Thi-Qar Medical Journal (TQMJ): Vol. (28), No. (2), 2024
Web Site: https://jmed.utq.edu Email: utjmed@utq.edu.iq
ISSN (Print):1992-9218 ISSN (Online): 3006-4791

The Effect of Sterol Regulatory Element-Binding Protein-1 C Modification on Fatty Acids in Alcoholic Liver Disease (ALD)

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Abstract : Among chronic liver diseases, alcoholic liver disease (ALD) is the most common in the world. The main cause of ALD is excessive alcohol consumption. The accumulation of fatty acids in liver cells is one of the oldest and most famous alcohol-related changes that cause the development of ALD . Although the mechanism by which excessive alcohol intake leads to fatty acid accumulation is far-fetched and complex, one of the mechanisms by which alcohol affects fatty acids is the regulation of the sterol regulatory element-binding protein-1 c (SREBP-1 C) which may be key to the treatment of ALD. In this review, we present evidence supporting the key important role of the SREBP-1 C in influencing the synthesis and accumulation of fatty acids that are a major cause of ALD, and we suggest that there should be future studies to evaluate the modification of the SREBP-1 C as a possible new treatment for alcoholic liver disease.

Introduction :Alcoholic liver disease (ALD) is a group of manifestations ranging from steatohepatitis, fatty liver disease and cirrhosis of the liver due to the constant consumption of alcohol, recently ALD is one of the most common diseases in the world that causes death [1][2] Alcohol intake is one of the global health problems, ALD caused by excessive and persistent alcohol consumption is a major risk factor for mortality among the world's population. [3][4][5]. Excessive alcohol consumption causes the highest degrees of liver tissue damage because the liver is the main site of ethanol metabolism .ALD is affected by alcohol-induced hepatitis and cirrhosis [6]. Due to the importance of alcoholic liver disease, many studies have focused on it, such as , inflammatory factors [7][8], studies on immune cells [9] , oxidative stress [10], autophagy [11], endoplasmic reticulum stress [12][13] linked to ALD. It is expected that the main cause behind hepatitis and cirrhosis causative agent of cumulative hepatitis is excessive lipids accumulation [14]. The early stage of alcoholic liver disease is the accumulation of lipids [15]. Early diagnosis of ALD is important to encourage abstinence from alcohol consumption to reduce the development and management of complications of ALD [16]. The chemical explanation of ALD revolves around the ability of ethanol metabolism to modify the state of reduction and oxidation inside the liver in addition to preventing the oxidation of fatty acids . Previous studies have found that alcoholic conditions lead to suppression of fatty acid oxidation and formation inside the liver .Alcohol regulates the activation of the sterol-1 regulatory protein, which leads to the stimulation of lipolytic enzymes [17]. Long-term ethanol intake causes liver hepatic steatosis or fatty liver disease [18]. In Hepatosteatosis, dyslipidemia occurs, where cholesterol and triglycerides

accumulate, and the cause of this is an imbalance of fat synthesis and analysis, which causes fatty hepatomegaly [19]. Evidence suggests that people who consume alcohol moderately are more likely to develop ALD compared to people who consume alcohol a lot [20][21]. One of the mechanisms by which alcohol affects fatty acids is its effect element binding protein 1C in ALD, but this mechanism is still unclear, In addition, the understanding of the mechanisms of the pathogenesis of alcoholic liver disease is still limited due to the complexity of ALD, In this review, we focused on the mechanisms by which the modification of the sterol regulatory element-binding protein-1 c affects the regulation of fatty acid synthesis in ALD, Because understanding the mechanisms of the pathogenesis of ALD creates new possibilities for treatment

Prevalence alcoholic liver disease : ALD is widespread and is one of the most common chronic liver diseases among the world's population, 48% of deaths are due to cirrhosis in the United States [22]. Due to ALD about 21.5 million years of life were lost in 2016[23]. Global deaths caused by excessive alcohol consumption account for 3.8 % of deaths worldwide due to cirrhosis of the liver and ALD [24]. The use of alcohol in large quantities, prevalence of ALD is constantly and progressively and at an early age among the world's population [25]. The death rate due to ALD reaches 5% worldwide, with the highest percentage in Europe . More than half a million deaths were recorded in 2010 due to cirrhosis of the liver caused by alcohol intake [22]. Out of ten deaths, one of them is due to cirrhosis of the liver caused by alcohol consumption , and 50% of deaths due to liver disease are caused by drinking alcohol [26]. The mortality rate in the US population is estimated at 5.5 per hundred thousand deaths, with the prevalence of ALD reaching 2% in 2010. In Europe, the percentage of deaths due to alcohol-related liver diseases is 41% [27]. In South Asia, specifically in India, the percentage of death due to cirrhosis of the liver is 34%, and 20% of patients with cirrhosis of the liver are alcohol consumers, which means that alcohol is the most common cause of death due to liver disease [28]. The prevalence of alcohol-related disorders is 8.6 % over a lifetime, the prevalence rate in Iraq (0.7%) is the lowest, while in Australia (22.7 %) it is the highest [29]

