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A Study on Functions of Liver to Sustain a Healthy Liver

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Abstract

The liver is the largest internal gland that has many important roles within the body. In an adult human it weighs between 1.5 and 2kg. It is divided into right and left lobes; the right lobe being larger than the left. It is located in the right upper quadrant of the abdomen and spans across the midline to the left upper quadrant. It plays an important role through the maintenance of blood glucose levels, and metabolizing drugs and toxic substances. It is an accessory organ in digestion, and also undertakes several metabolic processes, such as bile production, bilirubin synthesis; and protein, lipid, and carbohydrate metabolism. It has a remarkable capacity to regenerate its injured tissues. This study aims to provide an overview of function of the liver.

Keywords: liver functions, physiology, hepatocytes, metabolism

1. Introduction

The liver is the largest solid internal visceral vital organ of the body that carries out a complex array of functions. It is considered as the site of the soul, and the central place of all forms of mental and emotional activity. It is the powerhouse of the body for metabolism and a center for numerous physiological processes (Mohajan, 2024a, b). It is also an accessory organ of the gastrointestinal tract. ICentral functions of it are metabolism of nutrients and excretion of waste metabolites. It also performs protein, lipid, and carbohydrate metabolism (Jastrow, 1908).

The liver accomplishes many complex functions, such as metabolic homeostasis of many hormones in the systemic circulation, synthesizing virtually all plasma proteins, and serving as a nexus for myriad immune functions that balances innate and adaptive immunity to control tolerance and inflammation (Ebrahimkhani et al., 2014). Moreover, it is the only organ in the body that can regenerate itself. The functional unit of the liver is known as a “hepatic lobule” (0.8 to 2 mm in diameter) that is hexagonal in cross-section and contains a central vein from which cords of hepatocytes radiate outwards, and serve as the functional units of the liver. Hepatocytes have a unique ability to proliferate in response to any type of liver injury (Katawala, 2024).

At present acute and chronic liver diseases are increasing due to virus infection, pharmacological drug consumption, poor diet and lifestyle, alcoholism, cancer metastasis, and some other factors (LeCluyse et al., 2012). The liver comprises of five distinct cell types: hepatocytes (the largest cell mass that is about 60-80% of the cytoplasmic mass within human liver tissue), sinusoidal lining cells, such as endothelial cells, Kupffer cells, stellate cells, and cholangiocytes (the bile duct epithelial cells). Each type of cells possesses unique tasks and functions that collectively contribute to the overall support and functionality of the organ function at multiple levels (Zhao & Duncan, 2005).

The endothelial cells that line the sinusoids have large fenestrae, which provide a graded barrier between the sinusoid and space of Disse. The size of the fenestrae determines the exchange of fluids and size of molecules that can pass from the plasma into the space of Disse and the basolateral surface of the hepatocyte (Ohtani & Ohtani, 2008). About 25-30% of the cardiac output is directed to the liver which exceptionally receives both arterial blood from the hepatic artery. The portal vein supplies about 70-75% of hepatic blood flow that takes

directly from the gut (Mitra & Metcalf, 2009).

2. Literature Review

The literature review section is an introductory unit of research, which exhibits the works of previous researchers in the same field within the existing knowledge (Polit & Hungler, 2013). It often behaves with a secondary research source and does not study about future research work (Gibbs, 2008). Komang Trisna Sumadewi has provided an academic and comprehensive overview of the embryology, anatomy, and function of the liver (Sumadewi, 2023). Tasneem Katawala has discussed some physiology of liver, such as blood supply, protein catabolism, bile production; and metabolism of carbohydrate, protein, lipid, and bilirubin (Katawala, 2024). Zaenah Zuhair Alamri has shown that the liver maintains blood glucose levels during fasting by releasing glucose from glycogen and synthesizing glucose from amino acids (Alamri, 2018).

