A Quick Look at Biochemistry: Lipid Metabolism
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Abstract
Lipids and carbohydrates are the energetic molecules and one of the main components of the metabolic system. These molecules circulate in the blood stream and between the metabolic tissues and transfer energy throughout the body. They are degraded and release their energy in the form of adenosine triphosphate (ATP) to be used in anabolic reactions. Anabolic reactions are the energy consumer reactions for synthesis of molecules or energy storage. These include glycolgenolysis, glycolysis, tricarboxylic acid (TCA, citric acid or the Krebs) cycle, electron transfer chain, fatty acid beta oxidation and protein breakdown. Carbohydrates are the main energetic molecules that are consumed by active tissues like muscles. In excess consumption of carbohydrates, they are converted to lipid molecules to be stored in the adipose tissue for the time of starvation. This matter is one of the most important functions of the body in energy homeostasis. In this review, the main lipid groups are introduced and fat biochemical pathways are highlighted and illustrated in a way to facilitate follow up of the lipid biochemical pathways and to give the reader a better understanding of the pathogenesis of metabolic system disorders.

Keywords: Lipid; Carbohydrate; Lipoprotein; Atherosclerosis

Introduction
Lipids are a group of naturally occurring compounds and hydrophobic or amphiphilic molecules that form structures such as vesicles, liposomes or membranes in an aqueous environment. They are a large and diverse group of organic macromolecules; hence, it is always difficult for scientists to provide a specific definition for the word “lipid”. Therefore, due to the absence of a widely-accepted definition in this regard, lipids are categorized based on their different chemical properties including their ability for saponification, their chemical compositions and their building blocks. Saponification is the ability of lipids to be hydrolyzed by basic solutions into compounds such as glycerol and fatty acids (FAs). Based on their chemical composition, lipids are classified into simple and complex lipids. Simple lipids contain one or two different types of compounds. However, complex lipids frequently consist of three or more chemical identities (e.g., glycerol, FAs, and sugar) and they are usually amphiphatic. Based on their building-blocks, lipids are categorized into two ketoacyl and isoprene groups. In this categorization, lipids with ketoacyl subunits are divided into eight categories including FAs, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids, and polyketides while sterol lipids and prenol lipids derived from isoprene subunits. Regardless of all diversities in lipid classification, overlapping between different classifications still exist. This section simply introduces definitions of each category that is described in general books [1]. Nomenclatures, abbreviations and formulas are explained in the text and figures 1 and 2.

Lipid Categorization and their Definitions
In this section a general definition of ‘lipids, fats and oils’ is required that the differ between these terminologies be clarified. Fats consist of a wide group of compounds with the same chemical structure that are derivatives of FAs and glycerol bounded together via “ester” bonds. For instance, triglycerides are triesters of glycerol with three FAs. The properties of fats depend on their structure and particularly on the composition of their FAs. Long chain FAs (LCFAs) yield more energy per molecule during degradation and have a higher melting point compared to short chain FAs. Therefore, fats may be either solid or liquid at room temperature. “Oils” are referred to fats that are liquid at normal room temperature, while “fats” are usually solid at normal room temperature. “Lipids” is used to refer to both liquid and solid fats that are not soluble in water. Oil is also used for any substance that does not mix with water and has a greasy feel regardless of its chemical structure, for instance petroleum, heating oil, and essential oil. Fats are an important part of the diet and are broken down by lipases and serve both structural and metabolic functions. They play a vital role in energy storage in the body, health of skin and hair [2], promoting cell function and protecting body organs against shock and maintaining body temperature. They are sources of essential FAs and are required for the function of fat-soluble vitamins (A, D, E and K). The new fat tissues also function to dilute unsafe levels of substances in the bloodstream by storing them in their adipocytes. This helps to protect vital organs until the substances can be metabolized and/or removed from the body. It is also a useful buffer towards a host of diseases [3].

Fatty acids
FAs (C_{n}COOH) are amphipathic hydrocarbon chain molecules synthesized using acetyl-CoA and malonyl-CoA. They are terminated with a polar, hydrophilic carboxylic acid end and a non-polar, hydrophobic end that is insoluble in water. They usually have an even number of carbon atoms. FAs are used in other complex lipids and may be attached to functional groups containing oxygen, nitrogen, halogens and sulfur. Biologically important FAs are eicosanoids, docosahexaenoic acid, fatty esters and fatty amides. Eicosanoids include prostaglandins, leukotrienes, thromboxanes, which are derived primarily from arachidonic acid and eicosapentaenoic acid. Fatty esters include wax esters, FA thioester coenzyme A derivatives, FA thioester acyl carrier protein (ACP) derivatives and FA carnitine. Fatty amides

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Figure 1a: Abbreviations.

Figure 1b: Abbreviations.

- ABCA1: ATP binding cassette transporter A1
- ABCG1: ATP-binding cassette protein G1
- ACAT: Acyl-CoA:cholesterol acyltransferase
- ACC: Acetyl-CoA carboxylase
- ACP: Acyl carrier protein
- ACTH: Adrenocorticotropic hormone
- AGs: Acylglycerols
- Akt/PKB: Protein Kinase B
- AMPK: 5’ AMP-activated protein kinase
- Apo: Apolipoprotein
- AT: Adipose tissue
- ATGL: Adipose triglyceride lipase
- ATP: Adenosine-5’-triphosphate
- BAT: Brown adipose tissue
- bHLH: Basic helix-loop-helix
- cAMP: Cyclic adenosine 3’,5’-monophosphate
- CE: Cholesteryl ester
- CETP: Cholesterol ester transfer protein
- CM: Chylomicron
- CoA-SH: Coenzyme A
- COP: Coat protein complex II
- CPT-I: Acyl-carnitine palmitoyltransferase transferase I
- CREBP: cAMP response element binding protein
- DAG: Diglyceride (or diacylglycerol)
- DH: Dehydrogenase
- DHAP: Dihydroxyacetone phosphate
- DPG: Diphosphatidylglycerol
- ER: Endoplasmic reticulum and enoyl reductase
- ERK: Extracellular-signal-regulated kinase
- FAO: Fatty acid (FA) beta-oxidation
- FAD: Flavin adenine dinucleotide
- FADH2: Reduced flavin adenine dinucleotide
- FADH+: Flavin adenine dinucleotide
- FAID: Fatty acid-induced insulin pathway disturbance
- FAS: Fatty acid synthase
- FFA: Free fatty acid
- G3PDH: Glycerol-3-phosphate (G3P) dehydrogenase
- G6PDH: Glucose-6-phosphate (G6P) dehydrogenase
- GAP: G3P acyltransferase
- GPCR: G protein-coupled receptors
- GPx1: Glutathione peroxidase 1
- GR: Glucocorticoid receptor
- GTP: Guanosine-5’-triphosphate
- HCN: Hydrogen cyanide
- HDL: High-density lipoprotein
- HMG-CoAR: 3-hydroxy-3-methyl-glutaryl-CoA reductase
- HNF4a: Hepatocyte nuclear factor 4-alpha
- HSL: Hormone-sensitive lipase
- HSPG: Heparan sulphate proteoglycan
- IDL: Intermediate-density lipoprotein
- IL-6: Interleukin 6
- IMM: Inner mitochondrial membrane
- IMTG: Intracellular triglyceride
- IPP: Isopentenyl d(or pyro)phosphate
- KR: Beta-ketoacyl reductase
- KS: Beta-ketoacyl synthase
- LCAT: Lecithin: cholesterol acyltransferase
- LCFAx: Long chain fatty acids
- LD: Lipid droplet
- LDL: Low-density lipoproteins
- LDL-C: LDL cholesterol
- LPL: Lipoprotein lipase
- LPS: Lipopolysaccharide
- LTA: Lipoteichoic acids
- MAGL: Monoacylglycerol (MAG) lipase
- MAPK: Mitogen-activated protein kinases
- MAT: Malonyl/acyltransferase
- mCM: Mature chylomicron
- MVA: Mevalonic acid
- nCM: Nascent chylomicron
- MSH: Melanocyte stimulating hormone
- MUF: Monounsaturated FA
- NADH: Nicotinamide adenine dinucleotide
- NADH2: Reduced nicotinamide adenine dinucleotide
- NADPH: NADPH2
- NAE: N-acyl ethanolamine
- NEFA: Non-esterified fatty acid
- NFKb: Nuclear factor kappa B
- ox-LDL: Oxidized LDL
- OXPHOS: Oxidative phosphorylation
- PAF-AH: Platelet activating factor acetylhydrolase
- PC: Phosphatidylycholine
- PDE: Phosphodiesterase
- PDH: Pyruvate dehydrogenase
- PE: Phosphatidylethanolamine
- PG: Phosphatidylglycerol and prostaglandin E2 (PGE2)
- PIC-1α: PPARα coactivator-1-alpha
- PGJ2: Prostaglandin I2 or prostacyclin
- PI: Phosphatidylinositol
- P3K: Phosphoinositide-3-kinase
- PIP: Phosphatidylinositol phosphate
- PKA(C): Protein kinase A (C)
- PLA2: Phospholipase A2
- PON1: Paraoxonase 1
- PP1: Phosphoprotein phosphatase-1
- PP2A: Protein phosphatase 2A, HMG-CoAR phosphatase
- PPARα: Peroxisome proliferator-activated receptor-alpha
- PP1-1: Protein phosphatase inhibitor-1
- PS: Phosphatidylserine
- PUFA: Polyunsaturated FAs
- rCM: Remnant chylomicron
- rDL or LDL: Remnant Intermediate-density lipoprotein
- RCT: Reverse cholesterol transport
- S1P: Site-1 protease
- S1P: Sphingosine-1-phosphate
- SCAP: SREBP cleavage activating protein
- SCD: Stearoyl-CoA desaturase
- SM: Sphingomyelin
- SR-B1: Scavenger receptors class B type I
- SRE: Sterol regulatory element
- SREBP: Sterol regulatory element-binding protein
- SSS: Sterol-sensing domain
- TAG: Triacylglycerol, triacylglyceride
- TCA: Tricarboxylic acid
- TE: Thiolase
- TG: Triglyceride
- TM: Transmembrane
- TNFα: Tumor necrosis factor alpha
- TSH: Thyroid-stimulating hormone or thyrotropin
- USF: Upstream regulatory factor
- VLDDL: Very low-density lipoprotein
include N-acyl ethanolamines, such as cannabinoid neurotransmitter anandamide.

