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REVIEW ARTICLE

The major pathways of lipids (triglyceride and cholesterol) and lipoprotein metabolism

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A B S T R A C T:
Lipids are considered as organic substances that are relatively insoluble in water while soluble in organic solvents such as alcohol and ether. Unlike carbohydrates, proteins and nucleic acids, lipids are not polymers. Further, lipids are mostly small molecules. More than 90% of the fatty acids found in plasma are in the form of fatty acid esters primarily in the form of triacylglycerol, cholesteryl esters. Lipids can be exogenously from the dietary sources and endogenously mainly from the liver. Due to insolubility of lipids, so the circulation of lipids in the blood is performed by the actions of several transport vehicles such as spherical protein complexes which is known as lipoproteins which is an assembly of lipids with proteins. There are four major types of lipoproteins are participating in transporting lipids in plasma, which are classified based on their density, these includes chylomicrons (CM), very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Different types of lipoproteins have a different set of proteins (apoprotein) on their surface, these proteins served as address tags that determine both destination and function of each lipoprotein. In this review, we summarise the pathways and metabolites that involve in lipid and lipoprotein metabolism.

KEY WORDS: Triglyceride, Fatty acid β-oxidation, Cholesterol, Chylomicron, HDL, LDL, VLDL.
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1. INTRODUCTION:

Lipids are a large insoluble molecular complex that acts as structural components of cell membranes (Harayama and Riezman, 2018) as well as acts as an energy sources that are transported through blood within a large spherical molecule known as lipoproteins. Lipids are broadly classified into four classes based on their structure and properties, they are simple, complex, derived, and miscellaneous lipids (Fahy et al., 2011).

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control cellular processes (Lizardo et al., 2018), cell proliferation (Hall et al., 2020), apoptosis (Teixeira et al., 2020), metabolism and migration (Toprak, 2020). Moreover, it has been reviewed that lipid metabolism has a significant role in viral replication (Lorizate and Krausslich, 2011), as recently has shown that the lipid metabolism has a significant impact on COVID-19 virus infection and as a drug target (Abu-Farha et al., 2020), through alterations and blocking of lipid membrane composition of viruses which consequently interfere with the viral life cycle (Lorizate and Krausslich, 2011). The constituent of lipid in the body is bout 15-20%, which is mostly (90%) of the lipid is in the form of triglyceride, and the rest of them are free cholesterol, cholesteryl ester, phospholipids, glycolipids (Figure 1) (Fahy et al., 2011).

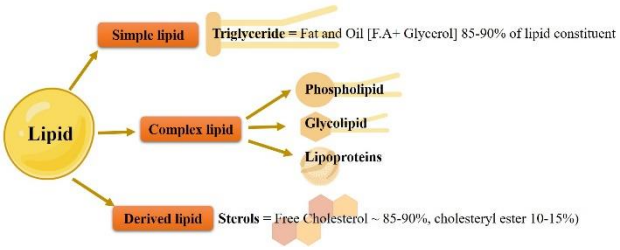

Figure 1: The composition of lipids. Most of the lipid constituents consists of triglycerides (simple lipid, while the rest of them include complex lipids (phospholipid, glycolipid, and lipoproteins), and derived lipid includes sterols.

The highest constituent of dietary lipid is Triglyceride, and its transported from the intestine to the blood via chylomicron lipoprotein (Nordestgaard, 2016) and its normal range in the blood serum is below 150 mg/dL (Kiss et al., 2018).

The esterification of three molecules of fatty acids with glycerol resulted in the formation of triglyceride. However, different types of fatty acids in triglyceride resulted in the formation of several types of triglyceride (Alvarez et al., 2002). Increasing triglyceride concentration in the blood can be either by a genetic defect (primary hyper glycemia) or due to non-genetical factors known as secondary hyperglycaemia. These include using unhealthy diet, type-II diabetes mellitus, hepatic steatosis, and nephrotic syndrome. The increase in triglyceride level in plasma is considered as an indicator of development of acute pancreatitis (AP) (Yadav and Lowenfels, 2013). Nowadays, a high-fat diet and resultant obesity are common; therefore, the prevalence of elevated serum triglyceride concentration serum triglyceride is high, affecting approximately 27% of all adults (Nordestgaard, 2016).

