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ALCOHOL -ASSOCIATED LIVER DISEASE: ETHANOL METABOLISM, MOLECULAR MECHANISMS, CLINICAL MANIFESTATIONS AND THERAPEUTIC STRATEGIES

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ABSTRACT

Alcohol-associated liver disease (ALD) is a major global health concern encompassing hepatic steatosis, alcohol-associated hepatitis, fibrosis, cirrhosis and liver failure. Chronic alcohol consumption contributes to hepatic injury through complex biochemical, metabolic, inflammatory and oxidative mechanisms. Ethanol metabolism involves alcohol dehydrogenase, aldehyde dehydrogenase, cytochrome P450 2E1 and non-oxidative pathways. These processes generate acetaldehyde and promote oxidative stress, mitochondrial dysfunction, lipid accumulation and inflammatory responses, accelerating hepatocellular damage and disease progression. Clinical manifestations range from asymptomatic steatosis to jaundice, systemic inflammation and advanced hepatic dysfunction. Diagnosis integrates alcohol consumption history, clinical assessment, biochemical investigations, imaging and non-invasive fibrosis evaluation, while liver biopsy is reserved for selected cases requiring diagnostic clarification. Management emphasizes sustained alcohol abstinence, nutritional rehabilitation, adequate protein intake and appropriate treatment of complications, including infections and hepatic decompensation. Selected patients with severe alcohol-associated

hepatitis may require pharmacological treatment and multidisciplinary evaluation. Early detection, accurate risk stratification and individualized therapeutic interventions are essential to improving clinical outcomes.

KEYWORDS: Alcohol-associated liver disease(ALD); ethanol metabolism; Acetaldehyde; oxidative stress; Alcohol-associated hepatitis; hepatotoxicity; nutritional therapy.

AIM AND OBJECTIVES:

- To review the causes and risk factors associated with alcohol-associated liver disease.
- To describe the clinical manifestations and complications of alcohol-associated liver disease.
- To evaluate current diagnostic methods and therapeutic approaches for ALD.
- To discuss preventive strategies and emerging treatment options that may improve patient outcomes.

1. INTRODUCTION

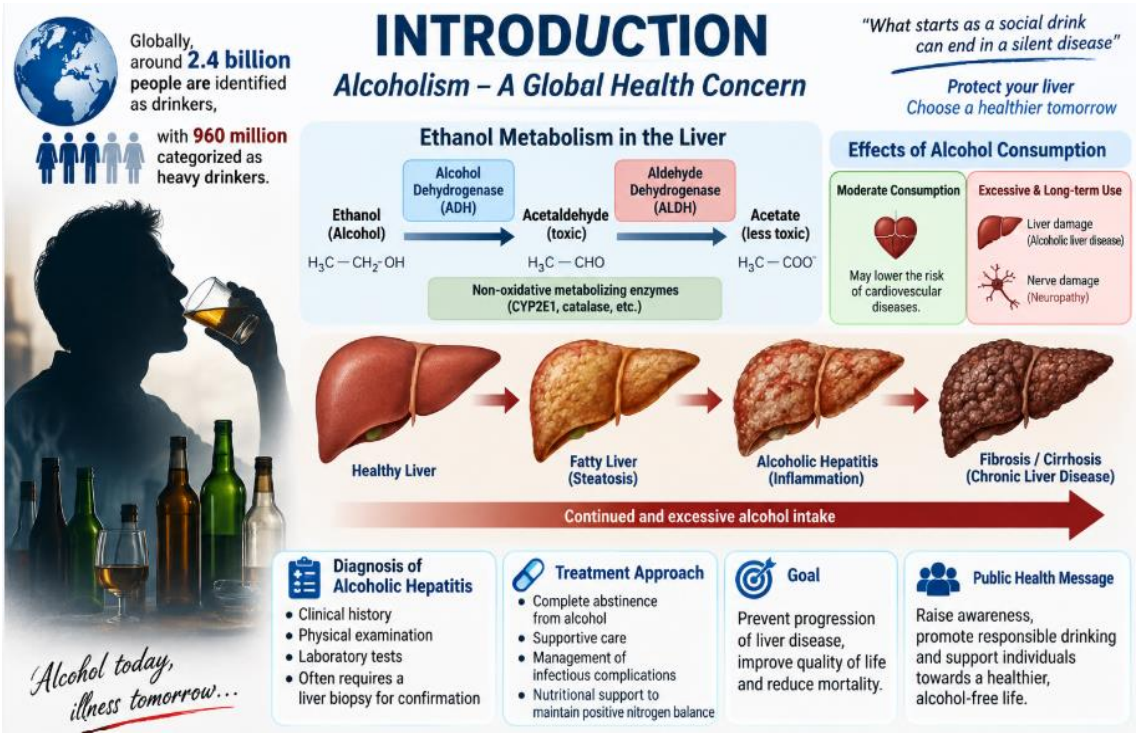


Figure:1 - Introduction: Alcoholism – A Global Health Concern.

According to the National Institute on Alcohol Abuse and Alcoholism, the amount of beverage containing approximately 14gm of pure ethanol is defined as a standard drink.

- A 12 -Ounce can of regular beer at 5 % alcohol by volume.

- A 5- Ounce glass of wine at 12% alcohol by volume.
- A 1.5- Ounce shot glass of distilled spirits at 40% alcohol by volume.

STANDARD DRINKS

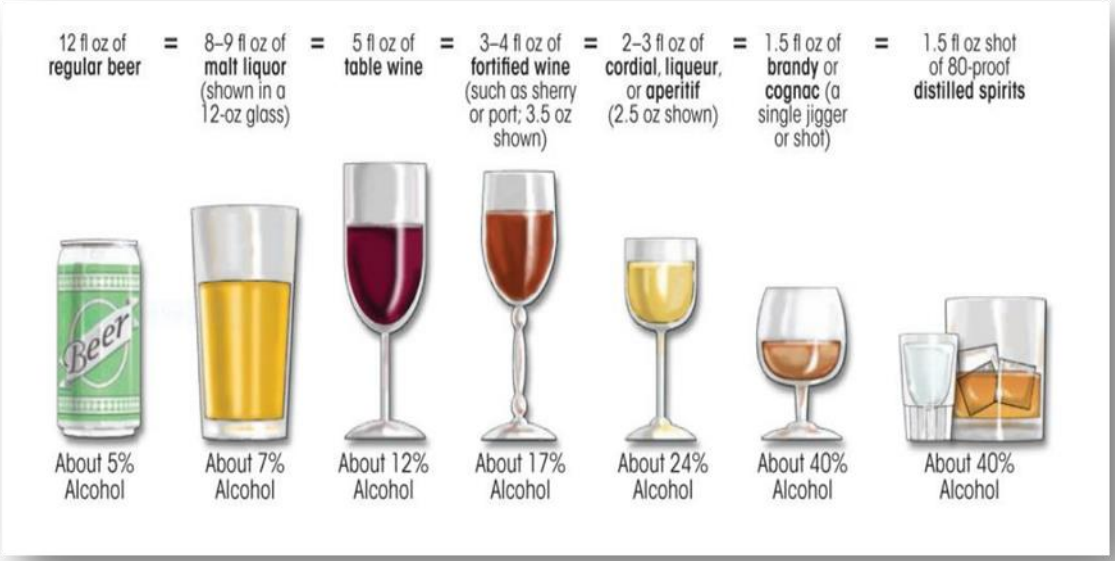


Figure:2- Standard Drink Equivalents and Alcohol Content of Different Beverages.

