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Systematic Review on Patterns, Causes and Mechanisms of Hepatotoxicity

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ABSTRACT

The liver, a important metabolic and detoxifying organ is noticeably susceptible to toxic damage due to its central function in drug metabolism and xenobiotic clearance. Drug-precipitated liver harm (DILI) remains a major impediment in drug development and a leading motive of scientific trial screw ups and drug withdrawals. Over 900 capsules, toxins and natural products had been implicated in liver harm contributing to more than 50% of acute liver failure cases. Hepatotoxicity arises thru diverse regularly drug-precise mechanisms consisting of oxidative pressure, mitochondrial disorder, immune-mediated responses, cholestasis and disruption of metabolic and vascular pathways. Cytochrome P450 enzymes, especially CYP2E1 play a crucial role in generating reactive metabolites and reactive oxygen species (ROS) which impair hepatocyte characteristic. Acetaminophen-brought on toxicity exemplifies direct hepatocyte injury through glutathione depletion and peroxynitrite formation even as mitochondrial damage characterised via impaired β-oxidation, altered respiratory and mitochondrial permeability transition is primary to NSAID, NRTI and alcohol-associated hepatotoxicity. Kupffer cell activation and neutrophil infiltration extend harm thru cytokine and ROS launch. Immune-mediated accidents contain drug-metabolite-brought about neoantigens that initiate allergy reactions as seen with Nevirapine, Diclofenac and Halothane. Cholestatic damage outcomes from bile acid accumulation and Fas-mediated apoptosis. Genetic polymorphisms, age, intercourse, alcohol use and preexisting liver sicknesses modulate man or woman susceptibility. Pathological manifestations variety from steatosis and hepatitis to cirrhosis and tumors. Despite advances in preclinical models and biomarker development translating mechanistic insights into predictive and preventive techniques stays a undertaking.

Keywords: Hepatotoxicity, Liver injury, Drug-Induced Liver Injury (DILI), Oxidative Stress, Cytochrome P450, Mitochondrial Dysfunction.

Introduction

The liver is the biggest stable organ and gland in the body crucial for survival and accountable for over 500 important capabilities, which include metabolism, detoxing and bile production. It receives a dual blood supply from the hepatic artery and the nutrient and antigen-rich portal vein, with blood flowing thru lobules composed of hepatocytes, Kupffer cells and LSECs. Beyond its metabolic responsibilities, the liver acts as a prime immune organ hosting numerous immune cells that clear out blood and preserve immune surveillance. Its specialized shape promotes immune tolerance specially to intestine-derived antigens helping save you pointless immune responses.[1,2,3,4,5]Functionally, the liver helps digestion thru bile secretion, manages bilirubin metabolism and detoxifies pills, hormones and pollution. It regulates nutrient metabolism, along with fats, proteins and carbohydrates, stabilizes blood glucose degrees and synthesizes plasma proteins and clotting elements. Additionally, it serves as a reservoir for vitamins and minerals (together with A, D, B12, iron and copper) performs endocrine functions like hormone activation and conversion and contributes to vascular law by storing and freeing blood. Together, those multifaceted roles underscore the liver's important importance in retaining systemic homeostasis and typical health.[6,7]Hepatotoxicity is liver dysfunction or damage caused by tablets or xenobiotics collectively referred to as hepatotoxins. The liver's key position in metabolism makes it in particular susceptible to such injury, which may also result from direct toxicity, reactive metabolites or immune-mediated mechanisms.[8,9,10] Over 900 marketers, inclusive of pills, herbs and pollution were implicated. Liver harm can be dose-structured as with acetaminophen or idiosyncratic taking place unpredictably at healing doses on occasion main to liver failure or demise. Injury may additionally present as hepatocellular or cholestatic patterns and is influenced by genetic and environmental factors. Management includes on the spot withdrawal of the offending agent, with N-acetylcysteine because the most effective specific antidote for acetaminophen toxicity; severe instances may require liver transplantation.[9,11,12,13]

Patterns of liver injury: -

Types of liver injury are as follows: -

Cirrhosis- Liver cirrhosis is the superior stage of liver fibrosis, marked by regenerative nodules and fibrous bands that distort regular liver structure and cause portal hypertension and liver failure. Common causes encompass alcoholic liver sickness, chronic hepatitis C and non-alcoholic fatty liver disorder. Diagnosis is based on medical evaluation, imaging and liver biopsy, although non-invasive equipment like Fibroscan and serum markers are increasingly

more used. The disease progresses from a compensated, regularly asymptomatic level to a decompensated phase with complications together with ascites, variceal bleeding and hepatic encephalopathy. Prognosis varies via severity and is classed the usage of Child-Pugh and MELD ratings. While once taken into consideration irreversible, cirrhosis might also regress if the reason is addressed, with liver transplantation being the definitive treatment for give up-level cases.[14,15,16,17,18,19,20,21,22]

