Lipidomics: Clinical Application

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Learning Objectives

1. The Lipidome and Clinical Application
2. Nutritional Influences on Composition and Function
3. Tools of the Trade for Lipid Therapy
4. Case Reviews

11.1 Introduction

The main global healthcare concern of the twenty-first century is chronic disease. Public health leaders around the world are working to quell the unsustainable widespread changing phenotype of populations. In the United States, more than two-thirds of the citizens are currently overweight or obese, and the trend is increasing. In 2012, there began an unprecedented decline in U.S. lifespan. Much of the trend toward chronic disease is due to dysfunction in the underlying mechanisms of cell signaling and the messages that operate at the organelle and cell membrane sites. This is where the DNA is expressed and put into action as body systems read the environment and determine how to respond to survive.

IFMNT is a person-centered approach with each individual assessed, and interventions developed, as personalized therapy based on the nutrition and medical data that is gathered during a comprehensive evaluation. For population of persons with the same diagnosis, there will be an equal number of uniquely designed protocols. Each disease has many causes, thus this chapter does not give a recipe for diagnosis and intervention rather provides principles and tools to draw from to form the best protocol to restore wellness.

In this chapter, we first examine the structure of the cell membrane, which is comprised of different regions of *microdomains* referred to as *membrane rafts* with varying percent lipids (e.g., fats, phospholipids, steroids), which are mainly formed from the food fats and oils we eat [1]. The structure of membranes determines the function of the "control tower" of our systems where communication and cell signaling occurs. Second, we assess function and how well the body can manage all its systems to enable them to produce a healthy organism. The evidence that the lipids we eat create the composition of our lipid structures and control our function is mounting in recognition of the metabolic plasticity of human metabolism [2, 3] (see ▶ Chap. 10). At the time of this publication, there is public and scientific interest in the comparison of the effects of high carbohydrate, low fat diets to those with low carbohydrates and high fat. The main thrust of this latter diet protocol is exchange of carbohydrates for fats. Nutrition professionals need to be aware of the metabolic implications of this dietary change and the science behind what is often referred to as paleo or ketogenic (keto) diets (see ▶ Chap. 23).

This chapter addresses emerging evidence about fatty acid metabolism and outdated misinformation that is still accepted dogma regarding dietary fat. Understandably, the public and even nutrition professionals are confused about dietary fats. We are on the brink of a new understanding of the science of lipids, food processing, and how one's unique personal genetics determine the type and amount of fats that may benefit an individual.

Table 11.1 Integrative and functional medicine principles

Focuses on patient/client-centered approach
Acknowledges biochemical uniqueness of each individual
Patient practitioner partnership
Appropriately uses conventional and complementary treatments
Considers genetic, environmental, and lifestyle factors
Seeks balance between mind, body, and spirit
Acknowledges all body systems are interconnected by physiological and metabolic factors
Identifies health as a positive vitality
Uses natural, effective, less invasive interventions, when possible

The goal of this chapter is to help the nutrition-trained professional understand the molecular structure of an individual's cellular membranes and how those structures affect the efficiency and proper functioning of metabolism. With that knowledge, one has the clinical skills in medical nutrition therapy for assessment and intervention. The practitioner must have working knowledge of foods and supplements, which support the body's *metabolic plasticity*. This approach is viewed through the lens of *systems biology*, which is the science of all systems interacting and influencing each other to produce the phenotype of an individual; it is often referred to as integrative and/or functional medicine (see Table 11.1).

11.2 History of Dietary Fat

It can be enlightening to think back on historical diets and events that led to the current recommendations about fat. Around the 1950s, recommendations to Americans concerning fat were promoted by publications from Gofman [3] and Keys (1953) [4], in which the dogma was propagated that "saturated fat and cholesterol were bad." A connection was made with respect to the rise of heart disease and epidemiologic correlations between dietary saturated fat, cholesterol and heart disease. Not much has changed in the last 70 years in recommendations to reduce total fat, saturated fat, and cholesterol-rich foods. Until the 1940s in the United States, heart disease and cancer were minor contributors to mortality statistics, but they have continued to grow to the number-one and -two causes of death in industrialized countries.

11.2.1 Human History

Fats used for dietary ingestion were "all natural" (not processed) prior to ~1900. Lipids, oils, and fats commonly used were:

- Fat or oil-rich foods
  - Meat
  - Poultry and skin
  - Fish, shellfish, roe
  - Egg yolk
  - Olives, olive oil
  - Other plants: nuts, seeds, avocado
  - Essential and/or medicinal oils
- Cooking oils
  - Butter, ghee
  - Lard
  - Tallow
  - Coconut oil
  - Olive oil, foot-pressed

The nutrition transition to the standard American diet (SAD) [5] at the beginning of the twentieth century paralleled the increase in the onset and progression of chronic human diseases as the food supply changed in quality and quantity, giving rise to obesity and a mismatch of gene–diet interactions. Cooking oils intolerant to heat, processed foods containing trans fats, and damaged oils have become commonplace. There is currently a debate regarding the impact of the increase in omega-6 on human health [6] and newer processing methods in the food oil industry that are allowing "damaged" oils and "new-to-nature" forms of oils into the food supply (e.g., hydrogenated vegetable oils, high heat processing of vegetable oils, changing proportion of linoleic acid, and monounsaturated fats to "high oleic" vegetable oils). Issues that need to be addressed include the influence of ingested food oils on the structure and function of cellular health and how these food oil changes have contributed to the epidemic of chronic disease?

11.2.2 The Nutrition Transition of Oils and Fats in the Early 20th Century

Processed oils:
- Heat-processed vegetable oil
- High heated commercial oil used for deep frying
- Hydrogenation of vegetable oils
- Charred red meats or high-temp-oil deep frying produce trans fats or acrylamides

Specialty foods available after 1950:
- *Natural*: nitrogen-packed seed/nut oils, refrigerated
  - Sunflower, safflower, flax (refrigerated), avocado oil, flax–safflower oil 4:1, macadamia oil
- Processed:
  - Deep frying with vegetable oils
  - Hydrogenated or partially hydrogenated vegetable oils

The ratio between the types of fats has changed dramatically during the past 70–100 years with a three-fold increase in dietary levels of the omega-6 (n-6) 18 carbon (C18), polyunsaturated fatty acids (PUFA), linoleic acid (LA; 18:2n-6) [5]. Horrobin [6] proposed an ideal ω6:ω3 ratio of 4:1, and most fatty-acid scientists agree optimum ratio somewhere with the range of 1:1 to 5:1 ratios [7, 8].

Chronic diseases are characterized as long-latency lifestyle and diet-related. Chronic diseases all have inflammatory pathophysiology promoted by injury, infection, or biological stressors (e.g., chronic inflammation, high visceral adiposity, emotional stress). For example, an acute infection may either be resolved by a healthy immune system or survive and continue as a subclinical infection that is often not recognized but continues to wear on the immune system. Lipids that participate in eicosanoid metabolism are largely responsible for control of inflammation and the ability of the metabolic resolution of an inflammatory event.

The healthy human body is equipped with defense features from conception throughout life to interact with the environment to protect it from infection and injury. All of the barriers' defensive functions are a reflection of their lipid-dominant structure. Much of the defense starts with the lipid-rich skin barrier and microbiome at all body orifices to protect from pathogens entering and infecting or causing injury.

11.3 The Lipidome and Clinical Application

The application of lipidomics in clinical practice is an important new tool for the healthcare practitioner due to expanding knowledge of the structural and functional properties of fat. Dietary fat is a key topic in government food policy, research, public media, and in the homes of families preparing food during a period of dramatic change in thinking about how we incorporate fat into diets. Many people feel confused about the amount and types of fat to eat. Is saturated fat bad? Is a low-fat diet good? Dietitians and healthcare professionals are beginning to learn about the emerging science of lipidomics and how that applies to the science of lipid metabolism and the use of dietary and food supplement to maintain health.

Lipids are highly diverse molecules that are as important for life as proteins and genes [2] with critical roles in membrane structure, cell signaling, energy storage, inflammation regulation, and as base units for constructing messenger hormones. Maintaining lipid balance and homeostasis is within a practitioner's capability when they are skilled at recognizing lipid imbalances and their relationship to disease pathology. One of the profound roles of lipid metabolism involves metabolic regulation of inflammation. It is essential to understand how to modulate lipid metabolism considering that the global epidemic of chronic disease in healthcare reflects prolonged and unresolved inflammation. All the "ingredients" of lipids (fatty acids, phospholipids, sterols, sphingolipids) and the associated enzymes and nutrient cofactors affect the control and resolution of inflammation. Knowledge of lipid modulation by dietary and lifestyle changes is a powerful addition to the toolbox of the IFMNT practitioner.

The two functions of the lipids that can be modulated by nutrition therapy are membrane structure and inflammation control.

- Membrane structure: the membrane is at least 50–75% lipids with embedded protein structures forming receptors, channels, and other structures [6] "You are what you eat." What fats and oils and sterols you eat become the structural composition of your membranes and influence their function of cell signaling, communication, and transport.
- Inflammation control: The lipid eicosanoid molecules play a key role in our survival. They are the primary metabolites teaming with the immune system to manage the immune response and control inflammation. Dysregulated lipid metabolism and nutrient status are thought to play a major role in the pathophysiology of every chronic disease. Since chronic prolonged inflammation is present in every chronic disease, the eicosanoids become priority in supporting their metabolic function. And the most effective way of modulating the eicosanoid cascade is nutrition lipid therapy guiding dietary intake of fats and oils and nutrient cofactors.

Each individual is unique. IFMNT is a person-centered approach with each individual assessed, and interventions develop as personalized therapy based on the nutrition and medical data that are gathered in the initial interview. For a population with the same diagnosis, there will be that many different protocols recommended. For one disease, there are many causes. That is why this chapter does not include specific interventions for a diagnosis but provides principles to consider and draw from in forming the best regulation of structure and inflammation control to restore wellness.