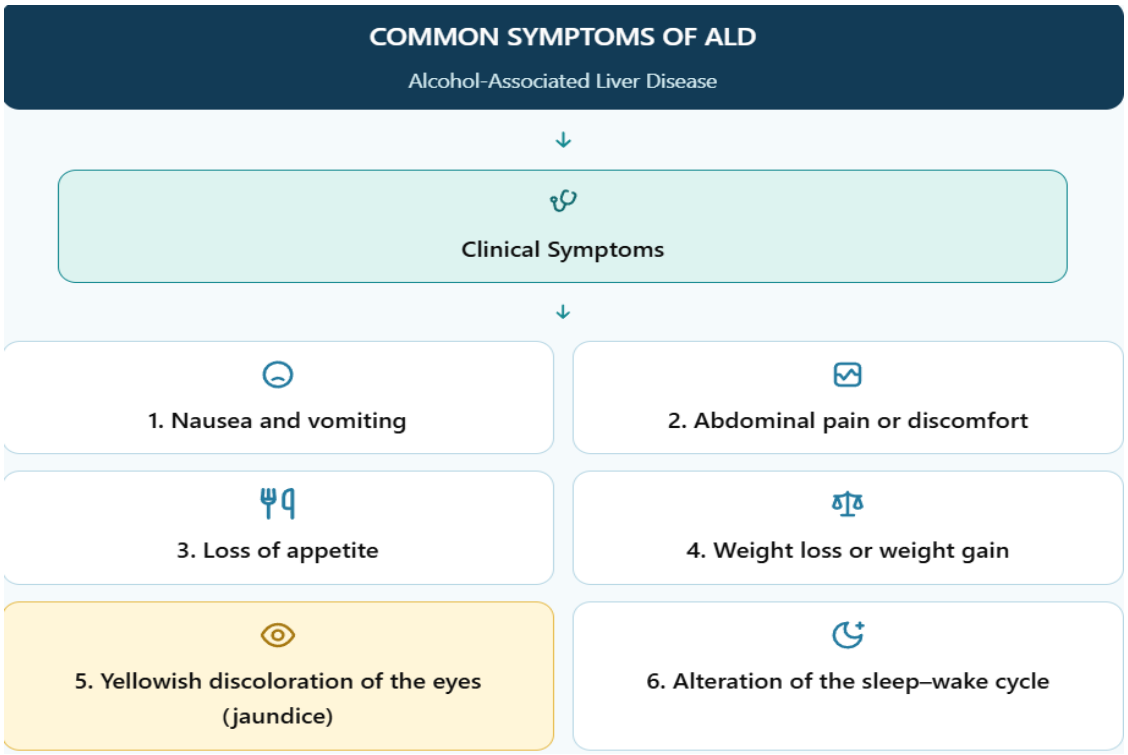
INTRODUCTION TO ALCOHOL-ASSOCIATED LIVER DISEASE

Alcohol-associated liver disease (ALD) poses a substantial global health burden, with rising mortality and pronounced sex-based disparities. Although men account for most alcohol use disorders, women exhibit greater hepatic vulnerability. Genetic variants, particularly PNPLA3, increase susceptibility to hepatic steatosis and disease progression. Additionally, Hispanic populations, especially Mexican Americans, experience disproportionate fatty liver disease burdens, influenced by genetic predisposition, metabolic comorbidities and healthcare inequalities.

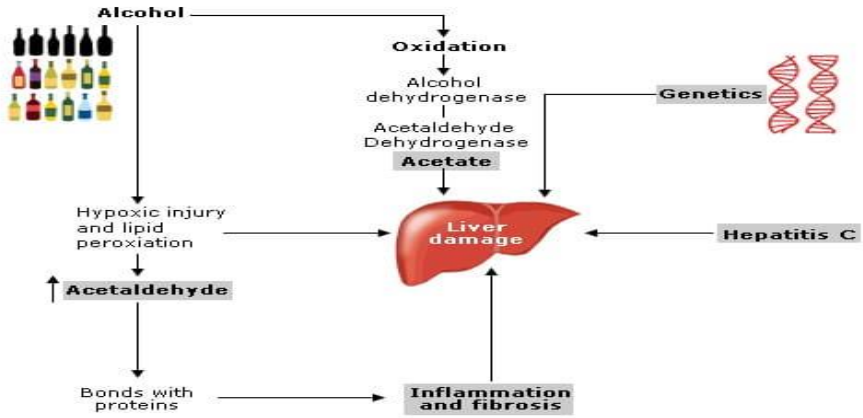
2. ETIOLOGY AND RISK FACTORS:

- ✓ **Alcohol Consumption** – Chronic and excessive alcohol intake.
- ✓ **Hepatotoxic Drugs** – Long-term use of medications that damage the liver.
- ✓ **Metabolic Disorders** – Obesity, diabetes mellitus and dyslipidaemia.

3. SYMPTOMS



4. PATHOPHYSIOLOGY OF ALCOHOL-ASSOCIATED LIVER DISEASE



Alcohol metabolism by the liver is primarily via two enzymes:

