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Nutrition, Inflammation, and Disease

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Inflammation has been recognized as an indicator of illness and injury for thousands of years. References to the physical symptoms of inflammation—"rubor" (redness), "calor" (heat), "tumor" (swelling), and "dolor" (pain)—date back to a medical treatise written in the first century AD by the scholar Celsus.[1] In 1908, the Nobel Prize in medicine was awarded to scientists Elie Metchnikoff and Paul Ehrlich for their work outlining the pathogenesis of inflammation.[1]

In more recent years, inflammation's role as a risk factor for various chronic illnesses, including cardiovascular disease, cancer, and diabetes, has been studied and described.[2,3] Recognizing the role of the inflammatory process in disease development has been accompanied by efforts to identify dietary factors that may promote or inhibit the inflammatory process, thereby affecting disease risk and severity.

This continuing education course explores the mechanisms involved in the inflammatory response, outlines the role of chronic inflammation in disease development, and summarizes the research investigating the influences of foods and nutrients in both promoting and inhibiting inflammation.

Types of Inflammation

Inflammation is characterized as acute or chronic. Acute inflammation is a normal and comparatively short-lived physiologic response (lasting minutes to days) to injury, irritation, or infection. The physiologic processes responsible for acute inflammation (increased blood flow, greater blood vessel permeability, and accumulation of white blood cells) lead to redness, swelling, heat, and pain at the affected site.[4] Physical symptoms are accompanied by the generation of new cells and synthesis of the collagen matrix, processes that promote healing of the damaged tissue.[5]

Chronic inflammation is a long-term physiologic response (lasting weeks, months, or years) to one or more factors, including exposure to environmental toxins, a microbial or viral infection, poor nutrition, stress, and processes related to aging. Chronic inflammation is activated when the mechanisms of acute inflammation fail to arrest infection or heal an injury. When unchecked, prolonged chronic inflammation generates a series of destructive reactions that damage cells and eventually lead to the clinical symptoms of disease. Ultimately, chronic inflammation is a failure of the body's immune system to maintain a healthy homeostatic state.[3,6]

Types of Immunity
The human immune system provides two types of immunity that interact to defend the body against injury and infection: innate and adaptive.

Innate immunity, an immediate response to localized injury or invasion by an infectious agent, is the body's first line of defense. Innate immunity is triggered when a large sensor protein produced by bone marrow—an inflammasome—detects a toxic substance and stimulates defensive white cells known as macrophages to attack harmful cells.[7] Macrophages recognize and react to the features of many different types of pathogens and can engulf harmful cells and initiate the phagocytosis process.[1]

Macrophages also synthesize regulatory proteins known as toll receptors that activate various mechanisms in the inflammatory process, including the production of "natural killer" lymphocytes; nuclear factor-kappa B (NF-kB), a transcription factor that regulates immune response; and cytokines, which are proteins involved in cell signaling.[8,9] Innate immunity has limited duration and potency; when overtaxed, the body's innate immune system triggers the more powerful activity of adaptive immunity.

Adaptive immunity, sometimes referred to as acquired immunity, occurs when innate immunity fails to combat infection or injury. The mechanisms of adaptive immunity are rooted in highly specialized responses to specific antigens.

There are two types of adaptive immunity: humoral immunity, in which B lymphocytes, produced by bone marrow, create antibodies in response to the presence of antigens; and cell-mediated immunity, in which T lymphocytes, generated by the spleen and lymph nodes, recognize peptide fragments on the surface of antigen cells that may escape detection by B lymphocytes. Both B and T lymphocytes can divide and develop into effector cells, which detect and destroy infected cells. Unlike the innate immune system, the adaptive immune system produces memory cells that recognize and react to repeated exposures to specific antigens.[10]

The systems of innate and adaptive immunity work together to fight infection and protect the body from disease. The following is a simplified explanation of their interaction[10]:

- A toxin, irritant, or microbe invades the protective epithelium of a tissue, generating the defense mechanisms of the innate immune system.

- Macrophages produced by the innate immune system detect and bind pathogens, causing T and B lymphocytes to be activated and develop into effector cells. Lymphocyte activation marks the initiation of the adaptive immune system's processes.

