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Review Article

A COMPENDIOUS STUDY REGARDING CONCEPTS OF PATHOGENESIS AND TREATMENT OF ALCOHOLIC LIVER DISEASE: A REVIEW

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ABSTRACT

Excess of alcohol consumption with consequent Alcoholic Liver Disease (ALD) is common cause of liver dysfunction, leading to morbidity and mortality. It encompasses a spectrum of disorders ranging from asymptomatic steatosis, alcoholic steatohepatitis, fibrosis, cirrhosis and its related complication. Multiple mechanisms include oxidative stress, mitochondrial dysfunction, alteration in gut permeability, and activation of TLR-4 has been proposed in pathogenesis. Various risk factors play key role in occurrence and worsening of condition are alcohol consumption, genetic factor, obesity and co-morbidity like hypertension, diabetes, lipid and inflammation. The mainstream of therapy of ALD patients, regardless of disease stage, is prolonged alcohol abstinence. Widely used Silybum marianum extract acts as lifesaving hepatoprotectant. Some medication like pentoxifylline, corticosteroids and N-acetyl cysteine are well established treatment for hepatic failure. Nutritional therapies are also important to meet the deficiencies of nutrients in patients with ALD. Liver transplantation remains emblem of concern for patients with end stage liver disease.

Keywords: Alcoholic Liver Disease, Mitochondrial Dysfunction, Genetic Factors, Abstinence, Nutritional Therapies, Liver Transplantation.

INTRODUCTION

Alcohol is the most commonly abused among youth [1, 2]. Alcoholism is the third leading cause of morbidity and the fifth cause of disease across the world. Globally, approximate 2.3 million people die each year due to the adverse and harmful use of alcohol, accounting for approximately 3.8% of all deaths [3]. The pure amount of alcohol is found as 354.8ml of beer (5%-12% alcohol content), 236.56ml of malt liquor (7% alcohol content), 147.87ml of wine (5% alcohol content), 44.36ml of a shot of 80-proof distilled liquor e.g. rum, vodka, whiskey (38%- 52% alcohol content) [4]. The pattern of alcohol consumption is defined in three categories: Binge drinking, which includes less than 5 drinks per occasion, Heavy drinking explains alcohol intake > 60g per day in men and > 40g per day in women, Moderate drinking indicates <20g per day in men and <10g per day in women [5]. Alcohol consumption across worldwide, personal or social use, which ultimately affects physiological processes leading to widespread of organ damage i.e. on cardiovascular system, liver, adipose tissue, skeletal muscle, brain, water and electrolyte balance and endocrine system[6]. Data reported from various epidemiologic studies over the last three decades have revealed complex associations between heavy alcohol utilization and cardiovascular system (CVS) conditions such as hypertension (HTN), peripheral arterial disease (PAD), coronary heart disease (CHD), cardiomyopathy causing damages to blood vessels, which leads to an increased risk of strokes and heart attacks [7]. Excessive use of alcohol affects not only the striated muscles of the myocardium, but also shows abnormalities to the skeletal muscle [8]. Further continuous drinking of higher amount over the years causes damages the brain tissue, causing alcohol-related brain damage (ARBD) [9]. Alcohol acts as diuretics and thus increases urine volume by suppressing vasopressin and the intake of fluid, resulting in kidney dysfunction [10]. Liver is a primary target for the detrimental effects of alcohol because it is metabolized by liver, which express high levels of two major alcohol oxidizing enzymes, alcohol dehydrogenase and CYP2E1 [11]. Liver diseases are ranked 27th as a major cause of death in world. In India, ALD 2.74% of all the causes of death [12]. Excess of alcohol consumption leads to Alcoholic Liver Disease (ALD), a leading cause which encompasses a spectrum of injury, ranging from simple steatosis to fibrosis and cirrhosis, attributing for 47.9% of all liver cirrhosis death [13]. In 2007, World Health Organization (WHO) reported mortality database, one can estimate for the Europe that 60% to 80% of liver-related mortality is due to excessive drinking [14].

