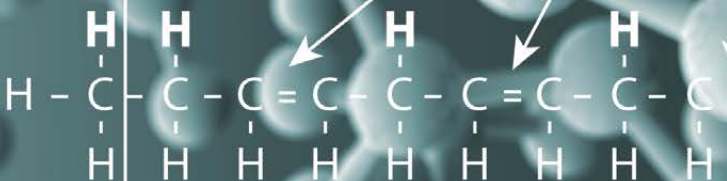


FATTY ACIDS SUPPORT GUIDE

Double-Bonds



EICOSAPENTAENOIC
20 carbons

GENOVA
DIAGNOSTICS

Methyl
Oil-soluble

Carboxyl
Water-soluble

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Essential & Metabolic Fatty Acids

NUTRITIONAL

Dietary fat is emerging as one of the most important nutritional modifiers for overall health. There are many health implications which make measuring fatty acids vitally important. Relying on dietary recall may not be accurate since fatty acids can not only be obtained from the diet, but also created endogenously. Imbalances in fatty acids have been implicated in many clinical conditions including but not limited to:¹⁻¹⁸

- Cardiovascular disease
- Chronic inflammatory conditions
- Autoimmune diseases
- Osteoporosis
- Cognitive decline
- Mood disorders
- Neurologic disease
- Cancer
- Diabetes
- Eczema and psoriasis
- Metabolic syndrome
- Polycystic ovary syndrome
- Chronic obstructive pulmonary disease
- Asthma



MEASUREMENT IN PLASMA VERSUS RED BLOOD CELL

Plasma and erythrocyte assessments are commonly used to assess fatty acid imbalances. Because the red blood cell life averages 90-120 days, it reflects a longer status than plasma. On the NutrEval, fatty acids are measured in the red blood cell as a weighted percentage of the cell membrane. Blood spot evaluation is whole blood, including RBC and plasma. This may reflect both short- and longer-term status, though internal data reveals good correlation between the two.

It should be noted that when dealing with percentages, the amount of each fatty acid can influence the others. For example, fish oil supplementation may increase the overall omega-3 percentage, which may lower the omega-6 percentage.

WHAT IS A FATTY ACID?

Fatty acids are simple in structure: a carbon backbone with a carboxyl group (COO) at one end, and a methyl group (CH₃) at the other. They are used as energy storage units, structural components of cell membranes, and precursors to eicosanoids, which are important signaling molecules in the inflammatory cascade. Fatty acids are made through the digestion of dietary fat or by endogenous production.

'Essential' fatty acids must come from dietary intake and cannot be made in the body. Dietary fat is digested and broken down into fatty acids which are then absorbed into circulation. In circulation, they can undergo beta-oxidation to become Acetyl-CoA to be used as energy in the Citric Acid cycle. They can also join in circulation to form triglyceride molecules.

Endogenous production of nonessential fatty acids happens one of three ways: synthesis, elongation, and desaturation.

- a. Fatty acids can be **synthesized** from carbohydrates. Dietary carbohydrates are metabolized to Acetyl-CoA which itself can form fatty acids outside of the mitochondria in the cytosol. Also, insulin can convert excess glucose into triglycerides in the liver and adipocytes.¹⁹
- b. **Elongation** is the adding of carbon molecules to an existing fatty acid to produce a longer fatty acid using an elongase enzyme.
- c. **Desaturation** is the process of adding double bonds to dietary fatty acid carbon backbones. The enzymes for this process are called delta-desaturases, further classified based on where the bond is being added. For example, adding a double bond between carbons 9 and 10 uses delta-9 desaturase.²⁰

FATTY ACID STRUCTURE AND NOMENCLATURE

Understanding the nomenclature of fatty acids can seem complex since there are several different naming conventions used by various laboratories and throughout literature. The basic structure of a fatty acid lays the groundwork by which it is named.

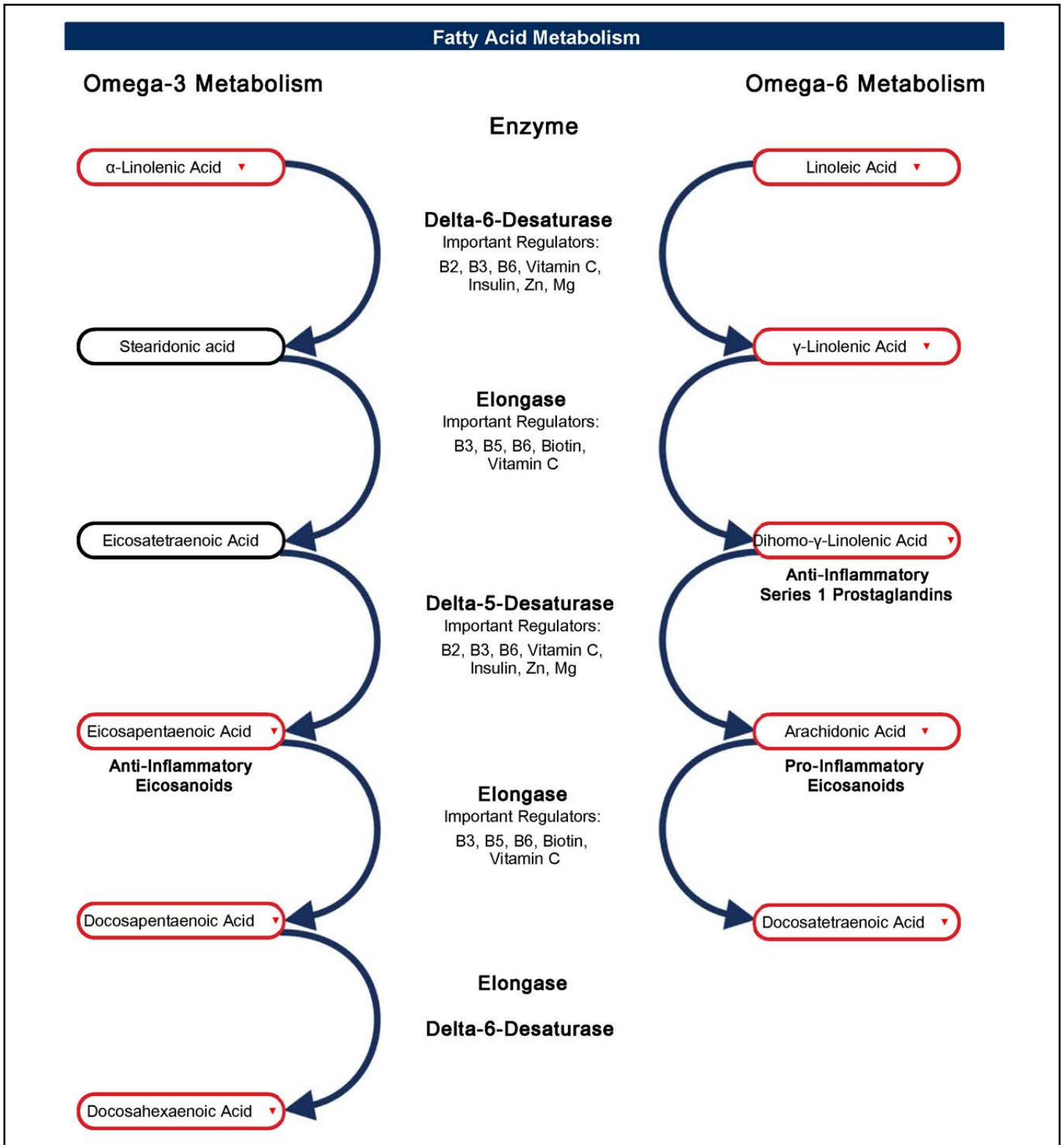
As mentioned previously, fatty acids consist of a carbon backbone with a carboxyl group at one end, and a methyl group at the other. That methyl group is referred to as omega (ω) or (Ω). The letter n is also frequently used. The length of each carbon backbone can range from 6 to 22, and sometimes longer. This is what differentiates them as short-chain, medium chain, long-chain, or very-long-chain fatty acids. The number of carbons delineating each of these (i.e. long vs. very-long-chain) varies somewhat in literature.²¹

A presence or absence of double bonds between the carbons reflects the degree of saturation. When the carbon backbone contains no double bonds, it is called saturated – filled with hydrogen as hydrocarbon chains. Unsaturated fatty acids contain one or more double bonds within that carbon backbone. Monounsaturated fatty acids contain one double bond while polyunsaturated fatty acids contain 2 or more. Because fatty acids are cell membrane structural components, the degree of saturation can play a role in membrane fluidity.²²

ESSENTIAL FATTY ACID METABOLISM

Dietary fatty acids can be converted into energy, stored, incorporated into cell membranes, or produce other fatty acids. There are only two essential dietary fatty acids: α -linolenic acid (omega-3) and linoleic acid (omega-6). All other fatty acids can either be obtained in the diet or be made from the essentials.