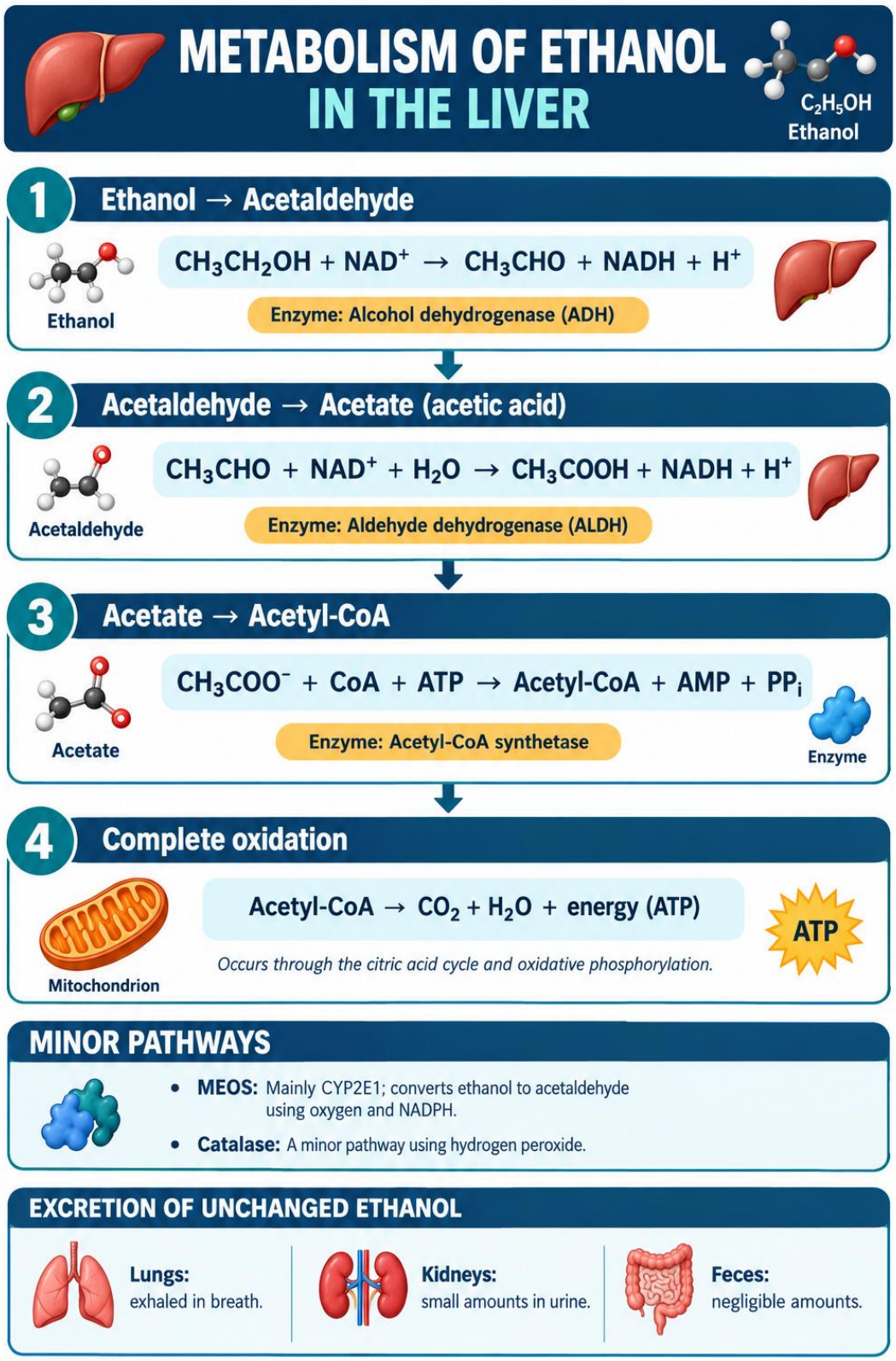
- **Alcohol dehydrogenase**
- **Aldehyde dehydrogenase**

KEY ENZYMATIC CONVERSIONS AND CONSEQUENCES

- Ethanol → Acetaldehyde (Alcohol dehydrogenase, ADH)
- Acetaldehyde → Acetate (Aldehyde dehydrogenase, ALDH)
- Increased NADH/NAD^+ ratio → Fat accumulation in the liver
- Inflammation and hepatocyte injury → Alcohol-associated hepatitis

➢ Persistent liver injury → Fibrosis and cirrhosis

5. ETHANOL METABOLISM PATHWAY



6. PHYSICAL EXAMINATION

ALCOHOLIC HEPATITIS

Alcohol-related inflammatory liver injury

↓

History of Heavy Alcohol Use

Often prolonged, heavy consumption; intake varies between patients

↓

Characteristic Clinical Presentation

Rapid onset of jaundice • Fever • Tender hepatomegaly

↓

Physical Examination

Jaundice • Enlarged liver • Possible splenomegaly • Spider angiomas • Possible ascites

↓

Clinical Evaluation

History, physical examination, liver function tests, blood counts and assessment of disease severity

↓

Assess for Complications

If new-onset ascites is present, perform diagnostic abdominal paracentesis to evaluate its cause and exclude infection.

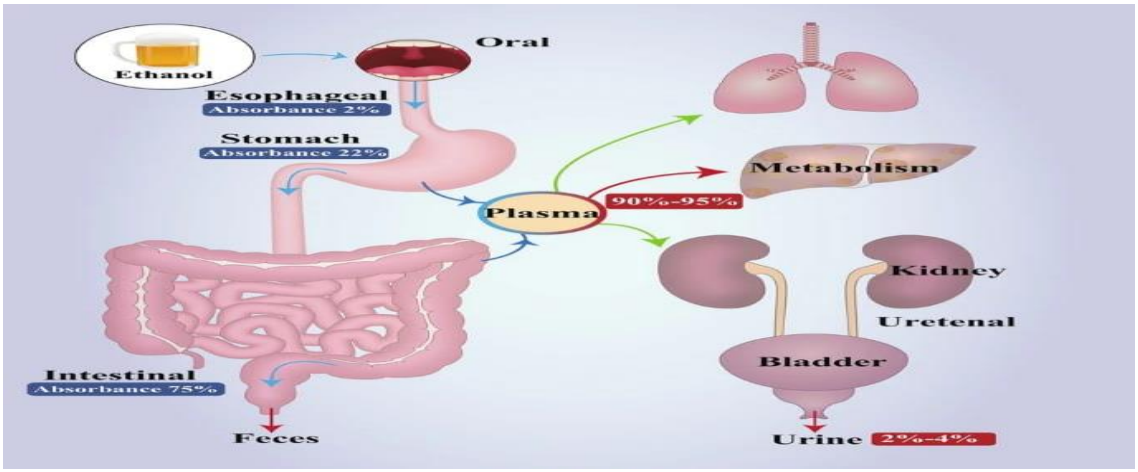


Figure:3- Absorption, Distribution, Metabolism and Excretion (ADME) of Ethanol.

