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Commentary

Alcohol Misuse and Pancreatitis: A Lesson from Meta-Analysis

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Alcohol misuse is a global health problem that includes the digestive diseases. However, compared to the liver diseases, much less attention has been paid to alcoholic pancreatic disorders. Alcohol misuse is the most common cause of chronic pancreatitis (CP) and is the second-most common cause of acute pancreatitis (AP) after gallstones (Yadav and Lowenfels, 2013). In Japan, for example, alcohol is the leading cause of both AP and CP (Hamada et al., 2014), accounting for 33.5% and 69.7% of such cases, respectively. One reason for the insufficient awareness of alcohol misuse as an important risk factor of pancreatitis is that only 2–5% of heavy drinkers develop pancreatitis (Yadav and Lowenfels, 2013; Lankisch et al., 2002), a number much lower than that for chronic liver diseases. Some individuals may develop alcoholic pancreatitis with alcohol intake as low as 20 g/day, whereas most individuals do not develop pancreatitis no matter how much they drink or how long. It has been suggested that an additional insult is required to precipitate pancreatitis (Apte et al., 2010). However, detailed mechanisms remain largely unknown.

In this issue of *EBioMedicine*, Samokhvalov, et al. (Samokhvalov et al., 2015) conducted a meta-analysis of 7 studies (5 case–control and 2 cohort studies) to assess pancreatitis risk and alcohol consumption. They showed that the risk of AP and CP increased monotonically according to the average alcohol consumption with no identifiable threshold in men. In women, the relation between average alcohol consumption and AP was J-shaped; the risk of AP was lower below the threshold of 40 g/day, whereas the risk increased above this threshold. This study has suggested several issues to be clarified when we study the relationship between alcohol consumption and the risk of pancreatitis. First, there are several confounding factors in patients with pancreatitis. Most patients with alcoholic pancreatitis are smokers, and it has been suggested that smoking is an independent risk factor for AP and CP. A recent meta-analysis revealed that tobacco use increases the risk of AP and CP by 2.12 and 2.07 folds, respectively (Alsamarrai et al., 2014). Another important confounding factor is gallstones, which is the leading cause of AP in many countries (Yadav and Lowenfels, 2013). This meta-analysis included a large number of female AP subjects, suggesting that most of these female patients developed biliary, but not alcoholic, pancreatitis. It remains unclear whether the beneficial effects of low-level alcohol consumption in the prevention of AP is indeed due to the prevention of gallstones, because the effects of low-level alcohol consumption could not be compared between the patients with biliary AP and those with non-biliary AP in women. Information regarding the smoking status and gallstones, stratified by the amount and pattern of alcohol consumption, would clarify these issues.

The second issue concerns the definition of AP and CP in respective studies. Although AP and CP were traditionally regarded as separate diseases, it has been increasingly recognized that the progression from AP to CP is not so rare, and that AP and CP represent a continuum of the disease (Sankaran et al., 2015). A recent meta-analysis showed that 10% of patients with a first episode of AP and 36% of patients with recurrent AP develop CP, and that the risk is higher among smokers, alcoholics, and men (Sankaran et al., 2015). AP often occurs in patients with CP, and the definition might be further complicated by the presence of recurrent AP. It remains unclear whether low-level alcohol consumption showed beneficial effects on the development of CP as well in AP in women, mainly because the number of female patients with alcoholic CP is very small. Obviously, further studies focusing on alcoholic pancreatitis in women are needed.

Third, ethnical and geographical differences might exist in the sensitivity to alcoholic pancreatitis. The risk of CP in Asian studies increased in a linear fashion with a higher slope than in Europe or the United States. One explanation may be related to differences in body size; the average body weight of Asian individuals is lower than those of Westerners. Another explanation may be related to genetic differences; a loss-of-function variant in the aldehyde dehydrogenase 2 gene, for example, is found almost exclusively in populations of Asian origin (Yokoyama et al., 2002). Therefore, the threshold determined based on a meta-analysis could not be applied worldwide. Nevertheless, this line of information would lead to re-define the amount of alcohol consumption in diagnosing "alcoholic" pancreatitis. Alcoholic CP is in general diagnosed based on the history of alcohol drinking >80 g/day, whereas the amount of alcohol consumed is not usually included in the definition of alcoholic AP (Ammann, 1997).

Attention should be paid to identifying individuals at high risk of pancreatitis, and genetic studies might be useful to identify such individuals. A recent genome-wide study have identified that the

Abbreviations: AP, acute pancreatitis; CP, chronic pancreatitis.
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polymorphisms in the *PRSS1–PRSS2* and *CLDN2-MORC4* loci are associated with an increased risk of alcoholic pancreatitis, but not with alcohol-associated cirrhosis or alcohol dependence (Whitcomb et al., 2012). In daily practice, patients with alcoholic AP are convenient targets for intervention to prevent them from progressing to CP, because an AP event indicates that they are sensitive to alcoholic pancreatic injury. In such individuals, lower levels of alcohol consumption might not be safe. Obviously, further prospective studies are needed to estimate accurately the risk of pancreatic disorders from alcohol consumption.

Conflict of Interest

None declared.

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