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Alcoholic Hepatitis – A Fatal Disease

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ABSTRACT

Liver is the vital organ that metabolizes and excretes nutrients. Failure of the liver leads to death in cases. The complication which causes liver failure is excessive alcohol consumption. Liver metabolizes ethanol and it faces the highest degree of injury by uncontrolled drinking. Alcohol use produces a broad spectrum of diseases; hepatosteatosis, Alcoholic hepatitis, fibrosis & cirrhosis. Pathogenesis of Alcohol related Liver Diseases (ALD) is explained by hepatic lipogenesis, deceleration of hepatic lipid breakdown, defective hepatic lipid export, macrophage induced alcoholic hepatitis (AH), Lipopolysaccharide (LPS) transport into the hepatic bloodstream, Malondialdehyde and acetaldehyde (MAA) adducts formation and hepatocyte stellate cell (HSC) induction. Main symptoms of AH include oxidative stress, metabolism interruption, inflammation, restoration process changes and bacterial byproducts misplacement from the gut into hepatic portal blood circulation. Diagnostic studies of ALD are concluded by medical records, clinical and laboratory declarations. Earlier, Glucocorticoids, Pentoxifylline, TNFα were used in the treatment of AH, alone or combined. Novel treatments include Metadoxine, Caspase inhibitors, Microbiome Modification, Microbial Phage Therapy, and liver transplantation. These treatments are prescribed in combination with addiction psychiatrists, social work, and family counselors. Recent studies confirmed that AH could be prevented by consuming capsaicin daily, which ultimately reduces the global burden.

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INTRODUCTION

Liver is the chief and vital organ that has a central function for the metabolism of minor and major nutrients and excretion of the metabolites. Liver controls the safety flow of the substances from the digestive tract into the systemic circulation. Damage to the liver could lead to severe sickness and death. Liver accounts for 2.5% of the body weight and weighs nearly 1500g with a smooth and dome shaped structure. Liver is located in the upper part of the abdomen, deep to the rib cage numbered 7 to 11 to the right side and is protected by the diaphragm and thoracic cage (Wakim, 1954).

Epidemiology of ALD

Worldwide, alcohol consumption disorder is one of the utmost common substance abuse disorders, with nearly cases of 1 million and 99 million disability-adjusted life years (DALY) in 2016.

According to WHO statistics, 2.3 billion citizens were vigorously consuming ethanol in 2016. Surprisingly, per-capita utilization of alcohol substance has inclined from 5.5 liters in 2000 to 6.4 liters in 2016 (Basra, 2011). ALD per-se records for 4% of death rate and 5% of DALYs having Europe being mostly worst affected. In 2010, nearly $\frac{1}{2}$ a million death reports were accounted to alcohol related fibrosis and cirrhosis. One in 10 deaths are attributed to alcohol abuse and is related due to alcoholic cirrhosis (Rehm *et al.*, 2013). This accounts to a yearly loss of 22 million DALYs. In the US population, a death rate of 5.5 per 100,000 was anticipated in 2010. In European Union, 41% of alcoholic hepatitis related death rate is attributed to alcohol. In India, alcohol consumption is the most common cause of cirrhosis (34.3%) and nearly 20% of all liver disease patients are presently alcohol consumers. AH is being diagnosed in around 30 to 40 percent of the worldwide patients stating chronic alcohol use with inclined short-term death.

Alcoholic Liver Disease

High alcohol intake is a major risk factor counting a huge number of unfavorable health reactions, which is the primary causes of avoidable morbidity and death. Excessive consumption of alcohol for many continuous years damages almost all organ of the body. However, it is the earliest, has the maximum level of tissue damage as it is the primary site of alcohol metabolism. Spectrum of liver damage includes ,

1. Steatosis or fatty liver,
2. Alcoholic hepatitis,
3. Fibrosis and cirrhosis.

Alcohol liver disease (ALD) is a common word used to submit to this spectrum (Nordqvist, 2018).

Hepatic Alcohol Metabolism

Alcohol is primarily metabolized at hepatocytes and its pathway is schematically represented in Figure 1. These articulate the highest planes of the ethanol oxidizing enzymes called ADH (alcohol dehydrogenase) and CYP2E1, which is placed in smooth ER. Hepatocytes contain high concentrations of catalase, an enzyme that is present in peroxisomes (Kong, 2019).

Alcohol dehydrogenase enzyme

ADH is a catalytically competent ethanol-metabolizing enzyme. ADH-catalyzed oxidation of ethanol makes use of nicotinamide adenine dinucleotide (NAD^+) cofactor, which generates reduced NAD^+ (NADH) and acetaldehyde. Acetaldehyde, which is formed as a product, is more toxic. It can co valently attach to lipids, proteins and nucleic acids to form acetaldehyde additional products, which can disturb the structure and utility of these macromolecules.

