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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 a 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.

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, periportal 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-chemotactic-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].

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 echinoccocosis [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 sensitizers such as D- galactosamine, CCl_4, dimethylnitrosamine, acetaminophene 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-1which contributes to collagen

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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 pre-hepatic 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- independent 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 extra-hepatic 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-α [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 H_20 and CO_2 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 adducts 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-morbid 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].

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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 (TGF-β) [45,46]. TNF-α and IL-6 are involved in cholestasis and synthesis of acute-phase proteins, however, TGF-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 TGF-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 abscesses 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-phrenic 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. intercalatum,* 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 Th1 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 melatonin 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 hepatosplenic candidiasis 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

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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 endotoxemia 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 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 fumarylacetoacetate 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 illnesse [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 [14]. 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

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liver cancer, NAFDL 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 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].

References

1. Tsung A, Monga DA (2011) Gross and cellular anatomy of the liver. In molecular pathology of liver diseases. edited by Monga SPS 3-6. Link: https://goo.gl/iMaEHq

2. Scharf J, Ramadori G, Braulke T, Hartmann H (1996) Synthesis of insulin like growth factor binding proteins and of the acid-labile subunit in primary cultures of rat hepatocytes, of Kupffer cells, and in cocultures: regulation by insulin, insulinlike growth factor, and growth hormone. Hepatology 23: 818-827. Link: https://goo.gl/Jaggwn

3. Shimada Y, Kato T, Ogami K, Horie K, Kokubo A, et al. (1995) Production of thrombopoietin (TPO) by rat hepatocytes and hepatoma cell lines. Exp Hematol 23: 1388-1396. Link: https://goo.gl/M452Tp

4. Sheikh N, Tron K, Dudas J, Ramadori G (2006) Cytokine-induced neutrophil chemoattractant-1 is released by the noninjured liver in a rat acute-phase model. Lab Invest 86: 800-814. Link: https://goo.gl/mBExmu

5. Sambasivam H, Rassouli M, Murray RK, Nagpurkar A, Mookerjea S, et al. (1993) Studies on the carbohydrate moiety and on the biosynthesis of rat C-reactive protein. J Biol Chem 26: 10007-10016. Link: https://goo.gl/3IvJUN

6. Ramadori G, Rieder H, Sipe J, Shirahama T, Meyer, Büschenfelde KH (1989) Murine tissue macrophages synthesize and secrete amyloid proteins different to amyloid A (AA). Eur J Clin Invest 19: 316-322. Link: https://goo.gl/cN47wu

7. Tron K1, Samoylenko A, Musikowski G, Kobe F, Immenschuh S, et al. (2006) Regulation of rat heme oxygenase-1 expression by interleukin-6 via the Jak/STAT pathway in hepatocytes. J Hepatol 45: 72-80. Link: https://goo.gl/GDgJOH

8. Ren X, Kennedy A, Colletti LM (2002) CXC chemokine expression after stimulation with interferon -gamma in primary rat hepatocytes in culture. Shock 17: 513-520. Link: https://goo.gl/YIi0uc

9. Afford C, Lalor F (2006) Cell and molecular mechanisms in the development of chronic liver inflammation in liver diseases. In: Liver diseases biochemical mechanisms and new therapeutic insights. Shakir Ali, Scott L Friedman and Derek A. Mann (eds.), 147-163.

10. Ramadori G, Saile B (2004) Inflammation, damage repair, immune cells, and liver fibrosis: specific or nonspecific, this is the question. Gastroenterology 127: 997-1000. Link: https://goo.gl/Suu6Cg

11. oMaher JJ, Lozier JS, Scott MK (1998) Rat hepatic stellate cells produce cytokine-induced neutrophil chemoattractant in culture and *in vivo*. Am J Physiol 275: G847-G853. Link: https://goo.gl/bkIXDH

12. Anthony B, Allen JT, Li YS, McManus DP (2010) Hepatic stellate cells and parasite-induced liver fibrosis. Parasites & Vectors 3: 1-7. Link: https://goo.gl/LkV81o