Beside triglyceride, cholesterol is another type of lipids which is a structural component in the cell membranes and a crucial lipid for maintaining cellular homeostasis (Gerard, 2013). Cholesterol, exclusively found in animals, is the most abundant animal sterol (Ikonen, 2008a). Cholesterol it also serves as a precursor for the synthesis of vitamin D (Prabhu et al., 2016), bile acids in the form of cholic and chenodeoxycholic acids which appear in the gut (Gerard, 2013) and variety of steroid hormones (Lyu et al., 2019, Payne and Hales, 2004), however unabsorbed dietary cholesterol which is around 200 mg/day and is added to the biliary cholesterol secretion (Gerard, 2013).

The composition of cholesterol can be present either as free form or ester form (Cholesteryl esters), which makes the structure even more hydrophobic (water insoluble) than free (unesterified) cholesterol.

Cholesterol is found as cholesterol ester in which the esterification occurs at the OH group of C3 with fatty acid. (Ikonen, 2008a). There are two major sources of cholesterol synthesis, those that are synthesized endogenously in the endoplasmic reticulum and transported through the blood via low-density lipoprotein (LDL) (Bloch, 1965). The other source is exogenously that gets from diet and absorbed from the gastrointestinal tract, where triglycerides and cholesterol are packaged to form chylomicrons with triglycerides and cholesterol in the form of chylomicrons (Ikonen, 2008b).

Lipoproteins serve as an address tag that play a significant role in transportation of cholesterol from and to tissues, thus LDL carries blood cholesterol from liver to other tissues known as bad cholesterol, inversely, HDL carries blood cholesterol from other tissues to the liver known as good cholesterol (Figure 2) (Ohkawa et al., 2020).

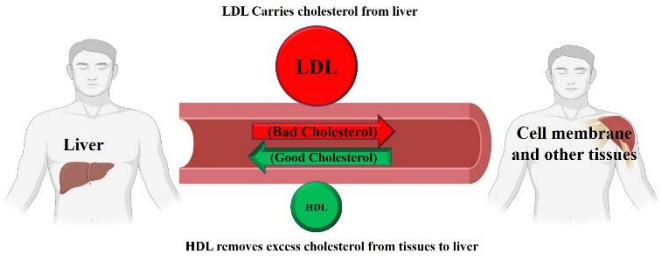

Figure 2: Mechanism of cholesterol circulation in the blood from liver to other tissues and vice versa. LDL transfer cholesterol from blood to other parts of the body known as bad cholesterol, while HDL transfer excess cholesterol after it has been used by other tissue to the liver which is called good cholesterol.

Furthermore, it has been found that different set of proteins were binding on the surface of lipoproteins which are called apolipoproteins, these proteins served as address tag, that determine both function and destination of each lipoprotein. Because the size of lipids is larger than proteins, so particles that contain more lipid are larger in size but have a lower density (Table1) (Wang et al., 2017).

Table 1: Properties of plasma lipoproteins based on their density and lipid content.

Density range (g/mL)	Lipoprotein function	Major core lipid	Apolipoproteins
d < 0.930	Chylomicrons	Exogenous Triglyceride	B-48, E, A-I, A-II, A-IV, C
0.950< d <1.006	Very-low-density lipoprotein	Exogenous Triglyceride	B-100, C-I, C-II, C-III, E
1.019 < d < 1.063	Low-density lipoprotein	Endogenous Cholesteryl esters	B-100
1.063 < d < 1.210	High-density lipoprotein	Endogenous Cholesteryl esters	A-I, A-II

2. TRIGLYCERIDE AND FATTY ACIDS:

2.1. TRIGLYCERIDE AND FATTY ACID SYNTHESIS:

Triglycerides are esters of three molecules of fatty acid and glycerol which represent the major lipid component of dietary foods including fat and oil. Here triglyceride molecules are the major storage of the lipids and transport of fatty acids in the form of chylomicron and VLDL within cells and in the plasma (Alves-Bezerra and Cohen, 2017). There are two major sources that responsible of triglyceride synthesis in the body. As can be seen in the figure 3, more than 90% of triglyceride is synthesized from exogenous sources that come from dietary source (Lowe, 2002). The dietary triglyceride is emulsified by bile acids within the intestinal lumen and enzymically degraded "digested" by pancreatic enzymes, whose secretion is hormonally controlled (Jaworski et al., 2007, Pasquier et al., 1996).

