Dietary Influence on Inflammatory Processes: A Literature Review

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Abstract

Objective – This article provides an overview of the scientific literature available on the subject of dietary influence on inflammatory processes. The degenerative manifestation of chronic inflammation and the factors that perpetuate this process will also be examined. The purpose of this review article is to demonstrate the etiological similarities between the most common chronic diseases and to propose basic nutritional guidelines to help manage these conditions.

Methods – Searches of the keywords listed below in the databases PubMed and EBSCO Host retrieved articles from indexed journals, literature reviews, cohort studies, meta-analyses, and randomized controlled trials.

Conclusion – Current research trends indicate a consistent underlying biochemical etiology for nearly all inflammatory processes. The typical Western diet has numerous adverse biochemical effects, all of which create an inflammatory state and predispose the body to chronic degenerative conditions. Evidence supports that an inadequate intake of fruits and vegetables can result in suboptimal intake of antioxidants and phytochemicals. Research also suggests that an imbalanced intake of essential fatty acids, as well as a deficiency in vitamin D can delay the healing process. Although specific disease entities may require specific medical treatments, nutritional management must also be considered to address the underlying inflammatory etiology.

Keywords – Chronic Inflammation; Chronic Disease; Plant Based Diet; Eicosanoids; NF-kB; Paleolithic Diet; Mediterranean Diet; Vitamin D; Omega-3; Western Diet

Introduction

The concept of the four cardinal signs of inflammation comes from antiquity as rubor et tumor cum calore et dolore, (redness and swelling with heat and pain).[1] It was Rudolf Virchow at the beginning of the 19th century who critically analyzed the meaning of the four key symptoms of inflammation (redness, swelling, heat, and pain) and postulated that inflammation cannot be represented as a single process, but rather constitutes various inflammatory processes. In addition he introduced functio laesa, denoting the restricted function of inflamed tissues. In the pathogenesis of inflammation, Virchow highlighted the importance of the inflammatory stimulus.[2]

Many types of stimuli can cause tissue inflammation including trauma, infection, ischemia, toxemia, or autoimmune injury. The process normally leads to recovery from infirmity and to healing. However, if targeted destruction and assisted repair are not properly phased, inflammation can lead to persistent tissue damage by leukocytes, lymphocytes, or collagen.[3] Inflammation participates in the restoration of normal tissue function, but it also contributes to the pathophysiology of many chronic diseases. A coordinated series of common effector mechanisms of inflammation contribute to tissue injury, oxidative stress, remodeling of the extracellular matrix, angiogenesis, and fibrosis in diverse target tissues.[4] In this situation, uncontrolled inflammation should be viewed as a disease process. Many diseases are, in fact, a manifestation of chronic inflammation. For example, chronic diseases, such as coronary heart disease and diabetes, may develop because of unchecked inflammatory occurring over decades.[5] The paradigm shift in rheumatoid arthritis therapy has changed from controlling symptoms to controlling the disease process with the abrogation of inflammation.[6] Mounting evidence shows

that inflammation plays a critical role in causing Alzheimer's disease.[7] A host of diseases such as asthma, respiratory distress syndrome, sarcoidosis, glomerularnephritis, psoriasis, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, and atherosclerosis have all been classified as inflammatory diseases.[8]

Chronic inflammation has been viewed as a disease for many years. Seaman[9] recognized that in the first edition of *Pathologic Basis of Disease*, published in 1974, Robbins clearly stated that numerous degenerative diseases are inflammatory in nature, such as gastritis, Crohn's disease, diverticulitis, ulcerative colitis, appendicitis, heart disease, cancer, cirrhosis, diabetes mellitus, and vascular disease. It is inappropriate to view inflammation as merely a component of the healing process, but rather as a key promoter of chronic diseases. Seven of the ten leading causes of death in America, from preliminary data in 2010, have been previously described as inflammatory in nature. These are, in leading order, heart disease, cancer, chronic lower respiratory diseases, stroke, Alzheimer's, diabetes, and nephritis.[10]

Prasad[11] suggests a link between lifestyle factors and degenerative disease and most chronic diseases such as cancer, cardiovascular disease, Alzheimer's disease, Parkinson's disease, arthritis, diabetes, and obesity are becoming leading causes of disability and death all over the world. Some of the most common causes of age associated chronic diseases are lack of physical activity, poor nutrition, tobacco use, and excessive alcohol consumption.[11] All the risk factors linked to these chronic diseases have been shown to upregulate inflammation. Therefore, down regulation of inflammation associated risk factors could prevent or delay these age associated diseases. Although modern science has developed several drugs for treating chronic diseases, most of these drugs are enormously expensive and are associated with serious side effects and morbidity.[11]

In this review, it is discussed how chronic inflammation leads to chronic disease, and how dietary and lifestyle factors precipitate this chronic inflammatory state. This paper outlines some of the most plaguing chronic conditions in the Western world and proposes a dietary strategy in dealing with them. An asserted effort will focus on fruits, vegetables, essential fatty acids, vitamin D, and the anti-inflammatory nature of the Paleolithic and Mediterranean diets.

Discussion

Underlying Inflammatory Mediators

It is likely that inflammatory mediators work in concert to create the inflammatory drive associated with chronic disease. Numerous mediators are known to perpetuate the inflammatory process including interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), and eicosanoids, such as prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and thromboxane A2 (TXA2).[9] Many inflammatory diseases are also associated with the improper activation of nuclear factor kappa B.[12] Combinations of these inflammatory mediators have been linked with several chronic pathologies such as cardiovascular, diabetes, rheumatoid arthritis, Alzheimer's, lung, autoimmune diseases, and cancer. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have been the cornerstone of treatment for these conditions because of their ability to inhibit eicosanoid production.[13]

Many of the same biochemical mediators that promote inflammation are also involved in the pathogenesis of heart disease, a condition associated with uncontrolled inflammation of the arteries. Gui[14] explained that cardiovascular disease is mainly caused by atherosclerosis, a chronic inflammatory disease, characterized by progressive arterial wall plaque formation

together with infiltration of immunocytes. The degree of influx of inflammatory cells to atherosclerotic lesions is determined by an intricate molecular network of innate signaling. TNF, for example, plays a pivotal role in orchestrating the production of a proinflammatory cytokine cascade. This cascade includes serotonin, TXA2, PGE2, IL-1, and several growth factors. TNF is thus considered to be a "master regulator" of proinflammatory cytokine production and possesses key proatherogenic properties.[14] IL-1, like TNF, contributes to slowly progressing inflammatory processes that take place in atherosclerosis. Clearly, a common inflammatory drive involving similar mediators promotes various chronic conditions including heart disease. Thus, it is not surprising that common oral antiplatelet agents such as aspirin are routinely recommended to reduce the risk of myocardial infarction and stroke. Aspirin's main mechanism of action lies in its ability to inhibit cyclo-oxygenase, therefore, reducing the production of the platelet activator TXA2.[15]