Mohammad Ebrahimkhani and his coauthors have provided perspective on the evolving landscape of bioreactor-based models to meet old and new challenges in drug discovery and development. They have emphasized on the design challenges in maintaining long-term liver-specific function and have tried to show how emerging technologies in biomaterials and micro-devices are providing new experimental models (Ebrahimkhani et al., 2014). Jevas C. Ozougwu has summarized various liver functions, such as secretion of bile, metabolism of bilirubin; synthesize of prothrombin, fibrinogen, and clotting factors; metabolism of nutrients; and storage of minerals and vitamins (Ozougwu, 2017).

Elijah Trefts and his coauthors have expressed that the liver is a critical hub for numerous physiological processes, such as macronutrient metabolism, blood volume regulation, immune system support, endocrine control of growth signaling pathways, lipid and cholesterol homeostasis, and the breakdown of xenobiotic compounds. They have stressed that it is important to emphasize that insight into hepatic pathologies and potential therapeutic avenues to treat these conditions requires an understanding of the development and physiology of specialized hepatic functions (Trefts et al., 2017).

3. Research Methodology of the Study

Research is the procedures of systematic investigations that requires collection, interpretation and refinement of data, and ultimately prepares an acceptable article, working paper, book chapter or a thesis by the appropriate use of human knowledge (Pandey & Pandey, 2015). Methodology is a guideline for the accomplishment of a good research (Kothari, 2008). Therefore, research methodology is the specific procedures that are used to identify, select, process, and analyze materials related to the topics (Somekh & Lewin, 2005).

In this study we have stressed on the secondary data sources. The valuable information of our research is collected from the published and unpublished data sources. We have used various research resources, such as journal articles, books written by famous authors, internet, websites, etc. to furnish our research fruitfully (Mohajan, 2017, 2018, 2020).

4. Objective of the Study

Main objective of this article is to discuss the functioning of liver. The liver is the largest internal solid organ in the body. It is considered as the centre for metabolism of nutrients and excretion of waste metabolites. At present the liver diseases, such as viral hepatitis, alcoholic fatty liver, non-alcoholic fatty liver, liver fibrosis, cirrhosis, and liver failure become major causes of morbidity and mortality worldwide (Mohajan, 2024e). Other minor objectives of the study are as follows:

- to focus on metabolism of liver,
- to highlight on endocrine functions, and
- to identify immunological functions.

5. An Overview of Liver

Liver is a wedge or cone shaped with the base on the right and the apex to the left. It is the largest internal organ in the body that weighs approximately 1500g, which is about 2.5% of adult body weight. It lies mainly in the right hypochondrium and epigastrium and extends into the left hypochondrium up to left lateral line (Ramachandran & Kumar, 2019). It is divided mainly into two lobes by the falciform ligament that connects the liver to the diaphragm and the anterior abdominal wall. These two lobes are right lobe and left lobe, of which right lobe is larger (about six times) than the left lobe. Additionally, the liver has quadrate and caudate lobes. It is protected by the rib cage and maintains its position through peritoneal reflections (Juza & Pauli, 2014). It has two main blood sources: i) the hepatic portal vein that transports nutrient-rich blood from the digestive system, and ii) the hepatic artery delivers oxygenated blood from the heart to the liver (Mohajan, 2024d).

6. Functions of the Liver

The liver performs a group of essential functions of the body, such as vascular, immunological, metabolic, and

secretory and excretory functions (Alamri, 2018). It plays an active role during digestion through the production of bile that is a mixture of water, bile salts, drugs and hormones, cholesterol, and the pigment bilirubin. The liver also acts as a temporary warehouse to store excessive amounts of nutrients and releases them at the time of need, such as fasting (Kalra et al., 2022). The functions of liver in brief are metabolism of carbohydrates, proteins and fat; storage of glycogen, vitamins (e.g., A, D, E, C), minerals (e.g., iron and copper); detoxification of drugs and toxins; excretion of bile and urea; reservoir of blood; filtration of bacteria, degradation of endotoxins and lactate metabolism; immunological functions with synthesis of immunoglobulins and phagocytic action by Kupffer cells; and Hematopoiesis in the fetus (Katawala, 2024).

