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Toxic Role of Alcohol is Ongoing Health Issue-A Review

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Abstract

Ethanol toxicity can occur in both acute and chronic settings, representing two different spectrums of disease. The toxicity results from the ingestion of ethanol, usually in large quantities from beverage ethanol, commonly as alcohol, and non-beverage ethanol as cough medicine (Vonghia L, 2008). Ethanol primarily metabolized in the liver by alcohol dehydrogenase to acetaldehyde. The primary site of acute ethanol toxicity is the central nervous system and later in liver. Alcoholic fatty liver disease (AFLD), a potentially pathologic condition, can progress to steatohepatitis, fibrosis, and cirrhosis or cancer, leading to an increased probability of hepatic failure and death. The objective of this study is finds out the biological effect and mechanism of ethanol toxicity. Search was done on pub med and Google scholar and extracted the data as per the PRISMA statement.

Ethanol act as a non-familiar chemical to body and provide xenobiotic action which interfere the biological action as toxin. Alcohol, as a hepatotoxin, causes hepatocellular damage via ethanol metabolism-induced oxidative stress and the inflammatory response in the liver Alcohol metabolism is attained by both oxidative pathways, which either add oxygen or remove hydrogen, and nonoxidative pathways. Acetaldehyde is the key toxin in alcohol-induced liver injury, that cause cellular damage, inflammation, extracellular matrix remodelling, and fibrogenesis.

Keywords: Ethanol, liver, hepatotoxicity

Introduction

The World Health Organization (WHO) estimates that 4.5% of the global burden of liver disease and injury, and 4% of all deaths worldwide are attributable to alcohol (Organization, 2011). The common alcohol consumption contains ethanol and methanol is high toxic among two further alcoholic beverages is known to be positively associated with lifestyle diseases, such as cancer (Pe ttigrew S, 2014) [22]. Ethanol is the product of sugar degradation by fermentation, and it is naturally present in carbohydrate rich fruits after reaching post-maturity. With a long history of alcohol consumption, it has not been usually regarded as a dangerous substance and in fact, it has been perceived as integral part of a meal.

Liver is the major site of alcohol metabolism, and it is one of the major targets for alcohol-induced organ damage. Ethanol is a water-soluble compound that rapidly crosses cell membranes, resulting in ready equilibration between intra-and extra-cellular concentrations (Marco CA, 1990) [17]. It is highly diffusible through cell membranes and is metabolized by most tissues. Fat accumulation (steatosis), inflammation, necrosis and fibrosis are found in affected tissues and effect of the alcohol to the target tissue is depends on quantity of drinking. Acetaldehyde is the key toxin in alcohol-induced liver injury, that cause cellular damage, inflammation, extracellular matrix remodelling, and fibrogenesis (CS., Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis, 2004) [6]. The factors effect on vulnerability to alcohol toxicity include genetics, gender, lifestyle or nutrition, exposure to environmental chemicals and drugs, and co-morbidities. Especially, alcoholic beverages and ethanol in alcoholic beverages are recognized as carcinogenic to humans and it consider as risk factor.

Material and Method

Search was done on pub med and Google scholar and extracted the data as per the PRISMA statement.

Metabolism of Alcohol: Alcohol metabolism is attained by both oxidative pathways, which either add oxygen or remove hydrogen, and nonoxidative pathways. Blood alcohol concentration (BAC) is determined by how quickly alcohol is absorbed, distributed, metabolized, and excreted from the body. Although the liver is the main organ responsible for metabolizing the alcohol, stomach alcohol dehydrogenase has been reported to contribute to first pass metabolism (LEE, CHAU, YAO, & AL., 2006) [14]. In oxidative pathway several processes are involved in alcohol metabolism and mostly two enzymes are relevant in metabolizing alcohol such as alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). With involvement of ADH enzymes alcohol molecules are broken into acetaldehyde which is highly toxic substance and known as carcinogen (Edenberg, 2007) [8]. Further, acetaldehyde broken into acetate then it is broken into water and carbon dioxide and make easy to eliminate from body

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(Alcoholism., 1997) [3]. Cytochrome P450 (CYP2E1) and Catalase also involved in liver and non-oxidative pathways of alcohol metabolism can be activated during high dosages, or during chronic ingestion, mainly driven by inhibition of the other pathways (Zakhari, 2006) [30]. During alcohol consumption due to gastric alcohol concentration reach molar range in stomach human ADH3 may play an important role in the first pass metabolism in stomach than liver (Baraona, Abittan, & Dohmen, 2001) [4]. Also, in brain alcohol is metabolized by enzymes cytochrome P450 and catalase via non oxidative pathway.