A great concern is the rising incidence of hepatocellular carcinoma (HCC) which evolves in approximately 1% to 2% of alcoholic cirrhotic per year [15]. Data derived from human studies and animal models; demonstrate that development of hepatic steatosis is an early and uniformly predictable occurrence after sustained moderate/ high alcohol consumption. Only a fraction of individual progress to more advanced disease characterized by inflammation (alcoholic steatohepatitis) and fibrosis, with cirrhosis ultimately occurring in approximately 10 to 20% of cases [16]. 3–10% of alcoholic cirrhosis patients ultimately develop HCC [17].

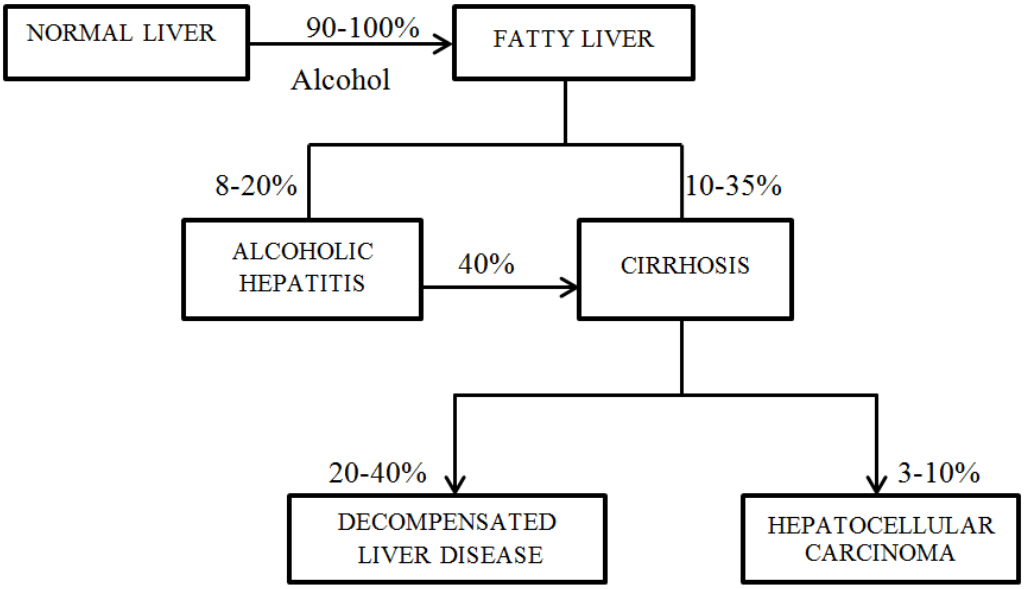

Figure 1: The spectrum of alcoholic liver disease, and percentage representing the proportion of patient progression [18].

PATHOGENESIS OF ALCOHOLIC LIVER DISORDERS

Alcoholic Fatty Liver (Steatosis)

Alcohol abuse leads to Steatosis, which is characterized by the accumulation of fat in hepatocytes, mainly triglycerides, phospholipids, and cholesterol esters. The prevalence of steatosis in developed countries ranges between 10% - 30% of the population [19]. Several studies have shown the increase in ratio of reduced nicotinamide adenine dinucleotide/ oxidized nicotinamide adenine dinucleotide in hepatocytes is due to alcohol consumption, which causes disruption of mitochondrial beta oxidation of fatty acids and leads to Steatosis [20]. Alcohol consumption directly increases transcription of Sterol Regulatory Element-binding Protein 1c (SREBP-1c) gene through metabolite acetaldehyde [21] and indirectly by activating processes and factors that stimulate SREBP-1c such as cell stress as the response to Endoplasmic reticulum [22]. It regulates the factors that increase SREBP-1c expression, such as AMP-activated protein kinase (AMPK), adiponectin and signal transducer and activator of transcription 3 (STAT3) [23]. Inhibition of fatty acid oxidation in hepatocytes due to consumption of alcohol mainly by inactivation of the peroxisome proliferator-activated receptor (PPAR), which is a hormone receptor controlling transcription of genes in fatty acid transport and oxidation [24]. Acetaldehyde, metabolite of ethanol, acts directly to inhibit transcription activity and DNA-binding ability of PPAR in hepatocytes. AMP-activated protein kinase (AMPK), a serine threonine kinase that inactivates acetyl-CoA carboxylase (ACC), rate limiting enzyme for fatty acid oxidation, enhancing Steatosis in hepatocytes [25].