Liver performs a wide range of vital functions, such as blood detoxification and purification; synthesis of plasma proteins; production of bile; the metabolism of carbohydrates, fats and proteins, etc. It is the only organ that has the extraordinary property of self-regeneration. If a part of the liver is removed, the remaining parts can grow back to its original size and shape (Ozougwu, 2014). Blood enters the lobules through branches of the portal vein and hepatic artery, and it flows through liver sinusoids toward the central vein (Ebrahimkhani et al., 2014). Liver function can be evaluated by various methods, employing imagery, liver biopsies, and blood tests (Schwenzer et al., 2009).

6.1 Functions of the Hepatocytes

The liver comprises of five distinct types cells: hepatocytes cells, sinusoidal endothelial cells, such as Kupffer cells, stellate cells, and cholangiocytes (Figure 1). Each type of cells possesses unique tasks and functions that collectively contribute to the overall support and functionality of the organ (Sumadewi, 2023). Hepatocytes are the main parenchymal cells of the liver that make up about 80% of the mass of the liver but 50-60% of total liver cell number (Singh, 2007). These are relatively large, mitochondrial and Golgi-rich cells as well as lysosomes and peroxisomes, and organized into epithelial plates and perform many of the functions ascribed to the liver (Wanson et al., 1979). These are cubical with sides of 20-30 nm (nanometer), and a typical volume of a hepatocyte is 3.4×10^{-9} cm^3 (Trefts et al., 2017).

The hepatocytes are the only cells in the body that produce albumin, fibrinogen, and the prothrombin group of clotting factors (Jeejeebhoy & Phillips, 1976). These are the main sites for the synthesis of lipoproteins, ceruloplasmin, transferrin, and glycoproteins. These synthesize lipoproteins, ceruloplasmin, transferrin, complement, and glycoproteins (Pavelka & Roth, 2015). These are the predominant cellular constituents of the liver that are responsible for the majority of hepatic functions, such as encompassing the synthesis and storage functions, and the filtering of blood from the portal vein (Trefts, 2017). The bile is produced in hepatocytes of the liver and then stored in the gallbladder. The hepatocytes also do some essential functions of liver, such as synthesis and storage of serum proteins; intermediary metabolism of amino acids, and carbohydrates; synthesis of lipids, bile salts and phospholipids; and detoxification, modification and excretion of exogenous and endogenous substances (Dunn et al., 1989). Numerous xenobiotics are metabolized by the mixed functions of mono-oxidases found in hepatocytes (Sirica & Pitot, 1979).

6.2 Functions of Sinusoidal Lining Cells

Radial spaces between the hepatocytes are called sinusoids and carry mixed hepatic arterial and portal venous blood towards centre of the lobule (Katawala, 2024). Sinusoidal endothelial cells comprise 15-20% of total liver cells and form a fenestrated endothelium that is unique among capillary beds (Ebrahimkhani et al., 2014).

Cholangiocytes: The cholangiocytes are identified as the second most prevalent cell type within the liver that form the biliary tree and serve the purpose of lining the lumen of the bile ducts. These collect the bile produced by hepatocytes and channel it to the gallbladder (Tam et al., 2018).

Kupffer Cells: The Kupffer cells are resident liver macrophages that comprise 8-12% of total liver cells in the body and reside within the hepatic sinusoids where they act as one of the first lines of defense against antigens passing through the gastrointestinal barrier (Basit et al., 2020). These are located within the sinusoid and are in constant contact with gut-derived particles that lead to low but constant amount of activation of these monocyte derived cells (Smedsrod et al., 1985). These are a distinct population of hepatic cells that possess specialized immune response and phagocytic activity functions, such as macrophages, bile canaliculi, and form a narrow gap between sinusoids and hepatocytes (Dixon et al., 2013). These have receptors that enable them to bind cells covered with immunoglobulins or bind to complement receptors and subsequently phagocytose cell (Figure 1). These actively remove macromolecules and particulate matter from the bloodstream, including old cells, foreign particles, tumor cells, bacteria, yeast, viruses, and parasites (Knook et al., 1977). Therefore, these can serve as a protective barrier against infection (Nguyen-Lefebvre & Horuzsko, 2015). These are even actively phagocytic in vitro and contain high levels of peroxidase, acid phosphatase and glucose 6-phosphate dehydrogenase (Munthe-Kaas et al., 1976). These also recycle hemoglobin by destroying senescent red blood cells through phagocytic action. These are integral in the innate responses of the immune system (Dixon et al., 2013). These