Necrosis- Liver necrosis refers back to the pathological loss of life of liver cells, commonly seen in both acute and persistent liver sicknesses. It happens thru diverse patterns—together with person cell, spotty, zonal (centrilobular or periportal) and big necrosis—each offering diagnostic clues. Causes consist of ischemia, drug toxicity (e.G., acetaminophen), viral hepatitis, autoimmune disease and cholestasis. Necrosis entails key mechanisms like ATP depletion, mitochondrial dysfunction, calcium imbalance and oxidative pressure, often triggering infection via DAMPs. While morphologically wonderful from apoptosis, each can coexist or overlap, prompted through factors like cell strength stages. Persistent necrosis drives fibrosis and liver failure, highlighting the want for targeted therapeutic techniques.[23,24,25,26,27,28,29,30]

Apoptosis- Apoptosis is a tightly regulated form of cellular dying vital for liver homeostasis however performs a key position in liver sicknesses whilst dysregulated. In the liver, it happens through extrinsic (demise receptor), intrinsic (mitochondrial), lysosomal, and ER strain pathways, frequently related to caspases and Bcl-2 family proteins. Excessive hepatocyte apoptosis contributes to inflammation and fibrosis, as engulfment of apoptotic our bodies by Kupffer cells and hepatic stellate cells triggers cytokine release and extracellular matrix manufacturing. Apoptosis is implicated in sicknesses like alcoholic liver disorder, cholestasis, NAFLD/NASH, viral hepatitis, ischemia-reperfusion damage and liver cancer. Therapeutic tactics include caspase inhibitors and TLR9 antagonists to modulate apoptosis and decrease liver harm.[31,32,33,34,35,36,37,38]

Fibrosis – Liver fibrosis is the excessive buildup of extracellular matrix proteins, broadly speaking collagen, as a wound-healing response to chronic liver harm. Persistent damage from reasons like viral hepatitis, alcohol, or NASH leads to innovative scarring, which could result in cirrhosis, liver failure and hepatocellular carcinoma. Key drivers include activated hepatic stellate cells, inflammatory indicators and fibrogenic cytokines like TGF-β1. Diagnosis historically is predicated on liver biopsy, but noninvasive assessments and imaging techniques like elastography are more and more used. Although no approved antifibrotic drugs exist, fibrosis can be reversible with removal of the underlying cause and through emerging therapies targeting inflammation, stellate cell activation and ECM degradation.[39,40,41,42,43,44]

Causes

Medications (Drug-Induced Liver Injury - DILI): The liver plays a critical role in drug elimination, particularly lipophilic drugs, making it a key target for drug poisoning. Drug-induced liver injury (DILI) encompasses a spectrum from asymptomatic liver test elevations to acute liver failure (ALF). It is classified as either predictable (intrinsic), like acetaminophen overdose which is dose-related and has a short latency, or unpredictable (idiosyncratic), which is unexpected and accounts for nearly all DILI in clinical settings. Idiosyncratic DILI can be categorized by the pattern of liver test abnormalities: hepatocellular, characterized by a high alanine aminotransferase (ALT) to alkaline phosphatase (ALP) ratio (≥5 times upper limit of normal (ULN) ratio), cholestatic (low ALT/ALP ratio, ≤2 times ULN ratio), or mixed (ratio between 2 and 5), although individual drugs can present with different patterns. Other forms include steatohepatitis, neoplasms, and vascular injuries. Antibiotics are the class of drugs most frequently associated with idiosyncratic DILI, particularly amoxicillin-clavulanate, which is the most common individual culprit. Herbal and dietary supplements (HDS) are also increasingly recognized causes, notably linked to severe outcomes like ALF and requiring liver transplant. Other commonly implicated drugs include antituberculosis agents like isoniazid, nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, sulphonamides, nitrofurantoin, phenytoin, and statins. DILI can also be immune-mediated, often presenting with fever, rash, and eosinophilia, or categorized as drug-induced autoimmune like hepatitis, which may require corticosteroid treatment.[45,46]

