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Review

Alcoholic liver disease: Clinical and translational research

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ABSTRACT

The present review spans a broad spectrum of topics dealing with alcoholic liver disease (ALD), including clinical research, translational research, pathogenesis and therapies. A special accent is placed on alcohol misuse, as alcohol is a legally commercialized and taxable product. Drinking alcohol, particularly from a young age, is a major health problem. Alcoholism is known to contribute to morbidity and mortality. A systematic literature search was performed in order to obtain updated data (2008–2015). The review is focused on genetic polymorphisms of alcohol metabolizing enzymes and the role of cytochrome p450 2E1 and iron in ALD. Alcohol-mediated hepatocarcinogenesis is also discussed in the presence or absence of co-morbidities such as viral hepatitis C as well as therapeutic the role of innate immunity in ALD–HCV. Moreover, emphasis was placed on alcohol and drug interactions, as well as liver transplantation for end-stage ALD. Finally, the time came to eradicate alcohol-induced liver and intestinal damage by using betaine.

Contents

Abbreviations: ALD, alcoholic liver disease; ASH, alcoholic steatohepatitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BAL, blood alcohol level; CI, confidence interval; CYP2E1, cytochrome p450 2E1; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IFN, interferon; IL, interleukin; LBP, lipopolysaccharides-binding protein; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; mRNA, messenger ribonucleic acid; NIAAA, National Institute on Alcohol Abuse and Alcoholism; OR, odds ratio; PNPLA3, patatin-like phospholipase domain-containing protein 3; ROS, reactive oxygen species; SAMe, S-adenosylmethionine; SIRT, sirtuin; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumor necrosis factor; UAL, urinary alcohol level; γ-GTP, γ-glutamyl transpeptidase.

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1. The new challenge of alcohol consumption

Alcohol consumption represents an ever-increasing global health burden (Lim et al., 2012).The magnitude of alcohol use is consistent with several chronic, non-infectious diseases. The impact of alcohol consumption was the subject of several meta-analysis including ischemic heart disease (Roerecke and Rehm, 2014a; Roerecke and Rehm, 2014b), atrial fibrillation (Larsson et al., 2014) and stroke (Chen et al., 2014a; Zhang et al., 2014). In addition, the risk of pancreatic injury in the general population revealed the important role of alcohol use as a contributory factor (Alsamarrai et al., 2014).

Alcoholic liver disease (ALD) is a major cause of chronic liver disease, leading to cirrhosis and liver cancer. The latest report from The National Institute on Alcohol Abuse and Alcoholism (NIAAA) shows that cirrhosis is the 12th leading cause of deaths in the United States, with a total of 29,925 deaths in 2007, of which 48% were alcohol-related. The spectrum of ALD includes steatosis, alcoholic steatohepatitis (ASH), cirrhosis, and hepatocellular carcinoma (HCC). The prevalence of heavy drinking patterns is on the rise in many countries such as Canada, USA, UK, as well as many Eastern European and Asian countries (Center for Disease Control and Prevention, 2012; Shield et al., 2013).

2. CYP2E1 polymorphisms and ALD

Cytochrome p450 2E1 (CYP2E1) induction by chronic alcohol consumption leads to a variety of complex cellular effects of enormous clinical significance. These include increased alcohol metabolism, increased production of reactive oxygen species (ROS) resulting in oxidative stress, increased cellular toxicity resulting in liver damage, and interactions with various drugs, xenobiotics and carcinogens. CYP2E1 expression and activation are induced in fatty liver disease, and oxidative stress plays a key role in the pathogenesis of ALD. In addition to ethanol, CYP2E1 also metabolizes linoleic acid and arachidonic acid to generate hydroxylated fatty acids which are further metabolized to cytotoxic dicarboxylic fatty acids. The associations between CYP2E1 polymorphisms and alcohol-related disorders were assessed in several recent studies (García-Bañuelos et al., 2012; Polonikov et al., 2013; Zeng et al., 2013; Plemenitas et al., 2015). For example, the presence of the *CYP2E1 c1/c1* genotype ($p = 0.011$) and the *c1* allele ($p < 0.05$) was higher among controls than among patients with alcoholic cirrhosis in a Mexican sample (García-Bañuelos et al., 2012).