Chemically, FAs are categorized into saturated and unsaturated forms. In saturated FAs (C\textsubscript{n}H\textsubscript{2n+1}COOH), their carbon chain is saturated with hydrogen during hydrogenation process. Unsaturated FAs (C\textsubscript{n}H\textsubscript{2n-1}COOH) contain double bonds within their carbon chain. Monounsaturated FAs (MUFAs) have only one double bond and polyunsaturated FAs (PUFAs or polyenoic FAs) contain two or more double bonds. Unsaturated fats can be further divided into Cis or Trans geometric isomers, which significantly affect the molecule’s configuration, structure and function of cell membranes. Most naturally occurring FAs are of the Cis configuration, while Trans configuration significantly increases the risk of coronary heart disease. Saturated and unsaturated forms differ in their energy content and melting point. Energy that is yielded during metabolism of unsaturated fats is less than that of saturated fats with the same number of carbon atoms. Moreover, saturated fats are typically solid at room temperature, while highly unsaturated fats are oily.

**Acylglycerols (AGs)**

Acylglycerols (glycerolipids, glycerides or neutral fats) are glycerol esters of FAs. Esterification of one, two or three FAs with glycerol yield monoacylglycerol (MAG), diacylglycerol (DAG) or triacylglycerol (TAG) respectively. TAGs function as energy store in the adipose tissues that are hydrolyzed to release glycerol and FAs for consumption of their energy in the shortage of energy. The other molecules in this category are glucosylglycerol (such as digalactosyldiacylglycerol and seminolipid), which are molecules composed of sugar residues and glycerol.

**Waxes**

Waxes are saponifiable, very hydrophobic compounds that are biosynthesized by many plants and animals. They are formed by esterification of long chain FAs (alkyl groups) with hydroxyl group of long chain fatty acids or alcohol such as sterols, aminoalcohols, hydroxy carotenoids or terpenols. They are organic compounds that are plastic near ambient temperatures. Above 45°C, they melt to produce a low viscosity liquid. Natural waxes are a mixture of waxes and other substances such as hydrocarbons, fatty aldehydes, FAs, terpenes, etc, that form a protective coating in plants and animals against desiccation and parasites. Synthetic waxes are long-chain hydrocarbons lacking functional groups.

**Phospholipids**

Phospholipids are complex lipid molecules in which phosphate group attaches to one alcohol that may be linked to fatty chains. Phospholipids are the major structural constituents of all biological membranes because they tend to form lipid bilayers corresponding to their ionic head and hydrophobic tails. They also may be involved in signal transduction. Phospholipids are classified into two main groups: glycerophospholipids and sphingosyl phosphatides.

Glycerophospholipids are amphipathic molecules that are formed by esterification of an alcohol to the phosphate of phosphatidic acid (1,2 diacylglycerol 3-phosphate). They are found in the neural tissue and lipid bilayer of cell and function in metabolism and cell signaling. They are subdivided into phosphatidylcholine (PC or lecithin), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), phosphatidylglycerol (PG) and cardiolipin or diphosphatidylglycerol (DPS). Phospholipids are a group of phospholipids whose structure one fatty aldehyde is substituted by the FA. Therefore, they are phosphatidyl molecules that are linked to ethanolamine, choline, serine or inositol. Glycerophospholipids can be hydrolyzed by phospholipases or by alkaline solutions.

Sphingosyl phosphatides are lipids containing (sphingo)ceramides linked by their hydroxyl group to a phosphate group, itself esterified to a polar head group such as choline (in sphingomyelins (SMs)), ethanolamine and glycerol or to a glycoside moiety (in glycolipids).

**Sphingolipids**

Sphingolipids comprise a complex range of lipids in which FAs are linked via amide bonds to a long-chain base or sphingoid. They are found in the neural tissue and lipid bilayer of cell and function in metabolism and cell signaling. They are subdivided into sphingadiylcholine (PC or lecithin), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), phosphatidylglycerol (PG) and cardiolipin or diphosphatidylglycerol (DPS). Phospholipids are a group of phospholipids in whose structure one fatty aldehyde is substituted by the FA. Therefore, they are phosphatidyl molecules that are linked to ethanolamine, choline, serine or inositol. Glycerophospholipids can be hydrolyzed by phospholipases or by alkaline solutions.
Ceramide is a product that is yielded by amide-linkage of FA to the sphingosine molecule. Combination of ceramide with one molecule of phosphocholine produces SM (or ceramide phosphocholine). Glycosphingolipids are molecules composed of one or more sugar residues linked to the sphingoid base via a glycosidic bond. Examples of glycosphingolipids are cerebrosides, globo sides and gangliosides. Cerebrosides are made by glycosidic linkage of the hydroxyl group of ceramide with one hexose molecule (glucose or galactose). In globo sides one hexose molecule is substituted with dimmers. The molecular structures of gangliosides are similar to cerebrosides. It has at least three sugars, one of which must be sialic acid. Sphingolipids protect the cell surface against harmful environmental factors. Certain complex glycosphingolipids are involved in cell recognition and signaling. Ceramide and sphingosine-1-phosphate are important mediators in the signaling cascades involved in apoptosis, proliferation, stress responses, necrosis, inflammation, autophagy, senescence, and differentiation. In experimental animals, feeding sphingolipids inhibits colon carcinogenesis, reduces low-density lipoprotein (LDL) cholesterol and elevates high-density lipoprotein (HDL) cholesterol.

**Terpenes**

Terpenes are lipids with the building blocks of isoprene units (2-methyl 1,3-butadiene, C=C(C)-C=C). Isoprene units may be linked in a head to tail or in a head to head fashion, and the resulting compounds can be cyclic or acyclic, and saturated or unsaturated. Terpenes are classified depending on the number of isoprene units incorporated into the basic molecular skeleton. Many terpenes are hydrocarbons, although oxygen-containing compounds such as alcohols, aldehydes or ketones (terpenoids) are also found. Moreover, isoprene units are also found within the framework of certain phenols (quinones) and indole alkaloids. Terpenes are probably the most widespread group of natural products such as essential oils, resins, waxes, rubber, carotenoids, etc. They are also involved in the synthesis of steroids, vitamins, and chlorophyll, as well as in the acylation of proteins.

**Steroids**

Steroids are modified triterpenes derived from squalene. They are lipid compounds based on the fundamental saturated tetracyclic hydrocarbon 1,2-cyclopentanoperhydrophenanthrene (sterane or sterol). Steroids are steroid alcohols or steroids with a hydroxyl group in the 3-position of the A-ring. Sterols form part of the cellular membrane where they influence their fluidity and function and participate in developmental signaling as secondary messengers. The most important sterols are cholesterol, which is an important component of membrane lipids, along with the glycerophospholipids and SMs. Other examples of sterols are bile acids and their conjugates, which in mammals are oxidized derivatives of cholesterol and are synthesized in the liver. Secosteroids, comprising different forms of vitamin D, are characterized by cleavage of the B ring of the core structure. Steroids are important components of cell membranes, hormones and vitamin D precursors.

**Prenol lipids**

Prenol lipids are compounds that are synthesized from the five-carbon-unit precursor isopentenyl di (or pyro)phosphate (IPP) and dimethylallyl diphosphate that are produced mainly via the mevalonic acid (MVA) pathway. The simple isoprenoids (linear alcohols, diphasphates, etc.) are formed by the successive addition of CS units and are classified according to the number of these terpene units. Polyterpenes are structures containing greater than 40 carbons. Carotenoids are important simple isoprenoids that function as antioxidants and as precursors of vitamin A. Another biologically important class of molecules is exemplified by quinones and hydroquinones, which contain an isoprenoid tail attached to a quinonoid core of non-isoprenoid origin. Vitamin E and vitamin K, as well as ubiquinones, are examples of this class.

**Saccharolipids**

Saccharolipids are compounds in which FAs are linked directly to a sugar backbone. In saccharolipids, a monosaccharide substitutes for the glycerol backbone of glycerolipids and glycerophospholipids. The most familiar saccharolipids in Gram-negative bacteria are the acylated glucosamine precursors of the Lipid A component of the lipopolysaccharides (LPS).

**Polyketides**

Polyketides are synthesized by polymerization of acetyl and propionyl subunits by classic enzymes as well as iterative and multimodular enzymes that share mechanistic features with the FA synthases. They comprise a large number of secondary metabolites and natural products from animal, plant, bacterial, fungal and marine sources, and have great structural diversity. Many polyketides are cyclic molecules whose backbones are often further modified by glycosylation, methylation, hydroxylation, oxidation, and/or other processes. Many commonly used anti-microbial, anti-parasitic, and anti-cancer agents are polyketides or polyketide derivatives, such as tetracyclines, erythromycins, avermectins, and antitumor epothilones.

**Cyanolipids**

Cyanolipids are made with FAs esterified to mono- or dihydroxy nitrile moieties. Cyanolipids are mainly found in cyanobacteria and plants, and their hydrolysis usually produces hydrogen cyanide (HCN), which has a protective effect.

**Phenolic lipids**

Phenolic lipids are mainly present in plants, fungi, and bacteria. This heterogeneous group includes simple phenols and polyphenols as well as their derivatives, and can be classified into coumarins, quinones, flavonoids and phenolics. They have a wide range of biological effects including antimicrobials, antioxidants, toxins, enzyme inhibitors, etc. The single-ring lipid compounds are made up of a catechol, a resorcinol or a hydroquinone nucleus alkylated by a variable non-isoprenoid carbon chain.

