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REVIEW SERIES

Chronic kidney disease in postmenopausal women

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Menopause is derived from the Greek words men (month) and pauses (cessation) and means permanent cessation of menstruation after the loss of ovarian activity. Chronic kidney disease (CKD) has recently been associated with cardiovascular events in several studies. CKD patients have a heavy burden of traditional cardiovascular risk factors in addition to a range of nontraditional risk factors such as inflammation and abnormal metabolism of calcium and phosphate. In this review, the association of CKD and cardiovascular disease (CVD), as well as of osteoporosis in postmenopausal women is discussed. CKD mineral and bone disorder, characterized by disturbances of calcium/phosphate/parathyroid hormone, bone abnormalities and vascular and soft tissue calcification, is highly prevalent in CKD and is a strong, independent predictor of bone fracture, CVD and death. Estrogen has been shown to: (a) decrease the expression of angiotensin type 1 receptors in vasculature and kidneys; (b) reduce the expression and activity of angiotensin-converting enzyme, and (c) cause the release of angiotensinogen substrate from the liver. However, the degree of activation or suppression of the renin–angiotensin–aldosterone system by estrogen has not been clearly established. Clinical data on the effects of estrogen therapy on bone mineral densities are extremely limited in the ESRD population. CVD is the most common cause of death in postmenopausal women with CKD and many contributing factors have been explored. Future research for prevention of CVD in postmenopausal women with CKD would focus on the biology of vascular calcification as well as bone loss.
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INTRODUCTION

Menopause is derived from the Greek words men (month) and pauses (cessation) and means permanent cessation of menstruation after the loss of ovarian activity. Clinically, menopause is defined as the absence of menstruation for 12 months.[1] In clinical medicine, it is well known that menopause is associated with accelerated progression of vascular diseases and osteoporosis as a long-term health risk in women. Indeed, menopausal status increases the risk of cardiovascular disease (CVD) by more than three-fold in women with normal kidney function.[2] Several factors such as the prevalence of hypertension,[3] diabetes,[4] dyslipidemia[5] and so on are known contributors to CVD. In addition to these factors, several studies reveal that chronic kidney disease (CKD) is closely related with CVD events.[6–9] Moreover, Perticone *et al.*[10] have recently demonstrated that the reduction of estimated glomerular filtration rate (GFR) was associated with the increased risk of death and CVD events, independently of traditional CV risk factors, menopause duration and presence of metabolic syndrome.

In addition to these risks in CVD, women lose an average of 25 percent of their bone mass from the time of menopause to age 60, due in large part to the loss of estrogen. Over time, this loss of bone mass can lead to osteoporosis and its related fractures are a serious problem affecting postmenopausal women.[11] Recently, two serious sequels of menopause have been closely associated with CKD. CKD is associated with accelerated progression of CVD, perhaps because CKD patients have a heavy burden of traditional cardiovascular risk factors in addition to a range of nontraditional risk factors, such as inflammation and abnormal metabolism of calcium and phosphate. Besides, CKD is associated with increased oxidative stress,[12] which is reported to be correlated with the development of coronary artery disease in patients with impaired renal function.[13] Although the cardiovascular burden of CKD is well documented, potentially beneficial therapies are sometimes underused in CKD patients of stage 3–4 and are rarely studied in patients on dialysis. The presence of kidney disease, manifested by low glomerular filtration rate and/or large amounts of protein in the urine, is independently associated with increased rates of CVD.[14] Moreover, the prevalence of low bone mineral densities (BMD) and osteoporosis increases with greater severity of CKD.[15,16] However, data regarding CKD in postmenopausal women are limited. In this review, the association of CKD and CVD, as well as of osteoporosis in postmenopausal women will be discussed.

ROLE OF ESTROGEN IN CKD

Hypertension is a major risk factor among a number of factors that contribute to deterioration of CKD and notably, the incidence of hypertension increases more rapidly in postmenopausal women. Although the mechanism responsible for this rapid increase is not fully understood[17–19] salt has an important role in hypertension and progression of CKD especially in postmenopausal women.[20]

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Our previous data clearly demonstrated that salt sensitivity correlated inversely with levels of circulating estrogens(estrone, estradiol and estriol) and progesterone. This suggested that decreases in estrogens and progesterone levels and increased sensitivity to dietary sodium may be important factors in the genesis of postmenopausal hypertension.[21] The World Health Organization (WHO) Cardiovascular Diseases and Alimentary Comparison Study proposed two possible explanations.[22] One is that women who have increased salt sensitivity after menopause may have been salt-sensitive before menopause. The other is that hormonal changes that occur immediately after menopause may lead directly or indirectly, to some extent, to an increase in salt sensitivity. Moreover, male Dahl salt sensitive (DS) rats became more hypertensive than female DS rats when given high dietary salt, suggesting that estrogen has an important role in regulating blood pressure (BP) in female DS rats.[23] From these studies, significant sodium–BP associations in postmenopausal women might be one of the mechanisms by which menopause exerts its effects on risk of CVD.