Through oxidative pathway due to the alcohol oxidation, a highly reduce cytosolic environment bring in liver cell that is more vulnerable to damage from the byproducts of ethanol metabolism, such as free radicals and acetaldehyde. These acetaldehyde and acetate contribute to cell and tissue damage in various ways. Acetaldehyde has the capacity to bind microsomal protein, enzymes and microtubules and with DNA to form carcinogenic DNA. Hence the adducts of the protein from hepatocytes impairs protein secretion leads to hepatic enlargement.

Alcohol is none oxidatively metabolized by at least two pathways. One is formation of fatty acid ethyl esters and other is involved with enzyme phospholipase D which breaks down phospholipids (primarily phosphatidylcholine) to generate phosphatidic acid. Oxidative and nonoxidative pathways of alcohol metabolism are interrelated. Inhibition of ethanol oxidation by compounds that inhibit ADH, CYP2E1, and catalase results in an increase in the nonoxidative metabolism of alcohol and increased production of fatty acid ethyl esters in the liver and pancreas (Werner, Saghir, & Warshaw, 2002) [28]. Though genetic variation is vital factor for alcohol metabolism but not related to tolerance of toxic effect.

Ethanol in Liver: Alcohol, as a hepatotoxin, causes hepatocellular damage via ethanol metabolism-induced oxidative stress and the inflammatory response in the liver (Lieber, 2004). Alcohol dehydrogenase is the most catalytically efficient ethanol-metabolizing enzyme. It reaches its half-maximal velocity when circulating ethanol levels are about 5 to 10 mg/dl, well below levels that cause intoxication and further catalysis to acetaldehyde which is more toxic (Addolorato, Capristo, Greco, & al, 1997) [2]. Though the catalytic efficiency of CYP2E1 is slow than ADH, it has a 10-fold higher capacity for binding ethanol, becoming half-saturated. Ethanol interacts directly with the CYP2E1 protein, causing it to assume a conformation that resists degradation by the ubiquitin-proteasome system and resulting in the accumulation of CYP2E1moleculs. This wide substrate specificity, increased levels of the enzyme also accelerate the conversion of excess amounts of substrates other than ethanol, such as the analgesic and antipyretic medication acetaminophen.

Present concept that the alcohol metabolised by the hepatocyte initiates a pathogenic process that involves production of protein-aldehyde adducts, immunologic activity, peroxidation of lipid, and release of cytokines. Alcoholic fatty liver is the common pathological condition with high ethanol consumption and characterized by the accumulation of fat mainly triglycerides, phospholipids, and cholesterol that, fat is diffused into zone 2 and zone 1of hepatocytes due to steatosis (Liu, 2014) [15].

Acetaldehyde increases the ratio of the reduced form of nicotinamide adenine dinucleotide (NADH) to the oxidized form of nicotinamide adenine dinucleotide (NAD+) in the hepatocytes to decrease the β-oxidation of fatty acids by the mitochondria, resulting in fatty liver. (Kane AB, 1994) Acetaldehyde also forms an adduct with tubulin that induces microtubule dysfunction, resulting in decreased lipoprotein transportation from the liver (Ugarte G, 1997) [26] Acetaldehyde is the key toxin in alcohol-induced liver injury, causing cellular damage, inflammation, extracellular matrix remodelling and fibrogenesis (Mello T, Alcohol induced hepatic fibrosis: role of acetaldehyde, 2008). Hence, hepatic steatosis is an early response to alcohol consumption and it happens in more than 90% of heavy drinkers, with about 30% of heavy drinkers developing more severe forms of alcoholic liver disease.