11.3.1 Clinical Imbalances

The conceptual diagram below (see Fig. 11.1) provides a guide to hearing the patient's whole story, so that an assessment can be as comprehensive as possible to narrow down root causes of the patient's condition. In seeking root causes of the etiology of a disease condition, one must investigate the health and *structural integrity* of the cell membrane. All cells in the body share the basic structure and function of a

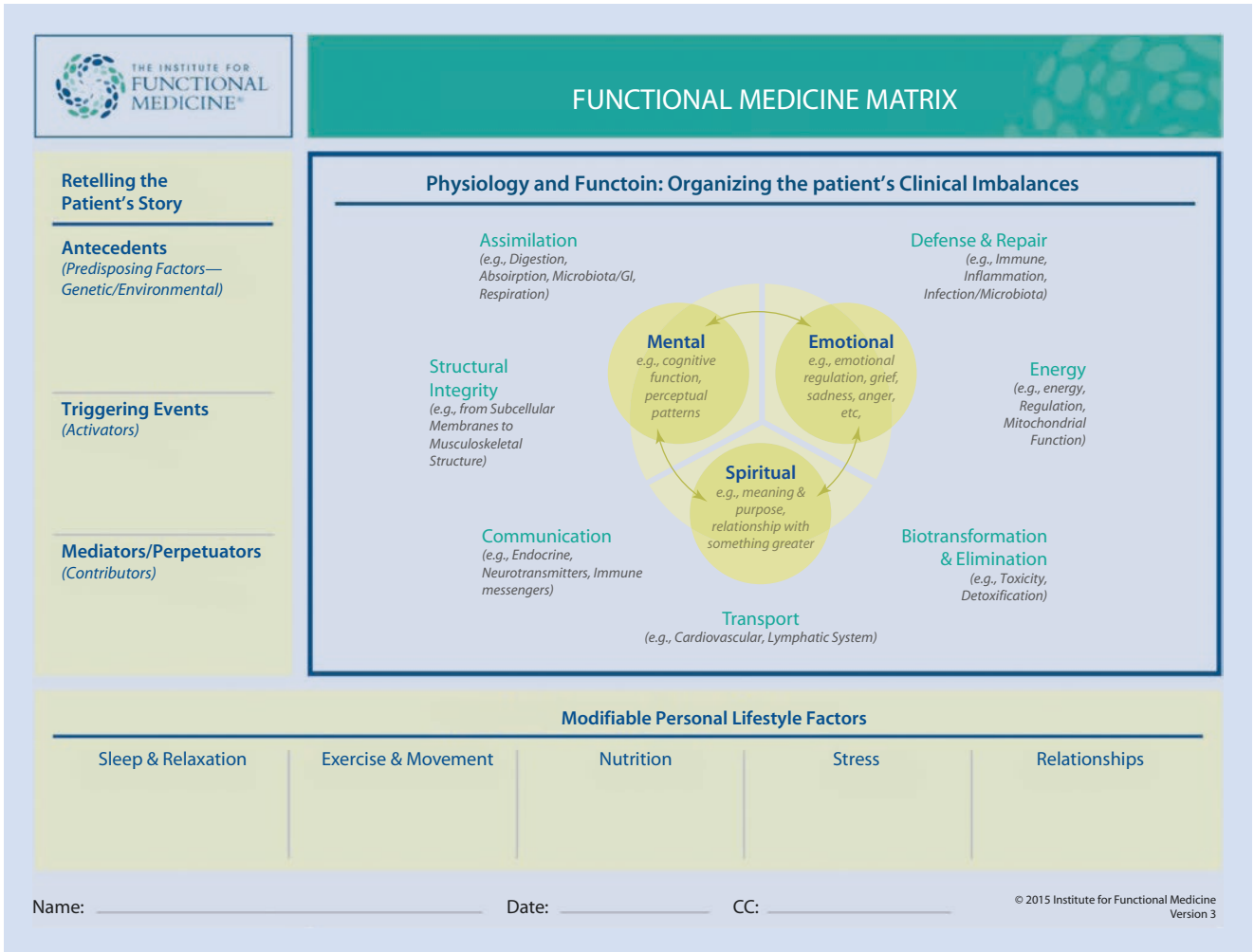


Fig. 11.1 IFM Matrix™ Conceptual diagram to guide the practitioner assessment procedure to hear the whole patient's story preparing for improved diagnosis of root causes of health issues. (Used with permission from The Institute for Functional Medicine ©2015)

bilayer membrane made of 50–75% phospholipids, fatty acids, cholesterol with embedded proteins forming channels, and receptors to facilitate ports of entry and exit to and from the intracellular to extracellular compartments. There are some carbohydrate molecules functioning as "antennas" extending from the surface of the cell for messaging and cell signaling [9, 10].

The other core physiological system to be investigated when assessing an individual's fatty acid status is *defense and repair*. Since lipids and fatty acids of the eicosanoid molecules are the primary influencers and regulators of inflammation, treatment of the defense and repair systems begins to reveal the etiology of the inflammatory aspect of an individual's condition. Once identified, utilizing the skill set of modulating lipid and fatty acid status will help target the intervention needed to restore structure, function, and wellness. The cell membrane is a primary determinant of the quality of an individual's health (see ► Chaps. 12 and 19) (◘ Fig. 11.1).

The structure and function of cells depend on membranes, which not only separate the interior of the cell from its environment but also define the internal compartments of eukaryotic cells, including the nucleus and cytoplasmic organelles. The formation of biological membranes is based on the properties of lipids, and all cell membranes share a common structural organization: bilayers of phospholipids with associated proteins. These membrane proteins are responsible for many specialized functions: some act as receptors that allow the cell to respond to external signals, some are responsible for the selective transport of molecules across the membrane, and others participate in electron transport and oxidative phosphorylation. In addition, membrane proteins control the interactions between cells of multicellular organisms. The common structural organization of membranes thus underlies a variety of biological processes and specialized membrane functions, which will be discussed in detail in later chapters [9].

11.4 Nutritional Influences on Body Composition and Function

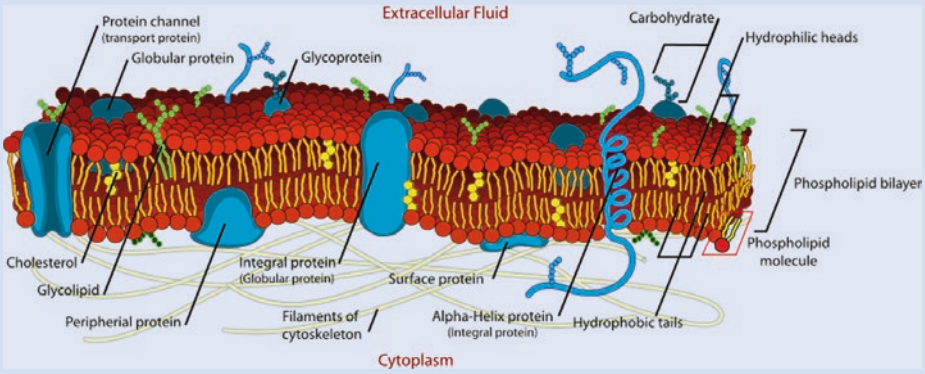
11.4.1 Structure and Functions of the Cell Membrane

11

The prevailing concept of cell membrane structure is the phospholipid bilayer that is impermeable to most water-soluble molecules, often referred to as the fluid mosaic model [9]. Most of the phospholipids in the membrane are present as a biomolecular sheet, with the fatty acid chains in the interior and exterior of the bilayer. Membrane proteins are located either on the internal or external faces of the membrane or projecting from one side to the other. An important feature of the membrane is "membrane permeability," allowing flexibility for molecules to move around [2, 11] (◘ Fig. 11.2).

The Cellular, Organelle, and Nuclear Bilayer Membranes of Each Cell [10]

- Protect and hold together each compartment.
- Protect cell compartments from their surrounding environment.
- Control movement of substances transported in and out of the cell.
- Manage immune responses regarding inflammation (eicosanoid metabolites).
- Maintain cell and mitochondrial membrane integrity—key to cell survival.
- Foundational to the core physiological clinical imbalances (see ◘ Fig. 11.1).
- Provide structural integrity



◘ **Fig. 11.2** Fluid mosaic model of membrane structure. (Reprinted from OpenStax CNX [88]. With permission from Creative Commons License 4.0: ► https://creativecommons.org/licenses/by/4.0/)

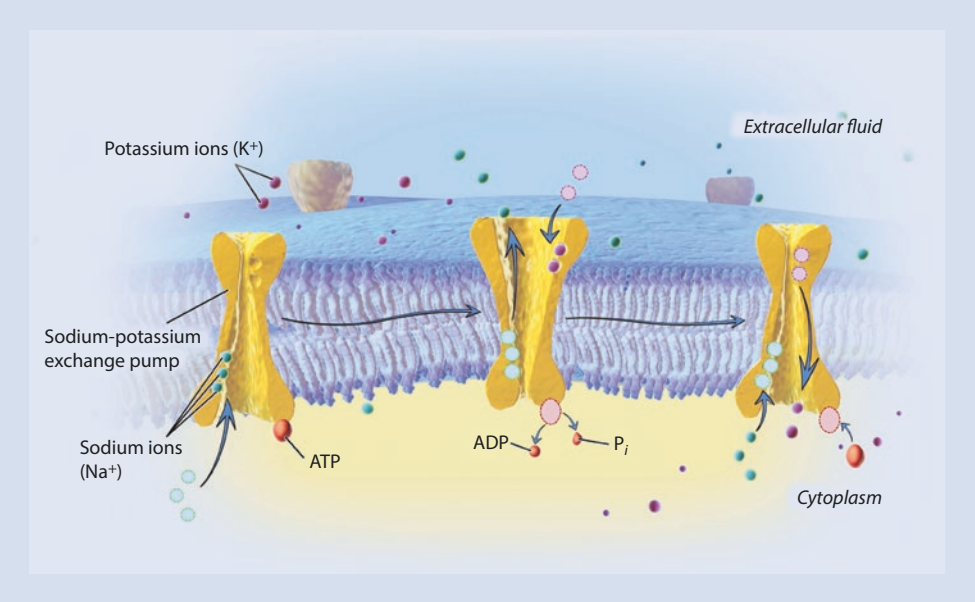


Fig. 11.3 Sodium-Potassium Pump. A transporter on the membrane that maintains high potassium and low sodium intracellular concentrations relative to the extracellular electrolyte concentrations. This pump functions at the expense of ATP energy and is influenced by the dietary intake of the minerals magnesium, potassium, and sodium. (Reprinted from ► Blausen.com staff [89]. With permission from Creative Commons License 3.0: ► https://creativecommons.org/licenses/by/3.0/deed.en.)

