Inflammation May Drive Comorbidities in RA

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BALTIMORE — Inflammation appears to underlie the increased risk for insulin resistance, metabolic syndrome, and cardiovascular morbidity in patients with rheumatoid arthritis, Dr. Joan M. Bathon said at a conference on rheumatic diseases sponsored by the Johns Hopkins University.

In addition to tightly controlling inflammation in RA patients, she advised physicians to "think about insulin resistance and metabolic syndrome in your patients with RA, and encourage them to lose weight, exercise, and eat less. This may also reduce insulin resistance."

Cardiovascular disease (CVD) is the largest contributor to the 1.28- to 3-fold increase in the Standardized Mortality Ratio in patients with RA, and to their 5- to 10-year reduced life span. Although overt CVD risk factors such as hypertension, diabetes, hypercholesterolemia, and body mass index do not appear to be elevated in RA patients, there is evidence that more subtle but nonetheless risky factors associated with CVD are increased in RA patients, particularly insulin resistance.

Inflammation and obesity both predispose to insulin resistance, and insulin resistance in turn is a potent risk factor for myocardial infarctions and stroke, she said.

Data suggest that RA patients have an increased prevalence of insulin resistance even in the absence of diabetes, more proatherogenic lipid profiles including reduced levels of HDL cholesterol, an increased percentage of body fat even in the absence of overall obesity, and higher rates of the metabolic syndrome, an inflammatory condition in the general population.

"Are CV risk factors more prevalent in RA patients? Not by clinical definitions. But, using some of these alternative definitions, the answer is yes," said Dr. Bathon, professor of medicine and director of the arthritis center at Johns Hopkins University, Baltimore.

Aside from systemic inflammation, factors such as drug toxicity also may contribute to the increased CVD risk in RA patients: Steroids are atherogenic, cyclooxygenase 2 inhibitors cause thrombosis, methotrexate is associated with hyperhomocysteinemia, and anti–tumor necrosis factor agents can cause congestive heart failure. RA might also be associated with increased thrombotic tendency, and patients with the disease often are less active, leading to cardiac deconditioning.

Current theory is that inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) explain the increased risk of CVD in RA patients. Both can induce insulin resistance—thus, inflammation could promote atherosclerosis, in part through its link with atherogenic metabolic pathways. Studies researching treatment with a TNF inhibitor, which temporarily or partially improves insulin resistance, dyslipidemia, and endothelial dysfunction, also support the theory, Dr. Bathon said.

Abdominal, and especially visceral, obesity also is linked to insulin resistance. Visceral adiposity, as opposed to subcutaneous fat, is thought to increase the proinflammatory milieu via the same cytokines, also leading to endothelial dysfunction, insulin resistance, and atherosclerosis.

Dr. Bathon and her associates at the university analyzed the body composition of 84 RA patients (58 men, 26 women) using total body dual-energy x-ray absorptiometry scanning. The group had a mean age of 61 years, and 89% of patients were white. About one-third each were classified as normal weight, overweight, and obese.

In the women, body fat percentage (BFP) was about 15% greater than that predicted from norms for age, race, and gender, a statistically significant increase. The mean increase in BFP was comparable across BMI strata. This increase was confirmed more recently in studies comparing RA patients with contemporaneous matched controls. In men with RA, however, BFP was not significantly greater than in controls.

"Women with RA classified as 'normal weight' have proportionally similar increases in BFP as those classified as overweight or obese, suggesting that RA patients may be at greater risk for disorders associated with increased adiposity than would be expected by their BMI values alone," Dr. Bathon noted.

Inflammation and increased fat mass may work together to promote insulin resistance and CVD in RA patients, so a coordinated program to reduce inflammation and control weight will likely be the most successful approach to reducing the prevalence of insulin resistance, she said. ■