As discussed above, elongase and desaturase enzymes convert the essential fatty acids into others by adding carbon molecules to the backbone, or by inserting double bonds. Omega-3 and omega-6 fatty acids are competitive in their use of desaturase and elongase enzymes.²⁷



Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been linked to healthy aging throughout our lifespan - from fetal development to prevention of Alzheimer's disease. Omega-3 fatty acids are anti-inflammatory and used in cell membrane production, function, and overall gene expression.²⁸

Most standard American diets are deficient in common n-3 food sources such as flax, oily fish, nuts, and green leafy vegetables. Deficiencies in n-3 have been correlated with many clinical conditions such as neurodevelopmental and behavioral disorders, cardiovascular disease, cognitive decline, mood disorders, skin abnormalities, visual changes, and cancer.²⁹⁻³⁵

Omega-3 Fatty Acids Low Levels:

The reference ranges for omega-3 fatty acids are one-tailed since their health benefits are well-studied and deficiencies are associated with many clinical conditions. Low levels can be seen with decreased dietary intake of n-3 containing foods. Gastrointestinal malabsorption or maldigestion should also be considered.

Additionally, desaturase and elongase enzymes are used to metabolize and create n-3 fatty acids from the essential alpha-linolenic acid. Lack of vitamin or mineral cofactors for these enzymes, or single nucleotide polymorphisms (SNPs) can contribute to lower, or sometimes higher levels of each. Nutrients such as zinc, vitamin B₆, vitamin B₃, and magnesium are important cofactors for fatty acid metabolism. Other enzymatic influences such as alcohol, cortisol, and adrenocorticoids can also influence these enzymes.^{36,37}

It should also be noted that there is competition between the omega-3 and omega-6 fatty acids for use of the desaturase and elongase enzymes which may alter levels of fatty acid metabolites.²⁷

Alpha-Linolenic Acid

Alpha-linolenic acid (ALA) is an essential n-3 fatty acid and must be obtained in the diet. Sources include green leafy vegetables, oily fish, flaxseed, soybean oil, canola oil, walnuts, and chia seeds.^{38,39} ALA has an 18-carbon backbone with 3 double bonds starting at the third carbon molecule (18:3n3). It is an important precursor to make eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), though these can also be obtained in the diet. Most dietary ALA is used to generate energy and only a small portion is converted to EPA and DHA.⁴⁰

High Levels

Increased dietary intake of ALA-rich foods or supplementation can elevate levels.

The delta-6 desaturase enzyme is used to convert ALA into other downstream fatty acids. Lack of vitamin and mineral cofactors or genetic single nucleotide polymorphisms (SNPs) in the enzyme may slow the enzyme and contribute to elevations. Some studies suggest that the conversion rates of ALA to downstream fatty acids are gender dependent. There may be direct estrogen effects to desaturase and elongase enzymes whereby women of reproductive age show substantially greater conversion rates.^{37,41}

Higher levels of ALA are beneficial and its positive effects have been studied in several clinical conditions such as cardiovascular disease, diabetes, cancer, neurodegenerative diseases, and autoimmunity.^{39,41-44}

Although there is limited toxicological data for ALA, no serious adverse effects have been reported. Research is inconclusive regarding increased risk of prostate cancer in association with high dietary ALA intake.^{41,45}

Eicosapentaenoic Acid

Eicosapentaenoic acid (EPA) is an omega-3 fatty acid with 20 carbons and 5 double bonds (20:5n3). EPA can either be made from the downstream metabolism of ALA or it can be obtained in the diet. Food sources include oily fish such as salmon, mackerel, cod, and sardines. In addition to diet and ALA desaturation, EPA is also available as a fish oil supplement. The desaturation of ALA to EPA is not a very efficient process, therefore dietary intake or supplementation is important.^{27,40}

As a precursor for prostaglandin-3 (which inhibits platelet aggregation), thromboxane-3, and leukotriene-5 eicosanoids, EPA carries special importance in the inflammatory cascade. EPA can also lower plasma triglyceride levels without raising low-density lipoprotein cholesterol levels. Some studies suggest that in cardiovascular disease, EPA may decrease plaque vulnerability, prevent progression, and decrease macrophage accumulation. It is also vasodilatory which can lower blood pressure.⁴⁶

High Levels

Elevations in EPA can be due to high dietary intake of EPA-containing foods as outlined above and from supplementation with fish oil.

Lack of vitamin and mineral cofactors, or SNPs in the elongase enzyme, may also contribute to elevations. It should also be noted that there is competition for the elongase and desaturase enzymes between the omega-3 and omega-6 fatty acids which may affect levels of fatty acid metabolites.

High levels of EPA and its downstream metabolite DHA have been used in treatment for many clinical conditions. Studies show benefit in cardiovascular disease, depression, cognitive decline, autoimmune diseases, skin diseases, inflammation, cancer, and metabolic syndrome.⁴⁷⁻⁵³

Because of EPA's anti-platelet effects, over-supplementation was once thought to increase bleeding risk, especially if taken with other anticoagulants. However, new literature finds no increased risk of bleeding in patients taking fish oil supplementation while undergoing surgery and invasive procedures. In fact, some literature demonstrates a reduced need for blood transfusion in these patients.⁵⁴⁻⁵⁶

Docosapentaenoic Acid

Docosapentaenoic acid (DPA) is an omega-3 fatty acid with 22 carbons and five double bonds (22:5n3). It is formed from its precursor, EPA, by way of the elongase enzyme which adds two carbons. It can be supplemented or obtained in the diet from foods such as marine oily fish. Not only is DPA found in most fish and marine foods but it is also present in lean red meat from ruminant animals.⁵⁷

DPA is often overlooked and overshadowed by the significant amount of research on its precursor EPA and downstream metabolite docosahexaenoic acid (DHA). Both EPA and DHA are widely studied and commonly available as fish oil supplements. However, DPA is also found to have significant clinical importance.

DPA inhibits cyclooxygenase-1 and is a potent inhibitor of platelet aggregation. It also has been shown to suppress lipogenesis to regulate lipolysis in favor of increased lipid oxidation for energy. Its beneficial role in cardiovascular disease has also been studied. DPA can be retroconverted to EPA. Some research suggests that DPA can function as a reservoir or buffer of the other omega-3 fatty acids.⁵⁷

High Levels

Elevated DPA is seen with high intake of marine fish and other food sources, as well as with supplementation. High levels are less likely due to problems with downstream metabolism to DHA since it's been shown to retro convert to EPA as a regulator and reservoir of the omega-3 fatty acids.

