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Review Article

Embryology, anatomy and physiology of the liver: Review

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ABSTRACT

The liver, located within the peritoneal cavity, is in the right upper quadrant of the abdomen. Additionally, it should be noted that the liver holds the distinction of being the largest gland within the human body, as well as the most extensive visceral tissue situated within the abdominal cavity. One of the factors contributing to the early migration of the developing intestines to an extracoelomic location during fetal development is their relatively bigger size in children, weighing between 1400 and 1800 g in adults. It contributes to the development of a distended abdomen in pediatric populations. The liver is situated in the right upper quadrant of the abdomen and spans across the midline to the left upper quadrant. The heart remains susceptible to regular injuries despite the protective presence of ribs and cartilage. The liver, functioning as an accessory organ in digestion, undertakes several metabolic processes, including drug metabolism, bile production, and bilirubin synthesis, alongside numerous other functions. For a considerable period, medical professionals and anatomists have encountered challenges in comprehending the complex functions of the liver. Significant advancements in the comprehension of liver anatomy have contributed significantly to the notable progress observed in various surgical and interventional radiologic procedures involving hepatic artery infusion pumps, liver ablation, transplantation, transarterial chemoembolization, selective internal radiation therapy, and portal vein embolization. The existence of hepatic structure is crucial for developing and implementing gradual therapies. This page aims to provide an academic overview of the embryology, anatomy, and function of the liver.

1. Introduction

Based on embryological principles, it is understood that the liver originates from the endoderm layer of the developing embryo.[1] This endoderm layer subsequently differentiates into both the morphological and functional components of the liver, as depicted in Figure 1.[2,3] The liver is protected by the structure of the rib cage and held in position through peritoneal reflection, which is alternatively referred to as ligamentous attachment. The location of this structure is within the right superior quadrant of the abdominal cavity, positioned under the right hemidiaphragm. The common hepatic artery, originating from the celiac trunk, is responsible for delivering oxygenated blood to the liver and serves as this organ's primary source of blood supply. The convergence of the central veins results in the formation of the hepatic veins. These veins facilitate the direct blood flow from the liver to the inferior vena cava (IVC), bypassing the diaphragm. Bile is vital as a fluid in facilitating the elimination of poisons that surpass the kidneys' capacity for removal. Bile facilitates the absorption and digestion of lipids by the secretion of bile salts and acids. The involvement of the liver in the metabolism and/or detoxification of xenobiotics is of utmost importance.[3,4]

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2. Embryology of Liver

During gastrulation, the germinativum endoderm layer, which would later give rise to the primitive gut, is created. Foregut, midgut, and hindgut are the three components that make up the primitive gut (Figure 1).[5] The liver diverticulum, an out pocket in the ventral foregut epithelium at the distal end, next to the growing heart, is where the liver primordium first develops in the middle of the third week. The liver and intrahepatic biliary tree will form in the diverticulum's anterior portion, while the gallbladder and extrahepatic bile duct will form in the diverticulum's posterior portion. Hepatoblast is a type of hepatic endoderm cell that separates from the epithelium and infiltrates the adjacent septum transversum mesenchyme to produce the liver bud. The connection between the liver diverticulum and the foregut (duodenum) narrows and produces a channel known as the biliary duct as the hepatoblast continues infiltrating the septum transversum. The gallbladder and cystic duct will then arise from the ventral bulge of this duct. The liver sinusoids are created during development when the epithelial liver cords connect the vitelline and umbilical veins. Fibroblasts, Kupffer cells, hematopoietic cells, and liver stellate cells are all developed by the septum transversum mesenchyme. Hepatoblasts can differentiate into both hepatocytes and Billiary Epithelial Cells (BECs). The portion of the hepatoblast closest to the portal vein will grow into BECs, which will line the intrahepatic bile duct (IHBD) lumen.[1,5–7]

