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UNVEILING HOPE: REVERSIBLE ALCOHOLIC FATTY LIVER DISEASES – A COMPREHENSIVE REVIEW

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ABSTRACT

Reversible Alcoholic Fatty Liver Disease (AFLD) represents a significant health burden globally, with its prevalence rising steadily. AFLD encompasses a spectrum of liver conditions, ranging from hepatic steatosis to more severe forms such as steatohepatitis and fibrosis, ultimately leading to cirrhosis if left untreated. Understanding the mechanisms underlying AFLD pathogenesis is crucial for developing effective therapeutic interventions. This review provides an overview of the etiology, pathophysiology, and risk factors associated with AFLD. The intricate interplay between alcohol metabolism, lipid metabolism, oxidative stress, inflammation, and genetic factors contributes to AFLD progression. Additionally, lifestyle modifications, including alcohol cessation, dietary changes, and exercise, are pivotal in AFLD management. Emerging therapeutic strategies targeting key molecular pathways involved in AFLD, such as mitochondrial dysfunction, lipid peroxidation, and inflammation, show promising results in preclinical studies. Furthermore, advances in precision medicine offer new avenues for personalized treatment approaches based on individual genetic susceptibility and disease severity. However, several challenges remain, including the need for large-scale clinical trials to validate the efficacy and safety of novel therapeutics. In conclusion, a comprehensive understanding of the complex pathophysiology of AFLD and the development of targeted treatment strategies hold the potential to mitigate the escalating burden of liver disease worldwide.

KEYWORDS: AFLD (Alcoholic fatty liver disease), Fibrosis, Steatohepatitis, Risk factors.

INTRODUCTION

Alcoholic Fatty Liver Disease (AFLD) is a consequence of excessive alcohol consumption.[1] Alcoholic fatty liver is a reversible consequence. Liver serves as primary organ for metabolism. Excess alcohol consumption leads to the build-up of fat inside the liver cells (steatosis) which leads to increase the size of liver in which a condition called hepatitis. Alcohol effects hepatic metabolism by accumulation of fatty acids and triglycerides. Hepatic fat accumulation occurs primarily around the central vein, it extends to center of hepatic lobe and at last at the portal area.

Alcoholic liver disease is due to the ethanol hepatotoxicity linked to its metabolism by means of the alcohol dehydrogenase and CYP450 2E1 pathways.[2]

Alcohol is a hepatotoxin that is commonly consumed worldwide and is associated with a spectrum of liver injury including simple steatosis or fatty liver.[3]

Alcohol effects the liver through its direct toxicity because of its predominant metabolism in the liver which is associated with Oxidation-Reduction changes which is mediated by the alcohol dehydrogenase (ADH) and Oxidative stress which is generated mainly due to the activity of microsomal ethanol oxidizing enzymes (MEOS).[2-3]

The oxidative stress cause by CYP2E1 induction and mitochondrial injury results in peroxidation and membrane damage'.

In AFLD due to fat disposition evolution of simple steatosis occurs.

Alcohol consumption is global healthcare problem. Chronic consumption produces hepatic lesions which lead to steatosis, hepatitis, cirrhosis.[4]

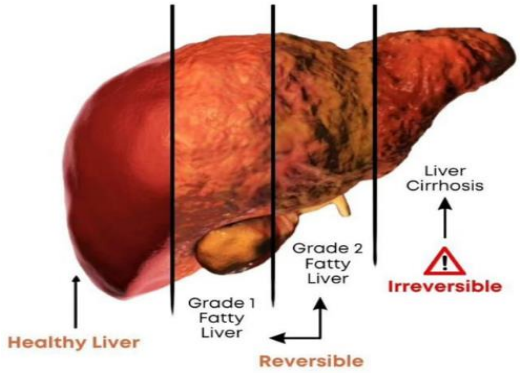

Figure 1: Grades of Fatty liver.