13. Omar HM Sanders RA Watkins III JB (1996) Minimal effect of acute experimental hepatitis induced by lipopolysaccharide/D-galactosamine on biotransformation in rats. Biochemical Pharmacolgy. Elsevier Science Inc 52: 1921-1924. Link: https://goo.gl/KHRTSl

14. Ramadori G, Moriconi F, Malik I, Dudas J (2008) Physiology and pathophysiology of liver inflammation, damage and repair. J Physiology and Pathophysiology 59: 107-117. Link: https://goo.gl/BLz5cP

15. Wallace K, Burt AD, Wright MC (2008) Liver fibrosis. Biochem J 411: 1-18. Link: https://goo.gl/Pz5AkB

16. Wynn TA, Thompson RW, Cheever AW, Mentink-Kane MM (2004) Immunopathogenesis of schistosomiasis. Immunol Rev 201: 156-167. Link: https://goo.gl/WYAdPQ

17. Grimaud JA (1987) Cell-matrix interactions in schistosomal portal fibrosis: a dynamic event. Mem Inst Oswaldo Cruz 82: 55-65. Link: https://goo.gl/ukwQhO

18. de Serres FJ (2002) Worldwide racial and ethnic distribution of alpha1-antitrypsin de ficiency: Summary of ananalysis of published genetic epidemiologic surveys. Chest 122: 1818-1829. Link: https://goo.gl/mJJGlE

19. Fairbanks KD, Tavill AS (2008) Liver Disease in Alpha 1-Antitrypsin Deficiency: A Review. Am J Gastroenterol, 103: 2136-2141. Link: https://goo.gl/V2h8FA

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

20. Nakajima T, Nakashima T, Okada Y, Jo M, Nishikawa T, et al. (2015) Parenteral fish oil-containing lipid emulsions may reverse parenteral nutrition-associated cholestasis in neonates: a systematic review and meta-analysis. *J Nutr* 145 : 277-283. Link: https://goo.gl/rK1046

21. Wood MJ, Gadd VL, Powell LW, Ramm GA, Clouston AD (2014) Ductular reaction in hereditary hemochromatosis: The link between hepatocyte senescence and fibrosis progression. Hepatology 59: 848–857. Link: https://goo.gl/BQB6Tz

22. Tomer G, Ahneider BL (2003) Disorders of bile formation and biliary transport. Gastroenterol. Clin N Am 32: 839–855. Link: https://goo.gl/2LwTmn

23. Jacques G (2009) Types of jaundices. Visual Understanding Environment (VUE). Enigma18:55.

24. Vendemiale G, Grattagliano I, Lupo L, Memeo V, Altomare E (2002) Hepatic oxidative alterations in patients with extra-hepatic cholestasis. Effect of surgical drainage. J Hepatol 37: 601-605. Link: https://goo.gl/1Gq2PG

25. Abshagen K, König M, Hoppe A, Müller I, Ebert M, et al. (2015) Pathobiochemical signatures of cholestatic liver disease in bile duct ligated mice. BMC Systems Biology 9: 83. Link: https://goo.gl/fAFnvS

26. European Association for the Study of the Liver (2009) EASL clinical practice guidelines: Management of cholestatic liver disease. Journal of Hepatology 51: 237–267. Link: https://goo.gl/B0vnkR

27. Assy N, Jacob G, Spira G, Edoute Y (1999) Diagnostic approach to patients with cholestatic jaundice. World J Gastroenterol 5: 252-262. Link: https://goo.gl/ftGxb8

28. Roelofsen H, Schoemaker B, Bakker C, Ottenhoff R, Jansen PL, et al. (1995) Impaired hepatocanalicular organic anion transport in endotoxemic rats. Am J Physiol 269: G427-434. Link: https://goo.gl/8Tv0c9

29. Moseley RH, Wang W, Takeda H, Lown K, Shick L, et al. (1996) Effect of endotoxin on bile acid transport in rat liver: a potential model for sepsis-associated cholestasis. Am J Physiol 271: G137-G146 Link: https://goo.gl/wXckJ3

30. Wang DQ-H, Cohen DE, Martin C, Carey MC (2009) Billiary lipids and cholesterol gallstone disease. J Lipid Res S406–S411. Link: https://goo.gl/mkq60R