Accumulating evidence shows that chronic inflammation is also associated with an increased risk of cancer. "Smoldering inflammation" is a component of the tumor microenvironment and is a recognized hallmark of cancer.[16] Mantovani[17] presented evidence which links inflammation to cancer in a number of ways. The most relevant connection was that NSAIDs reduce the risk of developing certain cancers and reduce the mortality caused by these cancers. Presumably, this is achieved as a result of their inhibitory effect on eicosanoid synthesis (Fig 1). Another important link identified that the inflammatory cells chemokines, and cytokines are present in the microenvironment of all tumors from the earliest stages of development. Lastly, Montovani[17] indicated that the targeting of inflammatory mediators (chemokines and cytokines, such as TNF and IL-1), key transcription factors involved in inflammation (such as NF-kB), or inflammatory cells decreases the incidence and spread of cancer. Although the initial

cause of cancer is still not understood, chemotherapeutic modulation of inflammatory processes lie at the heart of cancer treatment.

Inflammatory processes have a fundamental role in the most common neurodegenerative disorder to date, Alzheimer's disease (AD). The latest research shows brain inflammation to be a pathological hallmark of AD.[18] The characteristic inflammatory features such as swelling, heat, and pain are not present in the brain, and therefore researchers categorize AD as a chronic inflammatory state instead of an acute process. A characteristic feature of chronic inflamed tissues is the presence of an increased number of monocytes, as well as monocyte-derived tissue macrophages, know as microglia cells in the central nervous system. An important factor in the onset of AD inflammatory processes is the overexpression of IL-1. IL-1 produces many reactions that ultimately cause dysfunction and neuronal death. Other important cytokines in neuroinflammation are IL-6 and TNF.[18] Furthermore, it has been observed in epidemiological studies that treatment with NSAID's decreases the risk for developing AD.[19] This suggests that proinflammatory eicosanoids such as PGE2 may play a causative role in the pathogenesis of AD. In fact, rheumatoid and degenerative arthritis patients exposed to long term anti-inflammatory drug treatment have an inverse relationship in the incidence of AD.[19] Although a beneficial role of NSAID therapy for AD is understood to exist, a method of clinical application for treatment and prevention has yet to be determined.

Type 2 diabetes mellitus is fast emerging as one of the world's leading health concerns. It is estimated almost six percent of the world's adult population now live with diabetes and this number is expected to rise to 366 million in less than 30 years.[20] The proinflammatory etiology of diabetes is profound. Islets of patients with type 2 diabetes have the feature of an inflammatory process reflected by the presence of cytokines, immune cells, beta-cell apoptosis,

amyloid deposits, and fibrosis.[21] Beta-cells from patients with type 2 diabetes display inflammatory markers including increased interleukin IL-1 expression. Grimble[22] indicated a strong association between indices of inflammation, abnormal lipid and carbohydrate metabolism, obesity, and atherosclerosis, and that TNF may provide the very link between inflammation and insulin sensitivity. Recent studies on diseases which involve insulin insensitivity such as diabetes, obesity, and atherosclerosis also show increased cytokine production and markers of inflammation. Evidence favors chronic inflammation as a trigger for chronic insulin insensitivity, rather than the reverse situation.[22]

Obesity plays an unfortunate role in type 2 diabetes. Increasing adiposity activates inflammatory responses in fat and liver cells, with associated increases in the production of cytokines and chemokines. Immune cells including monocytes and macrophages are activated, and together these cause local insulin resistance.[23] Proinflammatory and proatherogenic mediators produced in adipose tissue such as in abdominal fat are referred to as adipokines. These adipokines create a systemic inflammatory disposition that promotes insulin resistance in skeletal muscle and other tissues, and atherogenesis in the vasculature (Fig 2).[24]

Although not a leading cause of death in Western society, osteoarthritis (OA) is the most common cause of disability among older adults in the United States, with the prevalence and incidence increasing rapidly.[25] OA is commonly described as a non-inflammatory disease in order to distinguish it from classic "inflammatory arthritides" such as rheumatoid arthritis or seronegative spondyloarthropathies. Despite this distinction, inflammation is increasingly recognized as contributing to the symptoms and progression of OA.[26] Clear evidence shows angiogenesis and inflammation are important processes in the pathophysiology of osteoarthritis (Fig 3). Pain, the major symptom of OA, can be caused or enhanced by inflammation and

angiogenesis. Angiogenesis may also introduce sensory nerves into the aneural cartilage and inflammation can sensitize these new nociceptors present in the joint. Inhibition of inflammation may provide to be an effective therapeutic intervention for the treatment of OA by improving symptoms and retarding joint damage.[26]

Nuclear Factor Kappa B

Nuclear factor kappa B (NF-kB) is an intricate player in inflammatory processes and its therapeutic modulation is a topic of current research. The inappropriate activation of NF-kB has been linked to a wide range on illnesses including cancer, arthritis, autoimmune diseases, and neurologic diseases such as Alzheimer's and Parkinson's.[27] As a ubiquitous transcription factor, NF-kB promotes the activation of genes that encode inflammatory mediators and enzymes. It is sometimes referred to as the major intracellular amplifier which ultimately increases the production of the direct mediators of inflammation such as cytokines, prostaglandins, leukotrienes, and free radicals.[28] NF-kB is highly activated at sites of inflammation in diverse diseases (Table 1) and can induce transcription of the many proinflammatory mediators discussed thus far.

From both nutritional and pharmacological standpoints the safe and effective inhibition of NF-kB is considered a major therapeutic goal for the prevention and treatment of conditions associated with an upregulated inflammatory response. Eicosanoid inhibition and proinflammatory drive reduction are integral components in the treatments of seemingly diverse and unrelated diseases. Essential to the focus of this article is that these different diseases demonstrate a common inflammatory etiology. It is evident that research points to chronic inflammation as a determinant of many of the diseases that afflict the industrialized world. The

most fundamental means for safely and effectively addressing the most common chronic inflammatory conditions is through skillful nutritional intervention. In particular, the importance of the nutritional modulation of fatty acid metabolism will be discussed.