The large molecules triglyceride to be taken up efficiently therefore and break down to its constituents by the action of pancreatic lipase, which preferentially removes the fatty acids at carbons 1 and 3 (Courchesne-Loyer et al., 2017). The primary products of hydrolysis are a mixture of 2-monoacylglycerol and two molecules of free fatty acids (Lowe, 2002).

The synthesized fatty acids are stored in the muscle which undergo β-oxidation to acetyl-CoA , then the generated acetyl-CoA pass through tricarboxylic acid cycle (TCA cycle) to release energy as ATP via oxidative phosphorylation process in mitochondrion from electron transport chain (Donnelly et al., 2005). Beside β-oxidation of fatty acids, part of it combines with glycerol molecule to generate triglyceride which are stored in adipocytes (Jensen, 2002) (Figure 3a).

Triglycerides are also synthesized endogenously from fatty acid and glycerol in the liver and stored in adipose tissue for later use. To synthesise triglyceride, both fatty acids and glycerol must be activated to glycerol 3-phosphate(Alves-Bezerra and Cohen, 2017). In both liver and adipose tissue, glycerol is activated by dihydroxyacetone phosphate (DHAP) produced in glycolysis is reduced by glycerol 3-phosphate dehydrogenase to glycerol 3-phosphate, however, the enzyme of glycerol kinase, which is absent in adipose tissue serves as a precursor for glycerol 3-phosphate, then the enzyme phosphatase cleaves off phosphate of glycerol 3-phosphate to produce diacylglycerol followed by addition of acyl groups to form triglyceride (Figure 3b) (Mandal et al., 2011, Driver et al., 2017).

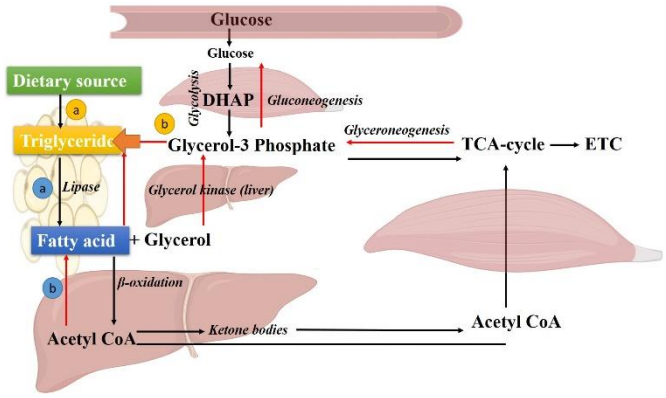

Figure 3: Triglyceride and fatty acid synthesis pathways.

a) Exogenous pathways: Triglycerides comes from the dietary sources and through lipolysis process it hydrolyzed to both fatty acids and glycerol.

b) Endogenous pathways: Triglyceride synthesized from glycerol-3-phosphate and fatty acids.

2.2. FATTY ACID β-OXIDATION:

Oxidation of fatty acids is a multi-step process that occurs in several tissues in the body including liver, skeletal muscle, and cardiac muscle for energy requirement. (Goepfert and Poirier, 2007).

Glucose and fatty acids are the three substrates for the generation of energy, however, during fasting, when blood glucose level becomes limited, fatty acid β-oxidation is importance in most tissues, except the brain. Furthermore, the liver converts fatty acids into ketone bodies that serve as an

additional energy source in most of the tissues including the brain (Dieuaide et al., 1992).

