Nutrition and Prevention of Diseases

Topic 20

Module 20.6

Moderate Alcohol and Cardiometabolic Risk in Type 2 Diabetes (T2D)

Iris Shai, RD, PhD
Professor of Nutrition and Epidemiology,
Department of Public Health, Faculty of Health Sciences,
Ben-Gurion University of the Negev, Israel

Learning Objectives
• Addressing the risks and benefits of alcohol consumption;
• Examining the associations and effects of moderate alcohol consumption in type 2 diabetes (T2D);
• Introducing the 2-year CArdiovaSCulAr Diabetes and Ethanol (CASCADE) Randomized Controlled Trial.

Contents
1. Risks and benefits of alcohol consumption
2. The associations and effects of moderate alcohol consumption in type 2 diabetes (T2D)
3. The 2-year CArdiovaSCulAr Diabetes and Ethanol (CASCADE) randomized controlled trial
4. Summary
5. References

Key Messages
• Alcohol is a toxic substance which risk-benefit balance depends on numerous factors;
• Heavy alcohol consumption has deleterious health effects, while drinking alcohol in moderation was demonstrated to have beneficial influence on cardio-metabolic health;
• Moderate alcohol consumption is defined as 10–30 g of alcohol per day, which is equivalent to ~0.5–2 drinks per day (up to 1 drink a day for women and up to 2 drinks/day for men);
• Beneficial effects of moderate alcohol on human health are documented in healthy populations as well as amongst patients with type 2 diabetes;
• Genetic polymorphisms in alcohol metabolizing genes may interact with the alcohol-health effects.
1. Risks and Benefits of Alcohol Consumption

The relationship between alcohol intake and alcohol-related health effects is a complex subject, since alcohol is associated with both, harmful and beneficial effects on health. Mounting evidence demonstrates a J-shape association for alcohol intake. It is well known that heavy alcohol drinking is positively associated with various social problems and adverse medical conditions. High alcohol consumption is associated with increased risk for numerous deleterious health outcomes, such as liver cirrhosis, dementia, and several types of cancers. Moreover, overall mortality is higher amongst individuals with a high alcohol intake compared with moderate consumers. High alcohol intake may result in acute cardiovascular damage (such as arterial hypertension and transitory ischaemic cerebral attack) as well as in harmful chronic effects on the heart (such as coronary heart disease, atrial dysfunction, ventricular dysfunction, and chronic arrhythmias), brain (such as ischaemic stroke, haemorrhagic stroke and subdural haemorrhage) and the vascular system (such as systemic atherosclerosis, arterial hypertension, peripheral artery disease, and adverse changes in inflammatory endothelial markers) (1,2).

On the contrary, moderate alcohol consumption decreases the overall mortality and has numerous health benefits. It was demonstrated to decrease the risk of type 2 diabetes and the cardiovascular risk, prevent thrombosis and plaques, and improve lipid profile (3, 4, 5, 6). These favorable effects were observed both in healthy populations as well as amongst patients with type 2 diabetes.

2. The Associations and Effects of Moderate Alcohol Consumption in Type 2 Diabetes (T2D)

With regard to diabetes and its complications, a J-shape association was suggested for alcohol intake (7, 8, 9), implying that moderate drinkers may benefit from a protective effect of alcohol on the risk of developing diabetes and its complications. Consistently, prospective studies confirmed an inverse relationship between moderate alcohol consumption and diabetes incidence, with moderate drinkers having a 43% to 46% reduction in risk for new-onset diabetes compared with abstainers.

In diagnosed type 2 diabetic patients, alcohol in moderation is linked to lower cardiovascular risk (10). Meta-analysis of observational studies (11) shows that among type 2 diabetics who reported alcohol consumption, a 21–36% lower total mortality rate, and a 25–66% lower rate of total and fatal CHD were observed, compared with abstainers. Intriguingly, the magnitude of these associations is even stronger than reported in observational studies in the general, non-diabetic population (12). However, the question whether it is acceptable to recommend patients start drinking to reduce the risk for cardiovascular disorders remains a controversial issue.

The apparent beneficial effects of alcohol on cardiovascular disease have been proposed to be mediated via effects on lipid metabolism (13), coagulation, fibrinolysis (14), and insulin sensitivity (15, 16). We have previously shown in an observational study among over 700 men with type 2 diabetes (17), that moderate alcohol intake was associated with decreasing levels of inflammatory biomarkers (sTNF-r2, sICAM-1, fibrinogen), as well as with elevated circulating levels of adiponectin. However, although these parameters may be regarded as good surrogate markers, it is unknown whether alcohol has direct effects on the atherosclerotic plaque.

Independent of the favorable biological effects of alcohol on the lipid profile, on homeostatic factors, and in reducing insulin resistance (18), phenolic compounds (19) (mostly resveratrol and quercetin) (20) of red wine appear to also exert beneficial effects (21, 22, 23). The mechanisms include antiplatelet actions, increases in high-density
lipoprotein, antioxidative function, reduced endothelin-1 production, and increased endothelial nitric oxide synthase expression. Comparison studies suggest (24) that wine is more protective against coronary disease than liquor or beer. However, others suggest that favorable traits or drinking patterns of wine drinkers might explain the comparative findings. As opposed to the experimental studies, epidemiological studies demonstrate a beneficial effect of alcohol consumption independent of the specific kind of alcoholic beverage consumed (25), suggesting that small doses (1-2 drinks a day) of wine, beer, or spirits are equally beneficial (26). In-vivo study suggests that both wine and ethanol alone reduce myocardial ischemic reperfusion injury. However, the mechanisms utilized by the various beverages in exerting their cardio-protective effect(s) differ (27). Thus, long-term intervention trials are needed to determine the net beneficial effect, of ethanol per se.