are able to secrete a vast range of inflammatory mediators, such as cytokines, reactive oxygen species, eicosanoids and nitric oxide (Knook et al., 1977).

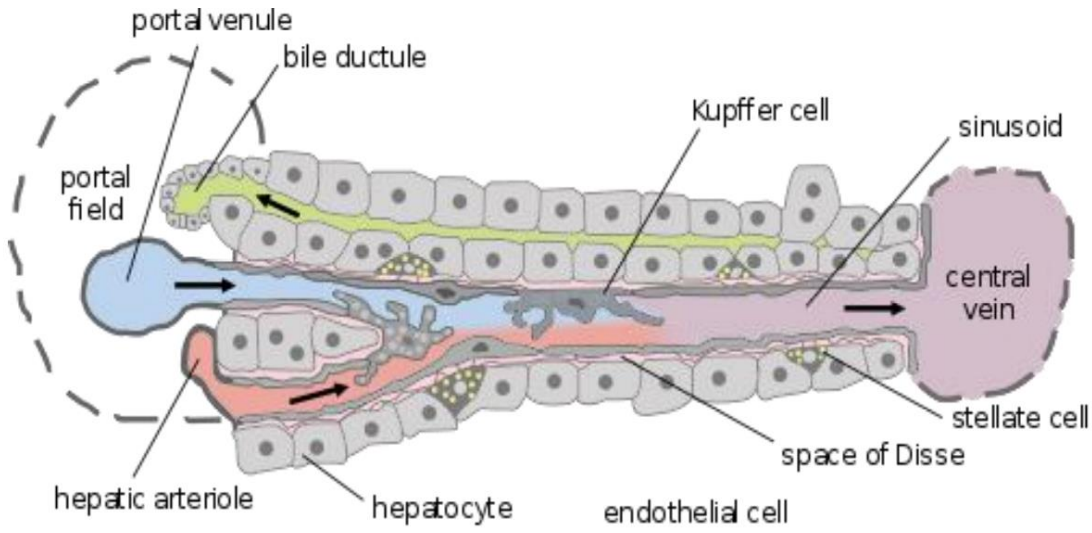

Figure 1. Different types of liver cells: Source: Ozougwu, (2017)

Stellate Cells: The stellate cells are derived from dividing progenitor cells in the white matter of postnatal cerebellum. These are neurons in the central nervous system (Figure 1). These represent a dynamic cell population that can exist in a quiescent or activated state (Rubenstein, 2013). The stellate cells, also called lipocytes or Ito cells, are smaller, and lie within the space of Disse, encircling the sinusoidal endothelium. These not only proliferate, but also produce increased amounts of extracellular matrix per cell (Kmiec, 2001). These generally protrude to come into contact with several sinusoids (Knook et al., 1982). These are involved in the progression of liver fibrosis, as they contribute to the organization of collagen within the diseased liver. During the quiescent state, these are the major storage site for vitamin A within lipid droplets that represents a key factor in regulation of immune responses (Costa & Kevan, 2011). Transforming growth factor leads to a higher transcriptional rate of mRNAs coding for extracellular matrix components, such as collagen I, fibronectin, and proteoglycans (Butura, 2008).