The increased production of NADH by ADH and ALDH2-catalyzed reactions reduces the usual intra-hepatocyte NAD^+/NADH ratio, and it is termed cellular redox potential. This alteration causes major metabolic transfer from oxidative metabolism to reductive synthesis, leads to fatty acids formation, which leads to steatosis (Singal, 2018).

Cytochrome P450 2E1

CYP2E1 is the main hepatic enzyme that catalyzes and converts ethanol to acetaldehyde. Catalytic competence of CYP2E1 is significantly slower than ADH. CYP2E1 is 10 times capable in binding ethanol and it can interrelate straight with the CYP2E1 protein, making it form a structure that opposes deprivation by ubiquitin proteasome system and leads to the accretion of CYP2E1 molecules.

Increased alcoholic metabolism by a high concentration of CYP2E1 gets the hepatic cells in metabolic threat as CYP2E1 also produce huge amounts of other reactive oxygen species (ROS), such as superoxide anions (O_2^-), hydroxyethyl radicals (i.e., free-radical forms of ethanol), and hydroxyl radicals (·OH) (Koop, 2006). Uninterrupted release of such molecules eventually generates oxidant stress. Under such circumstances, the pace of ROS production surpasses the liver's ability to neutralize the free radicals with naturally available antioxidants, like vitamins E, A, and C and glutathione, or to eliminate them by utilizing antioxidant enzymes (Zakhari, 2006).

Hepatocytes also contain elevated levels of catalase, which is present in peroxisomes.

Spectrum of ALD

Intense ethanol intake produces a broad spectrum of liver injuries, which is the most attribute to fatty liver (Steatosis), hepatitis, and fibrosis or cirrhosis.

Steatosis

Steatosis is an initial and common reaction that develops in nearly 90% of heavy drinkers who take 4 to 5 drinks per day for years. However, it also develops following binge drinking, which is the consumption of 4 to 5 drinks in less than 2 hours. It is defined as the accumulation of fat as lipid droplets, originally in the liver cells that enclose the liver's central vein (perivenular hepatocytes), then succeeding to mid-lobular hepatocytes, and at last to the cells that