Alcohol: Alcohol causes liver injury through multiple interacting pathways, primarily by inducing oxidative stress. Both acute and chronic ethanol exposure increase the production of reactive oxygen species (ROS), decrease antioxidant levels, and enhance oxidative stress in the liver. This oxidative stress arises from various sources, including changes in the cellular redox state, the formation of the reactive product acetaldehyde, damage to mitochondria, induction of CYP2E1, and the mobilization of iron. Chronic ethanol also stimulates Kupffer cells, which are activated by bacterial endotoxin, to produce free radicals and inflammatory cytokines such as TNFα, playing a significant role in alcoholic liver disease (ALD). Iron overload, often associated with alcohol consumption, exacerbates oxidative stress by catalysing the formation of potent oxidants and primes Kupffer cells for activation. Mitochondria are a critical target and source of ethanol-induced oxidants; chronic exposure depresses their function, increases ROS production, damages mitochondrial DNA, and alters mitochondrial permeability, leading to apoptosis. Ethanol metabolism and oxidative stress also generate reactive aldehydes that bind to proteins, forming toxic and immunogenic protein adducts. The induction of CYP2E1 by ethanol contributes substantially to ROS generation and oxidative stress, damaging cellular components like mitochondria and DNA, and stimulating hepatic stellate cells. Activated stellate cells, responding to inflammatory signals, become central players in fibrosis and cirrhosis by synthesizing and depositing extracellular matrix proteins. Furthermore, ethanol impairs cellular repair mechanisms, such as the ubiquitin-proteasome system, leading to the accumulation of damaged proteins and contributing to hepatocyte ballooning and Mallory body formation. The balance of reactive nitrogen species may also play a role.[47,48]

Infections: Hepatitis viruses (A, B, C, D, and E) and other viral infections like Epstein-Barr virus (EBV) and cytomegalovirus (CMV) cause hepatotoxicity primarily through direct viral infection of liver cells and the resulting immune response. Hepatitis A and E typically cause acute hepatitis by directly infecting hepatocytes, triggering an immune-mediated cytotoxic response that leads to liver cell death. Hepatitis B and C can establish chronic infections, with persistent viral replication and chronic inflammation that promote fibrosis, cirrhosis, and increase the risk of hepatocellular carcinoma. Hepatitis D, which depends on co-infection with hepatitis B, intensifies liver damage through enhanced immune activity. EBV and CMV, although not

primarily hepatotropic, can cause mild to moderate hepatitis by infecting immune cells and inducing a systemic inflammatory response that affects the liver, particularly in immunocompromised individuals. In all cases, liver injury results from a combination of viral replication, immune cell-mediated cytotoxicity, and the release of pro-inflammatory cytokines.[49,50,51]

Toxins and Chemicals: Hepatotoxicity is brought on by toxins and substances that either directly harm liver cells or interfere with normal liver function. Through oxidative stress, chemicals such as aflatoxins and carbon tetrachloride create reactive compounds that harm liver cells. Overdosing on acetaminophen results in harmful compounds that overwhelm the liver's detoxification system and cause damage to cells. Fatty liver disease is brought on by some drugs, such as alcohol, which accumulate fat in the liver. Furthermore, some medications may cause immunological reactions, which can lead to inflammation and additional liver damage. These procedures may eventually lead to liver failure or malfunction.[52]

Autoimmune diseases: Autoimmune liver injury occurs when your body's immune system attacks your liver by mistake. The main forms of this are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). These are complicated conditions likely resulting from a mix of your genetic background and environmental factors. Your genes particularly certain types of HLA (Human Leukocyte Antigen) can increase your risk. Things in the environment like infections or specific medications can also play a role. For instance, some drugs such as nitrofurantoin or minocycline can cause liver injury that closely resembles AIH. This type of drug-induced injury often involves having autoantibodies like ANA and SMA and elevated IgG levels, similar to idiopathic AIH. These autoimmune-like features typically decrease after stopping the medication. In autoimmune liver diseases immune cells such as T-cells, target liver cells or bile ducts, potentially because the immune system loses its ability to recognize the body's own tissues as safe. Problems with cytokine pathways like those involving IL-12 and IL-17 are also thought to be involved. This attack leads to inflammation and scarring which can progress to cirrhosis. It is common for these liver diseases to occur alongside other autoimmune conditions like autoimmune thyroid disease and Sjogren's syndrome suggesting a shared genetic risk or triggers. Distinguishing autoimmune liver diseases from liver issues caused by other autoimmune disorders or drug toxicity can be difficult and often requires a liver biopsy for accurate diagnosis. The presence and specific type of these other autoimmune conditions might also affect the progression of the liver disease.[53,54]