Fatty Acid Imbalances

Fatty acid imbalances may actually form the foundation on which the proinflammatory drive develops. Research demonstrates that an excess of omega-6 fatty acids (linoleic acid and arachidonic acid) and a deficiency of omega-3 fatty acids may be involved in the development of numerous diseases.[29] The omega-6 (n-6) polyunsaturated fatty acid, linoleic acid (LA), is a metabolic precursor for the synthesis of arachidonic acid (ARA), which is found in abundance in plasma membrane phospholipids. Once mobilized from the plasma membrane, ARA acts as a substrate for a number of proinflammatory eicosanoids including prostaglandins and leukotrienes. As discussed earlier, PGE2 has a number of proinflammatory effects including pyrexia, algesia, and inducing IL-6 production from macrophages. LTB4 is a potent chemotactic agent for leukocytes and promotes production of proinflammatory cytokines such as TNF, IL-1, and IL-6.[30]

Omega-3 (n-3) polyunsaturated fatty acids eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) are derived from alpha-linolenic acid (ALA) and formed into membrane lipids. EPA ultimately downregulates the expression of several genes involved in inflammation and decreases the production of TNF, IL-1, and IL-6 through several pathways including the NF-kB signal transduction pathway. In addition, DHA can have potent anti-inflammatory actions that include attenuation of leukocyte entry into sites of inflammation.[30]

The eicosanoids derived from LA and ALA attenuate the inflammatory process through a number of mechanisms (Fig 4).

Research further suggests an increased dietary intake of n-6 fatty acids may contribute to a proinflammatory environment by inhibiting the synthesis and incorporation of n-3 fatty acids.[30] A diet low in n-6 fatty acids with a favorable ratio of n6 to n3 fatty acid balance should promote an environment more tolerable to immunologic challenge. Epidemiological studies of Inuit and Japanese societies have supported this notion. Traditionally in these cultures, the major dietary source of n-3 fatty acids, EPA, and DHA were fish and other marine mammals in combination with a low intake of n-6 fatty acids. There were concurrently low incidences of chronic diseases such as cardiac and inflammatory bowel disease. Notably, these populations' diets are becoming increasingly Westernized and chronic disease rates are rising.[31] Another recent study concluded that reducing dietary saturated fat and replacing it with polyunsaturated fat is the main dietary strategy to prevent cardiovascular diseases and cancers. A moderate intake of plant and marine n-3 fatty acids in the context of the traditional Mediterranean diet, which is low in saturated and n-6 fatty acids, appears to be the best approach to reduce the risk of both cardiovascular diseases and cancers.[29]

Simopoulos[32] reviewed the importance of the n-6 to n-3 fatty acid ratio in various chronic diseases. Research suggests that human beings evolved on a diet with a ratio of n-6 to n-3 fatty acids of approximately one, whereas in Western diets the ratio is anywhere between 15 to 1 and 16.7 to 1. Western diets are deficient in n-3 fatty acids, and have excessive amounts of n-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Simopoulos[32] indicated excessive amounts of n-6 fatty acids and a very high n-6 to n-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases

including cardiovascular disease, cancer, and other inflammatory diseases. The therapeutic effects of n-3 fatty acid supplementation are acknowledged in Table 2. A lower ratio of n-6 to n-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries.[32]

The importance of balancing the n-6 to n-3 ratio was shown in a randomized, controlled, three-diet, three-period crossover study in which 22 hypercholesterolemic subjects were assigned to three experimental diets: a diet high in ALA, a diet high in LA, and an average American diet for six weeks.[33] Serum IL-6, IL-1, and TNF concentrations and the production of IL-6, IL-1, and TNF by peripheral blood mononuclear cells were measured. The ratio of n-6/n-3 was 10/1 in average American Diet, 4.1/1 in the LA diet, and 2/1 in the ALA diet. The results showed that in the ALA diet, IL-6, IL-1, and TNF production were lower than with the LA diet or average American diet. In this study the increased intake of dietary ALA elicited anti-inflammatory effects by inhibiting IL-6, IL-1, and TNF production in cultured peripheral blood mononuclear cells. The cardioprotective effects of ALA are mediated in part by a reduction in the production of inflammatory cytokines, IL-6, IL-1, and TNF.[33]

Although the anti-inflammatory benefits of n-3 fatty acids have been well documented, people who live in Western society likely consume a diet high in linoleic acid. There are two main ways in which humans increase tissue concentrations of arachidonic acid. First is the consumption of LA rich foods such as grain, corn, and vegetable oil.[35] Second is the consumption of ARA containing animal products such as beef, chicken, and eggs. Cordain[34] suggested the current practice of feeding linoleic acid containing grain to cattle not only increases the total amount of atherogenic saturated fats in the meat, but it also substantially reduces the concentrations of n-3 polyunsaturated fatty acids, while simultaneously increasing

the concentrations n-6 polyunsaturated fatty acids. Consequently, feed-lot produced beef does not contain an optimal fatty acid profile that would help to reduce the incidence of several chronic diseases.[34] In contrast, Westernized humans consume minimal amounts of foods that are rich in ALA, EPA, and DHA, such as green leafy vegetables, fish, and wild game. The outcome of this eating pattern is an excessive production of proinflammatory eicosanoids, essentially perpetuating the inflammatory drive seen in many chronic conditions.[35]

At present, the practice of n-3 supplementation remains a less than exact science as supplementation guidelines are nonexistent. The main goal of n-3 supplementation is to shift the balance of n-6 to n-3 ratios; keeping in mind the precise dosage will inevitably be dependent upon individual lifestyle factors. Since it has been shown that high n-6 diets are proinflammatory in nature, it is quite conceivable that a person who reduces the consumption of n-6 rich foods and ingests more n-3 rich foods may need less supplementation when compared to someone who predominates with n-6 rich foods. Meanwhile, studies with patients who have rheumatoid arthritis have provided some idea about supplementation levels. Kremer[36] studied the effects of n-3 supplementation on rheumatoid arthritis patients and found the number of tender joints on physical examination and the amount of morning stiffness is consistently reduced in patients who take n-3 supplements. It appears that a minimum daily dose of three grams of EPA and DHA is necessary to derived expected benefits. Fortunately, there are virtually no repots of toxicity in the dose range used for rheumatoid arthritis, and the oil is generally well tolerated.[36] On the basis of the available literature, Seaman[9] suggested supplementing the diet with one to three grams of n-3 fatty acids per day as both a therapeutic and preventive measure.

