Review Article

Review of Pathophysiological Aspects and Risk Factors for Liver Dysfunction

Abstract

The liver is accountable for many critical functions within the body and loss of those functions can cause significant damage to the body. Liver disease is an extensive term that covers all aspects that cause the liver to fail to perform its proper functions. Acute liver failure indicates the development of severe acute liver injury with impaired synthetic function without preexisting of clinical liver disease. However, chronic liver disease is characterized by destruction of the hepatic tissue. Early changes, such as fatty liver can progress via inflammation and fibrosis to cirrhosis. The main causes for liver dysfunction include dyslipidemia, obesity, viral and parasitic infection, drugs and environmental pollution, alcohol abuse, autoimmunity, and genetic defective such as hemochromatosis. The present review almost covers all the previous aspects that lead to liver dysfunction.

Hepatic stellate cells (HSC) have modulatory roles during inflammation by production of cytokine and chemokine [10] and modulating the recruitment and migration of mononuclear cells within the perisinusoidal space during liver injury [11]. Moreover, there is growing evidence that the HSC may be critically important in the progression of parasite-induced diseases. The interaction of parasites or parasite antigens with this cell can provide new insights in understanding of the pathogenesis of schistosomiasis and alveolar echinococcosis [12].

Kupffer cells are specialized macrophages scattered within the liver sinusoid, play a crucial role in the reticuloendothelial system to phagocytose spent erythrocytes. Kupffer cells become activated in the liver injury induced by hepatotoxins or by Gram-negative bacterial lipopolysaccharide (LPS), or in association with sensizers such as D- galactosamine, CCl₄, dimethylnitrosamine, acetaminophen and alcohol. Activation of Kupffer cells results in secretion of a large number of chemical mediators, can induce liver injury either by acting directly on the liver cells or via chemoattraction of extrahepatic cells [9]. However, D- galactosamine/ lipopolysaccharid induced liver injury was not accompanied by significant alterations in hepatic biotransformation enzymes [13]. Expression of adhesion molecules in Kupffer cells was similar to the sinusoidal endothelial cells during inflammation [14]. Kupffer cells may play a role in liver fibrogenesis [12], because the numbers of macrophages were increased around areas of tissue damage and fibrosis [15]. Activated macrophages produce proline and arginase–which contributes to collagen

Introduction

Pathophysiology of liver

The liver is the largest organ in the body and has a wide range of functions. Liver is consists of many different cell types, parenchymal cells (hepatocytes) make up the majority of liver mass and non–parenchymal cells includes Kupffer cells, sinusoidal endothelial cells, stellate cells, perportal fibroblasts, and hepatic dendritic cells [1]. Hepatocytes are able to synthesize hormones, like insulin–like–growth–factor (IGF–1) [2], thrombopoietin [3], IL–8 [4] and respond to acute phase mediators like IL–6, with the synthesis of C–reactive protein [5] or serum amyloid A [6]. Also, hepatocytes possess different intracellular defense proteins like hemeoxygenase-1 [7], cytokine–induced neutrophil chemoattractant and macrophage inflammatory proteins which are responsible for activation of resident macrophages [8]. The hepatic sinusoidal endothelial cells show low expression of IL–8, macrophage–chemoattract–protein–1and MIP–1α which are important for leukocyte recirculation and immunological surveillance under normal conditions. Moreover, under normal conditions the hepatic sinusoidal endothelial cells express platelet endothelial cell adhesion molecule–1, vascular adhesion protein–1 and intercellular cell adhesion molecule–2. Chemokine expression of the normal hepatic endothelium changed during inflammation with high levels of MIP–1β, IP–10, MIG and IFN–γ–inducible T cell chemoattractant. This expression characterized by the downregulation of PECAM–1, and upregulation of ICAM–1, vascular cell adhesion molecule VCAM–1, and P and E selectins [9].

Keywords: Liver disorder Jaundice Alcoholism Obesity Hepatitis Cholestasis Fatty liver Fibrosis Cirrhosis

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synthesis [16]. For example in fibrosis by schistosomiasis four stages were suggested recruitment of fibroblasts and/or differentiation of HSC proliferation of the HSC secretion remodeling of extracellular matrix [17].

