WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 1, 543-568. Review Article ISSN 2277– 7105

ALCOHOL INDUCED OXIDATIVE STRESS AND HEPATOTOXICITY- A REVIEW

Renu Malik[1]*, Dr. K. G. Singhal[2] and Ritu[3]

[1]Lord Shiva College of Pharmacy, Sirsa, Haryana. India.

[2]ASBASJSM College of Pharmacy, Bela, Ropar, Punjab, India.

[3]Delhi Pharmaceutical Sciences and Research University, New Delhi, India.

Article Received on
24 Oct. 2019,

Revised on 14 Nov. 2019,
Accepted on 04 Dec. 2019,

DOI: 10.20959/wjpr20201-16415

***Corresponding Author**
Renu Malik
Lord Shiva College of Pharmacy, Sirsa, Haryana. India.

ABSTRACT

This article is based on the various advances in mechanism of hepatotoxicity by alcohol. Liver is mostly target for various drugs, xenobiotics because of its unique metabolism. Alcohol metabolism in liver generates the various reactive oxygen species (ROS). These radicals lead to cell apoptosis by enhancing the production of kupffer cells and neutrofill infiltration. Kupffer cells trigger the release of cytokines, reactive oxygen species and chemokines, TNF-α. Alcohol depletes fatty acid oxidation and induces lipogenesis. This article also summarizes the molecular level of liver damage including PPAR, Adiponectin, SIRT1, SERBPs. Liver have wide range of metabolic enzymes which is use to metabolize alcohol specially CYT P450. CYP2E1 mediates ethanol oxidation reaction by two different kind of oxidation, which is elaborated here.

KEYWORDS: Alcohol, Oxidative stress, Hepatosis, Cirrhosis, CYT P450, Adeponectin.

1. INTRDUCTION

Alcohol abuse is one of the three high risk factors to health globally. Every year approximately 2.5 million death occur on vigorously use of alcohol. Among alcohol consumers, 4.2% are woman and 16.1% are men. Alcohol is second high source of income after tobacco in the world.[1]

62.5 million alcohol users estimated in India. Due to its large population, India has been identified as the potentially third largest market for alcoholic beverages in the world.

Alcohol consumption has a negative impact on various organ systems, affecting the central nervous system, gastrointestinal tract, the hematopoietic organs and immune system.[2] Besides, its consequences are multifactorial.[3] Not only alcohol abuse lead to health problems such as liver, hematological, pancreatic, gastrointestinal, cardiovascular and respiratory disorders as well as malnutrition, it may also interfere with fetal development.[4] Furthermore, heavy consumption may results in intoxication with respiratory failure, an increased risk of infections, such as pneumonia.[5] Alcoholic liver disease is a major cause of morbidity and mortality worldwide.[6] According to WHO fact sheets 2012, among alcoholic's mortality rates, 16.6% death occur due to liver cirrhosis and 8.2% due to liver cancer.

Liver damage due to Alcohol, is divided in to four stages:

i. Fatty liver (steatosis)

ii. Inflammatory liver (hepatitis)

iii. Fibrogen deposition in liver (fibrogenesis)

iv. Damage of liver (cirrhosis).

First three stages are reversible on alcohol withdrawal and fourth stage is irreversible.

Liver is a vital organ in human body and play an important role in metabolism and detoxification of various xenobiotics. It performs carbohydrate metabolism (gluconeogenesis, glycogenolysis, and glycogenesis), protein metabolism, amino acid synthesis, fat metabolism on emulsifying by bile acid. It mediates lipogenesis and synthesis of triglycerides, cholesterol. It also mediates the production of various hormone include insulin-like growth factor-1 (IGF-1) hormone and thrombopoietin.

2. SPECTRUM OF ALCOHOLIC LIVER DAMAGE

Alcohol induced liver injury progresses through different characterized stages[7,8] are characterized by fatty liver, inflammation, hepatocyte necrosis, fibrosis and ultimately cirrhosis.

