Functional Medicine University's Functional Diagnostic Medicine Training Program

Module 5 * FMDT 541D

Advanced FDM Testing: EFA Testing

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Required reading*: Butyric acid-producing anaerobic bacteria as a novel probiotic treatment approach for inflammatory bowel disease,* JMM Editorial, DOI 10.1099/jmm.0.017541-0; 2010 (This article can be found with this lesson on the FMU website www.FunctionalMedicineUniversity.com)

Fatty Acids

Fatty acids are present in serum or plasma in the form of lipoproteins. A small percentage of free fatty acids in the blood are bound to transport proteins, mainly albumin. The majority of fatty acids do not have a linear relationship to serum triglycerides[1].

Fatty Acid Classification

Fatty acids are a chain of carbons with a carboxyl group (-COOH) on one end and a methyl group ($-CH_3$) on the other. One system of classification of fatty acids is based on the number of double bonds.

- 0 double bonds – saturated fatty acids (e.g. stearic acid)
- 1 double bond- monosaturated fatty acids (e.g. oleic acid)
- 2 or more double bonds – polyunsaturated fatty acids (e.g. linoleic acid)

Fatty acids are also classified by the number of carbons*****.

- Short chain: 2-4 carbons
- Medium chain: 6-12 carbons
- Long chain: 14-22 carbons
- Very long chains 24-26 carbons

(***** some text differ in the relationship to exactly how many carbons a fatty acid should have to belong to one of these groups) MCFA's and SCFA's are absorbed directly and do not required chylomicrons for transport. They also do not require the use of the carnitine shuttle for oxidation.

Short Chain Fatty Acids (SCFA's)

SCFA's contribute to normal bowel function and prevent pathology through their actions in the lumen and on the colonic musculature and vasculature and through their metabolism by colonocytes.[5] Fiber is composed principally of polysaccharides that are subject to breakdown in the gastrointestinal tract. This is effected in the GI tract by a complex bacterial ecosystem, in particular, anaerobic bacteria. The intestinal bacteria can metabolize fiber to short chain fatty acid end products, mainly acetate, propionate, and butyrate. Butyrate is the preferred "food" of the colonocytes and is of clinical interest in the treatment of intestinal disorders, in particular, inflammatory bowel disease .

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Medium Chain Fatty Acids (MCFA's)

Three medium chain fatty acids are noteworthy; caprylic acid, undecylenic acid, and lauric acid. Caprylic acid is an eight carbon saturated fatty acid that has medicinal properties as an antimicrobial. Undecylenic acid, a 10 carbon unsaturated fatty acid derived for castor oil, is a natural fungicide. Lauric acid, a 12 carbon saturated fatty acid, is the main acid in coconut oil and in palm kernel oil. The MCFA's in coconut oil are known for their antimicrobial activity. After being ingested, they are transformed into monoglycerides, which kill bacteria, as well as viruses, fungi, and parasites.[6] Lauric acid and capric acid also enhance the ability of the pancreas to secrete insulin.[6]

Long Chain and Very Long Chain Fatty Acids

LCFA's and VLCFA"s include oleic acid, linoleic acid, linolenic acid and arachidonic acid.

Carnitine Shuttle

Cytoplasmic fatty acyl CoA is converted to fatty acyl carnitine by carnitine acyl transferase I (CAT I). Fatty acyl carnitine is then transported to the inner mitochondrial membrane. Fatty acyl carnitine is then acted upon by carnitine acyl transferase II (CAT II) into fatty acyl CoA and carnitine. This shuttle mechanism is required only for longer chain fatty acids. Medium and short chain fatty acids do not required carnitine to cross the mitochondrial membrane.