- Effector cells, consisting of lymphocytes, natural killer cells, and T helper cells (a subclass of lymphocytes), work together to remove antigens and destroy damaged cells.

Inflammation and Disease

If the mechanisms of innate and adaptive immunity ineffectively combat an infection, prolonged inflammation can result in illness. The progression of chronic inflammation to disease is a complex process involving many different biological pathways. Repeated or uncontrolled inflammatory processes unleash a host of defensive responses, including leukocyte proliferation, angiogenesis, oxidative reactions, and tissue fibrosis, that ultimately disturb the normal function of cells and set the stage for disease development.

Inflammatory Processes

The development of a specific disease depends on the site of the inflammatory response. For example, disruption of the action of glomerular epithelial cells in the kidney results in renal disease, whereas damage to intestinal enterocytes leads to inflammatory bowel disease (IBD).[1] Although the underlying factors that trigger different diseases may vary, the pathology linking chronic inflammation and disease onset is marked by the same processes.

Accelerated Cytokine Production

Cytokines are small peptides that act as signaling systems within the body and affect many biological processes. Because they facilitate communication between the innate and adaptive immune systems, cytokines are a key factor in fighting infection and maintaining homeostasis.

Proinflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-alpha) are released defensively in response to infection and trauma. Anti-inflammatory cytokines such as transforming growth factor beta (TGF-beta) and IL-10 oppose the action of the proinflammatory cytokines and promote healing.

Elevated plasma levels of proinflammatory cytokines are biomarkers of inflammation and/or disease. An imbalance between the activity of proinflammatory and anti-inflammatory cytokines is believed to affect disease onset, course, and duration.[11]

Blood Concentration of Acute Phase Reactants

The release of cytokines into the bloodstream signals the liver to produce a variety of proteins known as acute phase reactants (APRs) that respond to trauma or infection and serve as biomarkers of inflammation. During chronic inflammation, plasma concentrations of APRs either increase (positive APRs) or decrease (negative APRs) by at least 25% and sometimes by as much as 1,000%. Examples of positive APRs include C-reactive protein (CRP) and serum amyloid A (SAA), while negative APRs include albumin and transferrin.[12]

Stimulation of Inflammatory Signaling Pathways

Cell signaling pathways are the body's primary means of communication, directing and regulating all cellular activities. The body orchestrates a wide variety of these signaling pathways that often control more than one activity and engage in communication (crosstalk) with each other. For example, the cyclic adenosine monophosphate pathway responds to the effects of many hormones and neurotransmitters and helps regulate numerous biological processes, including glycogenolysis, lipogenesis, lipolysis, and neurotransmitter activity. The NF-kB signaling pathway is an example of a proinflammatory signaling pathway that drives macrophages and neutrophils to respond to pathogens.[13]

Inflammatory Biomarkers in Disease

Obesity

Obesity is associated with an increased risk of many chronic disorders, including cardiovascular disease, diabetes, hypertension, metabolic syndrome, and nonalcoholic fatty liver disease, as well as numerous cancers (eg, colorectal, gastric, esophageal, pancreatic, breast, endometrial, ovarian).[7,14] In particular, abdominal obesity is associated with chronic low-grade inflammation, which appears to be an adaptive response to overfeeding.[7]

Adipose tissue is metabolically active and produces a variety of bioactive molecules called adipokines, which include hormones, proteins, growth factors, cytokines, and macrophages. Adipokines have numerous and far-reaching biological effects, including the regulation of food intake, energy expenditure, and glucose and fatty acid metabolism. An increase in abdominal fat causes adipose cells to grow and change shape, leading to cell necrosis and the disruption of adipokine activity.

Adipose tissue macrophages respond to increased fat cell mass by stimulating the secretion of the proinflammatory cytokines TNF-alpha, IL-6, and IL-1 beta, which in turn signal the liver to produce CRP and initiate inflammatory pathway signaling. Compared with normal-weight individuals, healthy obese people have higher circulating levels of proinflammatory cytokines and CRP.[2,7]

Metabolic Syndrome

Metabolic syndrome, which is recognized as a risk factor for cardiovascular disease and type 2 diabetes, is defined as the occurrence of three or more of the following conditions: abdominal obesity, hyperinsulinemia, hyperglycemia, hypertension, low levels of HDL cholesterol, and hypertriglyceridemia.[7,15]

