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# Chronic kidney disease and menopausal health: An EMAS clinical guide

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ABSTRACT

Kidney diseases are related to the aging process. Ovarian senescence and the loss of estrogen's renoprotective effects are directly associated with a decline in renal function and indirectly with an accumulation of cardiometabolic risk factors. The latter can predispose to the development of chronic kidney disease (CKD). Conversely, CKD diagnosed during reproductive life adversely affects ovarian function.

*Aim:* To set out an individualized approach to menopause management in women with CKD.

*Materials and methods:* Literature review and consensus of expert opinion.

*Summary recommendations:* Menopause hormone therapy can be given to women with CKD. The regimen should be selected on the basis of patient preference and the individual's cardiovascular risk. The dose of hormonal and non-hormonal preparations should be adjusted in accordance with the patient's creatinine clearance. The management of a postmenopausal woman with CKD should focus on lifestyle advice as well as regular monitoring of the main cardiovascular risk factors and evaluation of bone mineral density. Tailored multidisciplinary advice should be given to women with comorbidities such as diabetes, dyslipidemia, and hypertension. Management of osteoporosis should be based on the severity of the CKD.

## 1. Introduction

Chronic kidney disease (CKD) is a progressive, lifelong condition with profound public health implications. It is defined by functional decline (e.g., a glomerular filtration rate (GFR) < 60 mL/min/1.73 $m^2$) or persistent structural pathologies of the kidneys or other signs of kidney damage, like albuminuria of a duration of at least three months [1]. A large number of studies have shown that CKD is a risk factor for cardiovascular disease, metabolic-associated fatty liver disease [2], as well as heart failure [3]. Apart from the well-documented cardiometabolic complications which are related to a decline in kidney function [4,5], CKD is also known to affect bone health adversely [3–7].

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The rate of CKD increases linearly with age [8]. The prevalence is lower in those aged 30–40 years than in those aged 70–80 years (rates of 13.7 % vs 27.9 %, respectively) [9]. The risk of CKD appears to be higher for women than for men. The US National Health and Nutrition Examination Survey (NHANES) reported the prevalence of CKD to be 15.3 % in women vs 12.4 % in men, based on estimations for the years 2017 to 2020 [10]. The risk of CKD is higher for women who are diagnosed with type 2 diabetes (T2DM) but also for men with the condition (17.8 % and 14.6 %, respectively) [11]. However, several lines of evidence suggest that the risk of progression of CKD to end-stage kidney disease (ESKD) is higher in men than women, with factors such as inadequate control of ambulatory blood pressure (BP) in men playing a significant role in this progression [12–14].

Observational data indicate an association between CKD and early menopause; women experiencing menopause before the age of 45 years have a higher risk of developing CKD [15,16]. Given that the global population of postmenopausal women will reach 1.1 billion by 2025 [17], CKD is a significant concern. This clinical guide explores the link between menopause and kidney health, along with the potential risks and benefits of menopausal hormonal therapy (MHT) for women with CKD.

## 2. Methodology

A literature search was performed by 3 investigators (ECC, CTE, IBOE) to identify all observational studies and meta-analyses available in PubMed, in the English language, and published through to May 2024. The search string was: [condition/disease of interest] AND [menopause OR (postmenopausal women)]. The title and abstract of the articles retrieved were reviewed and evaluated for relevance. Only those studies that included postmenopausal women with documented CKD and/or a history of renal transplantation were eligible for further evaluation.

## 3. Role of sex steroids in kidney function and the effect of menopause

### 3.1. Kidney function and the role of estrogen receptors

Estrogen receptors are present in the kidneys and their modulation can affect renal function. Estrogen inhibits the proliferation of glomerular mesangial cells, reduces mesangial expansion, decreases collagen deposition and interstitial fibrosis, and mitigates podocyte loss and glomerular hypertrophy [18,19]. Furthermore, estrogen prevents matrix accumulation, which is essential in the progression of glomerulosclerosis, via suppression of the synthesis of collagen type I and type IV [20].

### 3.2. Electrolyte and water homeostasis: the role of sex hormones

Water and electrolyte homeostasis are modified via estrogen's effect on osmoregulation [21,22]. At a cellular level, estrogen's role is summarized as follows: a) downregulation of the expression and function of the α-, β-, and γ-epithelial sodium channels (ENaC), which reduces sodium reabsorption [23–25]; b) regulation of the expression of alpha sodium/potassium adenosine triphosphatase (α-Na/K-ATPase) [23]; c) upregulation of the expression of the angiotensin type 2 receptor (AT2), and consequent suppression of aldosterone [26].

