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Review Article

Klotho and Postmenopausal Hormone Replacement Therapy in Women with Chronic Kidney Disease

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Kidney function is highly susceptible to age-related changes, with chronic kidney disease (CKD) serving as an important cause of morbidity and mortality in older patients. The prevalence of CKD in Korea is higher among the elderly, relative to the general population, with the most significant increases seen following the onset of menopause. Under normal conditions, estrogen attenuates renal superoxide production and protects the kidney from oxidative damage. As estrogen levels are known to decrease by as much as 80% during menopause, this represents a significant risk for older women. Postmenopausal hormone replacement therapy (HRT) modulates the renin-angiotensin system, thereby reducing the progressive deterioration of renal function. Use of estrogen-based HRT has been shown to ameliorate renal function in postmenopausal women, and delay CKD progression. Renal expression of klotho, an important suppressor of aging, is markedly decreased in CKD patients, making it a promising candidate for use as a prognostic biomarker in CKD. Here, we review the key links between renal function, sex, age, and estrogen levels during menopause, and discuss the use of postmenopausal HRT in CKD attenuation. **(J Menopausal Med 2018;24:75-80)**

Key Words: Estrogen replacement therapy · Hormone replacement therapy · Postmenopause · Renal insufficiency, chronic

Introduction

Chronic kidney diseases (CKD) are one of the many problems that arise in older populations. The prevalence of CKD increases with age, with significantly higher incidence seen among the elderly (22.0%), relative to both middle-aged (6.4%) and young individuals (2.8%).[1] In Korea, the prevalence of CKD varies based on sex and menopausal status, with an incidence of 7.4% in men and 4.7% in pre-menopausal women, compared to 20.1% in postmenopausal women.[2]

Development of CKD is associated with accelerated aging and is closely related with metabolic disorders (MD). Under normal conditions, estrogen attenuates renal pathology; however, as estrogen levels can decrease by as much as 80% during menopause,[3] this represents a significant risk for older women. It is therefore important to identify ways to preserve kidney function as patients' age.

Estrogen has been shown to protect against both the occurrence and progression of CKD, making it an attractive option for delaying CKD progression. Estrogen-based hormone replacement therapies (HRT) have been shown to confer protective effects on kidney-related diseases by attenuating kidney injuries caused by superoxide production. Klotho is a well-established anti-aging gene that is highly expressed in the kidneys. Expression of this gene has been shown to inhibit kidney diseases,[4] with significant evidence regarding its role in the pathophysiology of CKD.

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Here, we examined sex-specific differences in renal function and CKD, focusing on the relationship between estrogen levels and menopause in older populations. Furthermore, we review the effects of postmenopausal HRT and klotho expression on the incidence and progression of CKD.

Disease Burden of CKD

1. CKD incidence by sex and age

CKD is widely regarded as a disease of aging, with higher incidence seen in elderly populations. According to a nationwide survey, the prevalence of CKD in Korea was 8.2% among adults aged ≥20 years.[1] Kim et al.[5] reported that the prevalence was 13.7% among for residents aged ≥35 years of age in Korea. The overall incidence of CKD was shown to increase in accordance with age in both sexes, with the most significant changes seen in women aged >50 years.[2] Given the aging population of many countries throughout the world, CKD will represent an important public health concern in the years to come.

2. Aging and CKD

CKD is associated with accelerated aging due to the accumulation of uremic toxins, oxidative stress, and persistent inflammation.[6] As people grow older, accumulated kidney damage leads to decreases in both the estimated glomerular filtration rate (eGFR) and renal blood flow (RBF). eGFR is typically low at birth and does not reach adult levels until the late 20s, where it is maintained at ~140 mL/min/1.73 m^2 into the 40s,[7] after which levels decline by ~8 mL/min/1.73 m^2 per decade thereafter.[8,9] Similarly, RBF levels are maintained at ~600 mL/min into the late 40s, followed by declines of ~10% per decade.[7,10]

CKD is often accompanied by MDs as well as hyperparathyroidism, and vitamin D deficiency, which can lead to osteoporosis. Hyperparathyroidism in CKD results from hypocalcemia occurring partly from phosphate retention or 1,25-dihydroxy-vitamin D3 synthesis deficiency.[11] Due to the changes in calcium and vitamin D metabolism, mineralization defects may occur, which leads to osteoporosis.[12] Outside of MDs, Pituitary and gonadal alterations leading to disruptions in the hypothalamic pituitary gonadal axis are also seen in CKD patients, it may contribute to hypogonadism. Cardiovascular disease (CVD) is also common in patients with CKD regardless of age and severity of kidney disease.[13] CKD has also been shown to cause premature menopause in women, on average 4.5 years earlier than their healthy counterparts (47 years vs. 51.5 years, respectively).[14,15]