Plasma and Red Blood Cell Fatty Acids Analysis

Plasma fatty acids analysis reflects fatty acids status as it relates to ***dietary intake***. *Red blood cell membrane analysis of fatty acids* reflects ***metabolic functions*** within the cell. (RBC membrane analysis does not represent dietary intake or adipose tissue composition.) Red blood cell membranes consist of 45% fatty acids in the form of phosphatides and glycolipids[1]. RBC membrane analysis is the most common procedure for analyzing fatty acids, however plasma and blood spot test have also been used successfully.[1]

"It has become common for laboratory profiles of fatty acids to include more than 40 analytes that may be measured accurately from a specimen of plasma or erythrocytes from whole blood. In practice, clinicians generally do not evaluate each fatty acid individually but look for ***patterns****."* [1]

"Fatty acid testing can provide a great deal of information allowing for individualized interventions. Varying patterns can help to identify not only essential fatty acid deficiency or excess, but also signs of insulin resistance, hypertriglyceridemia, proinflammation, or omega-3 dominance." [2] Fatty acid analyses can also provide information with regard to dietary modifications, fatty acid supplements and the need for vitamin and mineral needs.[1] (You may recall from a previous lesson about the need for zinc as a cofactor for the desaturase enzymes.)

The long-term benefits of consumption the right proportions of fish oils and/or GLA-rich oil has been verified by past and present research studies. Essential fatty acids and conditional essential fatty acids are known to maintain and/or improve the health of the nervous system, cardiovascular system, endocrine system, and the musculoskeletal system. Fatty acid analysis guides and supports your recommendations for higher doses of fatty acid supplementation. Excessive intake of polyunsaturated fatty acid induces free radical production by increasing lipid peroxidation. Clinical management of fatty acid and antioxidant supplementation is aided by testing for fatty acid balance and measuring markers of oxidant damage.

Possible Signs and Symptoms of Essential Fatty Acid Deficiency

- Dry skin
- Scaly/flaky skin (esp. legs)
- Cracking/peeling skin on feet and hands
- Bumps (sandpaper-like feel on the back of the upper arms and thighs) [follicular hyperkeratosis- also check vitamin A and vitamin C]
- Dry eyes
- Dry mouth/throat
- Allergic conditions
- Stiffness/painful joints
- Vaginal dryness
- Skin atrophy
- Impaired vision
- Immune and mental deficiencies
- Edema

Note: Always rule out liver/gallbladder dysfunction as a possible cause of fatty acid deficiency. Considers bile salt supplementation (with fat containing meals), if the patient's gallbladder has been removed.

A substantial amount of research studies have been conducted on essential fatty acid status and neurological disorders; in particular, major recurrent affective disorders, such as major depressive and bipolar disorders, Alzheimer's disease, and cognitive impairment. Male and female patients with major depressive disorder and bipolar dipolar disorder exhibited selective erythrocyte DHA deficits relative to healthy controls, and this deficit was numerically greater in bipolar disorder patients[2.] Low levels of omega-3 fatty acids in plasma may be a risk factor for cognitive impairment and/or dementia[3.] There is also an association between carotenoids, omega-3 fatty acids and dementia severity. Lutein, beta-carotene and beta-cryptoxanthin were positively correlated with RBC DHA in Alzheimer's disease patients[4] These findings suggest targeting multiple specific nutrients, lutein, beta-carotene, and DHA in strategies to slow the rate of cognitive decline[4]. As functional medicine practitioners, we must always search for the answers of how and why the patient became deficient.

Essential and conditionally essential fatty acids, as well as fat-soluble vitamins, need an optimal functioning liver, gallbladder and gastrointestinal tract for proper absorption.

