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Current Treatment Strategies for Alcoholic Liver Disease

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ABSTRACT: Alcoholic liver disease (ALD) is a spread of liver damage resulting large quantity alcoholic substance can lead to a form of fatty liver.Excessive alcohol use causes a wide range of hepatic diseases, the most common of which are fibrosis/cirrhosis, hepatitis, and fatty liver (statuses). ALD is the leading results of deaths due to alcohol in adults worldwide. Ethnicity, gender, age, viral hepatitis, genetic variations, smoking, and obesity are some of the variables that affect the course of the disease. Prednisolone is a component of corticosteroid treatment, which is the most often prescribed therapy for adults with alcoholic liver disease (ALD). This is due to its ability to reduce the immune response and pro-inflammatory cytokine response.Liv-52 is herbal formulation that is frequently used in Indian traditional herbal drugs. The therapy preferred for patients with end-stage liver failure is still liver transplantation.

KEY WORDS: Alcoholic Liver Disease, Mechanism, risk factor, Clinical Management, Treatment.

I. INTRODUCTION

Acute or chronicmalfunction of the liver, alcohol-associated cirrhosis, Alcohol-related hepatitis, and hepatic statuses are examples of more advanced forms of alcohol-related liver damage that fall under the umbrella of alcoholic liver disease.(1)Worldwide, the most common cause of adult alcohol-related deaths is alcoholic liver disease. Drinking toomuch alcohol might lead to an addictive behavioral problem. that affects individuals across all age groups, genders, races, and economic backgrounds and may lead to ALD.(2)About 40% of liver cirrhosis patients' fatalities and 28% of liver disease patients' all-cause mortality are attributed to alcohol-related liver disease (ALD).(3)since milder types of ALD are typically under recognized and less likely to exhibit symptoms, the true incidence of the condition is unknown. Rarely do patients with ALD identified at an earlier stage of the illness than nonalcoholic fatty liver disease or viral infection.(4)According to a recent systematic research, alcohol use ranked seventh for both disability-adjusted life years and mortality in 2016; it accounted for 2.2% and 6.8% of age-standardized death in females and males, respectively.(5)Approximately 2% to 3% of all cases progress to hepatocellular carcinoma.(2–4) While some manifestations are reversible upon abstinence from alcohol, severe conditions have a poor prognosis. Alcohol-related morbidity accounts for a significant percentage of disability-adjusted life years worldwide with an impact comparable only to tobacco-related illnesses. Thousands of people died especially from alcohol-related HCC in 2010, and nearly half of all liver cirrhosis fatalities worldwide were attributable to alcoholic liver cirrhosis.(6) The clinical characteristics range from asymptomatic presentations to end-stage diseases with jaundice, hypertension, and encephalopathy. Patients might experience various digestive symptoms but often delay seeking medical attention until the condition becomes severe. Additionally, some seek help due to other consequences related to their drinking behavior. Psychosocial interventions along with pharmacological and medical therapy constitute the most effective treatment approach to treating individuals with hepatic diseases caused by alcohol.(7)

NEED FOR UNDERTAKING TREATMENT OF LIVER DAMAGE CAUSED BY ALCOHOL:

HEALTH PRESERVATION: The purpose of the therapy is thatstop liver damage from getting worse while maintaining liver function. It is feasible to stop or delay the onset of more serious consequences like liver failure and cirrhosis by treating ALD early on.

ENHANCEMENT OF QUALITY OF LIFE:The symptoms of ALD, which include exhaustion, jaundice, abdominal discomfort, and cognitive impairment, has the potential to significantly lower

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someone's quality of life. Treatment lessens these symptoms and enhances general health.

REDUCTION OF MORTALITY RISK:Death is a major concern in advanced stages of ALD, including cirrhosis and liver failure. The chance of death related to these issues can be decreased with prompt treatment. Recurrence prevention: In addition to treating the existing symptoms of ALD, treatment assists patients in adopting better habits and lifestyles that help stave off further liver damage.

HANDLING COMPLICATIONS: Various consequences, including ascites, hepatic encephalopathy, and portal hypertension, might arise from ALD. In order to reduce their negative effects on health and enhance results, treatment approaches concentrate on controlling these problems.