Alcoholic Hepatitis

Alcoholic hepatitis is a syndrome of liver occurring due to inflammation of cells and hepatocellular injury. The prevalence is believed to be 10% to 35% of heavy drinkers and spectrum of disease ranges from mild to severe, life threatening injury . Ethanol is metabolized into acetaldehyde by alcohol dehydrogenase in cytosol, cytochrome P450 in microsomes, and catalase in peroxisomes, in hepatocytes. There are many factors involved to alcohol induced inflammation and reactive oxygen species are generated by metabolism and causes lipid peroxidation, mitochondrial glutathione depletion, and S-adenosylmethionine depletion, thus leading to hepatocytes injury [26]. Hepatocyte apoptosis, also play important role in hepatic injury, which includes induction of oxidative stress and induction of proapoptotic signaling molecules (TNF and Fas ligand). In oxidative stress, direct cell injury occurs by DNA damage and tumor necrosis factor (TNF) production signaling via nuclear factor kappa B occurs due to excess pro-oxidants (i.e. NAD phosphate oxidase and inducible nitric oxide synthase) in Kupffer cells [27]. Alcohol consumption increases the gut permeability and translocation of bacteria-derived Lipopolysaccharide from gut to the liver [28]. In Kupffer cells, activation of MyD88- independent (Myeloid differentiation primary response-88) pathway, lead to the production of oxidative stress and proinflammatory cytokines, that occurs when lipopolysaccharides interacts with TLR4 (Toll-like receptor 4) attenuating to hepatocellular damage [29]. Alcohol consumption for long term causes to increase generating lipid peroxidation products like malondialdehyde and 4-hydroxynonenal that serves as antigen in response to activate the adaptive immunity [30]. Thus the patients with Alcoholic Hepatitis shows increased level of circulation of antibodies against lipid peroxidation and eventually increased number of T cells in liver, indicating activation of adaptive immunity, involved in pathogenesis of ALD [31]. The regeneration of liver after injury or damage of tissue, liver cell recovery occurs via proliferation of full grown adult hepatocytes, biliary epithelial cells and endothelial cells. Sever and long term consumption of alcohol not only leads to hepatocytes death but also inhibits hepatocyte proliferation in patients, which is involved in pathogenesis of ALD [32].

Alcoholic Fibrosis

Liver fibrosis is characterized by accumulation of collagen and extracellular matrix protein, a wound healing response to all types of chronic liver injuries [33]. Hepatocytes damage increases level and activation of cytokines, chemokines, angiogenic factors, neuroendocrine factors and components of innate immune

system, which induces Hepatic Stellate Cells activation and fibrogenesis [34]. Most of fibrogenic mechanism occurs at alcoholic liver fibrogenesis, and some contributes to alcoholic liver fibrosis [35]. Alcoholic Liver Disease patients are found with increased serum levels of Lipopolysaccharides which directly activates Hepatic Stellate Cells via TLR4, and also by stimulates Kupffer cells and cytokines for indirectly promoting the activation Hepatic Stellate Cells [36]. Signaling in immune cells (Kupffer cells) and liver nonparenchymal cells (HSC and endothelial cells) through TLR4 contributes to the pathogenesis of fibrosis [37]. Natural killer cells when activated inhibits liver fibrosis by producing interferon (IFN) or by destroying activated HSC, which leads to arrest of HSC cell cycle and thus causing apoptosis [38]. Daily alcohol consumption causes disruption of activity of natural killer cells and interferon as important factors in pathogenesis of alcoholic liver fibrosis [39].