Sex Differences in CKD

1. Renal function in men and women

Sex has been regarded as one of the important factors influencing kidney function and progression of renal disease. While both sexes show physiological and morphological differences in the kidneys, women and men exhibit numerous differences in clinical presentation, including differences in symptom presentation, disease tolerance, and responses to treatment.[16]

Specific outcomes include higher renovascular resistance, lower eGFR, and lower renal plasma flow in women compared to age-matched men.[16] In terms of histological findings, women's kidneys exhibit smaller mitochondria, fewer lysosomes, and abundant ribosomes in proximal tubular cells.[16] Furthermore, the renin-angiotensin system (RAS) has been shown to exhibit important sex-specific differences. The RAS helps to limit the progressive deterioration of renal function through reductions in blood pressure (BP) and proteinuria. Two different sex hormones, estrogen and testosterone, may play a role in RAS function. Estrogen has been shown to increase angiotensinogen synthesis, while decreasing renin and angiotensin-converting enzyme (ACE) synthesis. In contrast, testosterone increases renin release.[16] Similarly, estrogen mediates a decrease in arterial pressure via signaling through the AT2 receptor and ACE2, while testosterone increase arterial pressure via the AT1 receptor and classical RAS pathways. Women experience lower incidence of hypertension and chronic renal disease compared to men due to the divergent effects of estrogen and testosterone. Based on these observations, it is not surprising that studies have shown sex differences in the effectiveness of RAS inhibition via ACE inhibitors and angiotensin receptor blockers. Further studies will be necessary to clarify the

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clinical significance of these findings.

2. Sex differences in nitric oxide (NO) production and kidney disease progression

According to the most inclusive meta-analysis to date, comprising a total of 11,345 patients from 68 studies, women are likely to progress to end-stage renal disease (ESRD) more slowly than men.[17] Potential mechanisms for sex differences in kidney disease progression can be explained based on differences in NO metabolism, oxidative stress, sex steroids, lifestyle differences, and other sex-specific risk factors.[16]

NO is a potent regulator of vascular tone, with deficiencies in NO synthesis leading to endothelial dysfunction.[18] Within the kidneys, NO has been shown to inhibit the growth of mesangial cells, and limit production of extracellular matrix components.[18] Low NO levels in both blood and urine are generally observed in CKD patients.[19,20] Schmidt and Baylis[9] demonstrated that total NO production was nearly 9-fold lower in the peritoneal dialysis group (57 ± 26 μmol/24 h) relative to healthy group (525 ± 108 μmol/24 h), while Luksha et al.[18] observed ~2-fold lower total urinary NO excretion in CKD patients (410 ± 56 μmol/24 h) compared to controls (914 ± 129 μmol/24 h).

Sexual dimorphism in the NO system extends beyond humans, having been reported in several animal models of renal disease. These results suggest that sex difference in renal NO production is one of the contributing factors to the progression of renal disease. Ji et al.[21] reported that female rats with renal wrap (RW) hypertension (RWH) have higher NO levels than male rats, and that male rats with RWH are more susceptible to changes in NO production. Endothelial NO synthase (eNOS) production was 2.8-fold higher in the sham-operated female renal cortex compared to males. Furthermore, RWH had no effect on eNOS and neuronal NO synthase (nNOS) expression in the renal cortex and medulla of female rats, compared with males where eNOS expression was significantly upregulated in both the renal cortex and medulla, while nNOS protein expression was noticeably decreased in the medulla. These results suggest that the kidneys upregulate the expression of eNOS to compensate for the loss in medullary nNOS. A sustained, chronic loss of renal nNOS may therefore lead to hypertension and a decrease in GFR.

In human studies, sex differences in kidney diseases can probably be attributed to estrogen-mediated increases in renal NO synthase production.[22~24] Healthy premenopausal women show greater NO levels (2111 ± 139 μmol/36 h) compared with equivalent-aged men (1682 ± 87 μmol/36 h). Furthermore, urinary ^{15}N nitrate production by NO synthase over the course of 36 hours was positively associated with serum 7β-estradiol levels in females, suggesting a strong link between estrogen levels and NO synthase activity.[22]

3. Sex differences in superoxide production and renal function

Although men exhibit more rapid declines in renal function than women, the mechanisms underlying this sex difference have not been clearly demonstrated. Estrogens have protective effects on kidney-related diseases by attenuating kidney injuries induced by superoxide production, whereas testosterone inhibits antioxidant enzymes.[25]

Ji et al.[25] examined the renal cortex of males and females to determine if protection from renal disease progression is consistent with 17β -estradiol-induced reductions in superoxide production. Superoxide production was assessed by measurement of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in RW rats, as well as in ovariectomized rats treated with estradiol or vehicle control. Mean renal cortical NADPH oxidase activity was 1.3-fold lower in RW females than RW males. Similarly, ovariectomy increased NADPH oxidase activity 1.4-fold, whereas estradiol replacement prevented it. These results indicate that estradiol attenuates renal superoxide production and protects the female kidney. Furthermore, treatment with testosterone resulted in progressive kidney damage by increasing incidence of nephropathy (16-92%) in ovariectomized diabetic rats.[26]