Previously our study demonstrated a blunted or anti-natriuretic shift in the pressure–natriuresis relationship in DS rats when compared with Dahl salt-resistant rats.[24] Ovariectomy further impaired the pressure–natriuresis response in DS but not in Dahl salt-resistant rats. Harrison-Bernard *et al.*[25] further showed that in DS rats, despite a normal salt diet, ovariectomy promoted hypertension accompanied by left ventricular hypertrophy. These findings support the notion that cardiac remodeling and glomerulosclerosis may share common elements in their pathogenesis. It has been suggested that the renoprotective effects of estrogen may be related to their effects on glomerular mesangial cells (MCs) in a manner analogous to the effects of estrogens on cardiac cells in cardiac remodeling. It has been demonstrated that the cardiovascular protective effects of endogenous estrogens involve direct effects on blood vessels through modulation of endogenous vasoconstrictors, such as angiotensin (Ang) II and vasodilators such as nitric oxide (NO).[26] In addition, a close relation exists between estrogen and Ang II. Estrogen has been shown to: (a) decrease the expression of Ang type 1 receptors in vasculature and kidneys;[27] (b) reduce the expression and activity of angiotensin-converting enzyme[28,29] and (c) cause the release of angiotensinogen substrate from the liver. Although the degree of activation or suppression of the renin–angiotensin–aldosterone (RAA) system by estrogen has not been clearly established, RAA and NO systems have a central role in BP regulation and electrolyte balance and are involved in the phenomenon of salt sensitivity under the influence of estrogen.

Gragasin *et al.*[30] demonstrated that AII stimulation of endothelial cells increased the expression of NAD(P)H oxidase and NOS, which may contribute to oxidative stress, as evidenced by peroxynitrite formation. Several other studies support the notion that estrogen has the potential for exerting vasoprotective effects through modulation of pro-oxidant and antioxidant enzyme expression and activity by modulating the RAA and NO systems,[31] as well as enzymes such as NAD(P)H oxidase, Rho-kinase and superoxide dismutase,[32] and the transcription factor NF-κB.[33] The aforementioned findings demonstrated that in addition to the known effects on eNOS activity and expression, estrogen acts as an indirect antioxidant at the genomic level by downregulating the capacity of endothelial cells to generate reactive oxygen species, thereby improving their NO/O_2 balance. This add-on effect may have an important role in the known anti-atherosclerotic effect of estrogen in premenopausal women that contributes to their lower incidence of coronary heart disease and myocardial infarction (MI) than in age-matched men.[34]

The results of our previous study[35] might help in understanding these complex mechanisms. The study was conducted to elucidate the relationship between estrogen and the RAA system in the process of cardiac remodeling and nephrosclerosis in ovariectomized DS rats with MI. BPs in female DS rats with MI and with or without ovariectomy transiently increased at week 4, and then gradually decreased toward the end of the study. Administration of Ang receptor blocker (ARB) reduced BP in ovariectomized rats independently of estrogen supplementation. Urinary protein excretion was increased by ovariectomy, while it was decreased by estrogen supplementation and ARB administration. Ovariectomy resulted in increased activity in the RAA system, whereas estrogen supplementation and ARB suppressed the RAA system. Expression of ecNOS was decreased in the ovariectomized rats. This was reversed by estrogen supplementation in the heart but not in the kidneys, although administration of ARB reversed ecNOS expression in both the heart and the kidney. In the pathology of the kidney, in contrast to these physiological parameters, estrogen supplementation produced thrombotic microangiopathic lesions in the glomeruli. These changes were reversed by concomitant administration of ARB. From this study, the following working hypothesis will be proposed; (1) estrogen might protect from development of cardiac remodeling and deteriorating heart failure, (2) estrogen replacement promoted microangiopathy in the kidney due to thrombosis, (3) in overall, concomitant administration of estrogen supplementation and the blockade of the RAA system might be effective for protection of the heart and the kidney in ovariectomized DS rats.

In addition to these crucial roles of estrogen in a protective role against progression to renal injury, several other specific effects of estrogen have been reported described below.

MCs may be a target for estrogens. Estrogen action is mediated via estrogen receptor (ER) subtypes ERα and ERβ. Both ER subtypes are expressed in human and mouse MC. Using an estrogen-responsive reporter construct in transfection assays, it was also demonstrated that nuclear ER was transcriptionally active. Estrogen 2 increased both metalloproteinase (MMP)-9mRNA and MMP-9 activity in MC. This may be an important mechanism by which estrogens influence ECM turnover and protect against progression of diabetic glomerulosclerosis.[36] In renal tissue culture, estrogens inhibit the synthesis of type I and type IV collagens.[37] As accumulation of glomerular extracellular matrix after renal injury is a precursor to the development of glomerular obsolescence and progressive loss of renal function, the ability of estrogens to inhibit fibrogenic cytokine-stimulated collagen IV synthesis may contribute to the protective effect in females on the progression of renal disease.[37] Estrogen also stimulates the activity of two collagen degrading enzymes, MMP-2 and MMP-9. As matrix deposition and scarring contribute to the progression of renal disease, estrogens may affect progression rates by interfering with the fibrogenic process.[38] In addition to these findings, Guccione *et al.*[38] further demonstrated that estradiol suppresses type I and IV collagen synthesis and that estradiol stimulates MMP-2 activity in MCs. This suggests that estradiol shifts the balance of matrix metabolism away from matrix accumulation and glomerulosclerosis. These effects of estradiol on collagen metabolism may also contribute to the protective effect in females on renal disease progression. Finally, they concluded that continuous estrogen replacement therapy prevented the development of microalbuminuria and maintained normal glomerular structure in Ovx ROP Os/+ mice, a model of progressive glomerulosclerosis. The protective effects of continuous estrogen exposure were superior to those of endogenous estrogens that are secreted in a cyclical manner. Glomerular function and structure deteriorated during phases of chronic estrogen deficiency regardless of the timing of its onset, and the ensuing glomerular dysfunction and

morphological changes could not be prevented by subsequent estrogen replacement. The *in vivo* findings are mirrored in the MC phenotype. MCs remain estrogen-sensitive if exposed to continuous or cyclical levels of estrogens *in vivo* and irreversibly regress into an estrogen-insensitive, diseased cell type after prolonged estrogen deficiency. Another important finding was that tamoxifen reduced microalbumin excretion, and prevented the deterioration of the glomerular structure although not to the same extent as continuous estrogen replacement therapy. The implications of these findings could be far reaching if similar observations are made in women, especially those with a propensity to develop CKD.[39]