DPA's anti-inflammatory effects have been studied in many conditions such as inflammatory bowel disease, peripheral vascular disease, cardiovascular disease, cognitive decline, and stroke.⁵⁸⁻⁶³

Docosahexaenoic Acid

Docosahexaenoic acid (DHA) is an omega-3 fatty acid with 22 carbons and 6 double bonds (22:6n3). It can be obtained from the diet, supplemented, or created by conversion from DPA using elongase and desaturase enzymes. DHA is present in fatty fish such as salmon, tuna, and mackerel, and low levels of DHA can be found in meat and eggs.⁶⁴

Both individually or in combination with EPA, DHA is widely supplemented due to the enormous amount of research available regarding its anti-inflammatory role in many clinical conditions such as cardiovascular disease, cognitive decline, autoimmune disease, fetal development, visual disturbances, cancer, and metabolic syndrome.^{28,29,33,64,65}

High Levels

Elevations in DHA can be seen in high omega-3 dietary intake and in patients who are supplementing with fish oil.

In addition to the clinical implications outlined above, having adequate levels of DHA is important for neuroprotection, blood pressure regulation, protection from cardiac arrhythmia, inflammation, and tumorigenesis.⁶⁶

Much like EPA, oversupplementation with DHA was initially thought to increase bleeding, especially in patients also taking anticoagulants. However, literature is showing that fish oil containing EPA and DHA does not increase perioperative bleeding in patients undergoing invasive procedures. In fact, higher levels are associated with lower risk of bleeding in these patients.⁶⁷

Percentage Omega-3s

When assessing fatty acids in RBCs, Genova measures a weighted percentage of fatty acids taken up into the erythrocyte wall. The total omega-3 percentage is a combined total weight percentage. It is calculated by adding up each of the measured omega-3s. Higher total percentages of omega-3 fatty acids are anti-inflammatory, cardioprotective, and considered beneficial.

It should be noted that when dealing with percentages, the amount of each fatty acid can influence the others. For example, fish oil supplementation may increase the overall omega-3 percentage. By default, this may then lower the omega-6 percentage.

Omega-6 (n-6) Fatty Acids

Throughout evolution, the dietary intake of omega-3 and omega-6 polyunsaturated fatty acids has proportionately changed from a ratio of 1:1 to 20:1 or more, in favor of omega-6 fatty acids. This shift in Western diets toward omega-6s coincides with an epidemic of obesity, metabolic dysfunction, and many other significant clinical implications.⁶⁸⁻⁷⁰

The main concern with omega-6 fatty acids revolves around one of the downstream metabolites: arachidonic acid (AA). AA is a precursor for the inflammatory cascade. The potential pro-inflammatory nature of omega-6s, as well as their susceptibility to oxidation, can lead to many clinically deleterious effects. They also compete with the omega-3 cascade for use of the elongase and desaturase enzymes.

It should be emphasized that not all omega-6 fatty acids are concerning. In fact, some have important physiologic effects and can be anti-inflammatory. Omega-6 fatty acids act as structural cell membrane components and as precursors to eicosanoids. These eicosanoids modulate renal and pulmonary function, vascular tone, and the inflammatory response.⁷¹

Linoleic Acid

Linoleic acid (LA) is the only essential omega-6 fatty acid and must be obtained from the diet. From LA, other omega-6s can be created using elongase and desaturase enzymes. LA contains 18 carbons, with 2 double bonds, the first of which is at the 6th carbon position (18:2n6). LA is found in nuts and vegetable oils (corn, soybean, canola, sunflower, etc.) as well as most meats.⁷² When the double bonds of LA are arranged differently, the term conjugated LA (CLA) is used. Although technically CLA can be termed a trans-fat, a natural type of CLA can be obtained in the dietary intake of meat and milk from ruminant animals. There are many isomers of CLA – some beneficial and others are not as well defined.⁷³

There is some controversy regarding how much LA is needed from the diet for adequacy. Although LA is needed to synthesize downstream fatty acids, it may lead to increased inflammatory fatty acid production. Several studies show that LA lowers blood cholesterol levels and improves all-cause mortality. However, their current role in atherosclerosis and cardiometabolic disease are being revisited. There is difficulty in differentiating the

biological effects of LA from arachidonic acid in health and disease. In fact, it has been shown that LA is the most abundant fatty acid found in LDL and is one of the first fatty acids to oxidize. Studies are showing that LA promotes oxidative stress, oxidized LDL, and may be a major dietary cause of cardiovascular disease, especially when consumed via industrial vegetable oils.^{9,74-80}

High Levels

Elevations are seen with high dietary fat intake (especially vegetable oils), or with supplementation of CLA. The delta-6-desaturase enzyme converts LA to downstream fatty acids. Lack of vitamin and mineral cofactors, or a SNP in the enzyme may slow its ability to convert and elevate LA levels. Additionally, there is competition with the omega-3 fatty acids for use of this enzyme which may contribute to elevated levels depending on availability.³⁷

High levels of LA are associated with obesity, inflammatory conditions such as IBD, various cancers, cardiovascular disease, altered cognition, and brain development.^{79,81-85}

Low Levels

Linoleic acid deficiency is rare, especially given current dietary trends which include excess vegetable oils. However, lack or decreased intake of foods containing LA can contribute to lower levels. Additionally, a SNP in delta-6-desaturase may potentially alter the enzyme function and promote downstream metabolism.⁸⁶

Essential linoleic acid deficiencies have been mainly associated with skin conditions and impaired growth and development. Low levels of LA may contribute to impaired wound healing since it has been found to modulate a cellular response in wound healing by increasing the migration and functions of inflammatory and endothelial cells, and by inducing angiogenesis at the wound site.⁸⁷⁻⁸⁹

Gamma Linolenic Acid

γ -linolenic acid (GLA) is an omega-6 fatty acid containing 18 carbons and 3 double bonds (18:3n6). It is synthesized from LA by adding a double bond using the delta-6-desaturase enzyme. This enzymatic reaction is very slow and further impaired in vitamin and mineral deficiencies such as zinc and cobalt. Stress, smoking, alcohol, and systemic inflammatory conditions can also slow this conversion.⁹⁰

Since the synthesis of GLA is not efficient, dietary intake of organ meats may be considered to raise GLA levels. Also, many people supplement with GLA-containing products such as borage oil, black currant, and evening primrose. Primrose and borage oil supplementation have been studied as an effective treatment for many conditions such as rheumatoid arthritis, dermatitis, and diabetic neuropathy. They have been shown to decrease inflammation, improve bone health, regulate lipid metabolism, and have beneficial effects on the skin. But, whether it's the GLA component that is beneficial or GLA's downstream fatty acid metabolite is difficult to determine.⁹¹

The clinical importance of GLA is in its rapid conversion to its downstream fatty acid dihomo-gamma-linolenic acid (DGLA) which is anti-inflammatory. GLA itself, however, does have physiologic importance. It has been shown to exert some tumoricidal activity in various cancers and to inhibit metastases.⁹⁰ GLA has been studied for its clinical importance in neurovascular deficits in diabetes and has been shown to normalize nerve conduction velocity and endoneurial blood flow.⁹²

There is some concern regarding GLA supplementation leading to rapid conversion through DGLA to arachidonic acid. Supplementing the omega-3s EPA or DHA may help to mitigate the effects since there is enzymatic competition for the delta-5-desaturase enzyme. This enzyme is responsible for both AA production and EPA metabolism.⁹³

High Levels

Elevations are seen with supplementation of borage oil, primrose, and black currant. Additionally, the conversion to DGLA requires the elongase enzyme. Lack of vitamin and mineral cofactors, enzymatic SNPs, or competition for use of the enzyme by omega-3 fatty acids may contribute to elevated GLA. It should also be emphasized that smoking, alcohol, and systemic inflammation can slow the elongase enzyme and conversion to DGLA.^{37,90}

As noted above, GLA has important clinical implications. The issues of safety have been investigated and GLA appears to be nontoxic. Limited cases of soft stools, belching, and abdominal bloating have been reported. Long-term human studies show that up to 2.8 g/d are well tolerated. However, the possibility exists that GLA will be metabolized through to DGLA and then increase arachidonic acid causing inflammation.⁹² The addition of EPA or DHA may help to mitigate these effects.