The liver protrudes into the abdominal cavity due to liver cells invading the septum transversum. The omentum minus and ligament falciform are made of the mesoderm of the septum tranversum, which is placed between the liver and foregut and between the liver and the anterior abdominal wall. The ventral mesogastrium is the term used to refer to them all.[1,6,7]

Except in the superior region of the liver, the mesoderm that is superficial to the liver develops into the visceral peritoneum. The septum transversum, which will eventually form the diaphragm's central tendon, is connected to the liver in this superior region of the liver. The liver region next to the growing diaphragm is called the "bare area" and is not peritoneally lined.[1,6,7]

The liver makes up 10% of the body weight by the 10th week of development. The liver participates in hematopoiesis during the fetus before the bone marrow can take over this job by producing leukocytes and erythrocytes by a group of proliferating cells located between the liver cells and blood arteries. The liver's hematopoiesis function starts to be replaced by bone marrow by the seventh month of development, causing the liver's weight to decline and stay at 5% of the body weight.[1,6]

At development week 12, liver cells start to produce bile. Once the cystic duct and gallbladder have formed, the cystic duct merges the hepatic duct to create a bile duct, allowing bile to reach the digestive system. The bile duct moves from an anterior to a posterior location due to changes in the duodenum's position, placing it behind the duodenum.[1]

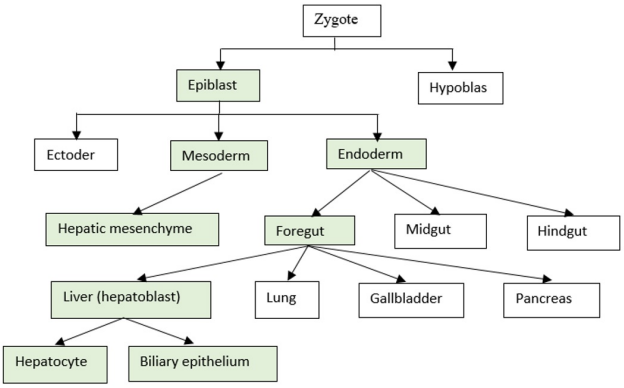

Fig. 1: Liver development [Figure adapted from reference[5]

3. Histology of the Liver

The hepatic lobule, which possesses a hexagonal form and is approximately the size of a sesame seed, serves as the liver's fundamental structural and functional unit. The hepatic lobule is characterized by the arrangement of liver cells (Figure 2). The liver lobule is comprised of several essential components, including hepatocytes, portal triad, central vein, liver sinusoids, Kupffer cells functioning as macrophages, bile canaliculi, and the space of Disse, which denotes the narrow gap between sinusoids and hepatocytes. A portal triad at each corner characterizes the hexagonal structure in question. This triad comprises the hepatic artery, portal vein, and bile duct. The blood circulation within the hepatocyte chord has distinct characteristics compared to conventional capillaries.

In contrast to the formation of tight connections observed in other capillaries, liver endothelial cells establish a sinusoidal network. This unique arrangement reduces the resistance between the hepatocytes and the blood as it traverses the sinusoids. The hepatic artery, which carries oxygen-rich blood, and the portal circulation, which carries nutrient-rich blood, converge in the sinusoids. Subsequently, this blood mixture passes via the lobule cells and proceeds toward the central vein. As a consequence, the composition of the fluid exiting the lobule exhibits distinct characteristics compared to the composition of the blood entering the lobule. During the circulation of blood within the lobule, cells use oxygen and the processing of nutrients, concurrently generating metabolites and waste substances. Deoxygenation occurs within the blood, whereas the removal of metabolic waste from the cells occurs along the sinusoids.[8,9]

The liver comprises five distinct cell types: hepatocytes, sinusoidal endothelial cells, Kupffer cells, Stellate cells, and