Although the mechanisms responsible for elevation of BP in postmenopausal women are complex and multifaceted,[40] a close relation between preeclampsia and CVD in later life is proposed. Several studies have shown that women who previously had eclampsia/preeclampsia have a 2–6 fold and 1.9-fold higher risk, respectively, of dying from ischemic heart disease than women who only developed hypertension at the time of the index pregnancy.[41] Endothelial dysfunction, which is one of the major contributing factors for ischemic heart disease, is closely linked with NO and oxidative stress.[42] Moreover, it is possible that estradiol conceals endothelial dysfunction until menopause. Women with a past history of preeclampsia might become hypertensive due to endothelial dysfunction as they approach menopause. Kaaja *et al.*[43] reported that women with preeclampsia and pregnancy-induced hypertension displayed hyperinsulinemia, hypertriglyceridemia and low high-density lipoprotein cholesterol. In addition, the same group demonstrated that women were characterized by significantly elevated immunoreactive insulin levels but normoglycemia 17 years after a preeclamptic first pregnancy.[44] Similarly, in our previous study,[45] insulin resistance was apparent in women with a past history of preeclampsia and these findings supported by several studies that insulin resistance and the resultant hyperinsulinemia are causally related to hypertension and renal injury.[46–48] A number of potential mechanisms can account for these deleterious effects. This is indirectly suggested by the fact that hypertensive patients with hyperinsulinemia excrete greater amounts of urinary albumin.[49] It is believed that the nature of nephrosclerosis is heterogeneous and factors other than BP are implicated in the development and progression of nephrosclerosis.[50] The mechanism by which insulin can induce renal injury is not completely clear, the deleterious influence of insulin on injury and dysfunction of endothelial cells has been shown. In addition to this, an increase of cholesterol and triglyceride synthesis as a consequence of hyperinsulinemia might promote vascular injury.[51]

HORMONE REPLACEMENT THERAPY AND CKD

The issue of hormone replacement therapy in postmenopausal women remains controversial although this therapy counters osteoporosis and prevents CVD.[52]

It is well known that menopause is associated with accelerated progression of vascular diseases. Ten to 15 years after menopause, women lose most or all of a lower risk for developing CVD, which associates with the leading cause of morbidity and mortality in postmenopausal women, compared with men.[53]

In general, hormone replacement therapy in postmenopausal women with CKD has been neglected, although the documented ability of estrogen to increase NO production and to reduce oxidative stress appears to be important in the improvement of nephropathy. Szekacs *et al.*[54] reported that 14 weeks of hormone replacement therapy in high-risk postmenopausal women resulted in a significant decrease in the proteinuria associated with progressive diabetic and hypertensive nephropathy. This was accompanied by a significant increase in creatinine clearance rate. These favorable effects were seen despite the fact they had already been treated for hypertension at entry. These data suggest that hormone replacement therapy can ameliorate nephropathy, in addition to the benefits of comprehensive conventional nephroprotective therapy. The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized, double-blind, placebo-controlled trial of daily use of conjugated equine estrogens plus medroxyprogesterone acetate (progestin) on the combined rate of nonfatal MI and CVD death among postmenopausal women with coronary disease.[55,56] Using this large scale clinical trial, Schlipak *et al.*[57] reported that moderate renal insufficiency (a serum creatinine level $>1.4\,mg\,dl^{-1}$) was associated with 60–80% increased risk of cardiovascular events. The association of renal insufficiency with cardiovascular outcomes persisted among subgroups with and without hypertension and diabetes and treatment with angiotensin converting enzyme inhibitors or hormone therapy. Even mild renal insufficiency (a serum creatinine $1.2–1.4\,mg\,dl^{-1}$) was associated with a 20–30% increased risk for CVD events. Later, Shlipak *et al.*[58] evaluated the association of worsened renal function (creatinine level increase $>0.3\,mg\,dl^{-1}$) during HERS with CVD outcomes that occurred during HERS-II. Only 9% of participants had worsened renal function during HERS, and they were characterized by a greater prevalence of diabetes, lower high-density lipoprotein cholesterol and higher triglyceride levels, and increased rate of CVD events during HERS. After adjustment for baseline characteristics, HERS cardiovascular events, and medication use, worsened renal function was no longer associated with CVD events. However, baseline creatinine levels from HERS were remarkably strong predictors of HERS-II events. Further, the same group reported that advanced kidney dysfunction in postmenopausal women is an independent risk factor for sudden cardiac death among women with coronary heart disease, an association that appears to be mediated in part by the development of congestive heart failure and incident MI.[59] Ginsberg *et al.*[60] reported that when standard dosage regimens were used for estrogen replacement therapy in postmenopausal women with ESRD, high-density lipoprotein cholesterol was increased to an extent that would be expected to improve their cardiovascular risk profile, although there were no differences in total or LDL cholesterol, other lipoprotein fractions including Lp(a), and triglycerides. In addition, estrogen may also heighten the risk of dialysis access thrombosis and other risks such as endometrial cancer that have not been adequately studied.