The Vitamin D Dilemma

Vitamin D insufficiency affects almost 50% of the population worldwide. An estimated one billion people, across all ethnicities and age groups, have a vitamin D deficiency.[37] This pandemic of hypovitaminosis D can mainly be attributed to lifestyle and environmental factors that reduce exposure to sunlight. The high prevalence of vitamin D insufficiency is a particularly important public health issue because hypovitaminosis D is an independent risk factor for total mortality in the general population.[38] Emerging research supports the possible role of vitamin D against cancer, heart disease, osteoarthritis, osteoporosis, autoimmune diseases, hypertension, type 1 and type 2 diabetes, depression, and multiple sclerosis.[39]

Vitamin D has potent anti-inflammatory benefits as indicated by its modulation of NF-kB, and suppression of systemic biomarkers of inflammation. Recent research investigated the link between vitamin D deficiency and inflammatory markers in type 2 diabetic patients with cardiovascular disease. A 12 week randomized controlled clinical trial demonstrated the therapeutic effects of vitamin D supplementation on several systemic inflammatory biomarkers such as high sensitivity C-reactive protein (hsCRP), IL-6, and TNF. Improvement of vitamin D status resulted in amelioration of these systemic inflammatory markers.[40] Research has also revealed that the binding of the active form of vitamin D yields a transcription factor which represses NF-kB activation, and additionally downregulates adaptive inflammation on multiple levels.[41] Notably, this counterbalance against inflammation works only when stores of vitamin D are abundant. Therefore is has been postulated by Hoeck and Pall[41] that a connection exists between lowered vitamin D metabolism, persistent NF-kB activation, and chronic inflammation.

Insufficient endogenous production due to lack of sun exposure necessitates oral supplementation of vitamin D3 to meet physiologic needs. If these physiologic needs are not met, a plethora of health conditions can ensue including conditions characterized by chronic proinflammatory states. In a review of the literature by Vasquez[39], oral supplementation in the range of 1,000 IU/day for infants, 2,000 IU/day for children, and 4,000 IU/day for adults is safe and reasonable to promote health and reduce the risk of numerous inflammatory diseases. Notably, vitamin D supplementation should be administered in its D3 form. The optimal serological range proposed by Vasquez[39] is 40-65ng/mL. Zitterman[42] concluded that serum vitamin D concentrations up to 100ng/mL are subtoxic. Safety and effectiveness can be assured by periodic monitoring of serum vitamin D and serum calcium levels.

The Anti-inflammatory Nature of Fruits and Vegetables

Fruit and vegetable consumption in Western civilizations including the United States are remote compared to recommended levels. Cordain[35] provided a more vivid picture of the Western population's modern dietary sources of calories. Dairy products make up 10.6%, refined grains make up 23.9%, refined sugars make up 18.6%, refined vegetable oils make up 17.6%, alcohol makes up 1.2%, added salt makes up 9.6%, and obese meats make up 15-20%.[35] This leaves less than 10% of modern dietary sources of calories attributable to fruits and vegetables. Such dietary habits can have catastrophic ramifications because evidence from prospective cohort studies indicates that a high consumption of plant-based foods such as fruits and vegetables are associated with a significantly lower risk of coronary artery disease and stroke, both of which have been identified as proinflammatory conditions.[43] The same diet that helps to prevent these inflammatory diseases can also be used to effectively reduce inflammation

and pain in patients with rheumatoid arthritis. Adam et al[45] compared the effects of a vegetarian-based diet versus a Western diet both with and without fatty acid supplementation in rheumatoid arthritis patients. The anti-inflammatory, vegetable-based diet was subject to a dietary intake of less than 90mg/day of arachidonic acid. The results showed a decrease of 14% in the numbers of tender and swollen joints in the vegetarian-based diet alone when compared to Western diet alone. This number improved to a 28% decrease when fatty acid supplementation was administered. This study concluded that a diet low in arachidonic acid ameliorates signs of inflammation in patients with rheumatoid arthritis and augments the beneficial effect of fish oil supplementation. Furthermore, Adam et al[45] suggested that the improvements seen in the patients on low ARA diets were the result of a shift in fatty acid consumption and was associated with eating more plant-based foods, which consequently resulted in the production of less inflammatory prostaglandins and leukotrienes.

A diet rich in fruits and vegetables tends to be anti-inflammatory, while a diet deficient in these foods is proinflammatory. Boeing et al[45] performed a recent comprehensive and critical analysis of the literature on the associations between the intake of vegetables and fruit and the risk of several chronic diseases. Results demonstrated that for hypertension, heart disease, and stroke, there is convincing evidence that increasing the consumption of vegetables and fruits reduces the risk of disease. There was probable evidence that the risk of cancer is inversely associated with the consumption of vegetables and fruit. In addition, there was possible evidence that an increased consumption of vegetables and fruits may prevent weight gain, the most important risk factor for type 2 diabetes mellitus. There was also possible evidence that increasing the consumption of vegetables and fruits lowers the risk of certain eye diseases, dementia, and the risk of osteoporosis. Likewise, current data on asthma, chronic obstructive

pulmonary disease, and rheumatoid arthritis indicated an increase in vegetable and fruit consumption may contribute to the prevention of these diseases. Boeing et al[45] concluded, the promotion of vegetable and fruit consumption by nutrition and health policies is a preferable strategy to decrease the burden of several chronic diseases in Western societies.

Research demonstrates children obtain the benefits from plant-based diets as well. One study showed the beneficial effects of fruit and vegetable intake on markers of inflammation are already present by early adolescence and provide support for the Dietary Guidelines for Americans "to consume five or more servings per day" of fruits and vegetables to promote health.[46] As illustrated in Figure 5, behavioral factors such as low fruit and vegetable intake are associated with chronic, low-grade states of inflammation, and therefore with many chronic diseases that are proinflammatory in nature.[47]

In general, it is known that nuts, seeds, whole grains, herbs, spices, fruits, and vegetables, contain a host of health promoting and disease-fighting nutrients, such as vitamins, minerals, antioxidants, essential fatty acids, and numerous phytochemicals. However, what remains hypothesized is what specific factors in each of these foods account for their anti-inflammatory and disease-preventing effects.[48] Two scientifically acclaimed dietary patterns generally considered to have beneficial, anti-inflammatory health effects are the Paleolithic and Mediterranean diets.