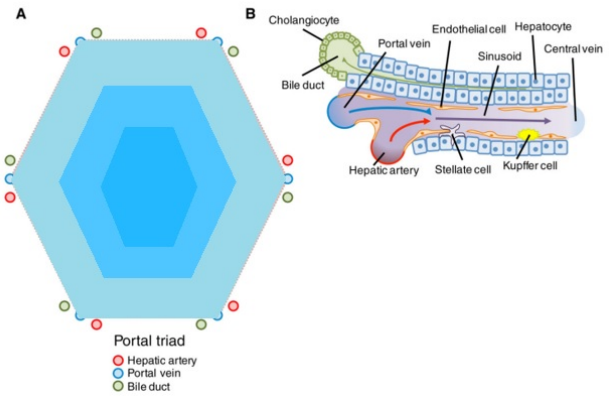

Fig. 2: Liver organization [Figure adapted from reference [8]

Cholangiocytes (Table 1). Hepatocytes, the predominant cellular constituents of the liver, encompass the sinusoidal capillaries in significant quantities. The hepatocytes are accountable for the majority of hepatic functions, encompassing the synthesis and storage functions and the filtering of blood from the portal vein. The Cholangiocyte, which serves the purpose of lining the lumen of the bile ducts, is identified as the second most prevalent cell type within the liver. Kupffer cells are a distinct population of hepatic cells that possess specialized immune response and phagocytic activity functions. Stellate cells, referred to as perisinusoidal cells or ito cells, are crucial components involved in the progression of liver fibrosis, as they contribute to the organization of collagen within the diseased liver. The cellular entity under consideration exhibits dynamic characteristics, displaying the ability to exist in a quiescent or active state. During the quiescent state, stellate cells store vitamin A within lipid droplets. The precise roles of stellate cells in their dormant condition still need to be fully understood. Hepatic sinusoidal endothelial cells exhibit distinct properties due to their specialized endothelial nature. The cells in question create pores inside the sinusoidal lumen, which possess a size range of 50-180 nm, effectively resembling a sieve-like structure. As mentioned above, the structure plays a crucial role in facilitating the transportation of proteins and particles between the plasma and liver cells. [8,9]

4. Anatomy of Liver

Humans have the largest smooth-surfaced organ, the liver. The liver makes up about 2-3% of the total body weight in humans. Men's livers typically weigh 1800 grams, while women's livers weigh only 1400 grams. [10] Located under the right hemidiaphragm in the right upper quadrant of the abdomen, costae surround and protect this organ. The liver is completely encased in the Glisson capsule except for the exposed area next to the diaphragm. [3,9,11] When viewed from the outside, The falciform ligament separates the liver into a right and a left lobe (Figure 3). The liver is joined to the anterior abdominal wall by this ligament. The ligament teres, containing the umbilical vein's final stages of development, are located at the base of the liver. [10] The diaphragm and visceral surfaces of the liver can be considered its two surfaces, with the unmarked anterior, lateral, superior, and posterior portions of the diaphragm surface. [12]

Table 1: Liver cells and functions

Cells Type	Functions
Hepatocyte	The primary cellular component of the liver. The processes of synthesis, storage, degradation, metabolism, and portal substances' endocrine and exocrine functions
Sinusoidal endothelial cells	The fenestrated plexus facilitates the communication between portal blood and hepatocytes
Kupffer cells	Phagocytosis and cytokine release
Stellate cells	The role of function in the process of regeneration after injury, as well as its function as a precursor to myofibroblast formation and storage of vitamin A
Cholangiocyte	The functions of the gallbladder include the transportation of bile, the secretion of bicarbonate, and the secretion of water

The umbilical fissure and the falciform ligament separate the liver into two lobes, with the right lobe more extensive than the left lobe (Figure 3). The caudate lobe and lobe quadratus comprise the right lobe of the liver. The lobe quadratus and caudate lobe are divided by the transverse hilar fissure, where the porta hepatis enters the liver. The gallbladder and umbilical fissure both surround the lobe quadratus on either side. Anterior to the hilar fissure is found in the caudate lobe, sometimes called Spigel's lobe. The liver contains two primary and two accessory lobes, each divided by easily recognizable fissures. [2]