Low Levels

Decreased intake of the essential LA can result in low levels. Also decreased conversion by the delta-6-desaturase enzyme can result in low levels of GLA due to lack of vitamin and mineral cofactors or SNPs in the enzyme. The competition for use of delta-6-desaturase by the omega-3s should also be considered.³⁷

Due to the important clinical implications of GLA and subsequent DGLA formation as outlined, supplementation with evening primrose, borage oil, and black currant may be beneficial.

Dihomo-gamma Linolenic Acid

Dihomo-gamma-linolenic acid (DGLA) is a 20-carbon omega-6 with 3 double bonds (20:3n6) derived from the essential linolenic acid. LA is metabolized to GLA, which is rapidly elongated to DGLA. There are only trace amounts of DGLA found in organ meats, otherwise it must be synthesized from GLA. The inability to convert precursor fatty acids to DGLA is associated with various pathologic and physiologic conditions such as aging, diabetes, alcoholism, atopic dermatitis, rheumatoid arthritis, cancer, and cardiovascular disease.^{94,95}

DGLA is a precursor to prostaglandin PGE1, which inhibits platelet aggregation and inflammation, produces vasodilation, inhibits cholesterol biosynthesis and thrombus formation, regulates immune responses and reduces blood pressure. It is also involved in inhibiting the formation of pro-inflammatory compounds from AA. PGE1 can also inhibit growth and differentiation of cancer cells. Although the mechanism of DGLA in cancer has not yet been identified, the potential benefits are being studied.^{94,96}

DGLA-enriched oils and fermented DGLA oil supplements are being developed with excellent safety profiles and studied in a variety of clinical conditions.^{94,97}

High Levels

Supplementation with DGLA or GLA, as well as high dietary intake of the essential LA, can lead to higher DGLA levels. Lack of vitamin and mineral cofactors, or SNPs in the enzyme which converts DGLA downstream to arachidonic acid, may also contribute to elevations.³⁷

Higher DGLA levels are mainly beneficial due to its anti-inflammatory role. Although there is some concern regarding DGLA being converted to its pro-inflammatory metabolite, arachidonic acid, the conversion is generally limited. The reason for this limitation is that inflammatory arachidonic acid-derived lipid mediators (eicosanoids) are made via several pathways two of which are cyclooxygenase (COX) and lipoxygenase (LOX). The synthesis of AA eicosanoids is dependent on DGLA since DGLA competes with AA for COX and LOX. When DGLA is in excess, it inhibits the synthesis of AA-derived eicosanoids due to its higher affinity for the COX and LOX enzymes.^{98,99}

High levels of DGLA are associated with elevated body mass index, waist circumference, body fat percentage, and other obesity-related parameters. It should be noted

that some of these clinical associations are related to increased overall intake of omega-6 fatty acids. But insulin itself can downregulate the enzyme delta-5-desaturase which synthesizes AA from DGLA. Therefore, obesity and insulin resistance can affect delta-5-desaturase resulting in higher DGLA levels.^{100,101}

Low Levels

Decreased intake of the essential LA, or inefficient metabolism of the omega-6 fatty acids can lead to decreased production of DGLA. Lack of vitamin or mineral cofactors, or SNPs in the elongase and desaturase enzymes can contribute to lower DGLA levels either from production to DGLA or increased metabolism to AA. It should also be emphasized that smoking, alcohol, and systemic inflammation can slow the elongase enzyme and conversion to DGLA.^{37,90}

Due to the anti-inflammatory and beneficial effects of DGLA, low levels have significant clinical associations such as diabetes, alcoholism, atopic dermatitis, rheumatoid arthritis, cancer, and cardiovascular disease.^{94,95} Decreased levels are associated with increased total mortality in patients with acute cardiac events and decompensated heart failure.¹⁰²

Arachidonic Acid

Arachidonic acid (AA) is a 20-carbon polyunsaturated n-6 fatty acid with 4 double bonds (20:4n6). Its double bonds contribute to cell membrane fluidity and predispose it to oxygenation. This can lead to several important metabolites which ensure a properly functioning immune system as well as regulate inflammation, brain activity, and other signaling cascades.

AA's metabolites are called eicosanoids which are signaling molecules. They can be produced via cyclooxygenases, lipoxygenase, cytochrome P450, and oxygen species-triggered reactions. These pathways yield molecules like prostaglandins, isoprostanes, thromboxane, leukotrienes, lipoxins, and epoxyeicosatrienoic acids.

AA can be obtained in the diet from eggs, fish, and animal meats and fats – or produced directly from DGLA using the delta-5-desaturase enzyme. Although often vilified, adequate AA intake is needed to achieve an equilibrium between its inflammatory and resolution effects to support a healthy immune system. It is also fortified in infant formulas due to its importance in growth and development.¹⁰³⁻¹⁰⁵

AA plays a crucial role in regulating innate immunity and inflammation resolution. When tissues become inflamed or infected, AA metabolites (eicosanoids) amplify those inflammatory signals to recruit leukocytes, cytokines, and immune cells to aid in pathogen resistance and clearance. Following the initial inflammatory signaling, these metabolites then balance those signals by producing resolving metabolites for host protection.¹⁰³

High Levels

Dietary intake of animal meats, fats, and eggs contribute to elevated levels. AA can also be produced from DGLA using the delta-5-desaturase enzyme, therefore high intake of omega-6 fatty acids or DGLA supplementation should be considered as a cause of elevations.

AA is then metabolized to docosatetraenoic acid using the elongase enzyme. Lack of vitamin and mineral cofactors, or a SNP in elongase, may slow the enzyme and contribute to elevations. It should also be noted that omega-3 and omega-6 fatty acids compete for use of the elongase and desaturase enzymes.

Because of its role in the inflammatory cascade and ability to induce oxidative stress, AA is a relevant factor in the pathogenesis of cardiovascular and metabolic diseases such as diabetes mellitus, non-alcoholic fatty liver disease, atherosclerosis, peripheral vascular disease, and hypertension. Neuroinflammation and brain excitotoxicity is also regulated by an AA cascade. Elevations are associated with Alzheimer's disease and mood disorders. There is also a substantial correlation between COX-catalyzed AA peroxidation and cancer development (prostate, colon, and breast).¹⁰⁶⁻¹⁰⁹

Low Levels

Reduced intake of animal meats and fats, or low dietary intake of omega-6 fatty acids in general, can result in lower levels of AA. Lack of vitamin and mineral cofactors for the desaturase and elongase enzymes upstream in omega-6 metabolism might contribute to lower levels.³⁷

Because of important immune and inflammatory signaling which requires AA, and its role in cell membrane phospholipid metabolism, lower levels of AA do have clinical significance. Psychiatric disorders such as schizophrenia, and neurologic disorders like tardive dyskinesia, show depletion of AA in RBC membranes. Improving AA levels decreased symptoms in some patients.¹¹⁰

Monitoring levels and ensuring adequate dietary intake of AA is important in pregnant women, infants, children, and the elderly due to its importance for the development and optimization of the nervous system, skeletal muscle, and the immune system.¹¹¹

Docosatetraenoic Acid (Adrenic Acid)

Docosatetraenoic acid (DTA) is a very long chain omega-6 fatty acid with 22 carbons and 4 double bonds (22:4n6). It is synthesized by adding 2 carbons atoms to the backbone of arachidonic acid using the elongase enzyme. It is sometimes referred to by its common name adrenic acid and is one of the most abundant fatty acids in the early human brain and the adrenal gland.¹¹²

DTA has not been well studied, though it has recently been shown to have important physiologic functions. It is now believed to be a pro-resolving mediator in inflammation by blocking neutrophilic metabolites and dampening the inflammation response. For example, in osteoarthritis DTA enhances phagocytosis by macrophages which clears products of cartilage breakdown in the joint space. Supplementation of DTA is being studied as a promising intervention in osteoarthritis to dampen inflammation and prevent structural damage.¹¹³

Much like AA (its precursor) DTA/adrenic acid is an important component of infant development. DTA is the third most abundant PUFA in the brain and it is necessary for neural tissue development.¹¹⁴

DTA is also prevalent in the vasculature. It is metabolized to biologically active prostaglandins and epoxyeicosatrienoic acids (EETs) which activate smooth muscle channels causing relaxation and vasodilation.¹¹⁵

There is some literature to also support DTA/adrenic acid's role in inducing oxidative stress and cell death through modulating superoxide dismutase enzymes.¹¹⁶

High Levels

Elevations of DTA/adrenic acid are seen in diets rich in omega-6s and arachidonic acid (animal meat/fats and eggs).