Acetaldehyde and oxidants are highly reactive molecules that can damage deoxyribonucleic acid (DNA), proteins and lipids. Changes in hepatic respiration and lipid metabolism can cause tissue hypoxia and impairment in the mitochondrial function in liver. Further both of this effect disruption of signalling pathways and ion channel function, the unfolded protein response and oxidative stress as well as the activation of adaptive immune response that is significantly triggered by acetaldehyde protein adducts. Continuity of this state leads to make mutation in genetic factor and liver cell carcinoma can be ultimate result. Toxicity role of the ethanol mainly depends on steatosis, form of cytokine (e.g. TNF-α) production, mitochondrial dysfunction and/or oxidative stress. Here are various histological stages through which alcoholic liver disease (ALD) is thought to advance: fatty liver (steatosis), steatohepatitis (alcoholic hepatitis, alcoholic steatonecrosis), fibrosis, cirrhosis and HCC. Hence excessive consumption of alcohol creates various pathological condition under alcoholic liver disease (ALD) that cause to increase mobility and mortality of the global death.

Alcoholic Liver Steatosis

Alcoholic liver steatosis is the earliest stage of ALD and is developed in 90% of heavy drinkers or with chronic ethanol consumption. Recent evidence indicates that alcohol-induced fatty liver is vulnerable to developing alcoholic steatohepatitis. Alcohol impacts multiple aspects of hepatic lipid metabolism including increased hepatic fatty acid uptake, increased hepatic new lipogenesis, decreased mitochondrial β-oxidation, and decreased very low-density lipoprotein secretion, the net effect of which is increased hepatic lipid accumulation (Jeon, 2020) [11]. In chronic alcohol consumption, increases adipose tissue lipolysis of triglyceride stored in white adipose tissue, which leads to an increase in circulatory free fatty acid available for hepatic uptake. Steatosis condition of the liver does not show specific sign or symptom but liver enzyme can be increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT) as well as an AST/ALT ratio, >2. Tissue histology reveal numerous large-and small-sized lipid droplets in the hepatocyte cytosol.

Alcoholic Steatohepatitis

The group of patients with alcoholic fatty liver, inflammation and fibrosis is defined as alcoholic steatohepatitis. Inflammatory processes are primary contributors to the development and progression of alcoholic steatohepatitis (ASH). Innate immune system signalling is involved in the early stage of ASH with simple steatosis even before the onset of inflammation. Mild and chronic ASH, the number of hepatic macrophages increases due to infiltrated monocytes. Endoplasmic reticulum stress activates interferon regulatory factor 3 (IRF3) via the adaptor molecule STRING and IRF3 is

activated with a single exposure to alcohol, preceding the development of inflammation (Petrasek J, 2013) [24]. In mild and chronic ASH, the number of hepatic macrophages increases; infiltrating monocyte derived macrophages are believed to contribute to this expansion and the pathogenesis of the condition (Wang M, 2014.) [1].

Alcoholic Hepatitis

Alcohol-related hepatitis (ARH) is a unique type of alcohol-associated liver disease characterized by acute liver inflammation caused by significant alcohol use. Clinical diagnosis that makes it difficult to come to an agreement on the signs and symptoms that define the alcoholic hepatitis. Though all symptoms are common in other liver disease patient history is quite critical in this condition because heavy alcohol consumption that develops jaundice with elevated liver enzyme which serum aspartate aminotransferase (AST). Anyway, the AST and alanine aminotransferase (ALT) levels are usually 2-6 times the upper limit of normal with and AST/ALT ratio of greater than 2 in alcoholic hepatitis condition (McPherson S, 2016). Further ethanol directly activates Kuppfer cells resulting in increased consumption of oxygen. Many stimulatory cytokines including prostaglandin E2, which increases the metabolic activity of hepatocytes are released by Kuppfer cells. Here after many essential molecules are broken down and formed because of activation of chemical reactions requiring oxygen, resulting in worsening of hypoxia induced cell damage to hepatocytes (II., 1998) [10].