2.1. Steatosis (Fatty liver, Hepatosis)

Steatosis develops in 10 - 90% population of alcohol drinkers.[9,10] Alcohol consumption leads to steatosis condition of a liver is result of metabolic imbalance such as increased fatty acid synthesis, increased triglycerides synthesis, mobilization of extra hepatic fat stores and decreased β-oxidation.[11] This is reversible and not a serious condition of liver.[12]

In steatosis, mitochondria become enlarge[13], hyperplasia of smooth endoplasmic reticulum (SER)[14], increases protein and water content of hepatocytes.[15] During steatosis stage fatty liver is prone to endotoxins, cytokine action and oxidative stress.[16,17,18]

Micro-vascular and macro-vascular are two types of fatty liver. Macro-vascular fatty liver is due to improper fat filtration and lateral displacement of nucleus. Fatty infiltration causes one large droplet of fat in each hepatocyte which leads to stetosis.[19] Micro-vascular steatosis is alcoholic foamy degeneration; hepatocytes are filled with tiny fat droplets (less than 1μm) with central placed nucleus.[20]

Experimental studies explored that the type and amount of dietary fat affects the fatty liver development. Long chain fatty acids content increases the steatosis condition and a decrease in fatty condition of liver is due to the diet of medium chain triglycerides.[21]

2.2. Hepatitis (Inflammation)

Acute alcoholic hepatitis condition develops in 10 to 30% of alcoholics.[22,23] The highly characteristic histological condition of alcoholic hepatitis is sclerosing hyaline necrosis of liver cells. In man, it is due to infiltration of polymononuclear leucocytes which mediates hepatocytes degeneration and finally necrosis of cells. In alcoholic hepatitis liver, an inclusion found in cytoplasm of liver cells called Mallory body as morphological alteration.[24]

Alcoholic hepatitis is a non symptomatic condition and reversible stage on cessation of alcohol.[25] Fatty liver is prerequisite to the development of inflammation because fat in liver is more vulnerable to various factors that trigger various inflammatory mediators.[26] Oxidative stress induced either by dietary polyunsaturated fatty acids or by iron supplementation may aggravate the inflammation.[27,28]

2.3. Fibrosis

Liver fibrosis refers to the accumulation of tough, fibrous scar tissue in the liver. Fibrosis occurs when excessive scar tissue builds up faster than it can be broken down and removed from the liver. In a healthy liver, the synthesis (fibrogenesis) and breakdown (fibrolysis) of matrix tissue are in balance. This is irreversible and progression may continue even after cessation of alcohol intake.[29]

When hepatocytes (functional liver cells) are injured due to infection with a virus, heavy alcohol consumption, toxins, trauma, or other factors, the immune system is activated to repair the damage. The injury or death (necrosis) of hepatocytes stimulates inflammatory immune cells to release cytokines (TNF-α, TGF-β), growth factors, and other chemicals in kupffer cells.[30,31] These chemical messengers direct activate hepatic stellate cells and transform these cells into the myofibroblasts. Myofibroblast activates and produce structural protein like collagen, matrix glycoproteins (such as fibronectin), proteoglycans, and other substances. These substances cause the overproduction of extracellular matrix (nonfunctional connective tissue).[31]

Alcohol metabolite acetaldehyde and oxygen-derived free radicals have been invoked in the stimulation of collagen synthesis.[32,33]

