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Review Article

The benefits of estrogen or selective estrogen receptor modulator on kidney and its related disease—chronic kidney disease—mineral and bone disorder: Osteoporosis

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Abstract

An umbrella concept addressing the relationship between chronic kidney disease (CKD) and mineral and bone disorders has been developed in recent years. Given the high prevalence of osteoporosis-related fractures in postmenopausal women with CKD, especially those undergoing chronic hemodialysis, the strategy used in the prevention and management of CKD and its associated osteoporosis in these postmenopausal women has become a topic of substantial debate. This controversy has ongoing relevance because osteoporosis results in a significant economic burden secondary to increased morbidity and mortality. The perfect goal of treatment and prevention includes both bone protection and renal protection, or at least protection of one disease without compromising the other disease. Both CKD and osteoporosis are frequently observed in the same patients, and often have parallel progression in postmenopausal women. Estrogen, the main female hormone during reproductive age, has been reported to have a protective effect on kidney fibrosis in several animal models, and is also considered one of the most effective drugs in the management of postmenopausal women with osteoporosis and prevention of osteoporosis. However, due to the many adverse events associated with the use of estrogen with and without progestin, some of which have contributed to significant morbidity and mortality, drug modification, which has had fewer reported incidences of adverse events without compromising the protective effect on both the kidney and bone, may have an easier road to acceptance. Therapeutic alternatives, such as the selective estrogen receptor modulators (SERMs), have shown the benefits of estrogen on bone, serum lipid levels, and renal protection, without any adverse effects on the breast and endometrium. The Multiple Outcomes of Raloxifene Evaluation trial (MORE) and its extension—Continuing Outcomes Relevant to Evista (CORE), a double-blind, randomized clinical trial encompassing postmenopausal women with osteoporosis, showed promising results in both bone and renal studies. Raloxifene increased bone mineral density (BMD) in the spine and femoral neck and reduced the risk of vertebral fracture. In addition, raloxifene slowed the increase in the rate of serum creatinine and also significantly slowed the decrease in the estimated glomerular filtration rate; of most importance, raloxifene use was associated with significantly fewer kidney-related adverse events. Hemodialyzed women on raloxifene treatment demonstrated increased trabecular BMD, a decrease in bone resorption markers, and a decrease in the low-density lipoprotein-cholesterol value. Thus, raloxifene and, most likely, other SERMs could be better in place of estrogen in the management of postmenopausal

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women with CKD and its associated osteoporosis, although much evidence should be provided in the advanced-stage CKD, especially in the Stage 5 CKD patients on dialysis.

Keywords: chronic kidney disease; estrogen; estrogen receptor; osteoporosis; raloxifene; selective estrogen receptor modulator

1. Introduction

Osteoporosis is defined by a decrease in bone mass and an alteration of microarchitecture, and a tendency toward subsequent fracture, which leads to debilitating health outcomes and consequently a considerable economic burden on the healthcare system.[1] In Taiwan, the incidence of vertebral fracture in women older than 65 years is approximately 20%, and the number of annual reported hip fractures in all populations age 65 years or older in Taiwan was 13,075 in 2002.[2–4]

There are many risk factors associated with osteoporosis, including advancing age, lack of estrogen (caused by menopause), vitamin D and/or calcium deficiency, low body weight or low body mass index (BMI), immobility, current smoking, excessive alcohol consumption, endocrine diseases, the use of certain medications (such as glucocorticoids, gonadotropin-releasing hormone agonists, or chemotherapy-induced early menopause), surgical intervention, family history, and chronic kidney disease (CKD).[5–10] Among the aforementioned risk factors, CKD is easily overlooked. In fact, an umbrella concept addressing the relationship between CKD and mineral bone disorders has been developed in recent years.[11]