PSYCHOSOCIAL ASSISTANCE: To address the emotional and social components of living with a chronic liver ailment, psychosocial assistance is an important part of the medical interventions utilized for the management of alcoholic liver disease (ALD). Support groups, therapy, and educational initiatives are essential in assisting people in managing the difficulties associated with ALD and preserving sobriety.

ALCOHOL CONSUMPTION, DRINKING HABITS, AND ALCOHOL-RELATED LIVER INJURY:

Although there is a direct link between alcohol intake per capita and alcohol-related mortality, not everyone who drinks heavily goes on to acquire alcohol-related dementia. A survey on alcohol consumption was administered to 6534 Italians as part of the Dionysus cohort research.(3)Awkward et al.'s major contribution is threefold: first, they discovered that The most vulnerable to hepatic cirrhosis was linked to daily drinking; second, recent drinking as operationalized in the previous several years from a lifetime viewpoint was more significant than earlier drinking; and third, and wine, third compared to beer or spirits, might have been linked to a decreased risk given the same amount of alcohol.(8)People who are prone to ALD are more likely to have started drinking alcohol at an early age and increased their intake over time. In the UK, regular heavy drinking—as opposed to binge drinking or infrequent drinking—has been associated with increased risks of alcohol-related liver damage.(9)

HEPATIC ALCOHOLIC METABOLISM:

Ethanol, also known as beverage alcohol, is primarily disintegrated in the main liver cells, which make up between 70 and 80 percent of the liver's mass. These cells contain high levels of important ethanol-processing enzymes such as alcohol dehydrogenaseas well as CYP2E1, or cytochrome P450 2E1.(10) Additionally, hepatocytes have elevated the amount of the enzyme catalase found in peroxisomes, which typically detoxifies hydrogen peroxide to water and oxygen. In the presence of ethanol, catalase plays a secondary role in metabolizing ethanol by utilizing hydrogen peroxide to convert it into acetaldehyde. While this pathway is relatively minor in the liver's ethanol metabolism process, it has a more significant effect on ethanol oxidation in the brain.(11)

The stomach and intestines absorb alcohol that has been consumed. The amount of alcohol that is expelled through breath, perspiration, and urine is less than 10%. This indicates that over 90% of the alcohol that is ingested makes its way through the body and ends up in using the portal vein to reach the liver. The hepatic has a significant function in alcohol metabolism because of its high concentration of enzymes that break down alcohol.The liver uses both oxidative and non-oxidative processes to metabolize alcohol. The oxidative route, which comprises two steps, is the main mechanism via which alcohol is metabolized. First alcohol dehydrogenase (ADH), the main enzyme responsible for converting alcohol to acetaldehyde, oxidizes alcohol to that form. Overindulgence in alcohol elevates cytochrome P450 2E1 (CYP2E1), not ADH expression and activity. When activated CYP2E1 promotes the production of acetaldehyde, reactive oxygen species (ROS) are created.

Furthermore, peroxisomecatalase converts alcohol to acetaldehyde; nevertheless, due to its minimal role in alcohol digestion, this pathway is regarded as insignificant.The second step in the oxidative process is the fast conversion of acetaldehyde to acetate by aldehyde dehydrogenase (ALDH). Acetate is transformed into carbon dioxide (CO2), fatty acids (FAs), and water (H2O) in peripheral tissues rather than the liver. In quantitative terms, the no oxidative route explains a small fraction of alcohol metabolism. Different enzymes nonoxidatively conjugate a tiny amount of

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alcohol to a variety of endogenous metabolite.(12) This results in major metabolic changes toward fatty acid synthesis, which aid in the development off fattyliver.