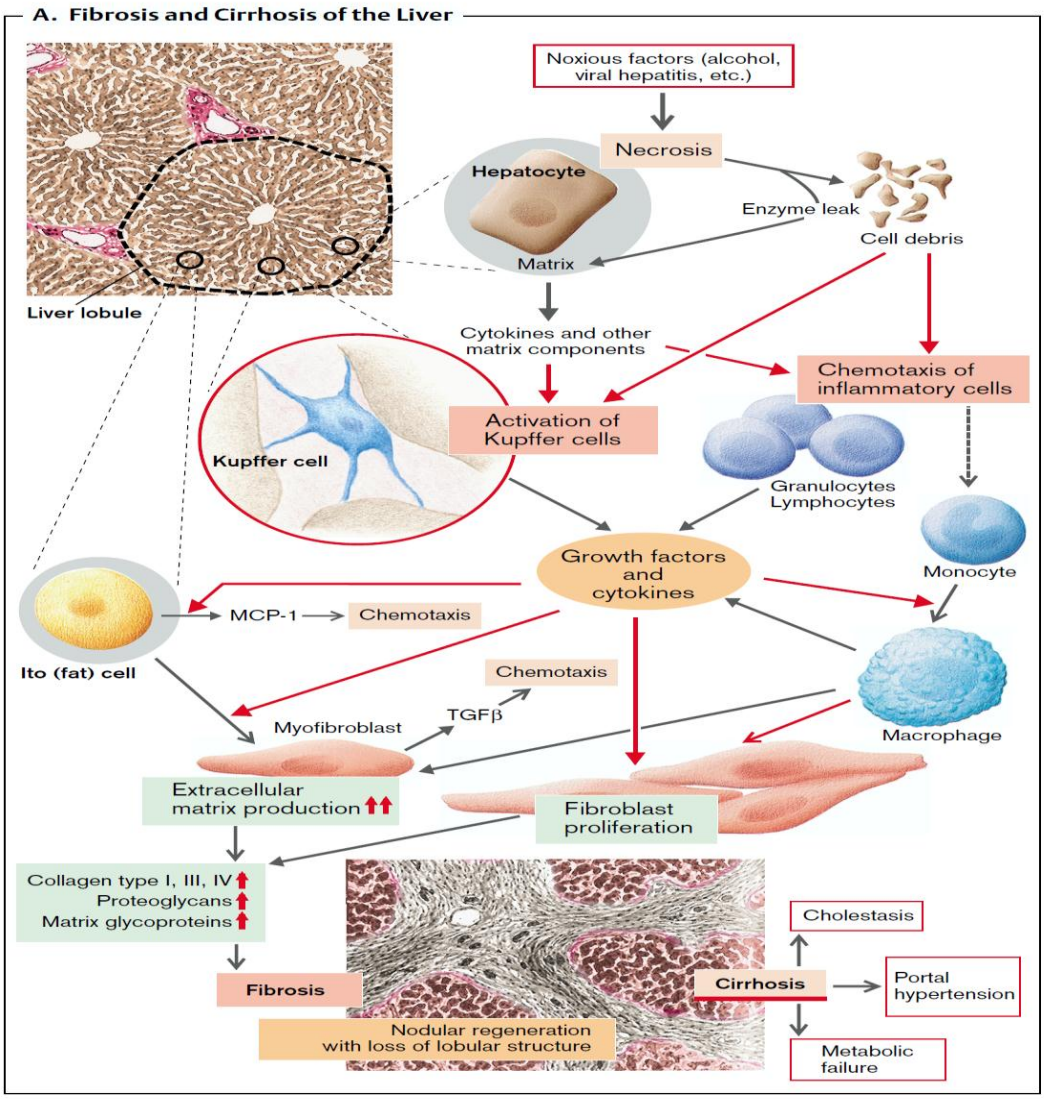

Fig. 1: Mechanism of Alcoholic Liver damage.

2.4. Cirrhosis

Cirrhosis is the most severe form of alcoholic liver injury; develop after 10-20 years of heavy drinking.[23,34] The term cirrhosis is describing the orange or tawny surface of the liver.

Liver fibrosis becomes so extensive that the architecture of the liver is altered as a result of excessive scarring, development of small nodules, and changes in liver tissue.[35,24] As cirrhosis further develops, scar tissue replaces healthy liver cells, stiffens blood vessels, distorted internal structure and the ability of the liver to perform its many functions.[36]

Cirrhosis is divided into two categories

- Compensated
- Decompensated

Compensated cirrhosis means that the liver is heavily scarred but can still perform many important bodily functions. Many people with compensated cirrhosis experience few or no symptoms and can live for many years without serious complications.

Decompensated cirrhosis means that the liver is extensively scarred and unable to function properly. People with decompensate cirrhosis eventually develop many symptoms and complications that can be life threatening.

3. Ethanol Metabolism

The liver is the main organ for metabolism of ethanol. Ethanol is mainly metabolized by the gastric alcohol dehydrogenase enzymes (ADH). The other route of metabolism of ethanol are microsomal ethanol oxidizing system (MEOS) that includes cytochrome p450 system mainly cytochrome p450 E1 (CYP2E1) and catalase (CAT).[21]

