Liver health and the interplay between obesity, alcohol and bariatric surgery

A. Geerts[1,2], L. Onghena[2,3], S. Lefere[1,2]

(1) Hepatology Research Unit, Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium; (2) Liver Research Center Ghent, Ghent University, Ghent University Hospital, Ghent, Belgium; (3) Gastrointestinal Surgery, Department of Human Structure and Repair, Ghent University, Ghent, Belgium.

Abstract

The prevalence of obesity and metabolic consequences, including non-alcoholic fatty liver disease (NAFLD) has become a global health problem. Obesity has an important impact on chronic liver disease even beyond NAFLD, as it accelerates the progression of alcohol liver disease. Conversely, even moderate alcohol use can affect NAFLD disease severity. Weight loss is the gold standard treatment but adherence to lifestyle changes is very low in the clinical setting. Bariatric surgery can improve metabolic components and cause long-term weight loss. Therefore, bariatric surgery could serve as an attractive treatment option for NAFLD patients. A pitfall is the use of alcohol after bariatric surgery. This short review integrates data about the influence of obesity and alcohol on liver function and the role of bariatric surgery. (Acta gastroenterol. belg., **2023,** 86, **313-317**.

Keywords: NAFLD, NASH, bariatric surgery, liver failure, alcohol, obesity.

Introduction

The global prevalence of obesity has become a public health issue (1). The obesity epidemic led to a significant increase in cases of non-alcoholic fatty liver disease (NAFLD), which can progress to non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis and eventually hepatocellular carcinoma (HCC). However, obesity is also an independent risk factor for developing liver fibrosis in other chronic liver diseases (2). In this short review we will briefly describe the impact of obesity on liver function in chronic liver disease, potential benefit of bariatric surgery and the impact of synergy of alcohol and obesity on liver function.

Obesity and progression of chronic liver disease

Obesity is a strong predictor of decompensation in patients with compensated cirrhosis of various etiologies, independent of other predictors such as disease etiology, albumin or portal hypertension. Berzigotti et al evaluated the role of obesity in the development of clinical decompensation in compensated cirrhotic patients. Patients who were obese and overweight at baseline developed liver decompensation at a significantly higher rate than patients with normal weight. One the underlying pathophysiological mechanism is the deleterious role of the visceral adipose tissue. The production of adipokines such as leptin, IL-1 and TNF-alfa may worsen the intrahepatic resistance and portal hypertension (3).

Obesity was also shown to be an independent risk factor for pre-transplant development of portal vein thrombosis, probably due to the existence of a proinflammatory and prothrombotic environment in obese patients (4). Furthermore, obesity is independently associated with infection in hospitalized patients with end-stage liver disease (5). In a US cohort of more than 100.000 patients, Sundaram et al studied the relationship between infection and obesity. Infection was most prevalent among obesity class III followed by obesity class I-II and non-obese patients, diagnosed respectively in 44%, 38.9% and 31.9%. Obese individuals had a significantly higher prevalence of bacteremia, urinary tract infection and skin/soft tissue infection as compared to non-obese patients. The same authors also showed that obesity class III is an independent risk factor for acute-on-chronic liver failure at the time of listing for transplantation (6). Regarding specific organ failures, patients with obesity class I to III had a greater prevalence of renal failure.

Beyond the repercussions of obesity in advanced chronic liver diseases of other etiologies, NASH is the fastest growing cause of HCC in liver transplant candidates. Data from the US liver transplant registry showed that the number of HCC developing on a background of NASH cirrhosis has increased eleven-fold during the last 10 years (7,8). Currently, NASH is the second leading indication for liver transplantation after alcohol-related liver disease. Recurrent and de novo NAFLD are also common after liver transplant due to metabolic comorbidities such as obesity. Identification and optimizing treatment before and after liver transplant is essential to maintain a healthy allograft (9,10).

