INTRODUCTION

Glucose metabolism disorders are frequent in liver cirrhosis. The liver plays a key role in blood glucose control, thus, in the presence of chronic liver disease, the metabolic homeostasis of glucose is impaired and results in glucose intolerance and diabetes mellitus (DM) ***(Garcia-Compean et al., 2009)***.

The liver functions to maintain normal levels of blood sugar by combination of glycogenolysis, gluconeogenesis, glycogenesis and glycolysis. These pathways are regulated by a number of hormones including insulin, glucagon, growth hormone and catecholamines. The sensitivity of the hepatocytes to insulin is responsible for the blood sugar buffering effect of the liver after oral carbohydrates load. In the fasting state, the liver contributes to glucose homeostasis by glycogenolysis and gluconeogenesis in response to hypoinsulinemia and hyperglucogonemia. Maintenance of the normal blood glucose levels through gluconeogenesis is ultimately related to catabolism of muscle protein, which provides the necessary amino acids precursors, especially alanine. In a complementary fashion in the postprandial state, the liver directs branched chained amino acids to peripheral tissues, where they are incorporated into for example muscle proteins, or used as an energy source ***(Hickman et al., 2007).***

Abnormalities of glucose homeostasis are common in cirrhosis. Most frequently hyperglycemia and glucose intolerance are observed. Glucose intolerance is associated with or increased level of plasma insulin, suggesting that insulin resistance rather than insulin deficiency may be responsible ***(Garcia-Compean et al., 2012).***

Aim of the Work

To determine the frequency of diabetes mellitus and impaired glucose tolerance in chronic hepatic patients and identify risk factors.

Chapter 1

CHRONIC LIVER DISEASE

The liver is a complex multifaceted organ that plays a fundamental role in many processes crucial to bodily function. To accomplish this, the liver is populated with multiple cell types, including hepatocytes, cholangiocytes, stellate cells, endothelial cells, and cells of the immune system (i.e., Kupffer cells). Each cell type performs unique functions essential to the overall performance of the liver ***(Grandmaison et al., 2001).***

The hepatocytes are the most numerous cells within the liver, constituting approximately 80 % of the total liver volume. These cells perform numerous functions that are essential to life. The hepatocyte is the only cell in the body that manufactures albumin, fibrinogen, and the prothrombin group of clotting factors. It is the predominant site for the synthesis of lipoproteins, ceruloplasmin, transferrin, and glycoproteins ***(Cucchetti et al., 2011).***

Mitochondria constitute about 20 % of the volume of the hepatocyte and are responsible for cellular respiration. They are the site of the tricarboxylic acid (TCA) cycle, fatty acid oxidation, and oxidative phosphorylation. Additionally, they participate in the urea cycle, fatty acid synthesis, gluconeogenesis, regulation of intracellular calcium, and heme

biosynthesis and play a key role in apoptosis ***(Schmelzer et al., 2001).***

Other liver cell types include endothelial cells, as well as fenestrated sinusoids; stellate cells, which normally function in vitamin A storage; biliary epithelial cells; and cells of the immune system, including lymphocytes and resident macrophages (Kupffer cells) ***(Kaneko et al., 1999).***

Chronic liver disease:

Definition:

Chronic liver disease in the clinical context is a disease process of the liver that involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis. "Chronic liver disease" refers to disease of the liver which lasts over a period of six months ***(NHS Choices, 2015).***

Pathophisiology:

Injured hepatocytes may show several potentially reversible changes, such as accumulation of fat and bilirubin (cholestasis); when injury is not reversible, hepatocytes die by necrosis or apoptosis. Necrosis is commonly seen following hepatic injury caused by hypoxia and ischemia. Apoptotic cell death predominates in viral, autoimmune, and drug- and toxin-induced hepatitides.

Widespread death of hepatocytes may produce *confluent necrosis*. This may be seen in acute toxic or ischemic injuries or in severe chronic viral or autoimmune hepatitis. Confluent necrosis begins as a zone of hepatocyte dropout around the central vein ***(Gouw et al., 2011).***

In longstanding chronic liver diseases, there is clear evidence that stem cell proliferation and differentiation make significant contributions to parenchymal restoration, probably following the replicative senescence of preexisting hepatocytes. The differentiating progeny of these tissue stem cells produce duct-like structures, called *ductular reactions,* a morphologic marker of stem cell–mediated liver regeneration ***(Kocabayoglu et al., 2013).***