There is a need for more effective treatment of alcoholic fatty liver disease as the severe form of the disease is life-threatening.

If the consumption of alcohol is continued, the alcoholic liver disease progresses to severe damage to liver cells known as "alcoholic cirrhosis".

STATISTICS OF ALCOHOLIC FATTY LIVER

Here are some key statistics related to alcoholic fatty liver

1. **Prevalence**: Alcoholic fatty liver is prevalent in individuals who consume excessive amounts of alcohol. The risk increases with the quantity and duration of alcohol consumption. It has been estimated that by 2030, the prevalence of end-stage liver disease will increase by 2 to 3 times in Western countries and several Asian countries. The share of the consequences of alcohol consumption as a cause of death is about 4.0% for women and about 7.6% for men worldwide.[5]

2. Onset: It can develop after as little as a few days or as long as several years of heavy alcohol use.

3. Symptoms: Many people with alcoholic fatty liver may not show any noticeable symptoms.

When symptoms do occur, they can include fatigue, abdominal discomfort, and mild jaundice.

4. Diagnosis: A definitive diagnosis is made through liver biopsy, but non-invasive tests like liver function tests and imaging techniques (e.g., ultrasound) are often used for initial assessment.[6]

5. Reversible: In the early stages, alcoholic fatty liver is usually reversible with abstinence from alcohol. If alcohol consumption continues, it can progress to more severe liver conditions, such as alcoholic hepatitis or cirrhosis.

6. Risk factors: The risk of developing alcoholic fatty liver is influenced by factors like the quantity and duration of alcohol consumption, genetics, and individual susceptibility.[7]

7. Complications: If left untreated, alcoholic fatty liver can progress to more severe liver diseases, including alcoholic hepatitis and cirrhosis, which can be life-threatening.

8. Prevention: The best way to prevent alcoholic fatty liver is to limit alcohol consumption or abstain from alcohol altogether.

MODIFIERS OF ALCOHOLIC FATTY LIVER DISEASE

Alcoholic fatty liver disease (AFLD) is influenced by various modifiers and risk factors that can affect its development and progression. Here are some key modifiers of AFLD.

1. Alcohol Consumption: The most significant modifier is the amount and duration of alcohol consumption. The risk of AFLD increases with higher alcohol intake.

2. Genetics: Genetic factors can play a role in an individual's susceptibility to AFLD. Some people may have genetic variations that make them more vulnerable to liver damage from alcohol.[8]

3. Gender: Men are generally more susceptible to AFLD than women. This may be due to differences in how alcohol is metabolized and processed by the liver.

4. Obesity: Obesity is a significant modifier of AFLD. People who are overweight or obese are at a higher risk of developing AFLD, especially when alcohol consumption is involved.[9]

5. Nutrition: Poor dietary habits, such as a high-fat diet or deficiencies in essential nutrients, can exacerbate the development of AFLD.

6. Metabolic Factors: Conditions like insulin resistance, metabolic syndrome, and diabetes can increase the risk of AFLD.

7. Age: The risk of AFLD can increase with age, as the liver's ability to metabolize alcohol may decrease over time.[10]

8. Duration of Alcohol Abuse: The longer a person abuses alcohol, the greater the risk of developing more severe forms of liver disease, such as alcoholic hepatitis and cirrhosis.

9. Liver Health: Individuals with pre-existing liver conditions or liver diseases are more vulnerable to AFLD and its complications.[11]

10. Medications: Some medications, when taken in combination with alcohol, can increase the risk of liver damage.

11. Lifestyle Factors: Smoking and other lifestyle choices can also influence the risk and progression of AFLD.

PROGRESSION OF ALCOHOLIC FATTY LIVER

AFLD can progress through various stages depending on extent of liver damage and inflammation.

Alcoholic steatosis (fatty liver)

- It is the earliest stage of AFLD
- Characterized by the accumulation of fat (triglycerides) within the liver cells.[12]
- It is often reversible if alcohol consumption is reduced.

