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Review Article

EXPLORING ALCOHOLIC LIVER DISEASE FROM BIOCHEMICAL DETECTION TO TREATMENT AND ITS COMPLICATIONS – A REVIEW

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ABSTRACT

Background: Alcohol consumption is the most common cause of developing alcoholic liver disease (ALD) all over the world. Chronic alcohol consumption has been known to induce a decrease in gut wall integrity in actively drinking alcoholics and patients with alcohol-induced liver disease. It is strongly correlated with the progression of three types of liver conditions as fatty liver, hepatitis and liver 'scarring' (cirrhosis). Fatty liver is a build-up of fat within liver cells in most people who regularly drink heavily. It is reversible if they stop the consumption of alcohol. However, in some people the fatty liver progresses and develops into hepatitis. Alcoholic hepatitis is the inflammation occurs in the liver. Methods: This is a systematic review about diagnosis, pathophysiology, detection of biochemical markers and various treatment methods for alcoholic liver disease. The search of databases including PubMed, EMBASE, Science direct, Alcohol and Alcoholism journals, Taylor and Francis data bases, Scopus, Google scholar, Web of Science. Results: The severe form of alcoholic hepatitis can quickly lead to cirrhosis. The main treatment for alcoholic hepatitis is to provide adequate nutrition in addition to steroids. Cirrhosis is a condition where normal liver tissue is replaced by scar tissue (fibrosis). The scarring tends to be a gradual process. The scar tissue affects the normal structure and regrowth of liver cells. So, the liver gradually loses its ability to function well. The interactions between acetaldehyde, reactive oxygen and nitrogen species, inflammatory mediators and genetic factors appear to play prominent roles in the development of ALD. The cornerstone of therapy for ALD is stopping the consumption to improve the survival of patients with all stages of ALD. Conclusion: Alcoholic liver disease comprises a wide spectrum of pathology ranging from mild fatty infiltration to advanced cirrhosis. No doubt as all these parameters in combinations may be useful indicator for identification and determination of severity of alcoholic liver diseases. During the past 3 decades, several pharmacologic interventions have been investigated in the treatment of ALD. To date, none are clearly effective with minimum side effects. Most of the final stage of recovery from ALD supports liver transplantation. There should be a need to pay attention in the development of new bio drugs with strong scientific validation approved by different clinical trials, nontoxic, cost effective, cheap, biocompatible and biodegradable to reduce the rate of mortality of individuals suffering from ALD.

Key words: Alcoholic liver disease; Alcohol dehydrogenase; Aldehyde dehydrogenase; Treatment.

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INTRODUCTION

Liver is the major organ to encounter the ingested food, micronutrients, drugs and environmental toxicants entering into the portal blood. It functions as a center of metabolism of nutrients

such as carbohydrates, proteins, lipids and excretion of waste metabolites. Additionally, it is also handling the excretion of drugs and other xenobiotics from the body thereby providing protection against foreign substances by detoxifying and eliminating them. Liver secrete bile into the small intestine to help digest fats and render them soluble for absorption. Nutrients are carried from the small intestine through the portal vein directly to the liver, which then synthesizes cholesterol, metabolizes or stores sugars, processes fats, stores vitamins, and assembles proteins for use within the liver. The liver also converts the products of protein metabolism into urea for excretion by the kidneys. In addition, it regulates blood-clotting mechanism. On a whole liver can mobilize a chemical and cellular arsenal for self-protection. Fortunately, its ability to regenerate helps this important organ survive the wear and tear of a lifetime.

Liver submitted to noxious stimuli may be functionally or structurally damaged, transitorily or permanently, depending on the strength and duration of the stimuli [1]. Long term administration of toxicants and therapeutics for different diseases can injure the hepatocytes. An observation on exposure of different hepatotoxicants has advanced the understanding of hepatic functions and its co relationship in cellular apoptosis. Researchers have identified mechanisms by which chemicals injure specific populations of liver cells. Among the wide variety of different toxicants high alcohol consumption is one of the most common factors that cause damage to the liver. Ethanol is more than a psychoactive drug [2]. In addition to its pharmacologic action, it has considerable energy value (7.1 kcal/g) and also promotes nutrient degradation or impaired activation [3]. Liver is the primary organ responsible for alcoholic metabolism, so it is highly vulnerable to alcohol-related injuries. As most of the advanced biochemical techniques and transgenic animal model research favors new insights in therapeutic values still there are some questions need to be resolved. Why 50% of cases of end stage liver disease have alcohol has a main aetiological factor. In addition the mortality from alcoholic cirrhosis is higher than that of non-alcoholic cirrhosis and the mortality rate in liver disease is more than that of many major forms of cancer, such as breast, prostate and colon cancer [4].