Despite clear epidemiological risks of obesity and the bulk of evidence showing that weight loss is beneficial in improving or reversing complications of liver disease, the management of obesity remains challenging. It has been shown that weight reduction of at least 7 to 10% with conservative lifestyle modification is necessary to resolve NAFLD (11,12). A prospective cohort study with paired liver biopsies in 261 patients demonstrated a 90% complete resolution of NASH as well as an improvement

Correspondence to: Anja Geerts, MD, PhD, Department of Gastroenterology & Hepatology, University Hospital Ghent, Belgium. Phone: +3293322371.
Email: anja.geerts@ugent.be

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of fibrosis in 45% after weight reduction of 10% or more. However, only 10% of patients achieved this degree of weight loss (11). We published findings from a prospective study in children and adolescents admitted for severe obesity at a tertiary center (Zeepreventorium, De Haan, Belgium). All children and adolescents underwent intensive and multidisciplinary lifestyle management encompassing caloric restriction, increased physical activity, education on a healthy lifestyle, and psychosocial support. After 6 months, the median body weight loss was 16.0%. A significant improvement of steatosis was seen, and more importantly, fibrosis improved in 75.0% of patients with baseline elevated liver stiffness (13).

Although weight loss reduction works, only 5 to 10% of patients will achieve the target weight loss with structured life-style interventions at 1 year and fewer than half of these patients maintain the weight loss 5 years later (14). Despite the increasing prevalence of NAFLD and NASH cirrhosis, there are still no Food and Drug Administration (FDA)-approved pharmacotherapies which halt progression in the spectrum of the disease and reduce liver-related complications in patients with NAFLD (15).

The bidirectional relationship between obesity and alcohol

Alcohol-related liver disease (ARLD) and NAFLD reveal astonishing histopathologic similarities. There is also a considerable number of individuals with both metabolic dysregulation and chronic alcohol consumption. The term nonalcoholic fatty liver disease (NAFLD) is based on the exclusion of harmful alcohol consumption. Recently Staufer et al showed that up to 29% of patients diagnosed with NAFLD are at risk of alcohol-related liver disease (16). A better terminology for NAFLD is proposed with as new name "Metabolic-associated fatty liver disease (MAFLD)" (17). With this new nomenclature, MAFLD can now also co-exist without contradiction with alcohol-related liver disease. Indeed, many patients diagnosed with obesity consume light, moderate or even excessive amounts of alcohol. It appears likely and plausible that the combination of 2 pathological mechanisms causes more harm than either of the 2 factors in isolation (18,19). Alcohol abstinence has been proven to prevent progression and complications in patients with ARLD. A critical association for hepatic fibrosis and cirrhosis development has been shown in obese subjects with heavy alcohol consumption (>40-60 g/day) (20-22). The risk of HCC is 3.1 times higher in alcohol users who have a BMI of 30kg/m² or greater as compared with nonusers with a BMI of less than 30kg/m², which is suggestive of multiplicative effect (23).

The classical threshold values of alcohol consumption thought to contribute to ARLD are 30 g/d for men and 20 g/d for women (24). However, there is conflicting literature on the impact of light to moderate alcohol use on the progression of fatty liver disease (25-27). No safe limit of alcohol use to avoid liver injury is reported in some meta-analyses, but others report that light to moderate alcohol use may have a protective effect against disease progression (25-27). Recently, we performed a meta-analysis on the impact of light (≤ 10 g/day or ≤ 1 drink/day) to moderate (≤ 30 g/day or ≤ 3 drinks/day) alcohol consumption on progressive NAFLD. Our analysis suggests a harmful effect on disease progression tot advanced fibrosis, cirrhosis and HCC. Light, but not moderate, alcohol consumption was associated with a protective effect on mortality, probably due to a decrease in cardiovascular events (28). In our view, NAFLD patients should be discouraged to drink moderate amounts of alcohol.

Beneficial effects of bariatric surgery in NAFLD

Bariatric surgery (BS) is the most effective and durable approach to obesity management. BS improves many associated comorbidities such as diabetes type 2, hypertension, sleep apnea, renal disease and stroke, which improve quality of life and reduce long-term mortality. The number of bariatric procedures performed in Belgium has been increasing in recent years, with around 14000 procedures in 2017. The two most commonly applied techniques in Belgium as well as worldwide are the Roux-en-Y-gastric bypass (RYGB) and sleeve gastrectomy (SG). Very low mortality and morbidity rates are associated with these procedures performed when performed laparoscopically (29).