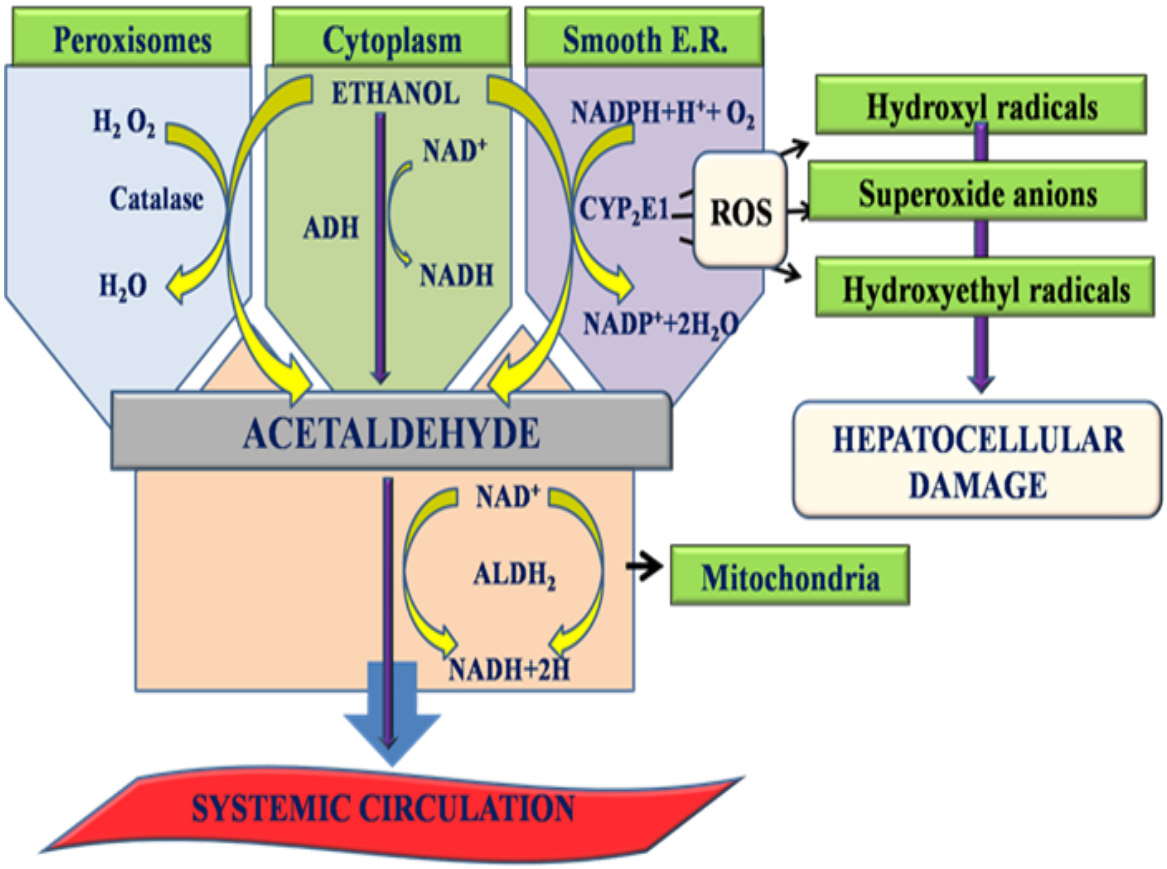

Figure 1: Hepatic alcohol metabolism: H_2O_2(Hydrogen Peroxide); H_2O (Water); ADH (Alcohol Dehydrogenase;NAD^+ (Nicotinamide Adenine Dinucleotide cofactor); NADH:(Nicotinamide Adenine Dinucleotide reduced); CYP2E1(cytochrome P450 2E1); $ALDH_2$(Alcohol Dehydrogenase 2); ROS: Reactive oxygen species

enclose the hepatic portal vein (periportal hepatocytes).

Alcoholic hepatitis

AH is a rigorous, inflammatory kind of liver damage defined by engorged and failing hepatocytes (Ballooning degeneration). It also leads to neutrophilic infiltration and formation of knotted proteins which are insoluble called Mallory-Denk bodies contained by the hepatocytes.

Fibrosis or cirrhosis

Fibrosis refers to the accumulation of atypical extracellular matrix proteins, which are mainly triggered by hepatic stellate cells (HSCs). The Patients primarily display vigorous pericellular fibrosis that may develop into cirrhosis, the last stage of liver scarring (Nordqvist, 2018).

Mechanisms concerned in Alcohol related Hepatitis

AH is diagnosed in nearly 30 to 40 % of the patients exposed to chronic alcohol use. It indicates the severe form of ALD and it is accompanied by elevated short-term mortality. The pathologic indications are,

1. Ballooning deterioration of hepatocytes which contains Mallory-Denk bodies,
2. Infiltrating neutrophils,
3. Fibrosis.

Detailed mechanisms involved in AH are described below, with all the mechanisms schematically presented in Figure 2.

Macrophages induced Alcoholic Hepatitis

The macrophages (immune cells) have an important role in the induction of liver tenderness. KCs are the liver residing macrophages representing nearly up to 15 percentages of hepatic cells and 50% of full macrophages. They exist in the liver sinusoids, which offer the first line of protection, serving as effective innate immune cells. In comparison, infiltrating immune macrophages are appointed as immature cell formed in the bone marrow, and maturation into macrophages occurs during inflammation in liver cells (Kumagi *et al.*, 2001).