**Lipids containing amino−compounds**

These compounds are made of linking FAs with the substances that contain amino groups. They are classified as (i) aminoalcohols, (ii) ceramides, (iii) lipoamino acids and lipopeptides and others like (iv) acyl-CoAs (thioester bond), acyl carnitines (ester bond) and dopamine (amide bond). Aminoalcohols are long carbon chains containing one or more alcohol groups and one amino group synthesized by condensation of an amino acid and an acyl-CoA. Aminoalcohols can be saturated or unsaturated, linear or branched and can have additional groups like ethanolamine, choline, and sphingosine. The most common aminoalcohols are sphingosine and their derivatives. Ceramides are
the simplest sphingolipids that result from the condensation of an aminoalcohol and a FA through an amide bond (when the condensation is through an ester bond the result is a wax). Free sphingoceramides are found in some tissues or are involved as messenger molecules, although their alcohol function is frequently linked to a glucose (glycosphinoglipids) or is esterified by a phosphoric acid linked to a polar group (SMs). Another important group of ceramides are N-acylthanolamines (NAEs). Lipopoemino acids and lipopeptides are amphipathic membrane lipids composed of one amino acid (lipopmino acids) or more amino acids (lipopeptides) linked to a FA through an amide bond. A second FA can be linked to the amino acid through an ester bond. They may act as virulence factors, or have pharmacological activity (e.g., lipstatin is a lipase inhibitor used against obesity).

**Glycolipids**

Glycolipids are complex membrane lipids containing a glycosidic moiety. They are classified into (i) glycosides of FAs, lipid alcohols and steroids, (ii) glycosphingolipids or glycolipids based on glycerol, (iii) glycosphingolipids or glycolipids based on ceramides, (iv) glycosides of lipoamino acids or lipoamino acids containing glycosyl moieties and (v) LPS.

Lipids of group (i) are made up of linking a glycosyl moiety (one or several units) to one or more FAs, fatty alcohols, and alkyl chains. Lipids of group (ii) consist of a mono-, di-, or oligosaccharide moiety that via the glycosidic bonds links to the hydroxyl group of glycerol, which may be acylated (or alkylated) with one or two FAs. Furthermore, these glycolipids may contain additional groups and chains. They form compounds such as lipoteichoic acids (LTA) of Gram-positive bacterial membranes, which consist of polymers of glycerol-1-phosphate linked to a (phosphatidyl) glycosyl diglyceride. Lipids of group (iii) are a mono-, di-, or oligosaccharide moiety linked to the hydroxyl group of a ceramide backbone. The ceramide and the glycosyl group(s), which can be neutral (unsubstituted) or acidic (substituted with carboxyl, sulphate or phosphate group(s)), can have further modifications. The best known ones are cerebrosides (a ceramide linked to a hexose) and gangliosides (a ceramide linked to an oligosaccharide containing sialic acid). Lipids of group (iv) including lipids having an amino acid with N-acetyl and/or ester linkages and lipids having a glycerol and an amino acid with ether linkage. LPS are the endotoxic O-antigens found in outer membranes of Gram-negative bacteria. The lipid part (Lipid A) is responsible for the toxic activity of these bacteria and septic shock and comprises of a backbone of β-1,6-glucosaminyl-glucosamine. The 3-position of glucosamine II establishes a glycosidic linkage with a long-chain polysaccharide. The other hydroxyl and amine groups are through an amide bond.

**Proteolipids**

Proteolipids or fatty acylated proteins are proteins that contain one or more covalently associated acyl moieties. Proteolipids are divided into (i) myristoylated proteins in which myristic acid is bound by amide linkage to glycine residue of the protein and (ii) palmitoylated proteins in which palmitic acids (or other long FAs) are bound by thioester linkages to cysteine residues of the protein. Acylation is one of the most widespread modifications of cytosolic and membrane proteins in all living things and can direct soluble proteins to membranes.

**Biological Functions of Lipids**

Fats are one of the main components of the body which are involved in many different functions. Mainly, they function in the structure of cell membrane and they are stored in adipose tissue in the form of triacylglycerol (TAG, triacylglyceride or triglyceride) as the source of energy in the body; hence, they are biologically active molecules.

**Membranes**

A biological membrane is a form of lipid bilayer in an aqueous system, in which the polar heads of lipids align towards the polar aqueous environment, while the hydrophobic tails tend to cluster together, forming a vesicle, micelles, liposomes, or lipid bilayers depending on the concentration of the lipid. The glycerophospholipids, SM and sterols (mainly cholesterol) are the main structural components of biological membranes.

**Energy storage**

Triglycerides are a major form of energy storage in adipose tissues. The complete oxidation of FAs provides about 9 kcal/gram energy that is higher than that produced from the breakdown of carbohydrates and proteins (4 kcal/gram).

**Signaling**

Lipid signaling is a vital part of cell signaling. Lipid signaling
may occur via activation of G protein-coupled receptors (GPCRs) and members of lipid categories as signaling molecules and cellular messengers. These include sphingosine-1-phosphate, diacylglycerol (DAG), PI phosphates (PIP2), PS, prostaglandins, steroid hormones such as estrogen, testosterone, cortisol and oestrogens such as 25-hydroxycholesterol.

Other functions

The “fat-soluble” vitamins (A, D, E and K), which are isoprene-based lipids, are essential nutrients stored in the liver and adipose tissues, with a diverse range of functions. Acyl-carnitines are involved in the transport and metabolism of FAs in and out of mitochondria during beta oxidation. Polyynoens and their phosphorylated derivatives also play important roles in transport of oligosaccharides across membranes. Polynoen phosphate sugars and polynoen diphosphate sugars function in extracytoplasmic glycosylation reactions, in extracellular polysaccharide biosynthesis (for instance, peptidoglycan polymerization in bacteria), and in eukaryotic protein N-glycosylation. Cardiolipins are a subclass of glycerophospholipids containing four acyl chains and three glycerol groups that are particularly abundant in the inner mitochondrial membrane. They are believed to activate enzymes of oxidative phosphorylation reaction.

Fats and their Importance in the Pathogenesis of Metabolic Disorders

Fats and carbohydrates are the energetic molecules of the body. This point highlights the metabolic functionality of these molecules in the body. However, lipids and carbohydrates have different biophysical properties; therefore, they influence the metabolic system of the body in different ways. Lipids are insoluble particles in the watery based circulation that require transporters for transfer. Transporters are soluble particles such as vesicles, endoplasmic reticulum (ER), the Golgi apparatus, intracellular lipid droplets and intra-circulatory lipoproteins [4,5]. These particles are made from lipids and proteins that influence the function of the particles; therefore, each particle has different biological functions in the body. However, carbohydrates are soluble crystal molecules that do not need carriers for transport. Both the carbohydrates and lipids influence blood viscosity, which has a significant effect on pathological events [6-8]. The change of viscosity affects cytoskeleton function and movement of intracellular organelles [9] and as an environmental factor changes gene expression [10]. Furthermore, viscosity has a shear stress effect in the circulation and together with constituents of the lipid particles influences the cardiocerebrovascular function [7]. During atherosclerosis, the environmental hyperviscosity could enhance atherothrombosis via influence on the membrane stretch [13].

With regard to biochemistry, lipids have almost double energy than carbohydrates and are considered as the energy storage molecules in the form of TAG in adipose tissues. Therefore, the main function of adipose tissue is the lipid storage capacity and not the catabolic function. Storage of energy in the form of TAG in adipose tissues is the best way for energy reservation in comparison with glycogen storage in the skeletal muscles and liver because of three reasons. Firstly, fats produce 9.3 kcal/gram, while this amount for carbohydrates is 4 kcal/gram. Secondly, lipid storage in adipose tissues requires less water than carbohydrate storage in the form of glycogen. Therefore, compared to the glycogen storage in skeletal muscle and liver the weight of adipose tissues is less than the amount of energy which is reserved in it [14]. Finally, the body cannot use the energy of lipids directly in the metabolic pathways. For this purpose, lipids should be degraded to acetyl-CoA, which is the intermediate molecule of glucose oxidation process, to be used in the mitochondrial oxidative phosphorylation (OXPHOS) reaction and release their energy. Therefore, there is a close interaction between lipid and carbohydrate pathways in cells. On the one hand, storage of carbohydrates in the body is regulated in balance of neutral lipids such as cholesterol esters, TAG or FA. In shortage of available energy in the form of carbohydrate, lipolysis is increased via FA oxidation (FAO) to produce acetyl-CoA to be used in carbohydrate pathways. This capacity of the body, which is nutritional storage in the form of lipids in the feeding state for usage in the form of carbohydrates in the starvation state, is one of the fundamental capacities of living things and is essential for life.

Lipid storage in the body happens normally in the white adipose tissue (WAT). Therefore, structurally the main cytoplasmic organelles of WAT-adipocytes consist of a nucleus and a (in mature adipocyte) or lots of (in small adipocytes) functional lipid organelles for sequestration of extracellular lipids (Figure 3) [14]. The number and activity of mitochondria in this tissue is not high. These lipid organelles that are also called lipid droplets (LDs) have almost the same structural properties as lipoproteins (Figure 4). They have an external layer of phospholipids that covers the intra-organelle TAGs. LDs exist in different organs, namely skeletal muscle, liver and pancreas; however, in adipose tissue they are highly specialized for lipid storage [14].

Carbohydrates are the energetic molecules that the body directly consumes in starvation and because of their solubility and availability have a strong influence on the metabolic system of the body. The required energy of the body is produced either directly via degradation of lipids or indirectly via nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH) oxidation during the OXPHOS reaction. Therefore, functional mitochondria are one of the fundamental parameters in proper cellular metabolism, mainly in the catabolic tissues such as hepatocytes and myocytes. Skeletal muscles, which require a huge amount of energy for movement, have highly functional mitochondria. In expert athletes, LDs of the skeletal muscles that are in close contact with mitochondria are expanded to store a high level of intramuscular triglyceride (IMTG). Athletes' muscle cells have high insulin sensitivity that could be because of this close functional proximity between the mitochondria and the LDs as well as the high ability of their LDs for intracellular-lipid sequestration [14]. In contrast, during physiological obesity the concentration of glucose and free FAs (FFAs) in circulation and consequently the metabolic functionality of metabolic tissues will increase to storage the excess energy level of the body in the form of triacylglycerol in their LDs. This leads to increase in the function of mitochondria for OXPHOS reaction of the energetic compounds of acetyl-CoA (product of both lipid and carbohydrate degradation). In the pathological obesity state, mitochondrial dysfunction lead to FAO reduction, lipotoxicity in the cytoplasm, ER stress and metabolic disorders [15-18]. In mitochondrial dysfunction, the amount of heat increases. Heat generation happens due to the high amount of ATP production following OXPHOS reaction as well as the leaky membrane of the inner mitochondrial membrane (IMM) during ATP production. In obese adults, the mass and function of the brown adipose tissue (BAT) are strongly low. Activated BAT could have a great effect in alleviation of the metabolic disorders during obesity [19]. BAT increases energy expenditure and weight loss and improves lipid and glucose homeostasis. Therefore, active BAT is able to uptake large quantities of lipid and glucose from the circulation [20]. Moreover, each ATP produces 8 kcal that is 20% of its total energy and the rest of the energy is wasted as heat to maintain body temperature. In obesity state, there is also defect in LD degradation and TAG lipolysis due to the low
level of adipose triglyceride lipase (ATGL) gene expression in skeletal muscles [21,22]. This matter increases the level of their bioactive lipid species such as diglyceride (or diacylglycerol, DAG) and ceramides that is known as "lipotoxicity" [22]. TAG accumulation in glycolytic muscles can induce FA-induced insulin pathway disturbance or (FAID) [14].