The Mediterranean dietary pattern can be identified by high consumption of fruits and vegetables, olive oil as the principal source of fat, low consumption of obese meat and dairy products, and moderate consumption of wine. The Mediterranean dietary pattern is classically associated with significant amelioration of multiple risk factors including modulation of

inflammation.[49] Trichopoulou and Critselis[48] reviewed five cohort studies on the Mediterranean diet and concluded that there appears to exist sufficient evidence that diet does indeed influence longevity. It was also concluded that an optimal diet for the prevention of both coronary heart disease and cancer is likely to extensively overlap with the traditional Mediterranean diet.[48]

Olive oil is considered the pillar of the Mediterranean diet since it improves major risk factors for cardiovascular disease and has several anti-inflammatory effects. Besides the monosaturated fatty acids, other minor components of olive oil such as hydrocarbons, polyphenols, tocopherols, sterols, triterpenoids demonstrate antioxidant, anti-inflammatory, and hypolipidemic properties.[50] Red wine's polyphenols are thought to be cardioprotective and the EPA and DHA in fish provide anti-inflammatory benefits as previously described.[50]

The Mediterranean and Paleolithic diets share common overlap. The Paleolithic diet is based on ancestral human diets of the hunter-gatherer populations throughout the world. The components of this diet when compared to today's modern Western diet includes much lower levels of refined carbohydrates and sodium, much higher levels of fiber and protein, and comparable levels of fat and cholesterol. Notably, the fat type is polyunsaturated with an ideal n-6 to n-3 ratio.[51] Figure 6 demonstrates how this ratio has maladapted over time to promote modern day proinflammatory states. Comparative analysis shows both the Paleolithic and Mediterranean diets' focus on plant- based foods, wild and lean sources of protein, and an abundance of n-3 fatty acids not seen in the Western diet. Paleolithic diets are higher in saturated fat intake than Mediterranean diets, but lower in sodium intake. They are both considered high in fiber, fruits, and vegetables, and low in refined grains and glycemic load.[52]

The Western diet may best be explained by O'Keefe and Cordain[52]. The genetic make-up of human beings has been shaped through millions of years of evolution, and determines nutritional and physical needs. Although the human genome has remained primarily unchanged since the agricultural revolution 10,000 years ago, diet and lifestyle have become progressively more divergent from those of ancestral hunter-gatherers. Accumulating evidence suggests that this mismatch between modern diet and lifestyle, and the Paleolithic genome is playing a substantial role in the ongoing epidemics of obesity, hypertension, diabetes, and atherosclerotic cardiovascular disease. Until 500 generations ago, all humans consumed only wild and unprocessed food foraged and hunted from their environment. These circumstances provided a diet high in lean protein, polyunsaturated n-3 fats, monounsaturated fats, fiber, vitamins, minerals, antioxidants, and other beneficial phytochemicals. Historical and anthropological studies show hunter-gatherers generally to be healthy, fit, and largely free of the degenerative inflammatory diseases common in Western societies.[52]

Conclusion

The inflammatory process is driven by various chemical irritants, in particular prostaglandins, leukotrienes, thromboxanes, and interleukins to name but a few. Without the release of these mediators, the inflammatory process does not occur and healing does not take place. If the release of these mediators does not resolve, inflammation will rage on. The end result of this chronic inflammation is pathological tissue expression and disease.

Both epidemiological studies and intervention trials support the important role of diet in reducing the risk of a variety of chronic diseases, including cardiovascular disease, and overall mortality. Scientific evidence supports that the generation of a proinflammatory drive might be

one mechanism through which unhealthy diets are linked to common disease that cause death and disability in the Western world.[53] Understanding the foundational link between diet and inflammation is the key by which modern society can proactively improve health.

Research clearly supports a consistent underlying biochemical etiology for nearly all inflammatory processes. The typical Western diet has numerous adverse biochemical effects, all of which create an inflammatory state and predispose the body to chronic degenerative conditions. Evidence supports that an inadequate intake of fruits and vegetables can result in suboptimal intake of antioxidants and phytochemicals. Research also suggests that an imbalanced intake of essential fatty acids, as well as a deficiency in vitamin D can delay the healing process. Although specific disease entities may require specific medical treatments, nutritional management must also be considered to address the underlying inflammatory etiology.