The liver is divided into eight functional parts, each with its portal pedicles, according to Couinaud's classification (Figure 3). The branches of the right and left hepatic arteries, the hepatic portal vein, and the hepatic duct form the portal pedicle. The liver's left lobe is divided into segments II, III, and IV. V, VI, VII, and VIII are the segments that make up the right lobe. Segment I is in the caudate lobe, though (Table 2). [10]

Table 2: Liver segmentation

Liver lobes	Liver segmentation	Location
Left lobe	II and III	Lateral segment
	IV	Medial segment
Right lobe	V and VIII	Anterior segment
	VI and VII	Posterior segment
Caudate lobe	I	On posterior liver

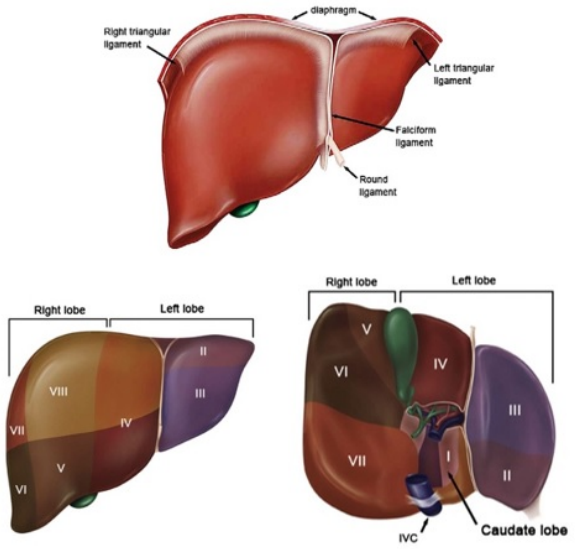

Fig. 3: Morphologic and functional of the liver [Figure adapted from reference [3]

Three veins—the portal and right and left hepatic veins—serve the liver. The right hepatic vein divides the right lobe of the liver into anterior and posterior portions. The right and left lobes of the liver are separated by the intermediate hepatic vein, which connects to the inferior vena cava. The left hepatic vein separates the medial and lateral parts of the left lobe. The portal vein divides the liver into superior and inferior parts (Figure 3). [10]

Understanding these liver parts is crucial because they provide guidelines for doing liver resection. According to the Couinaud classification, segmentectomy removes an anatomical segment (Figure 3). Segments II and III are resected using the left lateral segmentectomy technique, while segment IV is resected using the left medial segmentectomy technique. Segments V and VIII undergo a right anterior segmentectomy, whereas segments VI and VII have a right posterior segmentectomy. Left hepatectomy is used when the resection is done on segments II, III, and IV. Like removing segments V through VIII, right hepatectomy is also performed. Segments V, VI, VII, and VIII that reach segments I, IV, or both are removed during an extended right hepatectomy. While an extended left hepatectomy is when segments I, V, VIII, or a mix of segments IV, II, and III are removed. [9,10]

4.1. Ligamentum of the Liver

The liver is anatomically connected to the front wall of the abdomen and the diaphragm through four peritoneal folds, namely the falciform, coronary, and two triangular ligaments (Figure 4). The round ligament, also known as the ligamentum teres hepatis, is a fibrous structure that forms after dividing the left umbilical vein. Similarly, the ligamentum venosum is a connecting structure between the left branch of the portal vein and the left hepatic vein near the point of convergence with the inferior vena cava. The fibrous remnant being referred to is the ductus venosus. [3,13]

The falciform ligament traverses the anterior aspect of the liver and extends onto the hepatic dome. At this point, the ligament bifurcates, with the right leaf continuing as the superior layer of the coronary ligament. In contrast, the left leaf extends towards the elongated and slender left triangular ligament. The left triangular ligament connects the lesser omentum through the fissure that contains the ligamentum teres. The superior connections of the smaller omentum's bilayered peritoneal membrane consist of the ligamentum venosum fissure and the margins of the porta hepatis. The lesser omentum traverses from this attachment to the inferior curvature of the stomach. [12]

