
بسم الله الرحمن الرحیم


رَبَّنَا آتِنَا مِن لَّدُنكَ رَحْمَةً وَهَيِّئْ لَنَا مِنْ أَمْرِنَا رَشَدًا



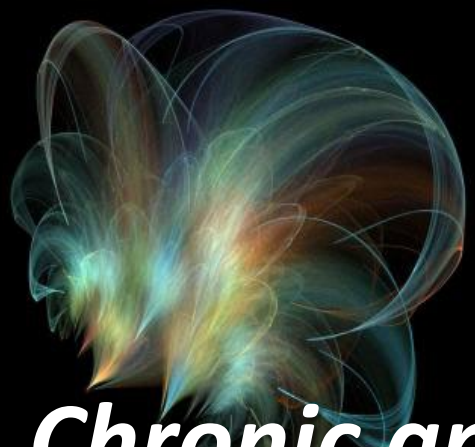
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- ***Alcohol Related liver Disease:***
- ***A comprehensive review of Epidemiology and pathogenesis***



- ***Chronic and excessive alcohol consumption is a global healthcare problem, which leads to clinical illness and pathological changes causing alcohol-associated liver disease (ALD).***

- *Alcohol is responsible for ~5% of all deaths globally and contributes substantially to liver-related morbidity.*
- *ALD is becoming more common, and it is killing more people and is driving increase in liver transplantation*
- *.*

- *Globally, alcohol-associated cirrhosis represents roughly 30–40% of cirrhosis-related deaths*
- *Men are affected more frequently than women, but the sex gap is narrowing because alcohol consumption among women has increased in many regions.*

- ***The risk is strongly related to cumulative alcohol exposure, but there is no completely safe level of alcohol consumption for liver disease.***

A particularly important 2026 trend

- *The epidemiology is changing from the traditional image of "ALD = isolated heavy alcohol use."*
- *Increasingly, patients have:*
- *Alcohol exposure + obesity/T2DM/MASLD → synergistic liver injury → earlier fibrosis/cirrhosis.*



- *ALD is associated with liver inflammation and injury or progressive fibrosis producing <u>three major classes,</u> each of which rarely exists in a pure form*
- *fatty liver,*
- *alcoholic hepatitis, and*
- *cirrhosis*



- ***Alcohol is considered to be a direct hepatotoxin, it is just around 20 % of all patients with alcohol use disorder, who subsequently develop into alcohol-associated hepatitis***

- ***The gender-dependent differences in the GI and hepatic metabolism of alcohol are likely to contribute towards the increased susceptibility of women to ALD***

A summary of risk factors causing ALD are

- *Quantity*
- *Gender and age*
- *Viral infection*
- *Genetics*
- *Malnutrition*
- *immune status*

Pathophysiology



- ***Alcohol is a direct hepatotoxin, and its ingestion causes the initiation of numerous metabolic responses that influence the final hepatotoxic response***

- *In the liver, alcohol is metabolized by oxidative and non-oxidative pathways*
- *The oxidative pathway is the major pathway for alcohol metabolism and is composed of two steps*

- *First, alcohol is oxidized to acetaldehyde by alcohol dehydrogenase (ADH), a primary enzyme that converts alcohol to acetaldehyd*

- ***The second step in the oxidative pathway involves the rapid conversion of acetaldehyde to acetate by aldehyde dehydrogenase (ALDH).***

- *Chronic consumption of alcohol produces a wide spectrum of hepatic lesions.*
- *Fatty liver (i.e., steatosis) is the earliest, most common response that develops in more than 90 percent of drinkers who consume 4–5 standard drinks per day.*

- *With continued drinking, alcohol-induced liver disease can proceed to liver inflammation (i.e., steatohepatitis), fibrosis, cirrhosis, and even liver cancer (i.e., hepatocellular carcinoma).*

- *The complex interaction of various distinct hepatic cell types is crucial to understand alcohol-mediated liver injury*
- *The main events in liver fibrogenesis include activation of stellate cells and production of collagen*

- *Overexpression of TNF-α mRNA in the liver activates the liver cell functions and macrophages and this caused the pro-inflammatory response and ROS elevation to reveal the liver toxicity.*
- *The mechanism of liver toxicity has been reported with activation of ROS, IL-6, and IL-8*

- *The fibrosis that results due to this, determines the extent of damage to the architecture of the liver following chronic alcohol ingestion*

- ***The liver and gut microbiota axis linked into the bidirectional actions, and this involved the integration factors of genetic, dietary, and environmental.***

- *The alteration of the intestinal barrier explains the interrelations of the gut, liver and sometimes leads to negative effects on the liver.*
- *The intestinal microbes in hepatic disease are mainly associated with alcohol.*

- *In the intestinal lumen, alcohol and its metabolites alter gut microbiota by decreasing the synthesis of saturated long-chain fatty acids by microbes.*

- *This mutual reciprocal action established by the gut derivatives directly enters the liver and leads to intestinal secretions*

- ***Alcohol-induced microbial peptides increase the level of proinflammatory mediators in the liver surroundings and this interconnected with the epithelial barrier, the lining of the mucus membrane, and the gut microbiome***

- *In the development of liver pathogenesis, alcohol directly acts on the liver parenchymal cells to initiate the abnormalities of intestinal barrier functions, alteration of microbiota, and increased toll-like receptors (TLRs) activation in liver cells*.

