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Review Article

Fat Facts: An Overview of Adipose Tissue and Lipids

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Abstract

The term fat evokes a multitude of ideas, images, and prejudices. It encompasses the different types of adipose tissue (AT) and cellular components as well as the myriad of lipid molecules. The AT and lipid molecules throughout the body carry out scores of vital functions ranging from thermal insulation to energy homeostasis to signal transduction. A fact that is not generally appreciated is that in addition to its roles in energy balance and thermoregulation, the AT is also an integral part of both the endocrine and immune systems. Fatty acids (FAs) are the primary building blocks of most lipids. They serve as fuel, structural components, and regulatory molecules (mediators). Most of the free FAs in the body are either obtained from the diet or released by the AT (lipolysis). However, most of the short-chain FAs such as propionate and butyrate are generated in the colon by the fermentation of dietary fiber by the gut microbiota. In addition to providing fuel for the colon enterocytes, these molecules act on specific G protein-coupled receptors in the gut cells stimulating the release of glucagon-like peptide-1 and peptide YY simultaneously improving insulin sensitivity and curbing appetite. The essential FAs linoleic and α-linolenic give rise to two distinct classes of omega FAs, *n*-6 and *n*-3, respectively, and hence to more complex lipid derivatives (eicosanoids) which are involved in virtually all aspects of cellular function including immunomodulation and inflammation. These include prostacyclins, thromboxanes, leukotrienes, and epoxyeicosatrienoic acids.

Keywords: Adipokines, adipose, free fatty acids, lipids

Introduction

The fat we eat and the fat we wear have profound effects on our health, quality of life, and how long we live. The fat we wear is the body fat we acquire, store, and maintain over the years in a specialized loose connective tissue known as the adipose tissue (AT). Whether we are lean, overweight, or obese depends on the quality of our diet, our energy balance, and the health of our metabolic regulatory systems. Energy balance is, of course, the difference between energy intake and energy expenditure (input–output). Metabolic regulation is a complex function involving multiple systems including the endocrine, nervous, immune, and digestive systems. Furthermore, it has become evident in recent years that the resident gut bacteria (commonly referred to as the microbiota or microbiome) play a critical role in metabolic regulation. The hormonal control of metabolism and the gut microbiome are heavily influenced by the nature of the food, drugs, or supplements we ingest.

The AT occupies a central position in the regulatory system responsible for energy homeostasis in addition to serving as an efficient energy store. Equally important is the fact that AT is an integral part of both the immune and thermoregulatory systems.[1-3] It also provides thermal insulation and physical protection (cushioning) for internal organs, and specific lipids (e.g., sphingomyelin) serve as an electrical insulator for nerve fibers.

Triglycerides (TGs) constitute the main lipid class in the AT, and fatty acids (FAs) are its primary energy currency. However, the role of FAs is not limited to energy production. Certain FAs participate in many critical cellular functions and are essential for the normal development and survival of the organism.

This is a narrative non-systematic review revisiting basic and clinically relevant fat facts. It provides an overview of the biochemistry and physiology of the AT and the various classes of lipids with emphasis on FAs.

Adipose Tissue

AT is widely distributed in the body, and its cellular composition varies depending on the anatomical location and

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environmental conditions. The two main locations are the subcutaneous and visceral (or internal) with the subcutaneous accounting for nearly 80% of total body fat. Three types of adipocytes are currently recognized: white (the vast majority), brown, and brite or beige.[4] White and brown adipocytes derive from distinct precursors while brite adipocytes are thought to derive mostly from the white adipocytes, hence their name (brown from white). It is important to note that although on average adipocytes account for nearly 80% of the AT volume, they represent approximately only 30% of the total AT cell count. In addition to the fully developed fat cells (adipocytes), the AT is made up of preadipocytes, lymphocytes, macrophages, vascular stromal cells, fibroblasts, pericytes, endothelial cells, and mesenchymal stem cells.

The subcutaneous white AT is found in a layer of variable thickness under the skin of the chest, belly, waist, cheeks, thighs, and buttocks. Visceral white AT is found in the thoracic and abdominal cavities, notably around and inside organs such as the liver, heart, and kidneys. The intra-abdominal visceral AT is further subdivided into mesenteric, omental, and peritoneal depots. Some white AT is located in breast tissue, within the liver, and around bundles of skeletal muscle fibers. Ectopic deposition of fat within the liver leads to fatty liver disease. This may be the result of excessive alcohol or carbohydrate intake. In the latter case, the result is nonalcoholic fatty liver disease (NAFLD). In most patients with long-standing diabetes mellitus type 2, visceral adiposity is widespread with ectopic fat deposition resulting in fatty liver, fatty skeletal muscles, and ultimately fatty pancreas and beta-cell failure.

Brown AT (BAT) represents a much smaller fraction of the total fat mass even in the infant where its contribution is substantially greater than it is in adults. In infants, BAT is located primarily in the back region while in adults, it is found specifically in the thoracic and supraclavicular regions. This is in sharp contrast to the wide distribution of the white AT. Two categories of body fat are distinguished – essential and storage. Essential or integral fat refers to the lipid molecules in cell membranes, nerve fibers, and bone marrow. These structural lipid components are indispensable for normal physiological functions whereas storage fat is the fat we gain and maintain as a result of the lifestyle we adopt, the food we eat, our physical activity, and the influences of our environment, sex, and genes. The level of adiposity is defined by the mass of AT relative to total body mass, and this is determined by the balance of macronutrients we consume, metabolic regulatory system, and the balance between energy intake and energy expenditure.

Adiposity is a function of the number and size of the adipocytes. Expansion of adipocyte number (hyperplasia) and size (hypertrophy) are influenced by genetic and environmental factors.[5] During the 14th week of pregnancy, the subcutaneous AT of the fetus begins to develop first in the head and neck region then in the trunk and limbs. By the end of the 28th week of gestation, all major AT depots are fully developed. Subcutaneous AT adipocytes continue to increase both in number and size throughout the first year after birth, and then, their number remains constant until adolescence when it begins to rise again. The picture is markedly different for the visceral AT, which does not begin to form until after birth and does not accumulate in significant amounts until adolescence.[6]

The development of obesity in children involves both hypertrophy and hyperplasia of the adipocytes whereas, in adults, it is almost exclusively a hypertrophic process. Thus, the number of adipocytes is primarily determined during the growth period in adolescence and remains substantially constant in both lean and obese adults.[7,8] By contrast, the adipocyte size varies depending on the amount of accumulated fat. Under conditions of sustained energy surplus particularly as carbohydrates, adipocytes become hypertrophic, and the AT expands to accommodate increasing fat gain.