Alcoholic liver disease (ALD) is unique in the way that it occurs when the person habitually consumes excessive amounts of alcohol through his or her own volition. It is an important lifestyle-related disease that is prevalent throughout the world. According to a WHO estimate, alcohol intake ranks third following hypertension and smoking, as a global disease burden [5]. Geographic variability exists in the patterns of alcohol intake throughout the world Some of the possible factors that affect the development of liver injury include the dose, duration, and type of alcohol consumption; drinking patterns; sex; ethnicity; and associated risk factors including obesity, iron overload, concomitant infection with viral hepatitis, and genetic factors [6]. One epidemiological study has estimated that for every 1-liter increase in per capita alcohol consumption (independent of type of beverage), there was a 14% increase of cirrhosis in men and 8% increase in women [7, 8] Alcohol abuse impairs reproductive activity [9] and fertility abnormalities with low sperm count and impaired sperm motility [10, 11]. It causes impaired testosterone production, enormous oxidative stress that results in testicular atrophy.

Accordingly priority should be emphasized to know about the acute and chronic alcoholic liver diseases because of its adverse long term effect in the human system and it is important to focus on more research studies in the invention of effective alternative medicines as a therapy to cure liver diseases induced by alcohol. Hence, in this review article, more attention has been given to generate extensive and informative data from various literatures, standard medical manuals and reference books.

METHODS

Medical reports including diagnosis, pathophysiology, biochemical markers, enzyme bioassays, different pharmacological therapeutic models were collected and grouped from specific medical and biomedical reference books and articles. The search of databases including PubMed, EMBASE, Science direct, Alcohol and Alcoholism journals, Taylor and Francis data bases, Scopus, Google scholar, Web of science, was carried out from 1988 to 2013. In addition, paper and printed information sources were searched manually in our library.

RESULTS AND DISCUSSION

ALD can emerge in 3 forms: fatty liver, alcoholic hepatitis, and cirrhosis. These are not necessarily distinct stages of evolution of disease, but rather, multiple stages that may be present simultaneously in a given individual [12, 13]. The form or severity of liver disease is not predicted by the amount of alcohol consumed. Between 90% and 100% of heavy alcohol consumers will develop fatty liver. Of those with fatty liver, 10% to 35% will develop alcoholic hepatitis, and 20% to 40% of these alcoholic hepatitis patients will progress to cirrhosis. Up to 20% of patients with fatty liver due to alcohol

consumption will progress directly to cirrhosis [14, 15].

Fatty liver

Fatty liver develops in about 90% of individuals who drink more than 60 g/day of alcohol [16] but may also occur in individuals who drink less [17]. Hepatic steatosis / fatty liver are considered reversible and to some extent non progressive if there is cessation or removal of underlying cause. At the beginning, the alcohol undergoes oxidation reaction to form a highly reactive molecule called acetaldehyde and finally produces acetate that changes the chemical redox state of the hepatocyte, favoring the rapid accumulation of the coenzyme NADH. The overproduction of NADH was fed to the electron transport chain that subsequently slows down the citric acid cycle. This sequentially stops the entry of acetyl COA into the citric acid cycle directing them to stimulate the biosynthesis of free fatty acids and ketogenesis [18]. This concurrent change affects several elements of liver metabolism. Gluconeo genesis (the metabolic production of glucose from non-carbohydrate sources) is prevented by the accumulation of fatty acids resulting in the form of reserve fuel called triglycerides. This leads to the deposition of fat in the liver, and can eventually lead to the condition called fatty liver .This condition arises due to the impaired ability of hepatocytes in synthesizing the lipoproteins and transport the lipids out of the liver.

Liver pathogenesis initially includes enlarged and distorted mitochondria with a proliferation of the endoplasmic reticulum [19] and small fat vacuoles (liposomes) around the nucleus (microvesicular fatty change). In this stage liver cells are filled with multiple fat droplets that do not displace the centrally located nucleus. In the later stages, the size of the vacuoles increase pushing the nucleus to the periphery of the cell giving characteristic signet ring appearance (macro vesicular fatty change). These vesicles are well delineated and optically empty because fats dissolve during tissue processing. Large vacuoles may coalesce and produce fatty cysts which are otherwise called as macro vesicular steatosis. This stage is characterized by the presence of irreversible lesions. The prolonged stage of fatty liver causes adverse effects including the enlargement of hepatocyte and disturbances in blood circulation.