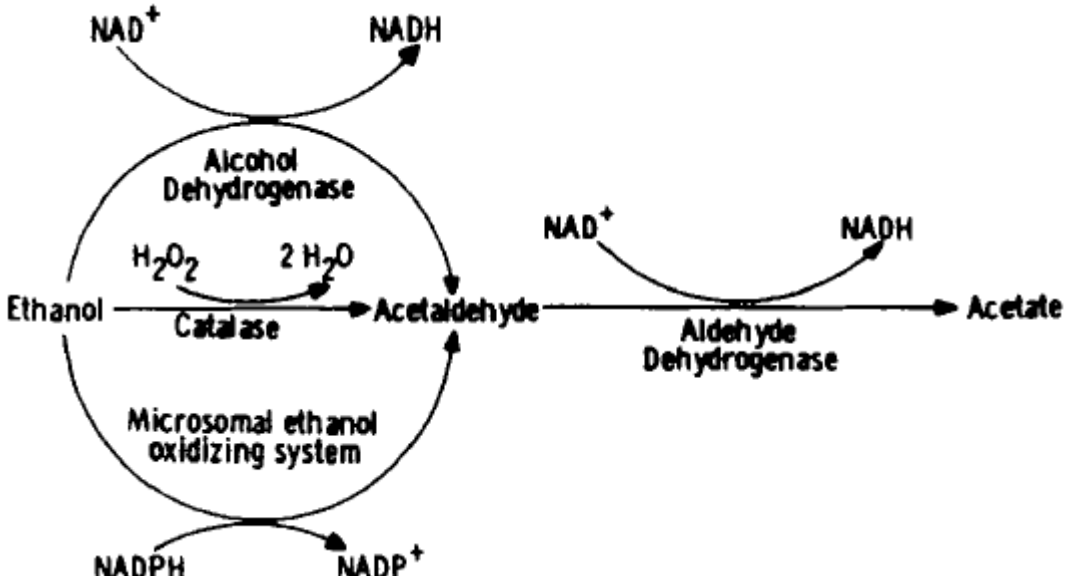

Fig. 2: Ethanol metabolism pathways.

3. 1. Alcohol dehydrogenase

ADH is located in hepatic cytosol and catalyzes the conversion of ethanol to acetaldehyde in presence of NAD^+ (Fig. 2). Acetaldehyde is a potent toxicant to lead various fatal effects in body.[33] Acetaldehyde is then converted in to acetate ion by catalyzing through Aldehyde Dehydrogenase (ALDH). ALDH is a mitochondrial enzyme which produces non toxic acetate ions with conversion of NAD^+ to NADH.[37]

$CH_3CH_2OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+$

The imbalance between $NADH/NAD^+$ ratio affects the metabolism of lipids and carbohydrate in cytoplasm and mitochondria. This imbalance leads to impaired glyconeogenesis and diverts the citric acid cycle towards ketogenesis and fatty acid synthesis on the Acetyl CoA step. Together with decrease in β oxidation of fatty acid and increase in fatty acid synthesis contribute in fatty liver i.e. steatosis.[38,39,40]

3.2. Microsomal ethanol oxidizing system

Beside ADH, CYP2E1 is another microsomal enzyme which metabolizes ethanol at high concentration**.** The mechanism becomes more significant in the case of alcoholic liver disease. CYP2E1 also metabolizes vitamin A, protease inhibitors and acetaminophen.[41,42] It implicates as a source of oxidative stress by inducing its activity 2-10 folds after chronic ethanol exposure.[43]

$CH_3CH_2OH + NADP^+ \rightarrow CH_3CHO + NADPH + H^+$

CYP3A, CYP1A are also involved in ethanol oxidation and get induced.[44,45]

3.3. Catalase

Catalase is present in peroxisomal membrane and plays a minor role in hepatotoxicity. It can oxidize ethanol in presence of hydrogen peroxide (H_2O_2) into acetaldehyde and water. *In-vivo* activity of catalase is limited due to bioavailability of hydrogen peroxide is very less in liver.

4. Genetic Factors Involved In Liver Damage

Genetic determinants play an important role in the development of alcohol dependence and alcohol-related disorders with heritability estimates in the range of 50-60%, gene coding for enzymes[46] that metabolizes both ethanol and acetaldehyde.[47] These genes encode for ADH, ALDH and C2 allele of the gene coding for CYP2E1affects alcohol dependence, sensitivity to alcohol and ALD cirrhosis development. Polymorphism of ALD and ALDH genes has been shown influence alcohol sensitivity for some races like Asians. In woman even consumption of low quantity of alcohol causes hepatotoxicity.[48] The polymorphism of C2 promoter alleles induces on alcohol consumption and exhibits a greater ability to metabolize alcohol this might increases lipid peroxidation and free radicals generation that's lead to fatty liver.[49] The XRCC1 gene encodes for XRCC1 protein, which repairs the damaged DNA through free radical generation.[50] Polymorphism of XRCC1 gene reduces the DNA repair activity on alcohol consumption. Alcohol also increases the polymorphism of CD14 encoding genes on kupffer cells and makes them more sensitive towards endotoxins.[51]