31. Bacq Y, Zarka O, Brechot JF, Mariotte N, Vol S, et al. (1996) Liver function tests in normal pregnancy: A prospective study of 103 pregnant women and 103 matched controls. Hepatology 23: 1030–1034. Link: https://goo.gl/rxUDkP

32. Caroline A. Riely, MD, FACG (1999) Liver disease in the pregnant patient. The American Journal of Gastroenterology 94: 1728-1783. Link: https://goo.gl/jxMxkj

33. Higuchi H, Gores GJ (2003) Mechanisms of liver injury: an overview. Curr Molec Med. 3: 483–490. Link: https://goo.gl/J3Zz02

34. Gramenzi A, Caputo F, Biselli M, Kuria F, Loggi E , et al. (2006) Review article: alcoholic liver disease- pathophysiological aspects and risk factors. Aliment Pharmacol Ther 24: 1151–116. Link: https://goo.gl/ZJIvZQ

35. Ikejima K, Enomoto N, Iimuro Y, Ikejima A, Fang D, et al. (1998) Estrogen increases sensitivity of hepatic Kupffer cells to endotoxin. Am J Physiol 274: G669–676. Link: https://goo.gl/42zpW9

36. Colantoni A, Idilman R, De Maria N, La Paglia N, Belmonte J, et al. (2003) Hepatic apoptosis and proliferation in male and female rats fed alcohol: role of cytokines. Alcohol Clin Exp Res 7: 1184-1189. Link: https://goo.gl/RWbKMn

37. Crabb DW (1999) Pathogenesis of alcoholic liver disease: newer mechanisms of injury. Keio J Med 48: 184-188. Link: https://goo.gl/KQnLwW

38. Cunningham CC, Coleman WB, Spach PI (1990) The effects of chronic ethanol consumption on hepatic mitochondrial energy metabolism. Alcohol Alcohol 25:127-36. Link: https://goo.gl/y27WiA

39. Cunningham CC, Van Horn CG (2003) Energy availability and alcohol-related liver pathology. Alcohol Res Health 27: 291–299. Link: https://goo.gl/ibJU3I

40. Wu D, Cederbaum AI (2003) Alcohol, oxidative stress, and free radical damage. Alcohol Res Health 27: 277–284. Link: https://goo.gl/1XOoBY

41. Zatonski WA, Sulkowska U, Manczuk M, Rehm J, Boffetta P, et al. (2010) Liver cirrhosis mortality in Europe, with special attention to central and eastern Europe. Eur Addict Res16: 193- 201. Link: https://goo.gl/5qEd6E

42. Ceni E, Galli A, Casini A (1997) Genetics, alcohol, and cirrhosis. Ann Intern Med 126: 1000. Link: https://goo.gl/mqM4YG

43. Piao YF, Li JT, Shi Y. (2003) Relationship between genetic polymorphism of cytochrome P450IIE1 and fatty liver. World J Gastroenterol, 9: 2612–2615. Link: https://goo.gl/7KLT8y

44. Vidal F, Lorenzo A, Auguet T, Olona M, Broch M, et al. (2004) Genetic polymorphisms of ADH2, ADH3, CYP4502E1 Dra-I and Pst-I, and ALDH2 in Spanish men: lack of association with alcoholism and alcoholic liver disease. J Hepatol 41: 744–750. Link: https://goo.gl/xSDX2Q

45. Tilg H, Diehl AM (2000) Cytokines in alcoholic and nonalcoholic steatohepatitis. N Engl J Med 343: 1467–1476. Link: https://goo.gl/yozMFg

46. Hoek JB, Pastorino JG (2004) Cellular signaling mechanisms in alcohol-induced liver damage. Semin Liver Dis 24: 257–272. Link: https://goo.gl/MVmKB6

47. Anthony RS, Farquharson M, MacSween RN (1983) Liver membrane antibodies in alcoholic liver disease. II. Antibodies to ethanol-altered hepatocytes. J Clin Pathol 36: 1302-1308. Link: https://goo.gl/esd4Gb

