

## Rheumatoid arthritis (RA) and HS-CRP

Rheumatoid arthritis (RA), systemic lupus erythematosus, and multiple sclerosis are among the group of diseases characterized by the presence of chronic inflammation contributing to significant loss of life expectancy and/or quality of life. Inflammation is increasingly being linked to conditions not generally considered to be among the group of inflammatory diseases, most notably cardiovascular disease and type 2 diabetes.

In a study of over 27,000 apparently healthy women, Paul Ridker, MD and colleagues measured LDL cholesterol and C-reactive protein (CRP), a non-specific indicator of inflammation. In assessing the value of the two measurements over an eight-year (mean) follow up, their data suggested CRP levels to be a stronger predictor of cardiovascular events than LDL cholesterol. An expert panel convened by the American Heart Association and the CDC has since issued recommendations for the highly sensitive C-reactive protein (hs-CRP) test for assessing heart disease risk.

Several studies have found an association between inflammatory markers and increased risk of developing diabetes. In an ancillary study of the NIH-funded Atherosclerosis Risk in Communities (ARIC) project, over 10,000 people who did not have diabetes were followed for nine years with blood sampling for a series of inflammatory markers. Those in the quartile of highest inflammatory marker levels were found to be at 20% to 60% greater risk for developing diabetes than those in the lowest quartile.

“Markers of inflammation don't necessarily mean that you've got an abscess somewhere, where your levels are extremely high,” says Vivian Fonseca, MD. “We're talking about a very tiny increase. The normal hs-CRP for someone may be 2 mg/L, and if that person was very sick with bronchitis it might go to 100. When you happen to have diabetes and heart disease, it's about 3 or 3.5 – slightly elevated, but we now have the ways to reliably measure it at that level. We can't be certain there is a cause-effect relationship in chronic inflammation. It's an association. There is a lot of heart disease in diabetes; there is inflammation in diabetes; there is a lot of inflammation in heart disease, so the two of them are linked. The inflammation seems to be related to the amount of fat that you have and it comes before the onset of diabetes. That is the most interesting thing that has come about so far.”

“It's certainly a revelation for cardiologists, given that some classical risk factors were typically diabetes, high cholesterol, and hypertension,” says Alisa E. Koch, MD, a rheumatologist at the University of Michigan. “Inflammation is being put into the vocabulary of thinking about CVD. Papers about the various inflammatory mediators have been coming out over the last 10 years or so, but I think this is only the tip of the iceberg. CRP is an old marker and a non-specific indicator of inflammation. If someone's CRP is up, it wouldn't tell me that individual has heart disease or RA, it would

just tell me that something is amiss. CRP can sometimes help us see if the patient is having a flare of an inflammatory disease like RA, but we take that only in conjunction with clinical signs and symptoms. To be honest, we really need better markers and that is why a lot of us are doing research.”

Dr. Koch compares the evolving understanding of inflammation in CVD and other conditions to the body of knowledge gained through inflammatory disease research. “In 20 years working with rheumatoid arthritis, we've gone from knowing none of the mediators that cause the disease to knowing many of them,” she explains. “We are now taking care of inflammation with specific biologic therapies that target specific inflammatory mediators known to be important in the disease. One of the mainstays in RA therapy now is to block tumor necrosis factor alpha (TNF $\alpha$ ), a protein one cell makes that influences other cells that causes inflammation. The TNF $\alpha$  blockers

were developed based on that specific pathway. The state of the art has advanced, and we're more advanced in rheumatology than in cardiology because they have only recently come to think about inflammation as part of their disease process. I predict there will be markers in CVD and other conditions based on things like TNFa that will be very useful in the future."

**Aspirin** has been demonstrated to reduce cardiac risk. **Studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce risk of Alzheimer's disease and various cancers. There is also evidence to suggest the cholesterol-lowering statin drugs may lower risk of Alzheimer's, diabetes, and cancer.** "We know that some of the drugs that we use for heart disease, such as the statins, slow inflammation," according to Fonseca. "Some of the drugs that we **use for diabetes, such as the glitazones and insulin, also lower inflammation.** We can't say they are working because they lower inflammation or because of the other actions have. Someday, we'll have to find something that does nothing else but lower inflammation and then we'll have to see if it cures diabetes and heart disease. It's a tantalizing concept. Everything we have currently to treat inflammation has other actions, so we don't know if the good effects are due to inflammation or something else."

"It's an exciting decade for thinking about inflammatory disease," says Koch. "The TNFa blockers are now being applied or thought about in other diseases. For example, prostatitis is now thought by many to have an inflammatory basis and there have been trials to apply some of the knowledge that we have from a disease like RA. And the knowledge we've gained about heart disease and inflammation has spilled over into rheumatology as well. It turns out that women with systemic lupus erythematosus are at greatly increased risk for cardiac disease compared to women in the general population, and RA patients are also at higher cardiac risk. The knowledge base has increased to make us think more about this, and think about it earlier. We have always diagnosed other systemic disease from our interest in rheumatology, but now even more so because of what is known about inflammation."