PEER REVIEWED

Liver Disease, Obesity and the Value of Treatment

Since 1990, the prevalence of obesity has more than doubled. In 2022, nearly one billion people were living with obesity.[1] The health risks of being obese or overweight are well understood and include higher mortality and morbidity due to cardiovascular disease, diabetes, cancer, neurological disorders, chronic respiratory disease, and gastrointestinal disease. Here we discuss the hepatic complications of obesity and the value of treatment for obesity for those liver complications.

Metabolic-dysfunction associated steatotic liver disease ('MASLD') is found in the majority of obese patients and the prevalence correlates with the degree of obesity (i.e., the higher the grade of obesity the greater the likelihood of finding MASLD).[2] Of patients with MASLD, 20–30% will have an inflammatory, fibrotic form of steatotic liver disease called Metabolic-dysfunction Associated SteatoHepatitis ('MASH') and 10–15% of MASH patients will progress to cirrhosis.[3] Among patients with co-existing type 2 diabetes and obesity of all degrees, the prevalence of MASLD, MASH, and cirrhosis has been found to be 55.5%, 37.3%, and 17%.[4] As well, obesity worsens the prognosis of patients with compensated cirrhosis due to other causes.[5] Obesity is an independent risk factor for the development of hepatocellular carcinoma ('HCC') and is associated with a 2–3 fold increased risk for the development of HCC, a 4-fold increase in HCC-related mortality, and a 2-fold increase in serious surgical complications following HCC resection.[6]

Obesity results in multiple metabolic derangements that contribute to the development of steatotic liver disease and HCC. Insulin resistance and resulting hyperinsulinemia lead to diminished insulin responsiveness and failure of target organs to dispose of blood glucose. Subsequently, there is hyperglycemia, loss of inhibition of lipolysis, increased circulating free fatty acids and increased intra cellular free fatty acid intermediaries (lipotoxicity), decreased glycogen synthesis, and liver production of glucose.[7] Lipid accumulation and lipotoxicity results from excessive lipid influx and impaired lipid export, and lipid accumulation in the liver is directly related to hepatic toxicity, oxidative stress, and endoplasmic reticulum stress. These stressors activate an inflammatory cascade that can recruit and activate inflammatory cells and trigger hepatic stellate cells ushering the transition from bland steatosis (MASLD) to MASH and increasing risk of HCC.[8]

Weight loss is the cornerstone of effective management of hepatic complications of obesity and is associated with improvement in all-cause mortality, MASLD, MASH, complications of cirrhosis, and HCC. A sustained weight loss of 5–7% of total body weight is required to achieve improvements in hepatic steatosis and hepatic steatohepatitis. Greater weight loss is required to show improvement in liver disease activity and fibrosis. Dietary modification and lifestyle interventions have been shown to achieve weight loss and improvement in MASLD, but sustained weight loss is rarely achieved with lifestyle interventions alone.[9]

Bariatric surgery (BS) is an effective method to achieve substantial and sustained weight loss for patients with obesity. Depending on the procedure, performed weight reduction between 20–35% are anticipated after BS.[10] Studies have shown marked improvement in hepatic disease after five years following BS with MASH resolution in 84%, fibrosis stage decrease in 70%, fibrosis resolution in 56%, and an 88% risk reduction in progression to major liver outcome. BS is also associated with a decrease in major adverse cardiovascular events and risk of obesity-related cancer.[11] A BS patient cohort has been observed to have reduced progression to MASH or HCC as compared to a propensity-matched control group.[12] Some have reported improvement and even resolution of cirrhosis after BS.[13] Bariatric surgery is recommended for patients with a comorbidity with a BMI ≤35. It is recommended for patients without a comorbidity who have been unable to maintain weight loss with lifestyle changes with a BMI > 35. Unfortunately, BS is unavailable to or not feasible for many patients due to expense, healthcare resources, or patient preference.

Endoscopic bariatric procedures have emerged as a less invasive alternative to BS to facilitate similar weight loss less invasively. The anticipated total body weight loss for endoscopic procedures ranges from 10–20%. Each procedure (*e.g.,* gastric balloon, transpyloric shuttle, endoscopic sleeve gastroplasty) works by reducing gastric volume and/or delaying gastric emptying. Some of these procedures are temporary and some patients experience weight gain after reversal.[14] Similar to BS, endoscopic therapies have been found to improve metabolic parameters, reduce liver steatosis, hepatic inflammation and fibrosis in MASH.[15] Long-term outcomes studies are ongoing to evaluate the efficacy of these procedures on liver-related, cardiovascular, and cancer-related events.

Pharmacologic therapy for obesity has been available for more than two decades and is currently recommended in adults with a BMI ≥30 kg/m^2, or ≥27 kg/m^2 with one or more comorbidities. These medications include orlistat, phentermine/topiramate combination, naltrexone, bupropion/naltrexone combination, GLP-1 agonist, and GLP-1/GIP receptor dual agonist. Sustained weight loss with orlistat, phentermine/topiramate and naltrexone/bupropion ranged from approximately 6–10% in clinical studies. With the introduction of GLP-1 agonists and dual agonist therapy, otherwise known as integrin therapy, sustained weight loss has been observed in 8–20% of patients. The dual receptor agonists showed higher sustained weight loss efficacy. Patients treated with orlistat have been found to reduce liver fat on MRI content; serum markers of fibrosis have not been shown to decrease with treatment. No long-term data is available to clarify the hepatic effects of orlistat therapy.[16] GLP-1 agonist therapy has been shown to improve liver steatosis on MRI, with a 2-fold increase in participants achieving a 30% reduction in liver fat over placebo. As well, histologic reduction in disease activity was observed

with GLP-1 administration. Long-term studies are ongoing to assess GLP-1 therapy in obesity and its impact on major liver outcomes and liver fibrosis.[17] Dual GLP-1/GIP receptor agonist has shown the greatest benefit thus far in percentage of weight loss, up to 20%. Dual agonist therapy is associated with a 50% reduction in hepatic steatosis on MRI PDFF, reduction of biomarkers of hepatocyte apoptosis and fibrosis. There are currently ongoing studies to evaluate histologic endpoints in MASH.[18] A variety of triple agonists are in early clinical development. These triple agonists may be able to achieve weight reduction that rival BS. Unfortunately, the GLP-1 agonist and multiple agonist therapies share an adverse even profile that includes delayed gastric emptying, nausea, vomiting, diarrhoea and constipation. Many patients are unable to continue therapy to achieve the desired weight loss. Overall, up to 25% of patients discontinue GLP-1 therapy by three months and nearly one-third by six months before the benefit of therapy is achieved. Patients impacted by early discontinuation were disproportionately African American, Hispanic, lived in areas of high economic need, or were on public insurance programs.[19] Further, the expense of these medications limit their long-term availability for many patients.

In conclusion, obesity is a growing health problem that impacts multiple organ systems. The liver is significantly impacted by the metabolic derangements associated with obesity. Weight loss, if achieved and sustained, can forestall and may even correct the hepatic complications of obesity. Recent advances in medical, endoscopic and surgical care have provided insight and hope for patients living with obesity.

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