Alcohol contributes to fatty liver in multitude ways.
Fatty liver exists in two stages.

- Grade 1 fatty liver.
- Grade 2 fatty liver.

Alcoholic hepatitis

- This is an intermediate stage, and it represents inflammation of the liver.
- Inflammation can range from mild to severe.
- It can be life threatening, especially in severe cases.[13]

Alcoholic Cirrhosis

- Cirrhosis is the advanced scarring of the liver tissue.
- Develops after years of chronic alcohol abuse and liver damage.
- This condition is irreversible damage to the liver leading to loss of liver function.

Hepatocellular Carcinoma

- In some cases, AFLD can progress to liver cancer, particularly in individuals with cirrhosis.[14]

PATHOGENESIS

The pathogenesis of alcoholic fatty liver involves a series of processes -

1. Ethanol metabolism: Alcohol metabolism ensues mainly by two enzymes - Alcohol dehydrogenase (ADH is a hepatocyte cytosolic enzyme) and Aldehyde dehydrogenase, where alcohol dehydrogenase converts alcohol into aldehyde and aldehyde dehydrogenase converts acetaldehyde into acetate/acetic acid which is less harmful and can be used for energy or stored as fat.[15]

2. Toxicity effects: In which both alcohol and aldehyde have toxic effects on liver cells and damage the liver cells.

It also promotes the production of reactive oxygen species (ROS) leading to oxidative stress.

3. Impaired fatty acid metabolism: Due to the increased alcohol metabolism, production of NADH is increased thereby reducing NAD, which in turn leads to the formation of glycerol phosphate.

Glycerol phosphate associates with the fatty acids which is formed due to the hepatic alcohol metabolism and converts into triglycerides which are going to accumulate within the liver.

When lipid oxidation stops fat accumulates in the liver cells or hepatocytes.

Besides the fatty acid synthesis and oxidation, ethanol also alters lipid metabolism in hepatocytes and VLDL secretion from the liver.[16]

All these alterations contribute to alcoholic fatty liver.

4. Inflammation: The accumulation of fats in liver cells triggers an inflammatory response. Immune cells are recruited, and pro-inflammatory cytokines are released, contributing to liver damage.

5. Lipid peroxidation: ROS can damage cellular membranes and lipids through a process called lipid peroxidation. This leads to the release of toxic byproducts and further leads to cell injury.

6. Fibrosis and scarring: Over time ongoing inflammation and oxidative stress can lead to the deposition of collagen resulting in the liver fibrosis.

The fibrosis can progress to cirrhosis if alcohol consumption endures.

HISTOPATHOLOGICAL FINDINGS

The histopathology of Alcoholic Fatty Liver Disease (AFLD) involves changes in liver tissues due to undue alcohol consumption.

There are some vital histopathological findings associated with AFLD.

1. Micro vesicular Steatosis: AFLD is characterized by the accumulation of fat within hepatocytes. In the early stages, this often appears as micro vesicular steatosis, where small lipid droplets accumulate in liver cells.[17]

2. Macro vesicular Steatosis: As AFLD progresses, micro vesicular steatosis can progress to macro vesicular steatosis, where larger fat droplets displace the liver cell's nucleus to the periphery of the cell.[18]

3. Mallory-Denk Bodies: These are abnormal protein aggregates seen in hepatocytes and are often a sign of liver cell damage and inflammation. They are a characteristic histological feature of alcoholic hepatitis.[19]

4. Inflammatory Infiltration: AFLD is associated with varying degrees of inflammation in the liver tissue, including the infiltration of immune cells like neutrophils, which contribute to liver injury**.**

5. Balloon Cells: In severe cases, hepatocytes can undergo ballooning degeneration, leading to enlarged, rounded cells with clear cytoplasm.