TABLE 5.5 – SIGNS AND SYMPTOMS ASSOCIATED WITH FATTY ACID ABNORMALITIES

Signs & Symptoms	Fatty Acid Association	Intervention
Emaciation, weakness, disorientation	Caloric deprivation	Balanced of fat, protein, and CHO
Reduced growth, renal dysplasia, reproductive deficiency, scaly skin	Classic essential fatty acid deficiency	Good quality fats and oils
Eczema-like skin eruptions, loss of hair, liver degeneration, behavioral disturbances, kidney degeneration, increased thirst, frequent infections, poor wound healing, sterility (m) or miscarriage (f), arthralgia, cardiovascular d., growth retardation	Linoleic acid insufficiency	Corn or safflower oils
Growth retardation, weakness, impairment of vision, learning disability, poor coordination, tingling in arms / legs, behavioral changes, mental disturbances, low metabolic rate, high blood pressure, immune dysfunction	Alpha or gamma linolenic acid insufficiency	Flax, primrose or black currant oils
Depression, anxiety, learning behavioral and visual development or cardiovascular disease risk	Long chain PUFA-dependent neuromembrane function Prostanoid balance	Fish oils Avoid hydrogenated oils
Cancer	Low stearic to oleic ratio, Prostanoid imbalance	n3 PUFAs (use n6 PUFAs with caution)
Rheumatoid arthritis	Low GLA & DGLA	Primrose oil
Myelinated nerve degeneration	Increased very-long-chain fatty acids	High-erucate rape or mustard oils
Fatty liver	Saturated and ω-9 accumulation in liver	Restrict alcohol Add lecithin Increase Met
Accelerated aging	High PUFA intake without increased antioxidants	Vitamin E and C and Se, Mn, and Zn

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Fatty Acids Profile Testing Options

- *Erythrocytes* – Red Blood cell membrane levels of fatty acids reveal metabolic effects and long-term balance in the tissues. This test is preferred to assess nutritional status of the critical eicosanoid and long chain fatty acids necessary for membrane stabilization. The red blood cell stearic/oleic ratio is a cancer therapy marker. *Oleic acid constitutes 15% of the fatty acids in the cell membrane. In tumor cells, stearic-acid falls as oleic-acid rises, causing a profound shift in the ratio of stearic to oleic acid. The stearic-oleic acid ratio is used as a monitor of the effectiveness of cancer therapy in certain types of cancer. Movement of a low ratio to higher levels provides an indicator for efficacy of a cancer therapy.*[2]

- *Plasma* – Plasma fatty acid levels reflect body stores as influenced by recent dietary intake and are useful for monitoring response to supplementation and dietary modifications, Plasma levels are preferred for assessment of dietary adequacy of these essential fatty acids as revealed by adipose tissue composition. Mead acid and the triene/tetraene ratio reveal chronic essential fatty acid insufficiency.

- *Blood Spot* (*Does not require venipuncture*) – The Bloodspot fatty acid profile measures key omega-3 and omega-6 fatty acids and calculates key indicators to establish optimal fatty acid balance. Trans-fatty acids are also measured.

- *AA/EPA Ratio Profile Plasma* – (usually included in plasma and bloodspot tests) this test measures the ratio of arachidonic acid (AA) to eicosapentaenoic acid (EPA) in plasma or serum. This ratio of the principle omega-3 and omega-6 fatty acids is a measure of the body's eicosanoid balance. Balancing the eicosanoids in the body is an excellent way for managing heart disease, and other chronic and inflammatory processes.

The Clinically Relevant Patterns

As previously stated, fatty acid interpretive patterns are more clinically relevant than individual analytes. The pattern can be further categorized in the seven steps of interpretation for clinical assessment. The seven steps are as follows:

1. General fatty acid deficiency
2. Omega-3 deficiency or excess
3. Omega-6 deficiency or excess
4. Hydrogenated oil toxicity
5. Micronutrient deficiencies
6. Metabolic and genetic disorders
7. Fatty acid ratio and indices