Like obesity, metabolic syndrome is marked by chronic inflammation, resulting in high circulating levels of the proinflammatory cytokines TNF-alpha and IL-6, and elevated serum CRP levels. Plasma CRP concentrations of 3 mg/L or higher are believed to be an independent predictor of metabolic syndrome.[7] The prolonged chronic inflammation of metabolic syndrome sets the stage for a feedback loop of worsening insulin resistance, impaired glucose tolerance, and abnormal lipid levels.[7,15]

Type 2 Diabetes

Abdominal obesity is believed to be the source of the chronic inflammation that accompanies type 2 diabetes. Diabetes is accompanied by increased circulating levels of the proinflammatory cytokines TNF-alpha and IL-6 as well as decreased levels of the anti-inflammatory cytokine IL-10. Plasma levels of the acute phase reactants SAA and CRP also are elevated.16 In addition, there are increased levels of fibrinogen, the protein involved in blood clotting, and higher levels of clotting factors VII and VIII. The net effect of these actions is hyperglycemia, increased insulin resistance, a higher risk of thrombosis, and abnormal lipoprotein metabolism.[7,15]

Atherosclerosis

Atherosclerosis once was believed to result simply from lipid accumulation in arterial walls. It's now known that inflammatory processes are the driving force behind atherosclerotic plaque development.

Cardiovascular risk factors such as cigarette smoking, hypertension, and diets rich in trans fat stimulate endothelial cells within the artery to release a sticky protein called the vascular cell adhesion molecule, which causes leukocytes to bind to the arterial intima. The continued depositing of white blood cells onto arterial cell walls stimulates the release of proinflammatory cytokines, which in turn cause macrophages called foam cells to engulf lipid fragments, leading to plaque formation and arterial damage. As damage to the arterial wall progresses, the cycle of inflammatory response intensifies, resulting in plaque instability and increasing the risk of aneurysm, stroke, or heart attack.[1,17]

Cancer

Chronic inflammation, infection, and tissue damage are associated with an increased risk of many types of cancer. Consider the following[18,19]:

- Inflammatory diseases such as IBD, Crohn's disease, and ulcerative colitis are associated with an increased risk of colon cancer.

- Chronic inflammatory conditions such as pancreatitis and Barret's metaplasia are linked with pancreatic and esophageal cancer, respectively.

- Inflammation resulting from microbial infection may lead to cancer of the affected organ. For example, chronic infection with the human papilloma virus or hepatitis B or C virus may result in cervical and liver cancer, respectively, whereas *Helicobacter pylori* infection is a strong predictor of stomach cancer.

- Inflammation arising from exposure to toxic agents such as asbestos and cigarette smoke is linked with increased risk of mesothelioma and lung cancer, respectively.

During the normal healing process, macrophages help fight infection, repair damaged cells, and restore homeostasis. However, macrophages' uncontrolled activity during chronic inflammation is strongly implicated as having a causal role in cancer development.[19] Highly reactive oxygen and nitrogen molecules released by macrophages during the healing process may produce harmful substances that lead to DNA mutation. Proinflammatory cytokines such as IL-1 and TNF-alpha block DNA repair and promote tumor growth and metastasis.[19]

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease marked by unrestrained growth of the synovial tissue of the joints, which leads to inflammation, pain, and joint damage. It develops when proteoglycans, structural proteins found in cartilage, act as antigens and stimulate T cells to produce various proinflammatory cytokines, such as TNF-alpha and IL-4, -5, and -6. The production of these cytokines leads to joint swelling, pain, and eventual joint destruction. In

addition, T lymphocytes promote the activity of macrophages and B lymphocytes, which intensify the inflammatory response and hasten joint damage.[3]

Nutrition and Inflammation

Nutrients play a key role in both promoting and combating inflammatory processes. Evidence linking nutrients with inflammatory processes comes from laboratory, clinical, and epidemiologic studies.

Proinflammatory Nutrients

Excess calorie intake: Excessive energy intake stimulates adipose cell growth and proliferation, and promotes abdominal obesity, thereby increasing the risk of diabetes, metabolic syndrome, and other chronic diseases.