6. Fibrosis: Fibrosis, the formation of scar tissue, can occur as a response to ongoing liver injury. It is an important feature, especially in advanced stages of AFLD.

7. Bridging Fibrosis: In more advanced stages, fibrous bands can extend and connect between portal areas and central veins, a condition known as bridging fibrosis.

8. Cirrhosis: The end stage of AFLD may involve the development of cirrhosis, characterized by extensive fibrosis, regenerating nodules, and loss of normal liver architecture.

Effects of Ethanol on AMPK

AMPK signalling pathway plays an important role in ameliorating lipid metabolism disorders. Upregulation of AMK can alleviate fatty liver.[20] Alcohol inhibits AMP-activated protein kinase. AMP-activated protein kinase (AMPK) is a multisubunit protein kinase, which is known to act as a key metabolic “master switch” by phosphorylating target enzymes involved in lipid metabolism such as acetyl-CoA carboxylase (ACC). ACC is generally regarded as the rate-limiting enzyme in fatty acid biosynthesis in liver and other tissues. The product of ACC, malonyl-CoA, is both a precursor for the biosynthesis of fatty acids and a potent inhibitor of

mitochondrial fatty acid oxidation at the carnitine palmitoyltransferase I (CPT I) step.[21] Further mechanistic studies led to the discovery that, in both rat hepatocytes and rat liver, metformin or AICAR-induced activation of AMPK leads to decreased messenger RNA (mRNA) and protein expression of SREBP-1c and its lipogenic target genes.[22]

SIGNS AND SYMPTOMS OF AFLD

1. Fatigue: This is a common early symptom of AFLD and can result from liver inflammation and dysfunction.
2. Abdominal Discomfort: Individuals with AFLD may experience a dull, aching pain or discomfort in the upper right side of the abdomen, where the liver is located.
3. Enlarged Liver: In some cases, a healthcare provider may be able to feel an enlarged liver during a physical examination.
4. Jaundice: Yellowing of the skin and the whites of the eyes (jaundice) can occur when AFLD progresses to a more severe stage. This is due to the impaired ability of the liver to process bilirubin, a waste product that is normally excreted.
5. Loss of Appetite: Many people with AFLD may experience a reduced appetite, which can lead to unintended weight loss.
6. Nausea and Vomiting: These symptoms can occur, particularly if AFLD advances to alcoholic hepatitis, which is a more severe form of liver inflammation.
7. Weakness: General weakness and feeling unwell are common, especially as AFLD progresses.
8. Dark Urine: Urine may appear darker than usual due to the presence of bilirubin.
9. Pale Stools: Stools may become pale or clay-colored, another sign of impaired bilirubin processing.
10. Ascites: In advanced cases of AFLD, a buildup of fluid in the abdominal cavity (ascites) may occur, leading to abdominal swelling and discomfort.
11. Mental Changes: Severe cases of alcoholic liver disease can result in mental changes, confusion, and in some cases, hepatic encephalopathy, a brain disorder caused by liver dysfunction.

METABOLISM OF ALCOHOLIC FATTY LIVER

The metabolism of alcohol and its impact on the liver are central to understanding AFLD. Here's a simplified overview of the metabolic processes involved in AFLD.