TABLE 5.3 — FATTY ACID IMBALANCES AND MICRONUTRIENT DEFICIENCIES COMMONLY EVALUATED BY FATTY ACID PROFILES

	Condition	Fatty Acid Pattern	Corrective Actions
General Fatty Acid Disorder	EFA deficiency	Multiple low n-3 and n-6; high mead; high T/T ratio, high palmitoleic	Add EFA-rich oils
	Hypertriglyceridemia	General elevation of most members of all families	Add fish oil Decrease dietary carbohydrate Antilipidemic medications
Omega 3 Deficiency or Excess	n-3 class deficiency	Low ALA, EPA, and DHA with normal or elevated AA	Add flax and fish oils
	Specific ALA deficiency	Low ALA with normal EPA & DHA	Add flax oil
	Specific EPA,- DHA deficiency	Normal ALA with low EPA & DHA	Add fish oils
	ALA or EPA excess.	High ALA or EPA	Decrease flax oil or fish oil and increase antioxidant intake
Omega 6 Deficiency or Excess	n-6 class deficiency (esp. with n-3 class excess)	All n-6s low with low DGLA/EPA and AA/EPA ratios	Decrease all n-3 supplementation and add corn, evening primrose, or other n-6 oils
	Specific GLA or DGLA deficiency	Low GLA or DGLA with normal LA & AA	Add primrose oil
	Specific LA excess	High LA (see desaturase deficiency)	Reduce LA-rich dietary sources
	Specific AA excess	High AA with normal levels of other n-6s	Check AA/EPA ratio, and decrease red meat intake accordingly
Hydrogenated Oil Toxicity	Toxic interferences from hydrogenated oil use	Elevated palmiteladic or C18-*trans*-fatty acids (elaidic, *trans*-vaccenic, *trans*-petroselinic)	Reduce hydrogenated oil intake
Micronutrient Deficiencies	Zinc deficiency	Elevated LA/DGLA or ALA/EPA ratios	Zinc supplementation
	Copper deficiency	Elevated stearic and docosadienoic with low oleic and linoleic acids	Copper supplementation
	Vitamin B_{12}, biotin deficiency	Elevated odd numbered fatty acids and vaccenic acid	Vitamin B_{12} and biotin supplementation

TABLE 5.4 — METABOLIC AND GENETIC DISTURBANCES EVALUATED BY FATTY ACID PROFILES

	Condition		Fatty Acid Pattern		Corrective Actions
Metabolic and Genetic Disturbances	The Metabolic Syndrome		Elevated C16, C18 and C20 fatty acids with low levels of other members in each class		Steps to increase insulin sensitivity and restrict dietary carbohydrate
	Multiple Acyl-coenzyme A Dehydrogenation disorders (MAD)		High capric, lauric and myristic acids		Riboflavin; 50 mg TID
	MCAT def		Pattern of high to low as chain length increases		Carnitine
	LCAT def or Metabolic Syndrome		Pattern of increase, then decrease with chain length		Carnitine, check insulin and insulin sensitization factors
	VLCAT def		Pattern of low to high as chain length increases		Add carnitine
	Peroxisomal insufficiency	Type 1. Single enzyme defects	X-linked adrenoleuko-dystrophy	Accumulation of fatty acids longer than 22 carbon atoms in length	Mixtures of glycerol trioleate and trierucate may correct the fatty acid status
			β-Oxidation disorders	Accumulation of fatty acids longer than 22 carbon atoms in length	
		Peroxisome Biogenesis Disorders	Zellweger spectrum	Pattern of VLCFA elevation (docosatetraenoic, nervonic, erucic, behenic, lignoceric and hexacosanoic)	Fish oils or CLA can activate PPAR and natural vitamin A containing the 9-*cis* isomer co-activates PPAR response