48. Izumi N, Hasumura Y, Takeuchi J (1983) Lymphocyte cytotoxicity for autologous human hepatocytes in alcoholic liver disease. Clin Exp Immunol 54: 219-224. Link: https://goo.gl/aNqm4Y

49. Pinzani M, Rosselli M, Zuckermann M (2011) Liver cirrhosis. Best Pract Res Clin Gastroenterol 25: 281-290. Link:© https://goo.gl/I7SU0o

50. Schuppan D, Ruehl M, Somasundaram R, Hahn EG (2001) Matrix as a modulator of hepatic fibrogenesis. Sem Liver Dis 21: 351–372. Link: https://goo.gl/rzncsK

51. Benyon RC, Arthur MJ (2001) Extracellular matrix degradation and the role of hepatic stellate cells. Semin Liver Dis21: 373–384. Link: https://goo.gl/k6AIpV

52. Riordan SM, Williams R (2006) The intestinal flora and bacterial infection in cirrhosis. J Hepatol 45: 744–757. Link: https://goo.gl/FJhR42

53. Friedman SL (2000) Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. J Biol Chem 275: 2247–2250. Link: https://goo.gl/x0EmZO

54. Bissell DM, Roulot D, George J (2001) Transforming growth factor β and the liver. Hepatology 34: 859–867. Link: https://goo.gl/h4XiPB

55. Schuppan D, Krebs A, Bauer M, Hahn EG (2003) Hepatitis C and liver fibrosis. Cell Death Differ 10: S59–67. Link: https://goo.gl/RfzurE

56. Cavalcanti MG, de AraujoNeto JM, Jose Mauro Peralta JM (2015) Schistosomiasis: Clinical management of liver disease. Clinical Liver Disease 6: 59-62. Link: https://goo.gl/rIu1u5

57. Gowda C (2015) Recognizing clonorchiasis: A Foodborne illness leading to significant hepatobiliary disease. Clinical Liver Disease 6: 44-46. Link: https://goo.gl/xkJkhI

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

58. Salit IE, Khairnar K, Gough K, Pillai DR (2009) A possible cluster of sexually transmitted Entamoeba histolytica: genetic analysis of a highly virulent strain. Clin Infect Dis 49: 346-353. Link: https://goo.gl/HB9HWC

59. Adams EB, MacLeod IN (1977) Invasive amebiasis. I. Amebic dysentery and its complications. Medicine (Baltimore) 56: 315-323. Link: https://goo.gl/sq7SZw

60. Miyauchi T, Takiya H, Sawamura T, Murakami E (2005) Cardiac tamponade due to intrapericardial rupture of an amebic liver abscess. Jpn J Thorac Cardiovasc Surg 53: 206-209. Link: https://goo.gl/k43KHX

61. Anesi JA, Gluckman S (2015) Amebic liver abscess. Clinical liver disease 6: 41-43. Link: https://goo.gl/zLrKIW

62. Sombetzki M, Loebermann M, Reisinger EC (2015) Vector-mediated microRNA-21 silencing ameliorates granulomatous liver fibrosis in *Schistosoma japonicum* infection. Hepatology 61: 1787-1789. Link: https://goo.gl/ia8dZv

63. Chuah C, Jones MK, Burke ML, McManus DP, Gobert GN (2014) Cellular and chemokine-mediated regulation in schistosome-induced hepatic pathology. Trends Parasitol 30: 141-150. Link: https://goo.gl/BmjiO4

64. Barron L, Wynn TA (2011) Macrophage activation governs schistosomiasis-induced inflammation and fibrosis. Eur J Immunol 41: 2509–2514. Link: https://goo.gl/lDpHuX

65. El-Sokkary GH, Omar HM, Hassanein AF, Cuzzocrea S, Reiter RJ (2002) Melatonin reduces oxidative damage and increases survival of mice infected with Schistosoma mansoni. Free Radical Biology & Medicine, Elsevier Science Inc 32: 319-332. Link: https://goo.gl/42tZ3k

66. Khurana S, Dubey ML, Malla N (2005) Association of parasitic infections and cancers. Indian J Med Microbiol 23: 74-79. Link: https://goo.gl/Nf5PDM

