

FIGHTING INFLAMMATION

It's not as simple as some claim

BY BONNIE LIEBMAN

Heart disease, cancer, Alzheimer's disease, the metabolic syndrome, physical disability. That's just a partial list of the illnesses that have been linked to chronic inflammation.

"It's different from the classic, red, swelling, white-cell kind of inflammation that we're used to thinking of," explains Walter Willett, chair of the Nutrition Department at the Harvard School of Public Health in Boston, Massachusetts.

Instead, it's more of a slow burn that's detected only by a rise in inflammatory signals, or markers—proteins produced by the immune system to fight infection or heal an injury (though not the kind of injury you can necessarily see or feel). The question is: how can you douse the flames?

So far, only one thing is clear, says Willett. "The most powerful way to reduce your inflammatory factors is to lose excess weight."

INFLAMMATION'S HARM

Judging by the advice from Andrew ("Anti-Inflammatory Food Pyramid") Weil, Barry ("The Zone Diet") Sears, Nicholas ("Get a Face Lift...in Your Kitchen?") Perricone, and others, you'd think that if you ate the right foods, it would be easy to fight inflammation.

But does less inflammation mean less disease, or is inflammation just a bit player or an innocent bystander? And if curbing inflammation matters, which, if any, foods can do it? The answers to both questions are elusive.

Heart Disease

"Inflammation plays two key roles in coronary heart disease," explains Penny Kris-Etherton of Pennsylvania State University.

First, it helps build the plaque that narrows arteries. The process starts when the immune system mobilizes to heal an "injury" in the artery wall, often caused by oxidized LDL cholesterol. Smoking, high blood pressure, and high blood sugar can also damage the arteries and lead to plaque buildup.¹ (See illustration, p. 10.)

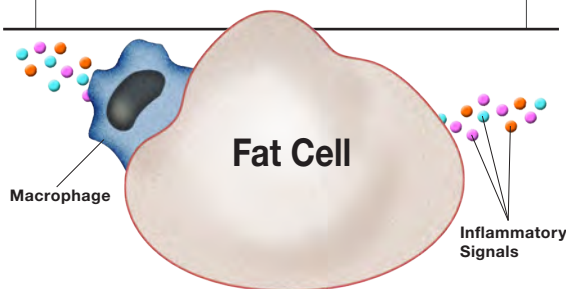
"And every single step of the way, inflammatory signals produced in the plaque fuel the process," says Kris-Etherton.

After decades, the plaque—now filled with cholesterol, calcium, and cell debris—gets covered with a fibrous cap of smooth muscle cells. Then, once again, inflammation wreaks havoc.

"Inflammation causes ruptures of

unstable plaque, which results in a clot," says Kris-Etherton. "That can block the flow of blood through the arteries, which can lead to a myocardial infarction, a stroke, or peripheral artery disease."

"So inflammation is very significant," she adds. Controlling it with "diet, lifestyle, and maybe even low-dose Aspirin is absolutely important."



Stuffed fat cells and invading macrophages send out interleukin-6, tumour necrosis factor-alpha, and other signals that cause inflammation.

Metabolic Syndrome

One out of five Canadians have the metabolic syndrome, which raises the risk of heart disease and diabetes. That includes you if you have at least three of the following:

- blood pressure: 130 over 85 or higher
- fasting blood sugar: 5.6 mmol/L or higher
- waist: at least 35 inches (women) or 40 inches (men)
- HDL ("good") cholesterol: below 1.3 mmol/L (women) or 1.0 mmol/L (men)

- triglycerides: 1.7 mmol/L or higher.

"The metabolic syndrome is clearly an inflammatory condition," says Ishwarlal Jialal of the University of California, Davis. That's because fat cells spew inflammation-causing markers into the bloodstream (see illustration below).

"Adipose tissue produces noxious factors like C-reactive protein, tumour necrosis factor-alpha, and interleukin-1, 6, and 8," says Jialal.