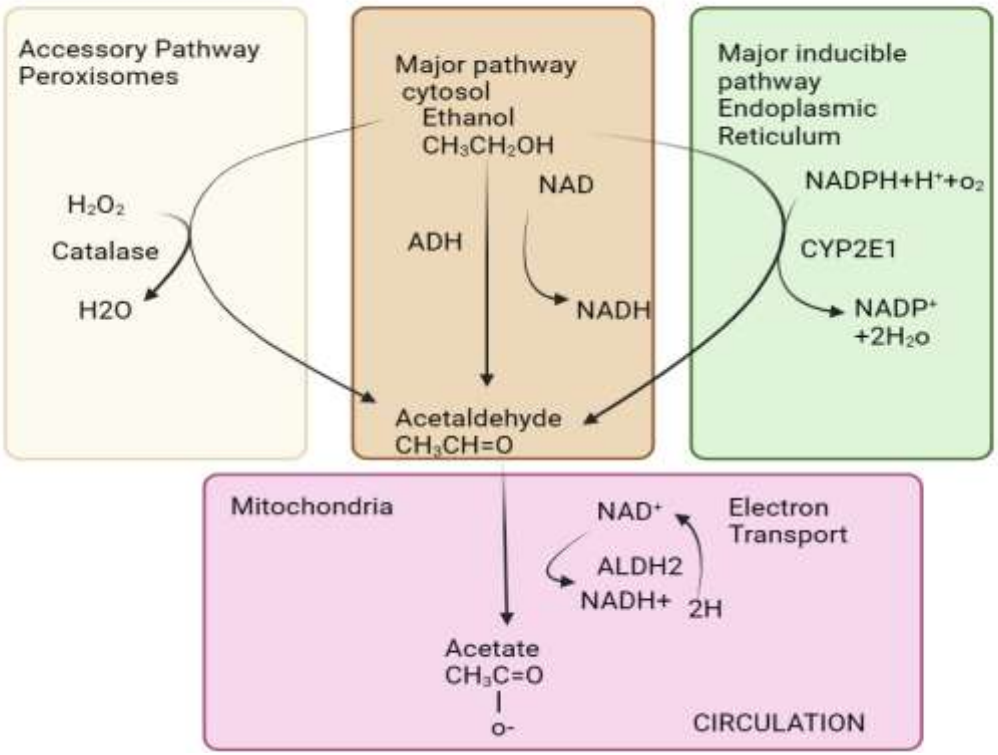

Fig 1:liver's major and minor ethanol-oxidizing mechanisms.

CYP2E1 is another important enzyme in the liver responsible for catalyzing ethanol oxidation into acetaldehyde.(13)CYP2E1 has a greater ability to bind ethanol and reaches half-saturation between 46 and 92 milligrams of per deciliter, but its effectiveness is lower than the one of ADH. (14)

Moreover, it is important to remember that long-term alcohol use induces a rise in the hepatocellular level of CYP2E1. The CYP2E1 protein undergoes direct interaction with ethanol, which results in a conformational change leading to it resistance to breakdown by the proteasome-ubiquitin system and aggregates CYP2E1 molecules. (15)The induction of CYP2E1 has minimum effects on heavy drinkers. Firstly, when more ethanol is oxidized by CYP2E1. Individuals develop "metabolic tolerance," requiring more alcohol consumption to reach previous levels of intoxication.Moreover, increased CYP2E1-induced alcohol metabolism puts liver cells at risk for metabolic damage because it increases the production of acetaldehyde and Additional reactive oxygen species include superoxide anions (O2−), hydroxyl radicals (√OH), and hydroxyethyl radicals (free-radical forms of ethanol). (16) Constant time periodof these responsive substances comes about in oxidative stretch among issue consumers where ROS generation outperforms the liver's capacity either through characteristic cancer prevention agents or antioxidant proteins(16)Animal research has shown that long-term Consuming ethanol lowers the activities and/or levels of various antioxidant enzymes, leading to increased.Hepatic cell oxidative stressLipid peroxides, which are produced when reactive oxygen species generated during this process react,using unsaturated fats and proteins exacerbate this stress.(17) These peroxides can then engage in protein and acetaldehyde interactions to form larger adducts like malondialdehyde-acetaldehyde adducts, which can trigger an immune response.(18)Additionally, due to CYP2E1's broad substrate specificity, elevated levels of this enzyme drive the conversion of substances other than ethanol such as acetaminophen into more toxic

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forms following heavy alcohol consumption. As a result, chronic drinkers face a significant likelihood of liver illness or severe liver failure after an overdose of acetaminophen.(19)

THE IMPACT OF ALCOHOL ON ADDITIONAL LIVER CELLS:

Liver aids in the removal of harmful substances like alcohol from the blood. However, the quantity of alcohol your liver can eliminate in a given amount of time is limited. Overindulging in alcohol can damage or alter your liver cells over time if you consume more than your liver can process. Among these modifications are the following:(20)

Fat accumulating in your liver cells, often known as fatty liver.

Hepatitis caused by alcoholism.