- Provide defense and repair.
- When compromised or damaged, allow healthy molecules to leave the cell and unwanted materials to enter. This can be referred to as "leaky cell membranes.
- Phospholipids, fatty acids, cholesterol, and proteins when in balance facilitate repair and maintenance of cell membranes.
- Sodium-potassium pump (see Fig. 11.3).
- Intracellular cytosol 97% potassium controlled by the sodium-potassium pump (Fig. 11.3).

11.4.1.1 Cellular Hydration

Among the many properties of the cells and organelles is hydration. Measurable aspects of cell hydration include total body water, intracellular water, and extracellular water [2]. These measurements are clinically available using bioelectric impedance analysis (BIA) (see ► Chap. 22). All metabolic characteristics apply to the balance of water between intracellular and extracellular fluids [2, 9]. In healthy cells, there is opposite composition of the intracellular potassium concentration versus the extracellular sodium managed by the sodium-potassium pump (Na-K pump) embedded in the cell membrane [9]. ATP production is the energy driving the activity of the pump [2, 10].

- Intracellular matrix (cytosol) is 97% potassium-controlled by the Na-K pump [9]
- Extracellular matrix is 97% sodium-controlled by the Na-K pump [9]
- Magnesium rate-limiting nutrient for the Na-K pump [10]

A deficit of any of the three minerals will affect the function of the Na-K Pump and cellular hydration.

11.4.1.2 The Membrane Barriers: Organelle, Cell, Tissue, and Organs

All membrane barriers contain the basic bimolecular bilayer membrane structure. That basic structure is found in every type of cell, organelle, tissue, or organ function, with only slight variation. Examples are that neuron cells have a higher percentage of phospholipids than liver cells and heart and muscle cells have a greater percentage than brown fat cells (see ► Chap. 12).

The most important barriers to be considered when assessing body systems are:

- Skin (see ► Chap. 54)
- Gastrointestinal barrier, with small intestine housing about 70% of immune cells in the lymphoid tissues (see ► Chap. 24)
- Blood–brain barrier (see ► Chap. 12)
- Respiratory-lung barrier, comprised of bronchi, bronchioles, and alveoli cells which together are responsible for exchanging oxygen intake and carbon dioxide waste exhalation (see ► Chap. 52)

Significant differences in the membrane structures of various cells, besides phospholipid composition, are in the presence and amount of cholesterol. Mitochondria have almost no cholesterol embedded in their inner and outer membranes. In all other eukaryotic cells (complex cells with organelles), cholesterol is present and is important to the stability of the cell, the sorting of protein structures [2], and guarding from toxic substances entering the cell.

During the twentieth century, cholesterol developed a bad reputation driven by the Ancel Keys' research concerning its relationship to cardiovascular disease. More recently, the scientific community has challenged Keys' research on cholesterol and saturated fat [4].

It is important to consider the beneficial role of cholesterol in the structure of the membrane. Cholesterol is a "lipid of its own" [2]. Cholesterol is a sterol and is different from phospholipids. Cholesterol has a steroid ring structure and polar head group (-OH). As an amphipathic molecule possessing both lipophilic and hydrophilic properties, cholesterol easily incorporates into lipid bilayers. Cholesterol has a "bulky and stiff tail and small head," contributing a stabilizing order to the cell membrane structure, making the membranes "stiffer" but allowing the membrane permeability to function. Membrane permeability is an important issue of chronic diseases and that the membrane signaling, therefore cell metabolism and viability, depends on the phospholipid, cholesterol, and fatty acid composition [1, 12]. The permeability of the organelle and cell membranes requires a balance that is not too rigid and not excess (leaky membrane). Membrane permeability is affected by several factors like age, dietary history, activity level, and hydration. A practical assessment of cell membrane permeability is the measurement of the *phase angle* (PA), a quantitative measurement available using the bioelectric impedance analysis (BIA) technology (see ▶ Chap. 22). The PA is used as a marker of cell membrane integrity and permeability. Although the biological significance of the PA is not fully understood, many studies have recognized that low PA values are associated with a poor prognosis and as a prognostic indicator for some cancers [11, 13, 14]. The BIA instruments have been used in research and clinical practice for over 30 years and are easy to operate in a clinical setting and relatively inexpensive. This BIA data when added to the information from a red blood cell (RBC) fatty acid analysis, blood lipid panel, and disease condition gives some indication of cell membrane permeability.

Cholesterol is essential to life by providing the base unit for production of hormones, neurological cells (neurons, myelin, brain tissue, etc.), bile, and others. As with all natural components of the chemical body, each cholesterol molecule has multiple functions. Each function depends on the balance of the amount of cholesterol deposited in the cell membranes. This balance is foundational to optimized cell function and may be related to compromised metabolism when cholesterol is too low (studies suggest hypocholesterolemia is total cholesterol <120–150 mg/dL). On the low-end of the spectrum, hypocholesterolemia is associated with increased incidence of mood disorders like depression, as well as cancer, and sepsis [15]. During a nutritional assessment, biomarkers for cholesterol status are important to quantify and should consider any medications that influence cholesterol synthesis. The IFMNT practitioner should be skilled at restoring cholesterol balance and managing hypercholesterolemia along with helping manage clinical symptoms.

11.5 The Eicosanoid Cascade: Acute and Chronic Tissue Inflammation Management

The eicosanoid cascade is comprised of a complex group of organic molecules with multiple metabolic functions. This section will focus on eicosanoid functions and their influence on the immune response to initiate and resolve inflammation [1, 16]. The 20-carbon eicosanoids are derived from the 18-carbon fatty acids omega-6 linolenic acid (LA) and omega-3 alpha-linolenic acid (ALA) by catalytic action of two enzyme groups, desaturases and elongases. The dietary amounts of omega-6 and omega-3 fatty acids affect this process of eicosanoid production. The eicosanoid metabolites are signaling molecules that determine the function of many metabolic pathways. The families of eicosanoids include prostaglandins, prostacyclins, thromboxanes, and leukotrienes [10]. Within each family, there are many metabolites, including recently discovered *specialized pro-resolving mediators* (SPM), involved in resolving inflammation [1, 6, 17]. Eicosanoid families may either produce or reduce inflammation depending on which molecules are produced by the immune response signaling. Eicosanoids also help regulate blood pressure, modulate the immune system, and affect blood clotting [7].

The IFMNT practitioner applies their knowledge of the eicosanoid cascade biochemistry and rate-limiting nutrient cofactors and lifestyle habits that affect elongation and desaturase enzyme functions. With skill in managing chronic inflammation, one can target nutritional interventions to restore optimum balance of the eicosanoid metabolites derived from the essential fatty acids, *linoleic acid* (LA C18:2 ω 6), and *alpha-linolenic acid* (ALA C18:3 ω3) (see ◘ Fig. 11.4). To assess an individual's eicosanoid and metabolite status, obtain functional lab testing and a diet history to assess the patient's fatty acid status and metabolites affecting inflammation. The initial assessment best includes an RBC fatty acid profile, blood lipid panel, and dietary history of fat and oil rich foods (see ▶ Chap. 58 on Fats and Oils Survey). From this data, one can assess fatty acid status and recommend changes to support inflammation control.

The two arms of the eicosanoid cascade share the desaturase and elongation enzymes and compete for their use, with preference toward omega-3 metabolites [18]. Each of the omega-3 and omega-6 metabolite families influence each other and cannot be converted from one family to the other due to lack of the required enzymes in the human metabolism. Even though the LA and ALA are the two essential fatty acids, their important metabolites like γ-linolenic acid (GLA), di-homo-γ-linolenic acid (DGLA), arachidonic acid (AA) in the omega-6 family, and EPA and DHA in the omega-3 family can be obtained from some foods rich in the converted forms. For example, for a person who did not eat