Patients with obesity who meet the criteria for BS, namely body mass index (BMI) > 40kg/m² or ≥ 35 kg/m² and at least one or more obesity-related co-morbidities, frequently have features of NAFLD or NASH (29-32). The presence of NAFLD and NASH prior to weight loss surgery is reported in 80.2% to 90% and 14.4%, respectively (30-33). A retrospective cohort study conducted by Aminian et al was the first to demonstrate a significantly lower risk for major adverse hepatic and cardiac outcomes in the bariatric surgery group compared with nonsurgical management in patients with biopsy-proven NASH and obesity (34). The cumulative incidence (CI) of major hepatic outcomes at 10 years was 2.3% in the BS group versus 9.6% in the nonsurgical group. In a recent meta-analysis, comprising 2374 patients, improvement of steatosis was seen in 88%, steatohepatitis improved in 59% and fibrosis improved or resolved in 30% of the patients (35). These beneficial findings were reported in several prospective and retrospective cohort studies and meta-analyses (36-40). The Long-term efficacy of BS has been nicely demonstrated by Lassailly et al (40). Resolution of NASH without worsening of liver fibrosis was achieved in 84% of patients and fibrosis regressed gradually and improved in 70% of patients compared to baseline fibrosis after 5 years of BS.

Despite the high prevalence of NAFLD/NASH in patients undergoing bariatric surgery, this co-morbidity is not consistently viewed as an indication. BS may be

an effective treatment for obese patients (BMI ≥ 35kg/m^2) with NASH fibrosis or obese patients with NASH fibrosis who otherwise meet BS criteria (BMI > 40kg/m^2). In this context, the ongoing randomized clinical trial (NASHSURG, NCT03472157) on BS for patients with class I obesity and NASH with advanced fibrosis or cirrhosis, will be instrumental in potentially broadening the indications for surgery.

Bariatric surgery in cirrhotic patients

Liver cirrhosis has long been a contra-indication for BS. The data are mostly retrospective cases from incidental findings of cirrhosis at the time of BS with a prevalence ranging between 0,14% to 1,5% (41).

The risk of 30-day mortality in decompensated cirrhotic patients undergoing BS was noted to be 16,3% and 19.4% versus 0,9% and 0.6% in compensated cirrhosis. Bariatric surgery is therefore absolutely contra-indicated in patients with decompensated cirrhosis (42,43). Other predictors of mortality were the type of procedure performed with 0.8% mortality after RYGB compared with 0% following SG, and the number of procedures performed in a given center each year (42,43).

A careful selection of patients, consideration of the type of procedure and local expertise are essential factors for successful BS in patients with cirrhosis. Recently published AGA clinical practice guidelines for BS in cirrhosis are in agreement and suggest that BS can be considered in selected patients with compensated cirrhosis (Child-Pugh A, MELD score < 12) and after assessing the grade of portal hypertension. It is necessary to exclude those with a history of decompensated cirrhosis or those with significant portal hypertension, which can be assessed by upper endoscopy (presence of varices) or measurement of hepatic venous wedge pressure gradient (> 10mmHg) (44). A laparoscopic SG is the preferred procedure and seems feasible in compensated cirrhotic patients. Another advantage of SG is the gradual weight loss, absence of malabsorption and the preservation of endoscopic access to the biliary tree.

Impact of bariatric surgery on liver function

An increase in liver enzymes can occur during the first few months after surgery. Liver function is however expected to return to normal within a year with reductions in AST, ALT and GGT levels already observed 6 months post-surgery (45). Contributing factors to the short-term elevation of enzymes are the metabolic changes due to rapid weight loss, for instance the significantly increased delivery of fatty acids to the liver, and slow adaptation of liver function after surgery.

The type of surgery is one of the criteria that should be considered in balancing the risks and benefits of BS. Procedures which induce severe malabsorption such as jejunoileal bypass and biliopancreatic diversion are associated with very rapid weight loss and malnutrition. These techniques were found to cause life-threatening complications including acute liver failure in up to 10% of patients, and should therefore be abandoned (46-48). Liver failure following RYGB and SG is rarely reported (49). However, extended limb or distal version of RYGB can behave like biliopancreatic diversion with higher potential for malabsorption and therefore should be carried out with caution.