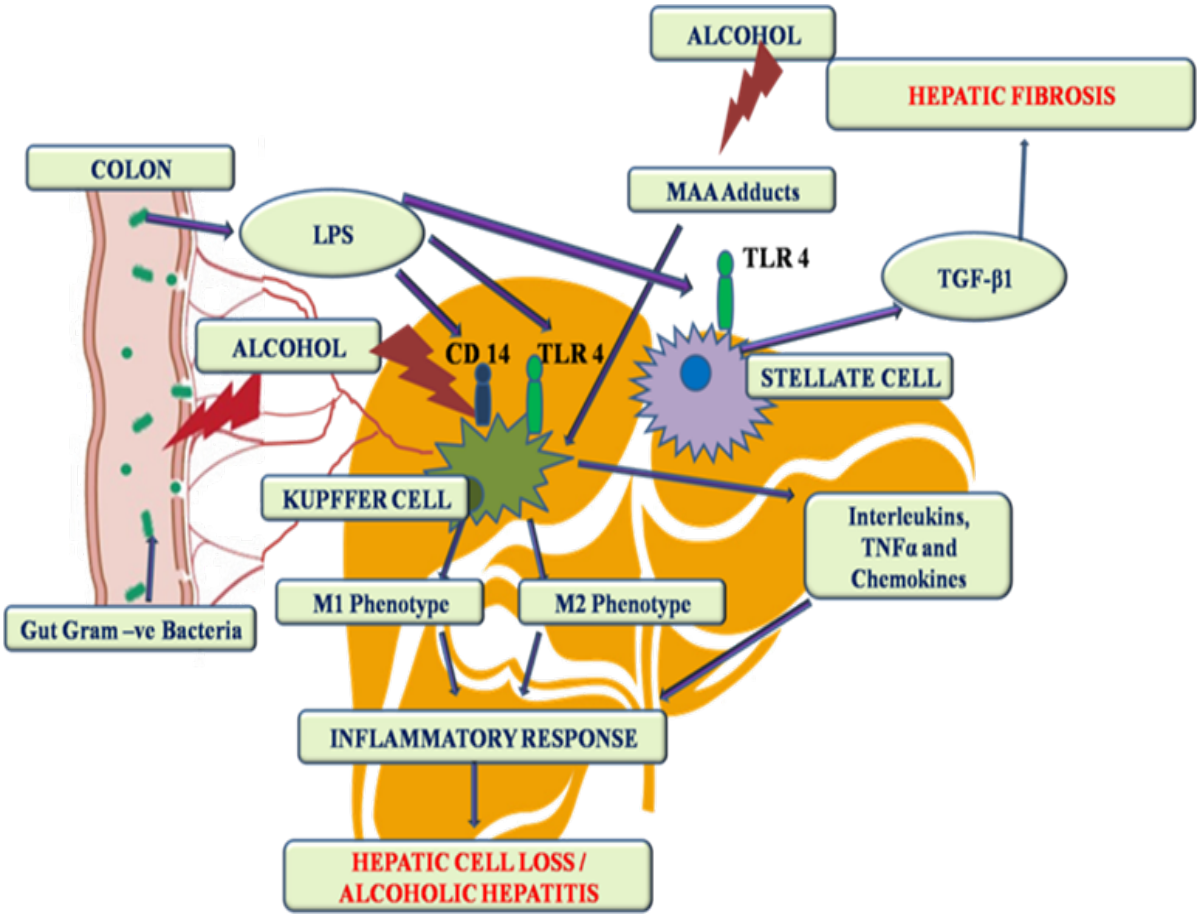

Figure 2: Mechanisms Involved in Alcoholic hepatitis andFibrosis: LPS- lipopolysaccharide; MAA - Malondialdehyde and acetaldehyde; TLR4 - and toll-like receptor 4; CD 14 - a cluster of differentiation 14; TGF-β1-transforming growth factor-β1

Polarization enables the macrophages to adjust inflammation and will develop any one of the functional states,

1. M1 (proinflammatory) or
2. M2 (anti-inflammatory) macrophages.

The polarization rests on the microenvironment, including flowing growth factors, pathogen-associated molecular pattern (PAMP), cytokines, and damage-associated molecular pattern (DAMP) molecules. Liver is open to the elements such as pathogens, antigens, and toxic particles that enter from the intestine through the portal circulation. Thus it should be secluded from having an immune reaction to these elements. As an outcome, KCs will not react to all types of antigens showing an immune response. However, extreme ethanol introduction will change KCs to proinflammatory M1 phenotype. More prominently, KCs can adjust the progress of inflammation, which depends on the capacity to either stimulate or repress proinflammatory modifications. These sort of effects have been related to the severity of the AH. In the intense scenario, KCs will distinguish themselves to the proinflammatory M1 phenotype, but in less severe forms, KCs change to the anti-inflammatory M2 phenotype. KCs also release many proinflammatory cytokines, like interleukins, TNFα and chemokines, which pulls inflammatory cells from the systemic circulation (Kumagi *et al.*, 2001).

Lipopolysaccharide-induced Alcoholic Hepatitis

One major factor which triggers KCs activity in alcoholics is an endotoxin, termed as lipopolysaccharide (LPS). It is a cell wall constituent of a Gram-ve bacterium that gets transported from the gut lumen into the blood circulation to arrive at the liver. Data reveals that overloaded ethanol consumption causes endotoxemia by the following two main mechanisms—by increasing bacterial growth beyond the limit and by enhancing intestinal permeability. Studies on animals have declared that increased endotoxin levels in the circulation relate to the seriousness of liver disease.

LPS can be sensed by two kinds of receptors—a cluster of differentiation 14 (CD14) and toll-

like receptor 4 (TLR4). These receptors stimulate the activation of KCs to release proinflammatory cytokines, further enhances free-radical configuration through the initiation of NADPH oxidase and CYP2E1. The formed highly reactive oxygen and nitrogen species sponsor the discharge of proinflammatory cytokines, in turn, amplify inflammasome augmentation in KCs, the discharge of chemokines draws circulating immune cells to cells of the liver (Zhang *et al.*, 2019).

MAA adducts induced Alcoholic Hepatitis

These are produced in hepatocytes that are exposed to alcohol. These adducts are grasped by scavenger receptors on Kupffer Cells, promote the proinflammatory reaction. Also, as macrophage metabolizes ethanol via CYP2E1, the alcohol initiation of oxidative stress boost up macrophage reliant discharge of proinflammatory cytokines, this also includes TNFα. Normally hepatocytes are anti to TNFα, but ethanol disclosure sensitizes these to form cytokines, leading to their loss through apoptosis. This result in the liberation of small vesicles called exosomes. KCs engulf apoptotic hepatocytes, thereby converting the phenotype to M1, which aggravates inflammation. Inflammation associated discharge of chemokines draws T-cells, macrophages, and neutrophils to the liver. These cells further endorse hepatocyte cell loss and the occurrence of alcoholic hepatitis (Tuma, 2002).