Liver disease is varied and there are many circumstances that affect this organ, including cirrhosis, alcoholic fatty liver and hepatitis. Primary sclerosing cholangitis is a type of inflammatory liver disease affecting the bile ducts. Hepatocellular carcinoma is a type of liver cancer that is among the most serious of liver diseases. Alpha-1-antitrypsin deficiency is an inherited metabolic disorder in which mutations in the coding sequence of the serine protease inhibitor [18]. Abnormal accumulation of the glycoprotein in hepatocytes results in programmed cell death, hepatic inflammation, fibrosis, and cirrhosis [19]. Accelerated hepatocyte ageing and the accumulation of senescent hepatocytes have been demonstrated in different chronic liver disorders [20,21].

Jaundice

Jaundice is the yellow discoloration of tissues due to an accumulation of bilirubin in serum. The causes of jaundice can be prehepatic, hepatic or posthepatic. The causes of prehepatic jaundice include hemolysis, where there is an increased breakdown of hemoglobin producing large amounts of bilirubin that overloads the conjugating mechanism. Such bilirubin is mostly unconjugated and commonly occurs in newborn babies due to low activity or inherited deficiency of hepatic UDP–glucuronyltransferase. Other causes of prehepatic hyperbilirubinemia include hemolytic disease of the newborn due to Rhesus incompatibility, viral hepatitis and acetaminophen poisoning [22]. Hepatic jaundice is occur due defect within the liver mainly in the hepatocytes. The liver captures bilirubin from plasma proteins mainly albumin, then after conjugation excretes in the bile via biliary system. Any pathological change in the liver leading to defect in capture, conjugation and excretion of bile can cause hepatic jaundice. Moreover, defect in the hepatic excretory mechanism of bilirubin can cause hepatic jaundice. Any defect in the excretory mechanisms that involve hepatocytic bile acid–dependent secretion, hepatocytic bile acid–dependent secretion and bile ductular secretion can lead to hepatic jaundice [23]. Post hepatic jaundice or obstructive jaundice is occurs due to obstruction in the hepatobiliary system, however, the major cause is extrahepatic biliary obstruction [24].

Cholestasis

Cholestasis is a decline in bile stream because of debilitated secretion by hepatocytes or to deterrent of bile flow through intra–or extrahepatic bile ducts. Clinically cholestasis is characterized as any condition in which substances regularly discharged into bile are detained. The cholestasis can be extensively hepatocellular due to disability of bile progress, and decrease in bile flow leads to stopping of bile in the interlobular bile ducts causes portal expansion and bile duct proliferation [25]. Extrahepatic biliary obstruction may be caused by stones, tumours and cysts [26]. Cholestatic jaundice is regularly joined by a wide range of lab variations from the norm incorporate expanded serum levels of basic phosphatase and gamma-glutamyltransferase (GGT), and rise of serum bilirubin, copper, ceruloplasmin, cholesterol, lipoprotein, and bile acids [27]. Endotoxins and pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF–α), interleukin (IL)–1, and IL–6 can downregulate hepatic transport mechanisms that affecting both bile acid uptake and canalicular secretion [28,29]. Cholesterol is essentially insoluble in water and is kept up in a fluid situation in vesicles joined with phospholipids and bile salts. Development of gallstones occurs when the proportion of cholesterol, phospholipids and bile salts surpasses the ordinary range [30].

Pregnancy causes not very many adjustments in the aftereffects of standard liver tests. The aminotransferases (AST and ALT), GGT, total bilirubin, and serum bile corrosive level stay inside the typical range. The alkaline phosphatase rises modestly in the third trimester. The albumin level is lower than in non-pregnant women, and the cholesterol level higher. Thus, elevations in aminotransferases or GGT signify pathology [31,32]. Intrahepatic cholestasis in pregnancy occurs because liver cannot manage the increased amounts of hormones, which reduces the flow of bile [33]. Alcohol induced liver damage is estrogen–dependent response to gut–derived endotoxin in the liver [34]. Since, estrogens, contribute expanding gut penetrability and entrance endotoxin levels and opening up the Kupffer cell affectability to endotoxin through expanded articulation of the endotoxin receptor CD14 and the star provocative cytokine TNF–a [35,36].