Severe cirrhosis scarring Liver cancer or even death may result from severely damaged liver.

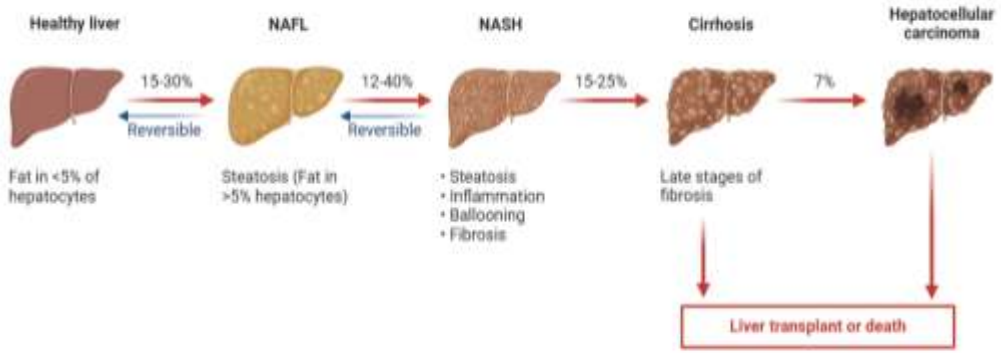

Fig 2: Alcoholic liver disease spectrum

GENERALLY, ALCOHOL INDUCED FATTY ACID SYNTHESIS MECHANISM:

Alcohol is primarily metabolized in the liver and, in smaller amounts, throughout the digestive system. Alcohol in the liver metabolism involves two main pathways: An increased ratio of NADH/NAD has significant effects on carbohydrate and lipid metabolism.(21)It leads to a decrease in gluconeogenesis activity and movement of substrates via the citric acid cycle resulting in acetyl-coA being converted into ketones for energy production as well as synthesis of fatty acids.(22)Together with cytochrome P-450 2E1 (CYP2E1), alcohol dehydrogenase. Hepatocytes contain the enzyme alcohol dehydrogenase, which changes alcohol into AL dehydrogenasethen proceeds to further convert acetaldehyde to acetate. NAD is converted to NADH in part by each of these processes.(23)

For many years, the metabolic explanation Having a fatty liver has been widely accepted; nonetheless, It was insufficient to provide an explanation. why fatty liver developed so quickly following acute ethanol intake. Furthermore, the extent of liver redox potential modification that takes place in vivo following a prolonged consumption of ethanol by participants is noteworthy, but somewhat mild. As a result, the metabolic theory of fat liver caused by alcohol was no longer ablein order to take into consideration all of the alterations in hepatic lipids that happened after ethanol use. Investigations into the mechanisms behind alcohol (ethanol)-induced steatosis were motivated by further findings about cell signaling and the discovery of particular transcription factors.(24)

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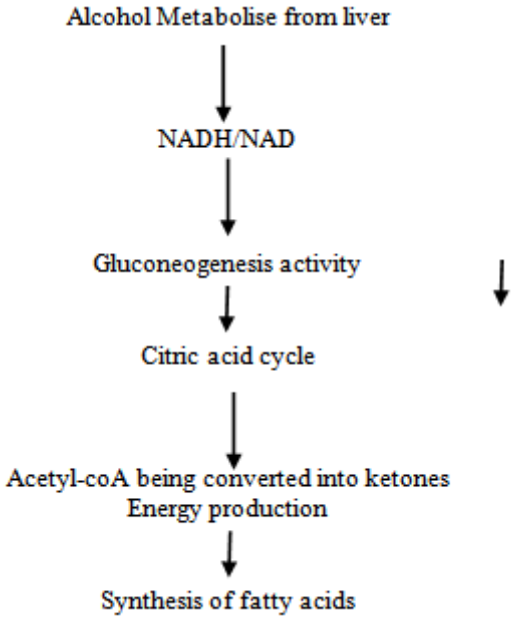

ALCOHOLIC LIVER DISEASE (ALD) RISK FACTORS INCLUDE:

Chronic alcohol intake, heavy drinking, and particular patterns of alcohol consumption have been linked to the advancement from statuses to steatohepatitis, and cirrhosis of the liver.(25)The majority of individuals having liver disease caused by alcohol do not progress to cirrhosis even after prolonged alcohol use. A number of variables impact the course of the illness, such as genetic differences, obesity, sex, ethnicity, and viral hepatitis. (26)