Hepatocyte Stellate Cell induced Alcoholic Hepatitis

HSCs have a double (stage dependent) role in directing liver inflammation. Essential roles of HSCs are to pass on signals from the sinusoid cells to hepatocytes. The chemokines and proinflammatory cytokines formed by the activated KCs excite the production of proinflammatory cytokines by stellate cells. An account of this LPS will directly activate HSCs via TLR4 to advance the emission of proinflammatory cytokines. All the roles of HSCs are being regulated by KCs. At the point of declaration of inflammation, KCs fabricate anti-inflammatory materials, like prostaglandin D2; it is being sensed by HSC receptors. Prostaglandin D2 codes HSCs to change their production capacity to anti-inflammatory factors, which includes transforming growth factor-β1 (TGF-β1), which is involved in promoting fibrogenesis (Osna *et al.*, 2017).

Diagnosis of alcohol related diseases

Physical assessment

A complete physical assessment must be carried out for examining a patient for proof of severe liver disease. Patients suffering from alcoholic hepatitis will possesssclera icterus, jaundice and mild hepatomegaly. If the hepatitis is intense, patients will suffer asterixis and show mental uncertainty on testing. They may also show signs of muscle wasting, heart failure and peripheral neuropathy.

Laboratory Studies

At the initial phases of testing, patients evaluated for ALD must possess a full blood count. The brief screening method combines three panels; transaminases, alkaline phosphatase, bilirubin, al-normalized ratio tested.

Serum transaminase levels

1. If a patient is proved with a hepatocellular injury which is indicated by increased serum transaminase readings, the patient must be tested for,
2. Severe viral hepatitis along with the establishment of hepatitis B core immunoglobulin g (IgG), hepatitis B surface antigen, and hepatitis C antibody.
3. Autoimmune hepatitis with anti-smooth muscle antibody, anti-nuclear antibody, and gamma-globulin levels.
4. Hemochromatosis having serum iron, serum ferritin, and transferrin
5. Alpha one anti-trypsin insufficiency
6. High levels of Serum ceruloplasmin

Usual hematological results in patients suffering from ALD includes macrocytic anemia, thrombocytopenia, increased erythrocyte sedimentation rate, lymphopenia, and an increased International Normalized Ratio (INR). Macrocytosis is a persistent disease and usually be next to toxicity levels of alcohol on the bone marrow, vitamin B12 shortage, or larger lipid accumulation in membranes of erythrocytes. Thrombocytopenia is present in about $1/3^{rd}$ of patients who are admitted to hospitals. High density lipids (HDLs), urate, and serum ferritin levels also boost as an outcome of excess alcohol consumption. Patients along with deprived hepatic synthetic utility will also show less serum albumin readings (Kong, 2019).

Patients having ALD regularly display confirmation of iron burden as indicated by an increased serum iron index (transferrin and ferritin saturation) and hepatic iron absorption. The clinical condition of iron buildup in alcoholics is not known, but it might

be because of alcohol inhibition of the liver transferrin formation or de-regulation of hepcidin formation in the hepatic cells.

The biochemical markers

The biochemical identifiers for severe alcohol intake, which have been mainly and commonly experimented are serum Aspartate aminotransferase (AST), Gamma-glutamyltransferase (GGT), mean corpuscular volume (MCV), Alanine aminotransferase (ALT), and carbohydrate-deficient transferrin (CDT). An AST to ALT proportion of more than 2 is extremely indicative of ALD. The patients who have non-ALD show AST to ALT proportion less than one. Particular IgA antibodies heading towards acetaldehyde formed protein changes are commonly seen in alcoholics and therefore increased IgA levels seen in severe ALD. An inclined proportion of IgA: IgG is extremely suggested for ALD. Severe alcohol utilization is well known for persuading an incline in serum GGT and is popularly used for examining extreme alcohol abuse. However, increased level GGT only has low specificity and sensitivity for alcohol use. GGT is mostly not particular to alcoholism, but it is seen increased in various other conditions like age, obesity, reasonable alcohol intake, other kinds of hepatic disease, which includes fatty liver and hepatocellular carcinoma, intra and extra hepatic biliary obstacle, and phenytoin usage. The usage of GGT as an indicator for alcohol intake in youngsters has shown to be poor even in situations of proved alcohol dependence (Kong, 2019). Sensitivity and specificity of the biological markers in determining ALD is listed in Table 1.