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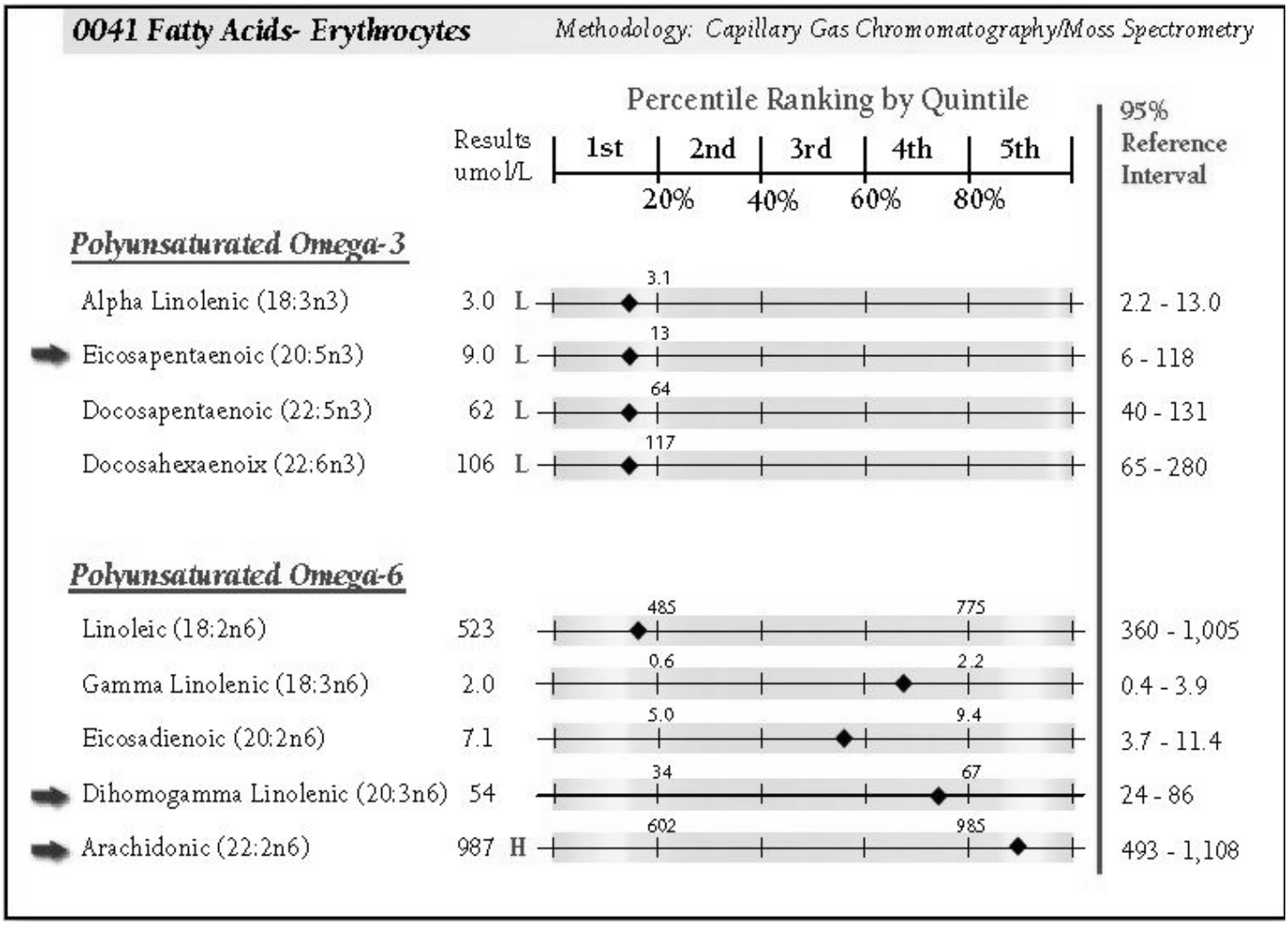