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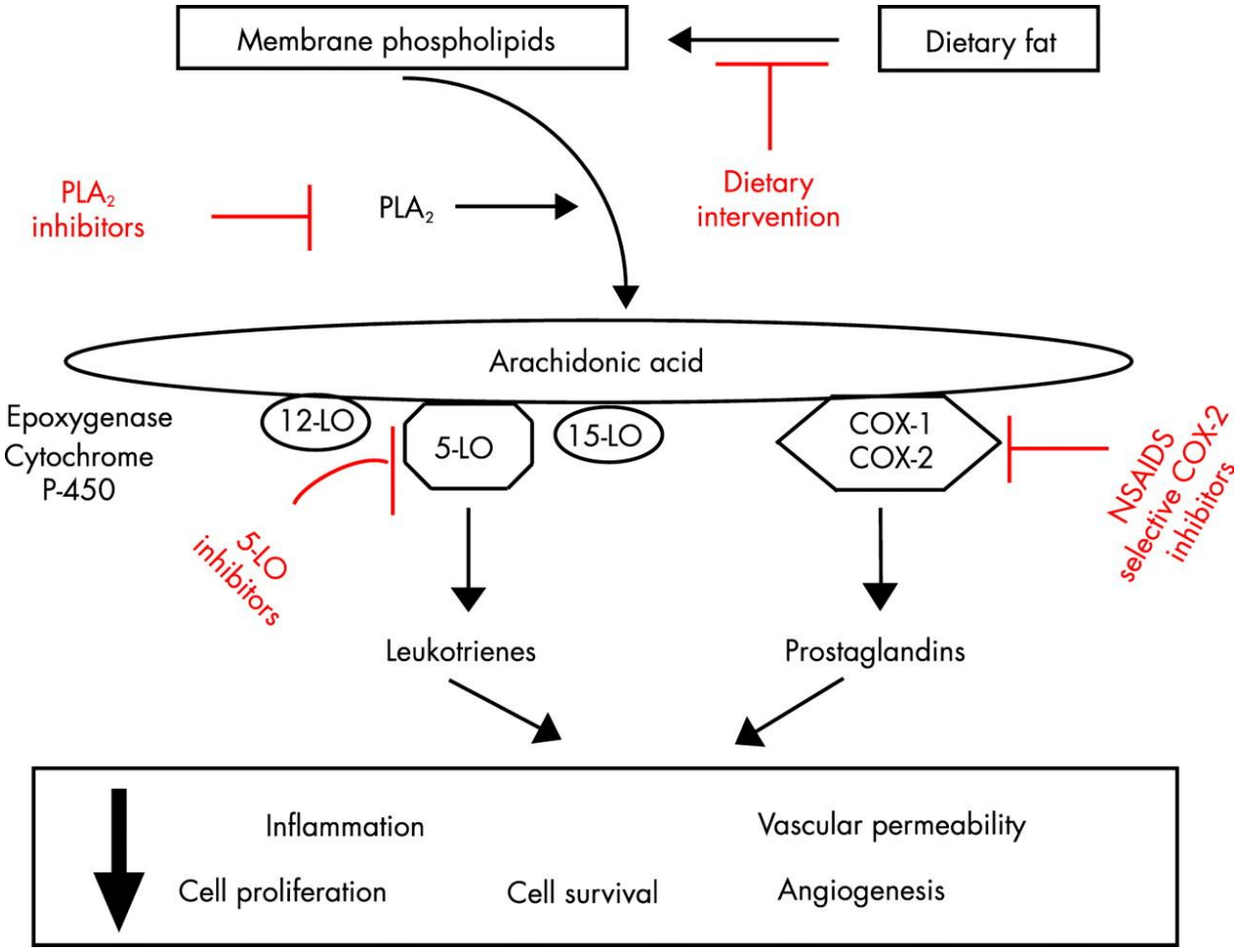
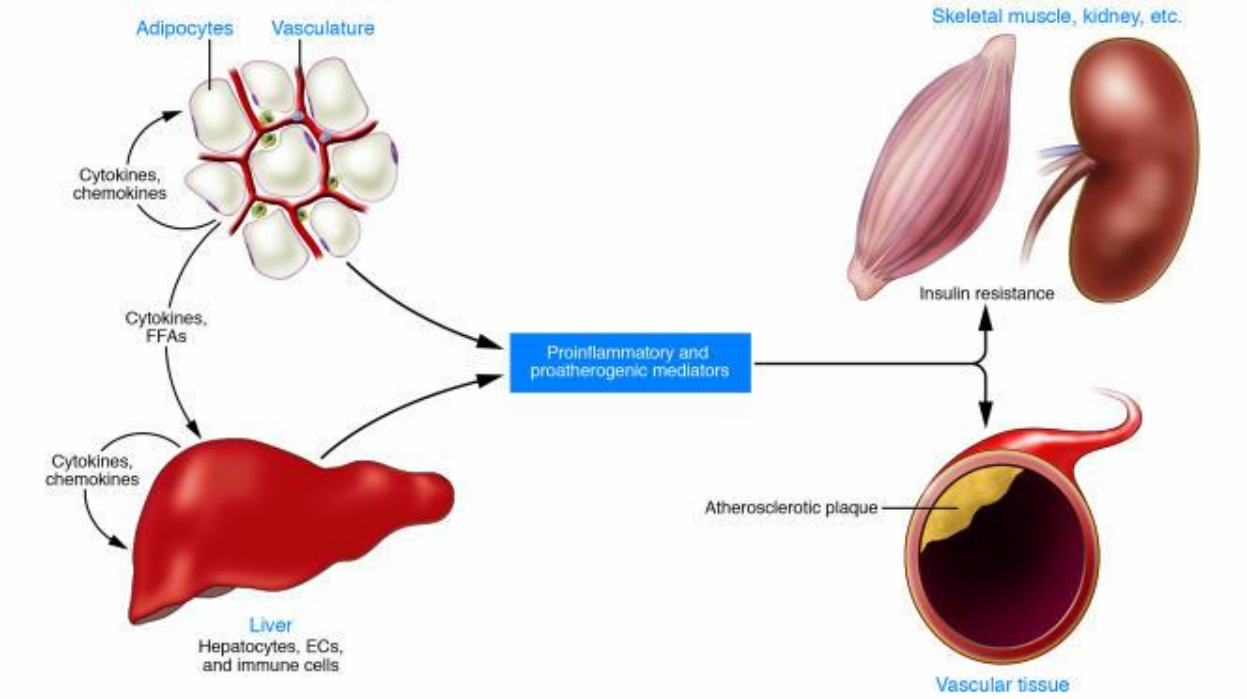
Figure 1



Source:

Nathoo N, Barnett GH, Golubic M. The eicosanoid cascade: possible role in gliomas and meningiomas. J Clin Pathol 2004;57:6-13.

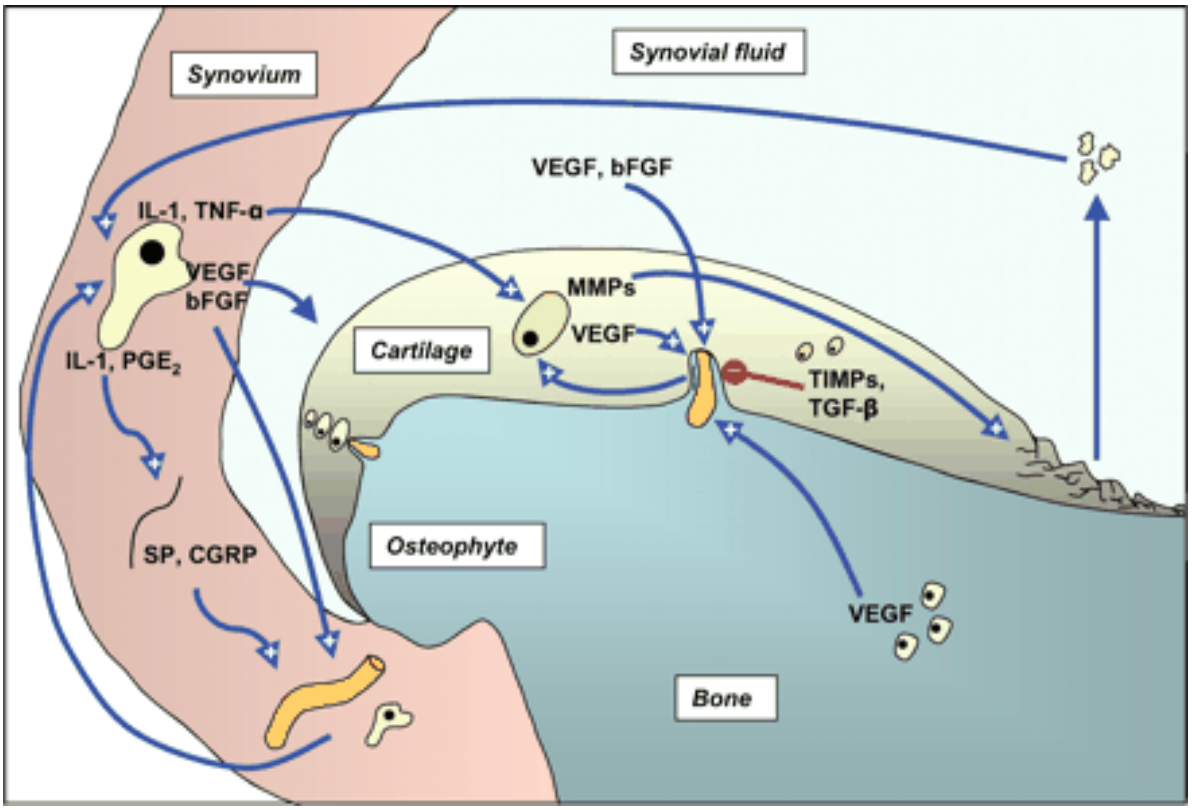
Figure 2



Source:

Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793-801.

Figure 3



Source:

Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. Rheumatology (Oxford) 2005;44:7-16.

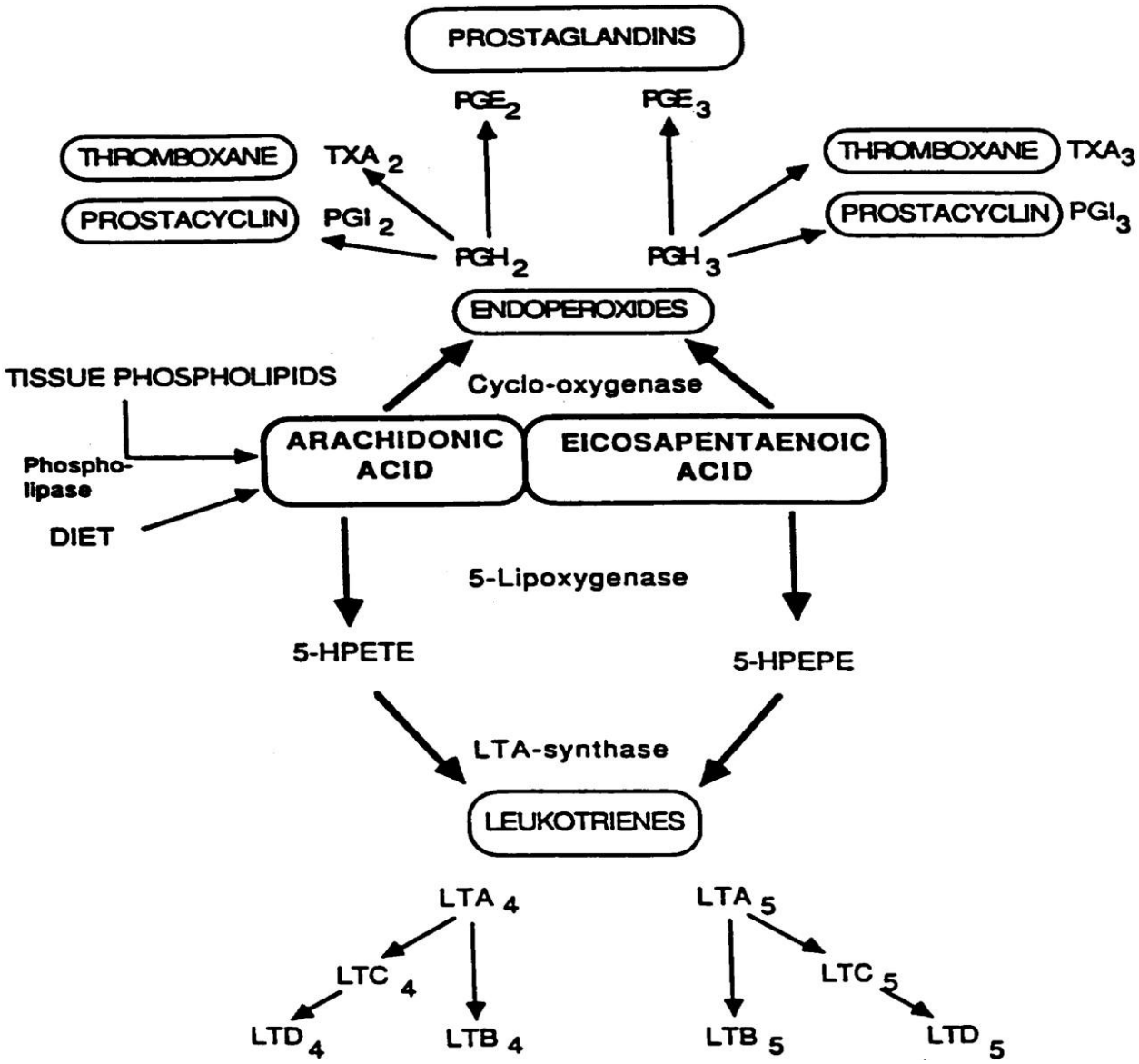
Table 1

NF-κB–activation inflammatory disease
Rheumatoid arthritis
Atherosclerosis
Multiple sclerosis
Chronic inflammatory demyelinating polyradiculoneuritis
Asthma
Inflammatory bowel disease
Helicobacter pylori–associated gastritis
Systemic inflammatory response syndrome

Source:

Tak PP, Firestein GS. NF-kappaB: a key role in inflammatory diseases. J Clin Invest. 2001;107:7-11.

Figure 4



Source:

Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med 2008;233:674-88.