Hepatocellular Carcinoma

Hepatocellular carcinoma is most common primary liver malignancy and is a leading cause of cancer death worldwide [40]. Major risk factor for HCC includes chronic liver disease (i.e. viral hepatitis) and alcoholic cirrhosis. Development of HCC is complex multistep process that involves sustained inflammatory damage, including hepatocyte necrosis and regeneration associated with fibrotic deposition [41]. Thus, the mechanisms involved are alteration of the micro-environment and macro-environment that promotes tumor cell survival and proliferation, complex and telomere shortening (induces chromosomal instability), impairment of hepatocyte proliferation and activation of oncogenic pathway [42]. Some unique mechanisms are involved in occurrence of HCC in ALD patients, i.e. formation of acetaldehyde (carcinogen with mutagenic properties), ethanol stimulated induction of CYP2E1 (metabolizes procarcinogenic compounds to alcoholic beverages) and immunosuppressive effects of alcohol [43]. Lipopolysaccharide when increased in levels, in ALD patients synergize with HCV infection to promote liver tumor genesis through formation of cancer stem cells, when analyzed by stem cell markers [44].

RISK FACTORS

Alcohol Consumption

Duration and quantity of alcohol intake are measured as key lay bare feature for progression of ALD[45]. According to National Institute of Alcohol Abuse and Alcoholism defines a strong drinkers men consuming >4 drinks day by day (48 gm. of ethanol) or > 14 weekly and women consuming >2 drinks day by day (24gm) or > 7 weekly [46]. A study involving meta-analysis showed 25gm of ethanol daily is sufficient to increase the risk of cirrhosis [47]. Liver related mortality is found among men or women consuming daily 12-24gm of ethanol were demonstrated in the study [48]. Some studies have given evidences that pattern of drinking is also identified as risk factors including binge drinking (by NIAAA as consumption of ≥ 5 drinks for male or ≥ 4 drinks for female in duration of 2 hours) and drinking outside meal increases the risk of ALD[49].

Obesity

Epidemiological study showed that obesity is risk factor for development of steatohepatitis or cirrhosis in alcoholic population when compared to non-obese alcoholic or obese non-alcoholic [50]. A study conducted in India/ USA, showed a potential synergism of alcohol and obesity via nitrosative stress mediated by type I macrophage activation, adiponectin resistance and accentuated endoplasmatic reticulum and mitochondrial response to stress [51].

Gender

Women are at higher risk to develop ALD than men, when reported for lower quantities of consumption of alcohol (up to 12gm/day) [52]. The accentuation in the risk factor is because of lower levels of gastric alcohol dehydrogenase, synergistic oxidative stress of estrogens and higher proportion of body fat [53].

Genetics

Genetic bias to ALD has visibly emerged. Studies on gene polymorphism suggest that genes encoding for enzymes that metabolize both ethanol and acetaldehyde control the predisposition to alcohol dependence, sensitivity to alcohol and ALD cirrhosis development [54]. These genes include encoding for alcohol-dehydrogenase (ADH), aldehyde-dehydrogenase (ALDH) and C2-promoter allele of the gene coding for cytochrome CYP2E1. Variants of ADH genotypes encoding for a smaller amount active alcohol-metabolizing enzymes capacity facilitate liver damage by any delaying acetaldehyde formation or diverting alcohol metabolism through non-ADH pathways, such as the CYP2E1 and other non-oxidative pathways, which are potentially noxious to the liver [55]. ALDH gene polymorphism has been known to influence alcohol sensitivity in a number of populations (e.g. Asian) and in women, who enhance ALD with steady consuming low amounts of alcohol [56]. The polymorphism of CYP2E1 gene (C2-promoter allele) much differs amongst races and heavy drinkers with ALD. Alcohol intake induces CYP2E1 and natives with the C2-promoter allele exhibit a considerably better ability to metabolize alcohol. This might enhance free radical initiation and lipid peroxidation, which promotes fatty revolutionize in the liver [57]. Polymorphism of the gene encoding for CD14 expressed on Kupffer faction has been concerned in the risk of ALD [58]. Persistent alcohol drinking leads to free radical generation that damage DNA , which is repaired by the origin excision-repair path connecting DNA ligase III, DNA polymerase b and poly (ADP ribose) polymerase. Condensed mending of DNA lesions represents an important lay bare aspect for the promotion of ALD [59].