His new study found that it's not just visceral (deep belly) fat, but also subcutaneous (under-the-skin) fat, that's to blame.² "There is no innocent fat," notes Jialal.

Some of those same inflammatory markers that are spit out by fat cells also cause insulin resistance—the body's inability to use insulin to admit blood sugar into cells—which leads to diabetes.³

"That's a fundamentally important observation," says Willett.

Cancer

"We have evidence that local inflammation can be related to cancer," says

Willett. A prime example: when a bacterium called *Helicobacter pylori* colonizes the stomach, it boosts the risk of stomach cancer (and ulcers).

"The infection causes an inflammatory reaction and that leads to cell multiplication, which may be part of the underlying cancer process," notes Willett.

But inflammation may be involved in some cancers even when bacteria aren't. "We have definitive evidence that Aspirin reduces colon cancer risk, and it's very likely through inflammatory pathways," says Willett.⁴

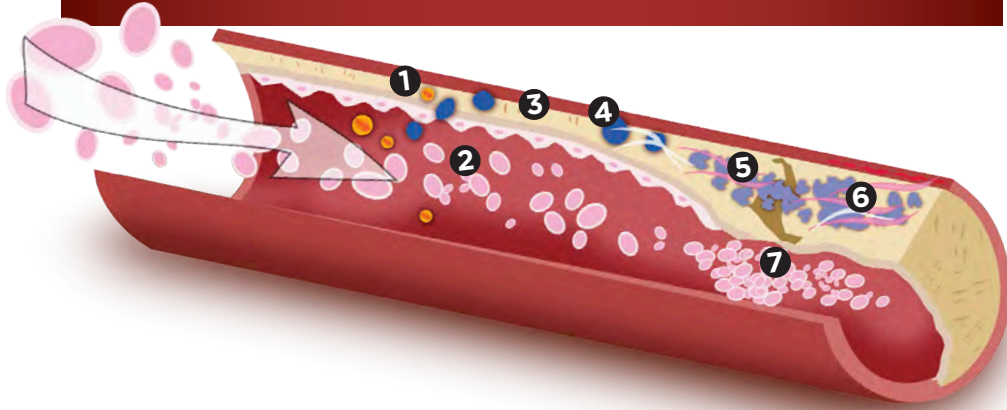
Other evidence suggests that inflammation may play a role in cancers of the lung, esophagus, cervix, and liver.^{5,6}

That's not to say that inflammation is linked to all cancers. For example, "it's less clear for breast cancer," says Willett. "There are associations with inflammatory factors but also with overweight and obesity, so it's difficult to separate the effect of inflammation from the effect of insulin resistance."

In fact, neither may be the key. "The clearest pathway is probably estrogen,"

>>>>

From Inflammation to Heart Attack



❶ Oxidized LDL cholesterol creates an “injury” by burrowing into the artery wall. ❷ The immune system sends inflammatory cells like monocytes to heal the injury. ❸ Monocytes enter the wall and turn into macrophages, which gobble up the LDL cholesterol. ❹ The LDL-stuffed macrophages form a “fatty streak.” ❺ Over decades, more cholesterol, connective tissue, calcium, and cell debris accumulate, turning the streak into plaque. Smooth muscle cells form a fibrous cap over the plaque. ❻ Macrophages break down the cap. ❼ The cap ruptures. When a clot forms around the rupture, blood flow is blocked, which triggers a heart attack or stroke.

says Willett, since it promotes most breast tumours, and fat cells are the chief source of estrogen after menopause.

Memory Loss

The first clue that inflammation is linked to Alzheimer’s disease came from autopsies.

“There is a very high concentration of inflammatory markers around the beta-amyloid plaques that are found in the brains of people with Alzheimer’s disease,” says Zaldy Tan, assistant professor of medicine at Harvard Medical School.

“And now several studies have found that people with higher levels of circulating inflammatory markers are at increased risk of developing dementia.”