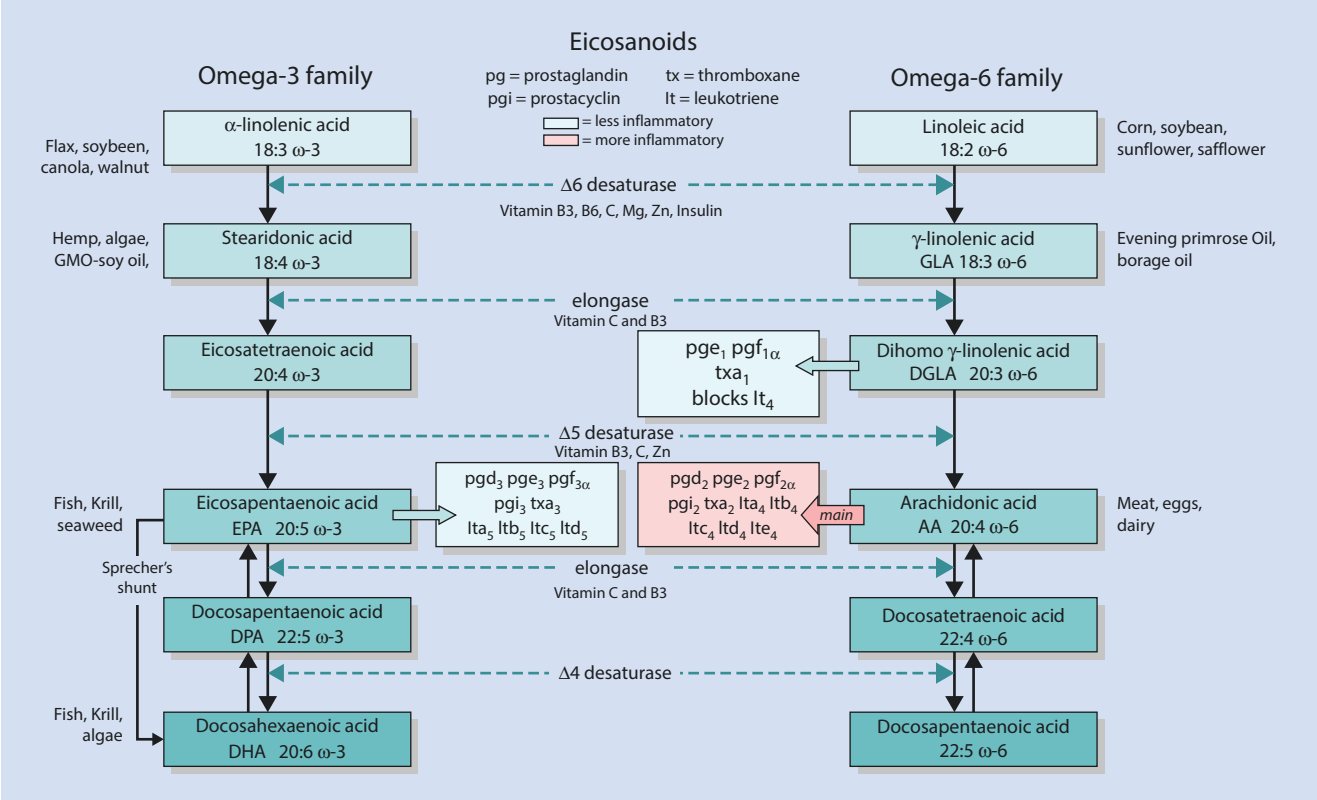


Fig. 11.4 The Eicosanoid Cascade of essential fatty acids, their metabolites, the nutrient cofactors, and foods rich in those cofactors. (Adapted with permission from: ► https://commons.wikimedia.org/wiki/File:EFA_to_Eicosanoids.svg)

any ALA sources like walnuts, flax oil, or vegetables, adequate EPA, and DHA could be provided by eating fish (EPA, DHA) or algae (DHA) sources. Another direct source of EPA, DHA, and LA is grass-fed or pasture-fed beef. If a person is depleted in the nutrient cofactors for the elongation and desaturase conversion biochemical steps, it would limit the efficiency of those enzymes. Repletion of those nutrient co-factors can increase the efficiency of the conversion enzymes.

11.5.1 Fatty Acid Elongation (See Fig. 11.4)

Elongation chemistry is dependent on the rate-limiting nutrients vitamin C and vitamin B3 (niacin). Any insufficiency or deficiency of those nutrients can significantly hamper achieving the balance of the eicosanoid metabolites. This balance is foundational to optimized cell function [19].

11.5.1.1 Elongase

The elongation of long chain fatty acids is derived from the omega-3 and omega-6 essential fats into very long chain fatty acids (VLCFA). The rate-limiting nutrient cofactors are zinc, magnesium, and vitamin B6. The elongation of very long (ELOVL) fatty acid by elongase enzymes is influenced by insulin and high carbohydrate diets [10]. It is important to assess glucose-insulin management when assessing of lipid status.

11.5.2 Fatty Acid Desaturation (See Fig. 11.4)

Desaturase enzymes delta-6-desaturase (D6D) and delta-5-desaturase (D5D) control the conversion of the essential fatty acids LA and ALA and eicosanoid metabolites. The key nutrient cofactors for the D6D and D5D are vitamins B3 (niacin), B6 (pyridoxyl-5-phosphate), C (ascorbate), and the minerals magnesium and zinc.

11.5.2.1 Delta-6-desaturase (D6D)

Interactions between dietary LA, D6D, and insulin resistance from the modern Western diet are associated with increased activity of the D6D enzymes, which result in the increased conversion of LA to excess pro-inflammatory AA [20, 21]. Alcohol and smoking can both suppress D6D activity, and those individuals may have poor conversion of LA to DGLA and AA. The GLA conversion to DGLA is a pivotal occurrence because the DGLA has two options for continued production of either the prostaglandin 1 series of metabolites or AA and the proinflammatory prostaglandin 2 series. The D6D and D5D enzymes determine how much the omega-6 metabolites proceed in either direction. If D6D is inhibited, not as much DGLA is produced. If DGLA is produced and D5D is increased in activity, DGLA will increase production of AA and lessen the ability to form the anti-inflammatory PG1 metabolites. For those who smoke and/or drink significant alcohol, the use of evening primrose or other GLA-rich

oil can support increasing DGLA conversion toward anti-inflammatory prostaglandin 1 metabolites and bypass the poor activity of D6D [6]. The D6D is encoded by the fatty acid desaturase (FADS2) gene and its function is rate-limiting in polyunsaturated fatty acid biosynthesis [22].

11.5.2.2 Delta 5-desaturase (D5D)

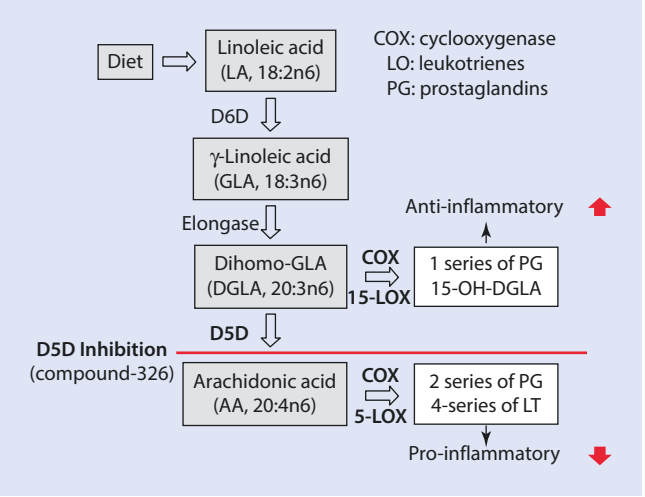
D5D activity is responsible for the conversion of omega-6 DGLA to pro-inflammatory excess AA. Elevated glucose, insulin metabolism, and obesity promote D5D activity, increasing AA formation and pro-inflammatory conditions. Dyslipidemia and the use of prescription medications (statins) are usually involved with increased D5D activity [3, 23]. Because of the epidemic of sarcopenic obesity and obesity overall, awareness of interventions such as supplemental GLA-rich sources can direct the omega-6 DGLA to its alternative anti-inflammatory pathway to prostaglandin 1 series metabolites and contribute to decreasing insulin resistance [23]. D5D is also involved in gonadal hormone metabolism. An example is when estrogen-dominant conditions develop, the D5D is more activated. This may increase conversion of DGLA to AA instead of a balanced conversion to the PGE1 anti-inflammatory molecules. Weight reduction to ideal body weight and weight maintenance can improve the healthy function of D5D [24].

It is important to remember that the omega-6 and omega-3 fatty acids cascades compete for the desaturase and elongase enzyme activities, so inhibiting the omega-6 DGLA to AA conversion will also affect the D5D activity that converts omega-3 ALA to EPA and then DHA. When inhibiting D5D, there may be an increased need for dietary intake of EPA and DHA by eating fish and/or fish oil supplementation. D5D enzyme activity is a target of research for diabetes management. D5D inhibitors are currently a target of the pharmaceutical industry [24]. The potential of nutrition therapy to optimize fatty acid status, reduce simple carbohydrate intake, and achieve weight management can be powerful modulators of these enzymes.

More comprehensive lipid blood tests have recently become clinically available that can improve assessment of a patient's status. The arachidonic/di-homo-gamma-linolenic acid ratio (AA/DGLA ratio) is a meaningful biomarker for assessing balance between AA and DGLA concentrations that affect the inflammation process and the function of D5D [25] (See ◘ Fig. 11.5).

11.6 Metabolic Stressors

Systems biology emphasizes the interactions of all systems to influence the phenotype of an organism. New stressors have arisen in the past century from environmental toxicants, decreased physical activity, highly refined foods, increased carbohydrate intake, and increased occurrence of metabolic syndrome to enable dramatic changes in phenotype due to chronic disease. Some of these stressors are known to influence the activity of the elongases and delta-5 and delta-6-desaturases, resulting in altered eicosanoid metabolism. Obesity is one metabolic condition that is associated with disturbed lipid metabolism and low-grade inflammation in tissues, and can vary based on the nutrigenomic profile of an individual for the FADS1 and FADS2 genes (See ▶ Chap. 17).



◘ **Fig. 11.5** Biosynthesis pathway of n-6 polyunsaturated fatty acids. D5D is a key enzyme affected by glucose, insulin, and stress status of metabolism and can be mediated by diet and lifestyle choices. (Reprinted from Yashiro et al. [24]. With permission from Creative Commons License 4.0: ▶ https://creativecommons.org/licenses/by/4.0/)

> The functional role of eicosanoids in the inflammatory etiology of diseases of metabolic syndrome (MetS) has been extensively studied in relation to immune cell recruitment and cytokine, chemokine production and their activation of inflammatory pathways in cancer, diabetes, and cardiovascular disease (CVD) [11, 26].

11.7 Tools of the Trade for Lipid Therapy

The toolbox for the IFMNT practitioner considering lipid therapy assessments and interventions includes all clinical and measureable parameters and modalities that influence lipid metabolism or are influenced by food intake, lifestyle, and/or environment. The following checklists and principles of gathering lipid data suggest laboratory testing and other clinical information to contribute to a comprehensive assessment, diagnosis, and intervention to promote the best outcome for an individual.