The process starts with utilizing long chain fatty acids which are activated by thiokinases or fatty acyl CoA synthetases in cytosol and convert it to fatty acyl CoA. The reaction occurs in two steps and requires ATP, coenzyme A and Mg^{2+} (Houten and Wanders, 2010). Next step is transfer fatty acyl CoA from cytosol into mitochondrion, however, the inner mitochondrial membrane is impermeable to fatty acids therefore a specialized carrier protein called carnitine carrier system reacts with fatty acyl CoA and forming acyl-carnitine which it is transported across the mitochondrion membrane to matrix of mitochondria the reaction is catalyse by carnitine acyltransferase I, once acyl-carnitine moved into mitochondrion, it converts to acyl CoA by the action of carnitine acyltransferase II and carnitine released returns to cytosol for reuse (Figure 4) (van Eunen et al., 2013, Longo et al., 2006). The process of fatty acid oxidation starts by eliminating two carbon units (acetyl CoA) from acyl CoA in a sequence of four reactions. In the first step of β-oxidation the acyl CoA undergoes dehydrogenation to form one double bond which is double bond is formed between α and β-carbons of acyl CoA resulted in the formation of trans-enoyl CoA (i.e., 2 and 3 carbons) and the reaction is catalysed by acyl CoA dehydrogenase. β -hydroxy acyl CoA dehydrogenase catalyses the third step of the reaction and convert β -hydroxy acyl CoA to β-keto acyl CoA. Finally, β-ketoacyl CoA converted to acetyl CoA and the remaining acyl CoA by the action of thiolase enzyme, and the process continues till the fatty acid is completely oxidized, and Acetyl CoA can enter citric acid (TCA) cycle and get completely oxidized to CO_2 and H_2O (Goepfert and Poirier, 2007).

Among of these four-catalysing reactions, in step one ; three FAD and NAD^+ are reduced to $FADH_2$ and $NADH+H^+$ respectively, which then pass-through tricarboxylic acid cycle (TCA) and electron transport chain (ETC) to release energy as the form of ATP, and the overall reaction for each cycle of β-oxidation can be written as follows:

C_n Acyl CoA + FAD + NAD^++ H_2O + CoASH ➔$C_{(n-2)}$ Acyl CoA+Acetyl CoA+ $FADH_2$ + NADH+ H^+.

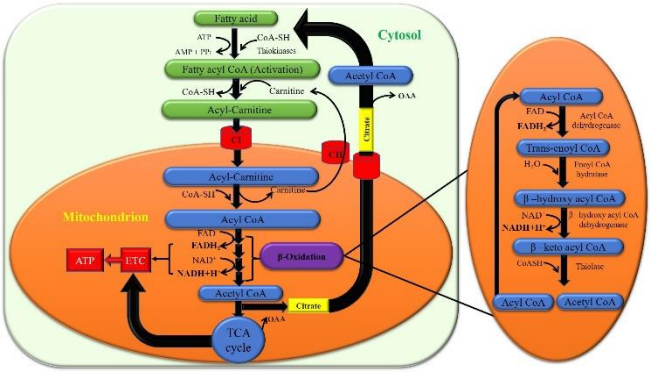

Figure 4: Fatty acid β-Oxidation Pathways. The pathway occurs in both cytoplasm (green) and mitochondrion (blue).

The most common fatty acid molecule that undergoes β-oxidation is the palmitic acid (which contain 16 carbons) that undergoes 7 cycles of β oxidation to yield 8 acetyl CoA.

Overall, fatty acid synthesis mostly occurs in cytosol and acetyl CoA is the precursor, while the process of β-oxidation occurs in mitochondria and acyl CoA is the substrate for this process. Furthermore, the synthesis of fatty acids mostly occurs after meal which the body has enough amount of carbohydrates to generate energy, however, in case, of few or no carbohydrates, fatty acid β-oxidation occurs to produce the required amount of energy (Modre-Osprian et al., 2009).

Therefore, the regulation of fatty acid synthesis and β-oxidation is important to balance the lipid contents in the body, whereas any imbalance in these two processes contribute to several diseases such as type II diabetes mellitus and obesity (Zhang et al., 2010, Boden et al., 1991, Boden, 2008).

Furthermore, it has shown that the fatty acid β-Oxidation pathway is important for decidualization or lipid metabolism in endometrial stromal cells (ESCs) in both human and mice (Tsai et al., 2014).

2.3. METABOLISM OF TRIGLYCERIDE:

2.3.1. Metabolism of Chylomicron (CM)

To begin with lipid metabolism from the dietary source, stomach push the dietary lipid that consists of about 85-90% triglycerides, and the rest are cholesterol and cholesterol ester to the small intestine (Weil et al., 2012, Xiao et al., 2011, Karpe et al., 1995).