- **Alcohol Metabolism**: When you consume alcohol, the liver is primarily responsible for its metabolism. The enzyme alcohol dehydrogenase converts alcohol (ethanol) into acetaldehyde, which is further metabolized into acetate by the enzyme aldehyde dehydrogenase. These metabolic reactions generate energy for the body.[23]
- **Acetate Utilization**: Acetate is a primary end-product of alcohol metabolism. In moderate alcohol consumption, acetate is efficiently used for energy production, and there's minimal impact on the liver.
- **Excess Alcohol and Fatty Acid Synthesis**: In cases of chronic and excessive alcohol consumption, the liver can be overwhelmed with acetaldehyde and acetate. The excess acetate can lead to increased fatty acid synthesis within liver cells. These fatty acids can then accumulate as triglycerides, leading to hepatic steatosis (fatty liver).
- **Oxidative Stress**: The metabolism of alcohol generates reactive oxygen species (ROS) and oxidative stress. These free radicals can cause damage to liver cells, leading to inflammation and further exacerbating liver injury.[24]
- ROS also play significant roles in various cell signaling pathways, such as NFκB, MAPK, ion channeling, and the ubiquitin proteasome response.
- **Lipid Export Impairment**: Chronic alcohol use can impair the liver's ability to export excess lipids, further contributing to fat accumulation in liver cells.
- **Inflammation**: The presence of fat in liver cells can trigger inflammation, and immune cells may infiltrate the liver in response. This inflammatory response can lead to alcoholic hepatitis, a more severe form of AFLD.
- **Fibrosis and Cirrhosis**: Prolonged alcohol-induced inflammation can result in the deposition of scar tissue (fibrosis) in the liver. Over time, this can progress to cirrhosis, where the liver architecture is severely disrupted, and liver function is compromised.

SPECTRUM OF AFLD

AFLD comprises a spectrum of histological abnormalities, ranging from bland steatosis to steatohepatitis, hepatofibrosis and cirrhosis. It is the most common liver disease worldwide.[25]
Heavy alcohol consumption produces a wide spectrum of hepatic lesions.[26]

The spectrum of AFLD can be categorized into different stages, which may progress if alcohol consumption continues.
1. Simple Steatosis: This is the earliest stage of AFLD, characterized by the accumulation of fat (steatosis) in liver cells. It is often reversible if alcohol intake is reduced or eliminated.
2. Alcoholic Steatohepatitis (ASH): In this stage, inflammation and liver cell damage occur in addition to fat accumulation. Symptoms may include jaundice, abdominal pain, and elevated liver enzymes. ASH can be severe and progress to more advanced liver disease.[27]
3. Fibrosis: With ongoing inflammation and liver damage, fibrosis (scar tissue) may develop. The extent of fibrosis can range from mild to severe.
4. Cirrhosis: If AFLD progresses, it can lead to cirrhosis, which is extensive scarring of the liver. Cirrhosis can cause liver dysfunction and various complications, including portal hypertension, liver failure, and an increased risk of liver cancer.[28]

Deposition of fat is due to.
Lipid droplets surrounds the liver central vein (Perivenular hepatocytes) then surrounds mid lobular

hepatocytes. These surrounds the hepatic portal vein (periportal hepatocytes).

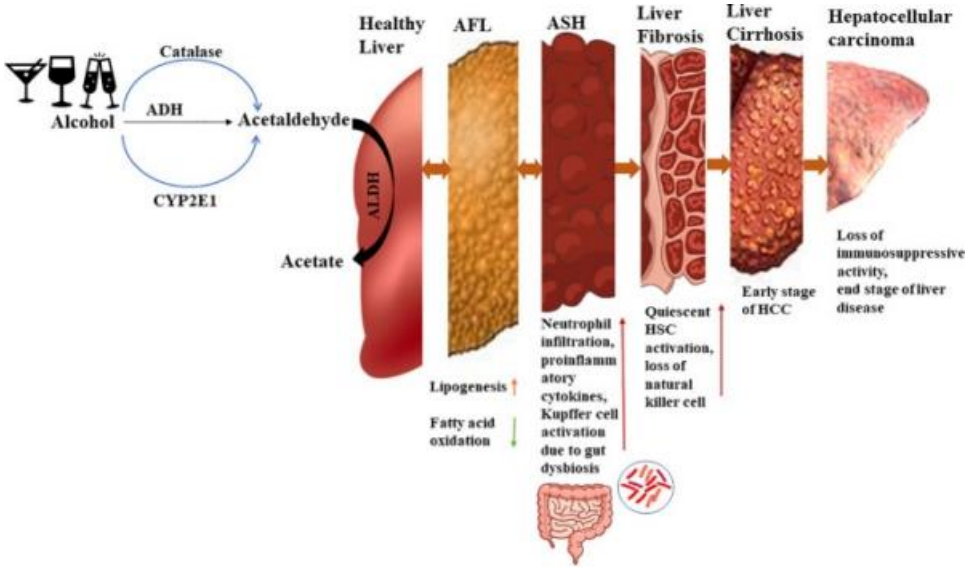

Figure 2: Deposition of fat in different stages.