One example: in Tan’s study of nearly 700 people in their 70s and 80s, those who had higher levels of inflammatory markers were twice as likely to be diagnosed with Alzheimer’s over the next seven years as those with lower levels.⁷

What’s more, “some studies found that people taking anti-inflammatory drugs like ibuprofen and naproxen for arthritis or other reasons seemed to have a lower risk of developing dementia,” says Tan.

However, clinical trials that gave anti-inflammatory drugs to people at risk for Alzheimer’s found that they had either the same or a greater decline in mental function as those who got a placebo.⁸

“It’s always possible that if you give the drugs for a longer time or earlier in the disease, the results might be different,” notes Tan.⁹ It’s also possible that curbing inflammation simply doesn’t help.

“We don’t know if inflammation is a cause or an effect of dementia,” says Tan. It could simply be the immune system’s

response to beta-amyloid plaques. “Inflammation could be a culprit or just an innocent bystander.”

Disability

Inflammation may eat away at your muscles as you age.

“There’s a strong association between inflammation and a loss of muscle mass and strength,” explains Barbara Nicklas, professor of geriatrics at Wake Forest Medical School in Winston-Salem, North Carolina.

For instance, in the Health, Aging, and Body Composition Study of 2,000 U.S. men and women aged 70 to 79, those with higher levels of inflammatory markers were more likely to lose thigh muscle and grip strength over the next five years.¹⁰

“People with higher levels of inflammatory markers are less physically able to do things,” says Nicklas.

And sarcopenia—muscle loss—can occur no matter what you weigh.¹¹ “Usually people who are obese have more muscle because they have to carry the weight around,” Nicklas explains. “But a sarcopenic obese person has a lot of fat and too little muscle.” And that can lead to falls.

It’s not clear why inflammatory markers go up with age. One possibility: “You gain fat and lose muscle as you age, no matter how hard you try,” says Nicklas.

Inflammation may also rise because of impending illness, she adds. “And some researchers think that the mucosal linings of the gut or nose or other organs break down as we age, and that leads to more pathogens in the body, so inflammation creeps up.”

But it’s still not clear if inflammation causes the loss of muscle or if something else causes both. Says Nicklas, “we don’t know if inflammation is the culprit.”

WHAT MAY HELP

Weight Loss & Exercise

It doesn’t matter if you lose weight by cutting calories, exercising more, or both. If you’re carrying extra pounds, losing them can curb inflammation. “Weight is the big factor,” says Harvard’s Walter Willett.

What about exercise? “For the normal, healthy, average person, exercise programs don’t really make a difference for inflammation,” says Nicklas.

“There are only two ways in which exercise training will make a dent in inflammation,” she adds. One is exercise that leads to weight loss.¹²

The second: “Exercise may also have a benefit if you’re highly inflamed to start with,” says Nicklas. “If you have arthritis or have heart failure or some other chronic condition, or if your inflammatory markers are at the higher end of normal.”

That includes many older people. In her study of 424 people aged 70 to 89, those assigned to do aerobic, strength, balance, and flexibility exercises several times a week had lower levels of interleukin-6 after a year.¹³

But think twice before you rush out to run that 5K race. “A single bout of exercise at a higher intensity *increases* inflammation,” warns Nicklas. “In an older person, the inflammation may contribute to overall muscle breakdown and fatigue.”

But that’s no reason to sit on the couch.

“If you keep up the exercise,” notes Nicklas, “the amount of inflammation isn’t as bad, because you get better fitness. Your muscles are getting stronger.”

And regardless of your age, exercise lowers the risk of heart disease, diabetes, colon and breast cancer, frailty, and more.

“There is no drug to maintain muscle mass,” says Nicklas. “The only thing you can do at any age is strength train.”

Omega-3 vs. Omega-6 Fats

Why would omega-3 fats—like the EPA and DHA in fish oil or the ALA in flaxseed—quiet inflammation?