Liver Cirrhosis

Liver cirrhosis is a late stage of scarring (fibrosis) of the liver caused by many forms of liver diseases and conditions, including chronic alcoholism. It results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis and histologically it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture (Dooley J, 2011) [7]. This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction. On the basis of complications presence cirrhosis is in four clinical stages and stage 01 is characterized by the absence of esophageal varices and of ascites. Stage 4 is characterized by GI bleeding with or without ascites. While stage two and three are presence of esophageal varices without ascites and without bleeding, characterized by ascites with or without esophageal varices in a patient that has never bled respectively (R, 2005) [25]. Cirrhosis is an end stage disease and after advance stage patient has to terminate the life.

Hepatocellular Carcinoma

An excessive alcohol intake has been shown to be a risk factor for Hepatocellular carcinoma and alcohol intake of >60-100 g/day increases the vulnerability (Persson EC, 2013;) [23]. When a large amount of ethanol is consumed, cytochrome P450 2E1 (CYP2E1), and catalase of peroxisomes also contribute to the metabolism. Correspondingly acetaldehyde can be carcinogen by forming direct DNA mutagenic mechanisms, by increasing the point mutation frequency in the hypoxanthine phosphoribosyltransferase (HPRT) gene in lymphocytes. (He SM, 1990) [9]. Acetaldehyde interacts with certain amino acids in proteins, for example, the formation of adducts with O6-methylguanine methyltransferase causes DNA repair system dysfunction. With regard to liver fibrosis, acetaldehyde produced in the hepatocytes can enter the hepatic stellate cell (HSC) and induces the expression of type I collagen genes *in vitro*. Taken together, the direct DNA mutagenic effect of acetaldehyde and the indirect carcinogenic effect through the formation of adducts may modulate hepatocarcinogenesis and liver fibrosis. Further polymorphism of the gene encoding for CD14 expressed on a Kupffer cell has been implicated in the risk of ALD and hepatocellular carcinoma (HCC).

The underlying causes of cancers related to alcohol consumption are not yet clear, although various factors have been proposed as having a role to play such as the localized effects of alcohol, cytochrome P4502E1, acetaldehyde, and interaction with retinoids (Lachenmeier DW, 2008) [13]. Also, acetaldehyde is not only extremely toxic, it is also carcinogenic. Cells or tissues are exposed to an amount of acetaldehyde after alcohol consumption which may be significant and could well increase carcinogenesis.

Summary

According to a WHO report, approximately 280 million individuals, or 4.1% of the population aged >15 years, meet the definition of Alcohol use disorders (World Health Organization, 2014). There is a positive dose-response relationship between the amount of alcohol intake and the risk of liver damage even with cancer. Therefore, alcoholic liver disease, a leading cause of morbidity, mortality, and cirrhosis, can range from simple steatosis to hepatocellular carcinoma. Multiple mechanisms such as oxidative stress, mitochondrial dysfunction, and alteration in gut-liver axis have been proposed for the pathogenesis of alcoholic liver disease. Abstinence from alcohol leads to resolution of alcoholic fatty liver disease which benign steatosis and it improves survival in alcoholic cirrhotic patients, even those with decompensated liver function.

Conclusion

Though the alcohol is a part of the meal it can be toxic substance when using in inappropriate manner. Due to the over consumption alcohol intoxication occur and cause to number of pathological conditions. It's a common fact that liver is capable in reversing damage but subjected to limitation. With over usage of ethanol and beverages liver is unable to maintain homeostasis. Under this scenario acetaldehyde create toxic effect to the liver cell. Lipid deposition in the liver gets rearrange and influence the liver cell steatosis and with continues usage of alcohol condition might be deteriorated. Thus, early abstention is critical in preventing liver damage with heavy consumers.

Liver steatosis is the early stage of liver damage and poor management will be ended with fibrosis of liver tissue. On other way the risk of having hepatocellular carcinoma is high with over usage of alcohol and beverages. Hence appropriate usage or abstention of Alcohol is vital fact for healthy liver

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