Several mechanisms for beneficial effects of ethanol uniquely in diabetic patients can be envisioned, and include improved glycemia and decrease in cardiovascular risk. Ethanol metabolism increases the hepatic cytosolic NADH/NAD+ ratio, thereby inhibiting gluconeogenesis which is abnormally elevated in type 2 diabetes, thus contributing particularly to fasting hyperglycemia. Current therapy of type 2 diabetes, including nighttime long-acting insulin and metformin, improves glucose homeostasis largely by addressing this abnormally-elevated metabolic pathway. However, just as hepatic glucose production can be over inhibited by excessive night-time insulin, alcohol can provoke hypoglycemia. This is particularly true when ingested in the fasting state (28). Since ethanol does not appear to significantly affect insulin secretion or glucose disposal, a hypoglycemic effect of ethanol is likely to be highly dependent on the nutritional status and fed-fast state of the person ingesting it (29). Several small short-term studies, of 5-20 patients with type 2 diabetes, reported a decrease in plasma glucose concentrations (30, 31) with moderate alcohol administration. However, other studies found no effect of alcohol on glycemic control (32, 33). Thus, the potential impact of moderate alcohol consumption on glycemic control in diabetics remains intriguing, but largely unproven.

The beneficial effects of moderate alcohol consumption inferred by observational studies form the need to test the hypothesis that initiating regular moderate alcohol consumption would be beneficial in patients with type 2 diabetes. Yet, as summarized in an editorial commentary, (34) proving the beneficial effect of moderate alcohol intake awaits results of randomized controlled intervention trials. To date, few such studies have been performed. In a randomized controlled crossover trial (35) of 63 healthy (non-diabetic) postmenopausal women over 8 weeks, consumption of 30 g/d of alcohol (2 drinks per day) reduced insulin and triglyceride concentrations and improved insulin sensitivity, but fasting glucose concentrations were not significantly affected. In a trial among young patients with diabetes after a first myocardial infarction (36), red wine, taken with meals, significantly reduced oxidative stress and pro-inflammatory cytokines. These important, but still anecdotal studies, provide proof-of-principle consistent with the hypothesis driving the present proposal, however, they are insufficient to determine whether initiating moderate alcohol intake, as a medically-prescribed long-term treatment, should be regarded as a safe therapeutic intervention for the general population of type 2 diabetic people.

To address these questions, we completed a three-month randomized controlled intervention pilot study (37) of alcohol (13 g/day) or a control nonalcoholic beer among 109 alcohol-abstainers with type 2 diabetes, and assessed the effect on fasting and postprandial glycemia. Within the alcohol intervention group, mean FPG decreased from 139.6 mg/dL to 118.0 after 3 months compared to 136.7 to 138.6 in the controls (p = 0.015). The effect was more pronounced among patients with higher baseline HbA1c.
levels, consistent with the proposition that elevated hepatic glucose production may be an important contributor to hyperglycemia in advanced diabetes.

3. The 2-year CARDioVASeCUIAr Diabetes and Ethanol (CASCADE) Randomized Controlled Trial

Currently there are only a few randomized controlled trials (RCT) examining the possible beneficial cardio-metabolic health effects of chronic moderate alcohol consumption. Moreover, long-term large-scale RCTs in type 2 diabetes patients are virtually lacking. Therefore, we conducted a 2-year RCT assessing whether initiating moderate alcohol intake in patients with type-2 diabetes is beneficial and, moreover, safe. 224 well-controlled alcohol-abstaining diabetics were randomized to mineral-water, white-wine or red-wine (150ml/dinner) groups. Wines and water were provided. All groups followed a Mediterranean diet without caloric restriction. Retention was 94% after one year and 87% after two. Overall, red wine was superior in improving cardiometabolic risk. While both wines were beneficial for glycemic control, the effect was mainly dependent on their polymorphism in alcohol-dehydrogenase 1B (ADH1B) gene. ADH1B is the main enzyme that metabolizes the first step of ethanol metabolism - catalytically oxidizing the ethanol into acetaldehyde. In the wine groups, slow-ethanol-metabolizers [homozygotic for the alcohol-dehydrogenase variants (ADH)1B*1] had favorable changes in glycemic control parameters as compared to fast-ethanol-metabolizers [carrying ADH1B*2 (Arg48His; rs1229984)]. Other parameters as blood pressure, liver function, adiposity, medications intake, and specific symptoms were not altered across groups. To summarize, initiating moderate wine intake among well-controlled type-2 diabetes patients as part of healthy diet is apparently safe. Wine induces modest improvements in several metabolic parameters. The significant interactions with genetic polymorphisms in alcohol metabolizing genes lend further support for a causal role of ethanol (38).

4. Summary

A complex interplay exists between alcohol and human health. To complicate the picture even more, not only the alcohol-related factors, such as drinking pattern with regard to alcohol dose consumed and the frequency of alcohol drinking, but also several additional features, such as age, gender, genetic factors, ethnicity, and the current health status, all have an influence on the effect of alcohol on health parameters. Therefore, alcohol consumption should be subject to careful consideration.
5. References

myocardial infarction of subjects with Type 2 diabetes mellitus Diabetic Medicine 23 (9), 974–981.