Adipocytes and their lipid contents undergo very slow turnover. The average lifespan of an adipocyte has been estimated at approximately 10 years and that of TGs at about 18 months.[9,10] The adiposity level depends on the cumulative balance of energy over some time and the individual's metabolic health (e.g., insulin sensitivity). Energy input is determined by the quality and quantity of food (and drink) consumed and the frequency of feeding. Energy output is determined primarily by the individual's basal metabolic rate plus any additional physical activity. Whatever degree of adiposity we gain over the years is likely to remain with us for a long time unless significant lifestyle changes are adopted. The social and health consequences of an individual's adiposity cannot be overestimated.

Because high whole-body fat content is a well-established mortality risk factor, an estimate of body fat percentage is used not only as a measure of overall fitness but also to assess risk and monitor changes in patients' health. There are several field tools for estimating the degree of adiposity including the body mass index (BMI) and waist circumference.[11] Despite its shortcomings, the BMI which is derived from the measurements of body weight and height has so far been the standard anthropometric method used in medical practice. It is easy, inexpensive, and correlates reasonably well with the actual mass of body fat in adults as validated by reference methods used in research such as magnetic resonance imaging (MRI), whole-body plethysmography, and dual-energy X-ray absorptiometry. If Wt is the body weight in kilograms and H is the height in meters, then BMI = Wt ÷ H^2. Values <18.5 indicate abnormally low weight. Values 18.5–25 indicate "normal" body weight while individuals with a BMI between 25 and 30 are considered overweight. Obesity is indicated by BMI >30. A major flaw of the BMI scale is that it does not give any clue as to the contribution of visceral fat which has much greater influence on metabolism and health than subcutaneous fat. For this reason, physicians and dietitians frequently use the waist circumference which better reflects central (visceral) obesity. As a rule, individuals should strive to maintain their waist circumference (W) at or

below half their height ($W \leq \frac{1}{2}H$). Recently, a more accurate anthropometric estimator of body fat percentage has been validated and found to be superior to the BMI.[12] The relative fat mass (RFM) is based on the measurements of height (H) and waist circumference (W) in meters: RFM (♂) = 64− ($20 \times H/W$) and RFM (♀) = 76 − ($20 \times H/W$).

Functions of adipose tissue

For decades, AT was regarded as a static long-term energy depot. However, it has become clear over the years that it is a highly dynamic and complex organ both concerning its cellular composition and its functions. In addition to the primary purpose of storing TGs and releasing FAs in response to metabolic regulatory signals, the AT plays a vital role in the integration of the body's metabolic and immunologic activities. The key to such functional capacity is the ability of adipocytes and the immune cells residing within the AT to secrete a number of cytokines (adipokines) including leptin, adiponectin, retinol binding protein 4, resistin, visfatin, angiotensin, interleukin-6 (IL-6), omentin, and tumor necrosis factor α. These are regulatory proteins with the capacity to modulate various metabolic functions thereby enabling the organism to adapt to a wide range of challenges such as brief periods of starvation or gross excesses of food intake (overfeeding). In addition, the AT is recognized as a significant player in the body's immune response owing to its ability to secrete pro- and anti-inflammatory mediators (cytokines, eicosanoids, and other lipid derivatives) and because it serves as host for a variety of immune cells that can be activated as needed in response to appropriate regulatory signals. Immune cells residing within the AT include neutrophils, macrophages, natural killer T cells, helper and regulatory T cells, and B cells.[13,14] Inflammation of the AT is a critical underlying pathology in the development of metabolic diseases such as metabolic syndrome.[15]

AT is an effective heat insulator and has the additional advantage of padding and physically protecting internal organs. It also serves as a sink for steroid hormones such as Vitamin D and the fat-soluble Vitamins A, E, and K. However, the primary importance of the AT lies in its role as the body's primary energy storage, a reservoir from which FAs are released into the circulation as needed to be used for the production of energy and the synthesis of complex lipids. In this respect, the AT may be thought of as an energy-buffering organ which stores excess FAs under conditions of positive energy balance and releases them when prompted by appropriate regulatory signals during negative energy balance.

BAT plays a significant role in the regulation of body temperature particularly in the newborn infant and to a limited extent in adults as well. Brown and brite adipocytes can dissipate a great deal of energy in the form of heat through the phenomenon of nonshivering thermogenesis. This phenomenon results from the uncoupling of mitochondrial oxidative phosphorylation leading to the dissipation of the potential energy in the proton gradient across the inner mitochondrial membrane in the form of heat instead of harnessing it as high-energy phosphate bonds (adenosine triphosphate, ATP). This process of uncoupling is induced by the expression of a particular mitochondrial protein known as uncoupling protein 1 (UCP1). The cold-induced adaptive thermogenesis helps maintain normal body temperature in neonates and to a limited extent in adults as well. Furthermore, the AT expresses β-adrenergic receptors which mediate cold-induced lipolysis and stimulate lipid uptake by the BAT adipocytes to fuel heat production.

Furthermore, stimulation of BAT β-adrenergic receptors leads to the activation of mitochondrial genes, mitochondrial biogenesis, and the expression of UP1. These processes require the expression and activation of the nuclear hormone receptor peroxisome proliferator-activated receptor-γ and its coactivator proliferator-activated receptor gamma coactivator 1-alpha.[16] Thermogenic stimuli such as exposure to cold stimulate the activity of brown and brite adipocytes and can also promote the browning of white AT, a process by which some white adipocytes in subcutaneous depots turn into brite adipocytes through the expression of UCP1.[17] Sluggish browning and/or dysfunction of the thermogenic cells may play a role in the pathogenesis of obesity at least in some individuals.[18,19]

Lipid classes

Lipids are organic compounds that include FAs and other molecules ultimately derived from FAs. They make up the bulk of all cellular membranes including the membranes surrounding cells as well as the membranes defining intracellular organelles such as the mitochondria, peroxisomes, Golgi apparatus, and endoplasmic reticulum. FAs are the main constituents in dietary fat and the lipid molecules stored in the AT. Lipids are of vital importance for the proper functioning of the various body systems. Dietary fat helps in the intestinal absorption of the fat-soluble vitamins and in their transport in the circulation.