Alcoholic hepatitis

Alcoholic hepatitis occurs in up to 50 percent of heavy drinkers [20]. Most of the people with alcoholic steatosis progress to steatohepatitis and subsequent fibrosis or even cirrhosis. Alcoholic hepatitis is characterized by widespread inflammation and more severe injury of the liver in which the body's own immune system responds and triggers the destruction of liver tissues. Hepatocyte injury caused by the generation of reactive oxygen species (ROS) through induction of cytochrome P4502E is a major determinant in alcoholic liver injury and fibrosis [21 – 24]. Some of the characterized symptoms may include fever, jaundice and abdominal pain. The condition can be fatal but may be reversible with abstinence. As alcohol induced liver disease progresses, appreciable cell death occurs; the functioning mass of the liver is replaced by the formation of scar tissue in the liver nodules called hepatic fibrosis. It is fact that liver fibrosis is a wound healing process characterized by the accumulation of extracellular matrix (ECM) proteins, especially collagen types I and III, as well as an increase in other extracellular matrix constituents such as proteoglycans, fibronectin and laminin in response to liver injury [25]. When the injury is recurrent or chronic, collagen deposition occurs in excess of collagen resorption as a result of an imbalance between fibrogenesis and fibrolysis leading to scar formation. As scarring progresses from bridging fibrosis to the formation of complete nodules it results in architectural distortion and ultimately liver cirrhosis.

Liver cirrhosis

Alcoholic cirrhosis, the end stage of ALD, is the most advanced form of liver disease which is diagnosed in 15 to 30 percent of heavy drinkers [26, 27]. This is characterized by extensive fibrosis that stiffens blood vessels with micronodular regeneration and distortion in the internal structure of the liver [28 – 30]. In addition to fibrosis, various admixtures of fat, inflammatory cells around the portal vein [31-33], stainable iron deposits and cholestasis are common in cirrhotic livers; especially this condition is observed in alcoholic subjects [34]. Liver metabolism is deficient in detoxifying the ammonia originated during the oxidative deamination of aminoacids and bilirubin derived from the catabolism of hemoglobin. Inadequate synthesis of blood clotting factors lead to development of irreversible uncontrollable hemorrhage with structural damage in the liver. This results in severe functional impairment in the liver, which may lead secondarily to malfunction of other organs, such as the brain and kidneys.

Alcohol metabolism

Liver is the primary organ responsible for the catabolism of alcohol. The consequences of ethanol on hepatic function can be dependent and/or independent of the metabolism of ethanol by the liver cells. Hepatocytes have very high constitutive activities of the phase I enzyme called alcohol

dehydrogenase that often convert ethanol into highly reactive electrophilic metabolite called acetalydehyde, which is a toxic by-product that may contribute to tissue damage. This reaction is further catalyzed by phase II enzyme called aldehyde dehydrogenase that yields acetate from the oxidation of acetaldehyde. At high concentrations, alcohol is eliminated quickly because of the presence of enzyme systems with higher activity [35].

$$CH_3CH_2OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+ \quad (1)$$
$$CH_3CHO + NAD^+ \rightarrow CH_3COO^- + NADH + 2H^+ \quad (2)$$

Alcohol dehydrogenases (ADH) generates NADH in the cytosol; the second catalyzed by aldehyde dehydrogenase (ALDH), also generates NADH, but in the mitochondrial matrix space. Alcohol oxidation generates a highly reduced environment by generating too much NADH in the liver cells. Some of the enzymes involved in gluconeogenesis (lactate dehydrogenase and malate dehydrogenase) and fatty acid oxidation (β – hydroxyl acyl – COA dehydrogenase) require NAD+ as a substrate. Thus these pathways are inhibited by alcohol intake as it depletes the NAD+ levels. This forced reduction in NAD+ leads to hypoglycemia and excess of lactate that rarely causes metabolic acidosis [36]. At this stage liver cells are vulnerable to damage from the byproducts of ethanol metabolism such as acetaldehyde, acetate and free radicals.