“It goes back to the idea that the omega-6 fatty acids produce eicosanoids that have pro-inflammatory effects,” explains William Harris of the University of South Dakota Sanford School of Medicine. (Corn, soybean, and sunflower oils are rich in omega-6s.)

“The omega-3 fats produce their own version of those eicosanoids, which are kinder and gentler,” he adds.

That’s how omega-3s got their anti-inflammatory reputation. “And it’s been seen in some rheumatoid arthritis trials,”

The Bottom Line

1. Inflammation has been linked to heart disease, cancer, metabolic syndrome, Alzheimer's disease, and muscle loss with aging. But the evidence is inconclusive that lowering inflammation prevents those diseases.
2. Losing excess weight is the best way to curb inflammation.
3. Exercise can reduce inflammation if it helps you lose weight or if you have high levels of inflammation, which are common among older people.
4. It's wise to eat a diet rich in seafood, beans, vegetables, fruit, and whole grains and to replace butter and margarine with oils. However, it's too early to know if those changes can curb inflammation.

where inflammation is rampant and “where relatively high doses of omega-3s reduce sore joints,” says Harris.

At first, the evidence that omega-3s could also quell inflammation in people with lower levels of inflammation seemed promising.

“Studies found that people with higher omega-3 intakes had lower inflammatory marker levels,” says Harris. But when researchers gave omega-3s to people with or without heart disease, inflammation didn't budge.¹⁴

“In the majority of studies where they've given fish oil to people in a randomized trial, it didn't lower inflammatory markers,” acknowledges Harris, who is also president and CEO of a company that measures omega-3 levels in red blood cells. “There are counter examples, but that's the usual experience.”

It's not clear why. “It could take years of a high intake to change the markers,” Harris suggests. “Or it could be that people who eat more fish are more careful about other lifestyle factors,” and that's why they have less inflammation.

Another possibility: maybe the studies aren't measuring the right thing.

“If you get exposed to bacteria or a virus, you want an inflammatory response because it helps with healing and fighting the infection,” says Penn State's Penny Kris-Etherton. “It's only when the inflammation smolders for a long time that it wreaks havoc.”

So she's launching a new study to test the body's response to infection. “We're giving people EPA and DHA”—the omega-3s in fish oil—“at different doses over a long period of time and then injecting them with *E. coli* bacteria at a very, very low dose,” she explains.

The question: “If you supersaturate your cells and membranes with omega-3 fatty acids, will that not only quell an inflammatory response, but also quicken a resolution?”

Fish oil may protect the heart whether or not inflammation plays a role. In one Italian trial, fish oil lowered the risk of a second heart attack.¹⁵ And in a Japanese trial on 18,000 people who were taking cholesterol-lowering statin drugs, EPA helped those who had high triglycerides and low HDL (“good”) cholesterol.¹⁶ “They had a 50 per cent drop in risk of cardiac events,” notes Harris.

In view of those trials and other evidence, the Heart and Stroke Foundation of Canada recommends that everyone eat at least two servings of fatty fish a week. So does the U.S. American Heart Association.¹⁷

Do you also need to cut back on the omega-6 fats that are found in many oils? No, says the Heart Association panel that Harris chaired.¹⁸

“Eating less omega-6 fat doesn't make a difference,” says Harris. The body doesn't convert much of it to inflammatory eicosanoids. “So the whole mantra—eat less vegetable oil and you'll make less inflammatory eicosanoids—is wrong.”

But eating more omega-3s may help since it means that “less of the omega-6-based inflammatory eicosanoids will be produced,” adds Harris.

Other Foods

■ **Mediterranean diet.** Italian researchers assigned 180 people with the metabolic syndrome to eat either a Mediterranean diet (rich in fruits, vegetables, whole grains, beans, and olive oil and low in saturated fat) or to follow advice on “healthy food choices.”