The liver plays a central role in uptake and storage of vitamins A and stores about 95% of retinoids found in the body. In the resting state, the stellate cells resemble fibroblasts but their cytoplasm contains numerous droplets in which vitamin A is stored. Upon activation, stellate cells elongate to resemble myocytes and exhibit contractile function that plays a role in regulation of sinusoidal tone and resistance, and progressively lose vitamin A stores (Chan-Palay, 1972). Stellate cells are also responsible for deposition and organization of collagen in the injured liver. This process contributes to scarring of the liver, which can progress to cirrhosis, a critical pathology contributing to end stage liver disease (Trefts et al., 2017). These function to control the turnover of extracellular matrix and regulate sinusoid contractility. These may become activated under stressful conditions and transformed into myofibroblast that play a key role in inflammatory fibrotic response (Kmiec, 2001).

Endothelial Cells: The sinusoidal endothelial cells have large fenestrae that provide a graded barrier between the sinusoid and space of Disse. These are a specialized endothelial population with unique characteristics (Butura, 2008). These cells form fenestrated sieve plates at the sinusoidal lumen. The size of the fenestrae (50-180nm in humans) determines the exchange of fluids and size of molecules that can pass from the plasma into the space of Disse and the basolateral surface of the hepatocyte (Figure 1). The endothelial cells have essential roles in the maintenance of hepatic homeostasis, such as regulation of the vascular tone, inflammation and thrombosis, and for controlling hepatic immune response (Gracia-Sancho et al., 2021). In general, the endothelial cells engulf smaller size particles and may play a role in clearance of viruses, but do not possess phagocytic function (Knook et al., 1977). These also have large endocytic capacity for extracellular matrix components and immune complexes. These may function as antigen presenting cells and secrete certain cytokines and eicosanoids (Kmiec, 2001).

6.3 Metabolism of Nutrients

6.3.1 Metabolism of Vitamins and Minerals

The liver absorbs and stores certain vitamins and minerals through the hepatocytes and releases them in

durations of need. The excess nutrients in the blood are glycogen; minerals, such as iron and copper; vitamins A, D, E, K and B_{12}, and release them when levels are very low (Ajjawi, 2022). The liver can store vitamins B_{12} and D for several months and vitamin A for several years. Iron is stored in the liver as ferritin, an iron-protein complex, and is released as needed for red blood cell production (Ozougwu, 2014).

6.3.2 Metabolism of Fat

Fat is synthesized from carbohydrate and protein, primarily in the liver. In the liver, fatty acids are used to synthesize triglycerides that are packed into very low density lipoprotein (VLDL). Also, fat is absorbed by lacteals in the intestinal villi and then enters the liver through the lymphatics as triglycerides (Ozougwu, 2017). In the liver the triglycerides can be hydrolyzed to glycerol and free fatty acids (FFA) and used to produce metabolic energy adenosine triphosphate (ATP). These FFA are also stored in the liver after conversion to neutral fat or can be released into the bloodstream as lipoprotein (Dijkstra et al., 2008). The lipoproteins are carried out by the blood to adipose cells for storage. These are made up of cholesterol, triglycerides, and proteins, which are transported to adipose tissue to be stored there (Stryer, 1995).

6.3.3 Protein Synthesis

Protein metabolism is a process in which proteins are broken down into smaller pieces. The liver has a central role in both protein metabolism and anabolism. It is responsible for 85-90% of circulating protein volume. It removes free amino acids, the end product of dietary protein digestion and cellular protein breakdown, from blood for gluconeogenesis and protein synthesis (Morris, 2002). The α-amino group is transformed into ammonia and combined into urea (about 80%) to be excreted in the urine through kidneys. A small amount (about 10%) is transformed by colonic bacteria into ammonia that may be important in de novo protein synthesis in the body during starvation. The other part of urea (about 10%) is excreted in the faeces (Rostom & Shine, 2018). Urea cycle enzymes in liver are regulated by glucagon, insulin, and glucocorticoids (Morris, 2002).