**Origin of Fats and Lipid Uptakes**

Fats originate from the external (TAG, cholesterol and phospholipids of food) and internal parts of the body (TAG and cholesterol storages of adipose tissues and lipoproteins). In the external origin, lipid solubilization (or emulsification) in the intestine happens by lipophilic bile acids, which are synthesized from cholesterol in the liver. This process renders fats accessible to the lipases. Fat digestion starts from the stomach by gastric lipase, which is active and stable in acidic environments [23]. The main part of lipid degradation takes place in the small intestine and via steapsin or pancreatic lipase and pancreatic phospholipase A2 (PLA2). These lipases affect TAGs, which are produced via esterification of three FAs with the carbon backbone of glycerol. Fifty percent of TAG degradation happens by pancreatic lipases that separate sequentially the acyl root (or FA) of the two outer positions (α1 and α2) of the glycerol carbon group of TAGs and produce monoglyceride. PLA2 is able to split off the FA of the middle position (β) of the glycerol carbon group of monoglycerides and release glycerol in 40% of TAG degradation. Ten percent of the TAGs can be directly absorbed from the intestine cells to the circulation.

There are different hormones in the small intestine that can affect fats. These hormones are (i) secretin and gastrin that stimulate secretion of pancreatic electrolytes, (ii) pancreozymin that stimulates the secretion of pancreatic lipase to degrade lipids and TAGs and (iii) cholecystokinin that causes contraction of gall bladder for entrance of bile salts in the duodenum.

Monoglycerides, following absorption in the intestinal enterocytes, are assembled again to produce TAGs. Heavy lipids such as LCFAs, TAGs, monoglyceride, DAGs, phospholipids and cholesterol enter the bloodstream via the lymphatic vessels. Short-chain FAs directly enter the circulation and form a complex with albumin and enter the liver via the portal vein [24].

In intestinal cells, lipids are used for chylomicron (CM) assembly and are then released to the lymphatic vessels and circulation. CMs have a bipolar external monolayer that covers the hydrophobic internal lipids. In the endothelial cells of tissues, they become degraded via lipoprotein lipase (LPL) and their FAs enter the liver cytoplasm for FAO.

**Retour of External Cholesterol in the Body**

Most of the external cholesterol is in the form of free cholesterol, which is the form that can be absorbed by the enterocytes. Therefore, esterified cholesterol loses its FA using cholesterol esterase and is converted to the free form. Inside the enterocytes, the free cholesterol becomes esterified again and are assembled together to form CMs, which enter the bloodstream via lymphatic vessels. In circulation, CMs are degraded by LPL and the esterified cholesterol enters the liver via the portal vein and converts to free cholesterol. Eighty percent of cholesterol in the liver is stored in the gallbladder in the form of bile salts and 20% is used for generation of other cholesterol-based products like sex hormones, phospholipids, CMs, cell membrane lipids, and vitamin D3. Cholesterol is released from the gallbladder to the intestine and is again absorbed via enterocytes.

**Lipoproteins**

The aqueous environment of the body poses problems with the transport of the hydrophobic substances between organs. Hence, animals have evolved plasma lipoproteins that facilitate transport of TAGs and cholesterol between the liver, adipose compartment and tissues [25]. Originally these structures were not thought to be of major importance for transmitting endocrinologically relevant signals, but this view is now changing. In 2006, Panakova and colleagues [26] showed that lipophorin (the Drosophila equivalent of very low-density lipoprotein (VLDL) in mammals) carried hydrophobic ligands activating Wnt signaling in atherosclerotic plaques [30,31]. Apart from hydrophobic morphogens, other hydrophobic signaling molecules may also reside in lipoproteins. Many hormones are highly hydrophobic and evidence

![Figure 5: Comparison between the structures of lipoproteins](image)

There is a reverse correlation between the size and density of lipoproteins that represent the percentage of the lipids and proteins in these particles. For instance, HDL has the highest density (and protein percentage) and conversely the lowest size (and lipid percentage).
is available that lipoproteins may be involved in their efficient transport through the body. In ApoE−/− mice for instance, both endocannabinoid [32] and glucocorticoid [33] signaling is disturbed and is strongly associated with inflammation, insulin unresponsiveness and hepatic steatosis, suggesting that endocannabinoid carrying by lipoproteins is a relevant process. Thus the lipoprotein compartment may have an underestimated role in the human endocrinology.

Lipoprotein constituents

Lipoproteins are biochemical transporters that are composed of proteins and lipids. The main function of lipoproteins in the body is transport of lipids through the circulation from the sources of lipids such as the intestine and liver to other tissues that require these fats as their energy suppliers or use them as structural materials in their membrane. Their structure consists of an amphipathic monolayer of lipids, which is composed of an assembly of hydrophilic head groups of phospholipids and free (non-esterified) cholesterol together with apolipoproteins (apo) that face the aqueous phase and cover the intra hydrophobic (non-polar) part of their structure which are TAGs and cholesterol esters [34]. The polarity of the surface lipoproteins prevents their aggregation and allows them to be solubilized in the circulation [35]. Lipids of the lipoproteins are TAG, free cholesterol, cholesterol esters, and phospholipids like PC, PE, PI and SM [25]. The particle proteins, via their interactions with each other and also with other proteins including enzymes and the cell surface proteins, determine whether the lipids should be absorbed from or exported to particular tissues. The overall metabolism and structure of lipoproteins is determined by apolipoproteins and also the interactions with the peripheral receptor molecules [36,37]. The main categorization of lipoproteins is based on their diameter and density as well as their proteins and lipids compositions. Based on the density, which results from the percentage of the proteins and lipids in their structure, they are mainly divided into five major classes including HDL, LDL, IDL, VLDL and CMs [38]. The density of lipoproteins is associated with the percentage of their protein. In contrast, there is an inverse association between the size of a lipoprotein and its density. HDL is the smallest lipoprotein and has more density with the highest percentage of proteins (Figure 5).

Metabolism of lipoproteins and atherosclerosis

LDL poses pathological challenges relating to atherosclerotic plaque formation through the distribution of cholesterol from the liver to the tissues and especially the endothelium [27]. Conversely, HDL is involved in the transport of lipids from tissues and back to the liver or excretion from the body, a process called reverse cholesterol transport (RCT) [39]. Thus, HDL has an anti-atherogenic and protective effect in the body. Chylomicrons and VLDL are involved in the transport of TAGs. Chylomicrons transport the newly absorbed TAGs from the intestine to the skeletal muscle for consumption, to the adipose tissue for storage or to the liver for synthesis of VLDL. VLDL is secreted from the liver to the circulation for transport to other tissues including adipose tissue.

Another nomenclature, which is used for explanation of the lipoprotein metabolism pathway, based on the origin of their lipid, is exogenous and endogenous lipoprotein pathways. In the exogenous lipoprotein pathway, the lipid components of the lipoproteins are synthesized by the intestine from dietary lipids, while in the endogenous lipoprotein pathway the lipid components are synthesized by the liver [40]. In the exogenous pathway, the intestinal lipids (TAGs, phospholipids, cholesterol) are absorbed by the epithelium and assembled with apoB48, apoA-I, apoA-II and apoA-IV to make the nascent chylomicron (nCM), which is secreted to the lymphatic vessels (via its apolipoproteins) and released directly (bypass liver) to the circulation via the subclavian vein. In the circulation, HDL delivers its apolipoproteins (apoC-II and apoE) to the rCM to make mature chylomicron (mCM). These exchangeable apolipoproteins protect the TAG-rich lipoprotein particles (CM and VLDL) from non-specific interaction with the plasma and lead to their correct configuration for the action of LPL. In the skeletal muscle and AT, mature chylomicron, via activation of the endothelial LPL in the presence of phospholipids and its cofactor apoC-II, ensures the hydrolysis of TAG to glycerol and FAs to be consumed or stored by tissues. Glycerol is returned to the liver and kidney to be converted to the glycolytic intermediates and the phospholipid and apoA and apoC of mCM is transferred to HDL. The hydrolyzed chylomicron, known as remnant chylomicron (rCM), contains cholesterol esters, apoE and apoB48. rCM is transferred to the liver through the circulation, which in turn rCM ends up with endocytosis mediated by the interaction of apoE with the rCM receptors in the hepatocytes [38,41-44]. Ultimately, rCM is degraded in lysosome, which results in release of FAs and glycerol [41].

In the endogenous pathway, liver is the main source of VLDL lipid constituent. The assembly of intracellular TAG and cholesterol in the liver is maintained by apoB100 and delivered to the circulation by lipid transporters [40,45]. Similar to CMs, circulating HDL provides apoE and apoC-II to VLDL [46,47]. VLDLs contain TAG, cholesterol, cholesteryl ester, apoB-100, apoC-I, apoC-II, apoC-III and apoE. Thus, VLDL plays an important role in the delivery of FFA to the adipose tissue to store energy as inactive fuel in the form of TAGs in the adipocytes-associated LDs or supply active energy for skeletal muscles and other tissues via FFA delivery [45]. LPL ensures release of FAs and glycerol via hydrolyzation of TAGs and loss of apoCs from VLDL to transfer back to HDL. The VLDL is then converted to remnant VLDL or IDL, which contains apoB-100 and apoE and is an interplayer between VLDL and LDL [38]. The released energy components in the form of glycerol and FAs are used by the skeletal muscles and adipocytes. As in CMs, the interaction of rVLDL or IDL with LDL receptors of the liver in the presence of apoB-100 and apoE ends in TAG hydrolyzation and loss of apoE to constitute the rLDL or LDL lipoproteins. ApoE is transferred back to HDL. Therefore, the predominant apolipoprotein of LDL is apoB-100. Lack of apoE in LDL decreases the affinity of LDL to its cognate receptors of the liver. Fusion of endosomes with lysosomes leads to degradation of apolipoproteins and hydrolyzation of cholesterol esters to free cholesterol, which is incorporated into the plasma membranes. Excess intracellular cholesterol enhances the activity of acyl-CoA: cholesterol acyltransferase (ACAT) for re-esterification of cholesterol to the cholesterol esters for intracellular storage.