Scar formation may follow very severe acute injury, but occurs more often as a reaction to chronic injury. The principal cell type involved in scar deposition is the perisinusoidal hepatic stellate cell. Following liver injury, stellate cells may become activated and convert into highly fibrogenic myofibroblasts, which produce the fibrous scar. Stellate cell activation involves complex interactions between Kupffer cells, hepatocytes, and inflammatory cells. When there is severe injury that causes death of large number of hepatocytes and the drop out of liver cells, there may be collapse of the underlying reticulin, precluding orderly regeneration of hepatocytes ***(Clouston et al., 2011).***

In such cases, there is activation of stellate cells, and the areas of liver cell loss are replaced by fibrous septae. Eventually, these fibrous septa encircle surviving, regenerating hepatocytes in late-stage chronic liver disease, many forms of which are described as *cirrhosis* ***(Friedman et al., 2013).***

Disorders Producing Chronic Hepatitis and/or cholestasis in children:

Table (1): Causes of chronic hepatitis and cholestasis in children.

1)Infectious Viral	Herpes simplex Varicella zoster Cytomegalovirus Adenovirus Enterovirus Hepatitis B Hepatitis C Rubella Parvovirus B19 Human immunodeficiency virus (HIV)
Bacterial	Syphilis Listeria Septicemia Pyogenic liver abscess
Fungal	Hepatosplenic candidiasis
Protozoal	Malaria Toxoplasmosis Congenital Chagas disease
2)Immune	Neonatal hemochromatosis Hemophagocytic lymphohistiocytosis Neonatal lupus Autoimmune hemolytic anemia with giant cell hepatitis Erythroblastosis fetalis Graft versus host syndrome Autoimmune hepatitis

3)Nutritional/toxic	TPN/intestinal failure Drugs/toxins/herbals Indian childhood cirrhosis
4)Metabolic	Tyrosinemia type 1 Galactosemia Organic acidemias Urea cycle disorders Fatty acid oxidation defects Cholesterol synthesis defects Mitochondrial/respiratory chain defects Congenital defects of glycosylation Bile acid synthesis defects Peroxisomal defects Niemann-Pick type C Lysosomal storage diseases Mucopolysaccharidoses Alpha 1-antitrypsin deficiency Cystic fibrosis Defects of biliary transport (PFIC) Wilson's disease
5)Syndromic	Trisomy 21 Trisomy 18 Trisomy 13 Cat-eye syndrome Alagille syndrome COACH syndrome Joubert syndrome Beckwith-Wiedemann syndrome North American Indian childhood cirrhosis Cri-du-chat syndrome GRACILE syndrome McCune-Albright syndrome Septo-optic dysplasia Smith-Lemli-Opitz syndrome
6)Endocrine	Panhypopituitarism Hypothyroidism Hypoadrenalism Hyperinsulinism
7)Cardiovascular	Ischemic hepatitis Heart failure Budd-Chiari

8)Neoplastic	Langerhans cell histiocytosis Hepatoblastoma Leukemia Other primary or metastatic liver Tumors

Clinical Manifestations:

Hepatomegaly

In children, the normal liver edge can be felt up to 2 cm below the right costal margin. In a newborn infant, extension of the liver edge more than 3.5 cm below the costal margin in the right midclavicular line suggests hepatic enlargement ***(Balistreri et al., 2007).***

Jaundice (Icterus)

Yellow discoloration of the sclera, skin, and mucous membranes is a sign of hyperbilirubinemia. Clinically apparent jaundice in children and adults occurs when the serum concentration of bilirubin reaches 2-3 mg/dL; the neonate might not appear icteric until the bilirubin level is >5 mg/dL. Jaundice may be the earliest and only sign of hepatic dysfunction ***(Balistreri et al., 2000).***

Pruritus:

Intense generalized itching can occur in patients with chronic liver disease often in association with cholestasis (conjugated hyperbilirubinemia).

Symptoms can be generalized or localized (commonly to palms and soles), are usually worse at night, are exacerbated with stress and heat, and are relieved by cool temperatures. Pruritus is unrelated to the degree of hyperbilirubinemia; deeply jaundiced patients can be asymptomatic. ***(Bunchorntavakul et al., 2012)***

Spider Angiomas

Vascular spiders (telangiectasias), characterized by central pulsating arterioles from which small, wiry venules radiate, may be seen in patients with chronic liver disease; these are usually most prominent in the superior vena cava distribution area (on the face and chest) ***(Garcia-Tsao et al., 2001)***.