67. Bhamarapravati N, Thamavit W, Vajrasthira S (1978) Liver changes in hamsters infected with a liver fluke of man, *Opisthorchis viverrini*. Am J Trop Med Hyg 27: 787-794. Link: https://goo.gl/cmepyY

68. Oshima H, Bandaletova TY, Brouet I, Bartsch H, Kirby G, et al. (1994) Increased nitrosamine and nitrate biosynthesis mediated by nitric oxide synthase induced in hamsters infected with liver fluke (*Opisthorchis vivverini*). Carcinogenesis 15: 271-275. Link: https://goo.gl/JhjoMH

69. Kirby GM, Pelkonen P, Vatanasapt V, Camus AM, Wild CP, et al. (1994) Association of liver fluke (*Opistorchis viverrini*) infestation with increased expression of cytochrome P-450 and carcinogen metabolism in male hamster liver. Mol Carcinog 11: 81-89. Link: https://goo.gl/Ubeabo

70. Wink DA, Kasprzak KS, Maragos CM, Elespuru RK, Misra M, et al. (1991) DNA deaminating ability and genotoxicity of nitric oxide and its progenitors. Science 254: 1001-1003. Link: https://goo.gl/Ujk8Yv

71. Ramachandran S, Perea MV (1976) Jaundice and hepatomegaly in primary malaria. J Trop Med Hyg 79: 207-210. Link: https://goo.gl/XLD3Bw

72. Anand AC, Pankaj P (2005) Jaundice in Malaria. J Gastroenterol and Hepatol 20: 1322-1332. Link: https://goo.gl/XQbCt4

73. Rupani AB, Amarapurkar AD (2009) Hepatic changes in fatal malaria: an emerging problem. Ann Trop Med Parasitol 103: 119-127. Link: https://goo.gl/BNxJPo

74. Ravdin JI (1995) Amebiasis. Clin Infect Dis 20: 1453-1466. Link: https://goo.gl/PC9uxN

75. Talwani R, Gilliam BL, Howell C (2011) Infectious diseases and the liver. Clin Liver Dis 15: 111–130. Link: https://goo.gl/MP4Ldd

76. Pandit A, Sachdeva T, Bafna P (2012) Drug-induced hepatotoxicity. A review. J Applied Pharmaceutical Science 02: 233-243. Link: https://goo.gl/DS8I8V

77. Kaplowitz N. (2005) Idiosyncratic drug hepatotoxicity. Nat Rev Drug Discov 4:489-99.

78. Boelsterli UA (2002) Mechanisms of NSAID-induced hepatotoxicity: focus on nimesulide. Drug Saf 25: 633–648. Link: https://goo.gl/9h19Up

79. Russmann S, Kullak-Ublick GA, Grattagliano I (2009) Current concepts of mechanisms in drug-induced hepatotoxicity. Curr Med Chem 16: 3041–3053. Link: https://goo.gl/gxrCAa

80. Robin MA, Le Roy M, Descatoire V, Pessayer D (1997) Plasma membrane cytochromes P450 as neoantigens and autoimmune targets in drug-induced hepatitis. J Hepatol 26: 23–30. Link: https://goo.gl/LLisfy

81. Rao RK, Seth A, Sheth P (2004) Recent advances in alcoholic liver disease I. Role of intestinal permeability and endotoxemia in alcoholic liver disease. Am J Physiol Gastrointest Liver Physiol 286: G881-G884. Link: https://goo.gl/dvIFfw

82. Hanck C, Rossol S, Bocker U, Tokus M, Singer MV (1998) Presence of plasma endotoxin is correlated with tumour necrosis factor receptor levels and disease activity in alcoholic cirrhosis. Alcohol Alcohol 33: 606–608. Link: https://goo.gl/Qa5BO6

83. Keshavarzian A, Holmes EW, Patel M, Iber F, Fields JZ, et al. (1999) Leaky gut in alcoholic cirrhosis: a possible mechanism for alcohol-induced liver damage. Am J Gastroenterol 94: 200–207. Link: https://goo.gl/TEW4Tp

84. Parlesak A, Schafer C, Schutz T, Bode JC, and Bode C (2000) Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. J Hepatol 32: 742-747. Link: https://goo.gl/vEIKkU