Toolbox to identify fatty acid/nutrition status

- Nutrition Physical Exam (see ▶ Chap. 40)
- Medical history: diagnoses, medical event history, residential location
- Signs and symptoms: Medical Symptoms Questionnaire (MSQ)
- Laboratory testing: basic nutrition, lipids, disease-specific and sometimes patient-specific markers
- Bioelectrical Impedance Analysis (BIA), if available

The nutrients in ◘ Table 11.2 are the most studied regarding lipid metabolism and should be considered as part of a nutritional assessment.

Table 11.2 Key lipid nutrient insufficiencies/deficiencies associated with subclinical or acute disease; key immune nutrients foundational for healthy lipid status

Nutrient	Clinical or biochemical implication of deficiency	Reference	Symptoms	Testing to consider
Immune modulators				
Omega-6 GLA	Eczema, Dermatitis GERD Viral infections	[6]	Broken skin lesions Rash, diabetes Long-term effects of chronic disease	RBC fatty acid Gamma linolenic (GLA) di-homo-gamma linolenic acid
Eicosapentaenoic acid (EPA, EPA, DHA, LA, ALA)	Altered mood Skin health Cardiovascular Cancer	[27]		RBC fatty acid
Malonaldehyde	Cancer Altered fatty acid Metabolism	[6]		RBC fatty acid
Choline phosphatidylcholine phosphatidylethanolamine phosphatidylinositol	Poor membrane permeability Impaired fat metabolism Fatty liver Mitochondrial dysfunction Released alanine aminotransferase (ALT) from liver cells	[28, 29]	Neurological Fat malabsorption Muscle damage	Homocysteine Creatine kinase Liver enzyme ALT Lipid panel Folate, RBC folate
Vitamin D	Immune modulator	[30–32]	Mood disorders Bone loss Joint pain Compromised immunity	Vitamin D25OH Vitamin D 1,25OH Parathyroid hormone (PTH) Ionized calcium
Vitamin A retinol	Mucosal immunity	[33, 34]	Mucosal bacterial/viral infections	Vitamin A, retinol B-carotene
Eicosanoids	Anti-inflammatory Pro-inflammatory Immune regulation Resolution biology	[35–37]	Pain Swelling Cancer	RBC fatty acid
Rate-limiting co-factors				
Folate	NK cell activity Cytotoxic cellular immunity Modulate T-cell responses	[38]	Fatigue Infection Mood disorder	Folate, serum RBC folate FIGLU
Zinc	Regulates intracellular signaling pathways in innate and adaptive immune cells	[38–40]	Skin conditions Poor smell Poor taste Frequent illness Nail spots	Zinc, serum RBC zinc
Magnesium	>300 enzymes cofactor Urine excretion under stress Muscle tension Camps	[10]	NHANES ~80% US population less than RDA magnesium	Magnesium, serum RBC magnesium
Antioxidants				
Vitamin C	Regulates cellular humoral immune function Increases macrophage Antihistamine Requirements increase during infection Anti-viral	[41]	Connective tissue impairment Skin conditions Poor wound healing	Vitamin C, blood CPT 82180 Urine, functional need for vitamin C test: urine *p-hydroxyphenyllactate* (HPLA)

(continued)

Table 11.2 (continued)

Nutrient	Clinical or biochemical implication of deficiency	Reference	Symptoms	Testing to consider
Vitamin E	4 tocopherols + 4 tocotrienols protective from oxidative stress/ lipid peroxides	[30, 42]	Oxidative stress Premature wrinkles Cysts Leg cramps	Serum: Alpha-tocopherol gamma-tocopherol
Selenium	Thyroid peroxidase metabolism with vitamin E Selenoproteins special effects on cellular immunity Resistance to viral infections Central to glutathione peroxidase structure	[38]	Hypothyroid Low glutathione blood levels Impaired detoxification	Selenium, serum RBC selenium
GUT secretions				
Short-chain fatty acids (SCFA)	Intestinal cells Anti-inflammatory Microbiome-gut- brain axis via immune system/vagal nerve Mucosal immunity	[43–48]	Inflammation Perturbed uric acid cycle Colon disease	Acetate Propionate (blood or fecal) Butyrate (blood or fecal)
Bile acids	Fat malabsorption Metabolic liver diseases Glyco and Taurochenodeoxycholic Acid	[49, 50]	Perturbed fat digestion	Bile acids US imaging gallbladder
Lipotoxic Conditions				
Dysfunctional regulation of lipid metabolism and homeostasis causes cellular lipotoxicity, impairs cellular processes and contributes to the pathogenesis of disorders such as obesity, atherosclerosis, and neurodegeneration	Neurological Cancer Autoimmune Developmental Cardiovascular Psychological	[51, 52]	Diagnosis specific	Diagnosis specific
Anti-Nutrients				
Endocrine-disruptors	Circadian rhythm disruption that can modulate immune function	[53, 54]	Hormonal imbalance Insomnia Cancer	GPL-TOX, Great Plains Lab toxic organic chemical profile
Damaged food components/ Western Diet & food preparation Trans fat Oxidized fat Toxic metals Toxic chemicals "new to nature molecules" (cookware, pest control, pollutants, processed, etc.)	Most damaged or toxic substance *Lipophilic* and embed into the fatty membrane and other tissues Damaged high-heat foods Chemicals Toxic metals ingested in foods and from food utensils during food preparation	[55]	Chronic disease Specific toxic symptoms Weakened immune integrity	Diet History RBC fatty acid analysis
Environmental Toxins				
Mold/mycotoxins Natural gas carcinogenic Chemical vapors Pesticides	Neuropsychiatric Immune disruption Vulnerable to poor cell signaling Insulin resistance	[56, 57] [58] [59]	Toxicities Chronic kidney failure Infertility Cancer Developmental Frequent infections	*Mold, pathogenic bacteria:* Multiple Antibiotic Resistant Coagulase Negative Staphylococcus (MARCoNS) nasal swab GPL-TOX, Great Plains Lab toxic organic chemical profile (pesticides, toxic chemicals)

11.7.1 Laboratory Principles

With laboratory data available, a diagnostic profile can clarify the priorities of core physiological imbalances and provide clues regarding nutrition and lifestyle therapy to restore structure and dynamic function of the membrane. From the IFMNT nutrition assessment, consideration of the two most likely physiological clinical imbalances is *structural integrity* and *defense & repair* (see ◘ Fig. 11.3).

11.7.2 Structural Integrity

The membrane's structural integrity affects the transport and communication of the cell membrane and receptors. If there is a history of head, neck, dentition, or back injury where there may be a possible structural misalignment in the cervical vertebrae, the brainstem and vagal nerve may be impaired. Someone with this history should be referred to a cranial specialist for evaluation and have their lipid status reviewed.

11.7.2.1 Assessment Checklist for Structural Integrity

- Cell membrane permeability and integrity (BIA phase angle, fatty acid status) [11]
- Dental periodontitis: infection of the tissues that surround the teeth-inflammation
- Structural-spinal alignment: neuronal membrane [1, 60]
  - Cervical C1-C7 – brainstem & vagal assessment – check vagal tone
  - Thoracic T1-T5 – stenosis or injury increased pain resulting in exaggerated immune inflammatory response
  - Lumbar L1-L5 – stenosis or injury increased pain resulting in exaggerated immune inflammatory response

11.7.3 Defense and Repair

Defense and repair are managed by a dynamic immune system that responds to endogenous and exogenous infection, injury, malnutrition, altered gut microbiome, stress, and other potential inflammatory triggers.

11.7.3.1 Assessment Checklist for Defense and Repair

Blood Markers

Vitamin D 25-Hydroxy

Vitamin D has many functions. It is a powerful immune modulator that plays a role in defense and repair.

> Vitamin 25OH serum levels have been associated with overseeing the dynamics of the cell membrane. Vitamin D seems to stimulate anti-inflammatory processes [31].

Vitamin A (Retinol) [61]

Vitamin A is a nutrient cofactor for the eicosanoid desaturase enzymes. It is increasingly recognized in experimental and human studies to enable suppression of inflammatory reactions and plays a significant role in normal mucosal immunity, regulation of T cell-dependent responses, antiviral activity, and cell communication.

Adequate vitamin A status, whether from intake of preformed retinol (e.g., animal sources: egg yolk, organ meats, fish, shellfish, and roe) or from b-carotene (e.g., yellow and green vegetables) is important for preventing excessive or prolonged inflammatory reactions and supporting the eicosanoid cascade [61].

Gut microbiome [55]

Gut commensal bacteria making up the microbiota are critical for the health of the immune system by defending and repairing the intestinal barrier where >70% of the immune cells reside. Stool testing provides biomarkers to assess GI ecology. From this data one can develop an intervention plan to correct and repair imbalances in the gut microbiome (see ▶ Chap. 24).

Inflammatory Load Assessment

- High-sensitivity C-reactive protein (hs-CRP): acute-phase-reactant and marker of systemic inflammation. It is often elevated due to bacterial infection, central adiposity, fatty liver, neoplastic activity, or traumatic injury. All clinical laboratory references include normal hs-CRP as ≤1.0. Its elevation implies potential bacterial infection or physical trauma. If no dental/oral infection is identified, begin further investigation of the root cause. It is important to rule out a recent traumatic injury that may be related, and hs-CRP should be retested in a month or two to observe if injury has affected the hs-CRP.
- CBC with differential
- Complete metabolic panel (CMP)
- Lipid panel
- Erythrocyte sedimentation rate (sed rate)
- TSH
- Bacterial/viral evaluation if indicated; saliva or blood
- Genomic testing (saliva), if available

11.8 Key Nutrient Cofactors and Foods Influencing the Eicosanoid Metabolism

11.8.1 Lipids

Lipids play critical roles in membrane structure, cell signaling, energy storage, control of inflammation, and as base units for constructing messenger hormones [2]. Each member of the family of lipids has specialized functions. Some provide cell signaling, cellular component transporting and regulate immune response of inflammation, hormonal modulation, and other undiscovered functions. When there is

poor structure, dysfunction occurs [62]. The following key nutrients below can be obtained from foods and/or dietary supplements:

11.8.1.1 Phospholipids (PL)

Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS). These phospholipids are ubiquitous in all membrane structures and especially important for the functions of neurological and mitochondrial membranes [6]. The body can synthesize them, and they can also be found in foods. Foods rich in phospholipids are animal meats and organs, egg yolk, and legumes.