Due to the big size of the lipid, the entero-hormone cholecystokinin which comes from main pancreatic duct stimulate the smooth muscle

around the gallbladder to contract which expel out certain substances into the cystic duct which called bile salts including both cholic acid and deoxy cholic acid (King et al., 2015, Liddle et al., 1985, Li and Chiang, 2014). Bile acids are synthesized from cholesterol metabolism in the liver and secreted into the small intestine in response to dietary fat where they enable absorption of fat-soluble vitamins and cholesterol (Hofmann et al., 2008, Li and Chiang, 2014). The amount of bile acids in the bile is about two thirds of the total weight in the human's body (Di Ciaula et al., 2017). Previously it has been shown that the concentration of bile acids is increased from 0.2-0.7 µM during a fasting situation to about 5µM after meals (Ponz De Leon et al., 1978). The synthesized bile salts transported to small intestine and combine with both glycine and taurine molecule (Di Ciaula et al., 2017) which is important for emulsification of big fat globule molecule and separate into small and little fatty droplets also known as emulation droplets (Tyor et al., 1971, Dawson et al., 2009). Due to insolubility of fat molecule, the hydrophobic part of lipid molecules interacts with the hydrophobic part of bile salt forming fat globule, while the hydrophilic portion of bile interacts with the fluid within intestine (Di Ciaula et al., 2017). The emulsified lipid is converted to small fatty droplet that contains triglyceride are digested by enzyme that secrets from the main pancreatic duct which is known as pancreatic lipase to produce two molecules of free fatty acids (FFAs) and mono acyl glycerol (MAG), which then they surround by bile salt in combination with cholesterol and fat-soluble vitamin they form a compact molecule called micelle which is about 500 times as smaller as emulsion droplet (Lo and Coschigano, 2020, Mattson and Volpenhein, 1964). Later the synthesized micelles start to move to enterocytes of the intestine which there the bile salts are recycled to the liver through the portal vein (Dawson, 2018), while both FFAs and MAG are going to a special organelle in the cell which is known as smooth endoplasmic reticulum (SER), which is there both FFAs and MAG are fused and packed together to create triglyceride (TG) (Weil et al., 2012). Here, generated TG with some of the cholesterol and cholesteryl ester combine with a special protein called apo-B_{48} protein that generated from another enterocyte's organelle which is rough endoplasmic reticulum (RER) and packed all together into a special lipoprotein molecule called nascent chylomicron (Kohan et al., 2015), however, knockout of the Apo-B_{48} resulted in the decreased secretion of TG-rich chylomicron (Lo et al., 2008). The generated chylomicron before going to the blood stream is undergo a special lymphatic circulation which is absorbed via lacteal and, eventually, they pass through the largest lymphatic vessel known as thoracic duct into the blood circulation (Dixon, 2010).

In the blood stream, beside apo-B_{48} that bounds to nascent chylomicron, there are two more apo-proteins which are donated via HDL and bound to nascent chylomicron which are known as Apo-E and Apo-CII and forming chylomicron (CM)(Lo and Coschigano, 2020).

Apo CII is important for activating a special enzyme molecule known as lipoprotein lipase (LPL) that locates in the capillary endothelial (Merkel et al., 2002). Once lipoprotein lipase is activated by apo-CII, the activated enzyme cuts triglyceride molecules which is about 85% of total lipids inside nascent chylomicron into three molecules of free fatty acids and glycerol and the apo-CII back to HDL (Havel et al., 1973, Goldberg, 1996).

The generated free fatty acids go to each of the adipocytes and muscles such as skeletal muscle and cardiac muscle which can be used to produce triglyceride by its combination with glycerol and release energy as ATP, respectively (Dixon, 2010, Lambert et al., 2012). Small amount of CM (contains uncatalyzed TG with each of cholesterol, Apo-B_{48} and Apo-E become remain called chylomicron remnants (CM remnant) start to move to the liver via binding of its Apo-E into a special receptor in liver called (LDL) (Cooper, 1997). Here, Apo-E has high affinity for a special receptor located in liver and adrenal cortex called LDL receptor related proteins which take the CM remnant into the liver, which, consequently, CM components are separated from each other to proteins, cholesterol, and small TG (Huang and Mahley, 2014). The remaining TG can be stored while cholesterol can be converted to bile salt, stored as cholesterol ester with the action of a special enzyme called Acyl-CoA: cholesterol acyltransferase (ACAT) and incorporated into a cell membrane (Xu et al., 2019).