CKD is defined as decreased renal function and/or renal damage persisting for at least 3 months.[11] Kidney dysfunction is indicated by a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2, and renal damage is most frequently manifested as increased urinary albumin excretion (e.g., a urinary albumin-creatinine ratio more than 30 g/g).[11] CKD is further classified into five stages: Stage 1 with GFR $\geq$ 90 mL/min per 1.73 m^2; Stage 2 with GFR of 60–89 mL/min per 1.73 m^2; Stage 3 with GFR of 30–59 mL/min per 1.73 m^2; Stage 4 with GFR of 15–29 mL/min per 1.73 m^2; Stage 5 with GFR less than 15 mL/min per 1.73 m^2.[11] CKD is often secondary to many medical illnesses and also leads to debilitating health outcomes, and consequently, a considerable economic burden on the healthcare system because CKD not only exacerbates the original precipitating diseases—diabetes and hypertension–and cardiovascular diseases—myocardial infarction, stroke, and congestive heart failure, but also induces many CKD-associated complications, such as end-stage renal disease (ESRD), and chronic kidney disease-mineral and bone disorders (CKD-MBD). CKD-MBD describes a broader clinical syndrome that includes mineral disturbance and abnormal metabolism of bone-regulating hormone, various bone disorders, and calcification of soft tissues.[11,12] In addition to renal osteodystrophy in patients with CKD, postmenopausal women on hemodialysis are at high risk of osteoporosis. In fact, both CKD and osteoporosis are frequently observed in the same patients and have parallel progress in postmenopausal women. Because estrogen deficiency is a key cause of osteoporosis in postmenopausal women, the role of estrogen and similar agents, such as selective estrogen receptor modulators (SERMs),is worthy of our attention,[13] and there has been evidence that these compounds might improve both CKD and osteoporosis in postmenopausal women.[14]

2. Estrogen and bone

Due to the close relationship between estrogen deficiency and osteoporosis, the use of estrogen therapy or its combination with progestogen after menopause has been theoretically reasonable.[15] The use of estrogen in these postmenopausal women significantly decreases the risk of osteoporosis and subsequent fracture, as reported in a large double-blind randomized clinical trial, the Women's Health Initiative (WHI) trial, in 2002.[16] The WHI was the first large, randomized clinical trial to show that estrogen-progestin therapy (EPT) reduces osteoporotic fractures, including a 34% reduction in both vertebral and hip fractures, and that this reduction occurred even though the study patients were at low risk for fractures.[16]

However, a recent Cochrane database systematic review, including 19 trials and 41,904 women, showed a significant increase in the risk of venous thromboembolism or a coronary event (after 1 year's use), stroke (after 3 years' use), and breast cancer and gallbladder diseases in relatively healthy women after continuous EPT, and an increase in all risks (thromboembolism: after 1 to 2 years' use; stroke: after 3 years' use; gallbladder disease: after 7 years' use), except breast cancer after estrogen-only treatment,[17] which impeded the acceptance of estrogen use in the prevention and management of postmenopausal women with osteoporosis. Therefore, pure estrogens might not be a good choice in the management of postmenopausal women with osteoporosis.

3. Estrogen and the kidney

The effect of estrogen on the kidney is uncertain.[18] There are at least three distinct estrogen receptors (ERs), including ERα, ERβ, and GPER (referred to as G-protein-couple protein 30) expressed in the kidney, although the distribution of the individual ERs seemed to be different in renal tissue, suggesting the potential role of estrogen in regulating renal function.[18] Estrogen can suppress collagen synthesis in glomerular mesangial cells by attenuating angiotensin II-induced mitogen-activated protein kinase activity and the

expression of the transcription factor AP-1, and indirectly inhibit proliferation of glomerular mesangial cells by modulating the synthesis of growth promoters and growth inhibitors, which might limit the progression of glomerulosclerosis, because increased generation and deposition of extracellular matrix proteins is considered as an initial step in glomerular injury and loss of renal function.[19] Various animal models of renal diseases have shown that the progression of renal injury is slower in female animals than in their male littermates, that disease progression in male rats could be slowed by estrogen substitution or orchiectomy, that estrogen application reduced proteinuria and glomerular fibrosis after experimental renal damage in different animal models, and that the expression of glomerular damage markers, including desmin, in spontaneously hypertensive rats and rats after puromycin treatment could be attenuated by estrogen treatment.[20−23] In the ischemia−reperfusion *in vitro* and *in vivo* models, estrogen also reduced postischemic glomerular endothelial hyperpermeability at least in part through receptor GPR30, and may regulate postcardiac arrest and cardiopulmonary resuscitation (CA/CPR) glomerular permeability in a similar fashion *in vivo*.[24]