Alcoholism

Alcohol is the main cause of liver disease, including liver cirrhosis. Alcoholic liver disease (ALD) encompasses a spectrum of injury, ranging from simple steatosis to cirrhosis. Fatty liver develops in about 90% of individuals who drink more than 60 g/day of alcohol, but may also occur in individuals who drink less [37]. Chronic alcohol consumption depresses the activity of all mitochondrial enzymes accordingly the rate of ATP synthesis in liver cells is reduced. Moreover, chronic ethanol administration enhances the oxygen uptake rate by liver cells as need for metabolism in the centrilobular area of the liver lobule [38,39]. Oxidation of ethanol to H2O and CO2 is mediated by three major hepatic enzyme systems: ADH in cytoplasm, microsomal ethanol oxidizing system in smooth endoplasmic reticulum of mitochondria and catalase in peroxisomal membrane. Consequently, alcohol increased hepatic oxidative stress via generation of highly reactive oxygen species (ROS) and adds such as malondialdehyde [40]. The mortality rate associated with cirrhosis has been considered indicator of alcohol–related mortality [41]. The cumulative amount of alcohol intake and alcohol consumption patterns and factors such as gender, genetic and nutritional factors, oxidative stress, immunological response and hepatic co–morbidd conditions play a key role in the alcoholic liver injury [34]. In addition, enzymes that metabolize ethanol and acetaldehyde alcohol–dehydrogenase, aldehyde–dehydrogenase and cytochrome CYP2E1 influence on the development of ALD–cirrhosis [42–44].

Citation: El-Din M Omar H, Omar OHM, Badr G (2016) Review of Pathophysiological Aspects and Risk Factors for Liver Dysfunction. Arch Clin Gastroenterol 2(3): 069-076. DOI: http://doi.org/10.17352/2455-2283.000025
Alcohol intake increases the intestinal permeability to lipopolysaccharide which bind with CD14 receptor on Kupffer cells and activates the nuclear factor kappa B (NF-κB) which causes blown up transcription of pro-inflammatory cytokines such as TNF-α, IL-6 and transforming growth factor beta (TGFB-β) [45,46]. TNF-α and IL-6 are involved in cholestasis and synthesis of acute-phase proteins, however, TGFB-β involved in fibrogenesis through the activation of HSC and progression of liver disease. Moreover, ethanol metabolites interact with the reactive lysine residues of proteins located on the membranes of hepatocytes and form neo-antigens that induce an immune reaction with antibody production or T-cell activation or both resulting in ALD [47,48].

Liver cirrhosis is a consequence of all chronic liver diseases and is characterized by tissue fibrosis and the conversion of normal liver architecture into structurally abnormal nodules [49]. The scar tissue in cirrhosis is composed of a complex of different extracellular matrix, comprising the fibril forming interstitial collagens type I and III, basement membrane collagen type IV, noncollagenous glycoproteins [50]. Toxins, viruses, cholestasis, or hypoxia can trigger fibrogenesis which is counterbalanced by removal of excess extracellular matrix by proteolytic enzymes [51]. Usually chronic damage favors fibrogenesis over fibrolysis [52]. Hepatic extracellular matrix was produced by myofibroblasts which activated by fibrogenic cytokines and growth factors that are released by Kupffer cells. The major profibrogenic cytokine is TGFB-β which drives fibrogenic gene expression in the myofibroblasts [53-55].

**Parasitic infection**

Schistosomiasis remains a critical reason for liver disease in regions of continuous transmission and presents as a test to finding in nonendemic ranges. Discovery of dynamic contamination and organizing of liver illness are the primary objectives in schistosomiasis administration [56]. Clonorchiasis, oriental liver fluke, is implicated in hepatobiliary disease ranging from asymptomatic infection to more severe liver disease including cholangitis or portal hypertension [57]. Amebic liver abscess by *Entamoeba histolytica*, a protozoan parasite that is obtained by ingestion of foods or water contaminated by human defecation [58]. Amebic liver abscesses burst into the peritoneum causing sub-aphasic abscesses and/or peritonitis and sometimes break into the pleural space creating empyema [59]. Rupture into the pericardium can be fatal due to purulent pericarditis [60]. Other complications include bacterial super-infection of the amebic liver abscess and thrombosis of the hepatic vein or inferior vena cava [61].