Metabolism of alcohol :Through the intestines and stomach, alcohol is absorbed . About 10% of alcohol is excreted through urine, breathing and sweat, while 90 % of alcohol remains inside the body Where the remaining alcohol is oxidized inside the liver[30]. The liver has an important role in the process of alcohol metabolism due to the presence of alcohol metabolism enzymes at high levels inside the liver [4]. By non-oxidative and oxidative pathways alcohol is metabolized inside the liver [31][32]. The main pathway of alcohol metabolism is the oxidative pathway, which is in two steps , the first step in which alcohol is oxidized by alcohol dehydrogenase to acetaldehyde [33]. The constant consumption of alcohol increases the activity of the enzyme cytochrome(CYP2E1). By forming reactive oxygen species (ROS) the cytochrome enzyme promotes the production of acetaldehyde [34]. Alcohol is hydrolyzed to acetaldehyde by peroxisomal catalase [10]. Then, in the second step, acetaldehyde is rapidly converted by aldehyde dehydrogenase to acetate .Acetate is metabolized to CO2, H2O and fatty acids within the surrounding tissues [10][12]. Quantitatively, the non-oxidative pathway hydrolyzes a

small part of alcohol metabolism. By means of various enzymes a small amount of alcohol with different endogenous metabolites is bound anoxically[35][36].

Metabolisem of alcholic [37]

Fatty acid and Alcoholic liver disease

By CYP2E1 ethanol metabolism is closely related to the overproduction of ROS in hepatocytes .

Protein carbonation ,lipid peroxidation and radical formation of lipids are promoted by oxidative stress .1-hydroxylation is catalyzed by the enzyme CYP2E1 to endogenous substrates such as (prostaglandins, steroids and fatty acids) this update occurs in microsomes [38]. Inside the microsomes, excessive alcohol consumption affects fatty acids, as alcohol facilitates the process of hydroxide of unsaturated fatty acids, including arachidonic acid (AA)[39][40]. In ALD, a decrease in the level of arachidonic acid was observed and its concentration was increased due to supplementation inhibiting the enzyme CYP2E1. Hepatic steatosis is a prominent feature of Alcoholic liver disease and is characterized by lymphocyte infiltration and hepatocyte hyperplasia. The accumulation of lipid droplets in the hepatic parenchyma occurs due to an imbalance in the synthesis and oxidation of fats (β-oxidation) associated with alcohol consumption[41]. Ethanol metabolism is related with down-regulation of peroxisome proliferator activated receptor alpha (PPARα) and regulation of sterol regulatory element binding protein 1c (SREBP-1c) [42][43]. The synthesis of fatty acids is enhanced by the above rather perverted expression and prevents β-oxidation [44][45]. The reason for the increase in alcoholic liver steatosis is the interference between fat balance and alcohol consumption, which promotes lipid formation . The newly synthesized free fatty acids (FFAs) are converted into triglycerides and diglycerides to form fat droplets inside the liver cells [46][47]. The most important causes of apoptosis and hepatomegaly are reactive oxygen species ROS and the accumulation of fat droplets [48].

