Linking obesity, inflammation, dyslipidemia and cardiovascular disease

By Constance Young

This issue’s DO Corner features an interview with Mehdi H. Shishehbor, DO, MPH, about issues relating to his research on the relationships between obesity, inflammation, dyslipidemia and cardiovascular disorders.

Dr Shishehbor is a National Institutes of Health scholar in the Department of Cardiovascular Medicine at the Cleveland Clinic where he is completing a fellowship in interventional cardiology. He is also currently pursuing a doctoral degree in Epidemiology at Case Western Reserve University. Dr Shishehbor is the author of numerous articles.

What is the impact of the frequently observed elevations of hsCRP (high sensitivity C-reactive protein) in obesity and metabolic syndrome?

Dr Shishehbor: The elevations of hsCRP found in people who are obese may indicate that there is a relationship between obesity and inflammation. Obesity, and also metabolic syndrome, are associated with higher levels of high sensitivity C-reactive protein.

Which comes first—obesity or inflammation?

Dr Shishehbor: That is the million dollar question. Most researchers think that obesity comes first and that the fat itself may play a role in the inflammatory cascade. Thoughts are that some of the fat in our body, particularly excess fat around our abdomen, can be a promoter of inflammation.

How specifically does our body’s fat promote inflammation?

Dr Shishehbor: That is a complex situation. Fat can stimulate chemokines and cytokines and through these pathways, enhance the inflammatory cascade putting our entire body at heightened levels of inflammation. In this state there are more inflammatory cytokines and chemokines, and can lead to elevations in high sensitivity C-reactive protein levels.

We don’t really understand how obesity heightens inflammation and its exact pathways, but we do know that chemicals that are released by fat cells activate our inflammatory system, which again leads to increased levels of inflammatory cytokines and other inflammatory proteins that enhance inflammation.

What are the health impacts of obesity and inflammation?

Dr Shishehbor: We have also long known that coronary artery disease is also an inflammatory disease, and that elevations of inflammation throughout the body may play a role in plaque formation and atherosclerosis. Since obesity is also associated with inflammation, we can assume that obesity also correlates with a high incidence of coronary artery disease and we know this is true.

Little by little we are learning that such conditions as osteoarthritis and
rheumatoid arthritis—associated with chronic low-grade inflammation—are also associated with atherosclerosis and coronary artery disease. So we can argue that obesity is another chronic condition that leads to low-grade inflammation and potentially plays a role in atherosclerosis.

C-reactive protein has gained official recognition as a cardiac test, since the federal Centers for Disease Control and Prevention and the American Heart Association have recently issued guidelines for measuring inflammatory markers such as CRP in assessing the risk of cardiovascular disease.

What happens when an overweight or obese person loses weight?

Dr Shishehbor: It has been shown that losing weight decreases hsCRP, so by losing weight a person is evidently decreasing inflammation. And by lowering levels of inflammation, that person also may be slowing or stopping the progression of atherosclerosis and its manifestations.

A recent study in the New England Journal of Medicine, called JUPITER, whose lead author was Dr Paul M. Ridker, MD, MPH, focused its attention on lowering high sensitivity C-reaction protein levels in apparently healthy people. JUPITER stands for Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin.

Study participants at the outset had slightly elevated levels of high-sensitivity C-reactive protein of about 2 mg/L, although their LDL cholesterol levels fell within normal limits—lower than 130 mg/dL. The study found that rosuvastatin treatment lowered hs-CRP levels by 37% as well as LDL-C levels, and this was accompanied by a 44% cardiovascular risk reduction.

There are many ways to treat the consequences of obesity. Obviously, the best way is exercise and weight loss. But getting patients to lose weight can be difficult, so we had best focus on treating the other related conditions—such as blood pressure and diabetes—while trying to get patients to lose weight.

There are a number of things a person can do to lower CRP—for example stopping smoking, exercising more and lowering weight. Lipid-lowering medications and aspirin also can decrease CRP.

The important question is whether hsCRP is a causative agent or just a bystander when it comes to coronary artery disease. Researchers are still trying to determine whether hsCRP is actually causing plaque to build in our arteries or if it is just a marker that doesn’t play a major role in creating plaque.

What are best therapeutic options for targeting obesity, dyslipidemia and inflammation?

Dr Shishehbor: This is a complicated issue that we still don’t fully understand. Right now I think the focus should be on treating dyslipidemia and obesity, not on treating inflammation.

Although we know that inflammation probably plays a role in atherosclerosis, we still don’t have a good sense of how it does this, when to treat it, or even how to measure it. Some basic science indicates that CRP may play a...
direct pathogenic role in arterial disease— that it is a mediator as well as a marker of atherothombosis, but other studies argue against this.

Because research findings are still uncertain, we should focus on the primary risk factors and what we know for certain. If lifestyle changes fail, elevated cholesterol should be treated with statins; elevated blood pressure with blood pressure medications; and obesity with lifestyle changes—exercise and diet modification.

People who smoke should stop smoking. Exercising has been shown to decrease levels of CRP so one could only guess that if you exercise and lose weight, that potentially you are decreasing levels of inflammation and changing your risk factors profile.

We should go back to the traditional risk factors, and in so doing patients’ levels of inflammation will probably decrease. If someone has already addressed all of those issues, and he or she still has elevated inflammation on CRP testing, then we don’t have a good answer for that right now.

There is currently no additional treatment to lower CRP. The only thing we can do is say, “continue doing what you are doing.”

What is the link between visceral adiposity and inflammation?

Dr Shishehbor: This is quite complicated, but I can tell you that there is a significant amount of research in this area and a significant number of people who feel that not all fat is the same and that visceral adiposity is more pro-inflammatory, and may have more inflammatory cells in it, such as macrophages, than other types of fat in the body. Those inflammatory cells and inflammatory markers may play a role in causing atherosclerosis.

**Should waist circumference as a marker of visceral adiposity, and hs CRP as a marker of inflammation, be added in our routine clinical evaluation to help identify the patient at risk?**

Dr Shishehbor: Waist circumference should definitely be considered because it is a very inexpensive tool. I think that waist circumference should definitely be part of the vital signs, just as we check blood pressure and height and weight, we should also measure waist circumference. There is a lot of evidence for this.

*An hs-CRP level of less than 1.0 mg/L is generally considered to denote low risk, 1.0 to 3.0 mg/L intermediate risk, and more than 3.0 mg/L high risk.*

