ω -6/ω-3 Essential Fatty Acid Ratios in Health and Disease

Over the last 20 years, there has been an explosion of knowledge gained from researching the connection of cardiovascular disease with abnormal lipid metabolism. These studies elucidated the importance of the balance of ω-3 and ω-6 polyunsaturated fatty acids (PUFA); intrinsic to the mechanisms underlying the inflammatory response.

Additionally, studies of Paleolithic nutrition and of modern-day hunter-gatherer populations show that humans have evolved on a diet that was much lower in saturated fatty acids (SFA) than is today's diet. Furthermore, the diet contained small but equal proportions of ω-6 and ω-3 PUFA; a ratio of 1:1. It is only since the industrial revolution that changes in food consumption have occurred rapidly. These changes are reflected in an increased consumption of animal fat and imbalances in the ω-6:ω-3 ratio over the last 100 years. Today, this ratio is reported to be up to at least 10:1, and even as high as 20-25:1, indicating that Western diets are deficient in ω-3 fatty acids. This is extremely significant especially when modern diets are compared with the diets of which humans have evolved on, and of which their genetic patterns have been based on.[1]

EVOLUTIONARY ASPECTS OF Ω-3 FATTY ACIDS IN THE FOOD SUPPLY:

Molecular biology has proven over the last couple of decades that genetic factors determine susceptibility to disease and that environmental factors determine which genetically susceptible individuals will be affected; i.e. **genes + environment = phenotype**. Since the beginning of the Agricultural Revolution, over 10,000 years ago, major dietary changes have occurred while at the same time, our genes have remained unchanged. In fact, our genes today are very similar to the genes of our ancestors during the Paleolithic period 40,000 years ago. Today, humans are subjected to a nutritional environment that differs significantly from that for which our genetic constitution was selected. Over the last 100 years, the consequences of a rapidly changing diet are proving to be very costly, particularly as a potent promoter of chronic diseases such as atherosclerosis, essential hypertension, obesity, diabetes and many cancers.[2]

Pre-agricultural humans ate an enormous variety of wild plants, lean meat, fish, green leafy vegetables, fruits, nuts, berries and honey. According to Simopoulos, a leading expert in essential fatty acid metabolism, they consumed fewer calories and drank many times more the amount of water than modern, westernized man does. Most of our food is calorically concentrated in comparison with wild game and the uncultivated fruits and vegetables of the Paleolithic diet. Today, however, 17% of the plant species provide 90% of the world's food supply, with cereal grains comprising the greatest percentage. Wheat, corn and rice account for 75% of the world's grain production. What is important to realize is that for the 99.9% of human existence, since the emergence of homoerectus 1.7 million years ago, humans rarely or never consumed cereal grains. Furthermore, we have had very little time to adapt to a food type which now represents humanity's major source of both calories and protein. Cereal grains are high in carbohydrates and ω-6 fatty acids, but low in ω-3 fatty acids and in antioxidants, particularly in comparison to green leafy vegetables. Additionally, industrialized societies are characterized by an increase in saturated fat, ω-6 fatty acids and trans-fatty acids, and a decrease in ω-3 fatty acid intake. Trans-fatty acids are detrimental to health because they increase LDL, lipoprotein A, platelet aggregation, and decrease HDL. Trans-fatty acids also decrease or inhibit incorporation of other fatty acids into cell membranes and inhibit delta-6 desaturase which interferes with the elongation and desaturation of essential fatty acids, thus decreasing the availability of ω-3 fatty acids for human metabolism.[2]

After World War I the modern vegetable oil industry began large-scale production of vegetable oil, where hydrogenation was applied to oils in order to solidify them and increase the shelf-life. This reduced the ω-3 α-linolenic acid (ALA) content of the oil while leaving a high concentration of ω-6 linoleic acid (LA). The process of hydrogenation also creates oils that are high in trans-fatty acids.[2] Due to recommendations by health professionals, "heart-healthy" concerned Americans were urged to reduced their use of saturated fatty acids and replace them with the vegetable oils of safflower, corn and soybean oils for frying and baking uses. These oils contain very high amounts of LA and are very low in ω-3 fatty acids.[10]

Agribusiness further contributed to the decrease in ω-3 fatty acids. Wild animals contain about five times more PUFAs per gram than is found in domestic livestock. Most importantly, 4% of the fat of wild animals consists of the ω-3 EPA. Domestic livestock are fed grains rich in ω-6 fatty acids and poor in ω-3 fatty acids and thus contain nearly undetectable levels of ALA in their meat. Similarly, green leafy vegetables, eggs and even fish contain less ω-3 fatty acids than those in wild food due to the agriculture industry's emphasis on production. For example, the wild plant purselane has eight times more ALA than cultivated plants. Eggs from free-range chickens have a ω-6/ω-3 ratio of 1.3 whereas the standard USDA egg has a ratio of 19.9. Farm raised fish contain less ω-3 fatty acids than do fish grown naturally in the oceans, rivers and lakes. Milk and cheese from animals that graze contain EPA and DHA, while milk and cheese from grain-fed animals do not.[2,5]

