**CLINICAL VIGNETTE**

# Semaglutide Affecting Alcohol Consumption

Lumbini Chandrasekara, Jennifer Han, MD and Aarthi Arasu, MD

A 59-year-old male with type 2 diabetes mellitus (T2DM), hyperlipidemia (HLD), hypertension (HTN), and gastroesophageal reflux disease (GERD) presented to endocrinology for diabetes management. He was initially diagnosed with pre-diabetes four years prior which was initially managed with diet and exercise. One year later his hemoglobin A1c (HbA1c) increased to 7.0 and metformin was started by his primary care physician. He presented to endocrinology on metformin 2000 mg XR daily with HbA1c of 7.5. At presentation, he reported drinking 12 to 18 servings of alcohol per week including beer, cocktails, and wine. He was started on semaglutide initially 0.25 mg subcutaneous q week for 4 weeks increased to semaglutide 0.5 mg subcutaneous q week. He reported that with increased semaglutide dose 0.5 mg subcutaneous q week, he immediately lost desire for alcohol due to a change in alcohol taste as well as no longer feeling enjoyable.

The patient lost 31 pounds since starting semaglutide. His BMI decreased from 33.91 kg/m2 to 29.70 kg/m2, and his hemoglobin A1c (HbA1c) improved from 7.5% to 5.9%. He reported brief mild nausea after semaglutide administration as well as constipation managed with over-the-counter stool softeners, magnesium supplements, and increased hydration. On physical examination, vital signs were normal with weight of 219 pounds. Laboratory data included total cholesterol of 169 mg/dL, with HDL 41 mg/dL, non-HDL cholesterol 17 mg/dL, LDL cholesterol of 111 mg/dL, triglycerides of 91 mg/dL, and eGFR of 79 mL/min/1.73.

***Discussion***

Harmful use of alcohol resulted in 3 million deaths in 2016, representing 5.3% of all worldwide deaths. It remains a leading global preventable risk factor for physical and social harms.[1] Mortality resulting from alcohol consumption exceeds that caused by tuberculosis, HIV/AIDS, and diabetes.[1] The COVID-19 pandemic had an impact on alcohol use with 60% of surveyed US adults reporting increased drinking compared to pre-COVID-19.[2] FDA approved drugs to treat alcohol use disorder (AUD) include: disulfiram which blocks the metabolism of alcohol and increases aversive responses to drinking; naltrexone which attenuates alcohol-induced opioidergic activity to reduce the rewarding effects of alcohol; and acamprosate which decreases neuronal hyperexcitability to help maintain abstinence from alcohol.[3] However, these therapies have limited success rates and mild to severe side effects including potential organ injury.[4]

Glucagon-like peptide 1 (GLP-1) is an incretin hormone and neuropeptide released from the gut to stimulate the release of insulin and inhibit the pancreas from secreting glucagon in response to food ingestion.[5] It also acts as a satiety signal and regulates gastric emptying to reduce additional food intake.[5] GLP-1 receptor agonists are the novel treatment for obesity, pre-diabetes, and T2DM.[5] Well-known analogues include exenatide, liraglutide, dulaglutide, and semaglutide.

Semaglutide is FDA-approved for treatment of adults with T2DM and obesity.[6] It has high affinity to GLP-1 receptors and long half-life, making it a long acting GLP-1 agonist suitable for once-weekly administration.[7] One study compared the efficacy of once-weekly semaglutide monotherapy versus placebo for 30 weeks in adults with T2DM. Semaglutide 0.5 mg weekly showed 1.45% decrease in HbA1c from baseline, 1.0 mg semaglutide showed 1.55% decrease from baseline versus 0.2% decrease from baseline with placebo.[8] This study also reported 3.73 kg decreased body weight from baseline with semaglutide 0.5 mg; 4.53 kg decrease from baseline with semaglutide 1.0 mg, and 0.98 kg decrease from baseline with placebo.[8] Semaglutide has greater effects on glycemic control and body weight compared to other GLP-1 analogues at standard doses. Three studies showed semaglutide 1.0 mg was significantly more effective in reducing HbA1c and body weight than exenatide ER 2.0 mg,[9] dulaglutide 1.5 mg,[10] and liraglutide 1.2 mg.[11]

Semaglutide has an association with alcohol aversion in patients. Causation awaits human clinical testing. Male Wistar rats, who were escalated on ethanol (EtOH) intake for an extended period of time, exhibited decreased voluntary EtOH preference and consumption with semaglutide treatment.[12] Semaglutide also demonstrated dose-dependent reduced binge-like alcohol drinking in both male and female mice as well as male and female rats.[13] The first investigation on primates showed GLP-1 receptor agonists, exenatide and liraglutide, can reduce the voluntary alcohol drinking in alcohol-preferring male African vervet monkeys.[14] To investigate the mechanism, a study examining the expression and distribution of GLP-1 receptors in the central nervous system demonstrated GLP-1 receptors are found in several reward-related brain regions such as the ventral tegmental area (VTA).[15] A further experiment measuring the alcohol intake of male Wistar rats before and after peripheral GLP-1 injection into the VTA, reported GLP-1 stimulation in the VTA leads to reduced alcohol intake.[16] Effect of GLP-1 on alcohol-related behaviors in humans has not yet been published.

For diabetic patients, alcohol causes metabolic dysregulation and is an additional barrier to the self-care adherence required to manage blood sugars.[17,18] HbA1c levels were significantly higher in drinking type 2 diabetics than in non-drinking type 2 diabetics.[19] Long-term alcohol consumption in well-nourished diabetics resulted in hyperglycemia, and alcohol consumption in fasting diabetics induced hypoglycemic episodes.[19] With decreased glycemic control, alcohol consumption worsened diabetes-related complications including disruption in fat metabolism, peripheral neuropathy, and retinopathy.[19] It is important to study the effects of GLP-1 receptor agonists on alcohol consumption in humans. If a GLP-1 agonist like semaglutide causes alcohol aversion it adds another beneficial effect for this medication. Additional anti-addiction effects may help diabetic patients who regularly consume alcohol. Investigation of the influence of GLP-1 analogues on neurological pathways for addiction can help develop new pharmacotherapies for those with AUD and perhaps other substance use disorders.

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