Alcohol-associated liver disease

Globally 43% of the population currently drinks alcohol. Heavy alcohol drinking is an important risk factor for illness, disability, and mortality worldwide. [https://doi.org/10.1016/j.jhep.2023.03.017]

Liver disease accounts for two million deaths annually and it is responsible for 4% of all deaths (1 out of every 25 deaths worldwide). [https://doi.org/10.1016/j.jhep.2023.03.017]

PROGNOSIS OF AFLD

The prognosis of Alcoholic Fatty Liver Disease (AFLD) can vary depending on several factors, including the severity of the disease, the individual's response to treatment, and lifestyle changes. Here's an overview of the potential prognoses associated with AFLD.

1. Reversible in Early Stages: In the early stages of AFLD, if an individual stops drinking alcohol, the condition is often reversible. The liver can heal and return to normal function. Abstinence from alcohol is the most critical factor in improving the prognosis.

2. Progression to Alcoholic Hepatitis: If AFLD continues without abstinence from alcohol, it can progress to a more severe condition known as alcoholic hepatitis. The prognosis for alcoholic hepatitis can be serious, and it may require hospitalization and medical intervention.[29]

3. Risk of Cirrhosis: For some individuals, long-term and heavy alcohol consumption can lead to the development of cirrhosis. Cirrhosis is a late and irreversible stage of liver damage. The prognosis for cirrhosis varies, but it can be life-threatening, and liver transplantation may be necessary in severe cases.[30]

4. Complications: AFLD can also lead to various complications, including liver failure, portal hypertension, and an increased risk of liver cancer (hepatocellular carcinoma). The prognosis becomes progressively worse with the development of these complications.

5. Coexisting Health Conditions: The presence of other health conditions, such as obesity, diabetes, or viral hepatitis, can worsen the prognosis and increase the risk of complications.

6. Response to Treatment: The prognosis may be influenced by an individual's response to medical treatment and interventions, including lifestyle changes, dietary modifications, and medications that may be prescribed to manage specific aspects of the disease.

7. Regular Monitoring: Regular medical monitoring and adherence to a healthcare provider's recommendations can improve the prognosis by detecting and addressing potential complications early. Alcoholic Fatty Liver Disease (AFLD) can range from being asymptomatic (showing no noticeable symptoms) to presenting with various signs and symptoms, especially as the condition progresses.

LIVER FUNCTION TESTS IN AFLD

In alcoholic fatty liver disease (AFLD), several liver function tests may be performed to assess the condition and its impact on the liver. These tests include.

1. Liver Enzyme Levels

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels: Elevated levels of these enzymes may indicate liver inflammation or damage. [: 10.3748/wjg.v20.i33.11684]

2. Gamma-Glutamyl Transferase (GGT)

GGT levels can be elevated in AFLD and may indicate alcohol-related liver problems.[31]

3. Alkaline Phosphatase (ALP)

Elevated ALP levels can be a sign of liver or bone issues and may be used to assess liver health in AFLD.

4. Bilirubin
High bilirubin levels can suggest liver dysfunction or obstruction of bile flow.[32]

5. Albumin and Total Protein
Reduced levels of albumin and total protein may indicate decreased liver function.

6. Prothrombin Time (PT) or International Normalized Ratio (INR)
Prolonged PT or elevated INR values can suggest impaired blood clotting, which may be associated with liver disease.