The liver maintains stability through the coordinated functioning of several components. The peritoneal suspensory ligament and the hepatic vein play a crucial role in maintaining the structural integrity of the liver. The ligament establishes a connection between the inferior side of the diaphragm and the superior surface of the liver via the coronary ligament and the right and left triangular ligaments. The liver is anatomically connected to the posterior aspect of the anterior abdominal wall through the teres and falciform ligaments. The anterior abdominal muscles play a crucial role in ensuring the stability of the liver. [12]

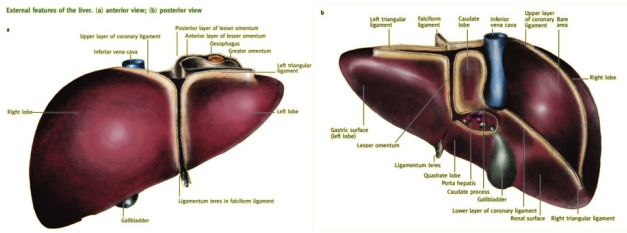

Fig. 4: External feature of liver [Figure adapted from reference] [12]

5. Liver Vasculature

The liver is the most vascular organ in the body and receives the highest cardiac output during rest, up to 25%. The hemodynamic factors that cause fluid shifts across most arterial beds have little impact on the liver's net fluid exchange. Four causes for this deviation from standard vascular control of fluid exchanges exist. [3,14]

6. Arterial Supply

Approximately 70-75% of the blood received by the liver is derived from the portal vein, while the remaining 25-30% is supplied by the hepatic artery, afterward entering

the liver sinusoids. The oxygen saturation in the blood falls as it traverses the liver sinusoids. The portal vein and hepatic artery traverse the hepatoduodenal ligament, a lesser omentum component, to reach the porta hepatis. The portal vein is situated in a posterior position relative to the pancreas and has a length of around 9-10 cm. It receives blood from both the splenic vein and the superior mesenteric vein. The portal vein additionally receives blood from the stomach through the right and left gastric veins. The absence of valves in the portal vein and its crucial role in supplying oxygen to hepatocytes renders the liver very intolerant to any obstruction in this vital vessel. The hepatic artery is a major arterial branch originating from the celiac trunk, responsible for transporting oxygenated blood derived from the aorta. The artery in question afterward emits right and left branches close to the porta hepatis. The right hepatic artery is responsible for providing blood supply to the right lobe of the liver. In contrast, the left hepatic artery supplies blood to the left lobe. [12]

The gastroduodenal artery encompasses multiple indirect branches that provide vascular support to the pancreas as it descends into the pylorus and proximal duodenum. Typically, the proper hepatic artery will emit a branch known as the cystic artery, which provides vascular supply to the gallbladder, the proximal segment of the common bile duct, and the common hepatic duct. Hepatic artery variations are frequently observed, with the most prevalent being a replaced right hepatic artery that arises from the superior mesenteric artery. A further variant observed is the presence of a replaced left hepatic artery, which arises from the left gastric artery and traverses the lesser omentum to provide vascular supply to the left lobe of the liver. Additional variations encompass early bifurcation in the common hepatic artery and the complete replacement of the common hepatic artery. [3,14,15]

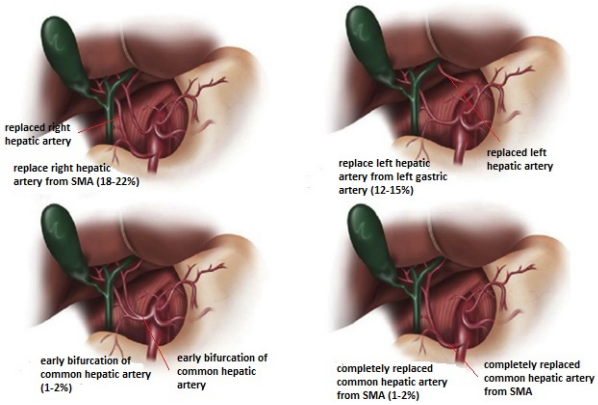

Fig. 5: Common variation of hepatic vasculature [Figure adapted from reference] [3]