At present, hormone replacement therapy cannot be recommended to women with established coronary artery disease and in postmenopausal women with CKD. As with estradiol–progesterone replacement therapy in postmenopausal women, it is likely that with androgen supplementation aging women would not have adverse cardiovascular consequences. However, in view of the increasing experimental evidence that androgens promote CVD and CKD, androgen supplement is considered with caution.[61]

BONE DISEASE IN POSTMENOPAUSAL WOMEN WITH CKD

CKD may have an increased risk for osteoporosis for several reasons, including shared risk factors for both conditions such as females and advanced age. Also, CKD may lead to metabolic abnormalities that accelerate bone loss, such as chronic metabolic acidosis, hypogonadism, hyperparathyroidism and abnormalities of vitamin D metabolism.[62] CKD mineral and bone disorder (CKD-MBD), characterized by disturbances of calcium/phosphate/parathyroid hormone, bone abnormalities and vascular and soft tissue calcification, are highly prevalent in CKD and are strong, independent predictor of bone

fracture, CVD and death.[15,16] Moreover, recent discoveries of fibro-growth factor (FGF) 23 and klotho shed a new light on calcium–phosphate regulation.[63] Huang[64] proposed a working hypothesis of the potential relationship between the effect of klotho on calcium and phosphate metabolism through FGF 23. According to this hypothesis, binding of FGF23 to the membrane klotho and FGF receptor co-receptor complex leads to inhibition of the synthesis of 1,25 vitamin D3 and inhibition of the expression of Na-dependent phosphate co transporter in the apical membrane of the proximal tubule. On the line of this hypothesis, dysregulation of calcium–phosphate in post-menopausal women with CKD will be investigated in the future, whether withdrawal of estrogen produce and/or change interaction of FGF23 and klotho. Osteoporosis, a 'brittle-bone' disease, occurs when the inside of bones becomes less dense, making them more fragile and likely to fracture. Irrespective of cause, individuals with CKD have a greater prevalence of osteoporosis and are at increased risk for clinical fractures. Despite the increased burden of osteoporosis among those with CKD, the majority of randomized trials evaluating the efficacy of pharmacological agents in preventing fractures in postmenopausal women with osteoporosis have excluded women with CKD. As therapies for osteoporosis typically have not included those with CKD, the beneficial effects of osteoporosis therapy remain to be determined.[65] CKD may be associated with a higher prevalence of osteoporosis and osteopenia for several reasons. Individuals with CKD are more likely to be older, female and vitamin D deficient; have increased PTH levels; and have had an earlier onset of menopause. In addition, there is concern that kidney disease itself may be a risk factor for lower bone mineral disease.[66] The biological basis for progressive bone loss among individuals with impaired kidney function resided in the greater rates of hip bone loss.[67,68] Increased rates of hip bone loss may potentially increase the risk or hip fracture among individuals with impaired kidney function. Nickolas *et al.*[69] reported an independent correlation between an estimated glomerular filtration rate-<60 ml per min per $1.73m^2$ and the prevalence of hip fractures using the cross-sectional National Health and Nutrition Examination and Survey. Ensrud *et al.*[70] reported a graded association between level of kidney function and the subsequent risk for hip fracture among older women. Similarly, elevated cystatin C concentrations have been independently associated with risk for hip fracture among women.[68] Estrogen has an important role in preserving bone mass and signals cells in the bones to stop breaking down. Epidemiological and clinical data have consistently shown that hormone replacement therapy results in a cessation of bone loss and an improvement in bone density with a subsequent reduction in risk of osteoporotic fracture.[71] Felson *et al.*[72] found that significantly higher BMD were demonstrated only in women who had taken estrogen replacement therapy for at least 7–9 years compared with those who had not taken estrogen. Such long-term studies would be very difficult to conduct in the ESRD population, which had such a high mortality rate. A review group on osteoporosis in CKD concluded that the use of osteoporosis therapies in patients with CKD is highly controversial, given the unknown effectiveness of these therapies on BMD and risk of fractures.[65] Miller *et al.*[73] demonstrated that risedronate led to similar increases in BMD and reductions in fractures irrespective of baseline kidney function. Jamal *et al.*[74] also reported that use of alendronate was associated with a reduced risk for clinical fractures irrespective of baseline kidney function. Alendronate use was also associated with a significant increase in total hip BMD compared with placebo. This effect was more pronounced in those with a CrCl <45 ml per min ($P<0.04$ for interaction between CrCl and treatment assignment). Adverse events were similar irrespective of baseline kidney function. Miller *et al.*[75] recently evaluated the effectiveness of teriparatide (recombinant human PTH (1–34))[76] among postmenopausal women with osteoporosis by the level of kidney function. They demonstrated that teriparatide increased BMD at the lumbar spine and femoral neck to similar degrees irrespective of baseline kidney function. Also, the reductions in risk for vertebral and nonvertebral fractures showed no differences by level of baseline kidney function; (1) however, teriparatide was associated with an increased risk for elevated uric acid in those with moderately impaired kidney function (CrCl 30–49 ml per min); and (2) women with a creatinine level >2 mg dl^{-1} were excluded from the study.