11.8.1.2 Fatty Acids:

- *Omega 9* Monounsaturated fatty acids (MUFAs): These oils are stabilizing components of structures and also have an anti-inflammatory effect in metabolism. Foods rich in MUFAs are olive oil, avocado/avocado oil, almonds, sesame, and peanuts. They are mildly heat sensitive and best raw or used with low heat.
- *Omega 6* Linoleic Acid (LA) (essential) and the eicosanoid metabolites GLA, DGLA and AA. LA is rich in seeds, some nuts, greens, grains and grasses.
- *Omega 3* Alpha Linolenic Acid (ALA) (essential) and the eicosanoid metabolites EPA, DPA, DHA recognized for their anti-inflammatory effects on metabolism. The balance between omega 6 and omega 3 fatty acids is important with most fatty acid scientists proposing an optimum ω6:ω3 ratio range of 1:1 to 5:1.
- *Saturated fatty acids* have been blamed as being detrimental for humans. But better understanding that there are beneficial saturated fatty acids when maintained at about 10% of dietary fat [63]. Natural and beneficial forms of the saturated fats are:
  - *Short chain fatty acids* (SCFA) with many critical roles of anti-inflammatory and fuel for colonocytes. Many health benefits are recognized reducing risk of colon cancer, autoimmunity, and gastrointestinal disease.
    1. Acetate (C2) and Proprionate (C3) SCFAs are formed in a healthy gut.
    2. Butyric Acid: butyrate: C4: butyrate-rich sources are butter, mother's milk, healthy gut microbiome consuming resistant and soluble vegetable and fruit fibers to produce SCFAs, and sodium or calcium-magnesium butyrate dietary supplements. If there are infectious or antibiotic insults to the gut microbiome, the production of butyrate may be notably reduced [64].
  - *Medium chain triglycerides* (MCTs) are composed of a glycerol backbone with three medium-chain fatty acids (MCFAs) (C6-C12). The MCTs are beneficial as part of dietary intake. They are heat resistant and recommended as cooking oil. Rich sources are coconut oil, palm kernel oil, and ruminant animal milk (cow, sheep, goat, horse). Therapeutic use of MCTs for liver failure and other gastrointestinal conditions is common due to their rapid absorption and not requiring bile salts for digestion and can be an easily metabolized source of energy.
  - *Saturated Fatty Acids (SFAs)*(C13-16) are made up of carbon chains with only single bonds. The body can synthesize SFAs and they are also found in SFA-rich foods such as animal meat fats like beef tallow, pork lard, poultry fat, and also cocoa butter.
  - *"New-to-nature" Fats:* with high heat and hydrogenation processing of vegetable oils, aberrant fatty acids and lipid structures can be formed that have been recognized as unhealthy for human metabolism, with some identified as carcinogenic. Examples of these compounds are trans fats and acrylamides.

11.8.2 Sterols

Sterols are naturally occurring unsaturated steroid alcohols, waxy lipids. The primary sterol for human metabolism is cholesterol, which is the base unit for all hormone production and vitamin D. Cholesterol is also an important component of cell membrane structure [2]. Most endogenous cholesterol is synthesized by the liver, but dietary cholesterol can influence total cholesterol levels. Foods rich in cholesterol are of animal origin: fats from animal milk, meat, egg yolk, poultry, seafood, and organ meats.

11.8.3 Minerals

11.8.3.1 Zinc

Zinc is a nutrient cofactor for the desaturase and elongase enzymes and a nutrient partner with copper. Zinc and copper should always be balanced in body fluids (see ▶ Chap. 8). When copper is elevated, it promotes increased fat deposition in some organs like the liver. Increased zinc intake can modulate the copper to a healthy level and reduce the fat deposition [65].

11.8.3.2 Magnesium

Magnesium functions as a nutrient cofactor for both the desaturase and elongase enzymes for eicosanoid conversions. When it is insufficient or deficient, restrictions in function can occur. In the case of magnesium as a cofactor in the sodium-potassium pump, the rate of conversion is decreased during a deficiency of magnesium. Magnesium is the cofactor catalyzing the enzymes driving the sodium-potassium pump, moving substances in and out of the cell through the lipid membrane [9, 66, 67] (see ▶ Chap. 17).

11.8.4 Methyl Nutrients

Vitamins B6, B12 (-cobalamins), B9 (Folate), B2 (riboflavin), B3 (niacin), choline (betaine, phosphatidylcholine/phosphatidylethanolamine), SAMe, and related Vitamin C, B1, B5 [68, 69].

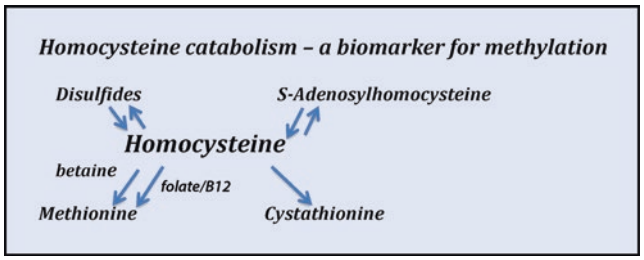


Fig. 11.6 Homocysteine major metabolic pathways in humans. (Adapted from Dudman et al. [70]. With permission from Oxford University Press)

Methyl nutrients support the process of methylation, having many roles within human metabolism with DNA methylation being the underlying mechanism, and they currently appear to be primary messengers of epigenetic expression (see ▶ Chap. 18) identified in the etiology of developing cardiovascular, cancer, and neurological disease conditions. Methyl nutrients are involved in the conversion of desaturase and elongase enzymes. Methylation involves biochemical pathways where the B vitamins and other cofactors like amino acids are rate-limiting cofactors [70] (Fig. 11.6).

11.8.4.1 B12 and Folate Metabolism

B12 in the natural bioactive forms (methyl-, hydroxy-, or adenosylcobalamin) is a nutrient cofactor that inhibits the excessive formation of arachidonic acid. B vitamins team together, and folate is an especially important teammate with B12. Folate is critical to many metabolic pathways like nucleic acid precursors, several amino acids, and erythropoiesis, which is the process in which new erythrocytes are produced. A biomarker that can suggest folate deficiency is an elevated mean corpuscular volume (MCV) on a complete blood count quantitatively measuring size of RBCs. Folate deficiency can be part of the etiology of enlarged RBC or megaloblastic anemia, from ineffective erythropoiesis. Additionally, Vitamins B6 and B12 are cofactors involved in erythropoiesis [71].

11.8.4.2 Niacin, Vitamin A, Vitamin C, and Zinc

- Rate-limiting nutrients for DGLA conversion to anti-inflammatory Prostaglandin 1 (PG1) series
- PG1 anti-inflammatory action primarily involved in mediating conditions of allergy, viral, autoimmune

11.8.4.3 Vitamin D, A [72]

These fat-soluble vitamins have many metabolic roles. Their influence on structural integrity and defense and repair (e.g., inflammation and immune response) modulates the lipid environment and metabolic dynamics. The fat-soluble vitamins function synergistically, with the vitamin D and A receptors sharing their nuclear receptor, influencing each other. Vitamin D2/3 and A are found in their food-rich sources together (e.g., liver, caviar, /roe, egg yolk). Vitamin A retinol is one of the key nutrient cofactors for the desaturase enzyme activity.

11.8.5 Phytonutrients: Protective Support for Lipid Structures

- Inflammation: Phytonutrients are antioxidants that protect the lipid membrane from oxidative stress through their powerful polyphenols found in a variety of pigment-rich fruits, vegetables, grains, nuts, teas, herbal spices, and legumes that have anti-inflammatory properties. The mechanisms of the plant chemicals include antioxidants, antibacterial, and antiviral. Even though phytonutrients are not considered essential nutrients, the evidence is mounting for their critical role in health maintenance and anti-aging.
- Biomarkers of poor phytonutrient status: Poor dietary intake of high polyphenol foods. Significant biomarkers for inflammation can be related to poor vegetable and fruit intake and lack of (or imbalance in) dietary intake of healthy fats and oils (see ▶ Chap. 58 Fats & Oils Survey)(Table 11.2)
- Resource: The Rainbow Diet. Color Can Heal Your Life [73].

11.9 Key Lifestyle Factors Influencing the Risk of Lipid Damage

11.9.1 Sleep [74] (See ▶ Chap. 35)

Sleep and circadian rhythm have a great influence on the integrity of the immune system. Much evidence has accumulated over the past decades associating poor sleep quantity and quality with weakening of the immune system, increasing vulnerability to the poor function of cellular structures.

11.9.2 Stress (See ▶ Chap. 47)

Chronic stress impacts every biological and psychological system. When the chemical microenvironment is under long-term stress, it pushes the immune system response into chronic inflammation and increased acidity. The vicious cycle continues until the threshold of resilience and adaptation is exceeded, leading to vulnerability to many chronic diseases including damage to lipid structures and influencing the eicosanoid metabolism.

11.9.3 Movement (See ▶ Chaps. 36 and 54)

As with all biological systems, there must be movement of structures like muscles, heart, lungs (breathing), as well as the fluids in the body to maintain health. Without movement, there is congestion that does not support healthy metabolism. The health of the immune system is dependent on the lymphatic system, which is supported by movement. The lymphatic circulatory system does not have a pump as compared with cardiovascular circulation. The lymphatic vessels are "pumped" by physical activity with arm and leg movement, abdominal breathing, laughing, etc.