In addition to animal studies, epidemiologic studies also supported the concept of renal protection with estrogen.[25−27] The physiologic decline of renal function during aging is significantly faster in healthy males than in females (loss of glomerular filtration rate [GFR] of 8.7 mL/min/1.73 m^2 per decade in healthy male kidney donors compared to 1.4 mL/min/1.73 m^2 per decade in females, as measured by inulin clearance).[25] Two large meta-analyses investigating sex differences in chronic renal disease or type I diabetes mellitus showed a favorable renal outcome and a decreased risk for the development of diabetic nephropathy in female patients compared to their male counterparts.[26,27] Taken together, evidence supports the beneficial effect of estrogen on the kidney. However, the relationship between estrogen therapy and renal function in postmenopausal women is uncertain, because some studies favored the relationship[28] and some argued against it.[29]

Based on previous reports, the substitution of estrogen does not provide a reasonable therapeutic option due to the significant adverse effects[30]; SERMs or nonreceptor- mediated estrogen metabolites may offer promising options for targeted therapy for renal diseases.

4. Estrogen and estrogen receptors

Before discussing SERMs, a brief introduction to the classic estrogen/ER pathway is needed. In this pathway, estrogen action at target sites around the body is mediated through related but distinct ERα and ERβ, which then bind as dimers to estrogen-response elements in the regulatory regions of the estrogen-responsive genes, and associate with basal transcription factors, coactivators, and corepressors to alter gene expression.[13] However, recent evidence has indicated that another pathway may exist.[31] The presence of specific, high-affinity estrogen binding in nonnuclear subcellular fractions, including plasma membrane and mitochondria, implies other sites of the ER location.[31] ERα and ERβ show 96% amino-acid identity in their DNA-binding domains, but only 53% homology is noted in their ligand-binding domains; the latter accounts for the differences in the responses of the two receptors to various ligands. For example, tamoxifen (TAM, Nolvadex; AstraZeneca, Wilmington, DE, USA) has been reported to be both an agonist and an antagonist for ERα, but only an antagonist for ERβ.[13] The recognition that TAM and other SERMs, for example, raloxifene (Evista, Eli Lilly, Indianapolis, IN, USA), have tissue-specific agonist-antagonist activity led to the realization that the classic model was incomplete and that estrogen action was more complex than had been thought.[32] The mechanisms of the tissue-selective, mixed agonist-antagonist action of SERMs, although still only partly understood, are gradually becoming clearer.[33] Most of the unique pharmacology of SERMs can be explained by three interactive mechanisms: differential ER expression in a given target tissue, differential ER conformation on ligand binding, and differential expression and binding to the ER of coregulator proteins.[33]

4.1. The efficacy of raloxifene in women with bone protection—results from three clinical trials (MORE, CORE, and RUTH)

There are three clinical trials addressing the influence of raloxifene on bone health, even though the primary end points of the individual trials were different.[34−43] The first trial was the MORE (Multiple Outcomes of Raloxifene Evaluation; 7705 postmenopausal women) study, which investigated the 4-year effect of raloxifene on the skeleton (on the risk of vertebral and nonvertebral fractures).[34−40] The second trial was an extension trial of the MORE— the CORE (Continuing Outcomes Relevant to Evista; 4011 women continuing from MORE, with a mean age of 65.8), which evaluated the efficacy of an additional 4 years of raloxifene therapy in preventing invasive breast cancer in women who participated in the MORE trial.[41] The third trial was the RUTH (Raloxifene Use for The Heart; 10,101 postmenopausal women, mean age, 67.5 years), which was originally designed to determine the effect of raloxifene on the incidence of coronary events (i.e., death from coronary causes, nonfatal, including silent myocardial infarction, or hospitalization for an acute coronary syndrome other than myocardial infarction) and invasive breast cancer.[43]

The bone mineral density (BMD) gains after 3 years were 2.1% in the spine and 2.6% in the femur. Significant concomitant decreases in osteocalcin (−26.3% vs. −8.6% in the placebo group) and urinary cross-linked N-telopeptides of type I collagen (NTX) (−34% vs. −8.1% in the placebo group) were noted. BMD gains after 4 years were 2.6% in the spine and 2.1% in the femur.[34] After 7 years of treatment (4 years in MORE and 3 years in CORE), BMD was higher in the raloxifene group than in the placebo group, by 2.2% in the spine and 3% in the total hip ($p < 0.01$).[42]