### 3.3. Estrogen complexes and the renin–angiotensin–aldosterone system

Estrogen signaling may regulate blood pressure through modulation of the renin–angiotensin–aldosterone system (RAAS) [27]. Estrogen receptor alpha (Erα) influences renin expression and sodium–potassium balance [28]. The inactivation of ERα results in an increase in renin expression, and conversely its activation by estrogen inhibits renin synthesis [29]. More specifically, estrogens have been found to suppress the transcription of the angiotensin 1 receptor gene in cultured rat vascular smooth muscle cells [30]. In vitro and in vivo evidence suggests that elevated levels of circulating FSH contributed to increased blood pressure, independent of estrogen levels [31].

Oral and transdermal estradiol have distinct effects on the RAAS, potentially influencing blood pressure regulation [27]. While oral estrogens, particularly conjugated equine estrogens (CEE), can elevate angiotensinogen levels, this effect may be clinically significant only in individuals with pre-existing hypertension or RAAS dysfunction. Increased angiotensinogen could lead to elevated aldosterone levels, which inhibit renin through negative feedback [27]. However, if this feedback mechanism is impaired, it may result in a rise in blood pressure [27]. To mitigate this potential adverse effect, transdermal estradiol or estradiol/drospirenone (with the latter acting as a selective aldosterone inhibitor) are often clinically preferred [27].

### 3.4. Erythropoietin production by the kidney and the role of estrogen

Animal studies have demonstrated that estrogen influences the effects of erythropoietin (EPO) either directly via the regulation of EPO production or indirectly via the regulation of EPO's tissue-specific response [32].

### 3.5. Parathormone, vitamin D and calcium metabolism: the role of estrogen

Aging and the ensuing state of hypoestrogenism are associated with higher rates of secondary hyperparathyroidism [33]. Postmenopausal estrogen deficiency leads to a heightened bone turnover, accompanied by renal calcium leakage and decreased calcium absorption from the intestine [34–37]. Growing old has been linked with a progressive reduction in serum calcium levels, leading to a corresponding increase in the level of parathyroid hormone (PTH) [38,39].

### 3.6. The role of progesterone on kidney function

Progesterone receptors are located in kidney tissues, mainly in distal tubule cells [40]. Progesterone has been demonstrated to stimulate renal reabsorption of sodium [24]. Progesterone molecules can also interact with androgen receptors upon being converted to testosterone and dihydrotestosterone [41].

## 4. Effects of CKD on the menopausal transition and postmenopausal health

### 4.1. CKD and age at menopause

The presence of chronic disease is linked to a higher risk of early ovarian senescence. A diagnosis of CKD during the reproductive years has been associated with a 2.64 times higher risk for early menopause, independent of cardiovascular risk factors or a previous diagnosis of diabetes or MHT use. Similarly, pre-existing cardiovascular disease (CVD) and related conditions such as hypertension and diabetes mellitus have been documented to increase the risk of early menopause, by 3.02 times, 2.11 times, and 1.75 times, respectively, independent of age, MHT use, traditional cardiovascular risk factors, and lifestyle [42].

Early menopause is reported for patients at CKD stages 3–5. In particular, CKD stage 5 leads to menopause at a relatively young mean age of 45.9 years [15]. Consequently, an inadequate rise in estrogen and progesterone prior to ovulation is insufficient to induce ovulation and results in amenorrhea and ultimately early menopause [43]. Menstruation was reported to resume, fertility to be restored, and successful pregnancies to take place in amenorrheic women with CKD of reproductive age who had received interventions such as hormone therapy [44], dopamine agonists [45], and successful kidney transplantation

[46]. Of note, menstrual cycles were found to recur within six months after transplantation, and the rate of ovulatory cycles was similar to that of healthy women [47]. In a study on hormone therapy use in kidney transplant recipients, MHT was effective in the long term and had no negative impacts on graft function [48].

### 4.2. CKD and postmenopausal health

Metabolic risk factors such as obesity, hypertension, and type 2 diabetes mellitus (T2DM) increase the risk of CVD as well as of CKD. Concomitantly, CKD during the reproductive years can increase the risk of CVD, independent of the postmenopausal cardiometabolic burden. CVD is in fact the leading cause of morbidity and mortality for patients with CKD [49].

#### 4.2.1. The interaction between CKD and CVD in women

Kidney function, expressed as estimated GFR (eGFR) values, declines with aging per se [50,51]. Furthermore, the menopausal transition per se is known to heighten the cardiometabolic burden by increasing the prevalence of T2DM, hypertension, abdominal obesity, dyslipidemia, and thus CVD. The high rates of cardiovascular morbidity and mortality observed in CKD and ESKD have long been attributed to a complex of traditional and non-traditional risk factors. The traditionally recognized risk factors for both CKD and ESKD are older age, male gender, hypertension, diabetes, dyslipidemia, and smoking, but, in addition, non-traditional risk factors, more specifically related to ESKD, are increasingly recognized, including electrolyte disturbances, mineral and bone disorders, anemia, oxidative stress, chronic inflammation, endothelial dysfunction, arterial stiffness, malnutrition, and autonomic nervous system (ANS) dysfunction [49,52,53].