Data obtained from studies of individuals enrolled in the Calorie Restriction Society, whose members voluntarily observe calorie-controlled diets as a route to increased longevity, showed that consuming approximately 1,800 kcal/day (an approximately 30% reduction from baseline) over several years decreased serum levels of CRP, TNF-alpha, proinflammatory growth factors, and body fat, improved BMI, glucose tolerance, insulin sensitivity, and lipoprotein profiles. These findings were duplicated in randomized, controlled clinical trials in which lean and obese subjects consumed 20% to 25% fewer calories for periods of six to 12 months.[20]

Dietary carbohydrate excess: Carbohydrate intake has been linked to chronic diseases such as obesity, metabolic syndrome, and type 2 diabetes. Of particular interest are foods low in fiber and rich in sugars and starches, and those that produce a high glycemic value based on the glycemic index (GI) scale.

A prospective study conducted in Australia among postmenopausal women demonstrated that the risk of death from inflammatory disease, including digestive, respiratory, nervous system, and endocrine disorders, was nearly three times greater among women consuming a high-GI diet compared with women eating a low-GI diet. In addition, levels of NF-kB were three times higher among lean subjects consuming high-GI meals.[21] High-GI diets rich in refined carbohydrate may stimulate proinflammatory IL-6 production and push the liver to generate CRP, according to one study.[22]

Trans fatty acids: Consuming trans fatty acids is a known risk factor for sudden cardiac death. A possible mechanism suggests that trans fatty acids induce an inflammatory response in cardiac tissue through their effect on cell membranes.

Data from an in vitro study published in the ***British Journal of Nutrition*** showed that trans 18:2 fatty acids were integrated into human aortic endothelial at twice the rate as cis 18:2 fatty acids, causing the cells to clump together and bind to arterial walls, stimulating the release of proinflammatory cytokines. In addition, studies of patients with chronic heart failure have demonstrated significant associations between the trans fatty acid level of red blood cell membranes and plasma biomarkers of inflammation, including IL-1, IL-6, and TNF-alpha.[23]

Saturated fatty acids: In vitro studies have shown that saturated fatty acids play a role in the inflammatory process by stimulating macrophage production and the secretion of the proinflammatory cytokines TNF-alpha, IL-6, and IL-8.[24] In mice, a diet containing 12% saturated fat (comparable with the level contained in the average American diet) resulted in increased body fat and elevated levels of proinflammatory cytokines.[25]

Omega-6 polyunsaturated fatty acids: During the last several decades, the consumption of oils rich in the omega-6 fatty acid linoleic acid (eg, soybean, corn, safflower, sunflower) steadily has risen in the United States, resulting in an increased ratio of omega-6 to omega-3 fatty acids in the American diet. Ideal dietary levels of omega-6 to omega-3 fatty acids are believed to be 1 to 4:1; however, the typical American diet now provides a ratio of about 10:1 to 20:1. This change has been associated with an increased risk of chronic inflammatory diseases, including atherosclerosis and cardiovascular disease, rheumatoid arthritis, and IBD.[26]

Omega-6 fatty acids are precursors to proinflammatory eicosanoids, signaling molecules that help regulate immune function and are active in the inflammatory process. Linoleic acid (C18:2n-6) is converted in the liver to the long-chain fatty acid arachadonic acid (C20:4n-6), which in turn is converted to three types of eicosanoids: prostaglandins, thromboxanes, and leukotrienes. These molecules have potent negative effects on platelet aggregation, blood pressure, and immune system function and trigger proinflammatory cytokine production.[26]

Anti-Inflammatory Nutrients

Omega-3 polyunsaturated fatty acids: The omega-3 fatty acids EPA and DHA, found in fatty fish and fish oil supplements, suppress the production of proinflammatory eicosanoids and stimulate the synthesis of anti-inflammatory eicosanoids (lipoxins) from arachadonic acid. Omega-3 fatty acids also reduce the generation of the proinflammatory cytokines TNF-alpha, IL-1 beta, IL-6, and IL-8. In addition, EPA and DHA can be converted to compounds known as resolvins, which inhibit proinflammatory signaling.[27]