Acetaldehyde readily forms covalent bonds with functional groups of mitochondrial proteins. These proteins further released the ROS includes superoxides and peroxy radicals capable of attacking nearby mitochondrial constituents. ROS can form adducts with reactive residues on membrane proteins or small molecules (e.g. cysteines) by blocking the normal biological processes and be directly toxic to the cell. These adducts may provide a sensitive marker to assess the past drinking activity of an individual [37]. The ROS modified biological molecules may also stimulate the host's immune response and cause an auto immune – like disease. Experimental trials conducted with a hybrid adducts of malondialdehyde and acetaldehyde (MMA) in human alcoholics and animals models has been shown to induce an immune response by generating antibodies against such oxidative modified proteins [38 – 40]. Liver have a limited capacity to oxidize the acetate, which is produced from the oxidation of acetaldehyde, to carbon dioxide (CO_2) because the TCA cycle is inhibited by high NADH and ATP levels during ethanol oxidation. Much of the acetate derived from ethanol escapes the liver to the blood. Virtually every other tissue like heart, skeletal muscle and brain cells oxidize it to CO_2 because the TCA cycle is inhibited by high NADH and ATP. Acetate is not an inert product; it increases blood flow into the liver and depresses the central nervous system, as well as affects various metabolic processes [41]. It is hypothesized that upon chronic alcohol intake the brain starts using acetate rather than glucose as a source of energy Acetate is metabolized into acetyl COA which involved in lipid and cholesterol biosynthesis in the mitochondria of peripheral and brain tissues [42].

Cytochrome P450 system

Cytochrome P4502E1, the central enzyme of (MEOS) microsomal ethanol oxidizing system, is induced primarily in the smooth endoplasmic reticulum and converts ethanol to acetaldehyde, which is then metabolized to acetate by ALDH [43]. Heavy drinkers exhibit approximately threefold higher activities of CYP2E1 than non-drinkers since ethanol is an inducer of Cytochrome P4502E1 system [44]. Research investigations carried out in ethanol induced HepG2 cells overexpress the production of CYP2E1. This supports the hypothesis that the co – localization of CYP2E1in hepatic lobular regions plays a casual role in the development of alcoholic liver disease [45]. In addition a research conducted in animal models showed that subsequent introduction of inhibitors for CYP2E1 partially blocked the pathology of hepatocytes [46]. CYP2E1 has been shown to be loosely coupled with cytochrome reductase, leaking electrons to oxygen to form $O_2^{\cdot-}$ radicals which further develop lipid peroxidation in the cells [47]. This implies the condition that increased expression of CYP2E1 is a metabolic marker in detection of ROS such as hydroxyl ethyl, superoxide radicals in the liver of alcoholics [48, 49].

Catalase

Another enzyme, catalase, located in cell bodies called peroxisomes, is capable of oxidizing ethanol in vitro in the presence of a hydrogen peroxide (H_2O_2)-generating system, such as the enzyme complex NADPH oxidase or the enzyme xanthine oxidase. Quantitatively, however, this is considered a minor pathway of alcohol oxidation, except in the fasted state [50]. The non-oxidative pathway for ethanol metabolism is minimal but its products have severe pathological effect. This reaction is catalyzed by fatty acid ethyl ester (FAEE) synthase, leading to the formation of fatty acid ethyl esters from the reaction of alcohol with fatty acids that play functional roles in human cells. FAEE concentrations are highest in organs susceptible to the toxic effects of ethanol, including pancreas and liver. FAEEs accumulate in the plasma membrane, as well as in membranes of organelles including mitochondria

and lysosomes, potentially having a negative impact on the activity of these organelles. FAEEs are detectable in serum and other tissues after alcohol ingestion and persist long after alcohol is eliminated. Accumulation of FAEE is currently being developed as a marker of long-term ethanol consumption [51].

Genetic polymorphism on dehydrogenase enzymes

The genetic and acquired differences in ADH and ALDH enzymes may explain why some persons are more susceptible to alcohol than others. Because polymorphisms of ADH and ALDH play an important role in determining peak blood acetaldehyde levels and the voluntary ethanol consumption [52] and in addition they also influences the vulnerability to alcohol dependence. This might be the allelic variation in ADH and ALDH genes which contribute to differential rates of ethanol elimination in human population. The polymorphisms of *ADH* and *ALDH* genes correlate with the occurrence of alcoholic liver disease in Japanese [53, 54] and with alcoholic cirrhosis in Taiwanese [55].

Alcohol dehydrogenase (ADH, EC1.1.1.1)

It is a zinc containing, cytosolic enzyme present in several tissues including the liver, which has the highest levels, but other tissues include the kidney, the lung and the gastric mucosa express ADH. This enzyme contributes to the overall oxidation of ethanol [19, 56]. Human ADH is a dimeric protein consisting of two 40 – kDa subunits. The sub units (α, β, γ, π and χ and sixth subunit known as σ or μ) are encoded by six different gene loci (ADH_1 through ADH_5, respectively, the sixth subunit (σ or μ) was originally reported to be encoded by gene ADH_7) [57, 58].