Ethyl glucuronide (EtG), phosphatidyl ethanol (PEth) and ethyl sulfate (EtS) have been in use with growing occurrence in past years to observe self-denial from alcohol consumption in outpatient. In an experiment on 40 patients, PEth analysis was done with CDT as one of the biomarkers for current alcohol intake and was established as +ve two times as regular as CDT in patients discharged from withdrawal in a voluntary outpatient healing program. Moreover, significant individual variability in PEth state was noted in the clinical examination, which might generate problems while interpreting the results and might bind the utility of PEth in the identification of reversion from withdrawal. The usage of EtG and EtSis comparable to the measurement of the level of blood alcohol, but it is limited to detect very recent consumption of minute and few drinks of alcohol (Amini and Runyon, 2010).

Patients suffering from AH will normally have reasonably increased aminotransferases (<500 IU/mL), an AST: ALT proportion of 2 or more and increased serum bilirubin (> 5 mg/dL). The patients having serious AH also show leukocytes is and increased C-reactive protein which indicates serious liver damage or associated infection.

Imaging

Current most widely accessible imaging utilities for the liver include ultrasonography (US), magnetic resonance imaging (MRI) and computed tomography scan (CT). These studies are helpful in the identification of the incidence of unnoticed liver related disease, but they could not validate that consumption of alcohol is the main cause of a patient's liver damage. Imaging is also used for the identification of cirrhosis and also to monitor and recognize hepatocellular cancer (Sahani and Kalva, 2004).

Ultrasonography is the non invasive method that has been normally used in the early testing of liver diseases. Visualization of fat on the liver is extremely unpredictable on ultrasonography, but in the usual case, a fat accumulated liver shows a hyperechoic surface and macroscopic fat, which appears as hyperechoic masses. Specificity and sensitivity of a hyperechoic model on ultrasound for hepatosteatosis in patients with liver diseases have 30% steatosis is 93% and 91%, respectively. MRI technique is a method in which fat and water are examined in and out of stages and could be the most specific and sensitive imaging method for detecting hepatosteatosis (98% sensitivity, 95% specificity). New imaging method is now under examination, which is used with temporary elastography, it shows capable performance in detecting and estimation of hepatosteatosis, but it is currently not available extensively. Other improved imaging methods are used to detect and compute cirrhosis and hepatic fibrosis; are acoustic radiation force impulse, FibroScan (transient elastography), and magnetic resonance elastography (Sahani and Kalva, 2004).

Liver Biopsy

Liver biopsy might be helpful to establish the liver diseases in few patients when testing results of ALD are unclear with respect to medical data and lab analysis. At present, liver biopsy is one of the mainly available methods to distinguish between steatohepatitis and bland steatosis. Liver biopsy will aid the identification and differentiation of normal steatosis and steatohepatitis, which and is based on diverse histological recordings. This has clinical significance where it grants vital prognostic details for patients (Dhanda, 2013). It's an invasive process in which patients might face complications, might be experiencing sampling faults and a solid cause for the basic hepatic disease might not be obtained

Table 1: Sensitivity and specificity of the biological markers in determining ALD

Biomarker	ALT	AST	CDT	MCV	CDT+GGT+MCV	CDT + GGT
Sensitivity	32 to 50%	47 to 68%	63to 84%	45 to 48%	88%	83 to 90%
Specificity	87 to 92%	80 to 95%	92 to 98%	52 to 94%	95%	95 to 98%

Serum Aspartate aminotransferase (AST),Gamma-glutamyltransferase (GGT), mean corpuscular volume (MCV), Alanineaminotransferase (ALT), and carbohydrate-deficient transferrin (CDT)

based on histological studies. The function of liver biopsy in the testing of alcoholic related hepatitis is much divisive as it may carry the considerable threat of bleeding while setting thrombocytopenia and coagulopathy while utilizing a normal percutaneous method.

Methods of Treatment

Glucocorticoids

Glucocorticoids were used first in the treatment of AH in earlier days, mainly because of the features of inflammation of hepatitis. Given that nearly 20 randomized, controlled trials were performed in patients with serious AH, it is defined by Maddrey's discriminant function (MDF) higher than 32. The multicenter clinical trial of methylprednisolone against placebo for the cure of serious AH detailed a major reduced 28-day death rate in the patients who are treated by administering methylprednisolone when judged against with usual care. Renal failure, active gastrointestinal bleeding, uncontrolled hyperglycemia, acute pancreatitis, psychosis, and infection in AH patients.

Pentoxifylline

Pentoxifylline has been reported to diminish mortality of the patients who were suffering from severe AH (mDF>32), studies have shown that combining treatment of PTX along with glucocorticoids has not confirmed any advantage in the endurance of patients suffering severe AH. Studies have shown that treatment of PTX with glucocorticoids did not confirm any advantage and PTX had no impact on survival compared to placebo.