THE IMPORTANCE OF EQUAL Ω-6/Ω-3 ESSENTIAL FATTY ACID RATIOS:

Currently, the ratio of ω-6 to ω-3 fatty acids is about 20-25:1 in Western societies. It has been calculated that thousands of years ago before agriculture, and when societies were hunters and gatherers and people consumed a primarily vegetarian diet, this ratio was approximately equal. Reports have ranged from a ratio of 5:1 to as low as 1:1.[7,1] In many industrialized nations, large increases in the intake of ω-6 fatty acids have occurred in the last 30 years. For example, in the UK, the PUFA to SFA ratio doubled between 1972 and 1988 and consisted primarily of ω-6 fatty acids. The intake of ω-6 PUFA rose from 4% of the dietary energy in the early 1970s to 6% at present.[9]

One other major nutritional factor disrupting normal lipid metabolism, is the failure of the gastrointestinal tract to absorb essential fatty acids (EFA) from the diet. Many people who have fat malabsorption problems, i.e. Crohn's disease, Celiac disease, pancreatic insufficiency, etc. will have difficulty absorbing the necessary EFA and will likely show an imbalance in proportions. In addition, Δ-6 desaturase activity in the liver has been shown to be vulnerable to a variety of factors, such as fatty liver, toxic burden and especially ethanol consumption. Similarly, diabetes mellitus, high alcohol ingestion, catecholamines released during stress, and diets rich in simple sugars, TFA, or SFA have been shown to impair conversion of dietary LA to DGLA and AA.[8]

The balance of EFA is crucial for good health and normal development. It has been suggested that the upsurge of inflammatory conditions, such as asthma, eczema, Crohn's disease, coronary heart disease, etc., are related to these increases in ω-6 PUFA intake.[9] Ethno-epidemiological studies of the Inuit in Greenland and in the Japanese, populations who are both exposed to a diet rich in fish oil, further elucidated the importance of PUFA in the prevention of inflammation. These later studies correlated the presence of high dietary intake of ω-3 fatty acids from fish oil, with lower incidence and prevalence of inflammatory conditions than in cultures with deficiencies in these PUFA. Additional investigations have confirmed the initial observations: when diets are supplemented with ω-3 fatty acids, the latter partially replace the ω-6 fatty acids in the membranes of practically all cells in the body. Thus PUFA composition of cell membranes is to a great extent dependent on dietary intake and therefore has a strong influence on eicosanoid metabolism and the resultant inflammatory cascade. [2,5]

THE ROLE OF ESSENTIAL FATTY ACIDS IN HEALTH AND DISEASE:

Eicosanoids are 20 carbon chain fatty acids derived from PUFA esterified to membrane phospholipids found in cell membranes. They include the prostaglandins (PG), thromboxanes, and leukotrienes. *Eicosanoids are the most potent regulators of cellular function in nature and are produced by almost every cell in the body*. They act as local hormones by affecting the cells that produce them or neighboring cells of a different type. Eicosanoids have many actions in the body, but are particularly involved in the inflammatory response.[6]

This inflammatory response is the sum of the body's efforts to destroy invading organisms and to repair damage.

Eicosanoids also regulate smooth muscle contraction, increase water and sodium excretion by the kidney, regulate bronchoconstriction and bronchodilation and are involved in regulating blood pressure. Eicosanoids often act like modulators in their actions on the body; some stimulate while others inhibit the same process. In addition, the actions of a given PG seem to vary in different tissue. Many eicosanoids have very short half-lives, in the range of a few minutes or less and they are rapidly inactivated and excreted.[6] There are 3 types of eicosanoids, referred to as series, which are determined by the number of unsaturated bonds present in the linear portion of the hydrocarbon chain. Prostaglandins (PG) are fatty acids containing 20 carbon atoms and are synthesized via the cyclooxygenase enzymes. Thromboxanes (TX) are also derived from the cyclooxygenase pathway and closely resemble PG in structure except that they contain a 6-membrane ring that includes an oxygen atom. Leukotrienes (LT) are sometimes considered the 4th series of eicosanoids. They are synthesized along the lipoxygenase pathway.