7. Vein Supply

The superior mesenteric vein, splenic vein, gastric vein, cystic vein, and pancreaticoduedenal vein are veins that empty into the portal vein. As it has no valves, the portal vein works at a low pressure of about 3-5 mmHg. The splenic vein connects with the superior mesenteric vein in front of the inferior vena cava and behind the neck of the pancreas to create the portal vein. The portal vein then travels upwards within the hepatoduodenal ligament, positioned posteriorly to the hepatic artery and common bile duct, towards the hepatic hilum, bifurcating into the right and left branches. The left portal vein first extends horizontally briefly before taking a cranial direction and subsequently dividing into branches that provide blood supply to the Couinaud hepatic segments I, II, III, and IV. The portal vein can be anatomically divided into two branches, namely the anterior and posterior branches. The anterior branch is responsible for supplying blood to segments V and VIII, while the posterior branch is responsible for supplying blood to segments VI and VII. The observed branching pattern of the primary pulmonary vein is prevalent in around 65% of persons within the general population. The inferior mesenteric vein has a notable degree of variety in its anatomical connections, with around 40% of cases demonstrating its convergence with the splenic vein, another 40% with the superior mesenteric vein, and the other 20% with the splenomesenteric confluence. [3,10,16]

The intrahepatic veins, including the left and intermediate hepatic veins, immediately empty into the IVC, the primary conduit for venous outflow from the liver. The right hepatic vein typically exhibits a comparatively shorter and wider extrahepatic trajectory, ultimately emptying straight into the IVC. Additional draining straight to the IVC is facilitated by the short retrohepatic vein and, on occasion, the accessory right inferior hepatic vein. (3) Compared to the portal venous system, the hepatic veins within the hepatic parenchyma are distinguished by the absence of the fibrous and protective Glisson's capsule. [9]

8. Biliary Ducts

The right and left hepatic ducts are the two primary trunks of the intercellular biliary passageways (bile capillaries), which join to form interlobular bile channels. The two lateral ducts combine at the port umbilical fissure, with the medial branch joining the newly formed duct. [12,13]

9. Functions of Liver

Bile is a vital physiological fluid crucial in eliminating poisons the kidneys cannot excrete. Furthermore, it enhances the assimilation and breakdown of lipids via the excretion of bile salts and acids. Hepatocytes

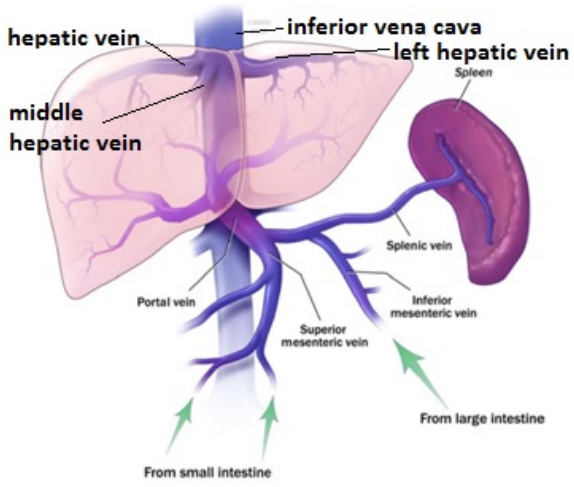

Fig. 6: Portal venous drainage [Figure adapted from reference][10]

are accountable for synthesizing bile, a multifaceted fluid primarily consisting of electrolytes, water, bile acids, bile pigment, bile salts, bilirubin, cholesterol, and phospholipids, among other components. Hepatocytes secrete bile into the bile duct, traversing via a network of channels of varying widths before reaching the duodenum or being deposited in the gallbladder for accumulation. The precise location is dictated by the pressures exerted by the duct and the sphincter of Oddi. Upon being released into the duodenum, bile undergoes circulation inside the enterohepatic system, which carries out its physiological role within the intestines. The constituents of bile that are not excreted undergo a process of recycling facilitated by intestinal bacteria, leading to their conversion into bile acids. Subsequently, the bile acids are absorbed within the ileum and transported back to the liver.[4]