The clinical significance of adrenic acid is still being studied. Its importance in fetal development, osteoarthritis, and vasodilation have been documented, though some of the research is in animal studies. It has also been found to be elevated in patients with nonalcoholic fatty liver (NAFLD) and nonalcoholic steatohepatitis (NASH).¹¹⁶

Because its precursor is AA, elevations due to high AA intake have deleterious associations as outlined above in the AA section.

Low Levels

Diets low in omega-6 fatty acids and arachidonic acid would result in lower levels of DTA/adrenic acid. The clinical significance of low levels may be relevant in infant and fetal development as previously described.

Eicosadienoic Acid

Eicosadienoic acid (EDA) is a rare, omega-6 fatty acid with a 20-carbon backbone and two double bonds (20:2n6). It is mainly formed through the downstream metabolism of omega-6s by elongating LA. EDA can be metabolized to form DGLA and AA. Literature is sparse regarding its role in the inflammatory cascade though it is known to modulate the metabolism of other PUFAs and to alter the responsiveness of macrophages to stimulate inflammation.¹¹⁷

High Levels

Elevations may be seen with high intake of LA and omega-6 fatty acid-rich foods. The clinical significance of elevations is presumed due to its role in the inflammatory cascade, though in and of itself, EDA hasn't yet been studied epidemiologically for disease associations.

Low Levels

Lower levels may be due to decreased dietary intake of omega-6 foods or decreased downstream metabolism of LA and other omega-6s. There is no known clinical significance of decreased levels.

Percentage Omega-6s

When assessing fatty acids in RBCs, Genova measures a weighted percentage of fatty acids taken up into the erythrocyte wall. The total omega-6 percentage is a combined total weight percentage calculated by adding together each of the measured omega-6s. Because some omega-6 fatty acids are less beneficial than others, each fatty acid abnormality should be addressed. However, in general, assessing the total omega-6 percentage as it relates to the omega-3 percentage is helpful. A more balanced ratio may decrease risk of many chronic diseases.¹¹⁸

It should be noted that when dealing with percentages, the amount of each fatty acid can influence the others. For example, fish oil supplementation may increase the overall omega-3 percentage, which may ultimately lower the omega-6 percentage.

Omega-9 (n-9) Fatty Acids

Monounsaturated fatty acids (MUFAs) contain one double bond within their carbon backbone structure. The placement of that bond is responsible for its nomenclature. These MUFAs have a double bond at the 9th carbon; therefore, they are omega-9 fatty acids. The double bond plays a role in increasing cell membrane fluidity.

Omega-9 fatty acids are not considered essential since the body can synthesize them, though they have many food sources. Olive oil is the most common source of n-9, and they are also found in various nuts and seeds. The overall health benefits to n-9s have been extensively studied as it relates to lowering inflammation, being cardioprotective, and important for brain health.¹¹⁹⁻¹²¹

Oleic Acid

Oleic acid (OA) has an 18-carbon backbone with one double bond at the 9th position (18:1n9). Oleic acid's main dietary source is olive oil, and it is also available as a supplement. OA can also be synthesized in the body by adding a double bond to stearic acid using the enzyme delta-9-desaturase.

Oleic acid is important in cell membrane fluidity and has attracted a lot of positive attention due to the amount of olive oil found in the 'Mediterranean diet.' OA's anti-inflammatory and immunomodulatory effects have been extensively studied and found to be beneficial in many conditions such as cancer, neurodegenerative disorders, inflammation, autoimmunity, cardiovascular disease, diabetes, wound healing, and infection. There is also literature to suggest that OA may be a selective biomarker of isolated impaired glucose tolerance regardless of fasting glucose.¹²²⁻¹²⁸

OA can lower blood lipids- mainly total cholesterol, LDL-cholesterol, and triglycerides. It also dampens the inflammatory response within the vascular endothelium.¹²⁹⁻¹³¹

High Levels

Elevations can be seen in diets high in olive oil, nuts, and seeds – or in patients supplementing with OA. In general, higher levels are beneficial and no adverse clinical associations are seen.

Low Levels

Decreased dietary intake of OA-rich foods, (olive/safflower/sunflower oils) will lower levels. Because stearic acid is its precursor, low levels of stearic acid may result in low OA. Lack of vitamin and mineral cofactors for delta-9-desaturase, or a SNP in the enzyme, may result in lower production of oleic acid.^{27,132}

Nervonic Acid

Nervonic acid (NA) is an omega-9 MUFA with a 24-carbon backbone and one double bond (24:1n9). It is a very important fatty acid in the white matter of the brain and is responsible for nerve cell myelin biosynthesis. There are small amounts of NA in cooking fats, vegetable oils and borage oil. It can also be synthesized in the body by elongating oleic acid (which is essentially desaturated stearic acid).

NA is essential for the growth and maintenance of the brain and peripheral nervous tissue enriched with sphingomyelin.¹³³

High Levels

Increased dietary intake of cooking fats, vegetable oil, or borage oil can elevate NA levels.

NA is elevated in clinical conditions marked by impaired white matter or altered desaturation enzyme activity such as major depressive disorder and Alzheimer's disease.^{133,134}

Due to its effects on overall lipid metabolism, higher levels of NA are also associated with improved metabolic parameters including blood glucose, insulin, and glucose tolerance. In animal studies, it has been shown that NA might play a role in treating obesity and obesity-related complications.¹³⁵⁻¹³⁷

Low Levels

Decreased intake of dietary sources and low levels of oleic acid may result in low NA. Lack of vitamin and mineral cofactors, or a SNP in the delta-9-desaturase enzyme, may also contribute to lower levels.

Clinically, low levels of NA results in a decreased ability to maintain or develop myelin in the brain. In fact, low levels may predict psychosis in schizophrenia. Supplementation with omega-3 fatty acids may offset risks conferred by low levels of NA in certain conditions.^{133,138}

Multiple sclerosis (MS) is thought to be an autoimmune reaction to myelin. A defect in the biosynthesis of NA causing lower NA levels may lead to breakdown of myelin which triggers the onset of the autoimmune response. Use of NA as nutritional support in MS is being studied.¹³⁹

Low levels of NA have been found to be an independent predictor of mortality in cardiovascular disease and chronic kidney disease.^{119,140}

Percentage Omega-9s

When assessing fatty acids in RBCs, Genova measures a weighted percentage of fatty acids taken up into the erythrocyte wall. The total omega-9 percentage is a combined total weight percentage calculated by adding up each of the measured omega-9s. In general, because the omega-9 fatty acids are beneficial, higher levels are preferred; though identifying root cause of elevations or deficiencies is important.

It should be noted that when dealing with percentages, the amount of each fatty acid can influence the others. For example, fish oil supplementation may increase the overall omega-3 percentage. By default, this may then lower the omega-6 percentage.