11.10 Chronic Disease and Impaired Lipid Metabolism (See Tables 11.3 and 11.4)

11.10.1 Heart Disease/Cardiovascular Association with the Lipidome

Lipids manage and resolve inflammation via the eicosanoid cascade. Chronic inflammation is a hallmark of cardiovascular disease, so if it is well controlled and resolved, the risk of a cardiovascular event is decreased. The current recommendation for eating fish or fish oil supplementation to benefit the cardiovascular system is primarily as a modulator of the eicosanoids to lower the pro-inflammatory excess omega 6 arachidonic acid [78].

11.10.2 Oncology

Several of the eicosanoid metabolites are evidenced to be tumor suppressive [79]. Eicosanoids, including prostaglandins and leukotrienes, are biologically active lipids that have been associated with many of the pathologies of chronic disease such as inflammatory cancer. Eicosanoid metabolites and their function of inflammation control give the IFMNT practitioner the ability to develop a targeted intervention for cancer by assessing the patient fatty acid status and analyzing the eicosanoid metabolism status [80].

Prostaglandins and leukotrienes can modulate tumor epithelial cell proliferation and apoptosis.

When the prostaglandin 1, 2, and 3 series are in balance, they can provide a change in the microenvironment toward wellness [81].

11.10.3 Neurological

11.10.3.1 Mitochondrial Dysfunction

Most neurological conditions involve underlying mitochondrial dysfunction. The mitochondrial inner and outer membranes are sensitive to influences from dietary fat. The inner membrane especially requires the phospholipid derived from choline, phosphatidylethanolamine (PE), and gamma-linolenic acid (GLA). Lipid nutrition therapy can use seed oils like evening primrose, black currant, sea buckthorn, or borage to provide adequate GLA in interventions to support mitochondrial repair. Evening primrose oil has also been shown to induce apoptosis and tumor suppression for cancer patients [82].

11.10.3.2 Alzheimer's Disease

The brain is approximately 70% fat and phospholipids. Restoring optimum lipid balance can benefit the structure and function of the nervous system. Comprehensive medical nutrition therapy supports high-fat diets in Alzheimer's and other neurological conditions. The brain can use glucose or ketones for fuel. Research on the ketogenic diet, where

Table 11.3 Laboratory: recommended biomarkers for lipid assessment

Blood tissue testing [75]
Lipid panel
Total cholesterol, HDL, LDL, triglycerides, lipoprotein particles [1]
RBC fatty acid analysis
Blood biopsy
Dietary fat intake reflected in RBC fatty acid membrane composition [76, 77]
Bioelectric impedance analysis (BIA) [11]
Phase angle: cell membrane permeability of the lipid bilayer
Capacitance: ionic potential, membrane surface biomarker
Intracellular and total body water
Organic acids [75]
Urine: first morning collection, fasting
View of all major systems (conventional and functional tests as indicated)
Inflammatory load
Clinical observation of any inflammation of the face, skin, pain, biomarkers?
Laboratory
CBC with differential
Sed rate
C-reactive protein-high sensitivity
Acute phase reactants per diagnosis or signs & symptoms
Nutrition physical exam: Barriers; rule out potential symptoms or history
Skin: tone, color, texture, lesions, skin tags, abnormal pigmentation
Lung capacity/O_2 Sat: optimum 98–100%; history lung disease or surgery
Gastrointestinal health: Comprehensive Digestive Stool Analysis (CDSA) abnormalities
Oral cavity: periodontal disease, swollen glands, tonsillectomy history
Esophagus: symptoms of esophageal pain/irritation, dysphagia, *Heliobacter pylori*
Stomach: pain, digestive upset, surgical history, vagal tone
Duodenum: structural changes, Small Intestinal Bacterial Overgrowth (SIBO)
Jejunum: structural changes
Ileum: structural changes, abnormal BM/bile circulation reentry
Colon: abnormal BM
Rectum: abnormal BM, hx colonoscopy
Pain: location, barrier involved
Fatigue
Time of day, meal timing, sleep quality and quantity, sleep apnea

Table 11.4 Lipid-supportive foods, herbs, and dietary supplements

Foods
Whole-foods, pesticide-free, vegetables and fruits in a variety of colors, adequate protein, healthy fats & oils, herbs, fluids; Minimize or avoid processed and high-sugar foods and beverages; avoidance of antigenic foods.
Oil-/fat-rich foods
Plant-based: avocado, raw seeds, olives, hearts of palm, nuts: macadamia, pine nuts, almonds, Brazil nuts, coconut oil
Animal source: organ meats, meat, poultry, fish, shellfish, roe, krill
Herbs
Turmeric/curcumin
Proteolytic enzymes: Bromelain, papain, trypsin, etc. (contraindicated for Alpha-1-Antitrypsin deficiency+ genetics)
Resveratrol
Boswellia
Diet
Macronutrient distribution
Insulin-glucose management
Meal timing
Intermittent fasting
Calorie restriction
Dietary supplements
Lipids
Phospholipids: phosphatidylcholine/phosphatidylethanolamine
GLA: evening primrose oil; black currant, sea buckthorn, and borage
Arachidonic acid: grass-fed meats, poultry, egg yolk.
EPA/DHA: various ratios are available; DHA vegan/algae; fish (ideally, lower on food chain)
ALA: cold nitrogen processed seed and nut oils flax oil and/or ALA-rich raw/soaked nuts, seeds, vegetables; sensitive to heat, light and oxygen.
LA: cold nitrogen processed seed and nut oils: refrigerated; sensitive to heat, light and oxygen.
Butyrate: short chain fatty acid (SCFA); sodium-potassium butyrate, calcium-magnesium butyrate, sodium butyrate, Rx: glycerol phenylbutyrate (Ravicti®), sodium phenylbutyrate (Buphenyl®)
MCT Oil: medium chain triglyceride; sources: coconut, palm and breast milk fats; MCT: Caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0)
Co-nutrients
Vitamin C (contraindicated for hemochromatosis mutation genetics)
Adequate methyl nutrients: B6, folate, B12, choline (betaine) and related B1, B2, B3, B5, Biotin, Vitamin D3, vitamin A (if indicated per personalized assessment)
Zinc: rate limiting nutrient to D5D, D6D, and elongase enzyme
Magnesium: rate limiting nutrient to D5D, D6D, and elongase enzymes
Personalize recommendations based on patient assessment

ketones are produced from high-fat low-carb diets, inducing a "nutritional ketosis", has shown therapeutic benefit in neurological conditions (see ▶ Chap. 23) [83–85].

11.10.3.3 Developmental Plasticity

Fetal and early childhood metabolic plasticity includes rapid growth of cells requiring lipids. The rapidly maturing brain and neurological system are high-fat cells that need lipids for membrane structure, cell signaling, and development of the immune system. Maternal health and nutrition status are important to secretion of fat-rich mother's milk, which lays the foundation for fetal growth [86].

11.10.4 Respiratory

The lung has a major protective barrier function in the body, and the lipid composition of the membrane is integral to modulating inflammation and promoting optimal function. Assessing and prioritizing the structural integrity and inflammation load using diet history, nutrition physical exam, and testing for nutritional status provide the foundation for developing a targeted intervention.

11.10.5 Autoimmune

Autoimmunity is the loss of immune recognition of self and non-self with resulting self-damage. Ongoing research has identified genetic relationships that have susceptibility to the development of autoimmune conditions (see ▶ Chap. 49). Chronic inflammation is present in all autoimmune conditions with resulting oxidative stress and reactive oxygen species that can damage lipid structures. Nutritional therapy considerations to reduce the chronic inflammation can be reducing or eliminating identified antigenic foods and replete nutrients that are insufficient or deficient.

11.11 Case Reviews

The following cases give examples of clinical application of lipid nutrition therapy. Each patient case presenting to an IFMNT practitioner needs to be approached as unique. Every diagnosis or symptom can have a multitude of root causes. The patient's story begins with an investigation to identify metabolic priorities and the focus of interventions using food, dietary supplements, and lifestyle to restore health. It is important to monitor interventions to assess effectiveness and determine if adjustments should be made.

Case Review: Simple Childhood Asthma

Diagnosis: Severe asthma
Male: age 8
Medical History:
- Asthma medications: Singular, albuterol inhaler, glucocorticoid inhaler- Budesonide and formoterol (Symbicort), salmeterol (Serevent). Fluticasone and salmeterol (Advair Diskus)
- Asthma emergency hospital ER event monthly

Laboratory Significant: CBC WBC 3.8, MCV 99 HI, Vitamin D 12 ng/mL; +grass and + casein IGE allergens

Nutrition Physical: depressed affect; depapillation pale tongue (low B6, B12, Folate, B2 and iron), corner lips cracked skin (low B2), pale skin, matty hair

Diet and Supplement history: Eighty percent fast food (hamburgers, hot dogs, cold cereal, cow milk casein, soda, yogurt, ice cream, toast, candy). No dietary supplementation.

Lifestyle: difficulty breathing, grass pollen allergy, no outside play (reduced sun exposure); poor sleep related to breathing difficulty.

Metabolic Priorities and Intervention Plan
- Remove antigen: cow's milk
- Remove empty calories: sugar, processed and refined foods, damaged oils
- Gut ecology: diet associated with poor gut pre and probiotics
- Get nutrients:
- EPA 350 mg/DHA 250 mg/GLA 130 mg supplement daily
- Vit D3 4000 IU emulsified D3 daily
- B Complex: bioactive forms – chewable
- Probiotic 450 billion powder in 6 oz. coconut yogurt daily
- Whole grain gluten-free bread for sandwiches, toast with organic butter
- Beverages: water, stevia-sweetened sodas, almond or coconut milk

Monitor: 6-Week Follow-up
- Happy affect, started 2 weeks able to take gym classes outside
- Nutrition: decreased probiotic; continued diet and remaining supplements

Follow-up plan: 3 Months
- Doctor removed four of the medications
- No hospitalization for asthma event

Outcome
- High school soccer team player, no asthma medications, continued casein-milk free diet and avoid high sugar foods, resumed gluten foods
- Annual physical: recommend Vitamin D25OH and maintain 40–60 ng/mL using vitamin D3 supplements and safe sun exposure.