4.1. Role of gender

Females are more sensitive toward alcoholic liver damage in spite of male due to ethanol pharmacokinetics differences. The same amount of alcohol increases the ethanol blood level in women due to small volume distribution, low total body water content, less weight and high proportion of fat mass than men.[52]

Low gastric ADH activity and high estrogen level makes female more sensitive towards alcoholic liver disease.[53] Estrogen increases gut permeability and portal endotoxin level on ethanol exposures. It also amplifies the kupffer cell sensitivity for endotoxins due to enhance expression of CD14 receptor on kupffer cells and TNF-α.[54] Estrogen also regulates generation and protection against oxidative stress.[55]

4.2. Ethnic's differences

Cirrhosis rates are higher in black and Hispanics men in comparison to whites[56] and blacks have a two fold increase in serum aspartate aminotransferase and gamma glutamyltranspeptidase in comparison to whites.[57]

5. Role of Inflammation in Liver Damage

5.1. Kupffer cells

Kupffer cell are involved in the defense against infection in liver by production of various inflammatory mediators. Kupffer cell increases circulating level of proinflamatory cytokines IL-6, TNF-α and some chemokines such as IL-8, MIP-1A, MCP-1, nitric oxide, monocytes and neutrophils to inhibit the proliferated microorganism.[58]

Alcohol increases the permeability of gut membrane for endotoxins. The high blood level of endotoxin lipopolysaccharides (LPS) andalcohol enhances CD14 receptor expression on kupffer cells[59] and increase production of inflammatory mediators[60] and oxygen free radicals.[61] The activation of kupffer cells activates the endothelium and induces neutrophills and mononuclear cell recruitment and infiltration.[62] Alcohol also increases intraluminal production of LPS and have synergistic effect. Alcohol decreases the cellular cAMP levels of kupffer cells and leads NF-kβ activation in hepatocytes by LPS and TNF-α production.[63]

In fibrosis, amplified Ito cell myofibroblastic transformation[64] and increase metalloproteinase (MMPs) production[65] takes place. Kupffer cells are involved in both processes by production of cytokines and growth factors.[66] Kupffer cell derived TGF-β regulates Ito cell transformation and induces production of collagen and proteoglycans by these cells. *In vitro* it has been observed that kupffer cells can also induce expression of platelet derived growth factor (PAGFs) receptors on Ito cells thus enhance Ito cell proliferation.[67] TNF-α, IL-1 and MCP-1 that are produced by activated kupffer cells, are also mutogenic and chemo attractant for Ito cells.[68] TNF-β and IL-6 induces mRNA expression of metalloproteinase (MMPs) and their specific inhibitors.[69]

5.2. Cytokines cells

Hepatic cellular dysfunction and death also have the ability to initiate immunological reactions, including both innate and adaptive immune responses. Hepatocyte stress and/or damage could result in the release of signals that stimulate activation of other cells, particularly those of the innate immune system, including Kupffer Cells, Natural Killer (NK)

cells, and NKT (Natural Killer T- Cells) cells. These cells contribute to the progression of liver injury by producing proinflammatory mediators and secreting chemokines to further recruit inflammatory cells to the liver. It has been demonstrated that various inflammatory cytokines, such as tumor necrosis factor TNF-α, interferon IFN- γ and interleukin IL-1β,[70,71,72], produced during Drug-induced liver injury (DILI) are involved in promoting tissue damage. However, innate immune cells are also the main source of IL-10, IL-6, and certain prostglandins, all of which have been shown to play a hepatoprotective role.[73,74,75] Thus, it is the delicate balance of inflammatory and hepatoprotective mediators produced after activation of the innate immune system that determines an individual's susceptibility and adaptation to DILI.

Table 1: Types of cytokines in liver and their function.