Saturated fatty acids (SFAs) are so named because they contain no double bonds among the carbon backbone skeleton; it is saturated with hydrogen atoms. This configuration contributes to a lack of cell membrane fluidity and difficulty for the body to convert them directly as energy. SFAs are not essential nutrients and are obtained mainly through dietary intake of animal fats and processed foods. Some SFAs can be synthesized in the body from carbohydrates via de novo lipogenesis. Attempts to lower SFA levels by removing dietary sources should also include a strategy of limiting carbohydrates.¹⁴¹

Compared to unsaturated fatty acids, SFAs have a higher heat index and better oxidative quality, making them ideal as a cooking oil at high temperatures.¹⁴²

SFAs alter overall lipid metabolism and elevate cholesterol levels. They are also involved in the inflammatory cascade which is implicated in dietary SFA disease risk. However, certain SFAs may play an important role in hormone production, gene transcription, cellular membrane structure, and protein signaling.¹⁴³⁻¹⁴⁵

Palmitic Acid

Palmitic acid (PA) is a 16-carbon saturated fatty acid (16:0) and the most common fatty acid in the human body. It can be obtained via diet or synthesized from carbohydrates, other fatty acids, and amino acids. As the name suggests, it is a major component of palm oil, but can also be found in meat, dairy, cocoa butter, coconut oil, and olive oil. Palm oil and palmitic acid are also found in many products ranging from skincare products, margarine, cereals, and baked goods.¹⁴⁶

Dietary intake of PA is counterbalanced by de novo lipogenesis depending on the physiologic needs of a specific tissue, or nutritional factors. Regardless of PA intake, the body makes it as needed. Excess PA is converted to palmitoleic acid via delta-9-desaturase or elongation to stearic acid. Homeostasis of PA levels is tightly controlled.

PA can be oxidized for energy production. It is also used structurally in cell membranes and cell adhesion molecules, as well as being a component of lung surfactant.¹⁴⁶

High Levels

Elevations in PA are seen in high dietary intake of saturated fats, proteins, and carbohydrates. Excessive intake of carbohydrates and a sedentary lifestyle can disrupt the PA homeostatic balance resulting in dyslipidemia, hyperglycemia, fat accumulation, lipotoxicity, altered immune responses, and stimulation of the inflammatory cascade. The disruption of this balance (implicated in atherosclerosis, neurodegenerative diseases, and cancer), is related to an uncontrolled endogenous biosynthesis regardless of dietary intake. Excess PA induces apoptosis through mitochondrial dysfunction and endoplasmic reticulum stress.¹⁴⁶⁻¹⁴⁹ Higher levels are correlated with the incidence of type 2 diabetes, cardiovascular disease, and cancer risk.¹⁴⁷

Low Levels

Decreased intake of saturated fat and PA may contribute to lower levels, however there is tight regulation of PA levels and the body will use carbohydrates, other fatty acids, and amino acids to maintain those levels. The liver plays a strong role in regulating the body concentration of PA using desaturase and elongase enzymes. Lack of nutrient cofactors, or SNPs in these enzymes, may interrupt this balance.¹⁴⁶

Stearic Acid

Stearic acid (SA) is a saturated fatty acid with an 18-carbon backbone (18:0). Although it is mainly abundant in animal fat, cocoa butter and shea butter are also very high in SA. It is also commonly used in detergents, soaps, cosmetics, shampoos, and shaving cream.¹⁵⁰ Additionally, it can be synthesized in the body from palmitic acid.

SA is not a strong substrate to make triglycerides compared to other saturated fatty acids and it generates a lower lipemic response.¹⁵¹ As compared to other saturated fats, SA doesn't raise plasma LDL cholesterol. This may be due to absorption of SA and the amount of energy metabolized from it. In fact, SA may have some beneficial effects in regulating mitochondrial morphology and function, though these mechanisms are still being studied.¹⁵²

The American Heart Association recognizes that a diet low in trans fats from industrial food sources and low in saturated fatty acids is optimal for cardiovascular health. SA is being studied as a solid-fat alternative to trans fatty acids in baking goods and shortenings since it is trans-free, oxidatively stable, and doesn't raise LDL cholesterol. (Unsaturated fats are not suitable for solid fat applications, like frying.) However, the safety of using SA substitutes in industrial products is still being studied and debated.¹⁵³⁻¹⁵⁵

High Levels

SA levels may be high with dietary intake, or through absorption of commercial products containing it. Because it can also be synthesized from palmitic acid, a diet generally rich in saturated fats can contribute to higher levels.

Saturated fatty acid levels are associated with many cardiometabolic conditions. SA alone seems not to exert the same detrimental effects as is seen with other saturated fatty acids, though these are often contained in foods alongside each other. SA itself can elevate serum lipoprotein(a), though to a lesser extent than trans fats.¹⁵⁵

Low Levels

Decreased intake of foods containing saturated fatty acids, or SA specifically, can contribute to low levels. Because it can also be made from palmitic acid, lack of vitamin or mineral cofactors for the elongase enzyme, or an enzymatic SNP, might also be implicated in lower levels. Clinically, lower levels have not been extensively studied in relation to disease.

Arachidic, Behenic, Tricosanoic, and Lignoceric Acids

Very-Long-Chain Saturated Fatty Acids (VLSFAs)

Very long saturated fatty acids (VLSFAs) are defined as having 20 carbons or more with no double bonds. (It should be noted that the amount of carbons needed to define VLSFAs varies in literature as 20-22 or more).¹⁵⁶⁻¹⁵⁹

These saturated fatty acids can be obtained in the diet, synthesized from precursor fatty acids (such as stearic acid and palmitic acid), or created *de novo* in mitochondrial microsomes.¹⁶⁰

Very long saturated fatty acids exhibit distinct beneficial functions compared to other saturated fatty acids. For example, they can influence liver homeostasis, retinal function, skin barrier, and may have anti-inflammatory effects. As important constituents of sphingolipids such as ceramides and sphingomyelins, levels can also be influenced by genetic factors related to sphingolipid synthesis.^{158,161,162}

VLSFAs are too long to be metabolized in the mitochondria and require peroxisomes for metabolism. Certain peroxisomal disorders (adrenoleukodystrophy, Zellweger syndrome) can be associated with high VLSFA levels.¹⁶³

- **Arachidic acid** is very long, 20-carbon backbone saturated fatty acid (20:0). It is found in various nuts, soybeans, peanut oil, corn oil, and cocoa butter. In addition to dietary sources, it can be synthesized by the hydrogenation of the omega-6 fatty acid arachidonic acid or the elongation of stearic acid.^{158,164,165}
- **Behenic acid** is a VLSFA which contains 22 carbons (22:0). Its name is derived from Ben oil (behen oil) from the *Moringa oleifera* tree. Commercially, products containing Moringa oil have high amounts of behenic acid in them such as hair conditioners, topical moisturizers, and other cosmetic oils. It can also be obtained through the diet in canola (rapeseed) oil and peanut oil. Using the elongase enzyme, it can be synthesized from arachidic acid.
- **Tricosanoic acid** is an 23-carbon, odd-chain saturated fat (23:0) synthesized initially from propionic acid and can be derived in the diet from sesame, sunflower, and hempseed oils.¹⁶⁶

- **Lignoceric acid** has 24 carbons and no double bonds (24:0). It can be formed from behenic acid using the elongase enzyme. It is found in peanuts, nut and seed oils. It can also be found in wood tar. Lignoceric acid is one of many fatty acids which compose brain tissue and myelin.

High Levels

Intake of foods containing these VLSFAs or use of products containing them can contribute to higher levels. Increased intake of precursor fatty acids, or SNPs in the elongase enzyme, may alter levels.