7. Complete Blood Count (CBC)
This may reveal changes in white blood cell and platelet counts, which can be related to liver inflammation**.**

8. Imaging Studies
Ultrasound, CT scans, or MRI may be used to visualize the liver and assess the extent of liver damage or fat accumulation.

9. Liver Biopsy
In some cases, a liver biopsy may be performed to provide a more detailed evaluation of liver tissue.[33]

TREATMENT FOR AFLD
The treatment for Alcoholic Fatty Liver Disease (AFLD) primarily focuses on stopping alcohol consumption and making lifestyle changes to promote liver health. Here are some key components of AFLD treatment.

- **Alcohol Cessation or Abstinence**: The most critical step in managing AFLD is to completely stop alcohol consumption. Abstaining from alcohol is essential to prevent further liver damage and allow the liver to heal.
- **Weight Management**: If the patient is overweight or obese, losing excess weight is often recommended. A healthy diet and regular exercise can help with weight management.
- **Nutrition**: A balanced and healthy diet is crucial. Reducing intake of saturated fats, refined sugars, and processed foods is important. Instead, focus on a diet rich in fruits, vegetables, whole grains, and lean proteins.
- **Medications**: In some cases, healthcare providers may prescribe medications to manage symptoms or complications of AFLD. These may include medications to lower cholesterol, manage diabetes, or address specific symptoms.
- **Vitamin and Mineral Supplements**: Patients with AFLD may be deficient in certain vitamins and minerals, such as vitamin D, vitamin E, and zinc. Supplements may be recommended to address these deficiencies.
- **Regular Exercise**: Engaging in regular physical activity can help improve insulin sensitivity and promote overall health. It's important to consult with a healthcare provider before starting any exercise program.
- **Close Medical Monitoring**: Regular medical check-ups and monitoring of liver function tests are essential to track progress and make necessary adjustments to the treatment plan.
- **Avoidance of Toxins**: In addition to alcohol, avoiding exposure to other liver toxins, such as certain medications or chemicals, is important.
- **Treatment of Coexisting Conditions**: If the patient has coexisting medical conditions like diabetes, high blood pressure, or high cholesterol, these conditions should be managed appropriately.
- **Support and Counseling**: Support groups or counseling may be beneficial for individuals trying to quit alcohol and maintain a healthy lifestyle.
- **Liver transplantation**: A surgical procedure to confiscate a diseased liver from a person and replace it with a portion of healthy liver.
- **Orthotopic liver transplantation**: Native liver was removed, and a graft was put in its place.

LIVER TRANSPLANTATION IN AFLD: Liver transplantation represents the ultimate therapy for patients with alcoholic cirrhosis.[34]

Liver transplantation is considered as a treatment option for individuals with end-stage liver disease, including severe alcoholic liver disease (ALD) or alcoholic cirrhosis, when other treatments have failed, and the liver damage is irreversible. However, liver transplantation for alcoholic liver disease, including alcoholic fatty liver disease (AFLD), has some specific considerations and criteria.

- **Abstinence Requirement:** Most transplant centers require a period of abstinence from alcohol for a minimum of six months to one year before considering a patient with ALD for transplantation. This demonstrates acommitment to sobriety and helps ensure the best chances of a successful transplant.[35]
- **Psychosocial Evaluation:** Patients with a history of alcohol abuse are typically subject to a thorough psychosocial evaluation to assess their suitability for transplantation. This evaluation considers factors like social support, mental health, and the likelihood of maintaining abstinence post-transplant.
- **Medical Evaluation:** A thorough medical evaluation is conducted to determine if the patient is a suitable candidate for transplantation based on the severity of liver disease and overall health.
- **MELD Score:** The Model for End-Stage Liver Disease (MELD) score is used to prioritize patients for liver transplantation. It is based on lab values and assesses the severity of liver disease**.**
- **Transplant Center Policies:** Each transplant center may have specific policies and criteria for accepting patients with ALD. These criteria can vary.