Herbal and Dietary Supplement: Herbal and Dietary Supplements (HDS) are a significant cause of liver injury accounting for about 20% of cases in the U.S. Drug-Induced Liver Injury Network (DILIN) prospective study a proportion that has increased over time. In a 2014 study HDS were responsible for almost half of the DILI cases identified through prospective surveillance in Delaware. Liver injury from HDS can have variable clinical, laboratory and histological phenotypes. Bodybuilding HDS often containing anabolic steroids typically cause prolonged cholestatic injury presenting as jaundice primarily in young men but are usually self-limiting without fatalities or transplantation. Non bodybuilding HDS, such as green tea extract or multi-ingredient nutritional supplements more commonly cause a hepatocellular injury pattern and notably may lead to more severe outcomes like liver transplantation or death compared to conventional medications or bodybuilding HDS. Challenges in diagnosing HDS-induced liver damage consist of the complicated multi-component nature of many merchandise, faulty labelling capability adulteration with prescribed drugs and variability in composition. Genetic elements, together with unique HLA alleles like HLA-B*35:01 were related to multiplied susceptibility to liver injury from sure HDS components, consisting of green tea extract and Polygonum multiflorum.[55,56,57]

Mechanisms of liver harm:

- (ROS) Reactive oxygen species
- Mitochondrial disorder
- Immune-Mediated Liver Injury
- Cholestasis and Liver Injury

Reactive oxygen species (ROS): Reactive oxygen species (ROS): Reactive Oxygen Species (ROS) are generated thru numerous mechanisms, such as the unfinished reduction of molecular oxygen, generally producing superoxide radical ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2). Major intracellular resources of ROS production in the liver encompass the mitochondrial breathing chain, peroxisomes, xanthine oxidases, cytochrome P450 oxidases (like CYP2E1 involved in xenobiotics metabolism), and NADPH oxidases (NOXs). The mitochondrial electron delivery chain produces $O_2^{\bullet-}$ from complexes I and III. NADPH oxidases are membrane-certain enzymes that generate $O_2^{\bullet-}$ and/or H_2O_2, with NOX4 predominantly generating H_2O_2. External stimuli, along with metal-based totally nanoparticles like Cadmium telluride (CdTe) quantum dots (QDs), actually have a sturdy capability to result in ROS production. While low degrees of ROS are worried in physiological signalling, an out of control upward push ends in "oxidative stress" or "oxidative misery," described as a disruption of the oxidant/antioxidant stability favoring oxidants, which causes tissue damage. In the liver, this imbalance can injure specific mobile sorts. Hepatocytes are sensitive to ROS-mediated harm, which includes lipid peroxidation which influences cell membranes and mitochondrial characteristic, exacerbating ROS production and potentially leading to dysfunction or demise. Oxidative strain can also induce hepatocellular dying through apoptosis or necrosis and disrupt bile go with the flow. Liver sinusoidal endothelial cells (LSECs) are touchy to oxidative pressure, which could harm them and impair their function, potentially main to fenestrae closure, disrupting molecular change, and contributing to sinusoidal dysfunction and portal high blood pressure. Kupffer cells (KCs), liver resident macrophages, are activated by way of stimuli, main to ROS manufacturing that complements the manufacturing of seasoned-inflammatory cytokines inclusive of TNFα, IL-6, and IL-1β. ROS generated via KCs, especially via NOX2, complements the manufacturing of pro-inflammatory cytokines. Hepatic stellate cells (HSCs) can be activated with the aid of ROS and lipid peroxidation products, causing them to differentiate into myofibroblasts that produce extracellular matrix components, contributing to liver

fibrosis. In essence, oxidative strain inside the liver disrupts mobile feature throughout a couple of cellular types, promotes irritation, and drives pathological processes like fibrosis, and can also make contributions to the pathogenesis of conditions like drug-induced liver harm and viral hepatitis. [58]

