steatohepatitis and non-alcoholic steatohepatitis. Indeed, the clinical presentation corresponds to the clinical diagnosis of alcoholic hepatitis (AH) (14,15), warranting a liver

biopsy for differential diagnosis (16). Here however, the anatomopathological analysis of the liver biopsy did not identify lobular neutrophil infiltration or satellitosis, thus excluding a diagnosis of alcoholic steatohepatitis (ASH) (14,15). There was also no Mallory-Denk bodies (14). This also argues against classical alcohol related liver disease (ALD), despite the potentially suggestive clinical presentation and the risk factors described (4,7,8). Finally, the histology revealed cholangitis, already described as a classical feature of malnutrition associated liver injury (2).

Concerning the pathophysiology of multifactorial origin (sarcopenia, bacterial pullulation, malabsorption, alcohol) (2,13), we would like to add a complementary hypothesis : the toxicity of bile acids. In cholestatic liver diseases, there is an increase in deoxycholic acid and cholic acid (17). Recent work showed that these two bile acids induce skeletal muscle atrophy through the Takeda G protein-coupled receptor 5 (TGR5) (17). Moreover, the existence of alterations in bile acid concentration, metabolism and hepatobiliary secretion has already been demonstrated in the context of gastric bypass (18), ALD (19), MAFLD (20) and systemic inflammation such as cancer cachexia (21). Those changes in the enterohepatic metabolism have therefore been considered as playing important roles in the potent metabolic effects of bariatric surgery (22,23). Here, the important elevation of fasted circulating bile acids reinforces this hypothesis. The level (288 µmol/L) is indeed much higher than the usual increase described after bariatric surgery (~9 µmol/L) (18) or in cases of alcoholic hepatitis (~140 µmol/L) (19). We can therefore suggest a chronological sequence starting with variable increase in circulating bile acids and skeletal muscle wasting secondary to malnutrition leading to the secretion of pro-inflammatory mediators, which then leads to cholangitis, exaggerated elevated bile acids and an additional toxicity of these on the muscle. Finally, this case report illustrates the importance of identifying this clinical presentation and potential complication of bariatric surgery. Reaching rapid diagnosis in similar cases will avoid unnecessary examinations, prolonged hospitalization with deleterious fasting periods, and allows for the initiation of rapid nutritional support.

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Conflict of interest

The authors declare that they have no conflict of interest.

Written informed consent

The patient agreed to the reporting of this case and gave her consent by signing a written informed consent form.

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