85. Boursier J and Diehl AM (2015) Implication of Gut Microbiota in Nonalcoholic Fatty Liver Disease. PLoS Pathog 11: e1004559. Link: https://goo.gl/8ERmNR

86. Kim JW, Park S, Lim CW, Lee K, Kim B (2014) The Role of Air Pollutants in Initiating Liver Disease. Toxicol Res 30: 65-70. Link: https://goo.gl/5OQicl

87. Moore JB (2010) Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the metabolic syndrome. Proc Nutr Soc 69: 211-220. Link: https://goo.gl/R0zySE

88. Kong AP, Chow CC (2010) Medical consequences of childhood obesity: a Hong Kong perspective. Res Sports Med 18: 16-25. Link: https://goo.gl/mHk7OK

89. Motlagh ME, Kelishadi R, Amirkhani MA, Ziaoddini H, Dashti M, et al. (2011) Double burden of nutritional disorders in young Iranian children: findings of a nationwide screening survey. Public Health Nutr 14: 605-610. Link: https://goo.gl/VlUwwg

90. Kelishadi R, Poursafa P (2 011) Obesity and air pollution: Global risk factors for pediatric non-alcoholic fatty liver disease. Hepat Mon 11: 794-802. Link: https://goo.gl/LUFSoq

91. Carbone1 M and Neuberger JM (2014) Autoimmune liver disease, autoimmunity and liver transplantation. J Hepatology 60: 210–223. Link: https://goo.gl/YyLBjI

92. Scorza M, Elce A, Zarrilli F, Liguori R, Amato F, et al. (2014) Genetic diseases that predispose to early liver cirrhosis. Int J Hepatology 2014: 713754. Link: https://goo.gl/skg7o2

93. Rosenstein BJ, Cutting GR (1998) The diagnosis of cystic fibrosis: a consensus statement. J Pediatr 132: 589–595. Link: https://goo.gl/A27RKQ

94. Debray D, Kelly D, Houwen R, Strandvik B, Colombo C (2011) Best practice guidelines for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros 10: S29–S36. Link: https://goo.gl/IL5GqW

95. Okada T1, Shiono Y, Kaneko Y, Miwa K, Hasatani K, et al. (2010) High prevalence of fulminant hepatic failure among patients with mutant alleles for truncation of ATP7B in Wilson's disease. Scand J Gastroenterol 45: 1232–1237. Link: https://goo.gl/1gsKme

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

96. Lalioti V, Sandoval I, Cassio D, Duclos-Vallée JC (2010) Molecular pathology of Wilson's disease: a brief. J Hepatol 53: 1151–1153. Link: https://goo.gl/Qp2Dn9

97. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS (2011) Diagnosis and management of hemochromatosis: practice guideline by the American Association for the Study of Liver Diseases. Hepatology 54: 328–343. Link: https://goo.gl/WbO4ca

98. Maillard E (2011) Epidemiology, natural history and pathogenesis of hepatocellular carcinoma. Cancer Radiother 15: 3-6. Link: https://goo.gl/E982Dm

99. Lalioti V, Sandoval I, Cassio D, Duclos-Vallée JC (2010) Molecular pathology of Wilson's disease: a brief. J Hepatol 53: 1151–1153 Link: https://goo.gl/Qp2Dn9

100. McKiernan PJ (2006) Nitisinone in the treatment of hereditary tyrosinemia type 1. Drugs 66: 743–750. Link: https://goo.gl/qH7pJZ

101. Lamperti C, Salani S, Lucchiari S, Bordoni A, Ripolone M, et al. (2009) Neuropathological study of skeletal muscle, heart, liver, and brain in a neonatal form of glycogen storage disease type IV associated with a new mutation in GBE1 gene. J Inherit Metab Dis 32: S161–S168. Link: https://goo.gl/jTb9wx

102. Higuchi H, Gores GJ (2003) Mechanisms of liver injury: an overview. Curr Molec Med 3: 483–490. Link: https://goo.gl/J3Zz02