7. DIAGNOSIS

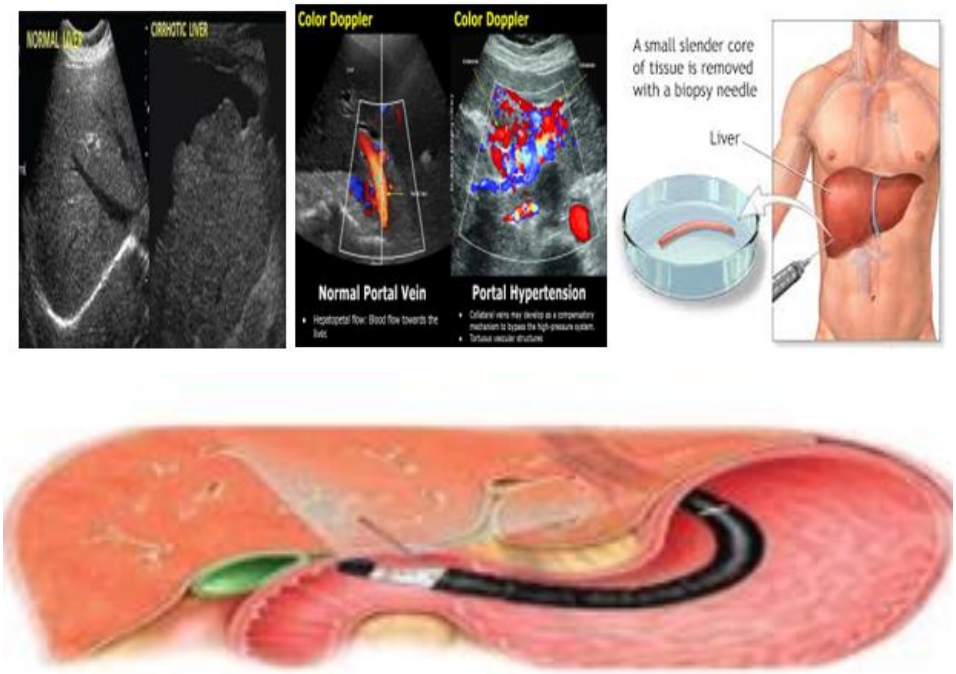
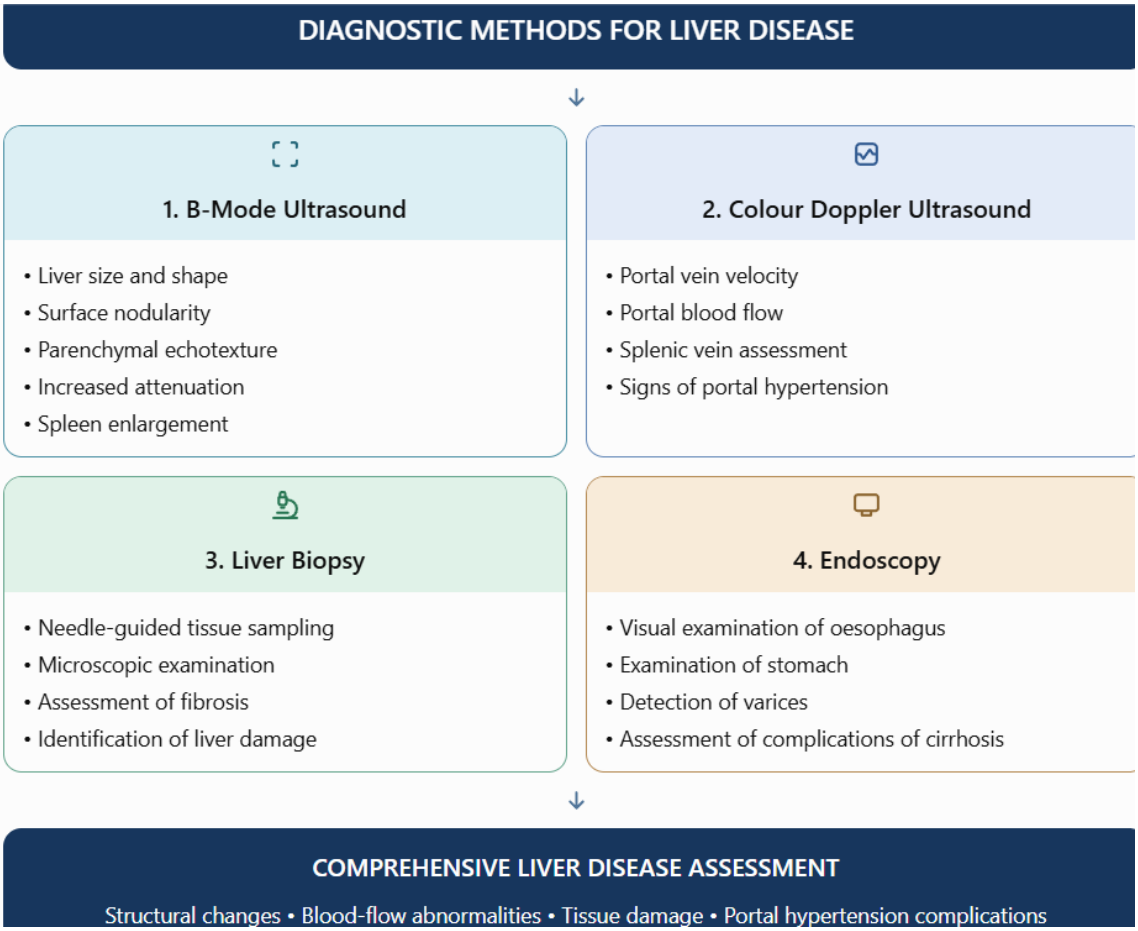


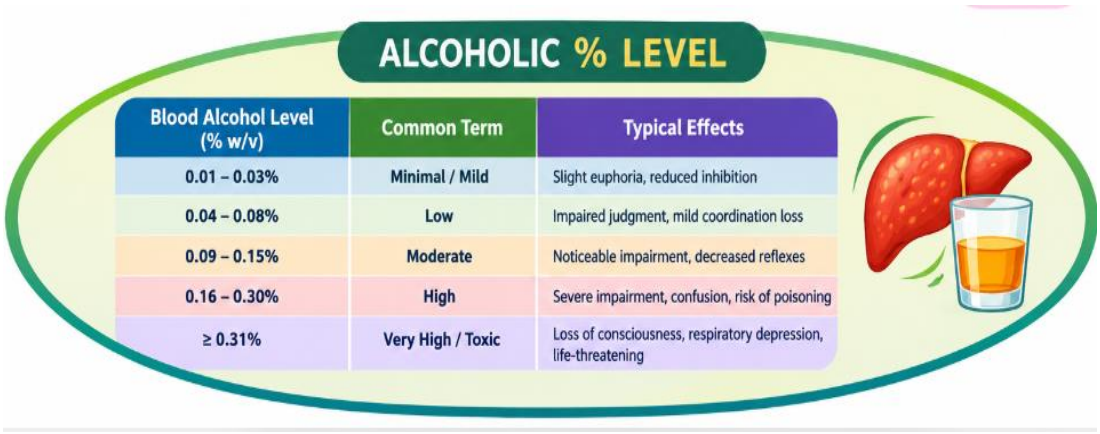
Figure 4- Various Approaches for Diagnostic Application of ALD.