The pathogenesis of liver failure after BS remains poorly understood. One important factor implicated in the pathogenesis of liver injury was intestinal bacterial overgrowth in the excluded small intestine segment. As we see no liver failure after equivalent intestinal resection, this may explain the role of excluded segment. Bacterial overgrowth leads to mucosal injury and increases gut permeability to especially endotoxins. When these toxins are absorbed via the portal vein to the liver, they can induce hepatocellular damage. Another factor in the pathogenesis of liver failure post-bypass surgery is protein and amino acid malnutrition, which can perpetuate or increase lipid accumulation in the liver. Rapid weight loss after severe malabsorptive procedures leads to massive depletion of adipose tissue in visceral deposits and release of free fatty acids into plasma (48).

The optimal daily protein intake should not be lower than the recommended 1.2 to 1.5g/kg (50). Oral multivitamins must be administered systematically during the weight loss phase and continuously after BS. A combination of malnutrition and non-adherence to nutritional supplements can lead to liver failure. Clinical improvement with conservative treatment and appropriate nutritional support seems to be effective, as recently described by Vandeberg et al and Van Golen et al (51-52). Consideration of a reversal of malabsorptive BS procedures can be considered in patients presenting with edema or ascites due to hypoalbuminemia in order to improve malnutrition and stabilization of liver disease. Liver transplantation needs to be considered if reversal of BS is not possible due to severe liver failure (47,48). To prevent recurrence of severe steatohepatitis and to rescue the liver graft, a reversal of the bariatric procedure needs to be done in the first weeks after post-operative period of liver transplant (47,53).

Alcohol use after bariatric surgery

The recent literature clearly indicates that the incidence of alcohol use disorder (AUD) increases after surgery. This phenomenon is mainly observed starting in the second postoperative year, with a prevalence ranging from 12 to 20% (54,55). The importance of the type of surgery has not been fully clarified yet. Ibrahim et al reported an identical risk after RYGB and SG in the second year, although several papers described a lower prevalence in restrictive procedures such as SG (55). The reasons for post-BS AUD are likely multifactorial. BS affects the pharmacokinetics of alcohol, leading to higher peak alcohol concentrations and a greater

feeling of drunkenness. Alterations in secretion of gut hormones like incretins and ghrelin, bile acid alterations and changes in gut microbiota might also contribute to a higher sensitivity for alcohol use (48).

The impact of BS on the development of ARLD is not yet clear. We have published single-center data showing that patients with a history of BS were significantly younger at the time of listing for liver transplantation. The liver decompensation was also more severe in the patients with a prior BS (56). A recent study reported similar data of BS patients presenting at a younger age with acute alcoholic hepatitis (57). In a retrospective observational analysis of obese adults based on insurance claims, women had undergone BS had twofold increased risk of alcoholic cirrhosis and alcohol misuse compared to women without prior surgery (58). However, prospective studies describing the prevalence of BS-related ARLD, the clinical course and prognosis, are currently lacking. Given the increasing use of BS, and the delay until development of ARLD, we expect that the prevalence will further increase in the next decade.

The possible risks of alcohol use which can lead rapidly to the development of alcoholic cirrhosis must be communicated with the patients in the pre-operative phase and surgeons should be reluctant to perform BS in patients with a history of AUD.

Conclusion

Obesity itself is a risk for worsening liver function in chronic liver disease and cirrhosis, with an impact on decompensation and infectious events. Weight loss is the cornerstone but difficult to reach and to keep long-term the target goals with only conservative lifestyle changes. Obesity interacts with alcohol to aggravate liver disease, and even moderate alcohol use can induce progression of NAFLD to more advanced stages of fibrosis. There is evidence that BS is beneficial in obese patients with NASH fibrosis and even in carefully selected patients with cirrhosis. De novo alcohol misuse, an increase of alcohol consumption and severe malabsorptive BS procedures are the most important risk factors for deterioration of liver function after BS.

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