Cardiovascular morbidity and mortality in CKD patients are associated with abnormalities in the calcium–phosphate balance and related vascular calcifications. The underlying pathophysiological mechanisms include apoptosis of vascular smooth muscle cells, osteochondrogenic differentiation, cellular release of vesicles loaded with phosphate and calcium, and elastin degradation. Towards the later stages of CKD, high phosphate levels contribute to accelerated mineral deposition in vessel walls [54], while high levels of sclerostin, an inhibitor of the canonical Wnt/β-catenin bone pathway, are associated with increased arterial stiffness and increased risk of cardiovascular events [55].

Vitamin K form 2 (menaquinone) plays a role in protein synthesis and is involved in cardiovascular and bone health [56,57]. At more advanced stages of CKD, phosphate binders simultaneously bind to vitamin K molecules, resulting in vitamin K deficiency [58,59]. The postmenopausal hypoestrogenic state also predisposes towards vitamin K2 deficiency. Vitamin K2 diminishes the menopausal development of hydroxyapatite within blood vessels by facilitating the carboxylation of matrix Gla protein and Gla-rich proteins [59]. Vitamin K2 hinders the apoptosis of vascular smooth muscle cells by promoting the expression of growth arrest-specific gene 6 and lessens the trans-differentiation of vascular smooth muscle cells into osteoblasts [60].

#### 4.2.2. CKD and bone health

Bone fragility in women with CKD G4–G5D is attributed to a complex combination of primary osteoporosis, drug-induced effects, and CKD-related bone abnormalities [61–64].

Primary osteoporosis, typically associated with aging or postmenopausal conditions, manifests at a younger age in CKD patients due to accelerated/premature aging of bone tissues. Moreover, the use of various drugs for a range of kidney diseases, such as corticosteroids and diuretics, can harm bone health [65]. The uremic environment, marked by inflammation and metabolic imbalances in CKD, also contributes to bone disease or renal osteodystrophy (ROD) [66–68]. ROD involves abnormalities in bone turnover, mineralization, and volume, potentially impairing bone strength. Abnormal bone turnover can be classified further into diseases that lead to high turnover (e.g., secondary hyperparathyroidism) and those that lead to low (mostly adynamic) turnover. The latter category has progressively become the more common bone condition in dialysis patients [65]. The uremic milieu also affects the biochemical composition of bone, impacting matrix composition and mineralization. On the other hand, primary kidney diseases like autosomal dominant polycystic kidney disease and systemic diseases that may also affect kidney function (e.g., systemic lupus erythematosus, diabetes mellitus) could be associated with specific bone phenotypes that predispose individuals to fractures [69,70].

Bone remodeling is regulated via paracrine and endocrine signals, particularly the Wnt/b-catenin pathway and Parathyroid Hormone (PTH). In the context of advanced disease, a decrease in free serum calcium levels leads to a secondary increase in PTH and in turn the continuous exposure to high circulating PTH levels promotes bone resorption. Signaling through PTH receptor type 1 in osteoblasts and osteocytes has the potential to elevate the ratio of receptor activator of nuclear factor B ligand to osteoprotegerin (the RANKL:OPG ratio) [65]. The OPG–RANKL–RANK pathway seems to be the primary mediator of PTH's catabolic effects. Prolonged exposure to PTH results in a sustained increase in the level of monocyte chemoattractant protein 1, promoting bone resorption. Conversely, the anabolic impact of PTH on bone appears to be predominantly facilitated through canonical Wnt/b-catenin signaling. PTH can enhance Wnt/b-catenin signaling both directly and indirectly, for example by suppressing the osteocytic expression of the Wnt antagonist sclerostin [71,72].

Conversely, the heightened expression of Wnt inhibitors can counteract the actions of PTH in the initial stages of CKD. There is a growing acknowledgment that PTH hypo-responsiveness is responsible for as much mineral and bone disorder (MBD) as are elevated levels of circulating PTH. [65]. Clinical and experimental evidence suggests that high PTH signaling predominantly causes cortical bone loss, explaining the increased prevalence of peripheral fractures in CKD patients.

Overall, bone fragility in patients with CKD G4–G5D is multifactorial; therefore, it is essential to consider the various contributing factors for effective diagnosis and treatment [73,74].

## 5. Menopausal hormone therapy (MHT) for women with CKD

Currently, there are no guidelines regarding menopause management in women with CKD, and almost half of kidney specialists report uncertainty about the role of MHT for this group [75]. Taking into consideration the sparsity of data, there are no contraindications to offering treatment in eligible symptomatic women, according to the well-documented indications for MHT [76]. The administration of MHT should ideally be planned to take place around the time of the "window of opportunity" for cardiovascular protection, as delayed administration is likely to have adverse cardiovascular effects [16].