Disorders of lipid metabolism can lead to serious pathological conditions such as those resulting from lipodystrophy or inherited enzyme deficiencies resulting in such diseases as Fabry, Gaucher, and Tay–Sach. Lipodystrophy is a rare heterogeneous group of conditions characterized by the progressive loss of AT. In addition, other defects in lipid metabolism which may or may not be associated with obesity can have serious negative effects on the function of such vital organs as the heart and brain. Furthermore, deficiencies in certain omega-3 FAs coupled with excess in the pro-inflammatory omega-6 FAs such as arachidonic acid (AA) can promote chronic inflammatory diseases and at critical stages of life can impede the healthy development and growth of the brain.

Lipids come in a vast array of molecular sizes, shapes, and compositions, but they all share the property of being readily soluble in organic solvent rather than water. Figure 1 shows a general classification of lipid molecules. These range from the simple, saturated short chain FAs such as the 2-carbon acetic acid (2:0) or the 4-carbon butyric acid (4:0) to the

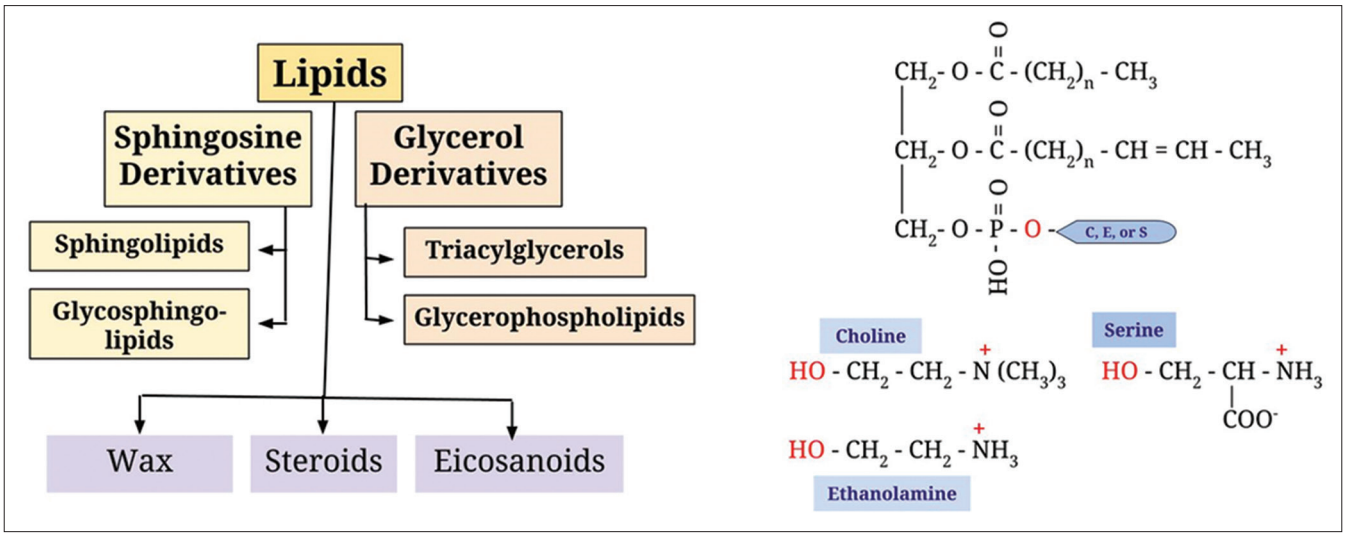

Figure 1: Left: Lipid Types. There are five major categories of lipids: glycerol derivatives (triacylglycerols and glycerophospholipids), sphingosine derivatives (sphingolipids and glycosphingolipids), steroids, eicosanoids, and waxes. Right: Glycerophospholipids consist of phosphatidic acid in which the phosphate group is linked through an ester bond to either choline to yield phosphatidylcholine (lecithin) or to ethanolamine to yield phosphatidylethanolamine (cephalin). The amino acid serine can also combine with phosphatidic acid in the same way to yield phosphatidylserine, also a cephalin

complex molecules of phospholipids, sphingophospholipids, glycosphingolipids, and waxes. The following is a brief, bare-bones description of each lipid class:

- Triacylglycerols (TAGs) or TGs are the most abundant kind of lipid. They consist of three FAs linked through ester bonds to a backbone of glycerol, which is a trihydroxy alcohol. The three FAs may differ from one another and may be saturated or unsaturated
- Phospholipids contain a phosphate group in ester bond with either glycerol or sphingosine. The latter is an unbranched 18-carbon amino alcohol with one *trans* C = C double bond, 2 hydroxyl groups, and one amino group
- Glycerophospholipids are triacylglycerol molecules in which one of the three FAs is replaced by a phosphate group to form phosphatidic acid. In glycerophospholipids, the middle hydroxyl group of glycerol is often esterified with an unsaturated FA. Further, the phosphate group may be attached through a second ester bond to either of the two amino alcohols – choline or ethanolamine [Figure 1, right] or to the amino acid serine. Choline forms phosphatidylcholine (lecithin), ethanolamine forms phosphatidylethanolamine (cephalin), and serine yields phosphatidylserine, a kind of cephalin. Lecithins and cephalins are found in neural tissue, liver, egg yolk, wheat germ, peanuts, soybean, and yeast. In animals, cephalins are critical components of the cell membranes of neurons and play crucial roles in cognition and cell apoptosis signaling
- Sphingosine derivatives are distinguished by the characteristic structure of sphingosine. In sphingophospholipids, a single FA is linked through an amide bond to sphingosine, and a phosphate group is connected to sphingosine through an ester bond and to choline or ethanolamine through a second ester bond. An example of a widely distributed sphingophospholipid is sphingomyelin [Figure 2, left], which is found primarily in the myelin sheaths of axons, but also in other locations including as a constituent of circulating high-density lipoprotein (HDL) particles[20]
- Glycolipids or glycosphingolipids are similar to sphingophospholipids except that instead of a phosphate group, a sugar moiety is linked through a glycosidic bond to the hydroxyl group (–OH) on carbon 1 of sphingosine. When the sugar is a monosaccharide such as galactose or glucose, the result is a cerebroside [Figure 2, right], but when the sugar is a more complex carbohydrate molecule, the result is a ganglioside
- Wax is a type of lipid consisting of long-chain alcohol in ester bond with a long-chain saturated FA. Waxes occur naturally on the surface of fruits, vegetables, leaves, insects, and the feathers of water birds. Wax is sometimes used to coat apples to prolong their shelf life.

