The slowing down of renal deterioration but acceleration of cardiac hypertrophy: is the estrogen receptor-α a hero or villain?

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CARDIOVASCULAR DISEASE (CVD) and chronic kidney disease (CKD) are complex diseases of multifactorial origin (8). One important fact has emerged over the years: there is a gender difference in the incidence and severity of these diseases, in that women, especially before menopause, have a significantly lower risk of CVD and CKD than men (10). Male gender is an independent risk factor for the development and progression of CKD, and men progress to end-stage renal disease (ESRD) from CKD faster than premenopausal women, regardless of previous renal status. In addition, the lifetime risk of ESRD is consistently higher for men at all ages and all estimated glomerular filtration rate strata than for women (9), although the renal function of postmenopausal women may be exacerbated.

Besides renal function, gender also affects cardiovascular function; for example, gender seems to have a real influence on endothelial function. One study used a validated tool able to detect endothelium function status, i.e., flow-mediated vasodilatation, to test the “endothelial dysfunction” of different genders (2). Endothelial dysfunction may be the earliest event in the atherosclerotic process. Ciccone and colleagues (2) found that reduced flow-mediated vasodilatation is related to older age (r = −0.34, P < 0.0001) and sex. Preservation of flow-mediated vasodilatation was significantly different between men and women: men maintained their stable flow-mediated vasodilatation before 40 yr of age, but women showed longer maintenance, with stability until their early 50s. However, similar to renal function, a steep decline in flow-mediated vasodilatation starts at menopause in women, and deterioration of function seems to be more severe and rapid in women than in men (2). Therefore, attention recently has been focused on understanding the features of gender differences relevant to the physiological, pathological, and pathophysiological features of cardiovascular and renal systems, including Diwan’s study (3) in a recent issue of the American Journal of Physiology-Renal Physiology. However, to date, there is uncertainty as to why gender differences influence physiological, pathological, and pathophysiological changes. Various factors that differ between women and men, including genetic, hormonal, reproductive, social, and lifestyle factors and age, can affect the incidence and severity of physiological and pathophysiological statuses, including CVD and CKD (2). Evidence supports the contribution of sex hormones, especially estrogen, as a possible key factor in the above-mentioned differences (8).

The action of estrogen is frequently mediated by estrogen receptors (ERs), which include at least three distinct ERs, i.e., ERα, ERβ, and GPER (referred to as G-protein-couple protein 30) and then controls many physiological functions and contributes to pathological processes, including various kinds of women’s cancers, such as breast cancer and endometrial cancers (6). Estrogen-ER action is usually thought to function as reno- and possibly cardioprotective (7). Various animal models of renal diseases have shown that the progression of renal injury is slower in female animals than in male littermates, that disease progression in male rats could be slowed by estrogen substitution or orchietomy, that estrogen can suppress collagen synthesis in glomerular mesangial cells by attenuating angiotensin II-induced mitogen-activated protein kinase activity and the expression of transcription factor AP-1, and that estrogen application reduced proteinuria and glomerular fibrosis after experimental renal damage, including in ischemia-reperfusion animal models (3,4). However, the contributory mechanisms of estrogen are uncertain. It has been proposed that the effect of estrogen-induced renal and possibly cardiovascular protection may be mediated by ERα (3). In fact, Kummer and colleagues (4) found that estrogen could suppress apoptosis of podocytes and glomerulosclerosis, which was mediated through ERα. Moreover, studies showed that both ERα and ERβ are expressed in the human cardiovascular system, including in vascular endothelial cells, vascular smooth muscle cells, and cardiomyocytes (1). However, the action of estrogen is more complicated, since studies have shown the different mechanisms of estrogen that provided vascular, myocardial, and renal protection. The adenine-fed rat model of Diwan (3) showed that an adenine diet significantly decreased ERα expression in male rat kidney, but significantly increased ERα expression in the heart of both genders. Their results regarding renal function showed female adenine-fed rats had significantly less kidney functional decline than male adenine-fed rats, but CKD-related molecular changes, including hemeoxygenase-1, tumor necrotic factor-α, and ERK 1/2, were similar between the two groups (3). In addition, compared with the female rats, the decreased expression of ERα in the kidney and changes in plasma estrogen and testosterone concentrations in males may be associated with this increased damage. All of this suggested the favorable role of ERα in the kidney.
However, the role of ERα in the heart is much more complicated. Two major vasculoprotective effects of estrogen, namely, atheroprotection and acceleration of endothelial healing, are clearly both mediated by ERα and involve profoundly different cellular and molecular mechanisms (7). The results of a study investigating ER expression in human cardiovascular pathology showed increased ERα and ERβ mRNA expression in left ventricular specimens from coronary heart disease and dilated cardiomyopathy patients compared with healthy individuals, suggesting that severely impaired left ventricular function per se might lead to a compensatory increase in ERs (7). Consistent with part of the above-mentioned study, the intake/output records and echocardiography results in Diwan’s study (3) showed that female adenine-fed rats presented with both pressure and fluid overloads, suggesting that expression of ERα and activation of the ERK1/2 pathway were significantly increased, which may be attributed partly to cardiac hypertrophy. However, it is uncertain why there was a difference in the pattern of cardiac hypertrophy between genders (a concentric pattern in males and eccentric pattern in females). Diwan did not investigate this issue.