PGE_1 has been shown to have many effects; in general these include keeping blood pressure regulated, modulating the secretion of the protective substances of the stomach, influencing mood and emotion and reducing inflammation.[7]

PGE_2 has a major role in the generation of the body's inflammatory response, a necessary and vital component of immune function. Some of its actions include increasing platelet aggregation, increasing temperature and pain, increasing blood vessel permeability and contracting the smooth muscle in blood vessels.[7] The 2-series prostaglandins (PGI_2, PGE_2 and PGD_2) have been shown to increase vasodilation and cAMP, and decrease the following: platelet aggregation, leukocyte aggregation, cytokine IL-2 formation and release, T-cell proliferation and lymphocyte migration. PGF_2 is known to increase vasoconstriction, bronchoconstriction and smooth muscle contraction. TXA_2 and PGI_2 have important antagonistic biological effects on vasomotor and smooth muscle tone and on platelet aggregation. PGI_2 inhibits platelet aggregation and causes vasodilation while

TXA_2 stimulates platelet aggregation and causes vasoconstriction.[6]

PGE_3 is responsible for decreasing the inflammatory response, regulates blood pressure, decreases platelet adhesiveness and serum triglycerides and improves the integrity of cell membranes. PGE_3 is a metabolite of the ω-3 fatty acids EPA and DHA. [7]

Diets high in omega-6 fatty acids have been shown to form larger quantities of inflammatory eicosanoid products than those formed by ω-3 fatty acids, especially EPA. A diet rich in omga-6 fatty acids shifts the physiological state to one that is pro-inflammatory, proaggregatory and prothrombotic. Some of the effects of ω-3 PUFA are brought about by modulation of the amount and types of eicosanoids made, and other effects are elicited by eicosanoid independent mechanisms, including actions upon intracellular signaling pathways, transcription factor activity and gene expression.[2,3]

EPA completes with AA for prostaglandin and leukotriene synthesis at the cyclooxygenase and lipoxygenase enzyme level. Studies on the human ingestion of ω-3 PUFA, especially in the form of EPA and DHA from fish oil, have shown the following important effects on prostaglandin metabolism:

1. decreased production of PGE_2 and its metabolites;
2. a decrease in leukotriene B_4 (LTB_4) formation, a powerful inducer of; inflammation and leukocyte chemotaxis and adherence;
3. an increase in leukotriene B_5 (LTB_5), a weak inducer of inflammation and a weak chemotactic agent;
4. a decrease in $TXA_{2,}$ which stimulates platelet aggregation and causes vasoconstriction.;
5. and an increase in TXA_3, a weak platelet aggregator and vasoconstrictor.[4]

The communication between immune and inflammatory cells are mediated by cytokines. TNF-α and IL-1 and IL-6 are three of the most important cytokines produced by monocytes and macrophages involved in the inflammatory process. Their production in appropriate amounts is a beneficial response to insult, however inappropriate amounts, or overproduction, are implicated in the pathological responses seen in inflammatory conditions. Furthermore, psychological stress in humans induces the production of these and other pro-inflammatory cytokines (IFNγ, IL-10). An increased intake of ω-6 relative or true to the amounts of ω-3 fatty acids cause a similar overproduction of pro-inflammatory cytokines (TXA_2, LTB_4, IL-1β, IL-6, TNF, and C-reactive protein). Extensive clinical and in vitro studies have demonstrated the suppression of these cytokines by the administration of ω-3 fatty acids and the restoration of the ω-6 to ω-3 ratio.

For example, Caughey et al. demonstrated that a diet enriched with flaxseed oil can inhibit the ex vivo production of IL-1 and TNF-α by 30% in four weeks. Adding nine grams of fish oil for an additional 4 weeks inhibited IL-1β by 80% and TNF-α by 74%. Interestingly, flaxseeds increased EPA but not DHA levels in monocytes. Coronary heart disease, major depression, aging and cancer are characterized by an increased level of IL-1. Similarly, arthritis, Chrohn's disease, ulcerative colitis, and SLE are characterized by high levels of IL-1 and LTB_4 which is produced by ω-6 fatty acids.[4] ω-3 PUFA have also been shown to suppress cellular and tissue hyperplasia and angiogenesis, thus explaining its effectiveness in treating hyperproliferative skin diseases and usefulness in cancer treatment.[4]

The well known Lyon Heart Study was a dietary intervention study which provided a diet with a 4/1 ratio of LA to ALA. It was achieved by substituting olive oil and canola oil for corn oil. Since olive oil is low in LA (8%) and corn oil is high (61%) in LA, the ALA incorporation into cell phospholipids was increased in the experimental group. The ratio of 4/1 LA to ALA led to a 70% decrease in total mortality at the end of the second year of this study, thus demonstrating how an imbalanced ratio of PUFA has a direct consequence on health.[2] Depending on the disease, the optimal ratio of ω-6/ω-3 varies from 1/1 to 4/1.[2] To ensure a more balanced ratio, research has shown that it is very important to decrease the amount of ω-6 intake while supplementing ω-3 fatty acids, which will ultimately result in more effective prevention and treatment of chronic diseases.

In the future, as the impact of this imbalanced ratio of PUFA on pathophysiology further elucidate, and as new biochemical mechanisms of gene expression, eicosanoid metabolism and cytokine production illuminate, one truth will remain: an equal balance of ω-6 and ω-3 fatty acids is essential for a healthy physiologic state of existence.

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