Raloxifene was efficacious (vertebral fracture reduction of 30% in women with and 55% in women without prevalent fractures in 3 years, respectively),[34] sustainable (a 50% reduction

in the 4th year versus a 55% reduction in years 0-3),[34] fast-acting (68% reduction, $p = 0.01$, in a 1-year *post hoc* analysis, and 90% reduction, $p = 0.01$, in a 6-month *post hoc* analysis),[37,38] and very fast-acting (80% reduction, $p = 0.034$, in a 3-month *post hoc* analysis).[38] The efficacious effect of raloxifene in decreasing vertebral fracture was also seen in the CORE study (170 fracture events (20.4%) with the placebo compared to 121 fracture events (14.1%) with raloxifene treatment).[42] Consistent with MORE and CORE trials, the RUTH trial clearly demonstrated the benefits of raloxifene in the prevention of clinical vertebral fracture (35% reduction, $p = 0.007$).[43]

Raloxifene not only offers benefits in the absolute reduction of the risk of vertebral fractures, but also ameliorates the severity of future vertebral fracture.[39] First, raloxifene can decrease the severity of all vertebral fractures; the risk of at least one new moderate/severe vertebral fracture was decreased by 61% in women without prevalent vertebral fractures (relative risk (RR) = 0.39, 95% confidence interval (CI) = 0.17 ~ 0.69), and by 37% in women with prevalent vertebral fractures (RR = 0.63, 95% CI = 0.49 ~ 0.83) at 3 years. Second, raloxifene also decreased the absolute number of vertebral fractures. The cumulative relative risks of multiple (≥ 2) new vertebral fractures through 4 years were 0.54 (95% CI = 0.38 ~ 0.77) with raloxifene compared with a placebo.[40]

However, these benefits of vertebral fracture prevention seemed to be absent with nonvertebral fracture. The risk reduction for nonvertebral fractures in the overall MORE population was not significant, although a reduction of 47% ($p = 0.04$) was noted in a *post hoc* analysis of patients with severe (semiquantitative grade 3) prevalent vertebral fractures.[40] the risk reduction for nonvertebral fractures in the overall CORE population was not significant.[41] The risk of at least one new nonvertebral fracture was similar in the placebo (22.9%) and raloxifene (22.8%) groups (hazard ratio [HR] = 1.00; Bonferroni-adjusted CI = 0.82~1.21).[42] The incidence of at least one new nonvertebral fracture at six major sites (clavicle, humerus, wrist, pelvis, hip, lower leg) was 17.5% in both groups. *Post hoc* Poisson analyses, which account for multiple events, showed no overall effect on nonvertebral fracture risk; however, a decreased risk (a reduction of 22%) was found at six major nonvertebral sites in women with prevalent vertebral fractures (HR = 0.78; 95% CI = 0.63 ~ 0.96, $p = 0.017$) and with severe (baseline semiquantitative technique (SQ) grade 3) vertebral fractures (HR = 0.64; 95% CI = 0.44 ~ 0.92, $p < 0.05$).[41] For hip fracture prevention, raloxifene did not show any advantage (HR = 1.04; 95% CI = 0.60 ~ 1.82).[42] Consistent with the MORE and CORE trials, the RUTH trial also showed that raloxifene was not sufficient to prevent nonvertebral fractures, because there was no difference in nonvertebral fractures between the raloxifene treatment and placebo groups.[43]

5. The efficacy of raloxifene in women with bone protection in Asian countries

The efficacy of raloxifene in osteoporosis prevention and treatment has been proven not only in populations in Western countries (the United States and Europe), but also in Asian countries.[44,45] One study included 968 healthy postmenopausal Asian women (mean age, 57 years) from Australia, Hong Kong, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, Taiwan, and Thailand. In comparison with a placebo, raloxifene significantly decreased osteocalcin and N-telopeptide by medians of 15.9% and 14.6%, respectively, and increased mean lumbar spine BMD (1.9%) at 1 year ($p = 0.0003$). In Japan, a similar result was noted.[45] Compared to baseline, women taking raloxifene had significant increases in lumbar spine (L2-L4) BMD at 24 weeks (+3.3%, $p < 0.001$) through 52 weeks (+3.5%, $p < 0.001$) of therapy.[45]