Many studies have shown that hypertriglyceridemia (with VLDL as TAG carrier) similar to hypercholesterolemia (with LDL as cholesterol transporter) is directly linked to the risk of cardiovascular morbidity and mortality and atherosclerosis [48]. Atherosclerosis is an inflammatory disease that is triggered by oxidation of LDL cholesterol (LDL-C), which in turn the oxidized LDLs (ox-LDLs) are trapped in the extracellular matrix of the sub-endothelial space [49]. The ox-LDL is absorbed by the tissue macrophages to form foam cells (macrophages loaded with lipids) and promote inflammatory gene expression (e.g., nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway) that initiate the inflammatory response. Inflammation primes the formation of fatty streak and in turn the arterial calcification [50,51]. This is the starting point for the aggregation of coagulation cells that express different coagulation factors for initiation and maintenance
**Fatty acid β-oxidation**

Utilized

- CoA-SH
- ATP, Mg

Yielded

- Acyl-CoA
- Acyl-CoA dehydrogenase
- FADH2
- H2O

**Dehydroacyl-CoA** (or 2-trans-enoyl-CoA)

- Enoyl-CoA hydratase
- 3-hydroxyacyl-CoA
- 3-hydroxyacyl-CoA dehydrogenase
- NADH2

**3-ketoacyl-CoA**

- 3-Ketoacyl-CoA thiolase (or acetyl-CoA acyltransferase)
- Acetyl-CoA

**Acyl-CoA (-2C)**

- Propionyl-CoA
- P-CoA carboxylase

**D-Methylmalonyl-CoA**

- Methylmalonyl-CoA epimerase

**L-Methylmalonyl-CoA**

- Methylmalonyl-CoA mutase
- Succinyl-CoA

**Figure 6:** Fatty acid beta-oxidation (FAO)
The cytoplasmic FAO reaction is a multistage process in which LCFAs are degraded to the multiple two carbon glycolysis intermediate (acytlate-CoA) as well as one three carbon component (propionyl-CoA) in the FAs that contain an odd number of carbon atoms. In this catabolic reaction, the reduced components of the OXPHOS reaction (NADH, FADH2) are produced. Abbreviations are explained in figure 2.

HDL also, via extraction of the free cholesterol from cell membrane, decreases the intracellular esterified cholesterol, which is mobilized to the membrane to replace the membrane cholesterol. This process happens via the action of ATP-binding cassette protein G1 (ABCG1). HDL moves to the liver to bind the scavenger receptors class B type I (SR-BI) and release its cholesterol esters to the hepatocytes through caveolae; however, it is not absorbed to the hepatocytes.

HDL has a different effect on vascular biology. In normal state, the apoA-I, GPx1, PON1 and PAF-AH of HDL have antioxidant properties; whereas in the inflammatory state, these properties become inactivated and HDL becomes proatherogenic. Besides, modification of apoA-1 by myeloperoxidase, which is produced from the atherosclerotic plaques, tends to lower affinity of HDL for interaction with macrophage and removal of cholesterol from foam cells.

HDL transfers its cholesterol esters to VLDL and LDL via the activity of CETP and its RCT property. In this situation TAG is transferred from VLDL to HDL. Ultimately, conversion of VLDL to LDL transfers these cholesterol esters to the hepatocytes via LDL receptors. However, some of the LDLs are oxidized in the peripheral tissues and induce atherosclerosis. Furthermore, TAG-rich HDL is targeted by hepatic lipase and becomes smaller and unstable and loses its apoA-I. In the absence of apoA-I, HDL is not able to act as RCT. One approach for increasing the circulatory level of HDL is inhibition of CETP. CETP blockade reduces cholesterol transfer to VLDL and LDL and decreases the level of ox-LDL and increases the level of TAG-rich HDLs [55].

**Lipoprotein Lipase (LPL)**

These pancreatic, hepatic, and endothelial lipases are soluble hydrolytic enzymes whose main function lies in the hydrolysis of TAGs of the circulatory TAG-rich lipoprotein particles, namely CMs and VLDL. LPL and converting their TAGs to non-esterified FAs (NEFA) and VLDL and converting their TAGs to non-esterified FAs (NEFA) and 2-monocarboxylicerol [17,56,57]. They also increase the cellular uptake of rCM, cholesterol rich lipoproteins and FFAs. The apolipoproteins of lipoprotein particles have a role in targeting of the lipoproteins to the tissues and also functions as a cofactor (especially apoC-II) for LPL although apoC-III is an inhibitor of LPL activity [58,59]. Apart from its enzymatic function, LPL has an important role in lipid metabolism and transport. LPL also acts simultaneously as a linker between lipoproteins and cell surface receptors, including proteoglycans such as cell surface related LDL receptors and heparan sulfate proteoglycans (HSPG) and thus facilitates the uptake of lipoproteins by the tissues [59]. In the literature, malfunctioning of LPL has been associated with a plethora of pathological conditions including atherosclerosis, obesity, diabetes, chylomicronemia, Alzheimer disease, and cachexia [60,61].

Expression of LPL is mediated through a complex interaction between sterol regulatory element-binding protein (SREBP), cytokines, LPS [60], peroxisome proliferator-activated receptor-alpha (PPARα), cyclic adenosine 3',5'-monophosphate (cAMP) response element binding protein (CREBP) and activator protein-1-like factors [60,62,63]. In addition, expression of LPL is enhanced by the differentiation of macrophage and adipocyte and is under the influence of specific nutritional factors, blood glucose levels, FAs, and the levels of hormones such as insulin, catecholamine, thyroid hormones, growth hormone, estrogen, prolactin, parathyroid hormone, retinoic acid and vitamin D3 [60]. LPL is produced in the parenchymal cells of adipocytes, heart, skeletal muscles as well as macrophages and is distributed along the vascular mesh [60]. Thereafter, it is secreted and translocated to the functional heparan sulphate proteoglycan (HSPG)-binding site on the luminal surface of the endothelium and hydrolyzes lipoproteins [64].
The level of LPL production in adipose tissue and the skeletal muscle determines whether dietary lipids are mainly stored in the adipose tissue (to induce obesity) or are used for energy consumption in the skeletal muscle (to induce weight loss). Thus, the control of LPL production is important for understanding obesity and pathological weight loss [65,66]. During fed state, the activity of enzymes is more in the adipose tissue than the skeletal muscle to store the extra energy, while exercise leads to a higher level of enzyme activity in the skeletal muscle [45,67]. Therefore, expression of LPL by adipose tissue and skeletal muscle is often considered to constitute an anti-atherogenic influence, while the expression of LPL by the endothelial cells and macrophages has a pro-atherogenic effect. In this way, import of LDL to macrophages and foam cell formation in the subendothelial space is the main trigger of atherosclerosis pathogenesis. Insulin is the main regulator of the LPL activity in adipose tissue. During fed state, insulin upregulates LPL expression and consequently FA storage in adipose tissue. However, in fasting state, the level of insulin is low and LPL expression is increased in the skeletal muscle that leads to absorption of fats by the skeletal muscles. Moreover, insulin unresponsiveness is associated with a proinflammatory state of adipose tissue in which production of cytokines such as Tumor necrosis factors alpha (TNFα) and interleukin 6 (IL-6) reduces LPL expression in adipose tissue [45]. This leads to hypertriglyceridaemia and susceptibility to coronary artery disease. Cytokine-induced inhibition of LPL expression in adipose tissue is also the pathophysiology of cachexia in cancers [67]. Thus, it is expected that anti-geriatric factors, if they exist, should also influence LPL activity.

**Fatty Acid beta-Oxidation (FAO)**

FAO is a mitochondrial (and peroxisomal for LCFAs) process in which the conserved energy of the FAs is released in a stepwise manner. FAs are long chain carbon molecules that during FAO and in each step, 2 carbon molecules of FA are degraded to produce the activated 2-carbone (2c-) intermediate, acetyl-CoA. In addition, reduction of NADH and FADH2 cofactors produces NADH2 and FADH2, during FAO. Degradation of FAs with odd number of carbons (produced in some bacteria) produces one molecule propionyl-CoA and one molecule acetyl-CoA instead of two molecules acetyl-CoA in the last step. Propionyl-CoA converts to methylmalonyl-CoA and succinyl-CoA to enter the Krebs cycle (Figure 6).

Oxidation of FAs happens in two stages in the cytoplasm and in the mitochondria. In the cytoplasmic stage, FAs are first activated via conversion to acyl-CoA by using fatty acyl-CoA synthase (or thiokinase), Mg2+ as cofactor, coenzyme A (CoA-SH) and ATP. Thereafter, acyl-CoA, by using acyl-carnitine palmitoyltransferase transferase I (CPT-I), forms a complex with carnitine (or beta-hydroxy-gamma-trimethylammonium butyrate) in order to pass the mitochondrial membrane. Carnitine is produced from the lysine amino acid in the liver and kidney cells. Therefore, any problem in the metabolism of lysine leads to disturbance in the formation of carnitine and consequently FA metabolism and storage of TAGs in cells. In cytoplasm, long chain hydrocarbons, acylcarnitine translocase enzyme transfers the acylcarnitine across the IMM.