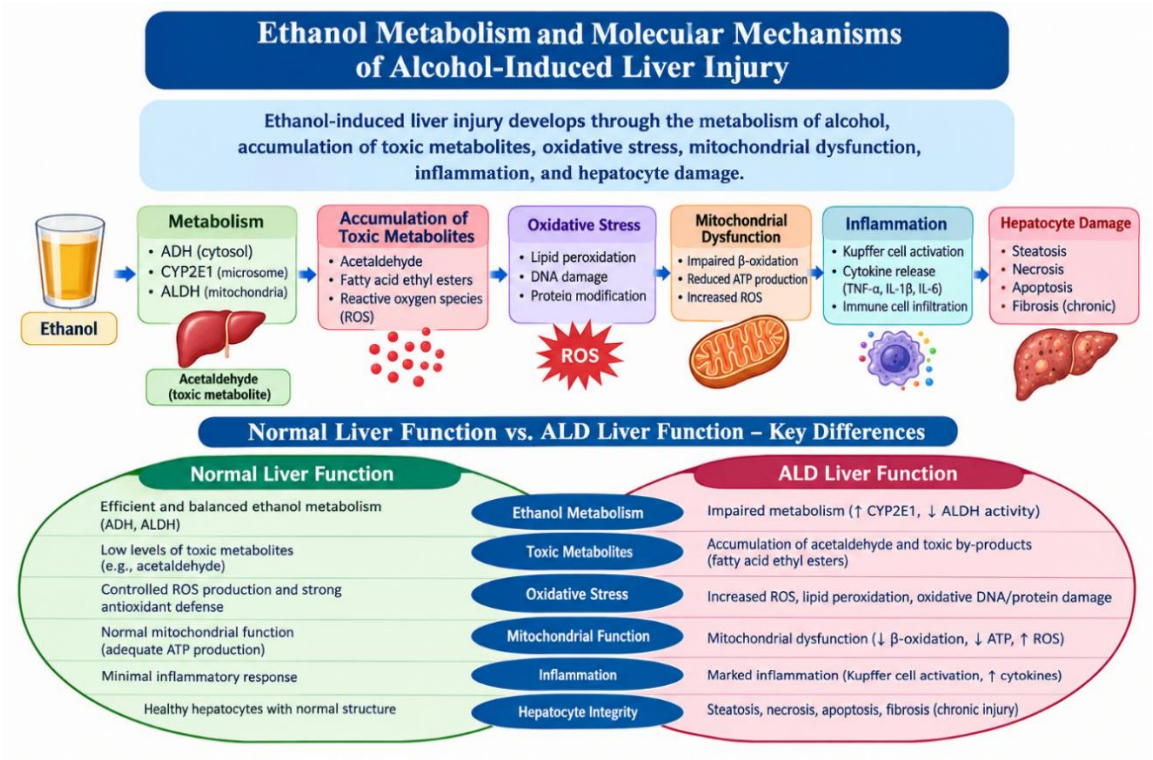
Modern Diagnostic Prediction For ALD

Diagnostic component	Key assessment	Key findings
Clinical history	Alcohol consumption pattern, duration, quantity, and associated symptoms	Chronic heavy alcohol use, fatigue, loss of appetite, nausea, jaundice, and abdominal swelling
Physical examination	General condition and signs of liver dysfunction	Hepatomegaly, jaundice, abdominal tenderness, ascites, and peripheral oedema
Laboratory tests	Liver function and evidence of liver injury	Elevated AST and ALT, often with an AST/ALT ratio greater than 1.5–2 in alcohol-associated hepatitis; increased bilirubin and GGT; reduced albumin and prolonged prothrombin time/INR in advanced disease
Imaging studies	Liver structure and complications	Ultrasound may reveal fatty liver, hepatomegaly, splenomegaly, or ascites; transient elastography assesses liver stiffness and fibrosis



8. Ethanol-induced liver injury develops through the metabolism of alcohol, accumulation of toxic metabolites, oxidative stress, mitochondrial dysfunction, inflammation, and hepatocyte damage.:





ETHANOL (CH_3CH_2OH)

Alcohol entering the liver

↓

Alcohol dehydrogenase (ADH)

$NAD^+ \rightarrow NADH + H^+$

ACETALDEHYDE (CH_3CHO)

Toxic and reactive metabolite

↓

Aldehyde dehydrogenase (ALDH)

$NAD^+ \rightarrow NADH + H^+$

ACETATE (CH_3COO^-)

Converted to acetyl-CoA in extrahepatic tissues and other metabolic pathways

↓

ACETYL-CoA

Energy production or lipid synthesis

9. MOLECULAR MECHANISMS AND THERAPEUTIC APPROACHES

Molecular target	Mechanism of injury	Drug action / therapeutic approach
ADH and ALDH pathways	Acetaldehyde formation and increased NADH/NAD^+ ratio	No established routine drug directly reverses all ethanol-metabolism effects; abstinence is the key intervention
CYP2E1 enzyme	Generates reactive oxygen species (ROS)	Abstinence reduces ethanol-driven CYP2E1 induction over time; antioxidant strategies remain limited in clinical evidence
Mitochondria	Oxidative stress and impaired energy metabolism	Supportive care and correction of nutritional deficiencies
Hepatic lipid metabolism	Increased triglyceride accumulation and fatty liver	Alcohol abstinence, nutritional management, and treatment of metabolic risk factors
Kupffer cells and cytokines	Inflammatory signalling and hepatocyte damage	Corticosteroids may benefit selected patients with severe alcohol-associated hepatitis after contraindications are assessed
Hepatic stellate cells	Collagen deposition and fibrosis	Sustained abstinence and management of liver disease complications; no, universally effective antifibrotic drug is established

10. MEDICINAL TREATMENT

- Corticosteroids (e.g., prednisolone): Reduce inflammation in selected patients with severe alcohol-associated hepatitis; they are not appropriate for every patient.
- Thiamine (vitamin B_1): Prevents or treats deficiency-related neurological complications in people with heavy alcohol use.
- Nutritional therapy: Corrects malnutrition and supports hepatic recovery.
- Naltrexone or acamprosate: May support alcohol-use-disorder treatment and reduce relapse risk in appropriate patients, with medication selection guided by liver and kidney status.
- Abstinence from alcohol: The most important intervention for preventing ongoing alcohol-induced liver injury.

11. MEDICINES USED IN THE MANAGEMENT OF ALCOHOL-ASSOCIATED LIVER DISEASE

DRUGS	INDICATION AND MECHANISM OF ACTION	PRECAUTION AND CONTRA INDICATION	COMMENTS

ALCOHOL ABSTINENCE

Acamprosate	**Reduces symptoms of alcohol withdrawal (e.g., anxiety, irritability, insomnia, cravings) Modulates the glutamatergic receptor system.**	**Contraindicated: Child–Pugh C cirrhosis , renal impairment (serum creatinine > 120 micromole / L) Caution : acute alcohol withdrawal , pregnancy**	**Not hepatically metabolised but requires dose adjustment in renal impairment.**
Naltrexone	Attenuates cravings and reduces the rewarding effects following alcohol consumption Reversible inhibition of opioid receptor	Contraindicated: opioid dependence , severe hepatic impairment , acute hepatitis Caution : renal impairment , liver enzymes > 3 times upper limit of normal	Risk of hepatotoxicity in hepatic and renal impairment Use non – opioid analgesics (paracetamol) if pain relief is required
Disulfiram	Irreversible inhibition of aldehyde dehydrogenase results in raised blood acetaldehyde concentration and unpleasant effects if alcohol is consumed	Contraindicated: ischaemic heart disease, severe myocardial disease , renal impairment , cirrhosis Caution: CVS, diabetes ,epilepsy, hypothyroidism	Adverse effects of a disulfiram – alcohol reaction can be severe, including respiratory depression, seizures, myocardial infraction. Numerous potential drug –drug interaction
NUTRITIONAL DEFICIENCY:			
Thiamine (B_1):	Chronic thiamine deficiency can lead to nutritional encephalopathy	--	Thiamine doses contained in over the counter oral supplements may be insufficient
Other B vitamins: Pyridoxine (B_6) , folic acid (B_9) , cyanocobalamin (B_{12})	Prevent complications of deficiency including cognitive dysfunction, anaemia Vitamin B deficiency is common in ALD	Caution: folic acid supplementation should be avoided in megaloblastic anaemia until B_{12} deficiency is corrected	Specific deficiency should be corrected , but evidence is lacking for long term use.
Vitamin D	Regulates absorption of essential minerals including calcium , magnesium and phosphate	Caution: severe renal impairment , hypercalcaemia	Evidence of vitamin D supplementation in chronic liver disease is inconclusive Supplement if deficient.