5.1. In vitro and in vivo models of renal protection with SERM treatment

As mentioned previously, accumulation of glomerular extracellular matrix after renal injury is a precursor to the development of glomerular obsolescence and progressive loss of renal function. A study on the inhibition of collagen synthesis or mesangial cell proliferation can be presented as a model to evaluate the effect of SERMs on renal function. SERMs, including tamoxifen and raloxifene, were reported to suppress *COL4A1* gene transcription (fibrogenic cytokines) and type IV collagen protein synthesis in a dose-dependent manner, with a potency identical to that of estradiol, and type I collagen synthesis was also suppressed by raloxifene in a dose-dependent manner, with a potency identical to that of estradiol, but greater than that of tamoxifen.[46] Tamoxifen prevented the accumulation of extracellular matrix by decreasing the expression of collagen III and fibronectin messenger RNA and protein, with a significant reduction in α-smooth muscle active-positive cells in the renal interstitium.[47] SERMs also reversed the stimulatory effects of angiotensin II and endothelin-1 on *COL4A1* gene transcription and type IV collagen synthesis via antagonisms of the autocrine/paracrine effects of transforming growth factor-β1 (TGF-β1).[47] In our previous study, we also found that raloxifene could induce apoptosis of fibroblast (for renal scar formation) via the G protein and PI3K/Akt pathways,[48,49] suggesting that proliferation of the fibroblast was inhibited by raloxifene, which might be associated with a lower degree of tissue scarring.

In an investigation of the vascular effect of raloxifene on isolated rat intralobar renal arteries, with and without a functional endothelium, raloxifene-induced renovascular relaxation was independent of the presence of the endothelium or ICI-182, 780-sensitive ERs (Sigma, St. Louis, MO, USA). This effect was approximately fivefold more effective than estradiol and was unrelated to ERs.[50] In addition, raloxifene reduced $CaCl_2$-mediated contraction and inhibited Ca^{2+} influx, which might be through L-type Ca^{2+} channels.[50]

In a study of the effect of SERMs on ameliorating renal damage in *db/db* mice, raloxifene suppressed TGF-β1–induced fibronectin promoter activity and AP-1 activation in cultured mesangial cells, suggesting that raloxifene has a beneficial effect on the kidney *in vivo* and may be more useful than estrogen as a clinical therapy for diabetic nephropathy.[51]

Taken together, SERMs have indeed provided an opportunity for renal protection in *in vitro* and *in vivo* studies.

6. Clinical studies showed the benefits of SERM treatment in renal protection

In the *post hoc* analysis of a MORE trial,[52] serum creatinine increased by 0.004 mg/dL per year on average ($p < 0.0001$), with women on raloxifene 60 mg showing a slower rate of increase over time than those women in the placebo group. The 3-year mean increase of serum creatinine was 0.01 mg/dL in the placebo group, but 0.0004 mg/dL with raloxifene treatment.[52] The 3-year mean decrease of the estimated GFR was 0.98 mL/min per 1.73 m^2 in the placebo group, but 0.56 mL/min per 1.73 m^2 in the raloxifene group, with women on raloxifene decreasing at a slower rate over time than those women in the placebo group ($p = 0.03$).[52] In addition, 28 women (0.6%) in the raloxifene group and 29 women (1.1%) in the placebo group had an adverse event related to kidney function, with a relative HR of 0.37 (95% CI = 0.18 ~ 0.77).[51] The risk of incident events related to kidney disease among those with probable kidney disease at baseline was also reduced by treatment with raloxifene (relative HR 0.27 (95% CI = 0.12 ~0.59).[52] Therefore, raloxifene showed a renoprotective effect in postmenopausal women.

7. Clinical studies showed the benefits of SERM treatment in postmenopausal women with CKD

A small, prospective, blinded, placebo-controlled, and randomized study that enrolled 50 postmenopausal women on chronic hemodialysis showed a significant decrease in the LDL-cholesterol value, suggesting that raloxifene might control hyperlipidemia and provide a favorable lipid profile for these postmenopausal women on chronic hemodialysis.[53] In addition, raloxifene lowered serum malondialdehyde and nitric oxide and decreased the LDL serum level, but increased HDL serum levels in postmenopausal women who were undergoing long-term hemodialysis treatment for chronic renal failure.[54]

