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Liver decompensation after rapid weight loss from semaglutide in a patient with non-alcoholic steatohepatitis -associated cirrhosis

Matthew Peverelle, Jonathan Ng, James Peverelle, Ryan D. Hirsch, Adam Testro

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Abstract

There is rapidly increasing uptake of GLP-1 (glucagon-like peptide-1) agonists such as semaglutide worldwide for weight loss and management of non-alcoholic steatohepatitis (NASH). remains a paucity of safety data in the vulnerable NASH cirrhotic population. We report herein the first documented case of liver decompensation and need for liver transplant waitlisting in a patient with NASH-cirrhosis treated with semaglutide. Rapid weight loss led to the development of ascites and hepatic encephalopathy and an increase in the patients Model for Endstage Liver Disease-Na (MELD-Na) score from 11 to 22. Aggressive nutritional supplementation was commenced and the semaglutide was stopped. Over the following months she regained her weight and her liver recompensated and her MELD-Na decreased to 13, allowing her to be delisted from the transplant waitlist. This case serves as a cautionary tale to clinicians using semaglutide in the cirrhotic population and highlights the need for more safety data in this patient group.

Key Words: Semaglutide; Non-alcoholic steatohepatitis; Cirrhosis; Non-alcoholic steatohepatitis cirrhosis; Glucagon-like peptide 1 agonists; Weight loss

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Core Tip: Patients with NASH cirrhosis who lose weight rapidly with semaglutide are at risk of liver decompensation. This complication requires the immediate cessation of semaglutide and aggressive nutritional rehabilitation with supplemental protein feeds and micronutrients. Restoration of lost weight can lead to liver recompensation; however, consideration of liver transplantation should be given to patients who fail to respond to treatment.

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TO THE EDITOR

We read with interest the systematic review and meta-analysis by Zhu *et al*[1] reporting on the efficacy and safety of semaglutide in patients with non-alcoholic fatty liver disease (NAFLD). Analyzing three randomized control trials involving 458 patients, they found that semaglutide was effective at improving histologic and radiologic markers of non-alcoholic steatohepatitis (NASH) activity but not histologic fibrosis. The risk of serious adverse events was similar compared to placebo, and importantly, no cases of hepatic decompensation occurred.

We herein present a case of liver decompensation in a patient with NASH cirrhosis after the use of semaglutide. A 68-year-old female with compensated NASH cirrhosis [Model for Endstage Liver Disease-Na (MELD-Na) score 11] was prescribed semaglutide 2.4 mg once weekly to manage her diabetes and obesity. Her other medications at the time included salbutamol for asthma. The semaglutide led to 10 kg weight loss (11% body weight) within 8 wk of treatment before it was stopped. After approximately 8% body weight loss she developed new onset hepatic encephalopathy (HE) requiring the use of lactulose and rifaximin. She also developed ascites requiring diuretic therapy (spironolactone 100 mg and frusemide 40 mg; further increases limited by postural hypotension) and two large-volume paracenteses. Patient adherence to prescribed medications was confirmed by her family during this time. Due to her rapid weight loss, her semaglutide was stopped. Despite stabilization of her weight, she continued to decompensate and her MELD-Na continued to rise (Figure 1). On referral to our service her MELD-Na was 22 (bilirubin 40 $\mu\text{mol/L}$, creatinine 44, international normalized ratio 1.6, Na 128). Investigations for alternate causes of decompensation including infection, alcohol consumption, hepatocellular carcinoma and portal vein thrombosis were negative. We concluded her liver decompensation was most likely secondary to semaglutide-induced rapid weight loss and malnutrition. She was commenced on high energy and high protein supplementation consisting of 60 g Sustagen twice-daily and micronutrient replacement with thiamine. She also underwent assessment for liver transplantation. Over the following 3 mo, she was reviewed each month by a transplant hepatologist and dietitian to assess her clinical progress, nutritional intake and adherence to treatment. Over this period, she managed to regain 5 kg (6%) of her ideal body weight, and this was associated with an improvement in her ascites and HE and a reduction in MELD-Na to 19 (Figure 1). By 6 mo her weight had returned to baseline, she no longer required abdominal paracentesis and her MELD-Na was 13. She was de-listed from the transplant waitlist and remains compensated at last follow-up.