Raloxifene is a benzothiophene derivative that binds to ERs to act as a selective ER modulator[77] and decreases oxidative stress. In the *post hoc* analysis of data from the Multiple Outcomes of Raloxifene Evaluation study, a randomized trial of the efficacy and safety of raloxifene treatment in postmenopausal women with osteoporosis, Ishani *et al.*[78] found that among postmenopausal women with osteoporosis and mild-to-moderate CKD (to stage 3), raloxifene therapy increased BMD at both the hip and the spine with a greater effect on hip BMD in those with mild-to-moderate CKD as defined by CrCl, reduces risk for vertebral fractures, but had no effect on risk for nonvertebral fractures. Several studies have indicated that individuals with end-stage kidney disease have a higher prevalence of osteoporosis as well as an increased risk of fractures[69,79,80] but bone disease is heterogenous and highly prevalent among those with CKD, stage 5 (CKD-5) patients. Although much is known regarding the risk factors and outcomes associated with renal osteodystrophy, less is known about osteoporosis in CKD-5. Factors that predict bone loss in the CKD-5 population are similar to those in the general population and include female gender, Caucasian race, older age, chronic disease and immobility. In addition, some studies suggest that chronic acidosis and renal osteodystrophy may also increase the risk for bone loss.[16,81,82] Little is known about associated adverse outcomes or the impact of therapeutic interventions for osteoporosis. Although it is known that the risk for hip fracture is high among CKD-5 patients and that fracture is associated with an increased risk for death, the role that bone loss has is largely unknown. Current recommendations suggest that risk-factor modification is the most appropriate treatment goal for CKD-5-associated osteoporosis.[83]

Clinical data on the effects of estrogen therapy on BMD are extremely limited in the ESRD population. In a preliminary study from Poland, 13 postmenopausal women with low estradiol levels (<30 pg ml^{-1}) were administered transdermal estradiol with the cyclic addition of noretisterone acetate for 12 months.[84] Compared with baseline measurements, BMD increased significantly, but only in L2–L4. Whether this increase in BMD will decrease the long-term risk of fracture will be difficult to evaluate owing to the presence of renal osteodystrophy in the ESRD population. Although data on raloxifene use during chronic hemodialysis in postmenopausal women is scarce, one study found increased bone density and reduction in frequency of bone fractures along with increased serum LDL levels.[85] Raloxifene was also associated with improvement in some serum lipid profile markers. Similar to these findings, Ozbasar *et al.*[86] recently reported that oral raloxifne administration for 3 months lowered serum malodialdehyde and NO levels as an index of oxidative stress in postmenoupausal women with ESRD under chronic hemodialysis therapy. Also, raloxifene was associated with improvement in serum high-density lipoprotein and triglyceride levels. This finding might have important implications, as serum lipid abnormalities in patients with ESRD have a causal relationship with CVD undergoing hemodialysis treatment.[87]

