Cardiovascular Disease, Estrogen Deficiency, and Inflammatory Cytokines

Jane F. Reckelhoff

The incidence of hypertension increases in women after menopause, as does the susceptibility to myocardial infarction and other cardiovascular diseases. The mechanisms responsible for increased cardiovascular disease risk after menopause are unknown. However, postmenopausal women exhibit increases in inflammatory markers, such as C-reactive protein and inflammatory cytokines, which have been suggested to increase the risk of cardiovascular disease. Arenas et al report data in this issue of Hypertension that support this hypothesis.

With menopause, the sex hormone levels decrease drastically. Estrogens have been shown to be antioxidative and to modulate both vasoconstrictor and vasodilator systems. For example, estradiol is known to increase NO synthase synthesis and activity and to reduce expression of the angiotensin (Ang) type 1 receptor (AT1R). Therefore, loss of estrogen production with menopause should be associated with increases in oxidative stress mediated by the renin–Ang system (RAS) because of increased expression of AT1Rs. This could occur even in the face of no change or lower levels of Ang II with aging. The consequences of increasing oxidative stress would lead to reductions in bioavailable NO because of the increased superoxide production but also the loss of antioxidant capacity. The combination of NO and superoxide produces peroxynitrite, a potent oxidant that is thought to reduce the levels of prostacyclin and increase the levels of thromboxane A2 because of peroxynitrite-mediated protein nitration. Both reactive oxygen species and Ang II are known to upregulate production of inflammatory cytokines, such as tumor necrosis factor (TNF-α), by activating nuclear factor κB.

Previously, Arenas et al made the observation that cytokine expression, particularly TNF-α, was increased in aging, ovariectomized female rats. In the present study, she and her colleagues carry this observation further and determine whether an increase in TNF-α caused by ovariectomy of middle-aged rats was associated with changes in mesenteric adrenergic vascular responses and whether these vascular responses were mediated via the RAS and/or TNF-α. They found that aged ovariectomized rats had increased plasma TNF-α and had increased sensitivity of their mesenteric vasculature to phenylephrine vasoconstriction. Estradiol repletion or blockade of TNF-α receptor with etanercept attenuated the phenylephrine vasoconstrictor response. In addition, the vascular response was also attenuated by candesartan, the AT1R antagonist. However, in ovariectomized rats in the presence of estradiol repletion or etanercept, there was no effect of candesartan on the phenylephrine response in mesenteric arteries. Finally, they found that mesenteric expression of AT1R, Ang-converting enzyme, and Ang II were reduced in estrogen-replete or etanercept-treated rats compared with untreated ovariectomized controls. These data support the hypothesis that estrogen depletion in aging female rats, as occurs in postmenopausal women, is associated with vascular hypersensitivity that is mediated by both TNF-α and the RAS.

These data then raise several important unanswered questions. First, because it has been established in many studies that, after menopause, women also exhibit increases in inflammatory markers, such as C-reactive protein, is the inflammatory process in postmenopausal women associated with upregulation of components of the RAS in their vasculature? It is known that Ang II can activate nuclear factor κB and thereby upregulate the expression of inflammatory cytokines including TNF-α. The subsequent activation of the RAS components by TNF-α, as postulated by the data presented by Arenas et al, would set up a positive feedback loop that would be deleterious to vascular function.

Probably the most important unanswered question, however, is why in recent clinical trials was hormone replacement therapy not protective against increases in C-reactive protein and cardiovascular disease outcomes? Data from the Women’s Health Initiative (WHI) Study showed that standardized hormone replacement therapy with conjugated equine estrogens (CEEs) and medroxyprogesterone acetate increased the incidence of both primary and secondary coronary events. It is possible that the use of medroxyprogesterone could have abrogated any beneficial effects of the estrogens on the inflammatory process in the WHI Study. This hypothesis is supported by a recent study by Reuben et al, who analyzed data from the Postmenopausal Estrogen/Progestin Intervention (PEPI) cohort and found that, in women given CEE-progestin regimens, C-reactive protein was increased and positively correlated with interleukin 6, which is secondary to TNF-α activation. This was not found in women in the CEE-only group.

However, in a recent reevaluation of the WHI cohort, there was no difference in the hazard ratio for coronary events between women aged 50 to 79 years who received CEE only.
compared with those receiving placebo. Thus, just as in women who received CEE + medroxyprogesterone, estrogen replacement without progesterone in the whole cohort was not protective against primary or secondary coronary events. In contrast, in women in the cohort who were 50 to 59 years of age, the CEE-only regimen did result in fewer events. Taken together, these data suggest that with increasing age, any benefit from estrogens to protect against cardiovascular disease after menopause may be adversely overcome by other factors associated with aging, such as additional increases in oxidative stress independent of estrogen loss. It is also possible that aging may abrogate the beneficial effect of estrogens in women by changing the vascular response either through changes in estrogen receptor expression or through changes in estrogen-mediated intracellular signaling pathways. In fact, Vitale et al9 reported that hormone replacement therapy was not successful in reducing inflammatory markers in women who were older and had a longer time since menopause.

Another reason why CEE may not have been effective in protecting against cardiovascular disease in the WHI Study is that the preparation was taken by mouth. Sumino et al10 have reported recently that transdermal hormone replacement with estradiol and medroxyprogesterone patches for 12 months resulted in reductions in monocyte chemoattractant protein 1 and vascular inflammatory markers, such as intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin. However, C-reactive protein concentrations in plasma did not change in this study compared with untreated control postmenopausal women.

The role that inflammatory mediators play in mediating cardiovascular disease in postmenopausal women is not clear. Perhaps there is a certain subset of postmenopausal women who are more sensitive to inflammation as a risk factor for cardiovascular disease. For example, Alexander and Clearfield11 contend that increases in C-reactive protein significantly amplify the cardiovascular risk in aging women who have the metabolic syndrome.

In conclusion, there is clearly a significant amount of research necessary to sort out the mechanisms responsible for the increase in cardiovascular disease in postmenopausal women. The studies of Arenas et al2 in this month’s Hypertension provide provocative data regarding the interaction between inflammatory markers and the RAS that may play synergistic roles in mediating vascular disease in aging women.

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References