After two years, the Mediterranean group had lower levels of several inflammatory markers, but that may be because they also lost more weight.¹⁹

■ **Olive oil & nuts.** In a Spanish study of roughly 100 people at risk for cardiovascular disease, inflammatory markers dropped more in those assigned to eat a Mediterranean diet with extra olive oil or nuts than in those who ate the same diet without extra olive oil or nuts.²⁰ But results from other studies differ.^{21, 22}

■ **Whole grains.** In three studies, inflammatory markers were no lower in people assigned to eat whole grains than in those who got refined grains.²³⁻²⁵

■ **Fruits & vegetables.** In a German study, men who were told to eat 8 serv-

ings of fruits and vegetables a day had lower levels of the inflammatory marker C-reactive protein (CRP) than those told to eat 2 servings a day, but the difference was partly due to a rise in CRP in the 2-serving group.²⁶ Another study found no change in CRP when overweight postmenopausal women were told to eat 2, 5, or 10 servings of vegetables a day.²⁷

■ **Legumes.** In a Spanish study of 30 obese men and women, those told to cut calories and eat four servings (each about a cup) of lentils, chickpeas, peas, or beans a week had lower CRP levels than those who cut calories without eating legumes.²⁸ (The bean eaters lost more weight, but the researchers adjusted for that.)

But none of that is enough evidence to be sure that beans—or any foods—matter.

“I wouldn't recommend making a decision based on one or two studies or on observational data alone,” says Alice Lichtenstein, director of the Cardiovascular Nutrition Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston.

The bottom line: replacing meats, sweets, and refined grains with beans, fruits, vegetables, whole grains, and fish—and substituting oils for butter and margarine—is smart, even if it doesn't change your inflammatory markers one iota.

“Can you change inflammation with diet?” asks Lichtenstein. “The data are equivocal. You can change it by losing weight. And there are lots of other good reasons for the majority of North Americans to lose weight.” 🍌

¹ *N. Engl. J. Med.* 352:1685, 2005.

² *J. Clin. Endocrin. Metab.* doi:10.1210/jc.2011-1577.

³ *J. Clin. Invest.* 121: 2111, 2011.

⁴ *Lancet* 369:1603, 2007.

⁵ *Cancer Epidemiol. Biomarkers Prev.* 14: 2413, 2005.

⁶ *Nature* 420: 860, 2002.

⁷ *Neurology* 68:1902, 2007.

⁸ *Arch. Neurol.* 65: 896, 2008.

⁹ *Alz. Res. Ther.* 2: 6, 2010.

¹⁰ *J. Gerontol. A Biol. Sci. Med. Sci.* 64:1183, 2009.

¹¹ *J. Appl. Physiol.* 102: 919, 2007.

¹² *Am. J. Physiol. Endocrinol. Metab.* 298: E824, 2010.

¹³ *J. Am. Geriatr. Soc.* 56: 2045, 2008.

¹⁴ *Inflamm. Res.* 60: 309, 2011.

¹⁵ *Lancet* 354: 447, 1999.

¹⁶ *Atherosclerosis* 200:135, 2008.

¹⁷ *Circulation* 106: 2747, 2002.

¹⁸ *Circulation* 119: 902, 2009.

¹⁹ *JAMA* 292: 1440, 2004.

²⁰ *Am. J. Clin. Nutr.* 89: 248, 2009.

²¹ *Nutr. Metab. Cardiovasc. Dis.* 21 Suppl 1: S14, 2011.

²² *Br. J. Nutr.* 97:1144, 2007.

²³ *Am. J. Clin. Nutr.* 92: 733, 2010.

²⁴ *J. Nutr.* 137: 1401, 2007.

²⁵ *Br. J. Nutr.* 104: 125, 2010.

²⁶ *Am. J. Clin. Nutr.* 82: 1052, 2005.

²⁷ *J. Nutr.* doi:10.3945/jn.111.139659.

²⁸ *Eur. J. Nutr.* 50: 61, 2011.