There are three main types of proteins: Albumin, globulin, and fibrinogen (Katawala, 2024). Albumin is one of the most found plasma protein that depict about 50% of the total plasma protein in our body on average, which is responsible for maintaining colloidal osmotic pressure and blood volume. It possesses carrier functions in transporting a number of critical molecules, such as lipids and hormones. It transports fatty acids and steroids to maintain correct pressure and prevent leakage of blood vessels. It maintains the oncotic pressure and maintains the body vascular volume. This protein consists of 585 amino acids and encoded by a gene molecular weight of 66 kDa on 4 chromosomes that is solely produced by liver cells. Albumin synthesis is an important function of the liver. When the functioning capacity of the liver decreases; the albumin level also decreases (Emma, 2022).

The majority of the plasma proteins (about 25% of all protein) except the immunoglobulin are produced by the liver; mainly in hepatocyte cells. About 12g of these including albumin are produced each day by the rough endoplasmic reticulum (RER). The liver cell also produces certain carrier proteins, such as transferrin, the transcobalamins, caeruloplasmin, and transcortin, and a variety of α_1 antitrypsin, α_2 macroglobulin, complement factors and haptoglobins, and β globulins that bind and conserve free haemoglobin (Rothschild et al., 1969).

The liver also synthesizes several non-essential amino acids and serum enzymes including aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and alkaline phosphatase (Ozougwu, 2017).

6.3.4 Protein Catabolism

Protein catabolism is the breakdown of proteins into smaller peptides and ultimately into amino acid that is important for digestion and absorption. It begins with pepsin, which converts proteins into polypeptides through the digestive enzymes (Gurina et al., 2022). This process begins in the stomach and continues in the small intestine. The nitrogenous end-product of amino acid degradation is ammonia that is a toxic end product and is eliminated from the body as urea. Creatinine is also synthesized in the liver from methionine, glycine and arginine; and is excreted in urine (Bauman et al., 2004).

6.3.5 Carbohydrates Metabolism

The liver makes the stability of blood glucose levels by releasing glucose during states of hypoglycemia and taking up glucose during states of hyperglycemia, and storing it as glycogen or converting it to fat (Ozougwu, 2017). Metabolism of carbohydrates is needed for keeping glucose levels stable in the body. The liver plays a critical role by maintaining concentrations of glucose to its normal level through the controlling metabolism of carbohydrates (Emma, 2022). It absorbs monosaccharaides, such as glucose, galactose, fructose, etc. After taking meal, glucose is produced and released in high level in blood by the portal system (more than 10nm). Two to three hours after the meal, blood glucose concentrations drops to the normal level, and later glycogen is synthesized and stored in the liver (Mitra & Metcalf, 2009).

A healthy liver normally contains about 100g of glycogen, and during fasting when glucose levels decreased this glycogen can be broken down into glucose and ketone bodies to release as free glucose into the bloodstream that

can be transported to other tissues for generating energy in the form of adenosine triphosphate (ATP) (Ajjawi, 2022).

During lengthy starvation, the liver glycogen reserve is depleted; the liver synthesizes glucose from amino acids, lactate, and glycerol to build up glycogen reserves in the body (Bechmann et al., 2012). Liver is also a major site for glycogen storage, glycogenolysis and gluconeogenesis when glycogen stores are depleted. Lactate is generated from glycogen breakdown in muscles and then transported to liver to be converted into pyruvate and then used in gluconeogenesis (Katawala, 2024).

6.4 Bile Production

Bile is an alkaline, bitter-tasting, yellowish green fluid that contains bile salts, cholesterol, bilirubin, electrolytes and water. It is stored in gall bladder and is discharged into small intestine through the bile duct. It is formed by hepatocytes and secreted into the canaliculi (Ozougwu, 2017). In quantity basis bile is primarily composed of water (95-98%) and also contains a number of endogenous solid, such as bile salts (0.7%), bilirubin, enzymes bilirubin phospholipid (0.2%), 0.51% fats (cholesterol, fatty acid, lecithin), 200 meq/L inorganic salts, electrolytes, and a small amount of heavy metals, amino acids, porphyrins, steroids, etc. (Puestow, 1931).

