

# Challenges of Type 2 Diabetes in Patients With Alcohol Dependence

Dalal Alromaihi, MD, Judith Zielke, RN, and Arti Bhan, MD

## PRESENTATION

S.E., a 53-year-old Caucasian woman, was referred to the endocrinology clinic for management of type 2 diabetes. She was diagnosed 2 years ago and failed to achieve acceptable glycemic control with metformin and glipizide. Her glucose values ranged between 300 and 500 mg/dl. The patient expressed fear of not getting the care she needs to achieve her glycemic goal because of the stigma of alcohol dependence.

S.E. had peripheral neuropathy but no history of nephropathy, retinopathy, or any macrovascular complications of diabetes. She has been drinking alcohol for the past 10 years. She reported that she has three 18-oz drinks per day, each composed of equal amounts of rum and regular cola. This is ~ 360 g of alcohol per day. She said she starts drinking from the time she wakes up until she goes to bed and has no intention of cutting back on the amount of drinking or enrolling in a detoxification program.

On physical examination, her blood pressure was 147/82 mmHg and her BMI was 33 kg/m<sup>2</sup>. Her skin showed spider telangiectasia and no evidence of acanthosis nigricans or thyromegaly. Her abdomen was soft and non-tender, and she had no organomegaly. She was able to sense pressure from a 10-g monofilament in all of 10 points bilaterally. The rest of the examination was non-contributory.

Laboratory results showed an A1C of 11%, creatinine of 1 mg/dl, albumin-to-creatinine ratio of 10.8 mg/g, aspartate transaminase of 113 IU/l, alanine aminotransferase of 69 IU/l, alkaline phosphatase of 276 IU/l, total bilirubin of 0.9 mg/dl, and thyroid-stimulating hormone of 2.04  $\mu$ IU/ml. Her total cholesterol was 280 mg/dl, triglycerides were 805 mg/dl, HDL cholesterol was 15 mg/dl, and direct LDL cholesterol was 182 mg/dl. Her vitamin B<sub>12</sub> level was > 1,500 pg/ml (reference range 250–900 pg/ml), and her folate level was > 24 ng/ml (reference range > 5.4 ng/ml).

Computed tomography of her abdomen showed diffuse hepatic steatosis and atrophic pancreas.

After extensive counseling about the health influences of alcohol and the risk of hypoglycemia, S.E. was initiated on basal-bolus insulin. She achieved an A1C of 7.5% without hypoglycemia. In addition to her clinic visits with the physicians and nurses, telephone conversations to follow up on her glycemic control and insulin administration were necessary. A team approach with gradual increases in insulin doses resulted in successful and safe management of her diabetes.

She later developed a gastrointestinal bleed related to esophageal varices and decided to quit drinking alcohol. Her insulin requirements are now markedly lower.

## QUESTIONS

1. What is the influence of alcohol consumption on a patient's risk of developing type 2 diabetes, ability to achieve diabetes control, and risk of complications?
2. What is the risk of hypoglycemia with insulin use in patients with heavy alcohol use?

## COMMENTARY

Managing patients with type 2 diabetes and alcohol dependence can be a challenge for a multitude of reasons. Patients may not be motivated to make lifestyle changes and are at an increased risk of hypoglycemia. This case exemplifies some of these practical challenges and describes our team approach in her care.

Alcohol consumption is prevalent in the United States, with an estimated 109 million Americans who drink alcohol. The effect of alcohol on causation or prevention of diabetes has been studied. Epidemiological and experimental studies suggest a protective effect of moderate alcohol consumption.<sup>1–4</sup>

Carlsson et al.<sup>1</sup> conducted a meta-analysis of 13 published epidemiological studies to evaluate this data further and concluded that the results showed that moderate alcohol consumption had a protective effect on the development of diabetes on the order of 30%. Moderate alcohol consumption was defined as ~ 5–30 g/day. This corresponds to about 0.5–2.5 drinks per day. There

was no protective effect from high alcohol consumption.

It appears that there may be a U-shaped relationship between alcohol and type 2 diabetes such that there is a higher risk of developing diabetes with both low and high intake levels and a lower risk with moderate intake. The possible protective effect of moderate alcohol consumption needs further evaluation; the influences of type of beverage, frequency of drinking, and interaction with other risk factors such as overweight and family history of diabetes are not yet clear.<sup>1</sup>

Several experimental studies evaluated the effect of alcohol consumption on glycemic control in patients with type 2 diabetes.<sup>2,5-9</sup> Alcohol consumption varied between studies with regard to being with or without food. Two studies<sup>8,9</sup> found a decrease in plasma glucose concentration after alcohol consumption with or without a meal. The decrease was statistically, but not clinically, significant in one study.<sup>8</sup> Another study<sup>7</sup> found a statistically significant decrease in plasma glucose after ethanol infusion during a fast. On the other hand, three other studies found that ingesting small to moderate amounts of alcohol with or without food had no acute effect on glycemic control.<sup>2,5,6</sup>

Two experimental studies<sup>10,11</sup> assessed the effect of alcohol consumption on medication-related complications. One<sup>10</sup> assessed the effect on troglitazone, a thiazolidinedione, and the other<sup>11</sup> evaluated sulfonylurea-related complications. There was no significant difference in the glycemic response to ethanol.