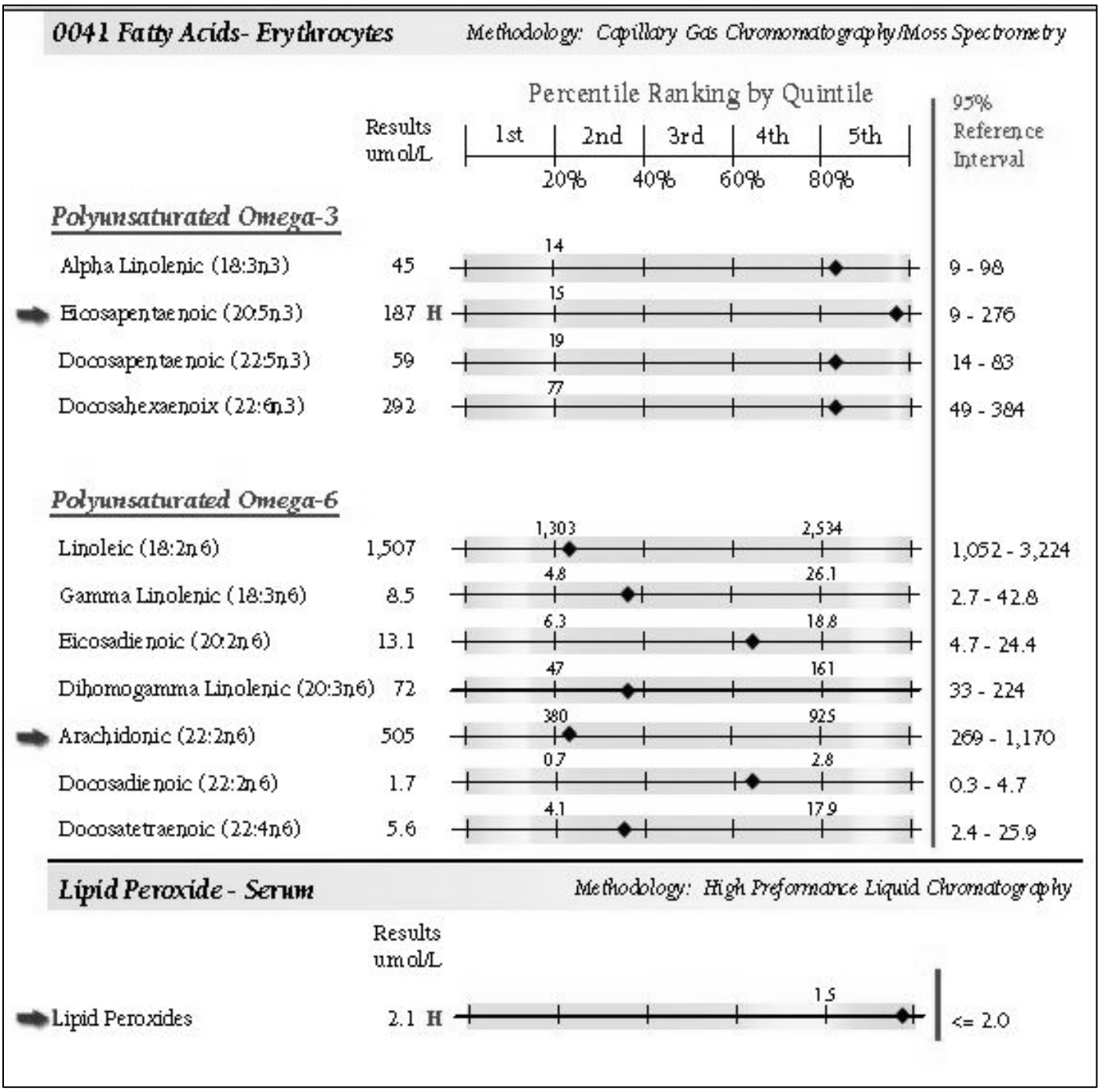
Case Illustrations