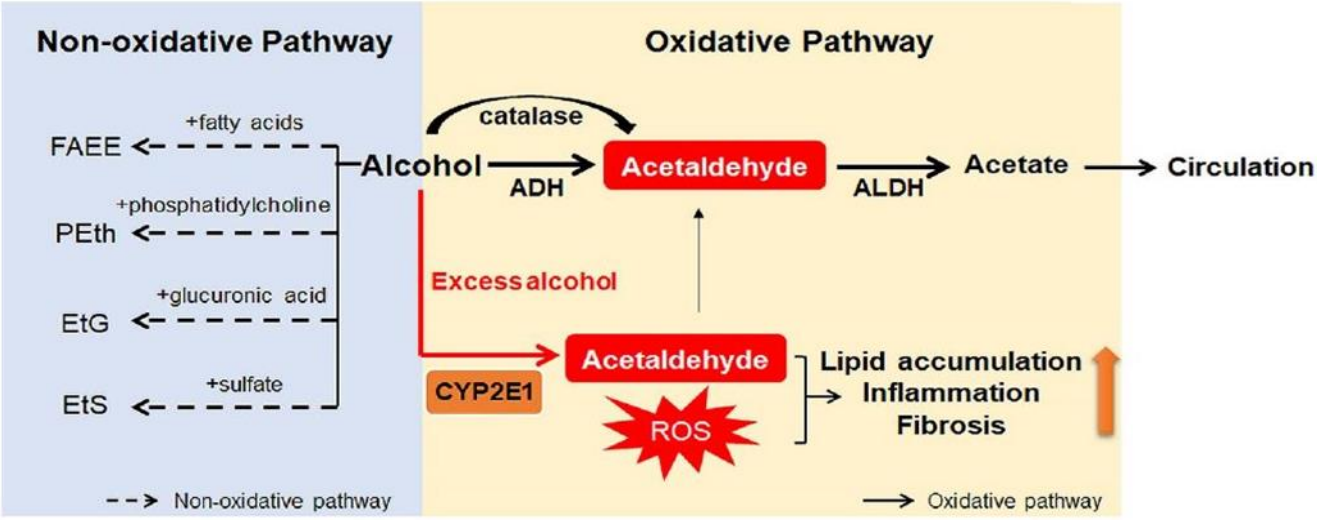

Figure (1).

Sterol Regulatory Element Binding Proteins (SREBPS)

SREBPs is an endoplasmic reticulum-linked transcription factor that controls the expression of genes for lipid absorption and synthesis [49][50], Has a role in lipid metabolism. SREBPs has three forms (SREBP-1a, SREBP-2 and SREBP-1c), which have an important role in the activation of more than 30 genes involved in the assimilation and synthesis of fatty acids, cholesterol, triglycerides and phospholipids in the liver[51]. SREBP-1c is a transcription factor that controls lipid synthesis, which is stimulated in response to dietary increase and is also stimulated to convert glucose into triglycerides and fatty acids for energy storage [52]. SREBPs controls fat synthesis by integrating cellular signals, which is expected to become an important treatment for alcoholic liver disease [53][54].

Some mechanisms affecting the role of SREBP-1c in the synthesis and regulation of fatty acids

Effect by Progesterone (P4) :P4 increases the levels of the SREBP-1 C and, consequently, increases the fatty acid content in the liver [55].

Delphinidin-3-sambubioside (Dp3-Sam) : Dp3-Sam Reduces the expression of the SREBP-1 C, which reduces blood lipids by regulating the oxidation of fatty acids in the liver [56].

Nuclear receptor 4A1 (NR4A1) :NR4A1 Affects the regulation of the SREBP-1, which affects the synthesis of fatty acids by modifying CD36 and fatty acid binding protein [57].

Kruppel-like Factor 2 (KLF2) is a Protein Coding gene.

KLF2 enhances fatty acid synthesis by activating SREBP1 by increasing the expression of SCAP which binds to SREBP1 [58].

Signal transducer and activator of transcription 3 (STAT3) :STAT3 directly regulates the expression of SREBP - 1 to promote the synthesis of fatty acids . STAT3 increases the synthesis and desaturation of new fatty acids through direct binding to to the promoters of SREBPF 1 and SCAP to activate the expression of SREBP-1 [59].

Nuclear factor Y (NF–Y) :overexpression of NF–Y causes an increase in the activation of SREBP1, which leads to the synthesis of fatty acids, so NF–Y is involved in alcoholic liver disease [60].

Alcoholic Liver Disease and Sterol Regulatory Element-Binding Protein-1 C

Some studies have indicated that alcohol consumption affects the main factors that affect lipid metabolism, including the binding protein of the (SREBP1c), which has an important role in causing ALD[38][61]. Where alcohol activates SREBP1c, which leads to enhanced synthesis of fatty acids inside the liver, SREBP1c is a major transcription protein through the regulation of fatty enzymes affects the synthesis of new fats such as fatty acid synthase and acetyl CoA carboxylase [62][63][64].

By alcohol SREBP-1c can be easily expressed by the accumulation of (ROS) and reduced regulation of protein kinase activated by a major regulator of energy metabolism) [38][65]. By regulating SREBP-1c, the cytokine signaling protein inhibitor increases the synthesis of fatty acids, presumably this process is carried out by persistent hyperinsulinemia and activators of transcription (STAT3) phosphorylation and suppression of signal transducer [66]. SREBPs have important roles in the synthesis of fatty acids . There are three types SREBP-2, SREBP-1c and SREBP-1a. SREBP-1c favors the fatty acid synthesis pathway ,as this protein dominates the liver . Transcription of the synthesis of genes involved in the synthesis of triglycerides and fatty acids is activated such as glyceraldehyde 3-phosphate acyltransferase , stearoyl-CoA desaturase (SCD) and the genes encoding fatty acid synthase by SREBP-1c [67][68]. In addition to the previous studies we have mentioned, the evidence indicates that SREBP-1c has important roles in the synthesis of fatty acids and is a major contributor to ALD [69].

Conclusion

Given the important roles played by SERPs in controlling the balance and synthesis of fatty acids in alcoholic liver disease, it will be interesting to explore additional and new mechanisms for regulating and modifying SERPs, because these new mechanisms may provide potential therapeutic methods to combat diseases, including alcoholic liver disease . We also suggest that modifying SREBPs may be useful in the management of alcoholic fatty liver disease.

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