The human ADH enzymes comprise nine subunits, all of which can combine as homodimers. In addition the α, β and γ subunits (and their allelic variants) can form heterodimers with each other. The different molecular forms of ADH are divided into four major classes. Class I contains ADH_1, ADH_2 and ADH_3 which can be considered isozymes. ADH_1 contains two alpha subunits or one alpha subunit plus a beta or gamma subunit. ADH_2 contains two beta subunits (which could be β_1 β_2 or β_3) or a beta subunit plus a gamma subunit (which could be γ_1 or $\gamma_{2)}$. ADH_3 contains two gamma subunits (which could be γ_1 or γ_2). ADH_2 enzymes that differ in the type of β subunits are known as allelozymes as are ADH_3enzymes that differ in the type of γ subunit. Accordingly ADH_2*1 is an allelozyme composed of β subunits; ADH_2*2 is an allelozyme composed of β_2 subunits and ADH_2*3 is an allelozyme composed of β_3 subunits. The class I ADH isozymes are responsible for the oxidation of ethanol and other small aliphatic alcohols. High levels of class I ADH are expressed in liver and adrenals, with lower levels in kidney, lung, blood vessels and other tissues but not brain. Class II contains ADH_4, which is made up of two π subunits (named as pi). Class II ADH is primarily expressed in liver (with lower levels in stomach), where it preferentially oxidizes larger aliphatic and aromatic alcohols. Class III contains ADH_5, which is made up of two χ subunits (chi – ADH). Class IV contains ADH_6 (originally named ADH7) which is made up of two subunits designated σ or μ [59].

Aldehyde dehydrogenase (ALDH)

There are twelve ALDH genes (known as ALDH1 to 10, SSDH and MMSDH) have been identified in humans, and a correspondingly large number of ALDH genes appear to be present in other mammalian species. The genetic deficiencies in any of the ALDHs impair the metabolism of other aldehydes, which is the underlying basis of certain diseases. For example, $ALDH_4$ deficiency disturbs proline metabolism and causes type II hyperprolinemia, symptoms of which include mental retardation and convulsions. A deficiency of $ALDH_{10}$ which detoxifies fatty aldehydes disturbs the metabolism of membrane lipids. This is the underlying basis of Sjorgen – Larson syndrome, symptoms of which include ichthyosis, neurologic problems and oligophrenia [60]. Genetic polymorphism in ADH, ALDH and Cyt P4502E1 are the potential contributors to variations in the susceptibility to alcohol dependence and/or organ damage in response to prolonged alcohol consumption [61, 62].

The best-known genetic polymorphism in ALDH genes is in $ALDH_2$. The allelic variants are $ALDH_2$*1 and $ALDH_2$*2, encoding for the high-activity and low-activity forms of the subunits respectively [63, 64]. Approximately 50 percent of Asian populations but virtually no Caucasians have the slow ALDH; alcohol consumption by people with this slow polymorphism leads to uncomfortable symptoms of facial flushing, increased skin temperature, heart rate and nausea due to high systemic levels of acetaldehyde [65 – 68]. Thus this slow detoxification polymorphism serves as a strong deterrent for alcoholism. The alcohol dehydrogenase fast polymorphism, which occurs in about 20 percent of Asian and less than 5 percent of Caucasian populations, has also been linked to a lower rate of alcoholism. These polymorphisms in gene products are responsible for alcohol sensitivity, especially in Asian populations, and that these individuals develop ALD while consuming less alcohol [69].

Consequences of alcohol metabolismHypoxia

Alcohol metabolism appears to increase oxygen utilization by liver cells, thereby reducing the availability of oxygen for other important cellular functions. The NADH generated in alcohol metabolism is oxidized by a series of chemical reactions in the mitochondria (i.e., the mitochondrial electron transport system, or respiratory chain) eventually resulting in the transfer of electrons to molecular oxygen (O_2), which then binds protons (H^+) to generate water (H_2O). This concludes that to have enough oxygen available to accept the electrons, the hepatocytes must take up more oxygen than normal from the blood [70]. This indicates that hepatocytes are supplied with oxygen rich blood by the arteries. But some strong evidences suggest that alcohol consumption result in significant hypoxia in zone 3 of the liver lobules, which normally is exposed to lower concentrations of oxygen than zone 1 or zone 2. The tendency of hypoxia to occur in zone 3, together with the fact that free radicals are more likely to be formed in this region, may account for the observation that alcoholic liver damage tends to concentrate in zone 3 [71]. Cells lining the liver sinusoids also may contribute to hypoxia by secreting endothelin, a potent agent that induces narrowing of blood vessels. The resulting narrowing of the sinusoids may decrease the delivery of oxygen-containing blood to zone 3.