ALCOHOL WITHDRAWAL SYNDROME

Benzodiazepines: Diazepam , oxazepam	Modulate neuronal hyperexcitability by stimulating gamma – amino butyric acid (GABA) receptor	Caution: may precipitate hepatic encephalopathy in patients with cirrhosis or acute liver failure	Short acting benzodiazepines with uncomplicated hepatic metabolism (oxazepam) are preferred in people with cirrhosis and the elderly

ALCOHOL HEPATITIS:

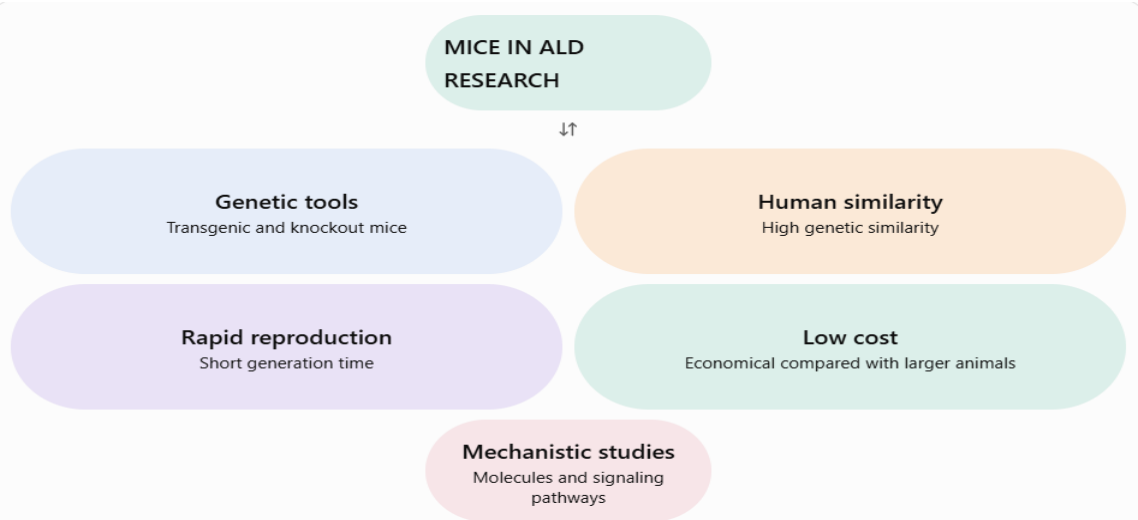
Corticosteroids: Prednisolone	Modulate inflammatory response	Contraindicated: untreated infection , GIT bleeding , pancreatitis Caution: diabetes, peptic ulcer disease.	Started in hospital with other supportive care . Short –term use only.

COMPLICATIONS OF ADVANCED LIVER DISEASE:

Non-selective beta blockers: Propranolol, carvedilol	Prevent bleeding from gastro-oesophageal varices	Caution: bradycardia(45-50beats/mins), severe hypotension, diabetes, asthma, severe hepatic impairment	Selective beta blockers(metoprolol, bisoprolol) are not effective Carvedilol is not PBS-listed for this indication
Antibiotic prophylaxis: Trimethoprim, sulfamethoxazole, quinolones	Prevent recurrence of spontaneous bacterial peritonitis Reduce pathogenic gut flora	Caution: renal impairment	Proton pump inhibitors can increase the risk of spontaneous bacterial peritonitis
Non-absorbable antibiotics : Rifaximin	Prevent recurrent hepatic encephalopathy Modify gut flora and reduce production of ammonia	Contraindicated: intestinal obstruction Caution: Child–Pugh C cirrhosis	Must be started by a gastroenterologist or hepatologist Use concomitantly with lactulose if tolerated
Diuretics: **Spironolactone, furosemide**	Treat fluid overload Promote excretion of sodium and water	Contraindicated: renal failure, severe sodium and fluid depletion Caution: renal impairment, electrolyte derangement	No significant pharmacokinetic changes in liver impairment, but patients may be at increased risk of harmful pharmacodynamic interaction Patients are usually on a salt-restricted diet

12. EXPERIMENTAL MODELS OF ALCOHOL-ASSOCIATED LIVER DISEASE

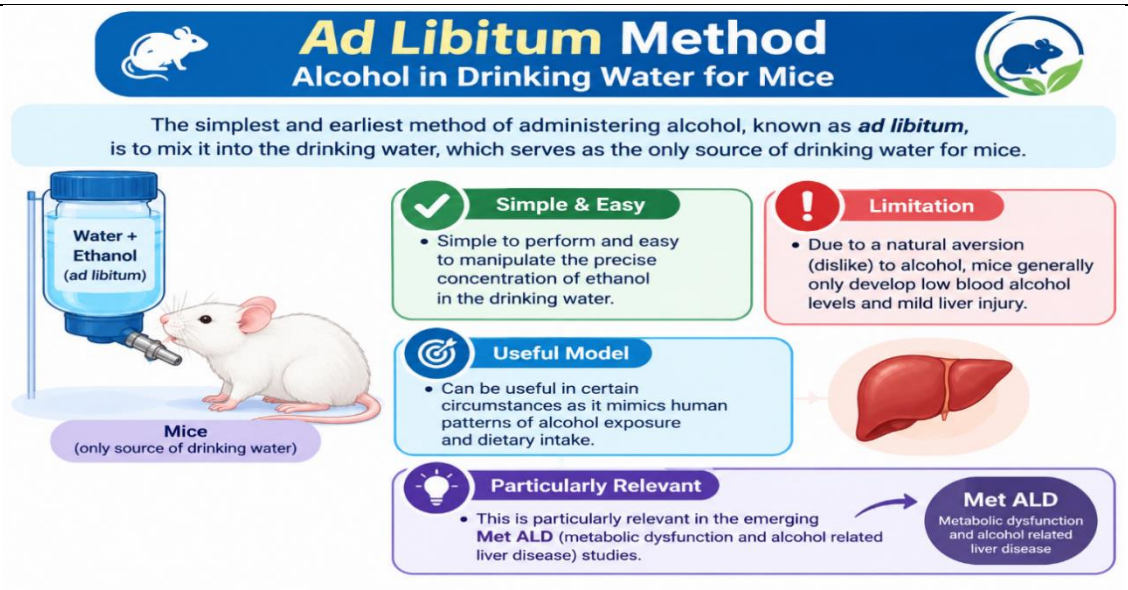
12.1 ALD Animal Models:

