

The dangers of inflammation

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It is the common bond between most chronic conditions. And it can be deadly. Jack Challem explains how this natural biological response often veers out of control — and which nutrients can help control it.

A few years ago, chronic inflammatory diseases were defined largely by arthritis and other ‘-itis’ diseases. Over the past several years, medicine has started to recognise the fundamental role of inflammation in nearly every disease process. Researchers and physicians have been redefining heart disease, Alzheimer’s, and even diabetes and obesity as inflammatory disorders.

Much of this new view of chronic inflammation in degenerative diseases has come from research showing that people with inflammatory diseases have elevated blood levels of C-reactive protein (CRP) and other markers of inflammation. Normally, inflammation helps fight infections and initiates the healing process after an injury. But it doesn’t always routinely fade away. Relatively minor inflammatory disorders, such as injuries or allergies, can rev up the immune system and be a prelude to more serious, chronic inflammatory diseases. In fact, considerable research now shows that arthritis, periodontal disease, obesity and diabetes all set the stage for coronary artery disease — through the common denominator of chronic, low-grade systemic inflammation. Because these conditions share common elements, they can be considered part of an ‘inflammation syndrome.’

The question, of course, is why does there seem to be a surge in inflammatory diseases? The answer is that modern food processing and eating habits are preludes to an array of nutrient deficiencies. These diets typically contain inflammation-promoting dietary oils and fats and large amounts of sugars and refined simple carbohydrates, which promote and sustain inflammation.

While a diet emphasising fish, chicken, vegetables and olive oil is of great value, studies have shown that specific types of nutrients have anti-inflammatory properties and can be integrated into finished foods.

Antioxidants

Free radicals stimulate inflammation in several ways. They increase the activity of genes involved in making pro-inflammatory cytokines such as interleukin-6 (IL-6).¹ Free radicals also activate several different kinds of adhesion molecules, which enable various types of white blood cells to stick to other cells – such as endothelial cells that line blood vessel walls.² Adhesion molecules should stick only to infectious microbes and damaged cells marked for cleanup. But in chronic inflammation, they can adhere to normal cells, including those in arteries and joints.

The natural antidotes for free radicals are antioxidants, which include vitamins C and E and the flavonoids found in vegetables, fruits and herbs. Many antioxidants directly counteract the pro-inflammatory effects of free radicals. For example, vitamin E helps turn off genes involved in inflammation, as well as some types of adhesion molecules.³ In addition, antioxidants lower CRP levels. They also curb inflammation by quenching free radicals, which would otherwise stimulate inflammation. In one study, researchers found that people with high blood levels of carotenoids, including beta-carotene and lutein, had the lowest CRP levels.⁴ Granted, those carotenoids may have simply been a marker for vegetable intake. But other studies have clearly shown that antioxidant vitamins have a large stake against inflammation.

Vitamin E supplements (800IU daily) can lower CRP levels from 30-50 per cent, and also lower IL-6 levels by 50 per cent.⁵ This effect may account for the vitamin's well-known heart benefits. The anti-inflammatory benefits of vitamin E were also noted in two clinical trials that found the vitamin of benefit in patients with rheumatoid arthritis.^{6,7} A clearer anti-inflammatory effect may be achieved at 800 or 1,200IU daily, and one of the studies noted analgesic properties of high-dose vitamin E therapy.⁶

More than any other nutrient, vitamin E can significantly reduce a variety of key indicators and promoters of inflammation. As an antioxidant, it quenches free radicals, thus reducing their ability to stimulate abnormal inflammatory responses. By the same token, it prevents LDL cholesterol oxidation, an early step in the development of coronary artery disease. Vitamin E also inhibits at least two transcription factors, preventing the activation of some of the genes involved in inflammation.⁸ It is a mild cyclooxygenase-2 (Cox-2) inhibitor. It has this action by reducing levels of pro-inflammatory prostaglandin E₂, which consequently reduces Cox-2 activity.⁹

The ability of vitamin E to lower CRP levels was demonstrated in a randomised, controlled human trial of 57 people with type 2 diabetes. After four weeks of supplementing with 800IU natural vitamin E, 500mg vitamin C or lycopene-rich tomato juice, only vitamin E lowered CRP levels, and by 49 per cent at that.¹⁰ Another study assessed 72 subjects, including some healthy and others with diabetes or heart disease, who took 1,200IU/day natural vitamin E for three months. Each group experienced an average 30 per cent drop in CRP as well as IL-6 decreases by 50 per cent.¹¹