Action of inflammatory agents in tissue damage

Chronic heavy alcohol consumption can cause an imbalance in inflammatory mediators such as eicosanoids, cytokines and TNFα that damage the liver tissues. Eicosanoids are a family of biological molecules with a wide range of functions. Different eicosanoids affect the liver in different ways: Prostaglandins and prostacyclins can protect liver cells from certain kinds of damage; conversely, thromboxanes cause blood vessels to narrow, which can promote hypoxia or directly cause inflammation or necrosis. Another type of eicosanoid, the leukotrienes (e.g., leukotriene B4), may cause liver injury by attracting and activating neutrophils, special white blood cells with phagocytic properties. Long-term alcohol consumption alters the balance of eicosanoids in the liver by decreasing the production of cell-protective prostaglandins and prostacyclins and by increasing the synthesis of the harmful eicosanoid thromboxane B2 and possibly leukotriene B4 [72]. Cytokines are a family of chemicals produced by various immune system cells, including the kupffer cells of the liver. They have many overlapping functions, and they can be harmful in the context of long-term heavy alcohol consumption [73]. TNF-α, produced primarily by Kupffer cells, may cause liver injury directly or indirectly. First, evidence suggests that TNF-α might be directly toxic to liver cells. Second, TNF-α stimulates the liver to produce other cytokines, which attract white blood cells to the liver and stimulate them to release free radicals and toxic enzymes that damage the liver.

Free radicals induced liver damage

Ethanol metabolism is a predominant factor by causing alcohol associated tissue damage through the generation of ROS in the tissues. The rate of oxidation of NADH generated by ADH and ALDH enter into the mitochondrial electron transport system requires two important factors such as oxygen and generation of ATP. If any of these two factors are limited it automatically reduces the efficiency of ETC activity in oxidation of NADH. This flux in electron transport proteins can divert the generated electrons by forming highly reactive superoxides, peroxy radicals [74] and initiate the direct injury to the liver. In contrast, CYP2E1, which also oxidizes ethanol, particularly following chronic alcohol intake, is found in many tissues in addition to the liver, including the brain, heart, lungs, and certain white blood cells (i.e., neutrophils and macrophages). Accordingly, metabolic consequences of CYP2E1 mediated ethanol oxidation would affect numerous tissues. In the liver, CYP2E1 mediated ethanol metabolism generates oxidative stress that leads to DNA damage and may thereby play an important role in alcohol-related development of liver cancer [75].

Hepatic cancer

Hepatocellular carcinoma (HCC) is one of the most frequent primary tumors that develop due to very long – term alcohol consumption. Even though ethanol is still not considered as carcinogen, its reactive metabolite acetaldehyde is a potent carcinogen that is proved in different experimental models. An inhalation of acetaldehyde increases the development of nasal adenocarcinoma and squamous cell carcinoma [76]. It interferes with DNA synthesis and causes point mutations in hypoxanthine phosphori bosyltransferase (HPRT1) locus of human lymphocytes and induces gross chromosomal aberrations. Moreover, ethanol and acetaldehyde inhibit adenosyl – L – methionine synthesis that helps cancer progression by decreasing methyl transfer to tumor suppressive genes and their subsequent transcription. It is evident that increased matrix metalloproteinases (MMP) activities are involved in the progression of cancer [77].

Kidney damage

Large amounts of ethanol have deleterious effects on the kidney. Chronic alcoholics may experience low blood concentrations of key electrolytes as well as potentially severe alterations in the body's acid-base balance. In addition, alcohol can disrupt the hormonal control mechanisms that govern the function of kidney by promoting liver disease. Chronic drinking causes further detrimental effects on the kidneys including impaired sodium and fluid handling and even acute kidney failure [78]. Most of the conventional therapies recommended for liver disease are based on the abstinence as well as general supportive and symptomatic care. Unfortunately, hepatocellular damage may still progress despite these measures, and so various specific therapies should be optimized for improving both the short and long term morbidity and mortality of this disease.