103. Maddrey WC (2000) Hepatitis B- an important public health issue. J Med Virol 61: 362-366. Link: https://goo.gl/WYFxmK

104. Lusida MI, Surayah, Sakugawa H, Nagano-Fujii M, Soetjipto, et al. (2003) Genotype and subtype analysis of hepatitis B virus (HBV) and possible co-infection of HBV and hepatitis C virus (HCV) or hepatitis D virus (HDV) in blood donors, patients with chronic liver disease and patients on hemodialysis in Surabaya, Indonesia. Microbiol. Immunol 47: 969-975. Link: https://goo.gl/YMDLhw

105. Gambarin-Gelwan M (2013) Viral hepatitis, non-alcoholic fatty liver disease and alcohol as risk factors for hepatocellular carcinoma. Chin Clin Oncol 2: 32. Link: https://goo.gl/NAmLjv

106. Fan JG, Cao HX (2013) Role of diet and nutritional management in non-alcoholic fatty liver disease. J Gastroenterol Hepatol 28 4: 81-87. Link: https://goo.gl/4x2hD1

107. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, et al. (2001) Nonalcoholic Fatty Liver Disease: A Feature of the Metabolic Syndrome. Diabetes 50: 1844-1850. Link: https://goo.gl/K5j3vS

108. Zivkovic AM, German JB, Arun J Sanyal AJ (2007) Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. Am J Clin Nutr 86: 285-300. Link: https://goo.gl/eLTnNB

109. Thuy S, Ladurner R, Volynets V, Wagner S, Strahl S, et al. (2008) Nonalcoholic fatty liver disease in humans is associated with increased plasma endotoxin and plasminogen activator inhibitor 1concentrations and with fructose intake. J Nutr 138: 1452-1455. Link: https://goo.gl/XW5laa

110. Ragab SMM, Omar HM, Sary Kh, Abd Elghaffar, El-Metwally TH (2014) Hypolipidemic and antioxidant effects of phytochemical compounds against hepatic steatosis induced by high fat high sucrose diet in rats. Archieves of Biomedical Science 2: 1-10. Link: https://goo.gl/n9SjoM

111. Ragab SMM, Abd Elghaffar SKh, El-Metwally TH, Badr G, Mahmoud MH, et al. (2015) Effect of a high fat, high sucrose diet on the promotion of non-alcoholic fatty liver disease in male rats: the ameliorative role of three natural compounds. Lipids in Health and Disease 14: 1-11. Link: https://goo.gl/39OMrr

112. Mohany M, El-Feki M, Refaat I, Garraud O, Badr G (2012) Thymoquinone ameliorates the immunological and histological changes induced by exposure to imidacloprid insecticide. J Toxicol Sci 37: 1-11. Link: https://goo.gl/E9Zf81

113. Badr G (2012) Supplementation with undenatured whey protein during diabetes mellitus improves the healing and closure of diabetic wounds through the rescue of functional, long-lived wound macrophages. Cell Physiol Biochem 3: 571-582. Link: https://goo.gl/UF6rrT

114. Badr G (2013) Camel whey protein enhances diabetic wound healing in a streptozotocin-induced diabetic mouse model: The critical role of β-Defensin-1, -2 and -3. Lipids Health Dis 1: 12: 46. Link: https://goo.gl/LhfOsT

115. Badr G, Al-Sadoon MK, El-Toni AM, Daghestani M (2012) Walterinnasia aegyptia venom combined with silica nanoparticles enhances the functions of normal lymphocytes through PI3K/AKT, NFκB and ERK signalling. Lipids Health Dis 11: 27. Link: https://goo.gl/OxnXC4

116. Badr G, Al-Sadoon MK, Rabah DM (2013) Therapeutic efficacy and molecular mechanisms of snake (Walterinnesia aegyptia) venom-loaded silica nanoparticles in the treatment of breast cancer- and prostate cancer-bearing experimental mouse models. Free Radic Biol Med 65: 175-189. Link: https://goo.gl/bhLqnr

117. Badr G, Mohany M (2011) Maternal perinatal undernutrition attenuates T-cell function in adult male rat offspring. Cell Physiol Biochem 27: 381-390. Link: https://goo.gl/1EFAyA

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