The −1293C allele [odds ratio (OR) 5.04, 95% confidence interval (CI) 1.23–20.70, $p = 0.03$] and the −1293GC genotype (OR 5.36, 95% CI 1.28–22.50, $p = 0.03$) were associated with an increased risk of essential hypertension in men compared to controls. Furthermore, both the −1293C allele (OR 6.82, 95% CI = 1.12–41.70, $p = 0.04$) and the −1293GC genotype (OR 7.61, 95% CI 1.2–48.4, $p = 0.03$) were associated with an increased risk of essential hypertension in men with alcohol abuse. There was no association between the risk of essential hypertension and the −1293C allele or the −1293GC genotype in men without alcohol abuse (Polonikov et al., 2013). There was no association between the *CYP2E1 Dra I* polymorphism and the risk of ALD or alcoholic liver cirrhosis (Zeng et al., 2013). While the *c2* allele in the *CYP2E1 Pst I/Rsa I* polymorphism was not associated with an increased risk of ALD, the homozygous *c2c2* genotype was a risk factor for developing ALD among alcoholic patients compared to the homozygous *c1c1* genotype (OR 3.12, 95% CI 1.91–5.11). The *c2c2* genotype was associated with ALD compared to alcoholics without ALD in Asians (OR 4.11, 95% CI 2.32–7.29 vs. c1c1). Both *c1c2* (OR 1.63, 95% CI 1.05–2.53) and *c1c2/c2c2* (OR 1.58, 95% CI 1.04–2.42) genotypes were associated with ALD among Caucasians. There were no differences between patients with ALD and controls with respect to *CYP2E1 Pst I/Rsa I* polymorphisms (Zeng et al., 2013).

The *CYP2E1* c.−1053C>T polymorphism was not associated with alcohol dependence in a sample of 101 currently alcohol-dependent patients, 100 formerly alcohol-dependent subjects and 97 healthy controls. On the other hand, the presence of the CC genotype ($p = 0.028$) in the *CYP2E1* c.−1053C>T polymorphism and the C allele ($p = 0.007$) in the catalase c−262C>T polymorphism were more predominant among healthy controls. As such, the catalase −262TT genotype (OR 2.55, 95% CI 0.852–7.636, $p > 0.05$) and the catalase −262T allele (OR 1.74, 95% CI 1.164–2.610, $p < 0.05$) were risk factor for alcohol dependence (Plemenitas et al., 2015).

3. CYP2E1 polymorphisms and hepatocellular carcinoma

The *CYP2E1 Pst I/Rsa I* polymorphism was not associated with HCC in a recent meta-analysis (overall OR 1.03, 95% CI 0.76–1.40 for heterogeneous carriers of the *c2* allele and overall OR 0.82, 95% CI 0.51–1.31 for homozygous carriers of the *c2* allele). Statistical significance was also absent when heterozygous and homozygous carriers of the *c2* allele were combined and compared to homozygous carriers of the *c1* allele (Liu et al., 2014). Drinkers who carry the *CYP2E1 Pst I/Rsa I c2* allele have an increased risk of developing HCC (OR 2.88, 95% CI 1.25–6.60) (Liu et al., 2014). No statistically significant association between the *CYP2E1 Pst I/Rsa I* polymorphism and HCC risk was observed in a previous meta-analysis (OR 0.73, 95% CI 0.50–1.06 for *c2/c2* vs. *c1/c1*, OR 1.00, 95% CI 0.76–1.33 for *c1/c2* vs. *c1/c1*, OR 0.99, 95% CI 0.77–1.26 for *c2/c2 + c1/c2* vs. *c1/c1* and OR 0.73, 95% CI 0.50–1.06 for *c2/c2* vs. *c1/c2 + c1/c1*). However, habitual alcohol consumption among