FUTURE PERSPECTIVES

CVD is the most common cause of death in postmenopausal women with CKD and many contributing factors have been explored. Among these factors, vascular calcification is recognized as a significant contributor to cardiovascular risk in CKD patients.[88] Recently, the processes of vascular calcification and bone loss in CKD patients have been considered to be driven by common mechanisms of damage, vesicle release and loss of mineralization, regulating proteins both locally and systemically.[89] If this is the case, future research for the prevention of CVD in postmenopausal women with CKD would focus on the biology of vascular calcification as well as bone loss.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Morse CA. Menopause transition. In: Wren BG (ed). *Progress in the management of the menopause*. The Parthenon Publishing Group: New York, NY, 1995.
2 Mosca L, Appel LJ, Benjamin EJ, Berra K, Chandra-Strobos N, Fabunmi RP, Grady D, Haan CK, Hayes SN, Judelson DR, Keenan NL, McBride P, Oparil S, Ouyang P, Oz MC, Mendelsohn ME, Pasternak RC, Pinn VW, Robertson RM, Schenck-Gustafsson K, Sila CA, Smith SC, Jr, Sopko G, Taylor AL, Walsh BW, Wenger NK, Williams CL. Evidence-based guidelines for cardiovascular disease prevention in women. American heart association scientific statement. *Arterioscler Thromb Vasc Biol* 2004; **24**: e29–e50.
3 Staessen J, Bulpitt CJ, Fagard R, Lijnen P, Amery A. The influence of menopause on blood pressure. *J Hum Hypertens* 1989; **3**: 427–433.
4 Owens JF, Stoney CM, Matthews KA. Menopausal status influences ambulatory blood pressure levels and blood pressure changes during mental stress. *Circulation* 1993; **88**: 2794–2802.
5 Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med* 1991; **325**: 1196–1204.
6 Zanchetti A, Hansson L, Menard J, Leonetti G, Rahn KH, Warnold I, Wedel H. Risk assessment and treatment benefit in intensively treated hypertensive patients of the hypertension optimal treatment (hot) study. *J Hypertens* 2001; **19**: 819–825.
7 Kumar J, Shah SV. Kidney disease as an independent risk factor for cardiovascular events. *J Ren Nutr* 2005; **15**: 99–104.
8 Amann K, Wanner C, Ritz E. Cross-talk between the kidney and the cardiovascular system. *J Am Soc Nephrol* 2006; **17**: 2112–2119.
9 Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52**: 1527–1539.
10 Perticone F, Sciacqua A, Maio R, Perticone M, Laino I, Bruni R, Cello SD, Leone GG, Greco L, Andreozzi F, Sesti G. Renal function predicts cardiovascular outcomes in southern italian postmenopausal women. *Eur J Cardiovasc Prev Rehabil* 2009; **16**: 481–486.
11 Saag KG, Geusens P. Progress in osteoporosis and fracture prevention: Focus on postmenopausal women. *Arthritis Res Ther* 2009; **11**: 251.
12 Dirican M, Sarandol E, Serdar Z, Ocak N, Dilek K. Oxidative status and prevalent cardiovascular disease in patients with chronic renal failure treated by hemodialysis. *Clin Nephrol* 2007; **68**: 144–150.
13 Jung HH, Choi DH, Lee SH. Serum malondialdehyde and coronary artery disease in hemodialysis patients. *Am J Nephrol* 2004; **24**: 537–542.
14 Saran AM, DuBose Jr TD. Cardiovascular disease in chronic kidney disease. *Ther Adv Cardiovasc Dis* 2008; **2**: 425–434.
15 Yendt ER, Cohanim M, Jarzylo S, Jones G, Rosenberg G. Bone mass is related to creatinine clearance in normal elderly women. *J Bone Miner Res* 1991; **6**: 1043–1050.
16 Lindberg JS, Moe SM. Osteoporosis in end-state renal disease. *Semin Nephrol* 1999; **19**: 115–122.
17 Oparil S. Hypertension in postmenopausal women: Pathophysiology and management. *Curr Opin Nephrol Hypertens* 1995; **4**: 438–442.
18 Reckelhoff JF. Sex steroids, cardiovascular disease, and hypertension: Unanswered questions and some speculations. *Hypertension* 2005; **45**: 170–174.
19 Oparil S, Miller AP. Gender and blood pressure. *J Clin Hypertens (Greenwich)* 2005; **7**: 300–309.
20 Pechere-Bertschi A, Burnier M. Female sex hormones, salt, and blood pressure regulation. *Am J Hypertens* 2004; **17**: 994–1001.
21 Tominaga T, Suzuki H, Ogata Y, Matsukawa S, Saruta T. The role of sex hormones and sodium intake in postmenopausal hypertension. *J Hum Hypertens* 1991; **5**: 495–500.
22 Yamori Y, Liu L, Ikeda K, Mizushima S, Nara Y, Simpson FO. Different associations of blood pressure with 24-h urinary sodium excretion among pre- and post-menopausal women. Who cardiovascular diseases and alimentary comparison (who-cardiac) study. *J Hypertens* 2001; **19**: 535–538.
23 Dahl LK, Knudsen KD, Ohanian EV, Muirhead M, Tuthill R. Role of the gonads in hypertension-prone rats. *J Exp Med* 1975; **142**: 748–759.
24 Otsuka K, Suzuki H, Sasaki T, Ishii N, Itoh H, Saruta T. Blunted pressure natriuresis in ovariectomized dahl-iwai salt-sensitive rats. *Hypertension* 1996; **27**: 119–124.
25 Harrison-Bernard LM, Schulman IH, Raij L. Postovariectomy hypertension is linked to increased renal at1 receptor and salt sensitivity. *Hypertension* 2003; **42**: 1157–1163.
26 Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; **340**: 1801–1811.