In an adult human, the liver assists intestinal digestion by secreting 700 to 1200ml of bile per day that passes into the gallbladder and gets concentrated to one-fifth of its original volume (Barrett et al., 2012). If bile does not develop, clotting factors will not be produced. Bile is produced by hepatocytes that are secreted into the canaliculi, and flows in a centrifugal direction to drain into a branch of the bile duct located in the corner of the lobule. The bile duct transports bile from the liver to the gallbladder, where it is concentrated and stored (Ajjawi, 2022). Bile acids are produced in the liver from cholesterol that serve as emulsifiers and form micelles. Bile is used for excess cholesterol excretion. Bile salts, which are conjugated bile acids, are required for the intestinal emulsification and absorption of fats. These are important for emulsification of fat and absorption of the fat soluble vitamins A, D, E, and K (Katawala, 2024). In the absence of bile, fats become indigestible and are instead excreted in feces as steatorrhea that leads to deficiencies in essential fatty acids and fat-soluble vitamins (Barabote et al., 2006).

6.5 Lipid Metabolism

Lipids are fats and composed of triglycerides and cholesterol that are hydrophobic and mostly insoluble in blood, and are either absorbed from food or synthesized by the liver (Ophardt, 2013). Cholesterol is a common constituent of cell membranes, steroids, bile acids, and signaling molecules; and triglycerides primarily store energy in adipocytes and muscle cells (Baynes, 2014). Lipoproteins are hydrophilic, spherical structures that possess surface proteins, such as apoproteins and apolipoproteins that are cofactors and ligands for lipid-processing enzymes (Freifelder, 1987). The liver forms fatty acids from carbohydrates and synthesizes triglycerides and phospholipids from fatty acids and glycerol (Jo et al., 2016).

The liver is critical for digestive absorption and performs uptake, synthesis, packaging, and secretion of lipids and lipoproteins. Its biliary synthesis and secretion system enables efficient absorption of lipid from digestion. Lipid metabolism is the synthesis and degradation of lipids in cells, involving the breakdown and storage of fats for energy and the synthesis of structural and functional lipids, such as those involved in the construction of cell membranes (Arrese & Soulages, 2010). Fatty acids and lipoproteins are synthesized, and the liver is the major site for endogenous cholesterol and prostaglandin production (Trefts et al., 2017).

6.6 Cholesterol Synthesis

Cholesterol is a main constituent of the biological membranes. Sex hormones, steroids, and bile acids are all derived from cholesterol (Luo et al., 2020). It is a required molecule for assembly of cellular membranes as well as maintenance of membrane fluidity (Razin & Tully, 1970). While a lack of cholesterol can be damaging, an excess is also harmful to health. Excess cholesterol from the diet can result in inappropriate cell membrane dynamics, and may result to cardiovascular disease and atherosclerosis (Trefts et al., 2017).

The daily cholesterol input in human is 100mg that represents about 1-1.5% of the entire cholesterol amount as about 300-500mg of cholesterol are absorbed daily from diets while 600-900mg of cholesterol is produced per day (Brunzell et al., 2008). Liver utilizes cholesterol to synthesize from 500-600mg of bile acids that enable the secretion of about 600mg of cholesterol into the bile (Agren et al., 2001). Cholesterol input is accurately well-adjusted of cholesterol output in order to maintain whole body cholesterol homeostasis as simply a minor (Chiang, 2014).

6.7 Metabolism of Bilirubin

Bilirubin is produced in the body through the breakdown of hemoglobin. It is a byproduct of destruction of aged red blood cells. It gives bile a greenish black color and produces the yellow tinge of jaundice (Ozougwu, 2017). This catabolism is a necessary process in the body’s clearance of waste products that arise from the destruction

of aged red blood cells that are taken up and destroyed by macrophages of the mononuclear phagocyte system, primarily in the spleen and liver (Braunstein, 2019).

The hemoglobin is separated into its component parts: heme and globin. The globin component is further degraded into its constituent amino acids that are recycled to form new protein. The heme moiety is converted to biliverdin by the enzymatic cleavage of iron. The biliverdin is enzymatically converted to bilirubin in the macrophage of the mononuclear phagocytic system and then is released into the plasma (Smith & Morton, 2010).

The iron attaches to transferrin in the plasma and can be stored in the liver or used by the bone marrow to make new red blood cells (Sedlak et al., 2009). In the plasma, bilirubin binds to albumin and is known as unconjugated bilirubin that moves from plasma in the sinusoids into the hepatocyte, and it joins with glucuronic acid to form water soluble conjugated bilirubin (Boron & Boulpaep, 2005).

6.8 Drug Metabolism

Drug metabolism in liver is the metabolic breakdown of drugs by living organisms through the specialized enzymatic systems (Simpson, 1981). It is the biotransformation of pharmaceutical substances in the body so that they can be eliminated more easily (Commandeur et al., 1995; Liddle & Stedman, 2007). The drugs are made water soluble excretable compounds in the bile that is called hepatic drug detoxification, which includes two phases (Hoffmann et al., 2012). The first Phase I is a sequence of reactions (non-synthetic reactions), such as oxidation, reduction, hydration, conjugation, condensation, hydrolysis, and isomerization (Vaja & Rana, 2020), followed by Phase II conjugation reactions (synthetic reactions) that increase the solubility of the drug through the modification with glucuronate, sulfate, or other polar molecules; and hence can be excreted in the urine or bile more easily (Jakoby & Ziegler, 1990). Phase I reactions may be carried out by any combination of a diverse group of over 50 cytochrome P450 (CYP450) monooxygenases, a subset metabolize 90% of drugs, such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 enzymes (Lynch & Price, 2007; Hoffmann et al., 2012). Some compounds move to Phase III transformations, such as glutathione conjugation via a peptidase-mediated intermediate (Commandeur et al., 1995).

6.9 Blood Supply

The liver is a very vascular organ. In every minute about 1500ml of blood flows through the liver that is about 25% of the cardiac output, which is more than any other organ. It is responsible for more than 20% oxygen consumption of the body. Almost all the blood coming from the intestine is collected and filtered through the liver, and serves as a blood reservoir. The liver has a unique dual blood supply: hepatic artery supply and hepatic portal vein supply (Sibulesky, 2013). The hepatic portal vein brings in nutrient-rich blood from the intestine while the hepatic artery brings oxygen-rich blood from the heart. From 50 to 80% of the liver's oxygen supply is furnished by the hepatic artery, the remainder comes from the portal vein (Lautt, 2009).

About 65-80% of the blood supplied to the liver is deoxygenated venous (portal vein) blood from the large and small intestines, spleen, stomach, pancreas and gallbladder that carries less oxygen; and the rest 20-35% of the supply is oxygenated arterial (hepatic artery) blood that carries a high level of oxygen. The arterial and portal blood ultimately mixes within the hepatic sinusoids before draining into the systemic circulation via the hepatic venous system (Nagrath, 2019).

7. Conclusions

The liver is a dynamic and heterogeneous internal organ that is controlled by highly regulated physiological system through the appropriate timing, localization, and intensity of signals. Liver plays an important role in metabolism through the preservation and regulation of the levels of lipid, glucose in the body as well as energy metabolism. The main functions of the liver are metabolism of bilirubin, nutrients, protein, lipid, and carbohydrate; storage of glycogen, vitamins, and minerals; secretion of bile, and bile salts; excretion of bile, urea and other wastes; detoxification of drugs and toxins; filtration of bacteria; and degradation of endotoxins and lactate metabolism. The liver maintains the blood glucose levels by a group of processes: glycolysis, glycogenesis, glycogenolysis, and gluconeogenesis. It also has adaptive and innate immunity cells to run immunologic functions. The liver also deals vascular, hemostatic, and hematologic functions. If an individual takes proper care of liver and maintains healthy lifestyle, can avoid many liver diseases that may progress to more dangerous conditions, such as liver cirrhosis or liver failure if does not take proper treatment. In this study, the functioning of the liver is discussed for the maximum exercise of healthy lifestyle to maintain a good health and to avoid liver diseases.

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