Fatty Acids

FAs are the primary building blocks of most lipids. From a chemical standpoint, a FA is a carboxylic acid consisting of a hydrocarbon chain of variable length (commonly, C2–C30) with a methyl group at one end and a carboxylic group at the other. FAs are classified based on 3 criteria – the number of C atoms, the number of carbon-to-carbon double bonds (C=C), and the position of the C=C closest to the methyl end of the chain. This is known as the "omega double bond." Based on the first criterion, FAs are divided into 4 categories: (a) short-chain FAs (SCFAs, C2–C5); (b) medium-chain FAs (MCFAs, C6–C12); (c) long-chain FAs (LCFAs, C13–C20); and (d) very

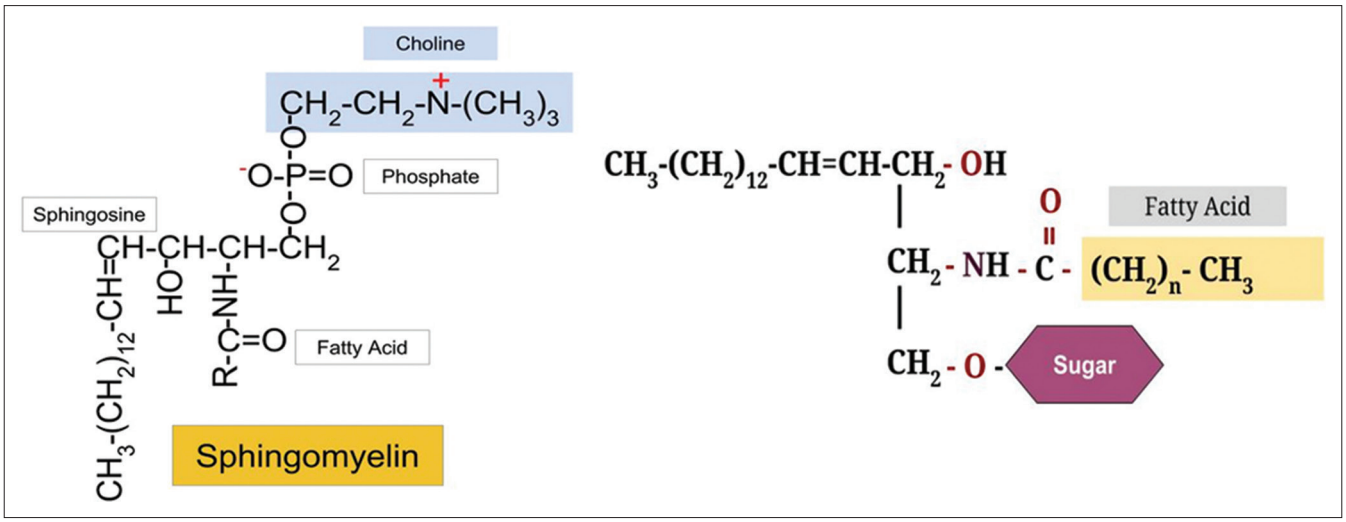

Figure 2: Left: Sphingomyelin is a sphingolipid with a phosphocholine headgroup. Sphingosine is an amino alcohol with 18 C atoms, 2 hydroxyl groups, one amino group, and one C=C double bond in the trans configuration. Right: Cerebroside is a glycosphingolipid with a sugar residue (galactose or glucose) attached to sphingosine through a glycosidic bond

long-chain FAs (VLCFAs, >C20). Caproic (hexanoic) acid is sometimes classified as an SCFA and sometimes as an MCFA. Most of the short-chain saturated FAs such as acetic (C2:0), propionic (C3:0), and butyric (C4:0) are generated in the colon by the fermentation of dietary fiber and resistant complex carbohydrates by the gut microbiota, an abundant and complex collection of bacteria residing particularly in the colon.[21] Acetate (CH_3COO^-) is readily absorbed and serves as a substrate for lipogenesis, while butyrate ($CH_3CH_2CH_2COO^-$) is the primary energy source for the epithelial cells of the colon (colonocytes). It has also been suggested that butyrate possesses multiple health benefits including stimulating mitochondrial metabolic activity, enhancing insulin sensitivity, preventing endotoxemia, and improving the integrity of the intestinal tight junctions. Propionate ($CH_3CH_2COO^-$) has been shown to inhibit cholesterol synthesis by inhibiting HMG-CoA reductase, the rate-limiting enzyme in the early steps of the cholesterol synthesis pathway. It is also thought to inhibit the expression of resistin, an adipokine implicated in a variety of disorders including insulin resistance, diabetes, cardiovascular disease (CVD), NAFLD, and autoimmune diseases.[22] The SCFAs generated by the gut microbiota act on specific G protein-coupled FA receptors (GPR43 and GPR41) in the gut epithelial cells stimulating the release of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY). GLP-1 helps in improving insulin sensitivity while the PYY acts on the hypothalamus to induce satiety thereby limiting calorie intake.[23] Besides, the combined effects of propionate and butyrate may help regulate body weight by boosting the expression of leptin and somehow activating other anorexigenic gut hormones.[24,25]

In clinical practice, MCFAs refers specifically to octanoic and decanoic acids (caprylic and capric acids, respectively). Triglycerides (TGs) containing exclusively these two saturated MCFAs are used in parenteral nutrition preparations because they are more easily formulated in lipid emulsions and readily transported in the circulation and oxidized. Combining medium chain TGs (MCTs) and omega-3 FAs spare the essential FAs from entering the oxidative pathway and allows them to exert their regulatory effects.[26] They are also used in preterm infant formula because they are more easily digested and absorbed. MCFAs do not require the assistance of carnitine palmitoyltransferase to cross into the mitochondrial matrix and enter the β-oxidation pathway to generate the energy needed for the growth and development of the infant.

The second criterion for classifying FAs is the number of C = C double bonds. Accordingly, FAs are divided into three major groups: saturated FAs with no carbon-to-carbon double bonds, monounsaturated FAs (MUFAs) with a single C=C double bond, and polyunsaturated FAs (PUFAs) with 2 or more C=C double bonds [Figure 3]. The so-called "saturated fat" is rich in saturated FAs and is typically solid at room temperature owing to its elevated melting point. In a saturated FA molecule, the hydrocarbon chain is typically linear, unbranched, devoid of kinks, and contains mostly an even number of carbon atoms. In addition to the SCFAs, metabolically important saturated FAs include caproic (hexanoic; 6:0), caprylic (octanoic; 8:0), capric (decanoic; 10:0), lauric (dodecanoic; 12:0), myristic (tetradecanoic; 14:0), palmitic (hexadecanoic; 16:0), and stearic acid (octadecanoic; 18:0).