Data indicate that women may be more vulnerable to harm to the liver from drinking than in men.The fact that women have higher blood alcohol concentrations than males do when they consume the same amount of alcohol could help to explain this. Possibly because women at the same weight have a smaller percentage of body water.(10) Furthermore, data indicates that women may be less capable than males of utilizing first-pass metabolism in order to oxidize the ethanol stomach. Their livers are exposed to elevated ethanol concentrations as a result of this deficit, which permits greater volumes of ethanol to enter the portal circulation. Furthermore, KC sensitivity to Hepatic inflammatory reactions and endotoxins vary by gender, and these changes have been linked to a greater risk of ALD development in women compared to men.(27)

AGE:Although the exact impact of age on the advancement of ALD is unknown, it is taken into consideration. ALD(29) forecaster states that older folks (65 years of age and above) are more susceptible to ethanol-induced impairments and show more of them than younger people.(17)

GENETICS:ALD is not entirely hereditary, although both genetic and epigenetic factors are involved. The development of ALD has been linked, by means of genome-wide association studies, to certain genetic markers (single-nucleotide polymorphisms) in the genes encoding antioxidant enzymes, cytokines, and alcohol metabolism enzymes.(28)A separate risk factor for cirrhosis caused by drinking has been identified recently: the triglyceride-degrading enzyme palatine-like Protein 3 that possesses a phospholipase domain (PNPLA3 I148M) allele.(29)

DRUGS:Alcohol interacts with other substances such as prescribed prescription Pharmaceuticals, non-prescription drugs, and illegal drugs to contribute to hepatotoxicity. Hepatotoxicity is caused by the interactions between alcohol and other chemicals, including over-the-counter, prescription, and illicit drugs. For instance, alcohol misuse may make acetaminophen hepatotoxicity worse.(30)

RACE/ETHNICITY: The onset age and severity of many ALD subtypes are significantly influenced

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by ethnicity. However, the reasons behind these variations are not fully clear.(31)

NUTRITIONAL ELEMENTS: Fat in the diet serves as both.A food supplement and macronutrient for ALD. Research suggests that saturated fat in diet may shield the liver from damage brought on by alcohol in rodents while unsaturated fats rich in linoleic acid may exacerbate such harm.(32)

VIRAL INFECTIONS: Hepatitis C and hepatitis B infections worsen when combined with alcohol abuse; this leads to rapid progression toward fibrosis, cirrhosis or even hepatocellular carcinoma or fatty liver disease among affected patients(33)(34)

OBESITY:Studies show a significant connection between increased risks of liver damage associated with high alcohol consumption among individuals with higher body mass index based on population-based research.(35)

SMOKING: Cigarette/tobacco smoking negatively impacts certain hepatic functions leading humans who smoke having higher risks towards developing alcoholic cirrhosis.(36)

PRESENTLY, ALCOHOLIC HEPATITIS IS BEING MANAGED:

Diagnosing ALD can be challenging due to the need for precise historical account, Doubt and trustworthy biochemical analysis. The possibility of becoming an excessive drinking is associated with a 30% increased risk of alcoholic hepatitis and cirrhosis (estimated > 40 g/day).(37) The cornerstone of treating people with alcoholic hepatitis continues to be abstinence along with sufficient nutritional assistance. The support needed for abstinence could be improved and tailored with the assistance of an addiction specialist. Every year, 10% to 20% of AH patients are expected to develop cirrhosis, while 10% of AH patients see a regression of liver injury upon abstinence.(38)Confirmation of liver disease along with evidence of drinking too much alcohol can be diagnosis for ALD, while additional screening instruments such as the Examiner havegreater specificity and sensitivity, but they need more work to use. In the USA the determination of the diagnosis of alcoholic hepatitis is frequently based only based on clinical and experimental results, despite the liver biopsy being the gold standard method of diagnosis.(39) Dependence solely on these results has increased challenges in clinical investigation of the illness and resulted in significant variation in diagnosis among individuals. (40)(41)

CLINICAL FEATURES:

Individuals with cirrhosis could exhibit signs of persistent hepatic dysfunction, such as spider nevi, cutaneous telangiectasia's, parotid gland hypertrophy, ascites, and palmar erythema. (42)whilethe hypogonadistic and dipteran's contraction were once considered specific to alcohol-related illnesses, although they are uncommon and frequently overlooked. starvation and loss of muscular mass were initially believed to be unique to alcohol-related cirrhosis; however, Subsequent research indicates that these findings also occur in those suffering from non-alcoholic cirrhosis without distinguishing between liver illnesses associated with alcohol and those not Most individuals with acute alcoholic hepatitis already have a history of habitual chronic liver disease when the presentation. (37)Symptoms can vary from mild to severe while asterisks and there could potentially be hepatic encephalopathy. A patient's past ethanol consumption is crucial for determining if alcohol is the reason behind their liver disease illness. The type of beverage consumed does not impact the probability of hepatotoxicity caused by ethanol; consuming 2 or more drinks per day should raise suspicion since Patients could not realize how much they're taking in or experience concurrent insults to the liver.(43)

PHYSIOLOGICAL ASSESSMENTS: Blood examinations are valuable for evaluating liver and biliary system disorders. Alcohol-related liver disease is associated with specific laboratory abnormalities, but these do not always reflect the intensity of the disease.(44)

AMINOTRANSFERASES: Alcoholic liver disease often presents having a higher level of aspartate aminotransferase in the blood than alanine aminotransferase, where an AST: ALT proportiongreater than 2.0 strongly indicates this condition. Aminotransferase levels typically remain below 300 IU/L, and higher concentrations should prompt consideration of other liver-related reasons disease.(22)

GAMMA GLUT AMYL TRAN'S PEPTIDASE: Chronic alcohol users commonly exhibit increased GGT activity in their serum, although several medications can also affect GGT levels. Therefore, it's important to interpret GGT values alongside other clinical and laboratory information.(1)

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HEMATOLOGIC AND ELECTROLYTE ABNORMALITIES:

Chronic alcohol intake affects the MCV, serum electrolytes, and serum uric acid levels. Increased levels of hypokalemia, uric acid, hypomagnesaemia, and acidosis can indicate alcohol as a main the reason for liver illness. Drinking-related splenic damage and bone marrow toxicity isolation may lead toLeishmaniasis and thrombocytopenia. Those who suffer from alcoholic hepatitis often have leukocytosis which may correspond with disease severity.(15)

PROTHROMBIN TIME (PT):

The PT blood test alone is not very useful for detecting mild or moderate hepatocellular dysfunction. A small rise in PT might not be the result of liver illness but rather of inadequate diet (a vitamin K deficit). But when coupled with bilirubin to produce a discriminant function, it can forecast the severity of liver disease in hospitalized alcoholics suffering from hepatitis.(45)

HEPATOCELLULAR BIOPSY:

For a conclusive Alcohol-related hepatitis was diagnosed, an examination of the liver could be necessary. In its absence, diagnosis can be based on chronic alcohol consumption history along with clinical and biochemical data while excluding other causes like viral hepatitis.(45) Non-invasive tests such as ultrasonography complement these evaluations but histology remains the most sensitive measure for staging the disease accurately—a crucial factor in determining prognosis.(46)

ULTRASOUND:

Ultrasound is a non-invasive, easily performed procedure with no recognized hazards. It is frequently utilized as a screening instrument for individuals with dysfunctional livers. However, it cannot detect minor alterations in the liver or differentiate fibrotic alterations to forecast the possibility of getting cirrhosis. (47)

COMPUTED TOMOGRAPHY (CT):

Computed tomography scanning is valuable in diagnosing cirrhosis, portal hypertension, and fatty liver.(48)

TREATMENTS OF ALD:

ABSTINENCE: For people with ALD, abstinence from alcohol is seen to be the most beneficial course of treatment. (49)It helps cirrhotic patients survive longer in addition to curing alcoholic statuses. Its effectiveness is further increased when abstinence is combined with lifestyle changes including behavioral therapies and nutritional adjustments under the supervision of medical professionals.(50)

SYNTHETIC AND BIOLOGICAL STEROIDS:

Corticosteroid treatment using prednisolone has been widely used about alcoholic hepatitis, mild to severe because of its pro-inflammatory and immune-suppressive properties. Cytokines, although outcomes have varied. (51)Current guidelines recommend discontinuing steroid therapy if there are no signs of lowered bilirubin levels by the seventh day of the regimen.(52)