PRE-TRANSPLANTATION

Pre transplantation achieves two main goals- It allows a window of opportunity for the liver to stabilize and also allows opportunity to examine the patient's commitment. The period of abstinence is important as it gives the time to access the patient support.

They also must be away from alcohol consumption for 6 months before the transplantation.

During pre-transplantation period they suffer from a wide range of comorbidities, including neurologic disorders, kidney dysfunction, cardiovascular diseases etc.

POST TRANSPLANTATION

The magnitude of post transplantation alcohol relapse is an issue of concern.

It can often be difficult to attain a healthy live.

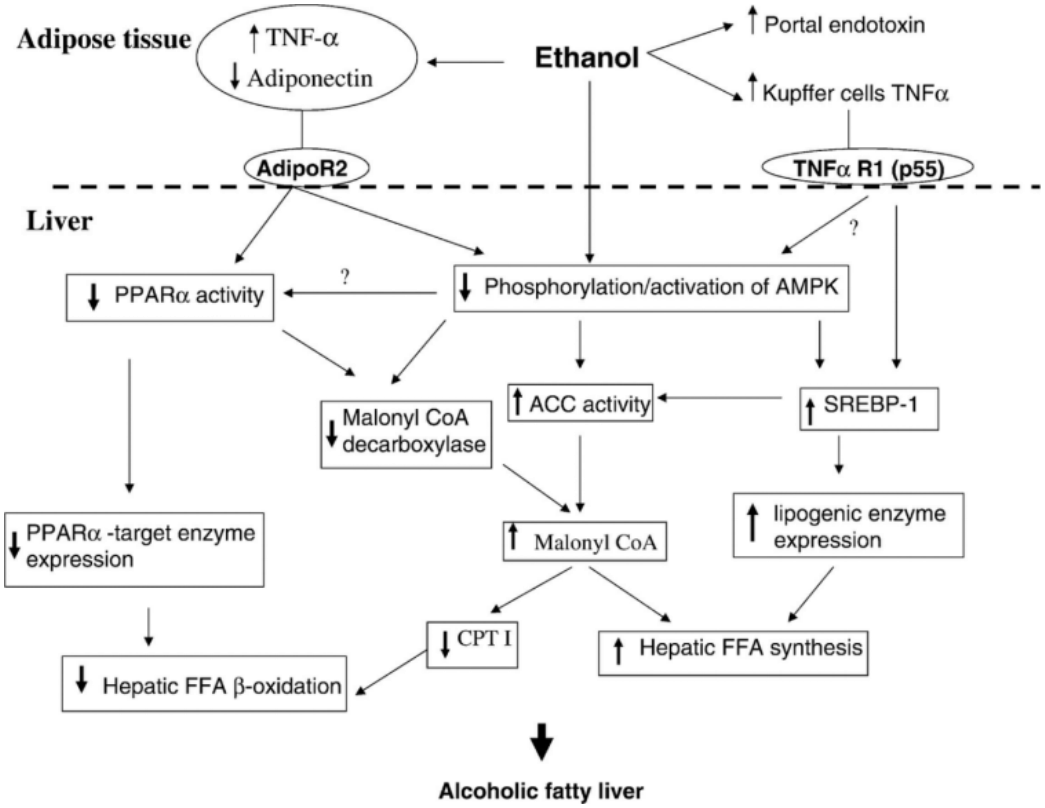

Figure 3: Mechanism of Fatty liver.

CONCLUSION

The reversible stage of alcoholic fatty liver disease suggests that with alcohol cessation and lifestyle changes, liver health can improve. However, if alcohol consumption continues, it may progress to more severe and irreversible liver conditions. Regular medical monitoring and adherence to a healthy lifestyle are crucial for managing and potentially reversing alcoholic fatty liver.

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