Treatment methods

Abstinence

Cessation of alcohol consumption or a significant reduction in alcohol intake improves histology and or survival of persons with any stage of ALD, [79] therefore; alcohol abstinence is the cornerstone of management for patients with ALD [80, 81]. Treatments that aim to reduce the alcohol intake in alcohol dependent patients include psychological and pharmacological approaches. Psychological treatments such as cognitive behavioral therapy and motivational enhancement therapy have been shown to reduce alcohol intake [82]. As an alternative, some patients may derive benefit from pharmacological therapy. Both acamprosate and naltrexone have been shown to reduce drinking days. Disulfiram, an inhibitor of acetaldehyde dehydrogenase, has been used for many years, although with conflicting results. In addition, family support is an essential component in the overall management of individuals with ALD.

Liver transplantation

Although it is controversial and situations are different in each country, the definitive treatment for ALD is liver transplantation (LT). In general, in order to be considered for LT, at least 6 months of proven abstinence is necessary [83]. Liver transplantation demonstrated in alcoholic cirrhotic patients demonstrated are successful and survival rates equal to those for nonalcoholic subjects.

Corticosteroids

These agents have well known effects on the immune response and reduce cytokine production, suppress the formation of aldehyde adducts and inhibit the production of collagen [84]. Natural corticosteroids are synthesized from cholesterol by the adrenal glands, which are located above the kidneys. Synthetic corticosteroids, such as prednisolone, are widely used medicinally to suppress inflammation [73]. Some studies demonstrate that corticosteroid therapy may improve survival in patients with severe alcoholic hepatitis [20]. Other studies have reported significantly improved survival rates only in patients suffering brain-related complications of alcoholic liver disease, however, and not in patients with milder illness [85].

Nutritional support

The protein-calorie deficiency could enhance the toxicity of alcohol, in part, through the influence of nutritional status on the integrity of the immune system and the capacity to respond to infection. A clinical trial conducted in patients with alcoholic hepatitis concludes that nutritional support improves the nutritional status and abnormal liver tests, but does not decrease the early mortality rate in patients [86]. Another study stated that nutritional support was associated with an improvement in serum albumin and reduction in mortality of patients treated with nutritional supplements [87]. Thus, although nutritional supplements are reasonable for any severely malnourished patient, their efficacy in the management of acute alcoholic hepatitis must be considered to be unproven.

Pentoxifylline

Pentoxifylline is a non-selective phosphodiestesase inhibitor that gives a moderate anticytokine effect attributed to a reduced transcription of the gene encodes tumor necrosis factor (TNF) [88]. The drug decreases blood viscosity, red cell, platelet aggregation and improves the flow of blood. Pentoxifylline is also thought to improve organ microcirculation and tissue oxygenation. A clinical trial of 101 patients with severe alcoholic hepatitis treated with oxpentifylline (pentoxifylline) (400 mg orally three times daily) vs. placebo concludes that 49 patients who received oxpentifylline (pentoxifylline) and 24 of the 52 patients who received placebo died during the initial hospitalization. Hepato renal syndrome was the cause of death in 50% of treated group and 91.7% in the placebo group [89]. Thus, the benefit of oxpentifylline (pentoxifylline) in treating acute alcoholic hepatitis appears to be related to a significant decrease in the risk of developing hepatorenal syndrome.

Anti-TNF therapy

Acute alcoholic hepatitis is a potentially important indication for the use of the direct anti TNF antibody, infliximab. This monoclonal antibody binds

to TNF and blocks its biological effects. There are two initial reports which demonstrated an improvement in biochemistry and satisfactory profile when used alone [90] or in combination with steroids.

Polyunsaturated Lecithin

Lieber and Colleagues [91] demonstrated that a mixture of fatty substances called polyunsaturated lecithin (PUL) dramatically reduced the incidence of cirrhosis in baboons fed alcohol for several years. In some cases, removal of PUL from the diet led to the development of cirrhosis, perhaps in an accelerated manner. PUL presumably exerts its beneficial effect by promoting the degradation of collagen, thereby inhibiting fibrosis. PUL also may help stabilize membranes and encourage the synthesis of cell-protective prostaglandins.

Antioxidants

Free radicals as a major cause of liver injury can be overcome by supplemented with exogenous antioxidants in ALD patients. Two main trials are conducted using silymarin (milk thistle) as an antioxidant. The results confirmed that silymarin has potent antioxidant properties in vitro and in vivo [92]. Glutathione depletion has been prevented in alcohol-fed animals by administering S-adenosyl-L-methionine (SAM), a precursor of glutathione. Interestingly, SAM's positive effect seems unrelated to its potential promotion of glutathione synthesis, but apparently derives from its ability to modify the mitochondrial membrane, thereby restoring normal transport of glutathione through that membrane. This effect helps to maintain normal levels of glutathione in the mitochondrion, where it is needed to prevent free radical damage in alcoholic cirrhosis. Mato and Colleagues reported a significant beneficial effect of SAMe treatment. A study of antioxidant supplementation in ALD patients has demonstrated that, it may have more protective role in alcoholic hepatitis than in alcoholic cirrhosis [93].