### 5.1. Exogenous estrogen and kidney function

- Experimental models suggest that estrogen replacement therapy may have nephroprotective effects. However, the results from human studies are inconclusive [77,78].
- Hormone therapy seems to be linked to lower odds of albuminuria, according to the results of the few relevant randomized controlled trials and observational studies (low level of evidence) [79].
- Despite the well-documented cardiometabolic benefits of MHT in the general postmenopausal population [76], the data on its cardiovascular effects in the CKD population remain sparse [80]. Furthermore, recent observational data indicate that MHT of any type is linked to a decreased likelihood of cognitive dysfunction related to CKD in postmenopausal women [81]. Levels of estradiol have been associated with all-cause but not specifically cardiovascular mortality in a large cohort of patients undergoing maintenance hemodialysis [82]. Estrogenic therapy has been reported to improve creatinine clearance, plasma lipid levels and insulin sensitivity in diabetic

postmenopausal women [83–85]. Preliminary data also suggest that raloxifene slows the progression of albuminuria in diabetic postmenopausal women [86]. Moreover, experimental data from rats support the beneficial effects of 17β-estradiol [87,88] as well as raloxifene [88] on urine albumin excretion and creatinine clearance [87].

- The postulated renoprotective effect of estrogen treatment appears to be related to changes in systemic and/or intraglomerular pressure, improved glomerular endothelial function and/or glomerular capillary wall integrity. Metabolic effects, such as raising insulin sensitivity, and lowering glucose levels, as well as cholesterol or triglyceride levels, may also be involved [89]. Beyond these effects, estrogen may lessen oxidative stress and diminish monocyte chemotaxis [90]. Further, 17β estradiol may attenuate tubulointerstitial fibrosis and glomerulosclerosis [91,92]. Moreover, the interaction between estrogen and autocrine-paracrine humoral hormones such as nitric oxide (NO), prostaglandin I2, and endothelin has been reported to contribute to the integrity of the glomerular capillary wall [93]. In vitro data also suggest that 17β estradiol and raloxifene exert their renoprotective effect by reducing the degree of fibronectin accumulation and mesangial expansion [88].

### 5.2. The dose and duration of MHT for women with CKD or renal transplant recipients

- Even though exogenous estrogen is mainly processed in the liver and gastrointestinal tract, CKD is known to alter the pharmacokinetics of the hormone [94,95].
- The guidelines produced by the American National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) recommend that for women with CKD, the dose of 17β-estradiol is 50 %–70 % lower than that which would be prescribed for women with normal kidney function, with no staging cut-off values [96,97]. There is no precise information on the dosing of progesterone for women with CKD. However, the risk of fluid retention is likely to be exacerbated in women with underlying CKD.
- Estrogen administration to women on treatment with calcineurin inhibitors like cyclosporine and tacrolimus requires close monitoring of the respective plasma levels. Both agents are metabolized through the cytochrome P450 system, implying the possible risk of cyclosporine and tacrolimus toxicity in women who are also on treatment with estrogen replacement [98].
- The risk of coronary heart disease, venous thromboembolism, and stroke is known to be higher in women with CKD [99]. However, large clinical trials are yet to be conducted on the safety of MHT in women with CKD and kidney transplant recipients, and so there is little information about the optimal dosing and duration, or the extent of the thrombotic risk. The menopausal symptoms of these patients remain neglected.
- For female kidney allograft recipients and patients with renal pathologies, the decision to initiate or continue MHT should be made individually, considering the severity and the type of renal disease, other risk factors, and the potential benefits of MHT. Collaboration between nephrologists and gynecologists in a multidisciplinary setting is crucial to provide comprehensive care and ensure optimal management of menopausal symptoms while minimizing potential risks to renal health [100].

### 5.3. The role of MHT in the control of climacteric symptoms and chronic health problems related to menopause

#### 5.3.1. Climacteric symptoms

There are conflicting data regarding the effects of MHT on climacteric symptoms in postmenopausal women with CKD or after kidney transplantation. In a large observational study, women with CKD were found to experience earlier menopausal transition than women with healthy kidney function and to report fewer and less severe vasomotor symptoms [101].

#### 5.3.2. Cognitive function

Patients with CKD can suffer from cognitive impairment due to multiple pathophysiological effects, including but not limited to white-matter injury, micro-bleeding in the cerebrum, vascular impairments, and endothelial dysfunction [102]. The degree of cognitive dysfunction has been found to parallel the severity of albuminuria [103,104]. While studies examining the correlation between MHT and dementia have yielded conflicting outcomes, no data have yet emerged on the phenomenon in women with CKD [96,105,106].

#### 5.3.3. Cardiovascular disease

It is well documented that the postmenopausal cardiometabolic burden leads to heightened cardiovascular morbidity and mortality [97]. Prevention of CVD is not included in the named indications for the administration of MHT; nonetheless, early initiation of transdermal treatment in eligible women can promptly aid in controlling cardiometabolic risk [107]. However, the role of MHT in reducing peri- and postmenopausal cardiovascular risk in women with CKD or kidney transplant recipients remains to be elucidated.