Saturated FAs are abundant in animal fat and dairy products (butter, cheese, etc.). The FAs used for energy may come from the diet or may be released from the internal stores (AT) when the need arises, and the metabolic conditions are favorable for lipolysis. Major plant sources of saturated FAs are coconut oil and palm oil, both products of tropical rainforests. Worldwide, palm oil may be the most widely consumed vegetable oil; it is found in most packaged products on supermarket shelves, ranging from chocolate and peanut butter to soap and toothpaste. The main FAs in palm oil are

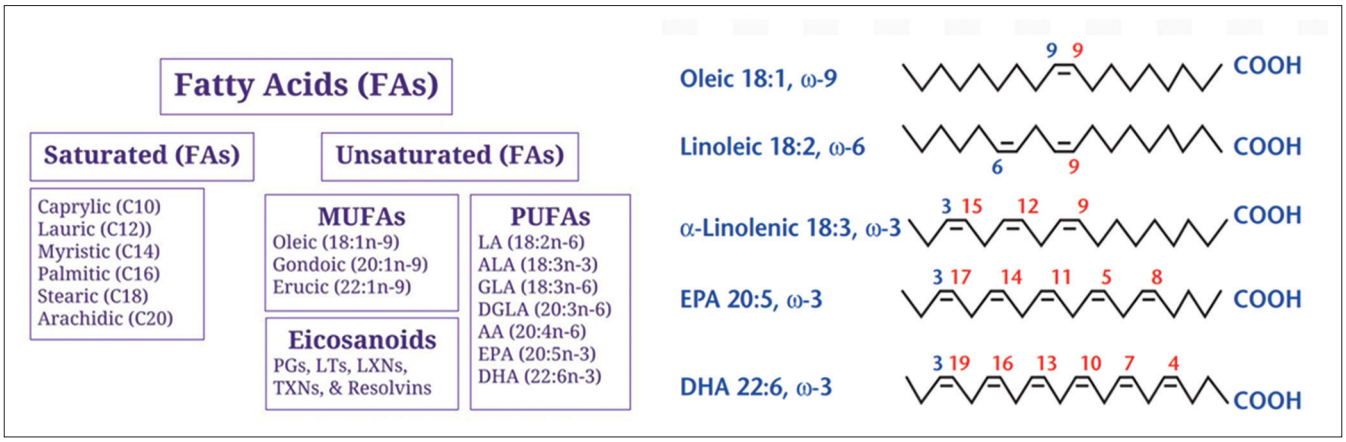

Figure 3: Left: divisions of fatty acids. Right: Unsaturated fatty acids. Schematic molecular structures showing two different numbering systems. The red digits indicate the number of the carbon atom starting with the carboxylic group as C1. The blue digits follow a numbering system beginning from the terminal methyl group as C1. The following fatty acids are shown in order: Oleic acid (C18:1 *n*-9) is a monounsaturated omega-9 FA; Linoleic acid (C18:2 *n*-6) is a polyunsaturated omega-6 FA; Alpha-linolenic acid (C18:3 *n*-3) is a polyunsaturated omega-3 FA; Eicosapentaenoic acid (C20:5 *n*-3) is a polyunsaturated omega-3 FA; Docosahexaenoic acid (C22:6 *n*-3) is a polyunsaturated omega-3 FA. MUFAs: Monounsaturated FAs, PUFAs: Polyunsaturated FAs, LA: Linoleic acid, ALA: Alpha-linolenic acid, GLA: γ-linolenic acid, DGLA: Dihomo-γ-linolenic acid, AA: Arachidonic acid, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, PGs: Prostaglandins, LTs: Leukotrienes, LXNs: Lipoxins; TXNs: Thromboxanes, FAs: Fatty acids

Table 1: Fatty acid composition of vegetable oils (%)

Acid	Canola oil*	Coconut oil	Corn oil	Olive oil	Peanut oil	Palm oil	Sunflower oil
Caprylic (C8)	0	7	4	0	0	0	0
Capric (C10)	0	8	7	0	0	0	0
Lauric (C12)	0	48	0	0	0	0	0
Myristic (C14)	0	16	0.5	0	0	1	0
Palmitic (C16)	4	10	10	11	7.5	40	4
Stearic (C18)	2	2	3.5	2	2	5	2
Oleic (C18:1 *n*-9)	56	0	0	75	71	45	25
Linoleic (C18:2 *n*-6)	26	0	0	7	16	8	70
α-linolenic (C18:3 *n*-3)	10	0	0	0	0	0	0

Values are expressed as percentages of the total fat content of the oil. Canola is also known as rapeseed. Unlike the other oils listed, canola oil contains 10% α-linolenic acid (C18:3 *n*-3). *Canola is extracted from genetically modified rapeseed to reduce its erucic acid content

palmitic (40%) and oleic (45%) acids [Table 1]. Coconut oil has become quite popular in recent years due to the popularity of the so-called paleolithic diet.[27] The main FAs in coconut oil are caprylic (C8; 7%), capric (C10; 9%), lauric (C12; 48%), myristic (C14; 16%), and palmitic (10%).

Saturated FAs represent the main constituent of AT, in which they exist mostly as TGs. Both saturated and unsaturated FAs serve as the primary metabolic substrates accounting for 15%–75% of the total daily calorie intake depending on the individual's diet; the high figure pertains to the "low carb high fat" ketogenic diet, which is gaining popularity among obese diabetic and prediabetic patients. In addition to supplying energy, saturated FAs are important structural components of the cell being part of the phospholipid bilayer, which accounts for at least 50% of the weight of the cell membranes. Besides, saturated FAs are necessary for vital, regulatory functions. The covalent bonding of saturated FAs to functional protein molecules serves to stabilize and modulate the function of membrane channels, receptors, and other signaling proteins. For instance, the addition of palmitate (palmitoylation) to one or more cysteine residues of the G-protein-coupled receptors (GPCR) is essential in the regulation of transmembrane signals.[28,29] GPCRs are integral membrane proteins and key intermediaries between external stimuli and the various intracellular signaling cascades. GPCRs play a central role in the signaling pathways controlling smell, vision, and taste.[30] In addition to their nutritional value, free FAs (FFAs) can also serve as signaling molecules for important energy regulatory processes and the modulation of taste preferences. These mechanisms are thought to involve insulin and incretin hormones as well as the sympathetic nervous system. The signaling function of FFAs is mediated through specific GPCRs known as FFA receptors (FFARs), which are categorized according to the length of the hydrocarbon chain of the FFA ligand that activates each FFAR. Free FAs act as ligands for at least 5 different receptors: FFAR1 (aka GPR40), FFAR2, FFAR3, FFAR4 (aka GPR120), and GPR84. These FFARs are thought to play critical roles in

some critical homeostatic processes. FFAR1 and FFAR4 are activated by medium-chain and long-chain free FAs. FFAR1 is expressed mainly in pancreatic β-cells and mediates insulin secretion, whereas FFAR4 is expressed in the cells of the small intestine and stimulates the secretion of the GLP-1 and cholecystokinin.