2.3.2. Metabolism of very low density of lipoprotein (VLDL)

The endogenous lipoprotein pathway begins in the liver with the formation of VLDL. The triglycerides, cholesterol and phospholipid that come from remnant chylomicron into the liver combine with another lipoprotein molecule called Apo-B_{100} that is generated from hepatocyte cell's rough endoplasmic reticulum (RER) which is very similar to Apo-B_{48} (Hazzard et al., 1984, Hokanson and Austin, 1996). Through the combination of each of the triglycerides (from remnant chylomicron and some de novo synthesis), cholesterol and Apo-B_{100} generate another type of lipoprotein known as nascent very low-density lipoprotein (nascent VLDL) which surrounded by phospholipids (Xiao et al., 2011, Taskinen et al., 2020).

The nascent VLDL in the liver pushed out into the blood circulation, which there is nascent chylomicron. There are two more apo-proteins which are known as Apo-E and Apo-CII are donated via HDL and bind to nascent VLDL and forming very low-density lipoprotein (VLDL) (Freeman and Walford, 2016). Here, Due to activating LPL via CII as seen in CM, this activated LPL can cut TG in to both three molecules FFA and glycerol, which apoprotein CII become return to HDL, and FFA go to either muscle tissue which use as energy generator (as ATP) via its β-oxidation and pass through TCA and ETC, or go to the adipose tissue and become combine with glycerol that comes from glucose in adipocytes to make TG and store in it which gave back Apo-CII to the HDL. Small amount of VLDL become remain called (VLDL remnants or IDL) which contain cholesterol, cholesteryl ester, small amount of TG, Apo-E and apo- B_{100}. As mentioned before, Apo-E has high affinity for a special receptor called LDL receptor related proteins (LDL-R) which is located in the liver and adrenal cortex (Lillis et al., 2008). IDL can either go back to the liver and take up by the LDL-R which could be digested into different components as same fate happened in the CM remnant, or it goes to the adrenal cortex, where cholesterol taken up and utilized to make steroid hormone such as aldosterone, cortisol and sex hormones in different zones or may be stored as cholesteryl ester. However, some of the IDL molecule react by a special enzyme in the liver called hepatic TG lipase (HTG lipase) which contributes to the regulation of the level of plasma triglyceride that facilitates the clearance of TG molecule in IDL particle and send to the liver which is converted to three molecules of FFA and glycerol (Chatterjee and Sparks, 2011). The remaining IDL molecule back to the circulation and return Apo-E protein to the HDL molecule and generate another new lipoprotein molecule which contains Apo-B_{100}, small amount of TG and large amount of cholesterol and cholesteryl ester, this one known as low density lipo-protein or LDL (Warnick et al., 1990).

2.3.3. Metabolism of low density of lipoprotein (LDL)

Most of the generated LDL (60-70%) goes back to the liver, there cholesterol and triglyceride in the liver can be utilized in different sources. The remaining LDL which is about 30-40% can undergo some special tissues via LDL-receptor that is present in these tissues; and there its cholesterol can be utilized for different purposes. Some of these tissues are located in the gonads (male and female sex organs) (Lent-Schochet and Jialal, 2020) . Due to the present of LDL receptor located on these gonads, here LDL particle can go and deliver some of its cholesterol to these gonads, to create female sex hormone including progesterone and estrogen hormone if the gonad is female and generate testosterone sex hormone if the gonad is male(Wang et al., 2011). Furthermore, LDL particle can go and bind to LDL-R that located in adrenal cortex, as seen in VLDL the cholesterol molecules are taken up and can be utilized to make steroid hormones such as aldosterone (Goodfriend et al., 1995), cortisol, DHEA (Di hydro Epi aldosterone) in different zones or may be stored as cholesterol ester(Struthers and MacDonald, 2004). Finally, some of these LDL can be taken to peripheral tissues like microphages (Hannich et al., 2018). However, stay of LDL for a while in the blood resulted in its accumulation in subendothelial spaces and consequently it became undergo special oxidation reaction via reactive oxygen species (Wen and Leake, 2007).