Chemokines	
Interleukin–8 (IL–8)	Attracts neutrophils to the site of an infection
Monocytes chemoattractant protein-1	Monocytes infiltration
Immunoregulatory cytokines	
Interleukin–10 (IL–10)	Inhibits proliferation of certain immune system cells and promotes proliferation of others; reduces production of inflammatory cytokines; promotes antibody secretion
Adipokines (Adiponectin)	Anti-inflammatory activity
Pro–inflammatory cytokines	
Interlukin-1 (IL-1)	Produces inflammatory responses; induces fever; stimulates growth and differentiation of the immune system)
Interlukin-6 (IL-6)	Promotes maturation of antibody–secreting B cells; acts with other cytokines to stimulate other immune system cells; stimulates production of mediators of inflammatory responses; stimulates liver regeneration
Tumor necrosis factor alpha (TNF–α)	Promotes inflammatory responses; stimulates neutrophils and macro-phages; induces fever; induces macro-phages to produce cytokines; induces both apoptosis and necrosis
Transforming growth factor beta (TGF–β)	Promotes collagen synthesis

6. Role of Oxidative Stress

Oxidative stress is an imbalance between reactive species concentration and free radical scavenging system that is antioxidants. Reactive species are generated mainly from oxygen and nitrogen molecules respectively reactive oxygen species and reactive nitrogen species.

In hepatocytes here are two suspected sites for production of pro oxidents i.e. Mitochondria and ethanol inducible CYP2E1. Mitochondria do not reduce completely all O_2 to H_2O. 1 to 2% O_2 consumption by mitochondria mediates production of O_2.[76] The increased yield of pro oxidants affects the mitochondrial protein and damaged it by stimulating mitochondrial mediated apoptotic pathways by activating modulators of apoptotic signaling (caspases, bad and bcl-2).[77] Alcohol consumption increases the formation of pro oxidants in mitochondria[78] and depletes mitochondrial GSH levels[79], which increase the response of hepatocytes to apoptotic signaling.[18]

6.1. CYP2E1

CYP2E1 was first characterized by Lieber 1997 and shown increase total content of P450 family specially CYP2E1 with high catalytic activity with ethanol. CYP2E1 is mainly found in liver but a significant amount is also present in various organs like intestine, brain[80] CYP2E1 level is highest in centrilobular zone of liver[81] and expressed mainly in hepatocytes and Kupffer cells[82] where it is induced by ethanol. It is also present in membrane of endoplasmic reticulum and plasma membrane[83,84] which is responsible for immune mediated hepatotoxicity.[85,86,87] Endogenous substrates of CYP2E1 are acetone[88], fatty acids and arachidonic acids.[89] Ethanol is exogenous substrates for CYP2E1. CYP2E1 catalyses ethanol oxidation reaction by two different kind of oxidation i.e. one electron oxidation reaction catalyses ethanol to 1-hydroxyethyl radical[90] since production can be inhibited by antioxidants[91,92] and two electron oxidation first oxidize ethanol to acetaldehyde and then oxidized to acetate because acetaldehyde is also a substrate for ethanol[93] which is likely to be negligible.[94]

Molecular oxygen is also an important substrate for CYP2E1. CYP2E1 act as a NADPH oxidase and poorly coupled with NADPH- cytochrome P450 reductase which is responsible for electron transport. Cytocrome reductase leaks electron to oxygen to form O_2- or catalyse lipid peroxidation.[95] Alcohol can cause modification to the cell that favours oxidative stress.

6.2. Hypoxia

Alcohol oxidation needs double consumption of oxygen[96] due to this intralobular oxygen gradient increases[97] and leads hypoxic condition in liver.[98] Alcohol impaired electrons transport in mitochondria due to the decreases in oxygen delivery and when alcohol level decreases in body oxygenation enhances pro oxidants production via hypoxia/reoxygenation.[99]

6.3. Iron

ROS produces superoxide radicals or hydrogen peroxide. In presence of certain metals in body like free iron or copper iron the most powerful ROS hydroxyl radical's produces via Fenton or metal catalyzed Haber Weiss reaction.[100] Iron amplifies oxidative stress by catalyzing the conversion of less reactive oxidant in to more reactive oxidants like super oxide or H_2O_2 converts in to hydroxyl radicals or perferryl type oxidants. An increase in hepatic iron concentration occurs in alcoholics and intake of iron leads to cirrhosis.