In the mitochondrial stage, acyl-CoA via acyl-carnitine transferase II, becomes separated from acyl-carnitine. Subsequently, acyl-CoA becomes dehydrogenated by using acyl-CoA dehydrogenase (a flavoprotein) and flavin adenine dinucleotide (FAD) coenzyme to produce dehydroacy-CoA (or enoyl-CoA). Dehydroacyl-CoA becomes hydroxylated by using hydratase and one molecule water to produce beta-hydroxyacyl-CoA. This product becomes oxidized by using dehydrogenase and NAD+ coenzyme to produce beta ketoacyl-CoA. Beta ketoacyl-CoA is degraded to acetyl-CoA and acyl-CoA molecule with 2 carbons less than the first acyl-CoA molecule by using beta-ketothiolase (or acyl-CoA acyl transferase) and one molecule CoA-SH. This acyl-CoA is dehydrogenated again to start the second cycle of the process to lose two extra carbons. This process continues till the long chain of FA becomes completely degraded to acetyl-CoA [68].

**Energy balance in FAO**

In the Krebs cycle, degradation of each acetyl-CoA produces 12 ATP molecules. Each propionyl-CoA produces 6 ATP that is yielded from 1 GTP, 1 FADH2 (equal to 2 ATP) and 1 NADH2 (equal to 3 ATP). Furthermore, conversion of propionyl-CoA to succinyl-CoA requires 1 ATP. Therefore, each propionyl-CoA at the end produces 5 ATP. In addition, in each cycle of beta oxidation, which leads to degradation of one acetyl-CoA from the LCFAs, 1 FADH2 (equal to 2 ATP) and 1 NADH2 (equal to 2 ATP). The number of cycles for each molecule of FA is calculated by subtracting one from the number of the final products. Moreover, the level of thiokinase reaction 1 ATP is consumed that should be considered in the final calculation.
Examples

1. How many ATP molecules are produced from a 6-carbon FA?
   
   **First stage:** Calculation of the number of products (including 2C-acetyl-CoA and 3C-propionyl-CoA) that is yielded from each molecule of 6C-FA. Each 6C-FA produces 3 2C-acetyl-CoA molecules, which produces 36 ATP.

   **Second stage:** Calculation of the number of cycles that is used for complete degradation of 6C-FA. The total number of cycles is equal to the total number of products (acetyl-CoA in the odd-numbered FAs) that is yielded at the end of the degradation (3 acetyl-CoA in this example) minus one. As in each cycle 5 ATP is produced, via OXPHOS reaction of 1 NADH2 and 1 FADH2, therefore, during degradation of each 6C-FA totally 10 ATP are produced in two cycles.

   **Third stage:** Consideration of the consumption of one ATP by thiokinase.

   This amount is used just one time; therefore, it should be considered at the end of the calculation.

   **Final calculation:** 36 ATP + 10 ATP - 1 ATP = 45 ATP

2. How many ATP molecules are produced from a 17-carbon FA?

   **First stage:** Each 17C-FA produces 7 2C-acetyl-CoA, which is equal to 84 ATP as well as one 3C-propionyl-CoA that produce 5 ATP.

   **Second stage:** Total number of cycles that is used for total degradation of 17C-FA is 7. This amount is calculated by consideration of the total number of products (8 molecules in this example) minus one. The total amount of energy production in each cycle is equal to 35 ATP.

   **Third stage:** Consideration of the consumption of one ATP by thiokinase

   **Final calculation:** 84 ATP + 5 ATP + 35 ATP - 1 ATP = 123 ATP

**Regulation of FAO**

The level of acetyl-CoA is one of the main determinant parameters in the regulation of FAO. Acetyl-CoA is the product of glucose degradation during glycolysis and pyruvate dehydrogenase (PDH) reaction as well as FAO. Therefore, acetyl-CoA is the main linker molecule between the carbohydrate and lipid pathways. Acetyl-CoA is consumed in different pathways including (i) the Krebs cycle, (ii) gluconeogenesis using pyruvate carboxylase (PC), (iii) oxaloacetate production by using CO2 to store glucose in the liver as glycogen, (iv) FA biosynthesis and (v) cholesterol synthesis [69]. One of the parameters that influence the concentration of acetyl-CoA in the body is hormones. In physiological states, insulin is secreted from the pancreas beta cells following feeding. Insulin is an antilipolytic hormone and the inhibitor of FAO [70]. This means that in excess of energy level in the body carbohydrate catabolism proceeds to lipid storage. In diabetic states, insulin unresponsiveness decreases the level of lipogenesis. This leads to lipolysis and elevation of the level of FFAs in circulation. FFAs are sedimented to non-adipose tissues such as skeletal muscle and liver to enhance FAID in these organs [14]. In type 1 diabetic state and shortage of insulin, FAO and acetyl-CoA production in the body is increased. Acetyl-CoA is the substrate of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA), which is the substrate of HMG-CoA lyase in the ketone bodies pathway.

**Fatty Acid Synthesis**

FA synthesis starts when the concentration of acetyl-CoA in cytoplasm is high. This cytoplasmic process happens via the enzymatic activity of a single, homodimeric, multifunctional protein, the FA synthase (FAS) complex. Each FAS monomer contains three catalytic N-terminal domains including beta-ketoacyl-ACP synthase (KS), malonyl/acetyl transferase (MAT) and dehydrase (DH) and four C-terminal domains including enzymatic and dehydration (DH) and four C-terminal domains including enoyl-ACP reductase (ER), beta-ketoacyl-ACP reductase (KR), (ACP) and thioesterase (TE) that are separated from each other by a structural core. The conserved ACP (central protein) acts as the mobile domain responsible for shuttling the intermediate fatty acid substrates to various catalytic sites. Coenzyme A is the source of the phosphopantetheine prosthetic group of the ACP domain, which contains thiol (central SH). One of the peripheral enzymes (KS) also contains thiol (peripheral SH), which belongs to the cysteine amino acid [71].

During FA synthesis, acetyl-CoA is carboxylated to malonyl-CoA in cytosol by using acetyl-CoA carboxylase (ACC), ATP, CO2 and biotin as coenzyme. Thereafter, malonyl transacylase and acetyl transacylase separate CoA-SH from malonyl-CoA and acetyl-CoA roots and join malonyl roots to the ACP domain (central SH) and acetyl roots to the active site of cysteine thiol of the KS domain (peripheral SH). Subsequently, one molecule CO2 is released from the malonyl root using carboxylase and the acetyl root joins to the rest of
molecule on the central SH to produce acetoacyl-ACP. Acetoacyl-ACP becomes reduced using reductase and NADH phosphate (NADPH) as coenzyme and produces β-hydroxyacyl-ACP. Thereafter, dehydrase separates one H₂O to produce β-dehydroacyl-ACP (or enoyl-ACP), which is reduced by using β-dehydroacyl-ACP reductase and NADPH, to produce butyryl-ACP (4C-acyl-ACP). Consequently, the butyryl root is again transferred from the central thiol to the peripheral thiol and the central thiol becomes free again for joining to a new malonyl root (Figure 7, 8).

The final product of this cycle is palmitoyl-ACP. Palmitoyl-ACP is released from the enzymatic complex using decarboxylase and one molecule water to produce palmitate, which is a 16C-FA. Mitochondria and microsomes produce FAs with longer chains or with unsaturated bonds [72,73]. Insulin is a lipogenic hormone that stimulates synthesis of both the FAs and cholesterol with the regulation of SREBP-1c and SREBP-2 in each pathway respectively [74].

Regulation of fatty acid synthesis

ACC is the main regulatory enzyme of FA synthesis that is regulated in three different ways including (i) allosteric reaction of the local metabolites, (ii) hormones and (iii) phosphorylation. AllostERICALLY, palmitoyl-CoA, a LCF, is the inhibitor and citric acid is the stimulator of ACC [75]. Excess of acetyl-CoA, through stimulation of the Krebs cycle and citrate synthesis, is converted to malonyl-CoA and stored as FAs [76]. Malonyl-CoA inhibits transport of FAs to the mitochondria for FAO [77]. Phosphorylation of ACC by 5’ AMP-activated protein kinase (AMPK) decreases the level of malonyl-CoA and inhibits FA synthesis [76]. AMPK is activated when the intracellular energy is low. AMPK also stimulates FAO by augmenting the inhibitory effect of malonyl-CoA for transport of FA to the mitochondria. In low level of glucose (e.g., in type 1 diabetes), stimulation of cAMP/PKA (protein kinase A) pathway by glucagon and epinephrine [78] inhibits AMPK; therefore, acetyl-CoA is consumed in ketogenesis pathway instead of FA synthesis [79]. Ketone bodies are the other energy source of the body in situations in which the level of glucose in the body is low. In high glucose level, insulin stimulates the pentose phosphate pathway [80] as well as ACC and FA synthesis [81]. Upstream regulatory factors (USFs) and SREBP-1 transcription factors mediate this process [82]. Polyunsaturated FA in the liver [83] and leptin in adipocyte inhibit expression of SREBP [84].

Triacylglyceride (TAG) Synthesis

Esterification of three FA molecules with glycerol produces TAGs. TAGs are the main lipid components of LDs and are stored in adipose tissues, skeletal muscles, liver, lungs and intestine to provide energy for the metabolic processes. In adipose tissue, there is a balance between degradation and synthesis of fats in normal state.

The first step of TAG synthesis is consumption of glycerol in the form of glycerol-3-phosphate (G3P). G3P is produced in two different ways in the liver and adipose tissue. In the liver, G3P is made by phosphorylation of glyceraldehyde using glyceraldehyde kinase and ATP. Glycerol is derived from degradation of adipocyte-TAGs and is transferred to the liver via circulation. In adipose tissue, synthesis of G3P via the liver pathway does not happen due to the lack of glyceraldehyde kinase; however, G3P is made from reduction of dihydroxyacetone phosphate (DHAP, glycogen metabolites) by glyceral-3-phosphate dehydrogenase (G3PDH).

