

Moderate Alcohol Consumption and Triglyceridemia

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Summary

The review aims to summarize current knowledge on the effects of moderate alcohol consumption (1 standard drink a day for women; 2 drinks a day for men) on triglyceride concentration in circulation. Current evidence suggests that the relationship between alcohol consumption and triglyceridemia is J-shaped. Triglyceridemia is lowest in subjects who drink 10-20 g/alcohol a day. Such a J-shaped association is comparable with that described for the relationship between alcohol and cardiovascular risk. On the contrary, alcohol taken with a meal increases and prolongs postprandial triglyceridemia. Such effects of alcohol consumption may be at least partially explained by the effects of ethanol on lipoprotein lipase (LPL) activity. Long-term moderate alcohol consumption increases LPL activity, which may explain its TG-lowering effect. On the other hand, LPL activity is acutely downregulated by ethanol, which explains increased postprandial triglyceridemia.

Key words

Alcohol consumption • Triglyceride • Lipoprotein lipase • Ethanol

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Introduction

Over the last few decades, compelling evidence has accumulated regarding the protective effect of moderate alcohol consumption on cardiovascular disease morbidity and mortality (Corrao *et al.* 2000, Costanzo *et al.* 2010, Ronksley *et al.* 2011, Wang *et al.* 2014).

Although the definition of a moderate dose somewhat differs among authors, one drink a day (10-15 g of alcohol) for women and 2 drinks a day (20-30 g of alcohol) for men may be generally considered a moderate level of ethanol consumption. The relationship between alcohol consumption and cardiovascular morbidity and mortality is J-shaped – Corrao *et al.* (2000) have shown that the protective effect of alcohol consumption reaches its maximal level at 20 g of alcohol/day and is preserved up to 72 g/day. The protective dosage of alcohol is lower in women compared to men (Corrao *et al.* 2000, Wang *et al.* 2014) and the protective effect of alcohol can even be seen in hypertensive patients (Wang *et al.* 2014). Importantly, the same protective effect of alcohol consumption is observed for wine, beer (Costanzo *et al.* 2011) and even for spirits (Rimm *et al.* 1996) as a source of ethanol. The authors of a recent meta-analysis (Ronksley *et al.* 2011) even conclude that alcohol taken in moderation may have overall health benefits that outweigh the risks in selected groups of patients. In their opinion, the evidence (especially for ischemic heart disease) is strong enough and so further observational studies may only have limited value. They also suggest that it is time to debate how to integrate the available evidence into clinical practice. Although the conclusions about the protective role of ethanol consumption were challenged by a recent Mendelian randomisation study (Holmes *et al.* 2014), even this study confirms the protective effect of alcohol consumption in drinkers compared to abstainers.

The positive effects of moderate alcohol consumption on cardiovascular disease outcomes might be mediated by the favorable effects on some cardiovascular disease risk factors. A meta-analysis of 63 intervention

studies documented that alcohol consumption favorably affects plasma HDL-cholesterol, apolipoprotein A-I, fibrinogen and adiponectin concentrations (Brien *et al.* 2011). Alcohol also decreases fasting insulin and glycated hemoglobin concentrations and, in women, improves insulin sensitivity (Schriecks *et al.* 2015).

On the other hand, alcohol consumption is recognized as a major cause of secondary hypertriglyceridemia (Baraona and Lieber 1979) and hypertriglyceridemia is currently accepted as a cardiovascular disease risk factor (Hokanson and Austin 1996, Sarwar *et al.* 2010, Jorgensen *et al.* 2013). However, the findings on the relationship between alcohol consumption in moderation and triglyceridemia are unequivocal and sometimes even confusing. The present review therefore aims to summarize the current knowledge of the effects of alcohol consumption in moderation on triglyceridemia in both fasting and postprandial states.

Metabolism of alcohol

Alcohol is carried to the liver, where it is enzymatically oxidized. The rate of alcohol elimination is influenced by factors such as diet, age, smoking, time of day, chronic alcohol consumption as well as genetics. Ethanol is metabolized in the liver by alcohol dehydrogenase (ADH) to form acetaldehyde. Consequently, acetaldehyde is rapidly oxidized to acetate by aldehyde dehydrogenase (ALDH2). The majority of the acetate resulting from alcohol metabolism escapes from the liver into the blood and is eventually metabolized to acetyl CoA, after which it is oxidized to CO₂ in the heart, skeletal muscle and brain cells (Zakhari 2006). This spares carbohydrates and lipids from oxidation, and they may be used for lipogenesis in the liver (Siler *et al.* 1999). However, the impact on lipogenesis and VLDL secretion does not seem to be quantitatively important when alcohol is consumed in modest doses (Siler *et al.* 1998b, 1999). Furthermore, the oxidation of alcohol to acetate results in an increase of NADH/NAD⁺ ratio in hepatocytes which inhibits gluconeogenesis, β -oxidation and the tricarboxylic acid cycle (Krebs *et al.* 1969, Siler *et al.* 1998a).