8. Clinical studies showed the benefits of SERMs on bone health in postmenopausal women with CKD

A significant increase in trabecular BMD and a decrease in bone resorption markers (pyridinoline crosslinks) suggest that raloxifene constitutes a therapeutic alternative for the improvement of bone metabolism in these postmenopausal women on chronic hemodialysis.[53] However, many factors might affect the efficacy of raloxifene in bone health in postmenopausal women with CKD. For example, the ER gene polymorphism may affect the efficacy of raloxifene in increasing BMD in postmenopausal women on chronic hemodialysis.[55] The level of intact parathyroid hormone is also reported to affect the efficacy of raloxifene in the prevention of BMD deterioration in postmenopausal patients undergoing dialysis.[56] One study showed that raloxifene significantly decreased serum calcium and increased intact parathyroid hormone in postmenopausal Japanese women on hemodialysis, suggesting that vitamin D and/or calcium salts should be added to raloxifene treatment to avoid secondary hyperparathyroidism.[14]

9. The potential risk of raloxifene in women

The potential risk of raloxifene treatment is thromboembolism. A meta-analysis evaluating the effect of raloxifene on the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) showed that therapy with raloxifene was associated with a 62% increase in the odds of either DVT or PE (odds ratio (OR) = 1.62; 95% CI = 1.25 ~ 2.09; $p < 0.001$).[57] Raloxifene therapy was associated with a 54% increase in the odds of DVT (OR = 1.54; 95% CI = 1.13 ~ 2.11; $p = 0.006$) and a 91% increase in the odds of PE alone (OR = 1.91; 95% CI = 1.05 ~ 3.47; $p = 0.03$),[57] although it was probably not associated with an increased risk of arterial thromboembolism.[58] Raloxifene might improve platelet metabolism in healthy postmenopausal women through an increase of the bioavailability of platelet nitric oxide by a reduction of inducible nitric oxide synthase and the beneficial effects on lipid metabolism.[59] However, other adverse effects, such as the higher frequency of hot flushes, cramps of the lower limbs, and fluid retention may be a reason for halting raloxifene use in menopausal women.[60]

10. Unanswered questions

Because the spectrum of chronic kidney disease-mineral and bone disorders is widely ranged, the following factors come into play: (1) some have severe high-turnover bone disease and the others have marked low bone turnover bone disease; (2) some have severe vascular calcifications whereas others do not; (3) the values of biochemistry determinations, including calcium, phosphorus, and parathyroid hormone vary widely among patients; (4) the variability may be influenced by the chronicity of the particular kidney disease, effects of therapies such as corticosteroids on modifying the course of kidney disease, and comorbid condition, there is no doubt that it is difficult to make strict protocol-driven therapeutic approaches in the management of these patients with CKD due to heterogeneities.[61] In addition, there is a good correlation between dual-energy X-ray absorptiometry measurements and bone fractures in the general population, but this is not the case with patients with CKD,[62] especially in the Stage 5 CKD population, which results in a lack of consensus on the diagnosis of osteoporosis in Stage 5 CKD patients.[63] Furthermore, although some of the small aforementioned trials suggested the potential benefits of SERMs on bone health in postmenopausal dialysis patients,[53,55,56] the benefits of SERMs might vary among the different stages of CKD. Finally, although *post hoc* analyses of many pivot trials (bisphosphonates, raloxifene, teriparatide, denosumab) have found similar results (benefits of the aforementioned drugs on bone health) in those with and without mild CKD, it is important to remember that patients with abnormal laboratory values were often excluded from these trials.[64] Therefore, it is relatively

difficult to suggest what is the best choice (SERMs or other medications) for those Stage 5 CKD patients with osteoporosis. By contrast, before consensus formed, considerable individualized or patient-tailored therapy is recommended, especially for those women with Stage 5 CKD and osteoporosis.[61]

In conclusion, these observations (MORE, CORE, RUTH trials) have shown the efficacy of raloxifene in terms of the prevention and management of osteoporosis, decreased bone turnover, increased BMD, and decreased incidence of fracture, as well as the slower yearly rate of increase in creatinine, significantly slower yearly rate of decreases in estimated GFR, and significantly fewer kidney-related adverse events. Furthermore, Asian populations do have a low risk of thromboembolism,[65] but a high percentage of these populations have gastrointestinal tract problems[66]; therefore, it is reasonable to use raloxifene in Asian postmenopausal women with CKD and osteoporosis. Raloxifene offers the best benefits for a specific population–climacteric symptom-free postmenopausal women, especially Asian women, who need renal protection and have CKD-MBD, although more evidence is required to support this recommendation.

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