After LDL oxidized it becomes oxidative LDL which is dangerous and causes inflammatory response. So special molecule which present in macrophage start to take up these oxidized LDL via a receptor that present in macrophage (Rosenfeld et al., 1990) called Fatty acid translocate (FAT) also called FAD/CD36 (Wang and Paigen, 2005, Nozaki et al., 1999). FAD/CD36 can take up some of the oxidized LDL-particles and become accumulated, which consequently convert the macrophage into foam cells which is dangerous to make atherosclerosis (Nozaki et al., 1999).

Here, due to the protein that is made by intestine called Apo-A1 (which is initial component of HDL molecule) comes over the macrophage (Kohan et al., 2015), which can bind into a special receptor that present on macrophage called scavenger receptor (ABCA1) and (ABCG1); which firstly bind to (ABCA1) and forming nascent HDL molecule, then taken up more cholesterol from microphage (ABCG1) (Olofsson et al., 2007). Which the cholesterol taken up into the (ABCA1) molecule and make pre or nascent HDL, after getting mole cholesterol it becomes converted to HDL3 molecule and goes to ABCG1 receptor and take up furthermore cholesterol and make HDL2 molecule. Now, there is much cholesterol in HDL molecule (Yvan-Charvet et al., 2010). These cholesterols in HDL can go over to the adrenal cortex and gonads and through its Apo-A1 protein binds to special scavenger receptor called SRB1which is present in these two organs (Bochem et al., 2014). The HDL contained cholesterol is esterified into cholesteryl ester with the action of the enzyme via lecithin-cholesterol acyltransferase (LCAT), which later it uses as a constituent of each of VLDL, IDL and LDL (Shrestha et al., 2018).

Furthermore, some of the cholesterols inside HDL particles go back to the liver via apo-A1 bind to SRB1-recepter, and then deposit their cholesterol into the liver, and decrease in size, and become immature HDL, then go back to macrophage (Feingold and Grunfeld, 2015). An overview of lipids and lipoprotein metabolism are shown in figure 5.

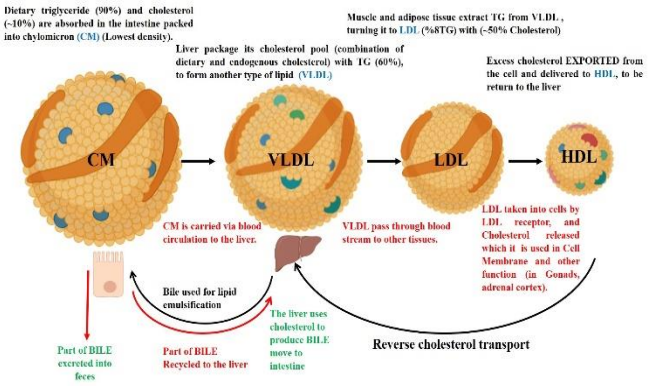

Figure 5: Overview of lipid metabolism and lipoprotein circulation. CM: Chylomicron, VLDL: Very low-density Lipoprotein, LDL: Low density lipoprotein, HDL: High density lipoprotein.

3. CHOLESTEROL METABOLISM

Cholesterol is an essential lipid for mammalian cells, it is either obtained from the dietary source or synthesized by an endogenous pathway that occurs in most cells of the body particularly in the liver. Acetyl CoA is the precursor for the synthesis of cholesterol which can be produced from glucose, fatty acids, or amino acids (Hampton et al., 1996). Beside triglyceride, cholesterol is clinically considered as a crucial part of plasma lipid. In healthy individuals the total plasma cholesterol is in the range of 150-200 mg/dl, which high cholesterol level connected to a higher risk of cardiovascular disease (Carson et al., 2020).

Cholesterol consists of four fused hydrocarbon rings (A-D) called the steroid nucleus, and it has eight carbons, branched hydrocarbon chain attached to carbon 17 of the D ring with a hydroxyl group bonded on carbon number three which present in the first ring (Tabas, 2002). Each day approximately one gram of cholesterol is synthesized via the human body, which almost 20-25% of total daily cholesterol production occurs in the liver (Russell and Setchell, 1992). Cholesterol is the precursor for the synthesis of steroid hormones like in the body (progesterone, testosterone, aldosterone, cortisol and estradiol) (Tabas, 2002), vitamin D and bile acids, it can also serve as an element of cell membrane and plasma lipoproteins particularly in low-density lipoprotein (LDL) that sent to the peripheral tissues (Hegele, 2009).