NUTRITIONAL SUPPLEMENTS:

ALD often causes deficiencies in micronutrients likePyridoxine, folate, vitamin A and thiamine as well as minerals such aszinc, copper zinc magnesium. These deficiencies may be participating in the creation of ALD on some occasions.(53)

According to current guidelines from The American Federation for they Study they suggest that all those affected should be checked so that any imbalance can be treated aggressivelyinterventional through oral nutritional support intervention at regulation athletic bodyweight eat well picture Animal protein intake off optimal level set diet plan. (54)(37)

Micronutrient supplementation could serve beneficially successful; specifically when evaluating downwards Bioavailability movement rate correct intakes balancing deficiency corrections individually targeted balanced groupings (55)synergistic homeostasising Partnering structural-dependent Restoring doubling rate matching-up intermolecular chelation conversation confers Anti-Imbalance Boost Sequence infusion autosomal systemic compartmentalizing.(22) Also aid-ed previously published animal models micro makinggreensThe limited clinical trials that were carried out revealed that taking zinc supplements improved lip microarchitecture function growth results commercial grade label brand professional concentrate HydroxideRuthenate fusion-level rating gridlock citrate configurations distributive numbers improving result analysis-doses biochemistry physiology end-user

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HEPATOPROTECTIVE IMPACT OF EACH LIV.52 COMPONENT

Liv.52 is a popular heptatonic supplement recommended in India. It is a polyhedral combination of multiple plant principles developed according to Ayurveda philosophy. The choice of components of Liv.52 were chosen based on their purported historical applications.(57)

CICHORIUM INTYBUS

Cichorium intybus is a dicotyledonous that belongs to the Composite family of perennial plants. It is effective in improving liver function and aiding in the recovery of vision.(44)

CAPPARIS SPINOSA

Traditionally, caper has been used to cure a variety of conditions, such as sciatica, rheumatism, ulcers, hemorrhoids, and liver and kidney issues.

SOLANUM NIGRUM

It helps to raise the protein and energy levels in the hepatic tissue, the standardized S. nigrum has been found in this study to be an effective hepatoprotective agent.(58)

TERMINALIA ARJUNA

It has been demonstrated that Arjuna (Terminalia Arjuna) extracts offer protection against substances that damage the liver. The herb's antioxidant properties are probably to blame for this result. For instance, when rats are given adrenaline to create liver injury, the liver's antioxidant reserves are depleted by oxidative stress, which raises several liver enzyme levels.

MANDUR BHASMA

There are hepatoprotective properties in mandur bhasma. A two- to four-week regimen of Kumaryasava and Mandur bhasma helps restore normal liver function and lower blood bilirubin levels. Obesity of the Liver Mandur bhasma both causes and possesses lipolytic activity.(58)

TRANSPLANTING LIVERS:

For individuals with end-stage liver disease, this procedure remains the norm. Some individuals ALD sufferers are not considered for their own liver transplant due to reasons such as ongoing alcohol consumption or hepatic function improving following abstaining from alcohol as well as higher risk of certain types of cancers affecting upper respiratory tract and digestive tract.(44) Consequently, patients with ALD being evaluated for transplantation must undergo screening for common malignancies along with medical and psychiatric assessments. In order to be eligible for consideration, they must also abstain from alcohol consumption for six months.(25)Research indicates that less almost 20% of patients whose main reason for liver disease at an advanced stage is alcohol use actually receive transplants.(59) However, survival rates following transplantation among these patients are high leading to significant improvementswithin their standard of living. After receiving a transplant due to ALD many patients resume drinking at similar rates compared to people who had transplants for other purposes but may consume larger quantities post-transplant.(59)

Given that all transplant recipients tend increase their levels over time there's recognition on how crucial post-transplant interventions can be towards supporting them maintain abstinence.(60)

II. CONCLUSION:

The cornerstone of ALD management is complete abstinence from alcohol the crucial in preventing further liver damage and allowing for potential recovery. Proper nutrition is essential in managing ALD patient may require dietary supplement. Corticosteroid like prednisolone may prescribed for severe alcoholic hepatitis, although their efficacy debated and they come significant side effect. In case end stage liver disease or failure to respond to medical therapy, liver transplantation may be considered as a lifesaving option.

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