Interaction of long-chain omega-3 FAs with GPR120 is thought to be involved in regulating the secretion of gastrointestinal peptide hormones, adipogenesis, and adipocyte differentiation. GPR84 is activated only by medium-chain free FAs. FFAR2 and FFAR3 are activated by short-chain free FAs. FFAR3 is expressed in endocrine cells of the intestine, and it is believed to exert its effects on the gut microbiota to help maintain energy balance. Thus, in the GI tract, the FFARs are supposed to function as sensors for food-derived free FAs and other digestion products.[31] However, FFARs are not limited to the GI tract; they are also found in AT, leukocytes, and macrophages. Dysfunction of these receptors may play an essential role in the pathophysiology of metabolic diseases such as obesity and type 2 diabetes (T2DM). Thus, in addition to being essential macronutrients, FAs act as signaling molecules in various metabolic regulatory processes.[32]

Saturated Fat and Cardiovascular Disease

The link between dietary fat and heart disease is often referred to as the fat-heart or the diet-heart hypothesis. Over the past several decades, the relationship between dietary saturated fat and the plasma levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and TGs has been documented by a large number of observational studies as well as controlled dietary intervention studies.[33-35] Elevated LDL-C and hypertension are well-established risk factors for coronary heart disease and stroke, respectively, and the link between a diet rich in saturated fat and cardiovascular risk factors is also well established.[35] Plasma TG level, the ratio of TC to high-density lipoprotein cholesterol (TC/HDL), and the TG/HDL ratio are all elevated in patients consuming diets high in saturated fat and are considered independent predictors of CVD. Besides, high dietary fat (including vegetable oil) can damage the endothelial lining of blood vessels leading to endothelial cell dysfunction (ECD) and promoting blood clotting. ECD decreases the release of endothelial nitric oxide (eNO), the most potent endogenous vasodilator. Nitric oxide inhibits the proliferation of smooth muscle cells, platelet aggregation, and the adhesion of monocytes to endothelial cells. Reduced availability of eNO is observed in patients with CVD or coronary risk factors such as hypertension, dyslipidemia, hyperhomocysteinemia, and diabetes.

The long-held views regarding the association between saturated fat and cardiovascular disease have been challenged several times over the past 10 years.[36-38] Naturally, contradictory conclusions generate a great deal of media attention and sensational headlines[39] and disseminate the notion that saturated fat is "healthy" confusing both consumers and healthcare professionals.[35,40] It is likely that such ideas will continue to circulate in the medical literature and famous press spawning fresh dietary recommendations. The debate of the diet-heart hypothesis is discussed in greater detail elsewhere.[41]

Unsaturated fatty acids

The distinguishing feature of an unsaturated FA molecule is the presence of one or more carbon-to-carbon double bonds (C=C). Virtually, all naturally occurring unsaturated FAs are in the cis configuration. The double bonds introduce kinks in the molecular configuration. They also lower the melting point of the FA; the higher the number of C=C double bonds, the lower is the melting point. At room temperature, most unsaturated FAs are in the liquid state (oils). Unsaturated FAs are divided into 3 groups: MUFAs, PUFAs, and eicosanoids [Figure 3].

The most common MUFA is oleic acid (OA) (18:1; *n*-9) which is found in abundance in olive oil, avocado oil, palm oil, and seeds and nuts of various kinds. The double bond in OA occurs in position 9 counting from the methyl end of the chain. Therefore, it is an omega-9 (indicated as *n*-9 or ω9) FA. In plant cells, a second C=C double bond can be introduced in position 6 to produce the omega-6 linoleic acid (LA, 18:2; *n*-6), a reaction catalyzed by Δ^{12}-desaturase. LA is the predominant dietary PUFA accounting for nearly 85% of all PUFAs in the average Western diet. LA may, in turn, undergo further desaturation catalyzed by the Δ^{15}-desaturase introducing a third C = C double bond to form the omega-3 alpha-linolenic acid (ALA) (18:3; *n*-3) [Figure 3, right]. ALA is the main dietary omega-3 PUFA. Both Δ^{12}- and Δ^{15}-desaturases are lacking in animal tissues; hence, there is the need to have LA and ALA in the diet. They are denoted as essential FAs because they are necessary for the proper functioning of the organism but cannot be synthesized *de novo* by animal cells due to the lack of the specific enzymes required for their production (Δ^{12} and Δ^{15}). These enzymes are, however, present in terrestrial plants, marine algae and microalgae, and various microorganisms including bacteria and fungi.

Essential fatty acids

Dietary fat is vital for the healthy growth and development of animals. This fact was not known before it was first suggested by Hans Aron in 1918 when he concluded, based on preliminary laboratory experiments, that fat possesses a "unique and specific nutrient value" that is unrelated to its caloric content and therefore cannot be replaced by other macronutrients. In 1927, Herbert M. Evans and George Oswald Burr attempted unsuccessfully to reverse the adverse effects of fat-deficient diet on laboratory animals by supplementing the diet with the fat-soluble vitamins. However, the definitive discovery of essential FAs is attributed to the work of George and Mildred Burr. In 1929, they demonstrated in laboratory rats that dietary FAs are necessary for the animal to thrive. Rats fed a fat-free diet became sick despite supplementing their diet with vitamins and alternative sources of calories. They called the condition "fat deficiency disease" and concluded that FAs were essential

nutrients. Subsequently, they showed that LA (18:2; *n*-6) prevented the "fat deficiency disease" which lead them to conclude that LA is an essential FA.[42]

Nearly 35 years later, it was discovered that LA serves as the precursor for prostaglandins (PGs), a family of locally acting hormones derived directly from AA (20:4; *n*-6), which is in turn derived from LA [Figure 4]. PGs are part of a large family of signaling molecules known collectively as eicosanoids, all of which derive from essential FAs. Eicosanoids include PGs, prostacyclins, thromboxanes, leukotrienes, and epoxyeicosatrienoic acids (EETEAs). In addition to their established role as local hormones (autocrine and paracrine) conveying signals to nearby cells, eicosanoids appear to participate in intracellular signaling cascades.[43]

Linoleic acid (LA, 18:2; *n*-6) and its derivative α-linolenic acid (ALA, 18:3 *n*-3) are both PUFAs with 18 carbon atoms, but they represent two distinct families of essential FAs (EFAs). The primary distinction between the two is based on the location of the first carbon-to-carbon double bond (C=C) counting from the methyl end of the chain (aka the omega carbon). LA is the most abundant and best-known member of the ω6 (*n*-6) family, while ALA belongs to the ω3 (*n*-3) family. Key members of both families are listed in Table 2.