Our case highlights the potential risk of rapid weight loss with semaglutide in the vulnerable NASH cirrhosis population. In our case, the rapidity of weight loss was significantly greater compared to the studies included in Zhu *et al*'s[1] meta-analysis (10 kg after 8 wk *vs* 6.5 kg after 48-72 wk). Loomba *et al*'s[2] study, included within the meta-analysis, involved patients with NASH cirrhosis and did not report any cases of hepatic decompensation. Of note, our patients pre-semaglutide MELD-Na score was higher (11 for our patient *vs* 7.6 in the study group), potentially conferring a greater predisposition to decompensation. It is interesting to note that despite stabilization of her weight after stopping semaglutide, our patient continued to decompensate until she was reviewed at our tertiary centre, as illustrated in Figure 1. Rapid weight loss is an established precipitant of hepatic decompensation in the post bariatric surgery population[3], with pathophysiological mechanisms thought to involve endogenous free-fatty acid oxidative damage, mitochondrial dysfunction and gut dysbiosis leading to hepatic inflammation and fibrosis[4-6]. However, it should be noted that decompensation has generally occurred later (up to 5 years post-surgery) and degree of excess weight loss (*i.e.* the amount of weight above the ideal body weight) was up to 110%[7]. Furthermore, the use of glucagon-like peptide 1 agonists such as semaglutide causes delayed gastric emptying, which may impact the absorption of concomitantly administered oral medications and therefore their efficacy. This may have contributed to our patients' diuretic-refractory ascites. In patients with liver cirrhosis, it is therefore important to consider inadequate absorption of medical therapies as a contributor to failure to respond to standard treatment.

Clinicians should consider the use of semaglutide cautiously in patients with underlying NASH cirrhosis and should strictly adhere to the prescribing information and dose escalation protocols as recommended and consider using a lower dose of the drug. Failure to follow strict dose escalation protocol may lead to significant gastrointestinal side effects including nausea and vomiting, which may precipitate weight loss and decompensation. Furthermore, clinicians must exercise a low threshold for cessation should weight loss occur rapidly ($\geq 1\%$ of body weight/week) or signs of liver decompensation develop.

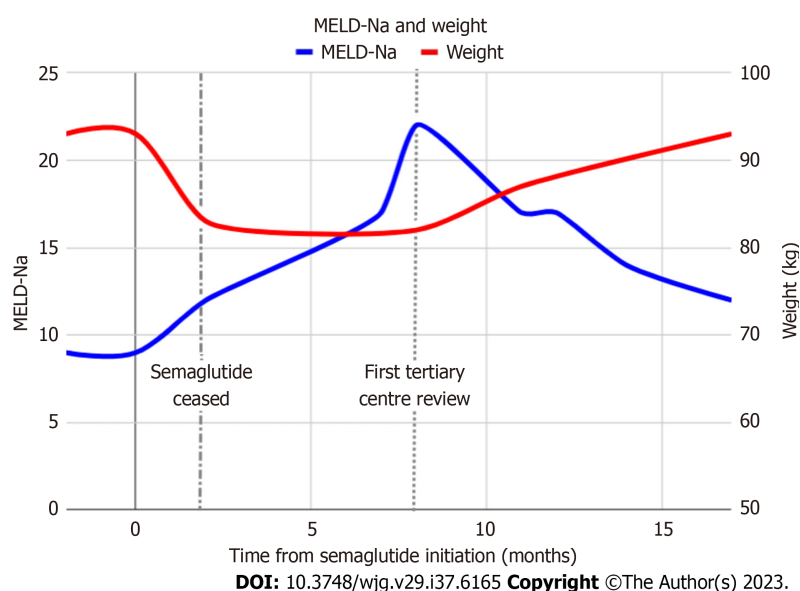


Figure 1 Patient's weight change with semaglutide use and MELD-Na score over time.

FOOTNOTES

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