

Menopause and reproductive endocrine dysfunction in CKD-associated osteoporosis

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ABSTRACT

Chronic kidney disease (CKD) is associated with multiple comorbidities and adverse outcomes, including cardiovascular disease and skeletal fragility. Women with CKD exhibit increased fracture risk, exacerbated by traditional osteoporosis risk factors and CKD-related alterations in mineral and endocrine regulation. Reproductive endocrine dysfunction, including hypogonadism, amenorrhea, and early menopause, is common in CKD. Mechanisms include accelerated uremia-related follicular atresia, hypothalamic–pituitary–ovarian axis disruption, and elevated prolactin, endorphins, and leptin. Amenorrhea may be misclassified as menopause, complicating risk assessment. These alterations contribute to impaired bone remodeling and increased cardiovascular risk, with early menopause linked to higher mortality. Kidney transplantation may restore hypothalamic–pituitary–gonadal function and fertility, pointing to a reversible component of CKD-associated hypogonadism. Hormone replacement therapy or selective estrogen receptor modulators may improve bone density and reduce fracture risk, although evidence remains limited. Long-term safety is not established in the setting of kidney dysfunction, and caution is required when prescribing these therapies to patients with CKD. Overall, reproductive aging and endocrine dysfunction in women with CKD remain under-recognized and warrant further investigation.

KEYWORDS

Chronic kidney disease, fracture, hormone replacement therapy, hypogonadism, osteoporosis, sex hormones.

Introduction: reproductive endocrine dysfunction in chronic kidney disease

Chronic kidney disease (CKD, Table I) is a common condition affecting approximately 10% of the adult population, although it is under-recognised due to its asymptomatic presentation in early stages^[1,2]. Across the globe, CKD is more common in women than in men^[3].

In the majority of cases, it has a multifactorial etiology, with contributions from other prevalent comorbid conditions such as hypertension, diabetes mellitus, obesity, cardiovascular disease, and atherosclerosis^[2,3]. Although kidney dysfunction itself may remain clinically silent for years, CKD affects multiple aspects of health and is a powerful marker of adverse outcomes. Cardiovascular disease represents the leading cause of death in this population, with epidemiological studies demonstrating a steep increase in cardiovascular mortality with declining kidney function^[4].

In addition to cardiovascular disease, skeletal fragility has emerged as a major and clinically relevant complication of CKD. Osteoporosis and fracture risk are increasingly recognized across the CKD spectrum and are driven by a complex interplay of traditional osteoporosis risk factors and CKD-specific disturbances in mineral metabolism, bone turnover, and endocrine regulation^[5].

Fracture risk is markedly increased in patients with CKD, spanning patients with CKD G3–5^[6], dialysis-dependent kid-

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ney failure^[7,8], and in the post-transplant setting^[9,10], with reported fracture incidences that are 2- to 4-fold higher than in age- and sex-matched individuals without CKD, rising progressively as kidney function declines^[5].

Women with CKD appear to be at particularly high risk of fracture. Large observational studies demonstrate that women consistently exhibit higher fracture rates than men across CKD stages, a pattern that persists after adjustment for age and comorbidity and becomes more pronounced in advanced disease and during the transition to dialysis^[6,11].

In the general population, this sex difference is well established and largely attributed to accelerated bone loss during the menopausal transition^[12–14].

However, whether and how menopause contributes to CKD-associated osteoporosis remains insufficiently understood. In particular, it is unclear to what extent skeletal fragility in women with CKD reflects chronological menopause versus CKD-related disturbances in reproductive endocrine function, which may modify both the timing and biological consequences of estrogen deficiency.

Sex hormones and bone health in CKD: an under-recognized clinical issue

Hypogonadism is common in CKD and affects women across the CKD spectrum, including those of reproductive age, with menstrual disturbances and gonadal dysfunction reported in both predialysis and dialysis-dependent populations [15-17].

Menopause is defined as the absence of menstrual cycles for at least 12 months associated with follicle-stimulating hormone (FSH) levels >30 mIU/L, and it represents the permanent cessation of ovulation [18]. In healthy women, this results from the progressive loss of ovarian follicles and the consequent reduction in estradiol production [19]. Menopause occurs when the number of ovarian follicles decreases to approximately 1,000, compared with about 2 million at birth, and the age at onset depends mainly on the rate of follicular atresia [20,21].