Comorbidity

Hypertension- At squat doses (<10 g for each day), alcohol has a temporary vasorelaxant effect at depressed dose, or in bender drinking; alcohol has a guide dose-dependent pressure effect[60]. Mechanisms of alcohol-induced main hypertension rope in a swell in significant adrenergic movement and vascular smooth-muscle tone, introduction of the renin–angiotensin–aldosterone system, and decreased liberation of nitric oxide [61]. In the Polish Public Multicenter Health Survey (WOBASZ) study, moderate alcohol intakes (15–30 g for each day) augmented the gamble of new commencement major hypertension by 37% [62]. According to the domino effect of a systematic reassessment and meta-analysis, the curve between hypertension and alcohol is linear in men at ≤40 g for each day (above which the take the risk of major hypertension plateaus), and J-shaped in women, with beneficial belongings at ≤20 g for each day. The connection between escalating alcohol intake and mounting attempt of hypertension has been corroborated worldwide, and is independent of age, smoking, obesity, salted intake, teaching level, and kind of alcoholic beverage [63]. The aura of the ALDH2 genotype raises blood force in alcohol consumers [64]. Alcohol intake has been reported in 16% of individuals with uninhibited arterial hypertension. Hypertensive subjects be supposed to be advised to evade high-dose alcohol, and clinicians be supposed to be mainly

knowledgeable of the stage of alcohol exploit in hypertensive patients [65].

Diabetes- Alcohol ingestion affects glucose metabolism in diabetic and non-diabetic individuals [66]. Light-to-moderate drinking (10–30 g for each day) inhibits in cooperation gluconeogenesis and glycogenolysis, and improves insulin sensitivity, follow-on in a minor incidence of mode 2 diabetes mellitus, [67] but excessive alcohol intake abolishes these favorable effects, ensuing in an U-shaped or J-shaped correlation between alcohol intake and diabetes incidence [68]. In a comparative study of men and women in Athens, Greece, neutral drinkers (<10 g for each day) had a 53% let down run the risk of diabetes than abstainers [69].

Lipids- Systematic reviews and meta-analyses of the property of low-dose alcohol consumption up on biological markers connected with Cardiac Heart Disease probability shows a dose–response correlation across beverage types, escalating levels of HDL cholesterol, apolipoprotein A-I, and adiponectin, and decreasing levels of LDL cholesterol[70]. Moderate alcohol intake increases the hazard of hyper triglyceridaemia by 25% and hyper homocysteinaemia by 46%[71]. The consequences of a randomized feeding trial demonstrated that moderate alcohol using up (30 g per day) increases serum HDL cholesterol by 5%, apolipoprotein A-I by 6%, and apolipoprotein A-II and adiponectin by 7%, in both women and men [72].

Inflammation- Systemic inflammation increases cardiovascular risk. Ethanol has anti-inflammatory special effects at minimal doses (<20 g for each day), but has a pro-inflammatory appearance at in height doses [73]. The mechanisms concerned in ethanol-induced swelling are diverse, comprising changes in the levels of inflammation, interleukins, cytokines, tumor necrosis factor, C-reactive protein, NADPH activation, and lipid peroxidation, with augmented oxidative stress, glutathione and superoxide dismutase (SOD) depletion, endothelial dysfunction, swell of endothelial nitric oxide synthase expression, and monocyte linkage to the endothelium[74].