$H_2O_2 + O_2^{\cdot -} \rightarrow {}^{\cdot}OH + OH^+ + O_2$ Haber- Weiss reaction

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\cdot}OH + {}^{-}OH$ Fenton's reaction (Fe dependent Haber - Weiss reaction)

$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + O_2^{\cdot -} + 2H^+$

${}^{\cdot}OH + H_2O_2 \rightarrow H_2O + H^+ + O_2^{\cdot -}$

$Fe^{3+} + O_2^{\cdot -} \rightarrow Fe^{2+} + O_2$

$Fe^{2+} + {}^{\cdot}OH \rightarrow Fe^{3+} + {}^{-}OH$

In kupffer cells increased iron content activates NF-kβ and ultimately for TNF-α production.[101] Oral iron chelators reduces these effects by reducing the increased non- heme iron concentration, lipid peroxidation and liver fat accumulation and injury.[101,102]

6.4 Hydroxyethyl radicals

Alcohol is hydroxyl radical scavenger, and produces hydroxyl ethyl radicals (HER) by liver microsomes in presence of NADPH.[90] The mechanism involves production of super oxides and H_2O_2 by CYP2E1, followed by an iron catalyzed generation of hydroxyl radicals like oxidants which interact with ethanol to yield HER.[91] On alcohol consumption HER binds to protein to produce ethanol derived protein adducts, which are immunogenic and production of antibodies that specifically recognize HER in alcoholic liver disease.[103]

7. Energy Metabolism

Chronic ethanol consumption affects all mitochondrial complexes activity except complex II [(104)] and also affects the mitochondrial respiratory chain system. Alcohol decreases activity and heme content of cytochrome oxidase[105], reduces ATP synthatase complex function, impaired proton translocation and electron transport through complex I[106], decreases cytochrome b content in complex III.[105]

7.1. Role of PPAR

PPAR-α is a ligand activated transcription factor which regulates lipid transport and metabolism, fatty acid metabolism and glucose homeostasis.[107] PPAR-α target genes also encode for apolipoprotein [Apo] B (protein involved in export), the microsomal triglyceride transfer gene, L-FABP and acyl-CoA dehydrogenase.[108] PPAR-α recognizes the influx of fatty acids and respond to them by stimulating the transcription of PPAR-α regulating gene.[109] PPAR-α also regulate some enzymes that are involved in fatty acid oxidation includes acyl CoA oxidase (AOX), 3-hydroxyacyl–CoA dehydrogenase, multifunctional β-protein (3-ketoacyl-CoA thiolase), acyl CoA synthase, malonyl CoA decarboxylase (MCD), liver carnitinepalmitoyl- CoA transferase (CPT-1).[110,111] Alcohol consumption impaired fatty acid metabolism i.e. decrease β-oxidation and enhanced lipogenesis in liver. Alcohol administration decrease expression of PPAR-α and PPAR-α regulated gene activity by depressing the transport system involved in fatty acid oxidation.[112,113] Acetaldehyde also decreases its expression by forming adducts with PPAR-α transcriptional complex.[114,115]

Chronic use of alcohol activates sterol regulatory element binding protein-1 (SREBP-1) which increases mRNA expression of lipogenic genes such as fatty acid synthase (FAS).[116] SREBPs are a family of transcription factors and synthesized as precursor bound to endoplasmic reticulum and nuclear envelope and release as mature protein by 2-steps cleavage processes. SREBPs regulate enzymes responsible for synthesis of cholesterol, fatty acids, triglycerides and lipogenesis in liver.[117] Acetaldehyde can increase the synthesis of the mature SREBP-1 protein, which increases lipogenesis in liver and leads to fatty liver.[116]

PPAR-α is able to inhibit inflammatory responses by preventing the NF-kβ and activator protein-1 activation through direct protein–protein interaction with p65 or c-Jun, respectively[118,119] and increase inhibitory kβ.[120,121,122] PPAR-γ is highly expressed in adipocytes, hepatic stellate cells and to a lesser extent in hepatocytes, spleen, skeletal muscles, macrophages.[123] PPAR-γ is involved in glucose metabolism, lipid storage, adipocytes differentiation[124] and inhibits inflammatory responses by decreasing IL-6, TNF-α, IL-1β secretion and iNOS production in macrophages and kupffer cells.[125] PPAR-γ agonists prevent the development of alcohol induced steatosis and inflammation.[126]

7.2. Adiponectin

Adiponectin is a 30-kDa bioactive protein, secreted by adipose tissue in circulation consist of four domain:

- N terminus with signal peptide,
- a short variable region,
- a collagenous domain,
- C terminal globular domain.

Adiponectin regulates fatty acid oxidation and lipid catabolism in the body. Deregulation of adiponectin on chronic ethanol exposure can lead to stetosis condition of liver. Chronic alcohol impairs lipid catabolism and fatty acid oxidation mediated by various transcriptional regulators including AMPK (adenosine monophosphate activated kinase), sirtuin-1 (SIRT-1), PPAR-α, SREBP-1 and cause excessive fat accumulation in liver.

