Estrogen and Different Aspects of Vascular Disease in Women and Men

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Considerable evidence indicates that sex hormones have an important influence on cardiovascular physiology and pathology. Recent work suggests that a mechanism based on estrogen receptor-alpha (ESR1) contributes to a range of structural and functional responses that relate to vascular disease. Most of this work focuses on ESR1 activity within the endothelium and yields variable findings due, at least in part, to differences in the vascular bed or species studied, as well as other experimental conditions such as age, estrogen status, degree of preconstriction, etc. But many findings in conduit arteries (eg, more frequent plaque erosion, increased wall stiffness, spasm, etc) and microvessels (eg, reduced coronary flow reserve, hot flashes, etc) implicate smooth muscle cells (SMCs) in gender differences in vascular disease. These cells are directly responsible for extracellular matrix production and assure the integrity of the artery wall. They may be decreased, apoptotic, or dysfunctional in terms of synthesis and repair of extracellular matrix, which is destroyed in vulnerable plaque by macrophages.

In this issue of Circulation Research, Montague and colleagues report that activation of ESR1 decreases human aorta SMC differentiation (Figure). Importantly, they found that SMCs of men, compared with women, had reduced ESR1 expression associated with increased differentiation markers. Their work suggests that ESR1 activation switches SMC to a form that may promote plaque vulnerability. Could different activation states of ESR1 be responsible for shifting the functional characteristics of SMCs toward a phenotype that explains some complexities of gender-related differences in vascular disease?

Differences in Vascular Disease Between Women and Men

Risk conditions and clinical findings indicate that the pathophysiology underlying ischemic vascular disease differs between women and men. A number of conditions are unique to women (eg, early age at menopause, hypertensive disorders of pregnancy, gestational diabetes, peripartum aortic or coronary dissection, polycystic ovarian syndrome, hypothalamic hypoestrogenemia, etc). Other factors linked with vascular disease or dysfunction are much more frequent in women than men (eg, migraine, coronary spasm, vasculitis, Raynaud phenomenon, etc). On this background, postmenopausal women more frequently have many traditional vascular disease risk conditions (eg, diabetes, obesity, hypertension, inactivity, etc) which occur and cluster more frequently in women than men. In addition to this greater burden of risk factors, the woman with vascular disease often is older and has more functional disability than her male counterpart.

Women have poor clinical outcomes compared with men with acute coronary syndromes, chronic coronary syndromes, coronary revascularization, and heart failure that cannot be explained by simply adjusting for age. So other factors must contribute to the increased severity of vascular disease in women compared with men.

Clinical Characteristics and Links With Sex Hormones

Although, ischemic vascular disease is the most frequent cause of death for women, its prevalence in women compared with men does not increase markedly until after menopause when major changes in sex hormones occur. During menopause estrogen levels are about one-tenth premenopausal levels and the predominant source, estradiol, changes to estrone produced by conversion of androgens in adipose tissue. Age-dependent aromatase expression in SMCs provides a mechanism for local production of estrogens from androgens. Aging attenuates many estrogen-related potentially beneficial responses. Yet, we have observed that central-induced endogenous estrogen deficiency in younger women is associated with a >7-fold increase in risk of coronary obstruction. One interpretation is the widely varying estrogen/androgen balance occurring throughout a woman’s life contributes to differences in vascular disease compared with men. This includes high levels of estrogen premenopause and decreasing estrogen and progesterone levels postmenopause, along with changing hormone balance during pregnancy, peripartum, and oral contraceptive or replacement therapy. Such varying estrogen/androgen balance interacts with the female unique and traditional risk conditions, as well as diet (eg, phytoestrogens, etc), physical activity, psychosocial characteristics, etc, to modulate differences in vascular disease.

Estrogen exerts effects via 2 receptors abundant in vascular tissue to transduce signals regulating expression of many genes, and it also has nongenomic effects. Considerable evidence implicates the ESR1 in vascular structure and function. Attempts to link estrogen receptor-alpha gene (ESR1) variation with adverse outcomes yield mixed re-
Hypothetical construct based on Montague et al suggests that the activation state of estrogen receptor-alpha (ESR1) governs the vascular smooth muscle (SMC) phenotype. Among men with lower ESR1 expression they identified higher levels of differentiation markers compared with women. However activation of ESR1 in SMCs containing low ESR1 expression reduced differentiation markers and promoted apoptosis. This was accomplished by the authors using lentivirus transduction. Conversely, inhibiting ESR1 in SMCs expressing high levels of interfering RNA (SiRNA). The balance between these mechanisms could contribute to vascular remodeling and plaque instability.

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None.

References


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