Vitamin C is another useful antioxidant nutrient. Indeed, humans' inability to convert blood sugar to vitamin C may very well predispose people to type 2 diabetes because excess glucose remains in the blood instead of being converted to vitamin C.¹² The chemical similarities between blood sugar and vitamin C lead to competition between them because both molecules enter the cell on the same transporter protein. Because diabetics have higher levels of CRP and IL-6 — markers of inflammation — increasing vitamin C levels can modulate both blood sugar spikes as well as its attendant inflammation. One report found that people with peripheral arterial disease were more likely to have greater inflammation and severe heart disease when their blood levels of vitamin C were low.¹³

Polyphenols and flavonoids by the thousands have been identified in plants, and probably all have some anti-inflammatory properties — and are likely a big part of the reason why vegetables are good for health. Flavonoids have been known since the 1930s for strengthening blood vessel walls and preventing bruising and they are synergistic with vitamin C (so it's worthwhile taking them in combination). Several specific flavonoids may be helpful in reducing inflammation, specifically quercetin, Pycnogenol and grapeseed extract.

Quercetin inhibits the activity of adhesion molecules, which enable inflammation-producing white blood cells to stick to other cells in the body.¹⁴

Researchers at Case Western Reserve University in Ohio recently reported that the antioxidant polyphenols in green tea had anti-inflammatory properties by inhibiting the pro-inflammatory compounds cyclooxygenase-2 (Cox-2) and tumour necrosis factor alpha (TNFα).¹⁵ Genistein inhibits prostaglandin E2 and Cox-2, and quercetin inhibits the activity of inflammation-promoting adhesion molecules. Because of its mild taste, green tea has the advantage of being consumed as a beverage.

Research has also shown that Pycnogenol and grapeseed extract also possess anti-inflammatory properties. It's likely these and other flavonoids work through similar mechanisms. In particular, Pycnogenol contains more than 40 polyphenols and flavonoids and has well-documented anti-inflammatory properties.¹⁶ Grapeseed extract, which has a slightly different chemical structure, also has notable anti-inflammatory effects.¹⁷

Omegas

The omega-3 family of fatty acids forms the building blocks of many of the body's natural anti-inflammatory compounds. The body makes two families of hormone-like compounds, called prostaglandins, which either promote or reduce inflammation. The parent molecules of these prostaglandins occur in dietary fats, also known as fatty acids.

Omega-3 EFAs form the foundation of the body's anti-inflammatory eicosanoids.¹⁸ Chief among the dietary omega-3s are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in cold-water fish. While both omega-3s have benefits in human health, EPA plays a more central role in the body's defences against inflammation. The omega-3s compete against omega-6s and reduce levels of three key pro-inflammatory compounds: thromboxane B2, prostaglandin E2 and interleukin 1-beta.¹⁹

In a lab study conducted at Cardiff University in Wales, Bruce Caterson, PhD, and his colleagues found that omega-3s inhibited the activity of enzymes known as aggrecanases, which break down joint cartilage.²⁰ Caterson first determined that chondrocytes, one of the key types of cells forming cartilage, readily absorbed alpha-linolenic acid (the parent omega-3 fatty acid) and displaced other fatty acids in the process. The same thing occurred when the researchers grew chondrocytes with EPA and DHA. Significantly, all of the omega-3s deactivated aggrecanases, which is a family of enzymes that break down cartilage. The omega-3s also stopped the genetic programming that increased levels of

pro-inflammatory IL-1, TNF α and Cox-2. This protective effect may help maintain joints in the face of rigorous physical activity.

Evidence of the broader anti-inflammatory effects of fish and fish oil supplements comes from other inflammatory conditions, such as asthma and Crohn's disease. For example, an Australian study found that children with asthma were half as likely to consume fish rich in omega-3s. As little as one fish meal per week was enough to reduce asthma occurrence.²¹

In addition, researchers in Italy conducted a study to see if omega-3s could have an effect on people with Crohn's disease, a type of bowel inflammation. In a year-long, double-blind, placebo-controlled trial published in the *New England Journal of Medicine*, they gave either 600mg/day EPA and 300mg/day DHA or placebo to 78 Crohn's patients. After one year, 59 per cent of the patients taking fish oil capsules were still in remission, compared to 26 per cent in the placebo group.²²

Gamma-linolenic acid (GLA) is the rare omega-6 fatty acid that behaves more like an omega-3. GLA works by boosting the body's levels of prostaglandin E1, an eicosanoid that suppresses inflammation. In fact, some research suggests that GLA and omega-3s have a synergistic anti-inflammatory effect in that both suppress pro-inflammatory prostaglandin E2 through different mechanisms.²³ GLA boosts production of dihomogamma-linolenic acid (DGLA), the immediate precursor of prostaglandin E1, which suppresses inflammation.²⁴