#### 5.3.4. Osteoporosis

- MHT prevents postmenopausal osteoporosis and reduces fracture risk [108], and women with CKD are at an elevated risk of osteoporosis and related fractures [109].
- The therapeutic approach for osteoporosis in women with CKD primarily involves reducing elevated serum phosphate levels while maintaining adequate calcium levels. Anti-resorptive therapy may be initiated if necessary [110].
- However, insufficient evidence exists regarding the impact of MHT on bone mineral density (BMD) and fracture risk in postmenopausal women with CKD [111]. In a meta-analysis, raloxifene for postmenopausal women produced notable improvements in lumbar spine (SMD 3.30; 95 % CI 3.21–3.38) and femoral neck (SMD 3.29; 95 % CI 3.21–3.36) BMD compared with placebo. A recent investigation indicated that bazedoxifene enhances renal function, potentially through increased renal phosphate excretion, in postmenopausal osteoporotic women without severe renal insufficiency [112].

## 6. The role of non-hormonal menopause treatments in women with CKD

The non-hormonal formulations typically used as alternatives to MHT for women with moderate to severe vasomotor symptoms can also be considered in patients with CKD. However, dose titration and monitoring for side-effects are recommended in all cases (Table 1).

## 7. Practical guide for the management of postmenopausal women with CKD

Women aged >50 years, especially if diagnosed with hypertension and/or diabetes mellitus, should be screened for CKD [113–115]. The screening should be based on estimated levels of GFR (eGFR) and the ratio of urine albumin to creatinine. Referral to a renal specialist is recommended in the following cases [113–115]:

- urine albumin-to-creatinine >300 mg/g
- a decrease in eGFR by at least 25 % or any eGFR <30
- evidence of hematuria or new diagnosis of nephrolithiasis
- hereditary renal disease
- renal dysfunction of unknown origin

**Table 1**
Hormonal and non-hormonal measures to control vasomotor symptoms in women with chronic kidney disease (adapted from [121–123]).

| Treatment agents | Recommended daily dose | Safety threshold for women with renal impairment | Contraindications and cautions |
|---|---|---|---|
| Transdermal 17β estradiol | 50–70 % lower than for women without CKD | • Not clearly defined | • Dose-dependent effects on cardiovascular and breast tissue |
| Anticholinergic modulators | • Oxybutynin 5–15 mg | • Not clearly defined | • Caution in patients with renal impairment |
| Central alpha-2 adrenergic agonist | • Clonidine 50 μg two or three times | • Start a low dose and titrate with caution<br>• For the initial dose, consider the amount of renal impairment | • Monitor carefully for bradycardia and hypotension |
| Gabapentinoids | • Gabapentin, starting dose 100–300 mg at night, titrated to a maximum of 2400 mg | Chronic kidney disease<br>Max daily dose:<br>• ClCr 50–79 mL/min: 1800 mg daily<br>• ClCr 30–49 mL/min: 900 mg/day<br>• ClCr 15–29 mL/min: 600 mg/day<br>• ClCr <15 mL/min: 300 mg/day<br>End-stage kidney disease<br>Max dose: 300 mg daily if dialyzed. Administer soon after hemodialysis | • Dose adjustment is required<br>• It is recommended to start at a low dose and slowly increase after 7–14 days<br>• Monitor for falls and altered mental status |
| Neurokinin B antagonists | • Fezolinetant 45 mg | • Mild to moderate CKD (eGFR 30 to <90 mL/min/1.73 m2): No dose modification is recommended | • Severe CKD (eGFR <30 mL/min/1.73 m2): Not recommended<br>• ESKD (eGFR <15 mL/min/1.73 m2): Not investigated |
| SNRI | • Venlafaxine 37.5-150 mg | Chronic kidney disease<br>• If administering the extended-release form, start with 37.5 mg daily<br>• Max daily dose depends on ClCr, as follows:<br>ClCr 30–89 mL/min: 150 mg daily<br>ClCr <30 mL/min: 112.5 mg daily<br>End-stage kidney disease<br>• If administering the extended-release form, start with 37.5 mg daily<br>• Max daily dose of 112.5 mg daily | • Can rarely cause serotonin syndrome<br>• Monitor for hyponatremia |
| | • Desvenlafaxine 100-150 mg | Chronic kidney disease<br>• Max daily dose depends on ClCr, as follows:<br>ClCr 30–50 mL/min: 50 mg daily<br>ClCr <30 mL/min: 25 mg daily or 50 mg every other day<br>End-stage kidney disease<br>• Max daily dose: 25 mg daily or 50 mg every other day | • Can rarely cause serotonin syndrome<br>Monitor for hyponatremia |
| SSRI | • Paroxetine 7.5 mg | Chronic kidney disease<br>The dosage as per ClCr is as follows:<br>• CrCl 30 to 60 mL/min: No need to change the dosing<br>• CrCl <30 mL/min:<br>o Immediate-release formulation: 10 mg/day; if needed, increase by 10 mg/day increments at an interval of at least a week; maximum dose 40 mg/day<br>o Controlled release formulation: 12.5 mg/day; if needed, increase by 12.5 mg/day increments at intervals of at least one week; maximum dose 50 mg per day. | • Caution, and plan dose as per CrCl |
| | • Citalopram 10-20 mg | • Mild to moderate CKD: No dose adjustment is necessary<br>• Severe CKD or ESKD requires close monitoring to avoid possible adverse reactions | • Monitor for side-effects in those with advanced CKD (e.g., drowsiness, insomnia, diaphoresis, nausea, vomiting, xerostomia, constipation, diarrhea) |
| | • Escitalopram 10-20 mg | • Mild to moderate CKD: No dose adjustment is necessary | • Severe renal impairment (CrCl <20 mL/min) requires caution |