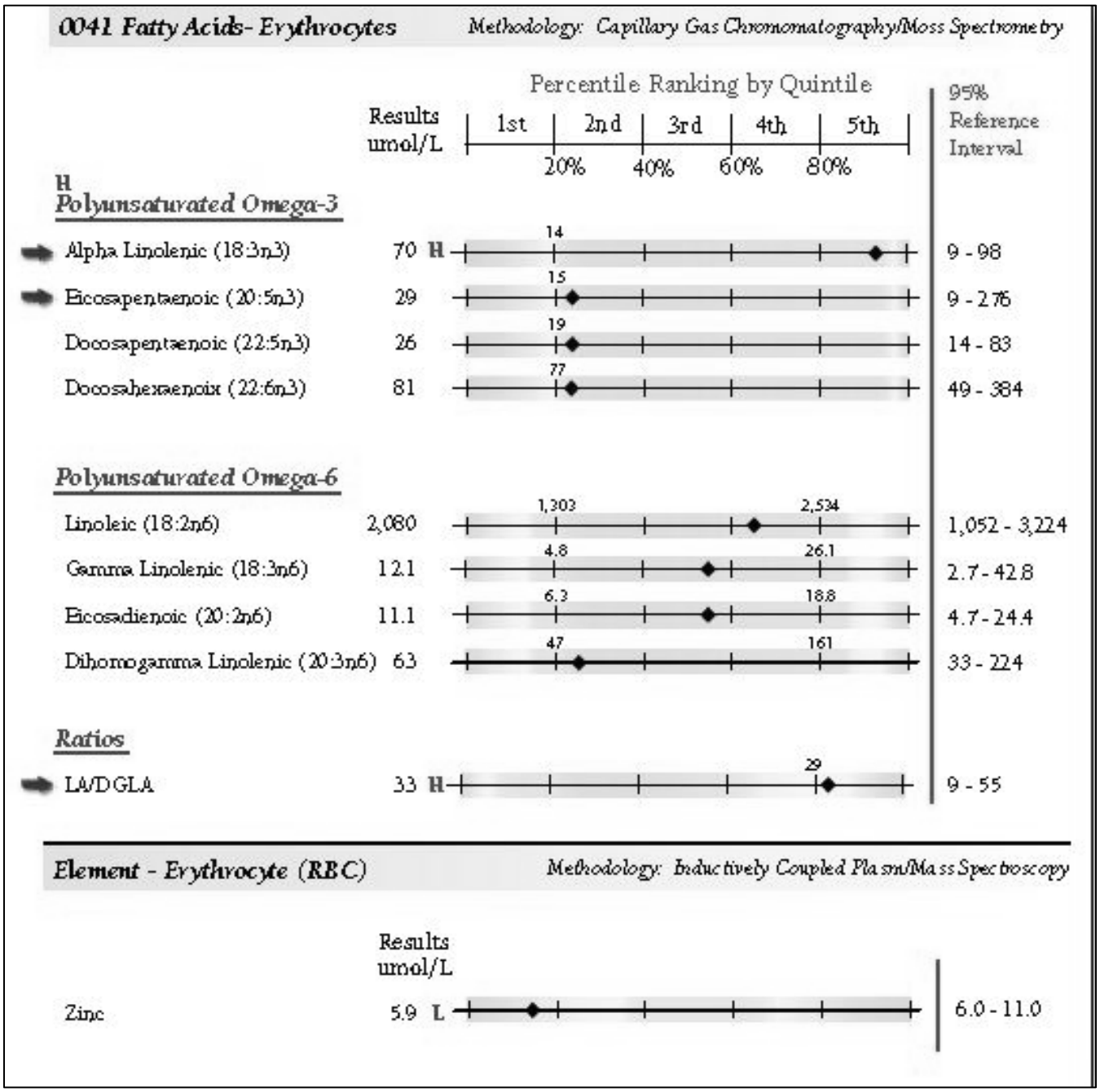
A Pro-Inflammatory Pattern



Omega 3 Dominant Pattern



Zinc Deficiency



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In Summary

In summary, assessing fatty acids is an integral part of functional diagnostic medicine. Fatty acids maintain cell membrane integrity and serve as precursors to the eicosanoid pathway. . As with all supplementation there is a therapeutic dose range that is generally patient specific. Functional testing will allow you to prescribe to the optimal dosage to achieve maximal patient outcomes. When prescribing essential and/or conditionally essential fatty acids, anti-oxidant status must be taken into considered to avoid excess lipid peroxidation.

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