Commentary

Alcohol and Steatosis: The Japanese Paradox

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1. Background

In this issue of *EBioMedicine*, Roerecke and Colleagues report that, in Japan, alcohol consumption as low as <20 g daily was associated with significant protection from incident and prevalent fatty liver; however, no such association was found in countries other than Japan (Roerecke et al., 2016). This systematic review is based on the analysis of 18 articles (11 of which are from Japan) which recruited, overall, 99,370 participants, 25,662 of whom had steatosis.

Moreover, sex was an important modifier of the risk of fatty liver when the whole range of alcohol consumption was considered. Indeed, while in men a non-linear and inverse dose-response risk relationship was reported, in women the risk curve was J-shaped and turned to a detrimental association with increasing alcohol consumption.

Finally, binge drinking was consistently associated with higher risk of liver steatosis.

2. Steatosis

Steatosis defines fatty changes either in >5% of hepatocytes based on histological analysis or >5.6% based on findings from proton magnetic resonance spectroscopy (EASL-EAS-EASO, 2016). Often, steatosis is diagnosed with ultrasonography both in clinical practice and in the research arena (Ballestri et al., 2015, 2016a).

A large variety of causes, notably including alcohol consumption, may eventually be conducive to accumulation of intrahepatic fat (EASL-EAS-EASO, 2016). In recent years nonalcoholic fatty liver disease (NAFLD) has reached massive proportions worldwide and has an epidemic diffusion in certain high-risk groups. However, the rationale for distinguishing alcoholic from nonalcoholic fatty liver disease has been questioned based on shared clinico-pathological commonalities (Völzke, 2012).

3. Relationship of Fatty Liver with the Metabolic Syndrome

Traditionally deemed to be the "*hepatic manifestation of the metabolic syndrome*", NAFLD is more correctly deemed to be bi-directionally linked with either the Metabolic Syndrome (MetS) or its individual components. Indeed, on the one hand metabolic derangements are a strong predictor of all the individual histological components of NAFLD (Ballestri et al., 2016b). On the other hand, NAFLD assessed with either liver enzymes or ultrasonography will predict the risk of incident MetS and type 2 diabetes (T2D) over 5 years (Ballestri et al., 2016a).

4. Relationship of Alcohol with MetS

Alcohol consumption exerts a complex effect on the MetS with light alcohol consumption reducing and heavy alcohol consumption increasing the risk of MetS (Sun et al., 2014). Consistently, a randomized controlled trial in 224 individuals reported that initiating moderate consumption of alcohol (particularly red wine) modestly decreased cardiometabolic risk in patients with well controlled T2D (Gepner et al., 2015).

5. How Little Alcohol Is Safe?

A consensus report concluded that the threshold of acceptability in healthy adults/elderly was ≤30 g ethanol daily for men and ≤15 g daily for women (Poli et al., 2013). Such a modest amount of alcohol does not necessitate any medical action (Poli et al., 2013). This study confirms that, irrespective of sex, alcohol <20 g daily is probably safe. In men the threshold of safety may even be higher, whereas women are more vulnerable and develop more severe toxicity for lower amounts of alcohol. This is of interest given that the drinking of moderate amounts of red wine regularly is probably associated with a relative health benefit thanks to antioxidants such as polyphenols, particularly resveratrol.

6. Japan vs. Other Countries: Reasons for the Discrepancy

Interestingly, findings from this study would suggest that the beneficial effect of modest alcohol consumption is restricted to Japan, and is not extended to other countries (the *Japanese paradox*). This conclusion may, though, be spurious given that quantity and quality of data vary across countries and are probably non-comparable. Alternatively, types of alcoholic beverages and pattern of alcohol consumption in Japan or interaction of host's metabolic factors (notably including obesity) may account for this discrepancy (Askgaard et al., 2015). Of note, binge drinking was consistently associated with increased risk of fatty liver across countries, suggesting that this pattern of alcohol consumption is universally harmful.

7. Conclusions

To sum up, the study by Roerecke et al. (2016) confirms, in Japanese individuals, that modest alcohol consumption does not exert any detrimental effects in healthy individuals. In this specific setting, it may even have beneficial effects by decreasing incidence and prevalence of steatosis. Future studies should evaluate the reasons why such benefits are not reproducible outside Japan, namely *the Japanese paradox*.

Acknowledgements

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