TREATMENT FOR ALCOHOLIC LIVER DISORDERS

Abstinence and lifestyle modification

Abstinence from alcohol leads to end of alcoholic fatty liver disease (benign steatosis) and self-discipline improves survival in alcoholic cirrhotic patients, unvarying individuals with decompensated liver function. Abstinence from alcohol not only resolves alcoholic steatosis but also improves survival in cirrhotic patients. Inpatient and outpatient psychoanalysis programs obtain demonstrated effectiveness in assisting patients to achieve and avow seriousness [75]. Studies indicate that heavy drinkers who collect remit interventions (less than 1 hour in extent and incorporating motivational psychotherapy techniques) are double as liable as domination patients to have personalized their drinking lifestyle 6-12 months after the interference [76]. Pharmacotherapy in number sequence with psychosocial interventions knows how to advance patients in maintaining abstinence from alcohol. Naltrexone and acamprosate have been exposed to assist in eliminating alcohol intake in unrelieved driving drinkers [77]. Disulfiram, which has long been official by the FDA for the treatment of alcoholism, is allay broadly but a reduced amount of clearly supported by clinical trial demonstrate[78]. Baclofen has proven effective in promoting alcohol asceticism in alcohol dependent patients with liver cirrhosis[79]. The effectiveness of abstinence is enhanced as soon as it combines with lifestyle modifications (e.g., behavioral interventions and food alterations) that are supervised by a nurse, prime care physician, or gastroenterologist/hematologist[80].

Nutritional Supplements

Nearly all patients with critical alcoholic hepatitis and cirrhosis are emaciated and their gradation of malnutrition correlates with disease severity and complications, such as variceal bleeding, ascites, infections, encephalopathy, and hepatorenal syndrome. Deficiencies in micronutrients (e.g., folate, vitamin B6, vitamin A, and thiamine) and minerals (e.g., selenium, zinc, copper, and magnesium) often arise in ALD and, in certain instances, are thought to be concerned in its pathogenesis[81]. According to the recent guidelines of the American Association for the Study of Liver Diseases, entirely patients with alcoholic hepatitis or advanced ALD be supposed to be assessed for dietetic deficiencies and treated assertively with enteral nutritional therapy. A protein intake of 1.5 grams per kilogram bodyweight and 35 to 49 kcal apiece kilogram body weight per day is not compulsory for ALD patients [82]. Micronutrient supplementation is supposed to be measured if deficiencies are detected. Supplementation with one such micronutrient, zinc, has been made known to be therapeutic in animal models of alcoholic liver injury. Mechanistic studies grasp showed that its safety is mediated by blocking or attenuating most mechanisms of liver injury, counting augmented gut permeability, oxidative stress, bigger TNF production, and hepatocyte apoptosis. Few clinical studies conducted to date evoke that zinc supplementation may possibly be an effectual beneficial manage for humans because liver task of ALD and HCV patients enhanced with 50 mg of basic zinc [83].

Pharmaceutical Therapy

Fastest renowned and widely used Silybum marianum (milk thistle) extract, which contains silibinin as the biologically most effective compound. The primary signal for silymarin treatment is Amanita phalloides (death chalice fungus) intoxication in which silymarin acts as a life-saving hepatoprotectant[84]. The popularity of silymarin goods in the midst of patients with chronic liver disease was promoted by a clinical test in 170 patients with cirrhosis of many etiologies which demonstrated a major survival help in individuals treated with silymarin[85]. Severe ASH in which therapeutic challenges reside in the renewal of liver synthetic function as well as falling hepatic and total inflammation. The key player of AH remedy are abstinence, corticosteroids and intensive problem addressing the complications of ASH such as renal collapse and sepsis. Corticosteroids comprise been old in the treatment of ASH for more than 40 years [86]. The most deliberate formulation is prednisolone 40 mg daily for 4 weeks. Prednisolone alone abridged the hazard of 28-day mortality. The response to prednisolone can be assessed based on the change in bilirubin after one week of therapy and quantified using Lille score [87]. With a bad response as indicated by a Lille score count ≥0.45, therapy is considered to be stopped. Based on these data, professional practice guidelines urge the consumption of corticosteroids in AH patients with a DF (discriminant function) >32, and the European guideline advises cessation thereof be supposed to answer after 7 days of remedy[88]. Abundant reports suggested a profit of pentoxifylline (PTX), an orally absorbed nonselective phosphodiesterase inhibitor approved for the cure of intermittent claudication, in reducing the happening of the hepatorenal syndrome in patients with Alcoholic Steatohepatitis [89]. N-ssacetylcysteine (NAC) is well-established in the management of fulminant hepatic failure due to paracetamol overdose, [90] and improves transplant-free survival in first scaffold non-paracetamol acute liver failure [91]. A contemporary randomized experimental showed that the code of NAC with