Intestinal schistosomiasis displays a special type of liver fibrosis. Five species of trematode Schistosoma are known to infect humans *S. mansoni*, *S. japonicum*, *S. intevalatum*, and *S. mekongi* affect the gastrointestinal tract. Adult worms reside within the mesenteric veins and produce numerous eggs per day. Eggs are mainly translocated into the gut by penetrating the vessel and the gut wall, but up to one-third of the eggs are flushed to the liver. Here, they become entrapped within the small pre-sinusoids and provoke infiltration with inflammatory cells and granulomatous lesions leading to hepatic fibrosis. In contrast to other chronic liver diseases, liver injury in schistosomiasis displays a delayed type of hypersensitivity reaction [62]. Tissue-entrapped eggs cause granulomatous response with a T helper response and secretion of pro-inflammatory cytokines, such as IL-1β, IL-12, TNF-α, and IFN-γ. During the chronic stage of infection, the onset of egg deposition is followed by Th2-mediated reaction, which is characterized by a pro–fibrotic cytokine profile with the secretion of IL-4, IL-5, IL-10, and IL-13 and the production of IgE [63]. Pro–fibrotic Th2 setting promotes the alternative activation of macrophages that are able to regulate granulomatous inflammation [64]. Moreover, oxidative stress at the site of inflammation in hepatic tissue are involved in the damaging effect of schistosomiasis and melanin as antioxidant is highly protective against the pathological changes associated with schistosomiasis [65].

The major aetiological agent for bile duct cancer is infection with flatworms *Opisthorchis viverrini*, *O. felineus* and *C. sinensis* which inhabit the human liver. Moreover, *Clonorchis sinensis* may be associated with cholangiocarcinoma [66]. Liver fluke infection causes chronic irritation and inflammation results in hyperplasia and adenomatous changes of bile duct epithelium [67]. Chronic inflammation around the bile ducts leads to generation of NO by inflammatory cells and endogenous formation of N-nitroso compounds. Therefore, bile duct epithelial cells are exposed continuously to high concentrations of nitroso compounds leading to neoplastic transformation [68]. N-nitrosodimethylamine is metabolized by cytochrome P-450 and the metabolite is DNA methylating agent that inducing DNA damage in proliferating bile duct epithelial cells [69]. Moreover, NO synthesized from L-arginine by macrophages, mast cells, eosinophils, and activated T cells, is a genotoxic leading to DNA damage [67, 70].

Malaria is disease caused by infection with protozoan parasite, Plasmodium (*P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*). Approximately 60% of patients with *P. falciparum* or vivax may have hepatomegaly and/or splenomegaly [71]. Jaundice was induced during malaria by intravascular hemolysis of parasitized erythrocytes [72]. Liver biopsy demonstrates Kupffer cell hyperplasia with pigment deposition due to phagocytosis of erythrocytes. Moreover, hepatocyte necrosis, portal inflammation, steatosis and cholestasis may be observed especially in fatal cases [73]. Infection with *Candida species* and *Entamoeba histolytica* causes hepatosplenomegaly and amoebiasis, respectively [74, 75]. During invasive amoebiasis, motile trophozoites invade the intestinal epithelium, causing extensive tissue damage characterized by acute inflammation and ulceration with necrosis and hemorrhage. In contrast to intestinal amoebiasis, invasion of the liver is characterized by the presence of nonmotile *E. histolytica* trophozoites that cause an acute inflammatory reaction [75].