In contrast to animal cells, plant cells can convert oleic acid (18:1; *n*-9) to LA and ALA, due to the presence of the two enzymes (Δ^{12}-and Δ^{15}-desaturases) required for the catalysis of two sequential desaturation reactions:

Oleic acid ═ Δ^{12}-desaturase ═ → LA ═ Δ^{15}-desaturase ═ → α-linolenic acid

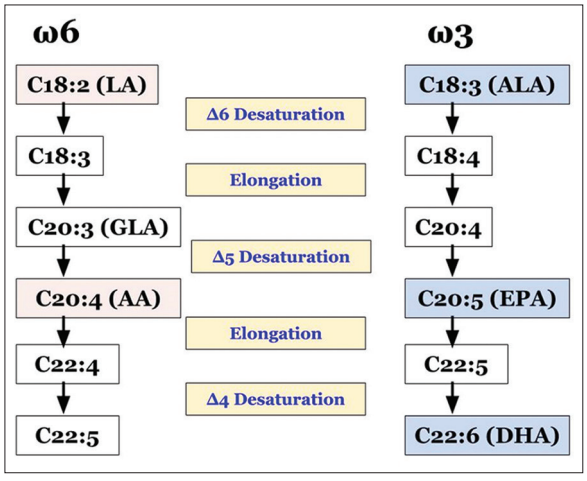

Figure 4: The parallel metabolic pathways of *n*-6 and *n*-3 polyunsaturated fatty acids. The series of alternating desaturation and elongation reactions in both pathways are catalyzed by the same enzymes. The two pathways compete for the same rate-limiting Δ6-desaturase. AA: Arachidonic acid (20:4; *n*-6); ALA: Alpha-linolenic acid (18:3; *n*-3), DGLA: Dihomo-gamma-linolenic acid (20:3; *n*-6), DHA: Docosahexaenoic acid (22:6; *n*-3), EPA: Eicosapentaenoic acid (20:5; *n*-3); GLA: Gamma-linolenic acid (18:3; *n*-6); LA: Linoleic acid (18:2; *n*-6). Adrenic acid (22:4; *n*-6) is found in significant amounts in the phospholipids of the adrenal glands and testes

LA is found in the seeds of most plants, while α-linolenic acid (ALA) is found in significant amounts in green leafy vegetables, flax seeds, chia seeds, and walnuts.

As mentioned above, animal cells cannot synthesize either LA or ALA because they lack the necessary enzymes. However, they do possess the enzymes required for the elongation and desaturation of LA and ALA to form a longer chain and more desaturated PUFAs (mostly up to 24 C and 6 C=C double bonds). As shown in Figure 4, LA is the precursor of all other ω6 long-chain PUFAs (LC-PUFAs) while ALA is the precursor of all other ω3 LC-PUFAs. The ω6 pathway includes γ-linolenic acid (GLA) (18:3; *n*-6), dihomo-γ-linolenic acid (20:3; *n*-6), and arachidonic acid (AA) (20:4; *n*-6) while the ω3 pathway includes eicosapentaenoic acid (EPA) (20:5; *n*-3) and docosahexaenoic acid (DHA) (22:6; *n*-3).

In the absence of the long-chain EPA and DHA in the diet, the presence of ALA becomes essential because it can be converted endogenously to EPA and DHA albeit at a slow rate. It should also be noted that in the animal body, ω6 and ω3 FAs are not interconvertible as evidenced by their parallel metabolic pathways [Figure 4]. The two pathways compete for the services of the same enzymes. Increased flux through the ω6 pathway is the reason for the slow conversion of ALA to EPA and DHA.

The functional differences between ω6 and ω3 FAs and their often opposing actions are illustrated in Figure 5. On the ω6 side, dihomo-γ-linolenic acid gives rise to PGE1, PGF1α, and TXA1. AA, through the cyclooxygenase pathway, gives rise to PGH2, which is then converted to PGD2, PGE2, PGF2α, PGI2, and TXA2, while the lipoxygenase pathway yields series 4 of the leukotrienes (LTA4, LTB4, LTC4, LTD4). Both the PG2 and LT4 series are established, pro-inflammatory mediators. On the ω3 side, EPA, through the cyclooxygenase pathway, gives rise to PGH3, which is then converted to PGE3, PGF3α, PGI3, and TXA3, while the lipoxygenase pathway yields the LT5 series (LTA5, LTB5, LTC5, and LTD5). Both PG3 and LT5 series are established as anti-inflammatory, pro-resolving mediators. DHA (22:6; *n*-3) can also give rise to some anti-inflammatory agents known as 17S resolvins (D1–D5). As already mentioned, LA accounts for over 85% of all omega-6 PUFAs in the "Western diet," and it is found in varying amounts in virtually all edible oils, nuts, and seeds [Tables 3 and 4]. Because of the widespread consumption of the ω6-rich vegetable oils [Table 3], Western diets provide a mix of omega FAs that is overwhelmingly dominated by ω6 with an ω6/ω3 ratio >10. This imbalance is thought to

Table 2: Omega fatty acids

Omega-3	Omega-6
α-Linolenic acid (18:3; *n*-3)	Linoleic acid (18:2; *n*-6)
Stearidonic acid (18:4; *n*-3)	Gamma-linolenic acid, (18:3; *n*-6)
Eicosapentaenoic acid (20:5; *n*-3)	Dihomo-gamma-linolenic acid, (20:3; *n*-6)
Docosapentaenoic acid (22:5; *n*-3)	Arachidonic acid, (20:4; *n*-6)
Docosahexaenoic acid (22:6; *n*-3)	Adrenic acid (22:4; *n*-6)
	Docosahexaenoic acid (22:5; *n*-6)