HRT for the Treatment of CKD

1. Role of estrogen in CKD

In women with CKD, disruption in gonadotropin-releasing hormone production leads to decreases in estradiol production. Low estradiol levels have been associated with abnor-

mal menstruation, hot flashes, sleep disturbances, and mood swings, as well as decreases in sexual desire and fertility.[27,28] In terms of disease pathology, estrogen administration may represent a viable therapeutic strategy for delaying CKD progression. In animal models, estrogen has been shown to confer antifibrotic and antiapoptotic effects in the kidney, with administration of estrogen decreasing glomerulosclerosis and tubulointerstitial fibrosis, and protecting renal tubular function by reducing the permeability of the glomerular endothelium.[16]

2. Effects of HRT in postmenopausal patients with CKD

Postmenopausal HRT is believed to affect the RAS, renal sodium excretion, renal endothelial function, BP, and albumin excretion.[29,30] Microalbuminuria, an early marker of vascular endothelial damage and CVD, is associated with a variety of kidney diseases, including CKD, BP, and eGFR. The relationship between postmenopausal HRT and progression of albuminuria remains controversial. The protective effects of estrogen-based HRT against progression of CKD diminishes in accordance with aging and menopause status.[3] A study of 1,518 postmenopausal women reported a higher prevalence of microalbuminuria in HRT users (14.2%) than nonusers (11.6%) in women with >5 years of postmenopausal therapy.[30] In contrast, a study by Schopick et al.[31] examining 2,445 nondiabetic women reported that women receiving HRT for >6 years exhibited lower overall urinary albumin-creatinine ratios than those not receiving treatment.[31] A third cross-sectional study of 1,044 postmenopausal women found that HRT was associated with better eGFR and BP levels than that of nonusers. Improvements in BP and decreases in urinary albumin excretion were observed during a 10 year follow up from 443 participants; however, there was no association between eGFR and continuous HRT.[32]

Therapeutic Role of Klotho in Kidney Disease

1. Klotho and CKD

Klotho was first identified as a potential anti-aging gene in 1997. Klotho is a single-pass transmembrane protein expressed in multiple tissues, though the highest levels of expression are seen in the kidney. Recent studies have shown a strong association between CKD and endocrine/renal Klotho deficiency status. Furthermore, many of the phenotypes exhibited by Klotho-deficient mice are similar to those seen in CKD patients, including ectopic soft tissue calcification, hyperphosphatemia, and high plasma FGF23,[33] suggesting a direct link between gene expression and disease outcomes. Significant decreases in both the secreted and membrane-bound forms of klotho mRNA have been observed in the kidneys of CKD patients ($P < 0.0001$),[34] indicating that klotho deficiency is not only a biomarker for CKD but also a pathogenic contributor to CKD development and progression, as well as complications including vascular calcification and cardiac hypertrophy.[35]

2. Sex steroid hormone and Klotho

Klotho expression in the kidney increases rapidly after birth, followed by gradual decreases thereafter. Comparisons of klotho expression in mouse kidneys at 2, 12, and 24-months by western blots revealed significant decreases in the 24-month group compared with other time points. To test whether these decreases were affected, at least in part, by sex hormones,[36] Hsu et al.[37] examined the effects of testosterone on renal klotho expression. Renal klotho and androgen receptor (AR) mRNAs were increased 3.6- and 3.5-fold, relative to controls after dihydrotestosterone stimulation for 24 hours. Interestingly, klotho expression was not affected by exogenous androgen stimulation, suggesting that renal klotho expression may be regulated by testosterone via an AR-dependent mechanism. In contrast to testosterone, estrogen deficiency increased klotho protein levels in aromatase-deficient mice.[38] While klotho expression was decreased after estradiol therapy in this estrogen deficiency model, the influence of sex-steroid hormones on renal klotho expression have not been confirmed in other animal research or human studies. Although renal klotho expression is affected by other regulators including epidermal growth factor, peroxisome proliferator activated receptor agonists, and tumor necrosis factor-α, the mechanisms underlying these effects are not fully understood.

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Conclusion

CKD is a common issue in older individuals and, therefore, a growing problem in aging populations, such as that seen in Korea. CKD incidence and disease pathology progresses in accordance with age and menopausal status due to the decrease in naturally occuring estrogen production. Estrogen has been shown to confer protection against CKD and diminished renal function via several mechanisms, including increased NO metabolism, reduced oxidative stress, selectivity of AT2 receptor signaling, and differential RAS activation. Despite numerous clinical research studies showing that HRT can ameliorate nephropathy in postmenopausal women, contradictory findings have been reported, making a link between HRT and disease outcomes uncertain. Although the relationship between renal klotho expression and CKD is well known, further research will be necessary to fully elucidate the effects of sex steroid hormones on klotho expression.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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