This decrease in plasma glucose concentration may be the result of enhanced insulin secretion or reduced hepatic gluconeogenesis. However, data on the long-term effects of alcohol consumption on

glycemic control are lacking, and further research is needed.

In terms of the effect of alcohol consumption on diabetes complications, four prospective cohort studies<sup>12-15</sup> assessed the relationship between alcohol consumption and the incidence of coronary heart disease or death in patients with diabetes. Each study reported a decreased risk of death resulting from coronary heart disease in association with alcohol use, and the results were statistically significant in three of the studies.

Two prospective cohort studies<sup>16,17</sup> assessed the association between alcohol consumption and risk for retinopathy. One study<sup>16</sup> found no association between alcohol consumption and incidence or progression of diabetic retinopathy, whereas the other study<sup>17</sup> found an increased risk of diabetic retinopathy with heavy alcohol use. The effect of alcohol use on other diabetes complications, including nephropathy and neuropathy, remains uncertain.

Alcohol has several effects on carbohydrate metabolism. Some are directly related to the influence of alcohol or its metabolic products (acetaldehyde and acetate), but others stem from an alcohol-induced increase within the liver cell of the ratio between reduced and oxidized nicotinamide adenine dinucleotide (NADH/NAD ratio). The increase of the NADH/NAD ratio contributes to inhibition of gluconeogenesis. After the consumption of 48 g alcohol (about four glasses), hepatic gluconeogenesis decreases by ~45%.

In addition, glycogenolysis is also impaired by alcohol by ~12% after the consumption of a moderate amount of alcohol. This effect may be confounded in patients with malnutrition and limited glycogen stores.<sup>18</sup>

Furthermore, alcohol consumption can lead to reactive hypoglycemia and the combination of a carbohydrate-rich meal and alcohol can lead to an exaggerated insulin response and result in hypoglycemia 2-3 hours after the meal. Studies do not show an increase of insulin or C-peptide after alcohol use in normal volunteers or in patients with non-insulin-dependent diabetes.<sup>18</sup>

Kiechl et al.<sup>19</sup> evaluated the relationship between regular alcohol consumption and insulin sensitivity in a cross-sectional study in Italy and found that fasting insulin concentrations were highest in those who did not drink alcohol and lowest in those who had heavy alcohol consumption, which was defined as > 100 g/day. Furthermore, post-glucose insulin concentrations and estimates for insulin resistance assessed by the homeostasis model assessment decreased significantly with increasing amounts of regular alcohol consumption. These trends were independent of sex, BMI, physical activity, cigarette smoking, medication, and diet.

Avogaro et al.<sup>20</sup> found that alcohol intake impairs glucose counterregulation in patients with type 1 diabetes while supporting it in nondiabetic subjects. In addition, alcohol intake in patients with type 1 diabetes and in nondiabetic subjects was associated with normal catecholamine responses and normal hepatic glucose production. Alcohol intake was noted to decrease plasma free fatty acid, and the authors hypothesized that depressed lipolysis in patients with type 1 diabetes led to deficient glucose recovery during alcohol intake.

Growth hormone level is increased in response to hypoglycemia, and that is associated with augmented hepatic glucose production and elevation of free fatty

acids, ketones, and branch-chained amino acids. Kerr et al.<sup>21</sup> showed that even modest ingestion of alcohol, to levels within the U.K. limits for driving, attenuated the usual growth hormone response to mild hypoglycemia.

### CLINICAL PEARLS

- Alcohol consumption is common, and its influence on the risk of developing type 2 diabetes appears to have a U-shaped curve.
- Alcohol consumption in patients with type 2 diabetes can result in hypoglycemia because of decreased gluconeogenesis, decreased glycogenolysis, and possibly reactive hypoglycemia in response to carbohydrate intake.
- Most data are retrospective or observational, and more research is needed to determine the long-term effects of alcohol consumption on glycemic control, self-management behaviors, and the complications of diabetes.

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*Dalal Alromaihi, MD, is a senior fellow; Judith Zielke, RN, is a nurse leader; and Arti Bhan, MD, is a senior staff physician at Henry Ford Hospital in Detroit, Mich.*