Fish oil supplementation in a dosage of 4 g/day for a minimum of six weeks resulted in significantly decreased plasma levels of TNF-alpha among individuals with type 2 diabetes and reduced cellular content of proinflammatory cytokines IL-1 beta, IL-6, and IL-8 in healthy subjects.[27] In addition, rheumatoid arthritis symptom relief was reported in several studies of individuals taking 2 to 4 g/day of supplemental fish oil for periods of three to six months.[27]

Although most studies have focused on the effects of fish oil, consuming approximately 3 oz of fatty fish (eg, salmon, herring) five times per week for eight weeks resulted in significant lowering of plasma levels of proinflammatory cytokines TNF-alpha and IL-6 among elderly Chinese women with dyslipidemia.[28]

Chia seed, walnuts, canola oil, and flaxseed oil are sources of the omega-3 fatty acid alpha-linolenic acid (ALA). Although ALA has shown some promise in counteracting inflammatory processes, EPA and DHA appear to be substantially more effective in their anti-inflammatory effects.[27]

Ascorbic acid: A powerful antioxidant, ascorbic acid (vitamin C) defends cells against lipid peroxidation and scavenges reactive oxygen and nitrogen species such as hydroxyl, peroxyl, superoxide, nitroxide radical, and peroxynitrite. Ascorbic acid supports phagocytosis by macrophages and stimulates the activity of natural killer lymphocytes generated during the innate immune response. Through its function as a cofactor in enzymes controlling collagen synthesis, vitamin C also reduces tissue damage at inflammation sites.[3]

Consuming approximately 70 mg/day of vitamin C from vegetable soup significantly reduced plasma levels of proinflammatory prostaglandins and CRP in a small clinical study of healthy subjects. Plasma vitamin C levels were inversely correlated with symptoms in a prospective study of the effects of the Mediterranean diet on rheumatoid arthritis, while supplementation with 1 g/day of vitamin C decreased measures of oxidative stress and improved endothelial function in a clinical study of individuals with hypertension.[3] In addition, dietary intakes of vitamin C, as measured by seven-day food records, were negatively associated with plasma levels of proinflammatory CRP and IL-6 in the Uppsala Longitudinal Study of Adult Men published in 2009.[29]

Vitamin E: Vitamin E exists in nature as different chemical structures; the most common forms in the diet are alpha- and gamma-tocopherol. Foods such as seeds, nuts, and vegetable oils are sources of gamma-tocopherol, while supplements commonly contain alpha-tocopherol.[3]

Alpha- and gamma-tocopherol have different biological activities. Alpha-tocopherol has long been recognized for its capacity to scavenge free radicals and prevent lipid oxidation. In addition, it inhibits the release of proinflammatory cytokines and reduces CRP levels. Gamma-tocopherol decreases proinflammatory NF-kB and TNF-alpha activity, and inhibits prostaglandin synthesis.[3]

Dietary intakes of alpha-tocopherol were inversely related to plasma levels of proinflammatory CRP and IL-6 in the Uppsala Longitudinal Study of Adult Men.[29] However, clinical studies examining vitamin E intake and measures of inflammation have provided mixed results.[3] There are several possible explanations for this.
Most clinical trials assessing the anti-inflammatory effects of vitamin E primarily have looked at alpha-tocopherol supplementation and not tocopherols from foods. Alpha-tocopherol significantly decreases circulating levels of gamma-tocopherol, decreasing its anti-inflammatory properties.[3]

In addition, alpha- and gamma-tocopherol may have a synergistic effect on inflammation.[3] This finding was observed in a randomized double-blind trial involving subjects with metabolic syndrome, in which supplementation with 800 mg/day of a combination of alpha- and gamma-tocopherol was more effective in reducing plasma CRP and TNF-alpha levels than were either supplement alone.[30]

Vitamin E shows some promise in the treatment of rheumatoid arthritis symptoms. A clinical study demonstrated a significant reduction in joint stiffness and pain following twice-daily supplementation with 600 mg of alpha-tocopherol, although plasma inflammatory biomarkers weren’t changed.[3]

Polyphenols: These aromatic compounds are found in fruits, vegetables, grains, chocolate, coffee, olive oil, and tea. To date, thousands of polyphenols have been identified and classified into different subgroups.[31] Two such groups are flavonoids and lignans.