Mitochondrial disorder: Mitochondrial perturbation and disorder represent a prime mechanism of drug-prompted liver injury (DILI). Given that mitochondria are critical organelles chargeable for strength homeostasis, mobile metabolism, and apoptosis, their damage can lead to various liver damage kinds. Typically, altered electricity production, excessive oxidative pressure, the discharge of pro-apoptotic indicators triggering cellular loss of life, and changed lipid metabolism leading to triglyceride accumulation (steatosis) are located. Impaired mitochondrial fatty acid oxidation performs a big function in NAFLD development and progression, contributing to triglyceride accumulation in hepatocytes. Mitochondrial dysfunction in non-alcoholic fatty liver disease (NAFLD) is characterized by ultrastructural damage, reduced respiratory chain activity, ATP depletion, increased membrane permeability, reactive oxygen species (ROS) overproduction, mitochondrial DNA (mtDNA) damage, and impaired β-oxidation. Excess ROS production, often linked to ETC disruption, can activate inflammatory pathways and contribute to hepatocyte necrosis. Alcohol metabolism produces acetaldehyde, a toxic metabolite that contributes to mitochondrial dysfunction, oxidative stress, and inflammation in alcohol-related liver disease (ALD). Alcohol-caused hepatic harm is related to mtDNA loss/mutation and decreased respiration chain complex pastime, exacerbating oxidative pressure and steatosis. Mitochondrial dysfunction is likewise a key element within the development of acute liver injury (ALI), in which challenges like LPS can disrupt mitochondrial biogenesis and oxidative metabolism. Predisposing elements which includes genetic predisposition, metabolic issues like weight problems and kind 2 diabetes (often related to NAFLD), and viral infections can impact drug-prompted mitochondrial dysfunction. Targeting alcohol-brought about mitochondrial dysfunction is considered a promising healing avenue for ALD.[59,60,61]

Immune-Mediated Liver Injury: Immune-mediated liver damage can be prompted by way of various factors, including drugs, immunological substances, or additives like the SARS-CoV-2 spike protein. This regularly entails capsules or their metabolites appearing as haptens, forming neoantigens through binding to self-proteins. Antigen-imparting cells (APCs) like dendritic cells (DCs), doubtlessly activated via harm-related molecular patterns (DAMPs) from injured hepatocytes, absorb and gift these drug-changed peptides within the context of HLA molecules. This presentation primes naive T cells in liver-draining lymph nodes, leading to their proliferation and differentiation into effector T cells. Host genetic elements, in particular HLA alleles, significantly influence susceptibility by using affecting this antigen presentation. Activated effector T cells then migrate to the liver. In the liver, those T cells and activated innate immune cells, including Kupffer cells, launch potent pro-inflammatory cytokines, drastically TNF-α and IFN-γ. TNF-α can without delay trigger hepatocyte apoptosis via TNF-receptor signalling and caspase cascades. Furthermore, TNF-α and IFN-γ can act synergistically to induce inflammatory cellular loss of life and tissue damage. Other mechanisms, including Fas ligand or TRAIL-mediated pathways, can also lead to hepatocyte dying, along with necroptosis. Intracellular signalling pathways, consisting of NF-κB and MAPK cascades, are inspired, gambling crucial roles in regulating the inflammatory reaction and figuring out mobile survival or dying. Released DAMPs perpetuate and extend the inflammatory cascade through further activating innate immunity.[62,63,64]

Cholestasis Liver Injury: Cholestasis manner bile glide is reduced, causing bile acids to accumulate inside the liver and blood. An early idea was that high bile acid stages immediately brought about liver cellular dying by way of apoptosis. However, recent studies advise bile acid concentrations inside the body is probably decrease than concept and no longer at once toxic sufficient. A more recent theory makes a speciality of sterile irritation. Bile acids, even at lower stages, can trigger liver cells to launch inflammatory alerts. These indicators attract immune cells, specifically neutrophils to the liver. Neutrophils then launch poisonous substances causing oxidant strain. This ends in liver cellular dying normally via necrosis not apoptosis in early harm in dwelling organisms. Neutrophil-brought about necrosis seems to be the main mechanism in early cholestatic liver injury within the body.[65,66]

Conclusion

Hepatotoxicity, especially drug-triggered liver damage (DILI), stays a primary undertaking in both scientific settings and drug development. The liver's primary role in metabolism and detoxing makes it fantastically liable to damage from capsules, alcohol, pollution, infections, autoimmune illnesses, and natural dietary supplements. Liver damage involves complex mechanisms together with oxidative strain, mitochondrial disorder, immune responses, and cholestasis. Clinical manifestations range from slight, reversible situations like steatosis to intense, irreversible damage inclusive of cirrhosis and liver failure. Despite advances in biomarkers, mechanistic research, and preclinical models, translating these findings into powerful predictive and therapeutic equipment stays tough. Ongoing studies into genetic elements, molecular mechanisms, and more secure tablets is essential to lessen hepatotoxic dangers and beautify drug safety.

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