SSRI = Selective serotonin reuptake inhibitor; SNRI = Serotonin norepinephrine reuptake inhibitors; ECG = Electrocardiogram; eGFR = Estimated glomerular filtration rate; CrCl = Creatinine clearance; CKD = Chronic kidney disease; ESKD = End-stage kidney disease.

Careful evaluation of cardiovascular risk factors is required for all women with documented CKD. According to the clinical practice guidelines for diabetes management in CKD produced by the Kidney Disease Improving Global Outcomes (KDIGO) study (2022) [113], the American Diabetes Association (2023) [114], and the International Society of Hypertension (ISH) and the European Renal Association (ERA) (2023) [115], the management of postmenopausal women with CKD can be summarized as follows:

- Routine evaluation of the 10-year cardiovascular mortality risk using international calculators is not required for women with CKD stages 3–5. Risk assessment depends on the eGFR and the severity of albuminuria (Fig. 1) [116].
- The evaluation of a postmenopausal woman with CKD should include an assessment of diet in combination with weight optimization if needed, physical activity measures, blood pressure assessment, estimation of the presence and severity of climacteric symptoms, and possibly an evaluation of bone density (Fig. 2) [113].

| Albuminuria categories (mg/g) | CKD GFR categories (mL/ min / 1.73 m²) | | | |
|---|---|---|---|---|
| | G3a (45-59) | G3b (30-44) | G4 (15-29) | G5 (<15) |
| < 30 | Moderate | High | Very high | Very high |
| 30 -299 | High | Very high | Very high | Very high |
| ≥ 300 | Very high | Very | Very high | Very high |

CKD = chronic kidney disease; GFR = glomerular filtration rate; CVD = cardiovascular disease

**Fig. 1.** Cardiovascular risk stratification by categories of GFR and albuminuria (CVD risk moderate to very high) (adapted from [116]).

- During a consultation of a postmenopausal woman with CKD with a menopause specialist, the following recommendations for health and well-being can be offered (Fig. 3) [117]:
  - o *Step 1.* General measures involve advice on smoking cessation and evaluations of blood pressure and serum lipid levels. Dietary measures should include a daily sodium intake of <2 g (or 90 mmol) for patients with hypertension and CKD. Exercise should consist of at least 150 min per week or as tolerated, depending on physical and cardiovascular well-being. Moreover, it is essential to emphasize the role of a healthy body weight and, if needed, to help manage obesity.
- *Step 2*. Specific measures involve recommendations for evaluating lipids, albuminuria, and blood sugar levels [113,118].
  - o With regard to the control of blood lipids, the guidelines recommend the use of statins targeting LDL-cholesterol <1.8 mmol/L (or 70 mg/dL) for women with high CVD risk and LDL-cholesterol <1.4 mmol/L (or 55 mg/dL) for those with very high CVD risk. Dialysis-dependent women who are already on statin (or ezetimibe) treatment at the time of initiation of dialysis may continue their hypolipidemic treatment. On the other hand, those on established dialysis without clinically prevalent CVD might not require ongoing hypolipidemic treatment. In the case of solid organ transplant recipients, statins should be offered as the first-line treatment. Treatment should be started at a low dose and cautiously titrated up with monitoring for potential drug-drug interactions.
  - o Regarding the prevention of CKD progression to ESKD, including control of albuminuria, early initiation of RAAS blockade is recommended even before referral to a kidney specialist. The typical treatment involves angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers titrated up to a maximum tolerated dose. The use of an SGLT-2 inhibitor for patients with diabetic or non-diabetic CKD and of finerenone for patients with diabetic CKD and albuminuria is recommended [113–115].
  - o Regarding blood pressure control, the recommended targets include systolic blood pressure < 130 mmHg and diastolic blood pressure < 80 mmHg, if tolerated, for patients with CKD or transplant recipients [115].
  - o Regarding the degree of glycemic control, the KDIGO 2022 guidelines [113] recommend an individualized target for glycated hemoglobin of <6.5 % to <8.0 % in patients with diabetes mellitus and CKD who are not dialysis dependent.

- o MHT management [76]:
  - ▪ For women classified as being at high cardiovascular risk, only topical (e.g., transdermal patch or gel) MHT should be offered if treatment is necessary.
  - ▪ For women at very high cardiovascular risk, MHT should ideally be avoided. If treatment is necessary, healthcare practitioners should consider offering only vaginal estrogen.

- For women with osteoporosis or high fracture risk, upon assessment with the FRAX algorithm, management involves the following (Fig. 4) [65,119]:
  - o Classification of the CKD stage. For CKD stages 3–5, consider referral to a specialist.
  - o Metabolic control of CKD in collaboration with a kidney specialist.

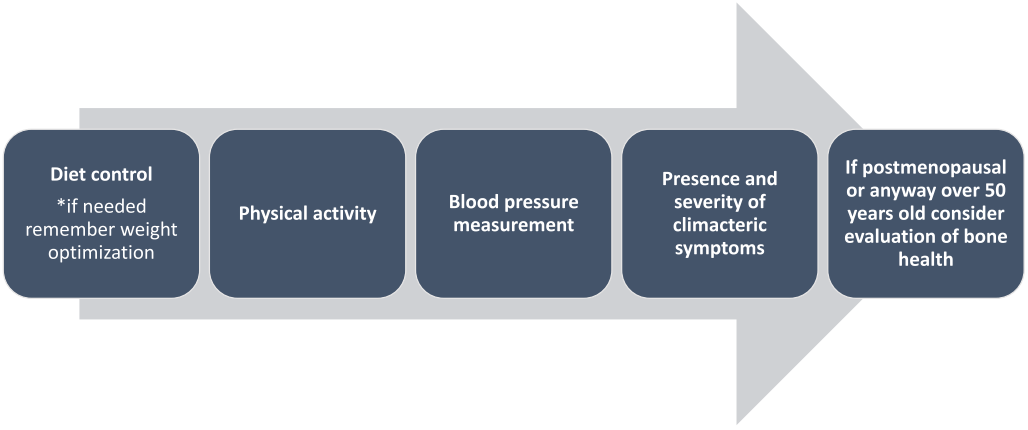
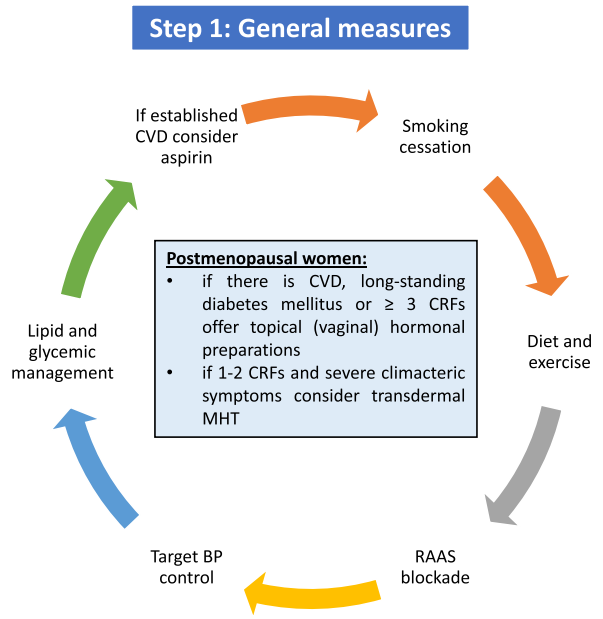



**Fig. 2.** Steps for the evaluation of a postmenopausal woman with chronic kidney disease (adapted from [76,116]).




BP = blood pressure; RAAS = renin–angiotensin–aldosterone system; CVD = cardiovascular disease; CRFs = cardiovascular risk factors; MHT = menopausal hormone therapy

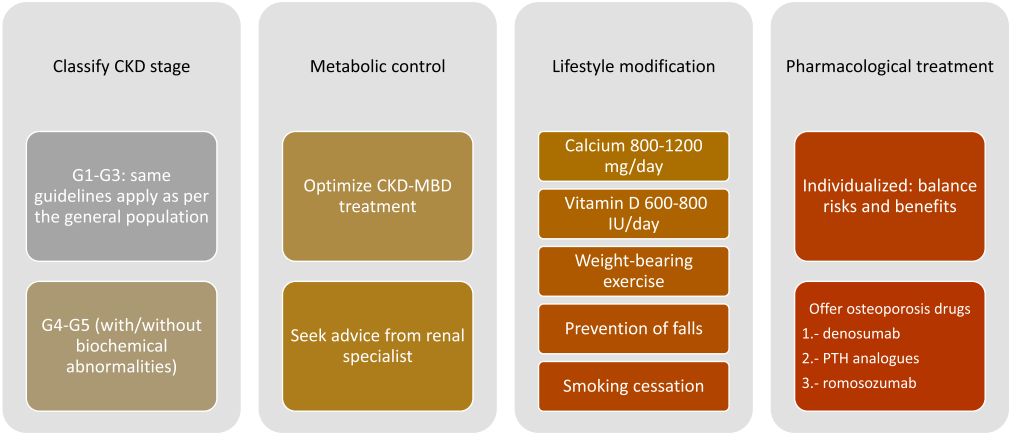
**Step 2: Primary prevention of specific risk scenarios**