Alcohol consumption and fasting triglyceridemia

The interpretation of the results of studies on the relationship between alcohol consumption and TG

concentration is complicated by the fact that these data come from uncontrolled observational studies. Since the data on alcohol consumption are obtained from questionnaires, the validation of these data is very intricate. Moreover, there can be many different confounders of alcohol consumption, the pattern of alcohol consumption can differ between sexes and countries, while lifestyle and physical activity can also have an effect. This could serve as an explanation for the inconsistency of the results of studies that analyze the impact of ethanol consumption on triglyceridemia. However, a recent study of 8396 participants (Whitfield *et al.* 2013) supplied evidence for a J-shaped relationship between alcohol consumption and triglyceridemia – triglycerides were lowest in people reporting between three and twenty drinks per week (or 4 to 30 g of alcohol per day) (Whitfield *et al.* 2013). These findings are in agreement with work carried out on 9584 subjects from the Copenhagen City Heart Study (Tolstrup *et al.* 2009). They also observed a J-shaped association between alcohol intake and non-fasting triglycerides in women ($p=0.006$), but not in men ($p=0.23$). Accordingly, moderate alcohol consumption has even been associated with lower triglyceridemia according to a recent Mendelian randomization study (Lawlor *et al.* 2013). Therefore, there is growing evidence that low-to-moderate alcohol consumption is associated with a reduction of plasma triglycerides. The consumption of 20 g or less of alcohol per day can have a positive effect on TG concentration.

Important information can also be obtained from short-term intervention studies. The first meta-analysis of such studies (Rimm *et al.* 1999) concluded that alcohol consumption increases triglyceridemia (0.06 mmol/l per 30 g of alcohol consumed a day). However, a recent meta-analysis of 63 studies (Brien *et al.* 2011) did not confirm these findings and did not find any significant impact of alcohol consumption on TG concentration. If the relationship between alcohol consumption and triglyceridemia is indeed J-shaped, then an increase in alcohol intake might have no effect in subjects who drink very little, which could in turn explain why there is no overall effect of alcohol consumption. This could also provide an explanation for the discrepancies between the studies.

Alcohol consumption and postprandial lipemia

Torres do Rego *et al.* (2013) studied the effect of the daily amount of alcohol on diurnal triglyceridemia

in 139 men. They showed that capillary triglyceridemia is lower in those who drink less than 10 g ethanol/day compared to abstainers and highest in those who drink more than 30 g ethanol/day. This may correspond with the idea that the relationship between TG concentration and the amount of alcohol consumed is J-shaped (Torres do Rego *et al.* 2013). On the other hand, studies on the effect of alcohol taken with a meal on postprandial lipemia consistently demonstrate markedly increased and even prolonged hypertriglyceridemia in the postprandial state (Pownall 1994, Chung *et al.* 2003, Mudrakova *et al.* 2013). However, the dose of alcohol used in these studies is in a range that is comparable to a high level in the above-mentioned study.

Alcohol consumption and lipoprotein lipase

Lipoprotein lipase (LPL) – a key enzyme in lipoprotein metabolism responsible for hydrolysis of TG in triglyceride-rich lipoproteins – is a rate-limiting factor of plasma triglyceride clearance (Kersten 2014). Consumption of alcohol in an amount considered moderate has been repeatedly shown to increase LPL activity in intervention studies when measured in the fasting state (Schneider *et al.* 1985, Nishiwaki *et al.* 1994, Kovar and Poledne 2004). Increased LPL activity could explain the decrease in TG concentration in subjects who consume a low amount of alcohol per day. On the contrary, LPL activity is acutely inhibited after alcohol consumption. This finding was previously documented by Nikkila *et al.* (1978) and Schneider *et al.* (1985) who measured LPL activity in post-heparin plasma after alcohol consumption. We confirmed these findings even *in vivo* using a repeated intravenous fat tolerance test to estimate LPL activity (Zemánková *et al.* 2015). The acute inhibition of LPL activity could contribute to the increased magnitude of postprandial lipemia when alcohol is taken together with a meal. The differences between the long-term response of LPL activity to alcohol and the acute inhibition of enzyme activity may explain the observed J-shaped relationship.

Alcohol consumption and lipolysis in adipose tissue

As far back as the 1960s, Crouse and colleagues showed that some metabolic effects of ethanol are mediated by acetate (Crouse *et al.* 1968). Recently, it has

been shown that acetate signaling through G-protein-coupled receptor 43 (GPCR43) in adipose tissue results in the suppression of lipolysis and increased insulin sensitivity (Ge *et al.* 2008). Decreased lipolysis should result in the lower availability of free fatty acids for TG synthesis and for VLDL production in the liver, which may explain the observed effect of alcohol consumption on triglyceridemia. The administration of vinegar as a healthful alternative to alcohol consumption has even been recommended in a recent review (Pownall *et al.* 2015).

Conclusion

In summary, evidence that the relationship between alcohol consumption and triglyceridemia is J-shaped has gathered recently; alcohol consumed in a low dose can even decrease triglyceridemia compared to abstainers. It remains to be determined whether this J-shaped association between triglyceridemia and alcohol consumption can explain the described J-shaped curve for alcohol and cardiovascular risk. The effects of alcohol on TG concentration can be at least partially explained by the combination of long-term and acute effects of ethanol consumption on LPL activity.

The recommendation of moderate alcohol consumption in the prevention of cardiovascular disease remains a controversial area in preventive medicine. Due to the risk associated with the development of addiction to alcohol, it does not seem wise to recommend abstainers to start drinking alcohol. With regard to triglyceridemia as an independent factor of cardiovascular disease, the most appropriate recommendation for the Czech population (who in 2012 consumed on average 21.4 g of ethanol *per capita* per day, including newborns (Ritschelová 2014)) should be to reduce alcohol intake.

Conflict of Interest

There is no conflict of interest.

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