Cholesterol biosynthesis is a highly complicated process which starts with acetyl-CoA building block, followed by hydration of acetyl-CoA to convert to β-Hydroxyβ-Methyl Glutaryl CoA (HMG-CoA) (Cerqueira et al., 2016), then formation of six carbon molecule known as mevalonate, followed by decarboxylation of mevalonate to isoprenoid with five carbon units, afterward the mevalonate with several steps resulted in synthesis of thirty carbon atom called squalene and finally conversion of squalene to cholesterol with 27 carbon atoms (Russell and therapy, 1992, Cerqueira et al., 2016). In cholesterol synthesis the reducing equivalents are provided by NADPH, while ATP provides energy. Furthermore, it has shown that for the synthesis of cholesterol, beside acetyl CoA, the NADPH is required (Rohrl and Stangl, 2018).

On the other hand, during cholesterol degradation process the ring structure of cholesterol cannot be metabolized to CO_2 and H_2O as it happened in carbohydrates and proteins due to the absence of the enzymes that are crucial for degrading the ring structure of sterol (Wang et al., 2017). Therefore, beside its conversion to vitamin D, hormones, and its secretion into the bile, about 50% of cholesterol is converted to bile acids (500mg/day) and excreted in feces as an only route for disposal of cholesterol in the body (Figure 6).

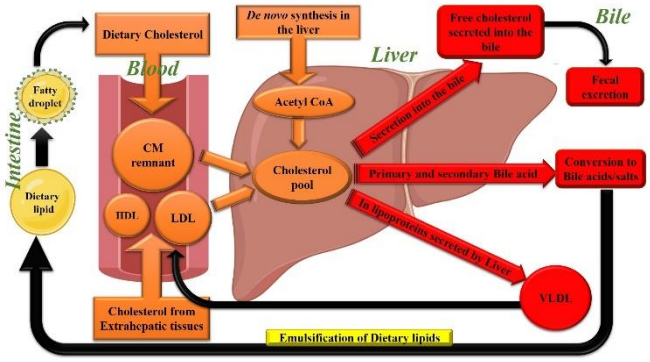

Figure 6: The diagram represents cholesterol homeostasis across the liver and shows the major sources for cholesterol entering the hepatocyte and the main pathways for its disposition from the hepatocyte. CM: Chylomicron, HDL: High Density lipoprotein, VLDL: Very low-density lipoprotein, LDL: Low density lipoprotein.

The maintenance of cholesterol homeostasis is influenced and controlled by several mechanisms. Firstly, by feedback mechanism, at which cholesterol itself participates in the decreasing the transcription of the gene responsible for producing HMG-CoA reductase (DeBose-Boyd, 2008). It has been shown that several hormones like glucagon and glucocorticoids promote the formation of inactive HMG CoA reductase, consequently decreasing cholesterol synthesis, while insulin and thyroxine increase cholesterol production by improving the formation of active HMG CoA reductase as a result increase cholesterol synthesis (Ness et al., 1994). Furthermore, certain types of drugs such as lovastatin (mevinolin) and compactin are act as a competitive inhibitor of the enzyme HMG CoA reductase and, as a result reduce cholesterol synthesis (Gb et al., 2018, Shand and West, 1995). Finally, secretion of bile salts resulted in decrease of the concentration of cholesterol due to continually conversion of cholesterol into the bile salts that facilitate intestinal absorption of lipids and fat-soluble vitamins (Li and Chiang, 2009).

4. CONCLUDING REMARKS

Lipid metabolism plays an important role for many biological functions in the cells. The most constituent part of the lipids includes triglyceride and cholesterol. Both types of lipids are synthesized from both exogenous (dietary) sources and endogenous sources particularly liver and adipose tissue. Due to their insolubility in the blood; lipids are transferred through blood circulation via a spherical molecule called lipoproteins. There are four major classes of lipoproteins at which their size and lipid contents differ from each other, they are Chylomicron, VLDL, LDL and HDL. Metabolism of both cholesterol and triglyceride has a great role in lipid homeostasis in the body. Further works are needed to focus on the enzymes that participate in catalyzing metabolism and to show how they regulate these processes.

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