prednisolone abridged 1-month mortality (8% opposed to 24%) and the incidence of hepatorenal syndrome and infection[92]. Oxidative stress is concept to compete a key in responsibility in the pathogenesis of ALD. Alcohol mediates oxidative stress in an amount of habits including lipid peroxidation, the fabrication of reactive oxygen species, and lessening of endogenous antioxidant capabilities[93].Vitamin E deficiency has been documented in ALD. Vitamin E has experimentally proven hepatoprotective capabilities including membrane stellate stabilization, reduced NFkB inauguration and TNF production, and inhibition of hepatic chamber creation[94]. In a study of patients with mild to moderate alcoholic hepatitis, 1000 IU of vitamin E per day has shown improvement serum hyaluronic acid. Another antioxidant, polyenyl phosphatidylcholine (lecithin), a lipid extract obtained from soybeans. It has been given away to put a stop to alcoholic liver cirrhosis and appears to engage in anti- inflammatory, anti-apoptotic, and antifibrotic property [95].

Liver Transplantation

This process remains the emblem of concern for patients with end-stage liver disease. Some patients with ALD are not programmed for the replacement of their in possession of liver by a donor organ (i.e., orthotropic liver transplantation) for reasons such as repeated alcohol consumption, restitution in liver occupation after abstinence, and a senior incidence of cancers of the better airways and high digestive tract. As a result, transplantation candidates with ALD habitually are screened for shared malignancies and must undergo an official remedial and psychiatric evaluation. They additionally have got to desist from alcohol for 6 months before being considered for liver transplantation. Data show that less than 20 percent of patients with histories of alcohol consume as the important basis of end-stage liver disease hear liver transplants[96]. However, enduring and organ survival is admirable in this patient population, with considerable improvement in their trait of being[97]. Following transplantation, ALD patients return to consuming alcohol at charge similar to those transplanted for other reasons, even if ALD patients may consume better amounts [98]. As every transplant recipient's exhibit increased levels of alcohol assistance over time, post-transplant interventions are deemed enormously valuable in at the bottom of patients to maintain self-denial [99].

CONCLUSION

Alcohol related toxicity is the third principal reason of morbidity; it enhances liver disease by performing as hazard for ALD. A number of factors responsible for the enlargement of liver injury include dose, duration, types of alcohol, amount of consumption, drinking pattern, sex obesity and infections with viral hepatitis and genetic factors. The pathophysiology of ALD is extremely complex. Numerous clinical manifestations ensue, ranging from benign condition, such as steatosis to deadly diseases, such as cirrhosis and hepatocellular carcinoma. Tainted metabolic pathways, energy metabolism impairment, immune-mediated dealings and oxidative stress cooperate in ALD pathogenesis. No foremost proceed has been made in the management of ALD, uniquely in the field of long-term treatments. Abstinence remains the basis of the cure to improve the overall survival, being able to decrease portal hypertension and cirrhosis progression. Malnutrition is a common condition in ALD, especially in alcoholic cirrhosis, thus a nutritional support is considered as essential in the patient management. Some medications, such as corticosteroids and pentoxifylline, are currently recommended for the treatment of liver imbalance of Alcoholic Hepatitis, no effective treatments have been yet approved for the long-term management of ALD. Lastly, liver transplant remains the only definitive treatment for end-stage alcoholic cirrhosis, in patients with adequate social support providing a 6-month period of abstinence, but the organ availability is still the major limiting factor.

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