Case Review – Early-Onset Alzheimer's

Patient Story: A 64-year-old male who presented with memory problems and diagnosis of early onset Alzheimer's disease by neurologist. Two months previous he showed no interest in activities, could not work. He was a building contractor for 35 years.

Medical History: Thyroid cancer, total thyroidectomy, and Hemachromatosis recessive.

Medical Data: Anthropometrics: BMI 30; height 76.2"; weight 250 lbs,

Dietary/Alimentation: High intake of soda (~2 quarts/day) and processed foods including gluten containing grains and starches; some candy, doughnuts, fried foods, fast food, and canned fruit; commercial lunch meats. Low intake of water, essential fatty acids, vegetables, and whole foods.

Nutrition Physical Exam: Memory deficits reported by wife and observed during exam, wrinkles beyond age appropriate (implies high oxidative stress), talks very slow and only when asked a question, poor dentition and dental hygiene, bleeding gums, very coated tongue with central crack.

Medications: Thyroid, Finasteride, Terazosin for prostate enlargement, and a baby aspirin daily.

Genotypic Risks: Family history of cancer (7 of 8 siblings and father); brother and uncle with Alzheimer's; son Hemachromatosis (BB polymorphisms).

Biochemical Lab: Mildly reduced GFR, high BUN, low TSH (0.03)/standard of care post thyroidectomy, PSA 1.19, high Homocysteine 18. Low albumin 3.9, Total Protein 6.3, Globulin 2.3.

Nutrition Assessment
- *Intake:* High sugar, processed foods and cured meats
- Digestion & Assimilation & Elimination: RZ reports a 1/week bowel movement
- *Utilization:* Cellular & Molecular Function:
- *Minerals:* Low magnesium, low-end blood electrolytes, BIA Capacitance 730 (goal ~ 1300)
- *Antioxidants:* Water Soluble: Vitamin C, Phytonutrients: severe skin wrinkles-poor Vit C, vegetable/fruit intake
- *Protein*: Low-end protein status; albumin 3.9
- Vitamin D & Fat soluble vitamins: Low vitamin D (25 ng/mL)
- *Oils/Fatty Acids:* Low omega-3 and omega-6:GLA intake foods; cholesterol panel is OK
- *Methylation*: elevated Homocysteine implying poor methylation; low folate, B12, MCV 101 HI, MCH 33

Plan: (Continued Early-Onset Alzheimer's)
1. *Elimination Diet*: Avoid sugars, soda-replace with tea or fresh lemonade; avoid cured meats, dairy, processed foods; eat more whole foods, sea salt, salads and no nitrate, eat high-quality meats; increase water intake to 2 qts/day (previous intake none). GOAL: reduce sugar intake and antigenic foods; increase phytonutrients, nutrient-dense-high-fiber food intake. Good family support.
2. Improve Methylation and Oils/Fatty Acids: Focused on neurological support;

Supplement with multivitamin, magnesium, EPA/DHA 1:1, GLA 370 mg QD, folate (5-MTHF 800 µg) QD, B12 (Methyl B12 1000 µg QD), D3 4000 IU QD; herbal laxative support until BM QD.

3. *Adjunctive Physician-Supported Nutrition Support Using IV Lipid Therapy:* [phosphatidylcholine (PC) × 2 months, Glutathione, phenylbutyrate, assessed methylation support] twice a week for 8 weeks then start oral protocol of PC, Glutathione and Butyrate, methylating nutrients (5-MTHF, B12) as needed)

Outcome: After implementation of herbal colon cleanse, magnesium and increased water intake, at 2 weeks bowel movements increased to 1/day; Memory improved ~70% within 4 weeks. Great family support. Client returned to work and driving at 6 months, showing significant improvement. Continue diet, oral supplements. Follow-up monthly for 14 months then every 6 months while continuing oral phospholipid, methyl nutrients and very low sugar nutrition program. Continues cognitive function as long as on supplements after 7 years. Blood homocysteine 9, MCV 92, MCV 30.5. Neurologist reversed Alzheimer diagnosis after 14 months.

Case Review: Complex Neurological Condition

Female AR, age 20
Weight 70 lb, 46 inches, BMI 15.7 Underweight
Diagnosis

- Cardiofaciocutaneous (CFC) syndrome (Q87.1 ICD10); Genes are: *BRAF* (~75%), *MAP 2K1* and *MAP 2K2* (~25%), and *KRAS* (<2%). [Congenital malformation syndromes predominantly associated with short stature]; 23andme.com nutrigenomics: homozygous MTHF +/+, heterozygous VDR –/+

The *cardiofaciocutaneous (CFC) syndrome* is a condition of sporadic occurrence, with patients showing multiple congenital anomalies and mental retardation. It is characterized by failure to thrive, relative macrocephaly, a distinctive face with prominent forehead, bitemporal constriction, absence of eyebrows, hypertelorism, downward-slanting palpebral fissures often with epicanthic folds, depressed nasal root and a bulbous tip of the nose. The cutaneous involvement consists of dry, hyperkeratotic, scaly skin, sparse and curly hair, and cavernous hemangioma. Most patients have a congenital heart defect, most commonly pulmonic stenosis and hypertrophic cardiomyopathy. ► https://www.cfcsyndrome.org/fact-sheet

- Epilepsy and recurrent seizures (G40 ICD10): ~200 seizures per month w/ anti-seizure Rx; three severe seizure hospitalizations per month.
- Severe mental impairment (*F79 ICD10*)
- Osteopenia (M85.80 ICD10)

Medical History

- Normal 9-month vaginal birth; 5 months developmental delay, 9 months diagnosed "failure to thrive"; started tube feeding; residential care at home parents
- Diet History: Tube feeding Infant Formula until 3 years old; 3–20 years old received Boost™ tube feeding; weight 78–80 lb. bedridden, Birth lab significant for hypercalcemia 10.9 HI (<10). No PTH was ordered. Hypothyroid Day 1 screen WNL.

Signs and Symptoms

- No eye contact
- Appears pain when touching arms and hands during bathing
- Tube feeding tolerated

Lab History: Significant Findings

- Methylmalonic acid 861 very HI (B12 functional marker)
- B12, serum >2000 pg/mL
- Lipid Panel: Total Cholesterol 128 mg/dL; LDL 55 mg/dL: Low-end
- Ferritin 24 – Low End
- Vitamin D >120
- GGT 88 HI (ideal <10) [can be suggestive of toxcity and/or low glutathione status]
- Differential: WBC 6.04; Neutrophils 40.2 low end/Lymphocytes 44.7 HI
- Specialty Lab: RBC Fatty acid analysis: Very low arachidonic acid, GLA, DGLA, Hi EPA, Hi DHA
- Specialty Lab: lymphocyte micronutrient analysis: LOW: vitamin D, B12, A, carnitine, zinc, magnesium, choline

PLAN: Complex Neurological Condition
Three-Month Plan

- Retest previous abnormal tests
- Monitor symptoms /behavior – report TF tolerance and any changes weekly
- Mother requested investigating possibility that AM and mother were hypothyroid - mother exploring possibility AM was hypothyroid and infant screening was done day of birth negative, but protocol is to be tested day 3 after birth. Early screening may have missed hypothyroid condition.

Three-Month Follow-up

- Review new lab. WNL: B12, serum, methylmalonic acid ABNORMAL:, +ANA Titer, +++ EBV, Total + IgG/+IgE, carnitine panel: low,
- Seizures reduced 50–60% no hospital trips, reduced anti-seizure Rx
- Eye contact; no pain appearance touching during bathing.

Nutrition Assessment Metabolic Priorities

- B12 deficiency; specific for adenosylcobalamin B12 2000 µg/day with L-5-MTHF (bioactive folate)
- Request doctor rule out subclinical infection with further viral/bacterial panel
- Depleted vitamin/minerals: D, A, B12, -5-MTHF, carnitine, phosphatidylcholine/phosphatidylethanolamine, Linoleic Acid,
- Home tube feeding Lipid Liquid Meal recipe 2 quarts
- 2 scoop vegan or beef protein powder
- 48 oz unsweetened almond or coconut milk; add water to achieve TF consistency
- 2 tsp Phosphotidylcholine/Phosphotidylethanolamine (mitochondrial support)
- 2 tsp evening primrose oil (GLA)
- Multivitamin/mineral powder 2 scoop (bioactive B vitamin forms)
- Active B12 w (adenosylcobalamin B12) w/ L-5-MTHF 1000 µg 1 tab in TF
- 1–500 mg L-carnitine – open capsule into TF
- 1 blanched egg yolk
- Blend and administer within 24 hours, refrigerate

Outcome 14 Months and beyond:

- Five months free of hospitalization due to severe seizures
- Eye contact daily
- Reach for objects
- Adult school; at 14 months mouthed quietly to Mom "I love you".
- Continues Lipid Shake daily, sometimes adds healthy variety of foods.

11.12 Conclusion

Lipids are the molecular components that comprise the *lipidome*—the complete lipid profile within the membrane, cell, tissue, or organism. The lipidome is in the dynamic metabolism of life expressing the genetic information in the DNA book of life. The membrane houses the receptors that receive information and direct the biochemistry to survive. The two functions of the lipids that can be modulated by nutrition therapy are membrane structure and inflammation control.

This chapter has described the association between a person's nutritional status and their vulnerability for impaired fatty acid status. Nutritional status of an individual is a determinant of how well their body can respond to and resolve an infection returning it to a state of wellness.

It is important to consider an individual's fatty acid status for several chronic disease conditions. Pathophysiology of chronic disease reveals its contrast to acute disease by its long-term development, often asymptomatic and not recognized. Subclinical chronic disease progression can "smolder" unrecognized for many years, even beginning in-utero and childhood. This biological stress often goes undiagnosed or with the patient being unaware of the significance. This chapter provides knowledge of lipid metabolism, as it relates to membrane function, the assessment of lipid imbalances, and specific membrane and anti-inflammatory nutrients that can contribute to targeted intervention and optimal health [87].

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