Additionally, as an odd-chain fatty acid, tricosanoic acid elevations can be seen with functional deficiency of vitamin B₁₂ since it is required for the conversion of propionate for oxidation. Tricosanoic acid can be high in microbiome dysbiosis with increased production of the short chain fatty acid propionate (its precursor). The health implications of elevated VLSFAs levels are evolving, though they are generally found to be beneficial in health and aging. Several meta-analyses suggest a beneficial association of very long chained saturated fatty acids with cardiovascular health outcomes as well as lower risks of type 2 diabetes, atrial fibrillation, heart failure, and coronary disease. These VLSFAs may also be important in neural development and cognition. The mechanisms of these very long chained saturated fatty acids are not fully known. Because VLSFAs are components of ceramides involved in apoptosis, there is strong evidence that VLSFAs are protective against apoptosis and cell death.^{156,161,167-172}

Low Levels

Decreased dietary intake of these saturated fatty acids, or avoidance of products containing them, can result in low levels. Some VLSFAs can be synthesized from other fatty acids. Therefore, decreased levels of precursors, lack of vitamin and mineral cofactors, or SNPs in the elongase enzyme may also contribute to low levels.

Specific deficiency in VLSFAs is not well studied. Though, due to their importance in brain development and their associations with improved health outcomes, as outlined above, research is evolving.

Tricosanoic, Pentadecanoic, and Margaric Acids

Odd-Chain Saturated Fatty Acids (OCS-FAs)

Most research in fatty acid metabolism has focused on even-chain fatty acids since they represent >99% of total human lipid concentration. For years, it had been concluded that odd chain saturated fatty acids (OCS-FAs) were of little significance and used only as internal standards in laboratory methodology. However, there is now a realization that they are, in fact, relevant and important physiologically.¹⁷³

OCS-FAs mainly originate from dairy fat since microbiome fermentation in ruminant animals is a primary source of production. The human body can also synthesize them by elongating propionic acid, a short chain fatty acid formed in the microbiome. New research is showing they may also be formed by shortening VLCFAs by removing carbon molecules using α -oxidation. Metabolism of OCS-FAs is a bit different than even-numbered chained fatty acids. Both odd and even chain fatty acids undergo oxidation, though OCS-FAs produce a molecule of propionyl-CoA and a molecule of acetyl-CoA instead of two acetyl-CoAs. Propionyl-CoA requires a vitamin B₁₂-dependent enzyme to be converted into succinyl-CoA and used in the citric acid cycle. It should be noted that the microbiome is not the only source for the OCS-FA precursor propionate. Endogenous propionate can be produced by the degradation of some amino acids, which can then lead to OCS-FA production.¹⁷³⁻¹⁷⁵

Several epidemiologic studies show a positive association between OCS-FA and reduced risk for inflammation, cardiometabolic disease, multiple sclerosis, and nonalcoholic steatohepatitis. They are also being studied as adjuvant therapies in cancer due to their cell signaling properties which induce targeted apoptosis. Additionally, it has been found that OCS-FAs increase membrane fluidity more than PUFAs, and they are being studied as a form of treatment for Alzheimer's disease.^{173,176-178}

- **Pentadecanoic acid** is a 15-carbon saturated fatty acid (15:0). Its major dietary source is the butterfat in cow's milk. It can also be synthesized from propionate via the mechanisms outlined above.
- **Margaric acid** is also known as heptadecanoic acid. It is a 17-carbon saturated fatty acid (17:0). Food sources mainly include milk and dairy products, though it can be endogenously made as noted.

- **Tricosanoic acid** is a saturated fatty acid which contains 23 carbons (23:0). It can be found in milk and dairy products, as well as some wild mushroom species. It can also be endogenously made.

High Levels

High dietary intake of dairy products can increase levels. Because propionate is a precursor for OCS-FAs, high fiber intake can induce the microbiome to produce propionate to be converted to propionyl-CoA. Because propionyl-CoA competes with acetyl-CoA, fiber intake can increase OCS-FAs levels at the expense of other saturated fatty acids. Some studies suggest that OCS-FA levels may act as a biomarker for dietary fiber intake.¹⁷⁹

Due to the broad health benefits of OCS-FAs, questions are being raised as to whether they should be considered essential nutrients.¹⁷⁸

Low Levels

Decreased dietary intake of dairy products and fiber may contribute to low levels. As noted above, literature is evolving as to their health benefits, and lower levels have been associated with risk for cardiometabolic diseases, inflammation, Alzheimer's disease, multiple sclerosis, and nonalcoholic steatohepatitis.

Percentage Saturated Fats

When assessing fatty acids in RBCs, Genova measures a weighted percentage of fatty acids taken up into the erythrocyte wall. The total saturated fatty acid percentage is a combined total weight percentage calculated by adding up each of the measured saturated fatty acids. It should be noted that when dealing with percentages, the amount of each fatty acid can influence the others. For example, fish oil supplementation may increase the overall omega-3 percentage, which then lowers the omega-6 percentage. Because some saturated fatty acids are beneficial, it is important to look at the levels of those specifically as well.

Omega-7 (n-7) Monounsaturated Fatty Acids

Monounsaturated fatty acids (MUFAs) have just one double bond throughout their carbon chain. The position of the double bond within that carbon chain distinguishes it from others and is responsible for the naming convention. If the double bond is at the seventh carbon, it is known as an omega-7 monounsaturated fatty acid.

Clinically, some literature suggests that a high-MUFA diet may be preferable to low-fat diets as it relates to cardiovascular disease. MUFA diets do not appear to increase triacylglycerol concentrations nor do they lower HDL levels. MUFAs have also been shown to decrease the oxidative susceptibility of LDL cholesterol. A high-MUFA diet can decrease platelet aggregation, increase fibrinolysis, and increase bleeding time which may protect against thrombogenesis.¹⁸⁰

Palmitoleic Acid

Palmitoleic acid (POA) is a monounsaturated omega-7 fatty acid (16:1n7). The main dietary sources of palmitoleic acid include dairy products, avocado oils, oily fish, and macadamia nuts. Macadamia nuts contain the cis- isomer of POA, while dairy products mainly contain the trans- isomer. Like many fatty acids, POA can also be endogenously made from the breakdown of triglycerides, the desaturation of palmitic acid, or de novo synthesis from carbohydrates.¹⁸¹

POA is an important signaling lipokine, produced mainly by white adipose tissue, that regulates important metabolic processes such as skeletal muscle glucose disposal, insulin sensitivity, and hepatic lipid deposition. It is also a modulator of adipocyte lipolysis, however, studies are mixed as to POA's specific role in obesity.^{181,182}

Epidemiologic studies show that circulating POA levels are involved in cholesterol metabolism and hemostasis, though the results are mixed as to their specific cardiovascular outcomes.¹⁸¹

High Levels

Elevations of POA can be seen with dietary intake of dairy products or macadamia nuts. Surplus dietary carbohydrates and high intake of its precursor palmitic acid might also result in higher POA.

As noted above, POA has many beneficial physiologic effects. In epidemiologic studies, higher intake of the trans-isomer of POA from dairy has been associated with lower levels of inflammation, improved insulin sensitivity, and decreased risk of diabetes. Alternatively, high POA levels have also been associated with various forms of cancers. There is a theory that endogenous production of palmitoleic acid may be an underlying cause of cell proliferation and survival in cancer progression. However, this needs more investigation.¹⁸³

Low Levels

Decreased intake of POA-containing foods, or palmitic acid can lower POA levels. Also, since POA can be made in the desaturation of palmitic acid, lack of vitamin and mineral cofactors, or a SNP in that enzyme, may contribute to lower levels.

Clinical associations of low POA levels are mixed as previously discussed.