The liver serves as the site for storing or metabolizing fat-soluble vitamins. The alpha- and gamma-tocopherol forms are how Vitamin E is transported to the liver. Despite the liver's inability to store or metabolize vitamin K, it remains an essential component for the liver enzyme gamma-glutamyl carboxylase.[4]

The liver is involved in metabolic detoxification, transforming both endogenous and exogenous substances, including medications and hormones, into metabolites that are less biologically active and less harmful. These metabolites are then eliminated from the body via the bowels or the kidneys. The liver plays a crucial part in detoxification concerning alcohol, amphetamines, hormones, steroids, and barbiturates. Its primary function is to prevent the excessive buildup of these substances and mitigate any potential negative effects. While metabolic detoxification is typically beneficial, there are instances where it can adversely affect hepatocytes. One illustration of the detrimental effects of alcohol abuse is the potential harm it can inflict upon hepatocytes, primarily due to the metabolic byproducts of alcohol, including acetaldehyde and hydrogen. The metabolic byproducts elicit an augmentation in adipose tissue deposition, which has the potential to impair hepatic functionality.[17,18]

Hepatocytes produce enzymes involved in detoxification, which can be categorized into phases: phase I and II. Phase I enzymes function by introducing hydrophilic polar groups, such as hydroxyl (-OH), to lipophilic molecules, thereby enhancing their hydrophilicity. In the interim, phase II enzymes conjugate hydrophilic components (e.g., sugar or peptide, such as glutathione) to the polar moieties introduced by phase I enzymes. The liver may be susceptible to harm if there is a disruption in the activity of phase II enzymes, leading to an accumulation of reactive chemicals generated during phase I metabolism.[18–20]

The process of heme oxidation predominantly occurs within the hepatic tissue. Unconjugated bilirubin is generated through the conversion of heme to biliverdin. Most of it is introduced into the bile and subsequently eliminated through the excretion of bile in fecal matter. A fraction of the substance dissolves within the bloodstream after filtration before renal excretion.[4,21]

The process of deiodination, specifically the conversion of thyroxine (T4) to triiodothyronine (T3), takes place inside the hepatic tissue, hence playing a significant role in the overall functionality of thyroid hormones. The liver is responsible for synthesizing most plasma proteins found in the human body, including albumin, protein C, binding globulins, protein C, protein S, and all clotting factors except for factor VIII, which are created through both the intrinsic and extrinsic pathways.[4]

The liver possesses a substantial capacity to retain a significant volume of blood due to its abundant presence of blood arteries. In hemorrhage, the liver can secrete blood to sustain the overall blood volume inside the circulatory system. Due to its anatomical connection with the gastrointestinal tract, the liver is prone to infiltrating germs or foreign particles introduced into the portal vein system. Kupffer cells can eradicate bacteria and serve as a protective barrier against infection.[18]

10. Conclusion

The article provides a comprehensive overview of the liver's development, anatomy, histology, and function. The liver undergoes development from the endoderm germ layer, whereas the hepatic mesenchyme arises from the mesoderm germ layer. The liver is in the right upper quadrant of the belly and is stabilized by several peritoneal folds. The liver comprises five distinct types of cells, each possessing unique tasks and functions that collectively contribute to the overall support and functionality of the organ. The liver plays a significant role in multiple physiological processes, including bile secretion, detoxification, heme oxidation, and deiodination. A comprehensive comprehension of the

anatomical composition of the liver is crucial in effectively managing disorders that specifically necessitate surgical intervention. By understanding the fundamental principles of the liver, one can effectively mitigate the potential for difficulties during surgical procedures or the treatment of various liver-related ailments.

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12. Conflicts of Interest

There were no disclosed potential conflicts of interest relevant to this article.

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