Besides the different actions of ERα on different organs, the different subtypes of ERs might also function differently. One study showed that ERα, but not ERβ, mediated estrogen’s regulation of serum lipid and cholesterol concentrations in mice, while estrogen reduced the histological complexity of atherosclerotic plaques in compound gene-targeted animals, suggesting that ERα may be involved in some elements of plaque formation (1). While ERβ seems to mediate myocardial protection, ERα is responsible for protection against vascular diseases (1). As mentioned above, Diwan reported an increased expression of ERα accompanied with cardiac hypertrophy, which might compensate for the contraction ability of the heart (3). Cardiac hypertrophy, transiently, might be needed for maintaining “normal” heart function, but in the long-term it may increase the burden of oxygen consumption of the heart and exacerbate the severity of existence of ischemic heart disease. The net effect might not be good for the heart itself (Fig. 1).

Therefore, the locations of ERs in nephron segments and in the heart might be required to study the role of estrogen in the evolution of CVD and CKD; however, this has not been fully elucidated, including in the study by Diwan et al. (3). Dr. Diwan concluded that ERα with increased phosphorylation of ERK 1/2 might be the molecular pathway for cardiac hypertrophy associated with CKD in both genders in the rat model, which supported the links between CKD and CVD (3); however, the end result of cardiac hypertrophy mediated by ERα, as suggested in Diwan’s study (3), is a worse sign of heart failure in human beings with CVD. Thus more studies aiming to elucidate the role of ERα or ERβ, including selective estrogen receptor modulators (5), in primary prevention or treatment of CKD and CKD-related cardiovascular disease, should add an interesting facet in the future. This in vivo adenine-fed rat model might be useful and applicable to the study of complications of CKD patients.

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![Fig. 1. Role of estrogen receptor-α (ERα) in the kidney and heart and the hypothetical mechanisms of chronic kidney disease (CKD) and CKD-related cardiovascular disease (CAD). Estrogen-ER action is usually thought to function as renoprotective and cardioprotective, including prevention of glomerulosclerosis and podocyte apoptosis in the kidney, atheroprotective by lowering plaque formation, and against endothelial dysfunction after injury, ischemia, and reperfusion. The adenine-fed rat model of Diwan (3) showed that an adenine diet significantly decreased ERα expression in the male rat kidney, but significantly increased ERα expression in the heart of both genders. Their results regarding renal function showed male adenine-fed rats had significantly more kidney function decline than female adenine-fed rats, suggesting the favorable role of ERα in the kidney. Since an increased expression of ERα with subsequent activation of the ERK1/2 pathway may be attributed partly to cardiac hypertrophy, cardiac hypertrophy, a compensation for the contraction ability of the heart, might transiently maintain “normal” heart function; therefore, it is a hero for the heart. However, cardiac hypertrophy may increase the burden of oxygen consumption and further exacerbate the severity of existence of ischemic heart disease or even worsen the “normal heart.” Therefore, the net long-term effect of ERα might not be good for the heart itself. CVS, cardiovascular system; RAAS, renin-angiotensin-aldosterone system; ANP/BNP, atrial natriuretic peptide/brain natriuretic peptide; NPR-A, type A natriuretic peptide receptor.](http://ajprenal.physiology.org/)}
DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES