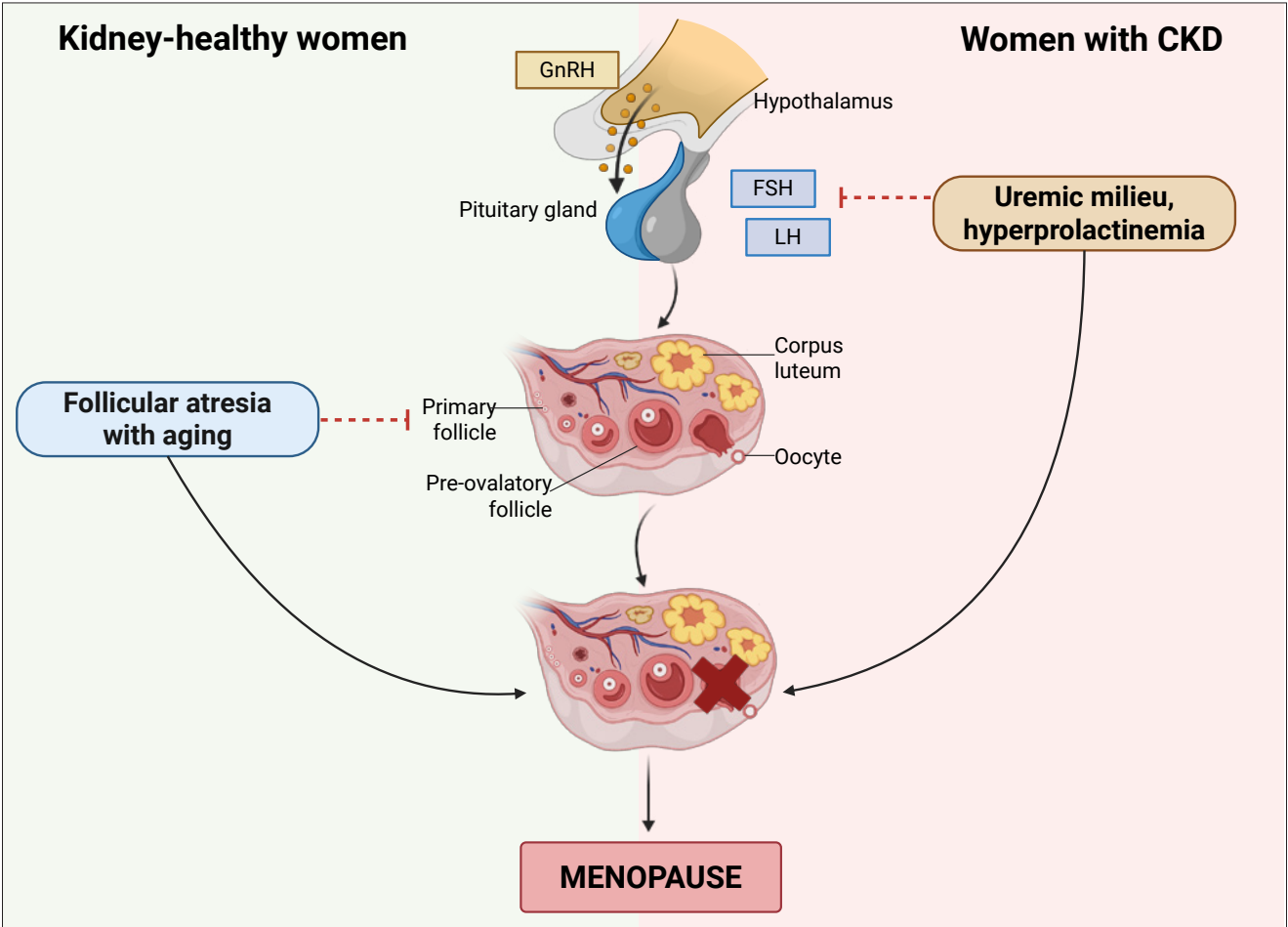
Amenorrhea, defined as the absence of menses for ≥6 months in women who have had menarche [22], is highly prevalent in women with kidney failure, affecting over 50% of patients [23]. Menopause has been reported to occur approximately 5 years earlier in these women than in the general population [24], and cases of early menopause (<45 years) have been reported even in earlier grades of CKD [25]. CKD is associated with disruption of the hypothalamic–pituitary–ovarian axis, characterized by impaired cyclic release gonadotropin-releasing hormone (GnRH), with documented abnormalities in follicle-stimulat-

Table 1 Classification of chronic kidney disease by estimated glomerular filtration rate (eGFR)

GRADE	DESCRIPTION	EGFR
G1	Normal kidney function despite kidney disease	>90
G2	Mildly decreased kidney function	60-89
G3a	Mildly to moderately decreased kidney function	45-59
G3b	Moderately to severely decreased kidney function	30-44
G4	Severely decreased kidney function	15-29
G5	Kidney failure	<15
G5D	Kidney failure with need of dialysis therapy	<15

ing hormone (FSH), luteinizing hormone (LH), estradiol and testosterone profiles across CKD grades [17,26,27]. Women with CKD have been shown to exhibit preserved GnRH secretion but absent midcycle LH surge, consistent with hypothalamic anovulation [24]. Notably, these abnormalities may arise despite preserved or only modestly reduced circulating estradiol concentrations, underscoring that central endocrine dysregulation (Figure 1) rather than primary ovarian failure predominates in CKD-associated hypogonadism [28]. Hyperprolactinemia repre-