Their size varies between 1 and 10 mm and they exhibit central clearing with pressure ***(Gugig et al., 2012).***

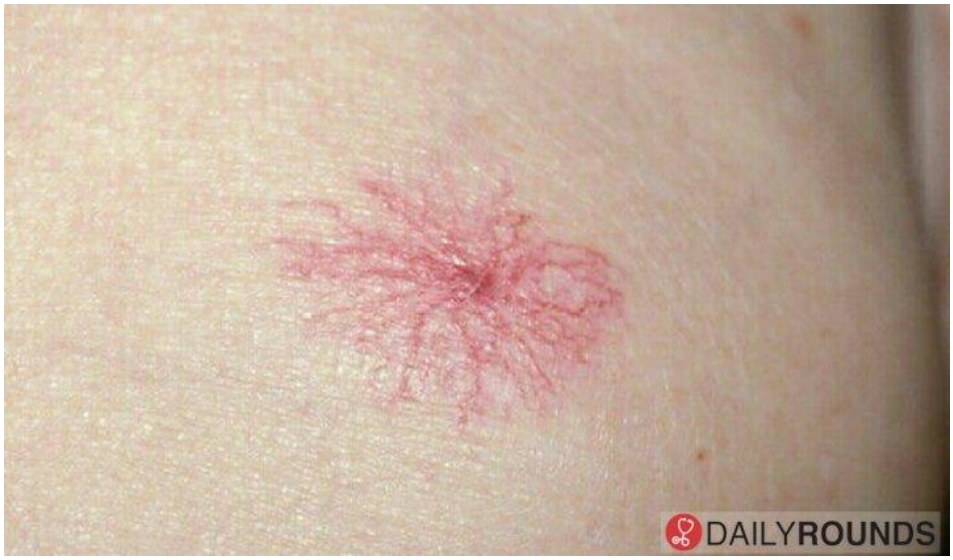

Figure (1): Spider angiomas.

Palmar Erythema

Blotchy erythema, most noticeable over the thenar and hypothenar eminences and on the tips of the fingers, is also noted in patients with chronic liver disease. Abnormal serum estradiol levels and regional alterations in peripheral circulation have been identified as possible causes ***(Jensen et al., 2013).***

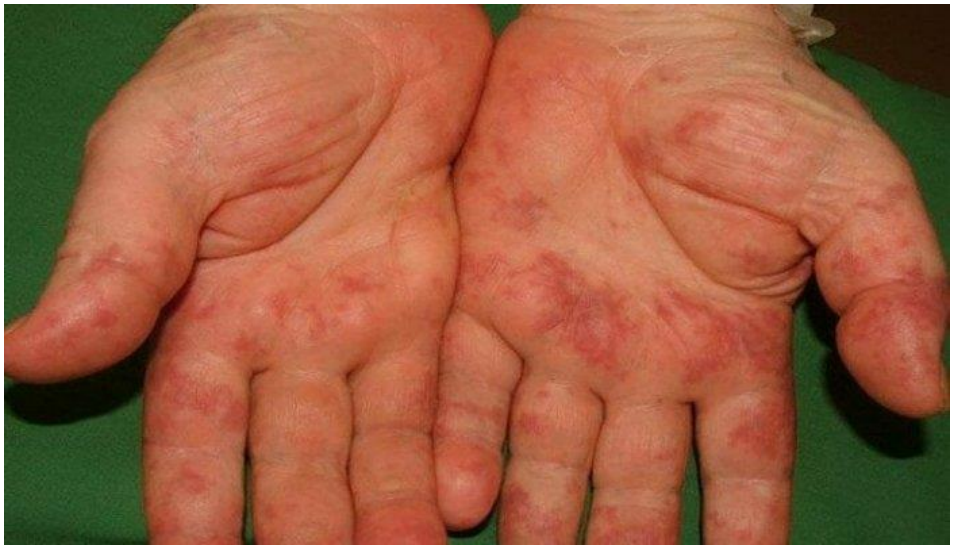

Figure (2): Palmar erythema.