**Drugs and environmental pollution**

The important mechanisms involved in non–allergic drug-induced hepatic injury can be divided into: (1) drug metabolism and reactive metabolite formation, (2) covalent binding, (3) ROS generation, (4) activation of signal transduction pathways that
modulate cell death or survival and (5) mitochondrial damage. Furthermore, immunological mechanisms can be triggered by these reactions [76]. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents such as those used in laboratories and industries and herbal remedies can also induce hepatotoxicity. Drug induced liver diseases are acute–dose dependent liver damage [77]. Environmental situation and in combination with an individual’s genetic susceptibility establishes the environment for the development of liver injury [78]. The initial steps of injury are triggered by the wrong drug, or drug metabolites that result from phase I drug metabolism by cytochrome P450 family or arise from conjugative phase II metabolism [79]. Injury from the drug is then propagated via cell stress, mitochondrial inhibition and/or specific immune reactions. Cellular stress may be exerted by a variety of mechanisms including glutathione depletion or the binding of metabolites to enzymes, lipids, nucleic acids or other structures. Mitochondrial inhibition occurs through inhibition of the mitochondrial respiratory chain resulting in ATP depletion and accumulation of ROS [80]. Specific immune responses evoked through the binding of the drug or its metabolite to HLA proteins, then presented to T cells and recognized as antigens. Then neo-antigens are sited on antigen presenting cells to activate formation of antibodies against themselves (auto–antibodies) [81].

Elevated intestinal permeability is the major factor involved in the mechanism of alcoholic endoxemia and the pathogenesis of ALD. Ethanol and its metabolic derivatives alter intracellular signal–transduction pathways leading to the disruption of epithelial tight junctions and increase paracellular permeability to macromolecules [82]. Patients with alcoholic cirrhosis showed significantly enhanced endotoxin plasma levels compared with healthy controls [83]. Leaky gut may be a necessary cofactor for the development of chronic liver injury in heavy drinkers because alcohol abuse impairs the function of the intestinal barrier which enhances the translocation of bacterial toxins and contributing in inflammatory processes [84,85]. Moreover, gut microbiota is another critical player in NAFLD [86].

Direct effects of articulate matter or carbon black on hepatocytes include the induction of oxidative stress and DNA strand breaks. In addition, airborne articulate matters contribute to the pathogenesis of steatohepatitis by alteration of lipid metabolism and induction of a pro–inflammatory milieu, resulting in non–alcoholic steatohepatitis [87]. Liver steatosis has various causes in the pediatric age group, such as inherited metabolic disorders, malnutrition, infections, and drug toxicity, and fatty liver disease. The majority of children with fatty liver disease are found to be obese and insulin resistant [88]. Low–and middle–income countries face the double burden of nutritional disorders, with an increasing prevalence of childhood obesity and NAFLD [89,90]. Moreover, both excess body fat and exposure to air pollutants are accompanied by systemic low–grade inflammation, oxidative stress, alterations in insulin/insulin–like growth factor and insulin resistance [91].

**Genetic defects**

Inherited liver diseases are a gathering of metabolic and hereditary deformities that normally bring about early and endless liver contribution. A large portion of these disorders are because of a deformity of a catalyst/transport protein that adjusts a metabolic pathway and applies a pathogenic part chiefly in the liver [92]. Alpha–1 antitrypsin synthesized by liver cells inhibits pro–inflammatory proteases such as neutrophil elastase [93]. Cystic fibrosis is a systemic disease that appears mainly with pancreatic insufficiency and pulmonary disease due to inflammation and opportunistic colonization that gradually causes respiratory insufficiency [94] (Rosenstein and Cutting, 1998). Altered activity of cystic fibrosis transmembrane regulator chloride channel on the apical membrane of cholangiocytes causes proliferation of HSC, cholangitis and fibrosis [95]. Wilson disease is an autosomal recessive disorder appears with liver disease in the second decade and neurological disorders in the third decade [96]. This disease depends on mutations in the gene encoding the ATP7B Cu translocase which regulates the levels of copper and modulates the synthesis of ceruloplasmin in liver [97]. Another, autosomal recessive disease is hemochromatosis which characterized by iron overload that prompted lipid peroxidation and hepatocellular damage. In this case, Kupffer cells deliver cytokines and HSC incorporate collagen and prompting cirrhosis [89,99].