Figure 1 Menopause in women with and without chronic kidney disease (CKD), (Created in BioRender).



sents an important contributing mechanism and has been consistently documented in women receiving dialysis, likely reflecting both reduced renal clearance and altered hypothalamic regulation [17,26]. Elevated prolactin levels may further suppress GnRH pulsatility and exacerbate gonadotropin deficiency. Importantly, kidney transplantation corrects the hyperprolactinemia induced by uremia and is followed by rapid restoration of hypothalamic–pituitary–gonadal axis function, supporting a central and potentially reversible mechanism underlying reproductive endocrine dysfunction in CKD [28].

These endocrine abnormalities have important implications for bone health. Chronic disruption of gonadotropin secretion and altered estrogen signaling contribute to disrupted bone remodeling [29], adding to the metabolic bone disease caused by CKD. With decreasing kidney function, disturbances in bone turnover, mineralization, and microarchitecture become evident, with a highly variable bone phenotype ranging from very low (adynamic) to very high bone turnover states with or without bone mineralization defects [30,31]. Regardless of the underlying uremic bone phenotype, the imbalance in skeletal remodeling favoring bone resorption induced by sex hormone disturbances is likely to exacerbate skeletal fragility in women with CKD.

Clinically, endocrine dysfunction may present as apparent early menopause; however, accumulating evidence suggests that this presentation often reflects functional and potentially reversible hypogonadism rather than irreversible ovarian failure, particularly in younger women. Following successful kidney transplantation, menstrual cycle and fertility may partially or fully recover, although variability in outcomes indicates that reversible and irreversible components may coexist [28,32,33].

Beyond skeletal outcomes, menopause-related endocrine changes in CKD have broader health implications. In postmenopausal women, the prevalence of hypertension and left ventricular diastolic dysfunction increases markedly, and the risk of cardiovascular disease increases nearly 3-fold [34]. A systematic review and meta-analysis demonstrated that postmen-

opausal status in women with CKD is associated with adverse health outcomes, including lower bone mineral density (BMD), increased fracture risk, and higher cardiovascular and mortality risk, even after adjustment for age [35]. These findings indicate that menopausal status independently influences risk in CKD and is not merely a reflection of age. Despite this, reproductive ageing and its consequences remain under-recognized in nephrology practice, and menopause is rarely incorporated into routine risk assessment or management strategies [36]. Furthermore, women with CKD-related amenorrhea may be incorrectly classified as menopausal, since the standard definitions of secondary amenorrhea and menopause can overlap [37]. In addition, hormonal testing (e.g., using the Women's Ischemic Syndrome Evaluation classification) is not a reliable method to determine menopausal status in women on long-term dialysis [38,39].

Therapeutic considerations: hormone-based interventions in CKD

Growing evidence suggests that sex hormone disturbances contribute to bone fragility in women with CKD, but the role of hormone-based treatment remains uncertain. At present, clinical decision-making is limited by a lack of high-quality evidence. No large, randomized trials have tested estrogen therapy or related treatments for fracture prevention in women with CKD, and most available data come from observational studies that rely on BMD rather than fracture outcomes (Table II). Despite these limitations, existing studies provide consistent and biologically plausible findings. Cross-sectional [40,41] and short-term longitudinal [42] studies in women on dialysis show that higher endogenous estrogen levels are associated with better bone health, including higher BMD and reduced bone loss over time, independent of traditional CKD–mineral and bone disorder markers. These results suggest that estrogen deficiency may worsen bone loss in CKD, even when other metabolic abnormalities are present.

Table II Studies investigating bone phenotype in women with chronic kidney disease in relation to sex hormone status.

AUTHOR	DESIGN	POPULATION	INVESTIGATIONS	RESULTS	INTERPRETATION
Jørgensen 2018 ^[40]	Cross-sectional	CKDG5-5D, N=146 (n=44 women)	Sex hormones, QCT BMD	Total and bioavailable testosterone positively correlated with lumbar spine BMD in postmenopausal women	High endogenous levels of sex hormones may preserve BMD in postmenopausal women with kidney failure
Sugiya 2011 ^[42]	Prospective, observational	CKDG5D (HD), N=112 post-menopausal women	Free estrogen index, DXA BMD	Free estrogen index showed a positive correlation with BMD Z-score and with annual percent change in BMD	Endogenous estrogen may prevent bone loss in postmenopausal women receiving hemodialysis therapy
Cueto-Manzano 2001 ^[43]	Cross-sectional	Kidney transplant recipients, N=30 (n=14 women)	Bone biopsy, DXA BMD	Serum estradiol levels were positively correlated with Z-scores of osteoblast surface, osteoid surface and trabecular wall thickness in women	High endogenous levels of sex hormones may preserve normal bone formation in women after kidney transplantation
Weisinger 2000 ^[41]	Cross-sectional	CKDG5D (HD), N=74 women <50 yrs	Sex hormones, DXA BMD	BMD was significantly lower in amenorrheic women (58%). Total estradiol levels directly correlated with BMD	Regular menstrual cycles and higher endogenous levels of sex hormones may preserve BMD in young women receiving hemodialysis therapy