Xanthomas

The marked elevation of serum cholesterol levels (to >500 mg/dL) associated with some forms of chronic cholestasis can cause the deposition of lipid in the dermis and subcutaneous tissue. Brown nodules can develop, first over the extensor surfaces of the extremities; rarely, xanthelasma of the eyelids develops ***(Bezerra et al., 2001).***

Complications of chronic liver disease:

Portal Hypertension

Portal hypertension occurs when there is increased portal resistance and/or increased portal flow. The portal system drains the splanchnic area (abdominal portion of the gastrointestinal tract, pancreas, and spleen) into the hepatic sinusoids. Normal portal pressure is between 3 and 6 mm Hg. Portal hypertension is defined as a portal pressure greater than 10 mm Hg. Clinically significant portal hypertension exists when pressure exceeds a threshold of 12 mm Hg or greater ***(Gugig et al., 2012).***

Portal hypertension is the main complication of cirrhosis, directly responsible for 2 of its most common and potentially lethal complications: ascites and variceal hemorrhage ***(Ryckman et al., 2001).***

Gastrointestinal Bleeding

Chronic liver disease may manifest as gastrointestinal hemorrhage. Bleeding may result from portal hypertensive gastropathy or varix rupture. Variceal hemorrhage is classically from an esophageal origin but may be caused by gastric, duodenal, peristomal, or rectal varices. It results from increased pressure within the varix, which leads to changes in the diameter of the varix and increased wall tension. When the variceal wall strength is exceeded, physical rupture of the varix results. Given the high blood flow and pressure in the

portosystemic collateral system, coupled with the lack of a natural mechanism to tamponade variceal bleeding, the rate of hemorrhage can be striking ***(Ryckman et al., 2001).***

Encephalopathy

Hepatic encephalopathy can involve any neurologic function, and it can be prominent or present in subtle forms such as deterioration of school performance, sleep disturbances, depression, or emotional outbursts. It can be recurrent and precipitated by intercurrent illness, drugs, bleeding, or electrolyte and acid-base disturbances. The appearance of hepatic encephalopathy depends on the presence of portosystemic shunting, alterations in the blood–brain barrier, and the interactions of toxic metabolites with the central nervous system. Postulated causes include altered ammonia metabolism, synergistic neurotoxins, decreased cerebral oxygen metabolism and blood flow, or false neurotransmitters with plasma amino acid imbalance ***(Balistreri et al., 2000).***

Endocrine Abnormalities

Endocrine abnormalities are more common in adults with hepatic disease than in children. They reflect alterations in hepatic synthetic, storage, and metabolic functions, including those concerned with hormonal metabolism in the liver. Proteins that bind hormones in plasma are synthesized in the liver, and steroid hormones are conjugated in the liver and excreted in the urine ***(Gugig et al., 2012).***

Renal Dysfunction

Systemic disease or toxins can affect the liver and kidneys simultaneously, or parenchymal liver disease can produce secondary impairment of renal function. In hepatobiliary disorders, there may be renal alterations in sodium and water economy, impaired renal concentrating ability, and alterations in potassium metabolism. Ascites in patients with cirrhosis may be related to inappropriate retention of sodium by the kidneys and expansion of plasma volume, or it may be related to sodium retention mediated by diminished effective plasma volume ***(Satapathy et al., 2011).***

Hepatorenal syndrome is defined as functional renal failure in patients with end-stage liver disease. The pathophysiology of hepatorenal syndrome is related to splanchnic vasodilation, mesenteric angiogenesis, and decreased effective blood volume with resulting decreased renal perfusion. The hallmark is intense renal vasoconstriction (mediated by hemodynamic, humoral, or neurogenic mechanisms) with coexistent systemic vasodilation. The diagnosis is supported by the findings of oliguria (<1 mL/kg/day), a characteristic pattern of urine electrolyte abnormalities (urine sodium < 10 mEq/L, fractional excretion of sodium of <1%, urine: plasma creatinine ratio <10, and normal urinary sediment), absence of hypovolemia, and exclusion of other kidney pathology. The best treatment of hepatorenal syndrome is timely liver transplantation, because complete renal recovery can be expected ***(Satapathy et al., 2011).***

Pulmonary Involvement

Hepatopulmonary syndrome is characterized by the typical triad of hypoxemia, intrapulmonary vascular dilations, and liver disease. There is intrapulmonic right-to-left shunting of blood resulting from enlarged pulmonary vessels that prevents red blood cells traveling through the center of the vessel adequate exposure to oxygen-rich alveoli. Shunting of vasodilatory mediators from the mesentery away from the liver is thought to contribute. It should be suspected and investigated in the child with chronic liver disease with history of shortness of breath or exercise intolerance and clinical examination findings of cyanosis (particularly of the lips and fingers), digital clubbing, and oxygen saturations <96%, particularly in the upright position. Treatment is timely liver transplantation; resolution of pulmonary involvement usually follows ***(Bunchorntavakul et al., 2012).***

Some causes of chronic liver disease:

Wilson's disease:

Definition:

Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder that can be associated with degenerative changes in the brain, liver disease, and Kayser-Fleischer rings in the cornea ***(Menchise et al., 2016).***