Anti–TNFα therapy

The limitation of TNFα is frequently seen as inclined in the patients suffering from serious AH. The primary data proposed that the anti-TNFα treatment method would be advantageous in serious AH, following clinical trials of etanercept (an antibody to TNFα receptor) and combined therapy of glucocorticoids with anti-TNFα treatment, which led to increased danger of infection and an increased death rate when compared to than standard treatment methods. Etanercept, Infliximab and a combination of glucocorticoids with anti-TNFα treatment led to increased risk of infection and mortality compared to standard treatment methods. Etanercept was also related to impaired liver regeneration. Infliximab has shown an increased frequency of severe infection within 2 months.

Novel treatment methods for Alcoholic Hepatitis

Metadoxine

Ion pairing of pyrrolidone carboxylate and pyridoxine will come from Metadoxine salt. There is slight proof that metadoxine will increase glutathione limits and decreases steatosis in animal's alcohol studies and may also act as an antioxidant. A study revealed a statistically enhanced 90-day endurance period in patients who are cured with a metadoxine and pentoxyfylline or prednisone combination when compared to PTX or prednisone (Kong, 2019).

Interleukin 1 Receptor Blockers

For patients suffering from AH, a combined treatment method would be necessary. A randomized, controlled trial study results were newly presented from combination therapy when compared to the usual method of treatment with methylprednisolone in patients with AH, which includes IL-1 receptor inhibitor-anakinra (reduces inflammation) and zinc supplementation (improves the function of a gut barrier). The combined treatment method was selected based on approved scientific studies, successful studies in animal models, and patient date interpretation (Mathews and Gao, 2013). Studies were not assuring whether inhibition of IL-1 signaling decreases AH-associated death and enhances patient outcomes (Mathews and Gao, 2013).

Caspase inhibitors to inhibit hepatic apoptosis

The inflammation pathway, which is triggered by Toll-like receptor (TLR) 4 or LPS, caspase-1 induces cell fatality. Thus, the caspase-1 inhibitor is of high significance for non alcoholic fatty liver disease (NAFLD) and AH. A phase 2 clinical trial in the patients having NAFLD revealed promised a cure for selonsertib (an apoptosis signal-regulating kinase inhibitor), but following trials in patients suffering from severe AH have been unsuccessful to deliberate any major dissimilarity between prednisolone and selonsertib and single prednisolone (Hao, 2017).

Modification of Microbiome (probiotics)

In the study of patients having mild to modest AH, short tenure intake of *Lactobacillus plantarum* 8PA3 and *Bifidobacteriumbifidum* regainedgut bacteria and enhanced lab indicators of liver damage (AST, GGT, ALT, serum bilirubin, lactate dehydrogenase). Supplements of *Lactobacillus rhamnosus* GG might progress integrity of mucosa inhibits the activation of endotoxin, which produces low TNFα, and lowersalcohol - mediated inflammation.

Microbial Phage Therapy

Bacteriophage is a virus that is usually selective for particular strain types of bacteria. It inserts their genome into the bacterial cell and stops the replication process of bacteria. Phage treatment method was experimentally used in the treatment of a drug resistant *Acinetobacter baumannii* infection. The authors of the research work illustrated that bacteriophage which has the specificity towards the cytolysin positive strain of *Enterococcus faecalis*, was capable of reducing the rigorousness of steatohepatitis in mice models. Considering a connection between cytolysin-positive *Enterococcus faecalis* and death rate in patients suffering with AH, an advancement to this sort of organism may provide good promise in treatment (Mitchell, 2018).

Stimulus of Liver rejuvenation

Granulocytes Colony Stimulating Factor

Intake of granulocyte colony stimulating factor (G-CSF) have shown an incline in the quantity of CD34+ cells, hepatocyte growth factor, and cells containing hepatic progenitor in the patients with alcohol related liver cirrhosis and hepatosteatosis. This examination recommended that G-CSF might encourage liver rejuvenation in patients having severe AH. A successive direct testing of G-CSF and the usual treatment plan, which includes PTX, revealed enhanced endurance of 78.3%, compared to in patients treated with a basic treatment plan on its own at 90 days. Mortality was reduced in glucocorticoid non responders when treated with twelve dosages of G-CSF 300 μg for 30 days when evaluated with patients who are administered with a basic treatment plan. Infection was lowered, and the model for end stage liver disease (MELD) number reduced significantly in patients who got treated with G-CSF (Kong, 2019).

Immunoglobulin-Rich Bovine

Colostrum Immunoglobulin rich bovine colostrum has revealed to have immune-modulatory properties, lesser endotoxin concentration in serum at animal studies, and an improved gut penetrability in seriously troubled patients.

Liver Transplantation

Liver transplantation (LT) presents outstanding short term endurance for healing patients suffering from serious AH, who have been unsuccessful by using usual medical treatment methods. Over the past 15 years, data revealed that patients with liver transplantation have increased. Many tests revealed that the probability of a reversion to binge drinking in the patients who got a liver replacement for ALD is mostly associated with aspects other than a certain period of self-restraint. Delayed death after LT for ALD is usually due to infections, cancer, and reversion to destructive limits of heavy drinking. Getting back to higher limits of drinking could be the main reason as LT still remains controversial (Osna *et al.*, 2017).