Flavonoids include the flavanones naringenin and hesperidin (found in citrus fruit); flavonols such as myricetin, kaempferol, and quercetin (found in apples, cocoa, and onions); and the flavones luteolin and apigenin (found in celery), catechins (found in tea), and anthocyanins (found in berries). Phenolic acids (caffeic acid, gallic acid, and ferulic acid) are found in coffee, olive oil, tea, grains, peanuts, and berries.
Lignans (secoisolariciresinol and matairesinol) are found primarily in flaxseeds. The polyphenol resveratrol, classified as a stilbenoid, is found in red wine and berries.

Many polyphenols show powerful anti-inflammatory effects. Laboratory investigations, clinical trials, and prospective studies suggest that polyphenols inhibit enzymes involved in prostaglandin and leukotriene synthesis, prevent free radical formation, decrease proinflammatory cytokine production, and block the activity of proinflammatory signaling systems.[31-33] However, the effect of dietary polyphenols on human inflammatory biomarkers requires further study because of wide variation in the polyphenol content of foods, differences in postprandial plasma concentrations, and inadequate knowledge of tissue stores.[31]

Prebiotics and probiotics: Prebiotics are defined as nondigestible, nonabsorbable substances that can be fermented by bacteria in the gut, promote the growth of desirable microflora, and impart improvements to health. Prebiotics include oligofructose, a short-chain fructose polymer, and inulin, a type of dietary fiber. Food sources of prebiotics include chicory, Jerusalem artichokes, and onions. Inulin is an additive in many commercially prepared foods and sold as a dietary supplement.[3]

The World Health Organization defines probiotics as “live microorganisms, which, when administered in adequate amounts, confer a health benefit to the host.” Probiotics are bacteria that are classified primarily as either lactobacillus or bifidobacteria; both are part of the normal gut flora and can ferment lactose. They’re found in cultured dairy foods such as yogurt and kefir and also are available in supplement form.[3]

Animal studies have shown that both prebiotics and probiotics can decrease the activity of proinflammatory cytokines and NF-kB, and increase levels of anti-inflammatory TGF-beta within the gut mucosa. Both prebiotics and probiotics appear to interact directly with gut epithelium cells to block pathogens from entering.[3]

Clinical trials have helped corroborate the anti-inflammatory effects of prebiotics seen in laboratory studies. Infants and children with diarrheal illness showed marked improvement in symptoms (eg, decreased diarrhea, vomiting, fever) when given supplemental inulin. Administered to patients with ulcerative colitis or precancerous colon polyps, inulin improved measures of disease activity and reduced levels of intestinal proinflammatory proteins.[3]

Studies investigating the efficacy of supplemental probiotics in alleviating inflammatory activity in Crohn's disease and ulcerative colitis have looked at both single strains of bacteria, such as *Lactobacillus acidophilus*, as well as mixtures of bacteria, such as *Streptococcus thermophilus* and *Bifidobacterium bifidum*. The results have been mixed but generally support a role for probiotics in decreasing disease activity and improving clinical symptoms. In addition, consuming cultured dairy foods has been found to alleviate symptoms of IBD, ulcerative colitis, and pouchitis.[34]

Anti-Inflammatory Foods and Dietary Patterns

Various foods and dietary patterns are effective in reducing the underlying inflammatory processes associated with chronic disease.

A diet high in fruits and vegetables may be one of the best defenses against chronic inflammation. Fruits and vegetables are a highly bioavailable source of vitamins, minerals, fiber, and polyphenols with anti-inflammatory activity. A cross-sectional study investigating self-reported fruit and vegetable intake among adults found that individuals reporting the highest consumption (more than two servings of fruit and three servings of vegetables daily) had significantly lower plasma levels of proinflammatory CRP, IL-6, and TNF-alpha as well as decreased biomarkers of oxidative stress. Four to five servings daily each of fruits and vegetables are recommended to combat inflammation and chronic disease.[35,36]

The Mediterranean diet is characterized by the generous consumption of vegetables, fruits, grains, legumes, and nuts; a minimal intake of red meat and whole-fat dairy products; increased fish consumption; moderate red wine intake; and liberal use of olive oil in cooking and food preparation. Compared with Western diets, the Mediterranean diet is rich in fiber, polyphenols, antioxidants, and omega-3 fatty acids and low in saturated fat and refined carbohydrate. Data from epidemiologic and clinical studies have demonstrated that consuming a Mediterranean-type diet reduces plasma levels of proinflammatory biomarkers, including endothelial adhesion molecules, CRP, TNF-alpha, and NF-kB.[37,38]