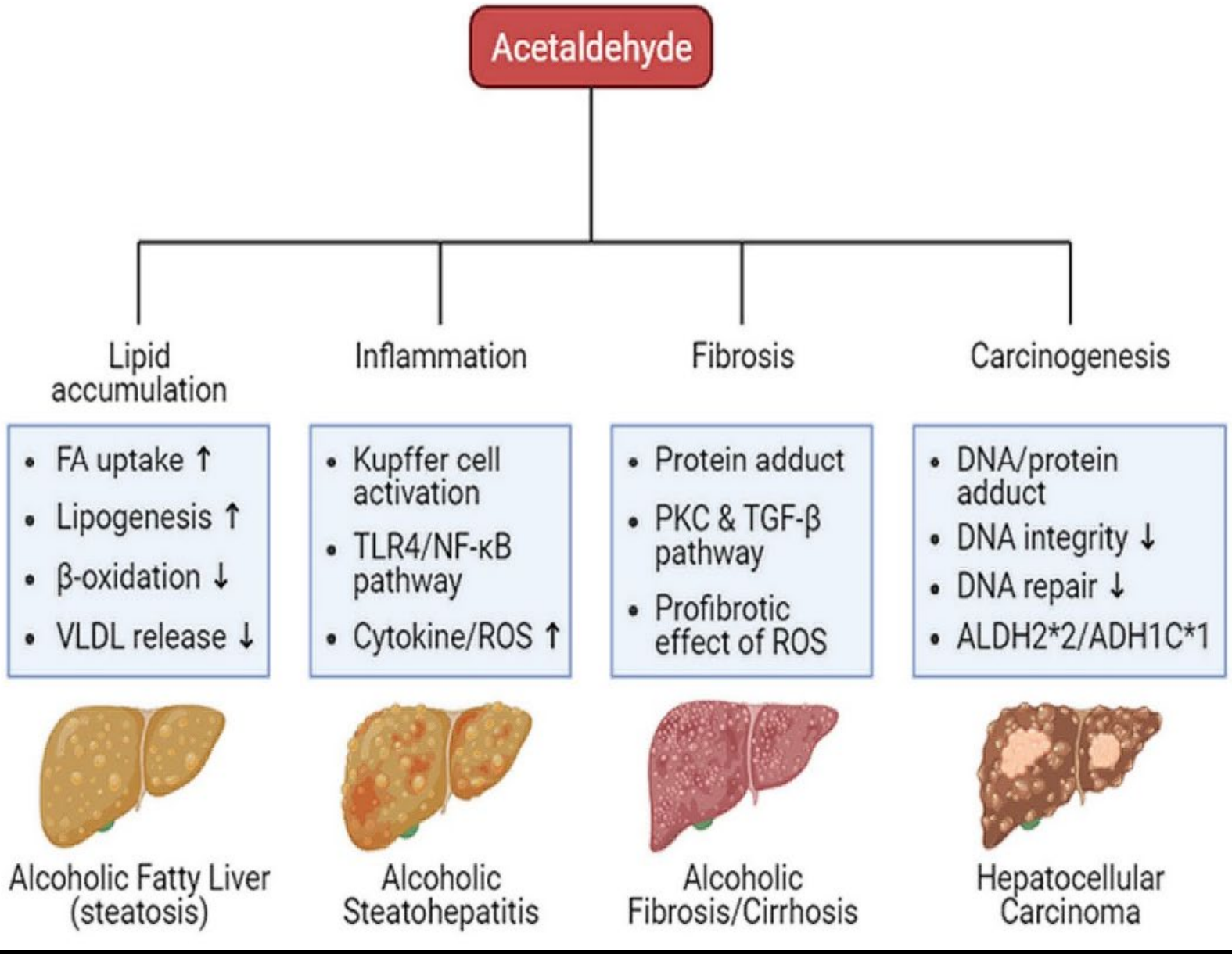


- *These mechanisms cause synergistic exacerbation of hepatocyte injury, resulting in*
- *lipid peroxidation,*
- *mitochondrial damage, and*
- *oxidative stress.*

- *Proinflammatory cytokines and chemokines, including tumor necrosis factor,mediate hepatic inflammation and recruit neutrophils and other immune cells.*
- *Activated stellate cells promote liver fibrosis and are the main source of extracellular matrix proteins*

- ***Hepatic regeneration, consisting of proliferation of the liver tissue, is impaired by alcohol-induced inhibition of hepatocyte DNA synthesis and microRNA signaling***

- *Imbalance from the proinflammatory response, hepatocyte injury, and insufficient regeneration appears to determine the outcome of severe forms of ALD*


Acetaldehyde
Lipid accumulation
Inflammation
Fibrosis
Carcinogenesis
• FA uptake ↑
• Lipogenesis ↑
• β-oxidation ↓
• VLDL release ↓
• Kupffer cell activation
• TLR4/NF-κB pathway
• Cytokine/ROS ↑
• Protein adduct
• PKC & TGF-β pathway
• Profibrotic effect of ROS
• DNA/protein adduct
• DNA integrity ↓
• DNA repair ↓
• ALDH2*2/ADH1C*1
Alcoholic Fatty Liver (steatosis)
Alcoholic Steatohepatitis
Alcoholic Fibrosis/Cirrhosis
Hepatocellular Carcinoma

In summary

- *Alcoholic hepatitis is still a major problem due to significant morbidity and mortality*
- *To reverse or inhibit the progression of ALD, identification of ALD risk factors and of mechanisms explaining their actions in ALD progression provides vital information for developing therapeutic targets for ALD.*



- *The main hepatotoxicity of ethanol-derived metabolites produced by oxidative alcohol metabolism (acetaldehyde and ROS) during excessive exposure to alcohol.*
- *However, the mechanisms of ALD pathogenesis remain unclear*

- *Limited understanding of ALD hampers the development of novel therapies for ALD.*
- *Therefore, further studies are necessary to elucidate the detailed mechanisms of ALD and to discover potential therapeutic targets for treating ALD*

Have a great day!