In the next step, two molecules of acyl-CoA (FAs) join to G3P using phosphatidic synthetase or fatty-acyl-CoA transferase to make phosphatidic acid. Phosphatidic acid, using phosphatase, loses one phosphate group and produces DAG. DAG, using TAG synthase, combines with one extra acyl-CoA and produces TAG (Figure 9). TAG is then transported to VLDL of the liver as well as the adipocytes-LDs for re-esterification in AT, for beta oxidation in AT, (iii) for re-esterification in AT, (ii) for re-esterification in AT, (iii) for beta oxidation in other tissues and (iv) for storage as phospholipids or other lipid types. Dysregulation of hormones such as insulin and androgens during stress (e.g., fasting) or metabolic system disorders such as obesity-induced metabolic syndrome and lipodystrophy affects the function of lipolytic enzymes in adipose tissue. Under fasting state, the level of the catecholamines increases in adipose tissue due to absorption by circulation or by sympathetic innervations. Catecholamines increase the adenylate cyclase activity and intracellular cAMP concentration and PKA activity and consequently phosphorylation and stimulation of hydrolytic activity of HSL, which is translocated to the adipocytes-LDs for TAG breakdown. Glucocorticoids, via stimulation of the desnutrin/ATGL enzymes, can also stimulate lipolysis [87]. In fed state, insulin inhibits lipolysis by dephosphorylation of HSL and activation of phosphatase.
of phosphodiesterase (PDE) that decreases the level of cAMP. Insulin, via phosphoinositide-3-kinase/AKT (PI3K/AKT (also known as PKB)) pathway, phosphorylates and inhibits PDE3B which has an inhibitory effect on the cAMP activity. Another inhibitory effect of insulin on lipolysis is through phosphoprotein phosphatase-1 (PP1) and its negative regulation on HSL [87].

Other pathways for phosphorylation of HSL are via 3',5'- cyclic guanosine monophosphate (cGMP) dependent kinase [89] and calcium-induced protein kinase C/ mitogen-activated protein kinases / extracellular-signal-regulated kinase (PKC/MAPK/ERK) activity [90,91] that activate HSL. AMPK inactivates HSL lipolytic property and has a competitive effect with PKA in HSL phosphorylation and activity [17,92]. Another regulator of HSL activity is perilipin A that associates with LD and enhances HSL lipolytic activity [92,93]. In basal states, perilipin A maintains a low rate of lipolysis in the LDs; however, under hormone stimulation, PKA-mediated perilipin phosphorylation through facilitating the HSL translocation to the LDs or its interaction with HSL, stimulates HSL activity. HSL has an effect on broad substrates of lipid molecules including TAG, DAG, MAG, retinyl and cholesteryl esters, but it mostly affects DAG and cholesteryl ester [94].

Desnutrin/ATGL contains a patatin-like domain that hydrolyzes TAG and does not hydrolyze cholesteryl and retinyl esters [86]. Desnutrin expression is limited to adipose tissue and is overexpressed in adipocyte differentiation and glucocorticoid stimulation and is downregulated during feeding and insulin stimulation [88]. Other parameters that are important in lipolysis are thyroid hormone, growth hormones [95], natriuretic peptide, alpha-melanocyte stimulating hormone (α-MSH) and TNFa that stimulate lipolysis [96,97]. Adenosine [98] and neuropeptide Y [99] inhibit lipolysis while prostaglandins such as PGE2 and PGJ2 have a biparal effect.

Regulation of Triglyceride Metabolism

Insulin has an antilipolytic effect and beta-adrenergic hormones have a stimulatory effect on TAG degradation. Another protein for regulation of TAG is lipin-1. It also has an effect on mitochondrial oxidation, development of mature adipocytes, storage and utilization of glucose and FAs of peripheral tissues [100,101]. They interact with some gluconeogenic nuclear receptors such as PPAR-gamma coactivator-1-alpha (PGC-1α), PPARa, glucocorticoid receptor (GR) and hepatocyte nuclear factor-4-alpha (HNF4α) [102]. During the acute phase of inflammation, LPS and proinflammatory cytokines negatively regulate lipin1 in adipose tissue and therefore the level of FFAs and VLDL is increased in circulation [101]. Both adrenaline and contraction-mediated events mediate TAG hydrolysis by HSL [103]. These events deactivate AMPK secretion and activate PKC/ERK and

Figure 10: Ketone bodies synthesis
Ketone bodies are the product of HMG-CoA, which is produced from assembly of three acetyl-CoA. During type 1 diabetes, shortage of insulin production by pancreatic beta cells stimulates intracellular FAO and the concentration of acetyl-CoA, which is used for Ketone bodies production. Ketone bodies are one of the energy sources of cells. Abbreviations are explained in figure 2.

Figure 11: Cholesterol synthesis
Excess amount of energy (or high concentration of acetyl-CoA) in cell is stored as lipid. Cholesterol synthesis happens in the cytoplasm of liver and adipose tissue following consumption of ATP and NADPH. Abbreviations are explained in figure 2.
cAMP/PKA pathways that are activated by muscle contraction-induced intracellular calcium release and epinephrine stimulation that lead to PKC and ERK activation and stimulation of HSL [17,104].

Adenylyl cyclase has an important role in lipid metabolism. Adenylyl cyclase, via conversion to ATP to cAMP, activates protein kinase using one ATP molecule. Activated PKA phosphorylates and activates TAG lipase [104]. Glycerol and FA, which are produced from TAG, are transferred to the liver via circulation.

Hormones through influence on adenylyl cyclase are able to regulate lipid metabolism. Epinephrine (adrenaline), norepinephrine (noradrenaline) [105], glucagon [106,107], adrenocorticotropic hormone (ACTH) [108], hydrocortisone [109], thyroxine [110], serotonin [111] and thyroid-stimulating hormone (TSH) [112] directly influence adipocytes and stimulate adenylyl cyclase and lipolysis [113]. Conversely, insulin has a negative regulatory effect on adenylyl cyclase and hence inhibits lipolysis. Therefore, insulin is an antilipolytic or lipogenesis agent; however, the antilipolytic effect of insulin is independent of this effect [114]. Insulin functions in different ways to inhibit lipolysis including (i) activation of PDE, which catalyzes the conversion of cAMP to 5’ AMP [115], (ii) stimulation of entrance of glucose to cells and glycolysis that increases DHAP concentration (substrate of FA synthesis), (iii) activation of FAS (enzyme of FA synthesis), (iv) inhibition of TAG degradation via inhibition of HSL, (v) activation of glycogen synthase to convert G3P to glycogen and (vi) activation of glucose-6-phosphate (G6P) dehydrogenase (G6PDH) that stimulates the pentose phosphate pathway and produces NADPH2 (cofactor for FA synthesis). In this stage also the concentration of DHAP increases and is reduced via G3PDH and produces G3P (substrates of TAG synthesis).

**Ketone Bodies**

Ketone bodies are acetone (C=CO-C), acetoacetic acid (C=CO-C-COOH) and beta hydroxyl butyric acid (C-C(OH)-C-COOH). Normally, the concentration of these products in the circulation is low (1 mg/dl); however, in type 1 diabetes, anesthesia and prolonged fasting their concentration increases and leads to ketosis and metabolic acidosis. When the concentration of ketone bodies in the serum exceeds the threshold of absorption by the kidney tubules, it is released in the urine (ketonuria). In normal states, the concentration of ketone bodies is not detectable in the urine. Ketone bodies are produced in the liver, testes and ovaries [116], and are transported to the brain and cardiac muscles for consumption as energy source via conversion to acetyl-CoA (Figure 10).

**Synthesis of ketone bodies**

In this cytoplasmic reaction, two acetyl-CoA produce acetoacetyl-CoA using beta-ketothiolase. Acetoacetyl-CoA produces HMG-CoA using HMG-CoA synthase and acetyl-CoA. HMG-CoA loses one acetyl-CoA using HMG-CoA lyase and produces acetoacetic acid, which follows two pathways; it becomes reduced and produces beta hydroxyl butyric acid using beta hydroxyl butyric acid dehydrogenase and NAD+ or it loses one CO2 and produces ketone using acetoacetate decarboxylase.

**Degradation of ketone bodies**

In order to use ketone bodies as energy source, the body only uses acetoacetic acid. Acetone evaporates quickly and is discharged via ventilation and beta hydroxyl butyric acid is converted to acetoacetic acid. During degradation, acetoacetic acid is converted to acetoacetic acid-CoA via thiokinase and using CoA-SH and ATP. Thereafter, acetoacetic acid-CoA combines with one CoA-SH and produces two acetyl-CoA using beta ketothiolase. In skeletal muscles, the first stage of ketone bodies degradation occurs in different ways. In skeletal muscles, succinyl-CoA (instead of ATP) is used for combination of CoA-SH to acetoacetic acid; therefore, totally 23 ATP are produced in skeletal muscles, while this amount in other cells is 24 ATP. Degradation of acetoacetyl-CoA to two acetyl-CoA produces 24 ATP because each acetyl-CoA produces 12 ATP during the Krebs cycle.

**Regulation of ketone body synthesis**

During fasting, TAG-adipocyte is degraded to release its energy. Over-supply of TAG in the liver induces synthesis of ketone bodies. This event happens when the insulin/glucagon ratio is decreased in fasting state. Therefore, in high level of glucagon, ACC is inhibited and consequently FAO is stimulated. In FAO, fatty acyl-CoA is converted to acetyl-CoA to be used in the Krebs cycle for energy production. In this state, NADH2 / NAD+ ratio increases. In high level of this ratio and when enough energy supply of the hepatocytes is prepared, the extra acetyl-CoA is consumed in the ketogenesis pathway. Moreover, oxaloacetate is converted to malate to generate glucose via gluconeogenesis. In the chronic fasting state, gene expression of mitochondrial HMG-CoA synthase is stimulated that induces the ketogenesis pathway.

**Cholesterol Biosynthesis**

Cholesterol is one of the main fat components of the body that has both external (foods like egg, meat and milk) and internal sources. Inside the body cholesterol is made from acetyl-CoA in hepatocytes, enterocytes, testes and ovaries [117] and contains less than 60% of the total proportion of cholesterol in the blood. Acetyl-CoA is yielded from oxidation of glucose and FAs.

In the cytoplasmatic process of cholesterol biosynthesis 3 acetyl-CoA are joined to each other to produce HMG-CoA. HMG-CoA can either follow cholesterol production by the function of HMG-CoA reductase or enter the ketogenesis pathway. NADPH2 is the cofactor of this process that is produced from the pentose phosphate pathway (Figure 11).