Vaccenic Acid

Vaccenic acid (VA) is a monounsaturated omega-7 fatty acid (18:1n7). VA is a naturally occurring trans-fat unlike those produced industrially. The trans-configuration occurs around carbon 11, therefore VA is sometimes denoted as trans11-18:1n7. Ruminant animals produce vaccenic acid in a fermentation process in their microbiome. The dairy products (cheese, milk, butter) or meat obtained from these animals contain VA. There is also a cis-configuration of vaccenic acid created by de novo lipogenesis. VA can then be converted to an isomer of conjugated linoleic acid (CLA) using a desaturase enzyme. CLA has been associated with anti-inflammatory activity and affects lipid metabolism.¹⁸⁴

VA, as a cis-isomer, has demonstrated associations with lower insulin resistance and decreased risk of diabetes. The trans-isomer has also been shown to be beneficial as it relates to insulin secretion and resistance. Both isomers have been studied in vitro (and in animal studies) and may suppress adhesion molecules in the vascular endothelium. Therefore, VA isomers are being studied as possible prophylaxis in patients with risk of atherosclerosis. However, human intervention studies are limited.^{24,185-188}

High Levels

Elevations in VA are seen in high dietary intake of meat and dairy products from ruminant animals. Overall, VA may not adversely affect health as compared to industrial trans fats, though studies are ongoing.

Low Levels

Decreased dietary intake of dairy and meat from ruminant animals may result in lower levels of VA. Because it can also be endogenously produced and further metabolized into CLA, lack of precursor fatty acids, or rapid metabolism by desaturation, may result in lower levels.

Trans fatty acids (TFAs) is a general term for unsaturated fatty acids with at least one double bond in the trans configuration. Dietary TFAs are primarily obtained in the diet from partially hydrogenated vegetable oils. Hydrogenation of oils has been used in the food industry to prolong shelf life of certain foods as well as to create semi-solid fats more suitable for cooking. In addition to artificial trans fats, vaccenic acid is a trans fatty acid naturally obtained from ruminant animal products. There is evidence that this difference in food sources of trans fatty acids contribute to differing biological effects with different clinical consequences.¹⁸⁹

Industrial trans fats have been extensively studied and shown to have significant adverse effects on the cardiovascular system. TFAs also contribute to obesity, cancer, inflammation, and endoplasmic reticulum stress.¹⁸⁹⁻¹⁹²

Elaidic Acid

Elaidic acid (EA) is an 18-carbon chained fatty acid with one double bond in the trans formation at the 9th carbon (18:1n9t). It is the trans isomer of oleic acid. EA is the principal and most abundant trans fatty acid in the Western diet. It is found in partially hydrogenated vegetable oil and margarine. There are trace amounts of EA in the meat and dairy products from ruminant animals.

EA has been shown to induce oxidative stress and alter mitochondrial signaling. It is quickly incorporated into triglycerides and cholesterol esters. Once incorporated into plasma membranes, it activates nuclear factor- κ B to induce adhesion molecules and become proinflammatory leading to endothelial dysfunction.^{193,194}

Intake of trans fats, specifically EA, has been implicated in cancer, cardiovascular disease, insulin resistance, neurotoxicity, obesity and many inflammatory conditions.^{193,195-198}

High Levels

Dietary intake of industrial hydrogenated oils and margarine, fried foods, baked goods, donuts, crackers, etc., can elevate levels. Due to the many deleterious health effects of EA as noted above, the recommendation is to limit intake of EA and trans fat.

Low Levels

Low intake of processed foods and hydrogenated oils lead to lower levels of EA. Given the health implications, low levels are preferred.

Delta-6-Desaturase Activity

Dihomo- γ -linolenic acid (DGLA) is an important anti-inflammatory n-6 fatty acid. Because it needs to be synthesized from precursor fatty acids, conversion steps in fatty acid metabolism must be optimal. Two enzymatic steps are required to synthesize DGLA from the essential LA – namely the use of the enzymes delta-6-desaturase and elongase. Although there are several vitamin and mineral cofactors required for each enzyme, the inability to convert LA to DGLA has been proposed as a functional biomarker of zinc status. Zinc not only directly affects desaturase activity, but can influence fatty acid absorption, oxidation, and incorporation into RBCs.^{199,200}

The inability to convert precursor fatty acids to DGLA is associated with various pathologic and physiologic conditions such as aging, diabetes, alcoholism, atopic dermatitis, rheumatoid arthritis, cancer, and cardiovascular disease.^{94,95}

High levels (Impaired activity)

Elevations may indicate impaired delta-6-desaturase activity. Literature points to zinc insufficiency as an important cause. Other considerations include lack of other vitamin and mineral cofactors, or SNPs in the delta-6-desaturase and elongase enzymes. Many clinicians supplement with evening primrose, borage, and black currant to bypass the delta-6-desaturase enzyme, though cofactors for elongase should be optimized as well. Additionally, keep in mind that there is competition between the omega-3 and omega-6 fatty acids for these enzymes. Therefore, supplementation with fish oils/omega-3 fatty acids can compete with omega-6 fatty acid metabolism.

Low Levels (Upregulated activity)

Anything that may increase DGLA might result in a lower LA:DGLA ratio. Patients who supplement with evening primrose, borage, and black currant may have elevated DGLA which may lower the ratio. Assessing the levels of linoleic acid is also warranted. If LA levels are normal, a higher DGLA may not be of concern. If LA is low, ensure essential fatty acid adequacy. A SNP in either the desaturase or elongase enzymes could alter the enzymatic conversions as well.

Fatty acid research is rapidly evolving due to their association with health and disease. However, conventional laboratories and published researchers use differing matrices to measure them, and differing reference ranges. To mitigate this, many use relative ratios to gain a better understanding of disease correlation. Because cardiovascular disease and fatty acid imbalances have been widely studied, several fatty acid ratios have been established as a way to assess risk.²⁰¹⁻²⁰⁴

Omega-6s/Omega-3s Ratio

There has been a significant change in the balance of n-6s to n-3s with the evolution of the Western diet. Close to a 1:1 balance existed throughout history. However, rapid dietary changes and food industry advances have altered this to now be vastly in favor of n-6s by upwards of 20:1. This change correlates with many chronic diseases such as cardiovascular disease, cancer, metabolic syndrome, obesity, mood disorders, autoimmunity, and neurodegenerative disease.^{68,202,203,205,206}

Dietary interventions which favor omega-3, in lieu of omega-6s, is recommended with elevations in this ratio to achieve a closer balance between the two.

Arachidonic acid/Eicosapentaenoic acid (AA/EPA) Ratio

EPA (n3) and AA (n6) both compete for use of the delta-5-desaturase enzyme to be synthesized. Increased dietary intake of animal fats alters fatty acid metabolism in favor of inflammation. There are many chronic diseases associated with elevations of this ratio including cardiovascular disease, mood disorders, and cancer.²⁰⁷⁻²¹²

Increasing dietary intake of fish oils, or omega-3 fatty acid containing foods such as flax, chia, oily fish, or walnuts, can shift delta-5-desaturase activity toward the metabolism of the more beneficial n-3 metabolites. Decreasing intake of animal fats is also recommended.

Omega-3 Index

The omega-3 index is defined as the RBC percentage sum of EPA+DHA, both of which are important anti-inflammatory omega-3 fatty acids. This index was first proposed in 2004 as a cardiovascular risk factor by Dr. William S. Harris and Dr. Clemons von Schacky as a way of assessing risk for coronary artery disease and related death. Since then, it has been repeatedly verified as an important cardiovascular biomarker, and studied in other diseases including obesity, mood disorder, and insulin resistance.²¹³⁻²¹⁹

A reasonable target for the omega-3 index is >8% to decrease disease risk. Drs. Harris and von Schacky stratified risk zones as high risk (<4%), intermediate risk (4-8%), and low risk (>8%). These percentages have been continually verified in outcome studies and risk assessment.^{213,220,221}

Dietary intervention to increase the omega-3 index should include oily fish, flax, walnut, and chia. Fish oil supplementation can also be considered.

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