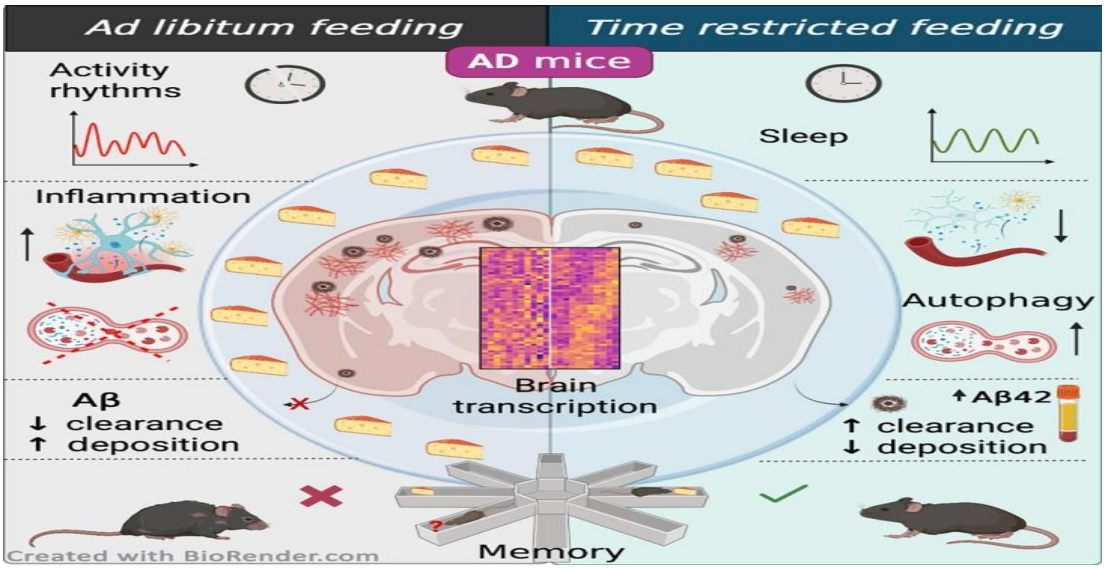


12.2 Animal Models of Alcohol-Associated Liver Disease (ALD)

S. No.	Factor / Animal Model	Description
1	Animal Strains	Select suitable mouse strains based on susceptibility to ethanol-induced liver injury.
2	Ethanol Dose	Optimize the amount of ethanol to induce liver damage.
3	Route of Administration	Use oral feeding, intragastric infusion, or oral gavage.
4	Duration of Exposure	Establish acute, chronic or chronic-plus-binge exposure protocols.
5	Ethanol Ad Libitum Feeding	Provide free access to ethanol-containing drinking water.
6	Tsukamoto–French Model	Administer ethanol through continuous intragastric infusion.
7	Acute Oral Gavage	Deliver a defined ethanol dose orally to study acute liver injury.
8	Lieber–DeCarli Diet Model	Provide ethanol in a nutritionally controlled liquid diet for chronic exposure.
9	Chronic-Binge Model	Combine chronic ethanol feeding with a single binge dose to induce liver injury over a relatively short period.

12.3 Ethanol AD Libitum Feeding:





12.4 INTRA GASTRIC INFUSION (Tsukamoto – French Model):

- **Higher Liver injury:** Intragastric ethanol feeding produces high blood alcohol levels (100–500 mg/dL in rats), hepatic steatosis, focal necrosis and severe liver damage.
- **Development of fibrosis:** Combining a high-fat diet with progressively increased ethanol intake can induce liver fibrosis in rats within 30 days.
- **Inflammatory mechanisms:** Mouse models revealed that Kupffer cell NADPH oxidase contributes to TNF-α production and liver inflammation.