Several human clinical studies have found that GLA controls inflammation and aids symptom reduction in patients with rheumatoid arthritis. In one double-blind, placebo-controlled human trial, researchers treated 37 patients who had rheumatoid arthritis and inflamed joints with either 1.4g/day GLA or placebo. After 24 weeks, the number of tender joints among patients taking GLA was reduced by 36 per cent, and the overall score on tests measuring tender joints declined by 45 per cent. In addition, the number of swollen joints decreased by 28 per cent, and the patients' overall score for swollen joints fell by 41 per cent.²⁵

In a follow-up placebo-controlled study, the researchers doubled the GLA dosage for six months. This higher dosage resulted in significant improvements — at least a 25 per cent improvement in four of eight measures of rheumatoid arthritis severity. For a second six-month period, both treatment groups received GLA, with improvements noted across the board.²⁶ GLA supplements are derived from the oil of evening primrose, borage and black currant seeds. However, the source is less important than the actual amount of GLA in each capsule.

Elevated blood levels of homocysteine, a known risk factor for coronary artery disease, reflect low levels of folic acid and possibly vitamins B6 and B12. Homocysteine is toxic to blood vessel walls, and evidence clearly indicates that it results in inflammation, ulceration and scarring of blood vessel walls. So although these three B vitamins are not

directly anti-inflammatory, they do reduce levels of an inflammation-promoting substance.^{27,28}

Connecting the dots

Considerable research now links many different types of inflammatory diseases to each other. Only in the past several years have researchers been able to connect the dots between these diseases and their common inflammatory roots. For example, it is well known that obesity increases the risk of diabetes, and both obesity and diabetes increase the risk of coronary artery disease.

Because the cause of chronic inflammation is largely nutritional, nutrition is the best way to reverse it. Vitamins E and C, the omegas, flavonoids, and other supplements are well documented for their roles in correcting pro-inflammatory nutritional imbalances and for reducing inflammation. By reducing inflammation in one disorder, they reduce the risk of developing other, more serious inflammatory diseases.

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State of the Science

C-reactive protein: more than just a marker

C-reactive protein (CRP) has long been recognised as an indicator of intense, systemic inflammation. Slowly, experts have come to see CRP as a promoter of inflammation instead of simply a marker. In a major study conducted at Harvard Medical School and published in the *New England Journal of Medicine*, 28,263 apparently healthy postmenopausal women were followed for three years to assess the risk of cardiovascular events associated with base-line levels of markers of inflammation. Of the 12 markers measured, high-sensitivity CRP (a more subtle marker of low-grade inflammation) was the strongest predictor of the risk of cardiovascular events; people with elevated CRP levels were at 4.4 times greater risk of having a heart attack. Second best, at 3.4, was the ratio of total cholesterol to HDL cholesterol.¹

Not only is elevated CRP more accurate than cholesterol in predicting heart attack risk, but high CRP levels have turned up in people with diabetes and prediabetes and in people who are overweight, leading to these conditions being redefined in part as inflammatory disorders.

Unlike cholesterol, CRP is not found in foods. However, its levels in the body are strongly influenced by diet. A study at Harvard Medical School found women who ate large amounts of high-glycaemic carbohydrates, including potatoes, breakfast cereals,

white bread, muffins and white rice, had very high CRP levels. Women who ate a lot of these foods and were also overweight had the highest and most dangerous CRP levels.²

The researchers noted that CRP is a marker of inflammation that predicts the risk of myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death among individuals with no history of cardiovascular disease, and recurrent events and death in patients with acute or stable coronary syndromes. CRP confers additional prognostic value at all levels of cholesterol, Framingham coronary risk score, severity of the metabolic syndrome, and blood pressure, and in those with and without subclinical atherosclerosis.³

Although many studies have found that vitamin E and other nutrients significantly reduce CRP levels, statin drugs are more commonly chosen.⁴ Statins, however, reduce the body's production of cholesterol by inhibiting the HMG-CoA reductase enzyme. The problem is that statins also turn off the body's production of all other compounds that depend on HMG-CoA-reductase, including coenzyme-Q10. Co-Q10 plays a vital role in energy production, and is especially accumulated in the heart. It is probably no coincidence the reason the Baycol statin drug was pulled from the market was because of 31 people who died of muscle tissue breakdown.

—JC

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Examples of the inflammation syndrome

Low-grade inflammatory disorders, if not properly controlled, can have chronic systemic effects. After many years, sustained inflammation can set the stage for more serious inflammatory diseases, such as heart disease, Alzheimer's and osteoarthritis.

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