High-fiber, low-GI foods appear to have a beneficial effect on inflammatory biomarkers. Adhering to a low-GI diet for one year resulted in significantly lower plasma levels of CRP in a clinical randomized trial of subjects with type 2 diabetes compared with adhering to high-GI and low-carbohydrate diets. The low-GI diet consisted of high-fiber breakfast cereals, whole grains, and legumes, and provided 52% carbohydrate, an average GI of 55, and 36 g of fiber per day. In contrast, the high-GI diet containing refined cereals, white bread, and potatoes supplied 47% carbohydrate, an average GI of 63, and 21 g of fiber per day; and the low-carbohydrate diet containing nuts, avocados, and olives, provided 39% carbohydrate, an average GI of 59, and 23 g of fiber per day.[39]

Whole grain foods consist of the unaltered grain with intact bran and germ components, which are valuable sources of fiber, phytochemicals, vitamins, and minerals. Prospective and clinical studies have suggested that consuming whole grain foods such as oats, barley, and brown rice may help decrease inflammation associated with metabolic syndrome, diabetes, and cardiovascular disease.[36]

Weight loss is known to have beneficial effects on metabolic syndrome, type 2 diabetes, and other chronic conditions. A small clinical study found that obese individuals who lost 10% or more of their body weight on a low-calorie liquid diet regimen significantly had reduced plasma levels of proinflammatory macrophage proteins and proinflammatory cytokines IL-6, -15, and -18. The greatest reductions were seen among subjects achieving a weight loss of 14% or more, suggesting that decreased caloric consumption has a beneficial effect on inflammation independent of nutrient intake.[40]

Future Directions

Evidence supporting the diet's role both in promoting and hindering inflammatory processes is mounting. Additional research is needed to identify the independent and interactive effects of foods and nutrients and to evaluate the protective role of supplements in fighting inflammation.

Clinical Recommendations

There are many simple dietary strategies that may effectively reduce levels of chronic inflammation and decrease disease risk. However, individuals with chronic disease often feel overwhelmed by the many lifestyle changes they're asked to make. In addition, they may be unaware of the role diet plays in affecting the inflammatory processes underlying many chronic illnesses.

Dietitians can support their clients and patients by emphasizing dietary changes that will help reduce inflammation levels in the body and begin to restore normal immune function. Encouraging clients to increase their intake of fruits, vegetables, whole grains, nuts, olive oil, and fatty fish is a positive message that can accompany advice to reduce their consumption of refined starches and sweets, and foods laden with trans and saturated fat.

It's important for dietitians to stress that anti-inflammatory benefits are derived from the synergistic effect of foods eaten together as well as from individual foods and that seemingly small changes can play a major role in improving health. Focusing on personalized goals and setting achievable objectives (eg, eat an extra serving of fruit at lunch) is key to helping clients make lasting dietary changes that will combat inflammation and enhance overall health.

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10 Ways Foods Can Reduce Inflammation

Many people with diabetes, high cholesterol, hypertension, and other chronic health problems have high levels of inflammation in their bodies that occur over time when the immune system tries unsuccessfully to repair cells and rid itself of harmful toxins. The right foods can help reduce the amount of inflammation in the body and improve health. Here are 10 suggestions for clients and patients for eating to decrease inflammation:

1. Boost consumption of fruits and vegetables. Aim to eat four to five servings each of fruits and vegetables daily. Choose fruits and vegetables that are deep green, orange, yellow,

and purple, since these have the greatest nutritional value. Ten servings per day may sound like too much, but serving sizes are small: one medium fruit, $^1/_2$ cup canned or frozen fruit, $^1/_2$ cup cooked vegetable, $^1/_2$ cup fruit juice, and 1 cup leafy raw greens.

2. Cook with olive oil as much as possible and use it to make salad dressings. Make a quick and easy dressing by combining $^3/_4$ cup olive oil, $^1/_4$ cup balsamic vinegar, $^1/_2$ clove minced garlic, and 1 T each of chopped fresh parsley and chives. (Use $^1/_2$ tsp dried herbs if fresh herbs aren't available.) Virgin olive oil is best since it has more inflammation-fighting antioxidants than refined olive oil.