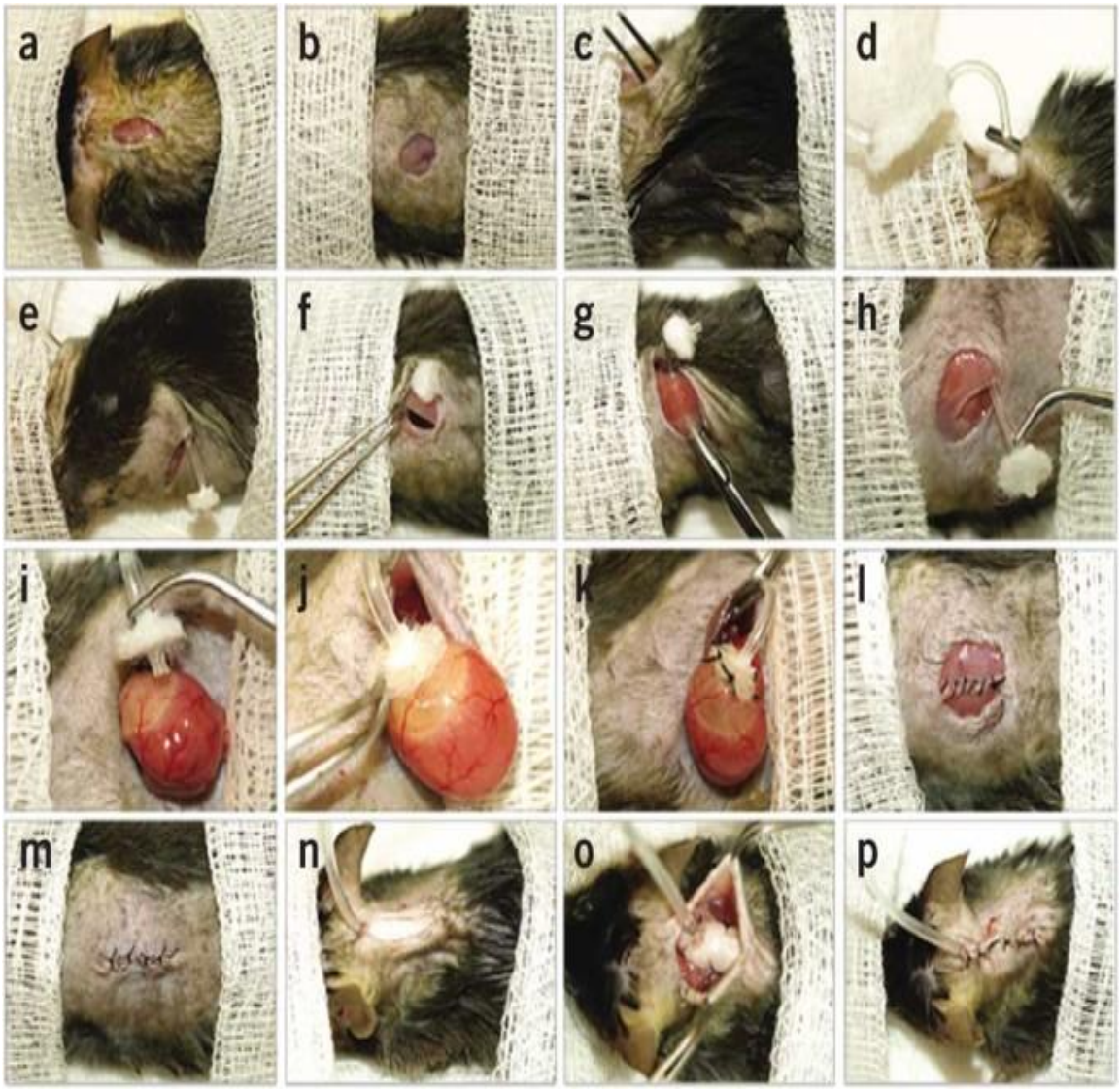


Figure:5- The Tsukamoto–French intragastric ethanol infusion model is a controlled rodent system for inducing alcohol-associated liver disease by continuously delivering ethanol and diet directly into the stomach to reproduce advanced ALD features, including steatosis, inflammation, and fibrosis.

- Modified Tsukamoto Model: Combining ethanol feeding with a Western diet produces inflammation, pericellular and perisinusoidal fibrosis, and increased proptosis.
- Limitations: The model requires specialized equipment, metabolic cages, surgical expertise and feeding cannulas, which may increase animal mortality and experimental complexity.

12.5 Chronic Lieber – Decarli Ethanol Diet with a Single Ethanol Gavage
(Gao – Binge Model)

Model development: Dr. Bin Gao's group developed the Gao-binge mouse model by combining chronic ethanol feeding with an acute ethanol binge.

❖ Initial feeding: Mice receive a control Lieber–DeCarli liquid diet for 5 days, followed by a 5% ethanol diet for 10 days.

❖ Acute ethanol binge: On day 11, mice receive a single oral ethanol dose of 5 g/kg (31.5% v/v), with outcomes assessed approximately 9 hours later.

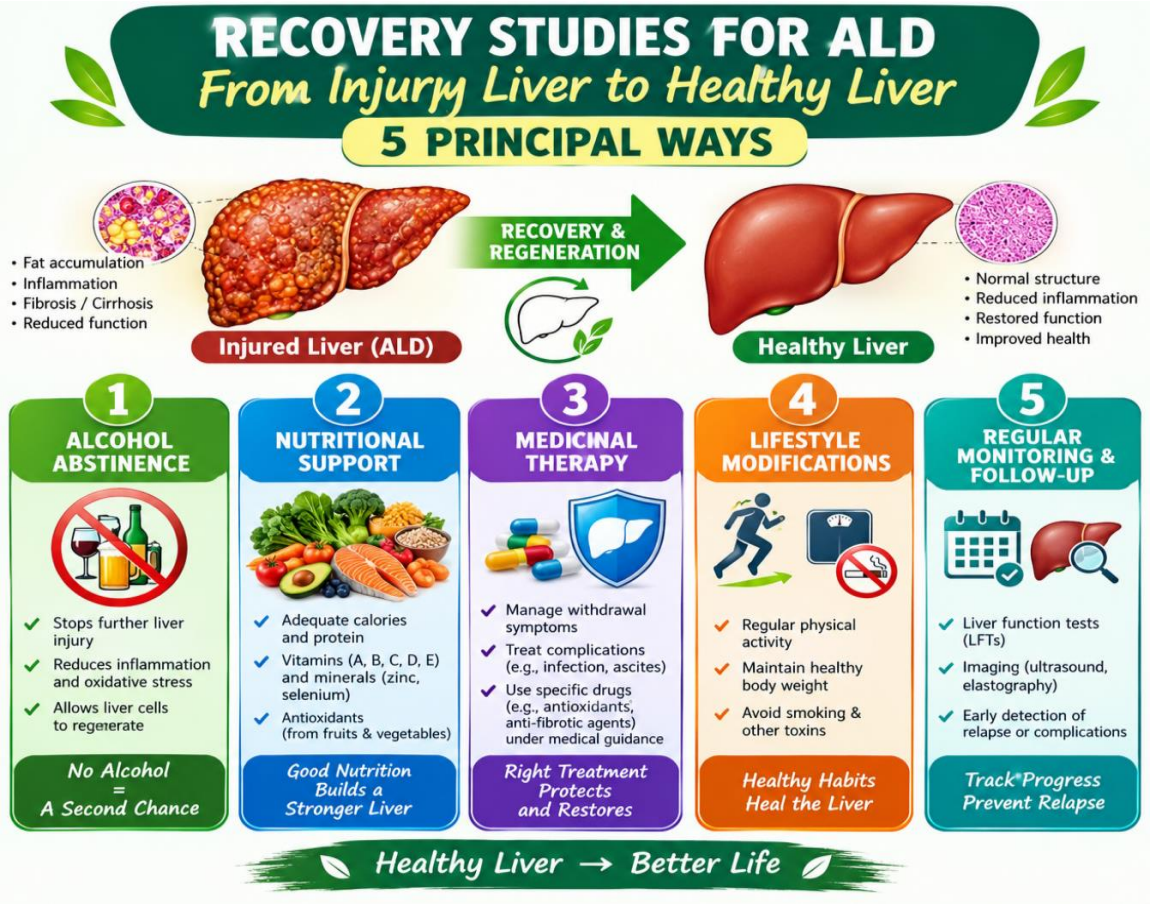
❖ Control group: Control mice receive a calorie-matched diet and a 45% maltose-dextrin binge.

❖ Liver injury: The model produces elevated ALT and AST levels, hepatic steatosis, and megamitochondria formation.

❖ Inflammation: Significant neutrophil infiltration occurs in the liver compared with chronic ethanol feeding or acute binge treatment alone.

❖ Advantages and limitations: The model is widely used because it is rapid and mimics binge-drinking behaviour; however, it produces limited fibrosis and does not reproduce advanced alcohol-associated liver disease (ALD).

13. RECOVERY STUDIES FOR ALD FROM INJURY LIVER TO HEALTHY LIVER



CONCLUSION

Alcohol-associated liver disease represents a significant and preventable cause of liver-related morbidity. Its progression reflects the interconnected effects of ethanol metabolism, oxidative stress, inflammation and metabolic dysfunction. Early diagnosis, sustained alcohol abstinence, nutritional optimization and evidence-based therapeutic interventions are fundamental to limiting hepatic injury and improving survival. Integrating non-invasive diagnostic tools, individualized risk assessment, and multidisciplinary care offers a promising approach to preventing disease progression and improving long-term clinical outcomes.

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