The Inflammation f

Scientists are looking at a potential new culprit in the development of heart disease and type 2 diabetes

By Terri D'Arrigo

We can predict whether a person will develop type 2 diabetes and heart disease by looking at a number of well-known risk factors: age, family history, race, and whether the person is overweight or leads a sedentary life. But now researchers are considering another potential culprit: inflammation.

When you think of inflammation, you might think of an infected cut or scratch—pain, redness, swelling, and heat at a wound site. That kind of inflammation is called "acute," meaning it comes on quickly and soon goes away.

The inflammation researchers are studying in relation to diabetes and heart disease is a bit different. It has no obvious symptoms. Instead, the evidence of its presence lies in high levels of certain proteins in the blood. Your body releases these proteins in response to injury. Normally this is a good thing, because these proteins limit tissue damage when you have a wound or injury. But if blood levels of these proteins remain high, that means there is ongoing inflammation somewhere inside your body, such as in your blood vessels, your gums, or your joints.

In the quest to understand inflammation, researchers are studying several different proteins, particularly C-reactive protein (CRP), tumor necrosis factor (TNF), and interleukin-6 (IL-6). CRP has made the most headlines, yet all three have led researchers down a winding road of inquiry and fueled more than one scientific debate.

In fact, these proteins are causing some controversy, says Allison B. Goldfine, MD, assistant director of clinical research at the Joslin Diabetes Center and Harvard Medical School in Boston. "It's a question of whether they're markers or mediators," she says. "Are they only signs that inflammation is going on in the body, or are they part of the inflammatory process? Are these the bad guys, and do they work together or independently?"

DIABETES RISK

In recent years, several studies have suggested a link between increased levels of these proteins and the risk of developing type 2 diabetes. Researchers in the Cardiovascular Health Study found that participants with the highest CRP levels were three to four times more likely to develop diabetes within 3 or 4 years of the study than those with the lowest CRP levels. The Nurses' Health Study bore similar results, but also suggested an association between TNF and IL-6 and the development of diabetes.

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factor

Other research indicates an association between these proteins and insulin resistance, a condition in which cells don't use insulin effectively—and which plays a major role in the development of diabetes. However, it remains unclear whether these proteins *cause* insulin resistance by changing how the cells work or react to insulin.

HEART TROUBLE

In the Physicians' Health Study, men with the highest levels of CRP were three times more likely to have a heart attack over an 8-year period than those with the lowest levels. For women, the association was even stronger: In the Nurses' Health Study, women with the highest CRP levels were 4.5 times more likely to have a heart attack than those with the lowest levels.

Scientists disagree about whether CRP is a sign of blood vessel damage or causes the damage directly. Some evidence indicates that high levels of CRP are a sign of both inflamed blood vessel walls and a build-up of sticky, clot-promoting plaque, says James B. Meigs, MD, MPH, associate professor of medicine at Harvard Medical School and Massachusetts General Hospital in Boston. In this scenario the damage comes first, and the body releases CRP in reaction to it. "Yet in test tubes and in some animal studies, these proteins actually *cause*" hardening of the arteries, he says.

TESTING AND TREATMENT

Researchers don't yet know whether lowering levels of these proteins also lowers the risk of diabetes or heart disease, so there are no uniform guidelines for testing and treatment. "The only modestly agreed-upon test for inflammation is a blood test for CRP levels," says Meigs. "But that's only for predicting heart risk, and even then, it's controversial. Different authorities have different recommendations, so it's a little bit in the eye of the beholder." What scientists *do* agree on is that high levels of these proteins are associated with obesity, itself a risk factor for both type 2 and heart disease.

"As fat cells get bigger, they produce cells that tell the inflammatory cells to come in, and these cells excite each other and produce new substances … that [further] mediate inflammation," says Steven E. Shoelson, MD, PhD, professor of medicine at Harvard Medical School and associate director of research at the Joslin Diabetes Center in Boston. "This inflammatory process may affect both insulin sensitivity and the risk of cardiovascular disease, which may explain the connection between weight gain and both diabetes and cardiovascular disease."

To that end, experts agree that losing weight is a safe bet all around. "We already know that diet and exercise are the best two things you can do to prevent and control diabetes and cardiovascular disease," says Shoelson. "But exercise decreases inflammatory proteins. Adding dietary changes on top of it is spectacular."

If you have other risks for heart disease, a high CRP level may nudge your doctor toward recommending drug treatment, says Meigs. Aspirin, cholesterol-lowering drugs called statins, and certain type 2 drugs have all been shown to lower proteins associated with inflammation. But again, there are no standard guidelines. These drugs have proven benefits to lower cholesterol or A1C, but keep in mind that they are not approved by the U.S. Food and Drug Administration specifically for protein levels.

In the meantime, scientists continue their research. "This is an active area of investigation," says Shoelson. "And we don't have all the answers yet."

Terri D'Arrigo is an associate editor of Diabetes Forecast.