Three adiponectin receptor: Adiponectin receptor-1 (AdipoR-1), Adiponectin receptor- 2 (AdipoR-2) and T-cadherin have been identified. AdipoR1 is expressed predominantly in skeletal muscles and AdipoR2 is expressed mainly in liver.

AMPK is heterotrimeric protein kinase, which act as a regulator of lipid metabolism by phosphorylation of substrates. Adeponectin–AMPK signaling promotes lipid catabolism and opposes triglyceride formation. Adeponectin stimulates hepatic AMPK which phosphorylates acetyl CoA carboxylase (ACC) and inhibits its activity. ACC directly induces lipogenesis and indirectly fat metabolism. ACC inhibition blocks malonylCoA production which is potent inhibitor of carnitine palmitoyltransferase-1 (CPT-1). CPT-1 mediates transport of fatty acid in to mitochondria.[127] Ethanol exposure inhibits adiponectin and thus enhances CPT-1 level which favors lipid deposition.[128]

7.3. SIRT1

SIRT1 also play an important role in controlling the lipid metabolism pathway.[129] SIRT-1-AMPK signaling acts as a central mechanism for lipid metabolism. SIRT1 regulates AMPK activity by modulation of an upstream AMPK kinase LKB1.[130,131,132] SIRT1 is down regulated by chronically use of ethanol.[133,134]

7.4. SERBPs

SERBPs are transcriptional factors that regulate fatty acid, triglycerides, cholesterol synthesis.[135] There are three isoforms SERBP-1a, SERBP-1c and SERBP-2. SERBP-1c predominantly presents in liver and regulates lipid synthesis. Chronic ethanol expouser stimulates hepatic SERBP-1c signaling and increases level of SERBP-1c gene regulated

enzymes include fatty acid synthase (FAS), steroyl-CoA desaturase (SCD), mitochondrial glycerol-3 phosphotase acyl transferase 1 (GPAT1), malic enzyme (ME), ATP citrate lyase (ACL) and ACC and leads to hepatic lipid accumulations.[136]

7.5. PPARα

PPARα is a transcription factor for mitochondrial and peroxisomal fatty acid oxidation.[137] PGC-1α is coactivator of PPARα and PPARγ. Interaction of PPARα / PGC-1α stimulate fatty acid oxidation enzymes, medium and long chain acyl CoA dehydrogenase, acyl CoA oxidase, very long chain acyl CoA synthase, CPT-1.[138] Adiponectin stimulates PPARα / PGC-1α activity and enhances fat acid catabolism.[139] Ethanol consumption leads to incomplete stimulation of its target genes which contribute to development of alcoholic fatty liver.[140]

CD36 is lipogenic gene responsible for transport of fatty acid in cell and it is targeted by PPARγ for lipogenesis.[141] Adiponectin inhibits CD36 activity and prevent influx of fatty acid in cell.[142] Ethanol consumption mediates up regulation of CD36 in liver.[143] Adiponectin suppress TNF-α expression and production in adipose tissue.[144] Chronic ethanol use increases TNF-α production in adipose tissue and regulates early stage of liver injury.

CONCLUSION

This article summarized the various pathways of alcoholic liver damage. Alcohol gives rise to state of oxidative stress by depleting the various antioxidant enzymes. In addition, alcohol also decreases the ATP production by damaging the mitochondria. Alcohol induces oxygen deficiency by utilizing more oxygen in its metabolism which amplifies the ROS production and prone the hepatocytes toward lipid peroxidation. Alcohol consumption increases level of gut derived endotoxin to the portal circulation. In response to endotoxins, kupffer cells are activated. Activated kupffer cells enhance the secretion of proinflammatory cytokines and suppress anti inflammatory cytokine secretion. This results inflammation of hepatocytes and causes cell necrosis. Alcohol administration decrease expression of PPAR-α and PPAR-α regulated gene activity by depressing the transport system involved in fatty acid oxidation. SIRT1 is down regulated by chronically use of ethanol which is responsible for controlling the lipid metabolism pathway. SERBPs are transcriptional factors that regulate fatty acid, triglycerides, cholesterol synthesis. Alcohol impaired the activity of SERBPs by increase acetaldehyde production and increases lipogenesis in liver and leads to fatty liver.

Adiponectin suppress TNF-α expression and production in adipose tissue. Chronic ethanol use increases TNF-α production in adipose tissue and regulates early stage of liver injury.

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