27 Nickenig G, Baumer AT, Grohe C, Kahlert S, Strehlow K, Rosenkranz S, Stablein A, Beckers F, Smits JF, Daemen MJ, Vetter H, Bohm M. Estrogen modulates at1 receptor gene expression *in vitro* and *in vivo*. *Circulation* 1998; **97**: 2197–2201.
28 Gallagher PE, Li P, Lenhart JR, Chappell MC, Brosnihan KB. Estrogen regulation of angiotensin-converting enzyme mrna. *Hypertension* 1999; **33**: 323–328.
29 Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. *Cardiovasc Res* 2002; **53**: 688–708.
30 Gragasin FS, Xu Y, Arenas IA, Kainth N, Davidge ST. Estrogen reduces angiotensin ii-induced nitric oxide synthase and nad(p)h oxidase expression in endothelial cells. *Arterioscler Thromb Vasc Biol* 2003; **23**: 38–44.
31 Hernandez Schulman I, Raij L. Salt sensitivity and hypertension after menopause: Role of nitric oxide and angiotensin ii. *Am J Nephrol* 2006; **26**: 170–180.
32 Hiroki J, Shimokawa H, Mukai Y, Ichiki T, Takeshita A. Divergent effects of estrogen and nicotine on rho-kinase expression in human coronary vascular smooth muscle cells. *Biochem Biophys Res Commun* 2005; **326**: 154–159.
33 Kalaitzidis D, Gilmore TD. Transcription factor cross-talk: the estrogen receptor and nf-kappab. *Trends Endocrinol Metab* 2005; **16**: 46–52.
34 Wagner AH, Schroeter MR, Hecker M. 17beta-estradiol inhibition of nadph oxidase expression in human endothelial cells. *Faseb J* 2001; **15**: 2121–2130.
35 Hoshi-Fukushima R, Nakamoto H, Imai H, Kanno Y, Ishida Y, Yamanouchi Y, Suzuki H. Estrogen and angiotensin ii interactions determine cardio-renal damage in dahl salt-sensitive rats with heart failure. *Am J Nephrol* 2008; **28**: 413–423.
36 Potier M, Elliot SJ, Tack I, Lenz O, Striker GE, Striker LJ, Karl M. Expression and regulation of estrogen receptors in mesangial cells: Influence on matrix metalloproteinase-9. *J Am Soc Nephrol* 2001; **12**: 241–251.
37 Neugarten J, Acharya A, Lei J, Silbiger S. Selective estrogen receptor modulators suppress mesangial cell collagen synthesis. *Am J Physiol Renal Physiol* 2000; **279**: F309–F318.
38 Guccione M, Silbiger S, Lei J, Neugarten J. Estradiol upregulates mesangial cell mmp-2 activity via the transcription factor ap-2. *Am J Physiol Renal Physiol* 2002; **282**: F164–F169.
39 Karl M, Berho M, Pignac-Kobinger J, Striker GE, Elliot SJ. Differential effects of continuous and intermittent 17beta-estradiol replacement and tamoxifen therapy on the prevention of glomerulosclerosis: modulation of the mesangial cell phenotype *in vivo*. *Am J Pathol* 2006; **169**: 351–361.
40 Reckelhoff JF, Fortepiani LA. Novel mechanisms responsible for postmenopausal hypertension. *Hypertension* 2004; **43**: 918–923.
41 Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N. Death rates from ischemic heart disease in womne with a history of hypertension in pregnancy. *Acta Obstet Gynecol Scand* 1995; **74**: 772–776.
42 Chambliss KL, Shaul PW. Estrogen modulation of endothelial nitric oxide synthase. *Endocr Rev* 2002; **23**: 665–686.
43 Kaaja RJ, Poyhonen-Alho MK. Insulin resistance and sympathetic overactivity in women. *J Hypertens* 2006; **24**: 131–141.
44 Laivuori H, Tikkanen MJ, Ylikorkala O. Hyperinsulinemia 17 years after preeclamptic first pregnancy. *J Clin Endocrinol Metab* 1996; **81**: 2908–2911.
45 Suzuki H, Watanabe Y, Arima H, Kobayashi K, Ohno Y, Kanno Y. Short- and long-term prognosis of blood pressure and kidney disease in women with a past history of preeclampsia. *Clin Exp Nephrol* 2008; **12**: 102–109.
46 Sarafidis Pa Fau-Ruilope LM, Ruilope LM. Insulin resistance, hyperinsulinemia, and renal injury: Mechanisms and implications. *Am J Nephrol* 2006; **26**: 232–244.
47 Lobo RA. Metabolic syndrome after menopause and the role of hormones. *Maturitas* 2008; **60**: 10–18.
48 Gaspard U. Hyperinsulinaemia, a key factor of the metabolic syndrome in postmenopausal women. *Maturitas* 2009; **62**: 362–365.
49 McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. *J Clin Endocrinol Metab* 2001; **86**: 713–718.
50 Tylicki L, Rutkowski B, Horl WH. Multifactorial determination of hypertensive nephroangiosclerosis. *Kidney Blood Press Res* 2002; **25**: 341–353.
51 Sarafidis PA, Ruilope LM. Insulin resistance, hyperinsulinemia, and renal injury: Mechanisms and implications. *Am J Nephrol* 2006; **26**: 232–244.
52 Michels KB, Manson JB. Postmenopausal hromone therapy in the 21st century: Reconciling findings from observational studies and randomized clinical trials. In: Lobo RA, (ed). *Treatment of the postmenopausal woman*. Raven Press: New York, NY,, 2007, 619–626.
53 Gorodeski EZ, Gorodeski GI. Epidemiology and risk factors of cardiovascular disease in postmenpausal women. In: Lobo RA, (ed). *Treatment of the postmenopausal woman*. Raven Press: New York, NY,, 2007, 405–452.
54 Szekacs B, Vajo Z, Varbiro S, Kakucs R, Vaslaki L, Acs N, Mucsi I, Brinton EA. Postmenopausal hormone replacement improves proteinuria and impaired creatinine clearance in type 2 diabetes mellitus and hypertension. *BJOG* 2000; **107**: 1017–1021.
55 O'Hare AM. Management of peripheral arterial disease in chronic kidney disease. *Cardiol Clin* 2005; **23**: 225–236.
56 Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; **280**: 605–613.