3. Snack on walnuts instead of chips. Walnuts provide fiber, minerals, antioxidants, and the kinds of fatty acids that are good for your heart.

4. Eat a whole grain cereal such as oatmeal for breakfast, and replace refined grains with whole grains, such as substituting brown rice for white rice.

5. Eat fatty fish such as salmon two to three times per week to get more omega-3 fatty acids. Wild salmon has more omega-3s than farmed salmon.

6. Eat fewer fast foods. Many tend to be cooked in oils that contain trans fatty acids, which increase inflammation. If you eat at fast-food restaurants, order a grilled chicken sandwich or salad with vinaigrette dressing.

7. Replace white potatoes with sweet potatoes. They're high in vitamins and delicious when baked with a little olive oil, garlic, and rosemary.

8. Cut down on sugary drinks such as juice, soda, and punch. Add small amounts of cider, fruit juice, or wedges of lemon or orange to plain water to enhance the flavor.

9. Eat more lentils and beans. They're good sources of protein and can replace red meat at meals. Try black beans and brown rice sautéed with onions and garlic and seasoned with cumin.

10. Munch on dark chocolate and fresh raspberries for dessert. Both are loaded with antioxidants.

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Examination

1. Abdominal obesity has which of the following effects?
A. It increases circulating levels of C-reactive protein (CRP).
B. It decreases circulating levels of proinflammatory cytokines.
C. It decreases fat cell necrosis.
D. It normalizes adipose cell adipokine activity.

2. Foods rich in polyphenols help fight inflammation by which of the following mechanisms?
A. They decrease anti-inflammatory cytokine production.
B. They destroy inflammasomes.
C. They inhibit enzymes involved in prostaglandin and leukotriene synthesis.
D. They reduce omega-6 to omega-3 fatty acid ratios.

3. What are the two types of adaptive immunity?
A. Innate and receptive
B. Humoral and cell mediated
C. Antigenic and phagocytic
D. Acute and chronic

4. Based on this article, which of the following statements about metabolic syndrome is true?
A. It's accompanied by circulating plasma levels of CRP of less than 1 mg/dL.
B. It's improved by increasing abdominal adiposity.
C. It's recognized as an independent risk factor for cardiovascular disease and type 2 diabetes.
D. It's caused by high circulating levels of anti-inflammatory cytokines.

5. Which of the following is true of prebiotics and probiotics, based on this article?
A. Both are strains of lactobacillus bacteria.
B. Both are found in foods and are available as dietary supplements.
C. Neither is effective in reducing gastrointestinal disease activity.
D. Both can be obtained by eating cultured dairy foods.

6. Which of the following are two examples of proinflammatory cytokines?
A. CRP and serum amyloid A
B. Interleukin 6 and tumor necrosis factor alpha
C. Transforming growth factor beta and nuclear factor kappa B (NF-kB)
D. Fibrinogen and clotting factor VII

7. Which of the following causes the anti-inflammatory properties of EPA and DHA?
A. Suppression of proinflammatory eicosanoids
B. Conversion of linoleic acid to arachidonic acid
C. Strengthening of the gut mucosa
D. Stimulation of collagen synthesis

8. Acute phase reactants are biomarkers of chronic inflammation. A positive acute phase reactant has which of the following effects?
A. Decreases during chronic inflammation
B. Increases during chronic inflammation
C. Increases when inflammation subsides
D. Decreases when proinflammatory cytokines are released

9. A diet low in refined carbohydrate and that limits high glycemic index foods may reduce inflammation in which of the following ways?
A. By stimulating interleukin 1 secretion
B. By decreasing free radical production
C. By shutting off CRP synthesis in the liver
D. By increasing NF-kB transcription factor activity

10. Which of the following causes difficulty in evaluating the effects of vitamin E on inflammation?
A. Alpha-tocopherol enhances the activity of gamma-tocopherol.
B. Few foods contain vitamin E.
C. Vitamin E is poorly absorbed.
D. The vitamin E supplements evaluated in clinical trials typically are composed of only alpha-tocopherol.