In order to overcome the adverse events and improve the epidemiology of alcoholic hepatitis, it is necessary to prevent the life-threatening disease. Recent studies have shown that capsaicin which is a naturally occurring alkaloid, plays a major role in the prevention of alcoholic hepatitis.

Capsaicin

Capsaicin(trans-8-methyl-N-vanilly-6-nonenamide) is an important pungent component in hot peppers. This is a naturally occurring alkaloid which is used as a food component with a distinguishing smell and flavor. *Capsicum annuum, C. baccatum, C. chinense, C.frutescens, and C. pubescens* (family – Solanaceae) are the most prominent species used for the extraction of capsacinoids. The capsaicinoids are capsaicin, dihydrocapsaicin, nondihydrocapsaicin, homohydrocapsaicin, homodihydrocapsaicin and nonivamide (Antonious, 2018).

With its wide variety of pharmacological effects, it has been widely studied and its pharmacological properties include anti-inflammator (Antonious, 2018), anti-obesity (Zhang *et al.*, 2019), antioxidation and lowering of lipid peroxidation properties (Reyes-Escogido *et al.*, 2011).

Meghana koneru investigated the effects of capsaicin on the hepatic tissue of mice treated with alcohol and concluded a drastic improvement. The results from the study indicated that capsaicin may prevent alcohol-induced acute liver injury (Koneru, 2018).

The mentioned study by Megana Koneru also was published in the Times of India in the issue on October 25, 2017. It was published that a team of researchers from the Indian Institute of Chemical Technology (CSIR-ICT) and Andhra University has conducted a study on the liver protection properties

of capsaicin and it was found that capsaicin has antioxidant properties that fight damage caused to the liver by alcohol (Koneru, 2018).

At the International Liver Congress 2015 of the European Association for the Study of the Liver (Science Daily), it was revealed that capsaicin was found to reduce the activation of hepatic stellate cells (HSCs) in CCl4-treated mice models, which further prevents liver damage caused by alcohol.

Bitencourt S et al., at EASL 50^{th} International Liver Congress, Vienna, stated the inhibitory effects of capsaicin as a dietary supplement on HSC activity in mice with artificially induced liver fibrosis. Mice fed capsaicin prior to toxin exposure were protected against the development of liver injury and up-regulation of fibrosis activation markers (Bitencourt, 2015).

On 27^{th} April 2015, it was posted in South a China Morning Post published that the capsaicin can prevent liver damage caused by alcohol.

Hui Zhang et al., stated that capsaicin pretreatment significantly reduced TNF-α and IFN-γ levels in both serum and liver of Concanavalin A-challenged mice, which may contribute to the protective effects of capsaicin on Con A-induced hepatitis. It was also stated that Capsaicin pretreatment suppresses oxidative stress. These findings, together with the fact that capsaicin down regulated proinflammatory cytokines, support the inhibition of apoptosis by capsaicin *in vivo* (Zhang *et al.*, 2019).

Hui Zhang et al. also found that Capsaicin pretreatment inhibits lymphocyte activation and promotes myeloid-derived suppressor cell (MDSC) accumulation. Findings highlight capsaicin as a potential therapeutic agent that can protect the liver from autoimmune hepatitis (Zhang *et al.*, 2019).

Several methods have been improvised to forecast the threat of reversion to heavy alcohol consumption in patients suffering from ALD. These systems have shared few regular components, which includes the extent of unlimited use, or chief social penalty, and breakdown of preceding efforts to suspend drinking at high dangerous levels. The method to treat ALD is combined with addiction psychiatrists, social work, and family counselors.

CONCLUSIONS

Excessive consumption of alcohol for many continuous years destroys nearly all organ of the human body. The liver is the first and has the maximum level of tissue damage as it is the principal site of ethanol metabolism. Spectrum of liver damage includes steatosis or fatty liver, alcoholic hepatitis, fibrosis, and cirrhosis forming in a sequence. In the majority of patients, the disease analysis will be customized by thorough medical history, clinical and laboratory results. However, in doubtful situations, it will be able to be sustained by imaging and liver biopsy. With a clear knowledge of the pathogenesis of AH, the probability of developing novel treatment methods will be increased. Novel approaches to treat AH might concentrate on decreasing the inflammatory constituent and augment restoration of the liver functions while keeping differentiated liver functions which are in need. Quick expansion of awareness and estimation of this disease should be able to make possible progress of development of new treatments. However, prevention of AH might be possible by dietary intake of Capsaicin, which would ultimately reduce the global burden of alcohol and improve the national economy.

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Conflict of Interest

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