Type I tyrosinemia is two forms: the 1st shows up with an extreme liver expression in the principal months of life that may advance to ascites, jaundice, and gastrointestinal dying while, the 2nd include cases with intense liver disappointment at around one year and an unending development with renal–tubular brokenness [100]. Type I tyrosinemia is because of the adjusted action of fumarylacetocetate hydrolase, which causes the rise of plasma and pee succinylacetone and high plasma centralization of tyrosine, methionine, and phenylalanine [101]. Glycogen stockpiling ailment sort IV is an autosomal latent infection because of transformations in the quality encoding the glycogen expanding compound that catalyze the alpha 1,6 obligation of the primary glucose in the side chains of glycogen [102].

**Viral infection**

The most common cause of acute hepatitis is viral infections, for example hepatitis A, B, C, D and E viruses which leads inflammation, and necrosis of the hepatocytes. Moreover, drugs, toxins and autoimmune reactions can leads to acute hepatitis [103]. Hepatitis B infection (HBV) and hepatitis C infection (HCV) are the main sources of endless liver illness [104,105]. Removing the insult and stopping the persistent inflammatory stimuli is the best way to prevent progression of fibrosis as in many patients with chronic hepatitis C and in smaller numbers of patients with autoimmune hepatitis [16]. Vaccination of infants at birth for hepatitis B is highly effective in decreasing the incidence of HBV. Antiviral therapies decreased but not eliminated the risk of HCC in both hepatitis B and C individuals. However, as antiviral therapies continue to improve in efficacy and will decrease HBV– and HCV-related
liver cancer, NAFLD is becoming a main cause of HCC in developed countries [106].

Diet and physical activity

Non-alcoholic fatty liver disease (NAFLD) includes a range running from steatosis to non-alcoholic steatohepatitis, which causes an expanded danger of cirrhosis, type 2 diabetes, and cardiovascular complexities. Dietary examples and supplements are the vital benefactors to the improvement and treatment of NAFLD and related metabolic comorbidities [107]. NAFLD, in the presence of normoglycemia and normal or moderately increased body weight, is characterized by clinical and laboratory data similar to those found in diabetes and obesity [108]. Dietary effects on whole-body metabolism and its regulation via effects on hormones, transcription factors, and lipid metabolic pathways are plays a central role in NAFLD. Both excessive carbohydrate intake and fat intake could play a role in increasing blood glucose, FFA, and insulin concentrations, independently or together [109]. Dietary fructose intake, increased intestinal translocation of bacterial endotoxin, and plasminogen activator inhibitor may contribute to the development of NAFLD in humans [110]. Moreover, primary hypothyroidism and other endocrinopathies are important factors as possible causes in patients with NAFLD or primary hypothyroidism and other endocrinopathies are important factors as possible causes in patients with NAFLD or with abnormalities of liver biochemistry [111]. In experimental model of NAFLD, rats fed HFS diet showed alterations of serum and hepatic dyslipidemia, metabolic enzyme activities, micro and macrovesicular steatosis in liver and the downregulation of peroxisome proliferator-activated receptor γ (PPARγ) in adipose tissue and the liver. These changes were ameliorated by supplementation of rats with phytochemical compounds, quercetin, o-coumaric and berberine [112,113]. Interestingly, dietary supplementation with natural antioxidants affects generally the metabolism and subsequently ameliorates the liver functions, which in turn, affect the hematopoiesis, complement system and enhances the immune response to infections. Natural antioxidants play central roles in enhancing immune system function via oxidative stress–dependent mechanisms. In this context, we provided great evidences for the beneficial effects of thymoquinone (TQ) on insecticide-induced immunological and histological damage in a rat model [114]. Similarly, it has been shown that supplementation of camel whey protein accelerates wound healing through activation of macrophages, alteration of the free radicals and upregulation in the expression of β–defensins in a streptozotocin (STZ)–induced diabetic mouse model [115,116]. Other studies have demonstrated that natural antioxidants isolated from snake venoms enhance normal lymphocyte functions and exert general antitumor effects in various human and animal cells by decreasing oxidative stress [117]. Moreover, evidence for the importance of diet on the metabolism, liver functions and T cell immune response has been proved [11].

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