**Regulation of cholesterol synthesis**

Cholesterol synthesis is regulated through the enzymes of this pathway. These are 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoAR) and acyl-CoA: cholesterol acyltransferase (ACAT), for regulation of intracellular free cholesterol as well as LDL receptor-mediated uptake and HDL-mediated reverse transport that regulate the plasma cholesterol level. HMG-CoAR is the rate limiting and key sterol synthetic enzyme that has 8 transmembrane (8TM) spans and is anchored to the ER membrane. It is regulated by the level of cellular cholesterol. High level of cholesterol has a negative feedback effect on HMG-CoAR and its gene expression. In addition, cholesterol stimulates HMG-CoAR polyubiquitination and degradation which is modulated by its transmembrane (TM) sterol-sensing domain (SSD) and its role in proteasome degradation. HMG-CoAR is also regulated by phosphorylation and dephosphorylation. Phosphorylation of HMG-CoAR inhibits its function. HMG-CoAR phosphorylation happens either via activated AMPK [118] or activated protein phosphatase inhibitor-1 (PPI-1). The phosphorylated forms of AMPK and PPI-1 are active. Activated PPI-1 inhibits HMG-CoAR phosphoryase (also called PP2A), which dephosphorylates (and activates) HMG-CoAR. Activated PPI-1 also inhibits PP2C, which dephosphorylates (and inactivates) AMPK. Inactivated HMG-CoAR phosphatase and phosphorylated AMPK maintain HMG-CoAR in the phosphorylated (and inactivated) states [119]. Glucagon and epinephrine decrease...
cholesterol synthesis through activation of the PPI-1 inhibitor, while insulin dephosphorylates (and activates) HMGCroA [120].

SREBP is the master regulator of lipid homeostasis [121] and a transcription factor that enhances lipogenesis in adipose tissue by controlling the gene expression of enzymes of lipid synthesis. These genes are cholesterol synthesis enzymes (HMGCroA synthase, HMGCroA reductase, farnesyl diphosphate synthase and squalene synthase), FA synthesis enzymes (ACC, FAS, stearyl-CoA desaturase (SCD)) and TAG synthesis enzyme (G3P acyltransferase (GPAT)) and also for lipid uptake (e.g., LDL receptor) [122]. The concentration of cholesterol in ER determines the regulation of gene expression in cholesterol synthesis. The synthetic sterol, through a negative feedback loop, inhibits the cleavage of SREBP and synthesis of additional sterol.

SREBP is in three isoforms of SREBP-1a (involved in the FA and cholesterol synthesis), SREBP-1c (involved in FA synthesis) and SREBP-2 (involved in cholesterol synthesis and LDL receptor gene expression). The inactive precursor of SREBP is bound to the ER membrane. The three TM proteins of ER membrane (SREBP2, SREBP cleavage activating protein (SCAP) and Insig) and the two cleavage proteins (site-1 protease (S1P) and site-2 protease (S2P)) regulate formation of SREBP. SREBP precursor protein is a 2TM-protein that belongs to the basic helix–loop–helix (bHLH) transcription factors and contains one cytosolic C terminal SCAP binding domain and one cytosolic N terminal SREBP domain that mediates the dimerization, nuclear entry and DNA binding to sterol response element (SRE) -segment to enhance the genes encoding for biosynthesis of lipids. The cholesterol-sensing protein, (SCAP), is an 8TM-protein containing SSD domain similar to HMGCroA. Its cytosolic domain binds to the cytosolic C terminal domain of SREBP protein. High level of sterol forms a complex with 6TM-Insig and SCAP and induces binding of the SSD of SCAP with the Insig protein. The Insig protein which always stays in the ER membrane, retentis SREBP-SCAP precursor complex in the ER and inactivates it.

In low concentration of sterol, the complex does not interact with the Insig protein. Conformational change in SCAP leads to SREBP-SCAP complex translocation to the Golgi apparatus using COPIII vesicles. Subsequently, two separate site-specific proteolytic cleavages by S1P and S2P proteins happen that release the membrane-bound SREBP to the cytoplasm. The released SREBP2 translocates to the nucleus to function as transcription factor for upregulation of cholesterol synthesis genes including HMGCroA. After a short period, SREBP is ubiquitinated and degraded to become inactive (Figure 12) [123].

**Conclusion**

Lipid-carbohydrate interaction is one of the fundamental parameters in regulation of the energy metabolic system. Disturbance in the function of the adipose tissue as the main fat storage organ of the body leads to FAID and consequently metabolic disorders. In this review, the biochemical pathways of the main energetic molecule of the body (lipids) are summarized in such a way that researchers can follow the association between these pathways easily. Understanding these biochemical pathways will help biologists to comprehend the pathophysiology of metabolic diseases properly.

**Nomenclatures**

**Acetyl group**, (also named methylhydroxicon or ethanoyl group) is the organic group of acetic acid (C-CO-OH). Acetyl group is the acetyl chemical formula C-CO-. The acetyl group contains a methyl group single bonded to a carbonyl. The acetyl moiety is a component of many organic compounds such as acetyl-CoA, acetylcycteine, acetylcholine, acetaminophen (or paracetamol) and acetylsalicylic acid (or aspirin).

**Acyl group** is an alkyl group attached to a carbon-oxygen double bond (R-CO-). Acylation is the substitution of an acyl group into a carbon-containing compound or an acetyl chloride, ethanol (C-CO-) or formyl group is the aldehyde group without R group. Acetyl chloride is made by joining a chloride atom with an ethanoyl group (C-CO-).

**Aldehyde** is an organic compound with the structure R-CHO consisting of a carbonyl center (CO) bonded to hydrogen and an R group, which is any generic alkyl or side chain. In aldehydes, carbonyl is located at the end of a carbon skeleton, while in ketones carbonyl is placed between two carbon atoms.

**Aldehyde group** or formyl group is the aldehyde group without R (-CHO).

**Aliphatic** molecules are basically non-cyclic or cyclic molecules that are not aromatic. Thus, instead of the normal benzene ring that has 3 double bonds inside, it is just a saturated closed ring.

**Amphipathic** molecules are molecules that contain both polar (hydrophilic) and non-polar (hydrophobic) regions.

**Alkane** is an acyclic structure of saturated hydrocarbon that consists of only hydrogen and carbon that join together with single bonds. Their general chemical formula is CnH2n-2. Each carbon atom is able to bind to four hydrogen or carbon atoms and each hydrogen atom can join to one carbon atom. Carbon skeleton or carbon backbone is a series of linked carbon atoms that are joined together. The size of the alkane depends on the number of carbons that makes the molecule. The simplest alkane is methane (CH4).

**Alkoy group** is an alkyl group singular bonded to oxygen (R-O). The simplest alkoy groups are methoxy (R-O-C) and ethoxy group (R-O-C-O-C).

**Alkyl** is an alkane missing one hydrogen atom. An acyclic alkyl has the general formula CnH2n-1. The simplest alkyl group is methyl.
group is a hydrocarbon and an alkyl derived from methane, containing one carbon atom bonded to three hydrogen atoms (-CH₃). An alkyl group is symbolically abbreviated with R. A cycloalkyl is generated by removal of a hydrogen atom from a cycloalkane and formation of a ring with the general formula CₙH₂ₙ₋₁.

**Aryl group** is the substituent derived from an aromatic ring, including phenyl, naphthyl, thiophenyl, indolyl, etc. A simple aryl group is phenyl, C₆H₅, which is derived from benzene.

**Aryloxy groups** have an aryl group singular bonded to oxygen (R-O-aryl). An alkoxy or aryloxy group bonded to an alkyl or aryl (R₁-O-R₂) is ether. If bonded to H it is an alcohol. An alkoxide (RO⁻) is the ionic or salt form; that is a derivative of an alcohol where the proton has been replaced by a metal, typically sodium.

**Carbonyl group** is a functional group composed of a carbon atom double-bonded to an oxygen atom (C=O). This structure is found in different compounds including aldehyde (R-CO-H), ketone (R₁-CO-R₂), carboxylic acid (R-CO-OH), ester (R₁-CO-OR₂), amide (R₁-CO-N(R₂)-CO-R₃), anhydride (R₁-CO-O-CO-R₂), and imide (R₁-CO-N(R₂)-CO-R₃). X represents the halide, acid anhydride (R₁-CO-O-CO-R₂), or imide (R₁-CO-N(R₂)-CO-R₃).

**Carboxyl group** (or carboxy) is a functional group consisting of a carboxyl (C=O) and a hydroxyl (OH) group, which has the formula -CO-OH or -COOH.

**Carboxylic acid** is an organic acid in which at least one carboxyl group is present. Its general formula is R-COOH, where R is some monovalent functional group. The simplest examples of these groups are formic acid (H-COOH) and acetic acid (C₂-COOH). Acids with two or more carboxyl groups are called dicarboxylic, tricarboxylic, etc. The simplest dicarboxylic example is oxalic acid (COOH₂), which is just two connected carboxyls. Other important natural examples are citric acid. Salts and esters of carboxylic acids are called carboxylates.

**Esters** are chemical compounds consisting of a carboxyl (CO) adjacent to an ether linkage (C-O-C). They are formed from the reaction of an oxoacid (like carboxylic acid) with a hydroxyl compound such as an organic alcohol or phenol. For instance, triglycerides are the FA esters of glycerol. Esters are usually derived from an inorganic acid or organic acid in which at least one hydroxyl (-OH) group is replaced by an alkyl (-O-alkyl) group, and most commonly from carboxylic acids and alcohols. Esters are formed by condensing an acid with an alcohol.

**Ethers** are organic compounds that contain an ether group.

**Ether group** is an oxygen atom connected to two alkyl or aryl groups (R₁-O-R₂) such as in anesthetic diethyl ether, (C₃-H-O-C₃).

**Isoprene** (or 2-methyl-1,3-butadiene) group is one of the common building blocks of the lipid structures with the formula C₅H₈(C≡C=C).

**Ketoacyl group** (R-CO-C=CO-) is the other building block of the lipid structure that consists of one acyl group (R-CO-) binding to one acetyl group (C=C=O).

**Methyl group** is a hydrocarbon group that is an alkyl derived from methane, containing one carbon atom bonded to three hydrogen atoms (CH₃).

**Oxoacids** are acids that (i) contain oxygen (ii) contain at least one other element, (iii) have at least one hydrogen atom bound to oxygen (iv) form an ion by the loss of one or more protons.

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**References**


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