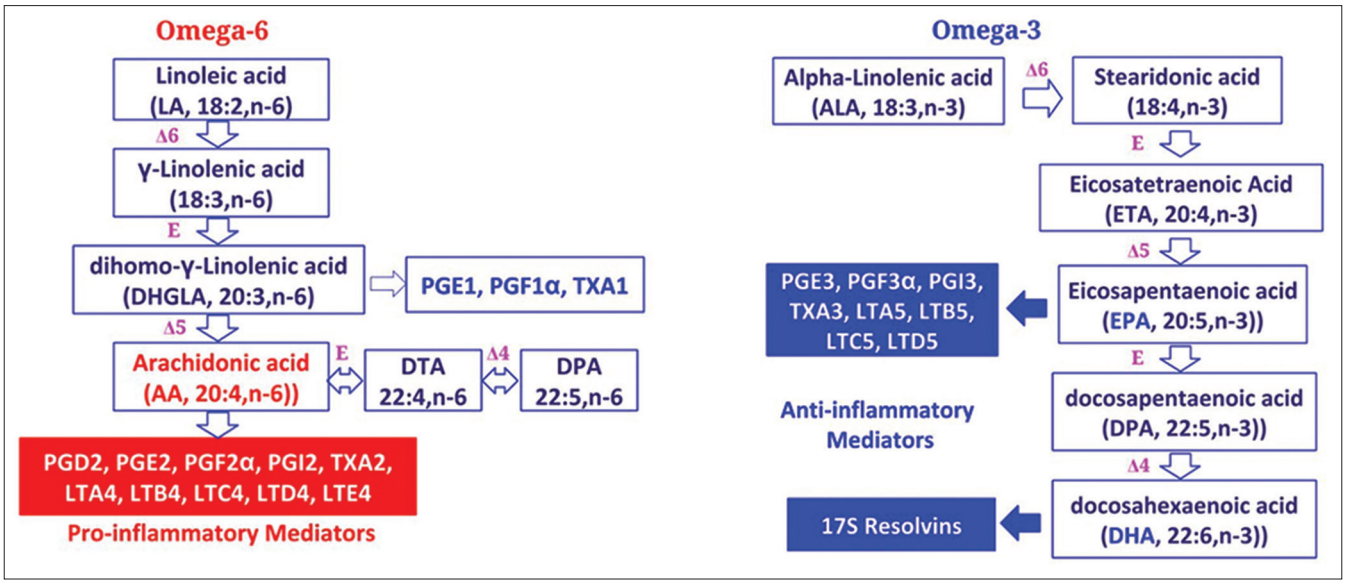

Figure 5: The parallel metabolic pathways of omega-6 and omega-3 FAs. LA is converted to AA through alternating desaturation and elongation reactions. The same enzymes catalyzing these reactions are also required for the conversion of dietary ALA to its physiologically active derivatives EPA and DHA. Thus, the two pathways compete for the same rate-limiting desaturase enzymes. Excess of AA will severely limit the endogenous production of the critical omega-3 PUFAs, EPA, and DHA. AA is important for the integrity and function of cell membranes, and like DHA, it is essential for the normal development and function of the nervous system. Derivatives of AA play important roles in transmembrane signal transduction. However, AA is also converted to pro-inflammatory prothrombotic mediators. Excess AA promotes the development of inflammatory diseases such as obesity, diabetes, metabolic syndrome, and atherosclerosis. Δ: Desaturase enzyme, E: Elongase enzyme, DTA: Docosatetraenoic acid, DPA: Docosapentaenoic acid, LT: Leukotriene, PG: Prostaglandin, TX: Thromboxane, LA: Linoleic acid, AA: Arachidonic acid, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, ALA: α-linolenic

Table 3: Fatty acid composition of common fat sources (%)

Source	Saturated fatty acids	Unsaturated fatty acids
Canola oil (rapeseed)	Palmitic 4%; Stearic 2%	Oleic 58%; LA 25%; ALA 9%
Coconut oil	Lauric 48% Myristic 16%, Palmitic 9% Caprylic 8%, Capric 7%, Stearic 2%	Oleic 7%; LA 2%
Corn oil	Palmitic 13%; Stearic 3%	Oleic 52%; LA 31%; ALA 1%
Linseed (flaxseed) oil	Palmitic 6%; Stearic 4%	Oleic 22%; LA 21%; ALA 47%
Olive oil	Total 12%; Palmitic 12%; Stearic 2%	Oleic 78%; LA 7%; ALA 1%
Palm oil	Palmitic 44%; Stearic 4%	Oleic 40%; LA 10%
Peanut oil	Palmitic 13%; Stearic 3%	Oleic 41%; LA 38%
Safflower oil	Palmitic 7%; Stearic 3%	Oleic 75%; LA 14%
Soybean oil	Palmitic 10%; Stearic 4%	Oleic 51%; LA 23%; ALA 7%
Sunflower oil	Palmitic 4%; Stearic 2%; Arachidic 2%	Oleic 31%; LA 60%

ALA: α-Linolenic acid, LA: Linoleic acid

Table 4: Fatty acid composition of some nuts and seeds (%, w/w)

	Saturated fatty acids	Oleic acid (ω-9)	Linoleic acid (ω-6)	α-Linolenic acid (ω-3)	ω6/ω3
Almonds	4	32	12	0.007	1714
Brazil nuts	15	25	21	0.02	1050
Cashews	9	27	8	0.06	128
Hazelnuts	4	46	8	0.09	87
Macadamias	12	59	1.3	0.2	6.5
Pecans	6	41	20	1	20
Pines nuts	9	23	25	1	25
Pistachios	5	23	13	0.25	52
Walnuts	6	9	38	9	4.2
Chia seed	3.20	2.00	6	17.3	0.33
Flax seed	3.53	7.41	6	22.5	0.26
Pumpkin seeds	26	25	9	0.07	117

play a significant role in the epidemic of chronic, low-grade inflammation and attendant chronic inflammatory diseases such as obesity and T2DM. A healthful diet should provide a ω6/ω3 intake ratio in the range of 1–4. As shown in Table 4, plant-based sources rich in omega-3 FAs include flax seeds, chia seeds, and walnuts. Animal sources include fatty fish such as freshwater salmon (1.5%), sardines (1.6%), and tuna in water (0.26%).

Conclusions

The adipose tissue is far from being a static fuel depot. It is an active dynamic organ teaming with a variety of cells including adipocytes and all kinds of immune and endocrine cells secreting a myriad of signalling molecules. Thus, in addition to its roles in energy balance and thermoregulation, the adipose tissue is an integral part of both the immune and endocrine systems. lipids fulfill multiple functions ranging from energy provision to electrical insulation. fatty acids, the chief lipid, are not merely a rich source of calories, but function also as signaling molecules through their interactions with specific G-protein linked receptors. Fat in general and omega fatty acids in particular are essential for healthy development and maintenance of health. An omega-6/omega-3 intake ration close to 1-4 is important to resolving chronic inflammation and preventing related metabolic disease.

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Compliance with ethical principles

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