57 Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furberg CD. Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol* 2001; **38**: 705–711.
58 Shlipak MG, Stehman-Breen C, Vittinghoff E, Lin F, Varosy PD, Wenger NK, Furberg CD. Creatinine levels and cardiovascular events in women with heart disease: Do small changes matter? *Am J Kidney Dis* 2004; **43**: 37–44.
59 Deo R, Lin F, Vittinghoff E, Tseng ZH, Hulley SB, Shlipak MG. Kidney dysfunction and sudden cardiac death among women with coronary heart disease. *Hypertension* 2008; **51**: 1578–1582.
60 Ginsburg ES, Walsh B, Greenberg L, Price D, Chertow GM, Owen Jr WF. Effects of estrogen replacement therapy on the lipoprotein profile in postmenopausal women with esrd. *Kidney Int* 1998; **54**: 1344.
61 Reckelhoff JF, Yanes LL, Iliescu R, Fortepiani LA, Granger JP. Testosterone supplementation in aging men and women: Possible impact on cardiovascular-renal disease. *Am J Physiol Renal Physiol* 2005; **289**: F941–F948.
62 Pitts TO, Piraino BH, Mitro R, Chen TC, Segre GV, Greenberg A, Puschett JB. Hyperparathyroidism and 1,25-dihydroxyvitamin d deficiency in mild, moderate, and severe renal failure. *J Clin Endocrinol Metab* 1988; **67**: 876–881.
63 Komaba H, Tanaka M, Fukagawa M. Treatment of chronic kidney disease-mineral and bone disorder (ckd-mbd). *Intern Med* 2008; **47**: 989–994.
64 Huang CL. Regulation of ion channels by secreted klotho: Mechanisms and implications. *Kidney Int* 2010; **77**: 855–860.
65 Cunningham J, Sprague SM, Cannata-Andia J, Coco M, Cohen-Solal M, Fitzpatrick L, Goltzmann D, Lafage-Proust MH, Leonard M, Ott S, Rodriguez M, Stehman-Breen C, Stern P, Weisinger J. Osteoporosis in chronic kidney disease. *Am J Kidney Dis* 2004; **43**: 566–571.
66 Bianchi S, Bigazzi R, Baldari G. Microalbuminuria in patients with essential hypertension: Effects of several antihypertensive drugs. *Am J Med* 1992; **93**: 525–528.
67 Jassal SK, von Muhlen D, Barrett-Connor E. Measures of renal function, bmd, bone loss, and osteoporotic fracture in older adults: The rancho bernardo study. *J Bone Miner Res* 2007; **22**: 203–210.
68 Fried LF, Biggs ML, Shlipak MG, Seliger S, Kestenbaum B, Stehman-Breen C, Sarnak M, Siscovick D, Harris T, Cauley J, Newman AB, Robbins J. Association of kidney function with incident hip fracture in older adults. *J Am Soc Nephrol* 2007; **18**: 282–286.
69 Nickolas TL, Leonard MB, Shane E. Chronic kidney disease and bone fracture: A growing concern. *Kidney Int* 2008; **74**: 721–731.
70 Ensrud KE, Lui L-Y, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antoniucci DM, Cummings SR, for the Study of Osteoporotic Fractures Research G. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med* 2007; **167**: 133–139.
71 Keating FSJ, Stevenson JC. Interventions for osteoporosis. In: Lobo RA, (ed). *Treatment of the postmenopausal woman*. Raven Press: New York, NY,, 2007, 351–375.
72 Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PW, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med* 1993; **329**: 1141–1146.
73 Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the cockcroft and gault method: A pooled analysis of nine clinical trials. *J Bone Miner Res* 2005; **20**: 2105–2115.
74 Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. *J Bone Miner Res* 2007; **22**: 503–508.
75 Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH. Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. *Osteoporos Int* 2007; **18**: 59–68.
76 National high blood pressure education program working group report on high blood pressure in pregnancy. *Am J Obstet Gynecol* 1990; **163**: 1691–1712.
77 Walsh BW, Kuller LH, Wild RA, Paul S, Farmer M, Lawrence JB, Shah AS, Anderson PW. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA* 1998; **279**: 1445–1451.
78 Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE. The effect of raloxifene treatment in postmenopausal women with ckd. *J Am Soc Nephrol* 2008; **19**: 1430–1438.
79 Stehman-Breen CO, Sherrard DJ, Alem AM, Gillen DL, Heckbert SR, Wong CS, Ball A, Weiss NS. Risk factors for hip fracture among patients with end-stage renal disease. *Kidney Int* 2000; **58**: 2200.
80 Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 2000; **58**: 396.
81 Ureña P, Bernard-Poenaru O, Ostertag A, Baudoin C, Cohen-Solal M, Cantor T, de Vernejoul MC. Bone mineral density, biochemical markers and skeletal fractures in haemodialysis patients. *Nephrol Dial Transplant* 2003; **18**: 2325–2331.
82 Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL. Prevalence of abnormal serum vitamin d, pth, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. *Kidney Int* 2006; **71**: 31–38.
83 Stehman-Breen C. Osteoporosis and chronic kidney disease. *Semin Nephrol* 2004; **24**: 78–81.
84 Matuszkiewicz-Rowiska J, Skrzewska K, Radowicki S, Sokalski A, Przedlacki J, Niemczyk S, Wdarczyk D, Puka J, Switalski M. The benefits of hormone replacement therapy in pre-menopausal women with oestrogen deficiency on haemodialysis. *Nephrol Dial Transplant* 1999; **14**: 1238–1243.
85 Hernandez E, Valera R, Alonzo E, Bajares-Lilue M, Carlini R, Capriles F, Martinis R, Bellorin-Font E, Weisinger JR. Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int* 2003; **63**: 2269–2274.
86 Ozbasar D, Toros U, Ozkaya O, Sezik M, Uzun H, Genc H, Kaya H. Raloxifene decreases serum malondialdehyde and nitric oxide levels in postmenopausal women with end-stage renal disease under chronic hemodialysis therapy. *J Obstet Gynaecol Res* 2010; **36**: 133–137.
87 Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, Klag MJ. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the choice study. *J Am Soc Nephrol* 2002; **13**: 1918–1927.
88 Shanahan CM. Mechanisms of vascular calcification in renal disease. *Clin Nephrol* 2005; **63**: 146–157.
89 Schoppet M, Shroff RC, Hofbauer LC, Shanahan CM. Exploring the biology of vascular calcification in chronic kidney disease: What's circulating? *Kidney Int* 2008; **73**: 384–390.