| | High CVD risk | Very high CVD risk |
|---|---|---|
| LDL-cholesterol target | < 1.8 mmol/L (or 70mg/dL) | <1.4 mmol/L (or 55 mg/dL) |
| | · **Non-dialysis dependent** → statins ± ezetimibe<br>· **Dialysis dependent**→<br>a) at the time of the initiation of dialysis, if already on hypolipidemic treatment consider continuation<br>b) during ongoing dialysis, without clinical atherosclerotic CVD, commencement of statin is not recommended. | |
| Albuminuria | Consider RAAS inhibition independent of BP | |
| Blood pressure | Target SBP < 130 mmHg when tolerated<br>For transplant recipients, target SBP < 130mmHg and DBP < 80mmHg | |
| T2DM or non-DM kidney disease and eGFR > 20 mL/min/1.73m$^2$ or HF | Consider SGLT2 inhibition | |
| Additional drugs for heart and kidney protection | GLP-1 RA; Non-selective MRA; Antiplatelet therapies | |

LDL=low density lipoprotein cholesterol; CVD = cardiovascular disease; RAAS = renin-angiotensin aldosterone system; BP = blood pressure; T2DM = type 2 diabetes mellitus; eGFR = estimated glomerular filtration rate; HF = heart failure; SGLT2 = sodium glucose co-transporter 2; SBP = systolic blood pressure; DBP = diastolic blood pressure; GLP-1 RA = glucagon-like peptide-1 receptor agonists; MRA = mineralocorticoid receptor antagonists

**Fig. 3.** General and risk-specific recommendations for women with chronic kidney disease (adapted from [76,113]).

- Lifestyle modification should incorporate calcium 800–1200 mg/day and vitamin D 600–800 IU/day in people without secondary hyperparathyroidism. For people with secondary hyperparathyroidism or adynamic bone disease, the treatment of osteoporosis should be modified according to existing guidelines for the treatment of CKD-MBD, in close collaboration with a kidney specialist [120]. Exercise, particularly weight-bearing, is recommended. Lifestyle modification should also include smoking cessation and the prevention of falls.
- Pharmacological treatment. For women with low bone density that is not attributed to CKD or for women with insufficient response to treatment for CKD-induced bone pathologies, the typical anti-osteoporosis drugs can be offered. Agents that can be used safely in postmenopausal women with CKD include denosumab, PTH analogs, and romosozumab. These agents are not retained by the kidneys and have exhibited good efficacy in preclinical studies. Post-hoc studies report reduced fracture rates in postmenopausal women on treatment with denosumab or PTH analogs, with a significant increase in BMD levels in women with advanced CKD. Safety concerns in the postmenopausal population include the risk of atypical fracture, hypocalcemia, or osteonecrosis of the jaw for denosumab; the risk of hypotension for PTH analogs; and the risk of hypocalcemia and adverse cardiovascular events for romosozumab. Specific attention should be given to the offset of effect when offering treatment with denosumab or romosozumab, while PTH analogs may require dose adjustment. \, The treatment interval with PTH analogs can be extended only up to 24 months.




PTH = parathyroid hormone; CKD = chronic kidney disease; MBD = metabolic bone disease

**Fig. 4.** Management of postmenopausal women with osteoporosis and CKD (adapted from [65]).

## 8. Conclusion and summary recommendations

- Both menopause and CKD have a significant impact on cardiovascular and bone health.
- Estrogen influences renal function and may be renoprotective; however, the results of epidemiological studies on the possible role of MHT are conflicting
- Vasomotor symptoms are the main indication for MHT. However, no dosing studies are available for women with CKD or renal transplant recipients.
- Recommended doses of systemic estradiol for women with CKD are 50–70 % lower than for those with normal kidney function. Women treated with calcineurin inhibitors such as cyclosporine and tacrolimus should have their estradiol levels closely monitored after MHT initiation.
- Topical rather than systemic estrogens are preferred for women at high or very high cardiovascular risk.
- Protection of kidney function could be considered as an additional indication for MHT in women with primary ovarian insufficiency (POI) or early menopause.
- Non-hormonal treatments for hot flushes and osteoporosis are not contraindicated in women with CKD.
- A multidisciplinary approach is recommended.

## Contributors

E. Cansu Cevik, C. Tamer Erel and Ipek Betul Ozcivit Erkan prepared the initial draft, which was circulated to all other named authors (EMAS board members and advisors) for comment and approval. Irene Lambrinoudaki and Margaret Rees coordinated production.

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