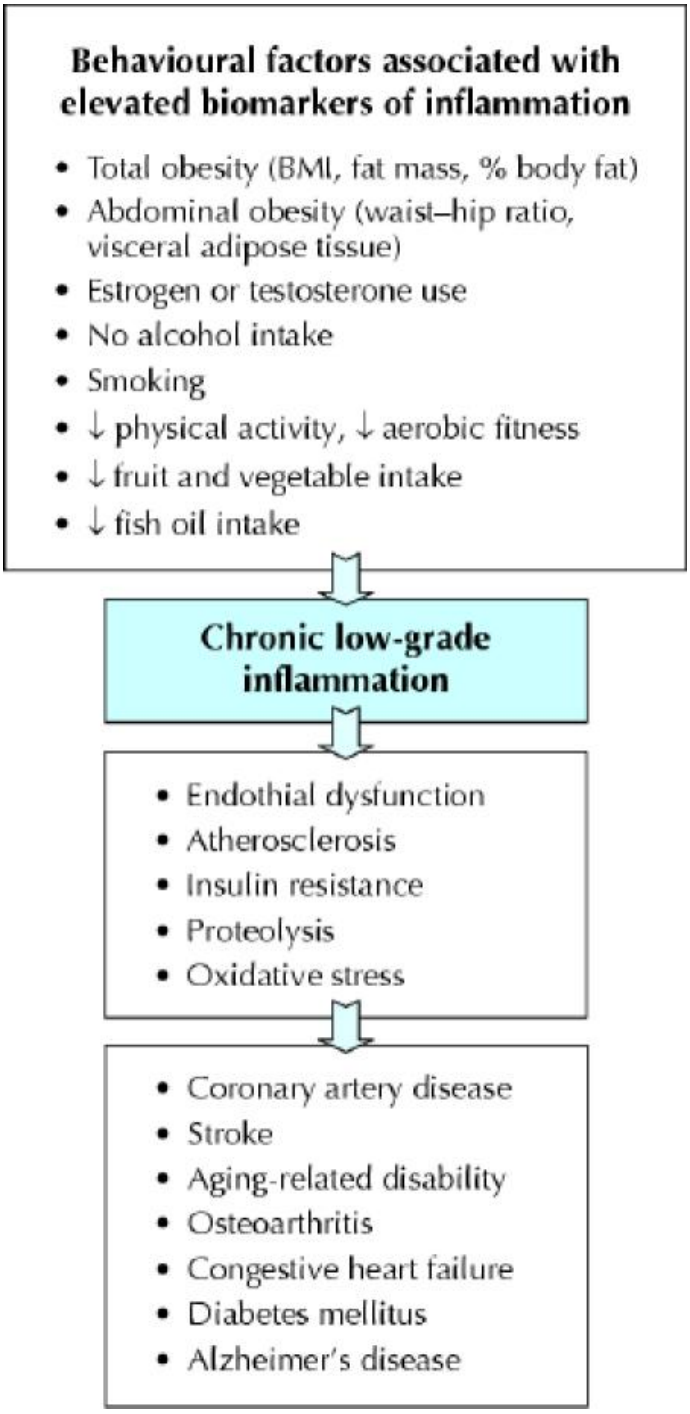
Table 2

Decreased production of prostaglandin E_2 (PGE_2) metabolites
A decrease in thromboxane A_2, a potent platelet aggregator and vasoconstrictor
A decrease in leukotriene B_4 formation, an inducer of inflammation, and a powerful inducer of leukocyte chemotaxis and adherence
An increase in thromboxane A_3, a weak platelet aggregator and weak vasoconstrictor
An increase in prostacyclin PGI_3, leading to an overall increase in total prostacyclin by increasing PGI_3 without a decrease in PGI_2, both PGI_2 and PGI_3 are active vasodilators and inhibitors of platelet aggregation
An increase in leukotriene B_5, a weak inducer of inflammation and a weak chemotactic agent

Source:

Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med 2008;233:674-88.

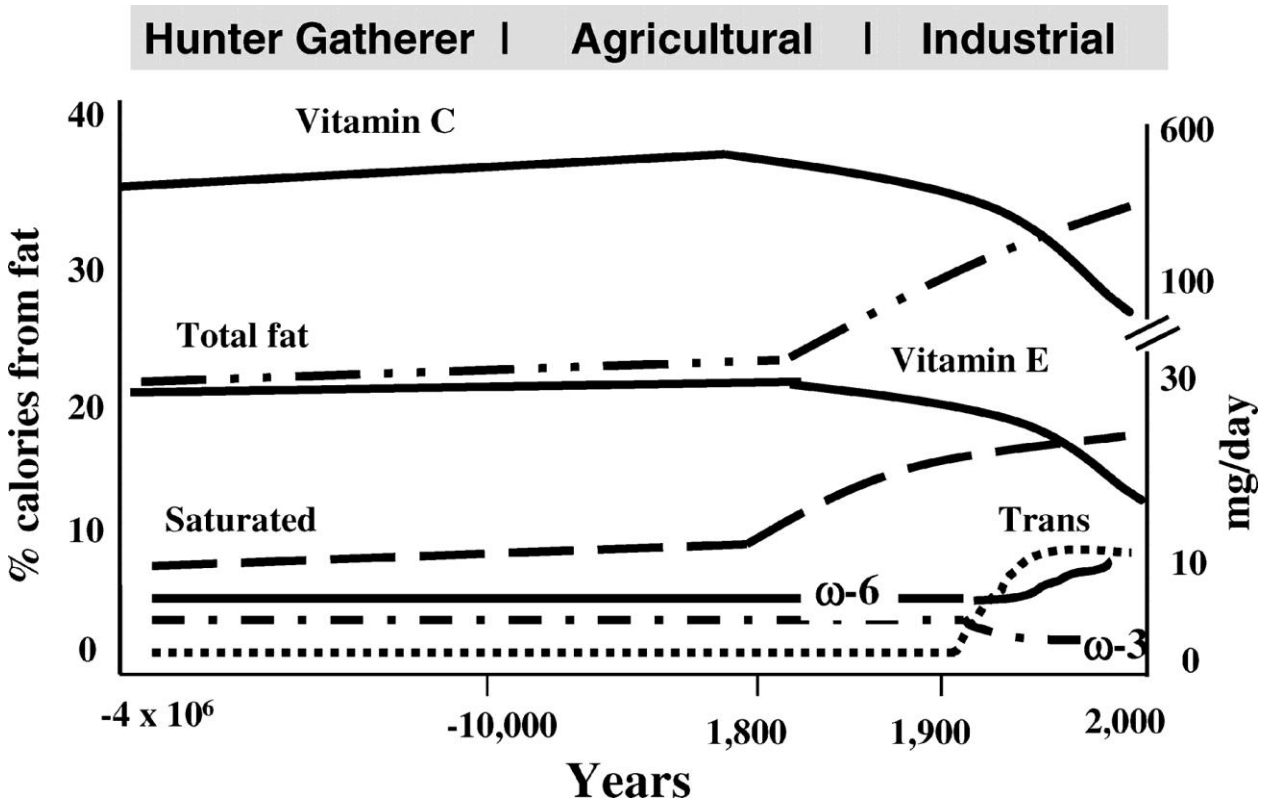
Figure 5



Source:

Nicklas BJ, You T, Pahor M. Behavioral treatments for chronic systemic inflammation: effects of dietary weight loss and exercise training. CMAJ 2005;172:1199-1209.

Figure 6



Source:

Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med 2008;233:674-88.