N-acetylcysteine (NAC)

N-acetylcysteine is an antioxidant substance and replenishes glutathione stores in hepatocytes. NAC treatment (1g/Kg.b.w) diminishes oxidative stress by increasing antioxidant enzymes and restoration of oxidant/antioxidant balance (reflected by lower levels of transaminases, ALP and GGT) [94]. In a randomized controlled trial of N-acetylcysteine alone versus placebo there was no evidence of a significant effect [95]. In another randomized trial, N-acetylcysteine alone was inferior to corticosteroids in terms of short-term survival [96]. More recently, a randomized controlled trial observed that patients treated with combination therapy (corticosteroids and N-acetylcysteine) had better 1-month survival than patients treated with corticosteroids alone [97]. The rates of hepatorenal syndrome and of infection were lower in patients treated with corticosteroids and N acetylcysteine. However, there was no significant difference in survival between the two groups at 6-months, the primary planned end point. Therefore, corticosteroids and N-acetylcysteine may have synergistic effects.

Melatonin

It protects against alcoholic liver injury by attenuating oxidative stress, inflammatory and apoptotic responses. It significantly attenuates the increased level of serum aminotransferase, reduces the severe extent of hepatic cell damage, steatosis and the immigration of inflammatory cells. In addition melatonin decreases serum and tissue TNF – α levels, tissue lipid peroxidation, neutrophil infiltration and apoptosis of hepatocytes [98]. Researchers are also investigating vitamins A and E as therapeutic agents for alcoholic liver disease. Vitamin E is reported to have antioxidant activity and prevents the lipids from oxidation. A randomized clinical study has shown that it improves serum hyaluronic acid, although no beneficial effects is observed on liver function tests in patients with mild to moderate alcoholic hepatitis.

Vitamin C

Liver diseases are highly related with reduced ascorbic acid levels in leukocytes of patients in ALD especially in primary biliary cirrhosis (Beattie & Sherlock, 1976). Ascorbic acid supplementation causes faster restoration of reduced glutathione content in the regression of alcohol induced hepatotoxicity in male guinea pigs [99].

Flavonoids

Flavonoids are reported to have antioxidant property that protects against ALD. It ameliorates the alcohol induced liver injury by inhibiting NFκB activation. It also attenuates inflammatory pathways and activates antioxidant enzymes [100]. However, a randomized double – blind clinical trial has demonstrated that 3-palmitoyl-(+)-catechin at a dose of 1500mg daily for 3 months fails to produce statistically significant clinical, biochemical or histological benefit in patients with biopsy-proven alcoholic liver disease. Another randomized double – blind clinical trial has shown similar results, with no significant benefit; although both reports have documented significant reduction in alcohol consumption during therapeutic studies.

CONCLUSION

Long term consumption of alcohol is the one of the major factor that indirectly damages the liver cells and alters the cellular oxidant and antioxidant system. Alcoholic liver disease comprises a wide spectrum of pathology ranging from mild fatty infiltration to advanced cirrhosis. The association between alcohol abuse and liver disease has been supported by most of the research work; the exact mechanisms of alcohol induced liver injury remain incompletely understood. Most of the advanced diagnostic techniques and new biomarkers or identifier proteins for detecting the alcohol abuse can accurately diagnose ALD. No doubt as all these parameters in combinations may be useful indicator for identification and determination of severity of alcoholic liver diseases. In the stage of therapy the only treatment of ALD that has been proven to be of value in improving mortality, is the combination of abstinence from alcohol, life style changes, supportive care, and adequate nutrition. During the past 3 decades, several pharmacologic interventions have been investigated in the treatment of ALD. To date, none are clearly effective with minimum side effects. Most of the final stage of recovery from ALD supports liver transplantation. This is not the affordable treatment method for people all over the world. There should be a need to pay attention in the development of new bio drugs with strong scientific validation approved by different clinical trials, nontoxic, cost effective, cheap, biocompatible and biodegradable to reduce the rate of mortality of individuals suffering from ALD.

Ethical considerations

Ethical issues like plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and / or submission, redundancy, etc. have been completely observed by the author.

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