Abbreviations: DXA=Dual-energy X-ray absorptiometry; BMD=bone mineral density; CKDG5-5D=chronic kidney disease grade 5 to 5D; HD=hemodialysis; QCT=quantitative computed tomography

From a therapeutic perspective, these findings support careful, individualized consideration of hormone-based approaches in selected patients with severe hypogonadism and high fracture risk. However, estrogen therapy carries potential risks, including thromboembolic events, malignancy, and cardiovascular complications [44], which may be particularly relevant in CKD. Alternative strategies, such as selective estrogen receptor modulators (SERMs), may offer a safer option, but evidence in CKD populations is limited (Table III).

A small, controlled study provided evidence of benefit of hormone replacement therapy (HRT) in young women with sex hormone dysregulation in CKD. In a 12-month study of pre-menopausal women on hemodialysis with secondary amenorrhea and low estradiol, transdermal estrogen with cyclic progestin restored physiological estradiol levels, normalized menstrual cycles, reduced prolactin concentrations, and resulted in an increase in lumbar spine BMD, while untreated controls experienced bone loss [16]. Notably, these skeletal effects occurred without significant changes in parathyroid hormone or calcium–phosphate parameters, suggesting a direct effect of estrogen on bone. Reported adverse events were limited, but thrombotic risk remains a concern in dialysis patients. No CKD-specific dose adjustments were defined, and optimal

dosing and monitoring remain unclear. These findings raise the question of whether premature hypogonadism in young female dialysis patients should be managed similarly to that in kidney-healthy women [55], with careful individual risk–benefit assessment.

Although small proof-of-concept studies of HRT have been conducted in postmenopausal women with CKD [45–47], none have investigated outcomes relevant to skeletal health. In contrast, potential bone-protective effects of SERMs have been demonstrated in both early and later stages of CKD. Post hoc analyses of large, randomized trials demonstrate that raloxifene and bazedoxifene increase lumbar spine BMD and reduce vertebral fracture risk in postmenopausal women with mild to moderate CKD, with similar safety profiles across kidney function [49,53]. Smaller trials have also indicated a positive treatment effect in kidney failure [48,50–52]. Importantly, these benefits appear to be independent of classical CKD–mineral and bone disorder parameters. A systematic review and meta-analysis found that raloxifene improves spine BMD in women with advanced CKD and kidney failure, although effects at cortical sites and fracture outcomes remain uncertain [56]. Available evidence suggests that SERMs do not accumulate in bone and may avoid concerns related to oversuppression of bone turno-

Table III Studies investigating hormone replacement therapy (HRT) or selective estrogen receptor modulators (SERMs) in women with chronic kidney disease.

STUDY	DESIGN	POPULATION	N	INTERVENTION	DURATION	OUTCOME	RESULT
Ginsburg 1998 ^[45]	RCT (placebo)	CKDG5D (HD), post-menopausal	11	Oral HRT	8 wks	Lipid profile	Increase in HDL cholesterol, no change in LDL. No bone outcome.
Matuszkiewicz-Rowinska 1999 ^[16]	Controlled clinical trial	CKDG5D (HD), <45 yrs, amenorrhea	23	Transdermal estradiol	1 yr	Hormonal status; BMD	Return of regular menstrual cycle, increase in estradiol and decrease in prolactin. Spine BMD improved.
Szekacs 2000 ^[46]	Non-controlled clinical trial	Diabetic nephropathy, post-menopausal	16	Oral HRT	14 wks	Lipid profile	Decrease in proteinuria, increase in creatinine clearance. Decrease in fasting blood sugar and cholesterol. No bone outcome.
Park 2000 ^[47]	RCT (control)	CKDG5D (HD), post-menopausal	65	Oral HRT	12 wks	Lipid profile, haemostatic factors and homocysteine	Increased HDL cholesterol and triglycerides; decreased LDL cholesterol, lipoprotein(a), PAI-1 and t-PA. No bone outcome.
Hernandez 2003 ^[48]	RCT (placebo)	CKDG5D (HD), post-menopausal + low BMD	50	Raloxifene	1 yr	BMD, lipid profile	Decrease in LDL with no change in HDL. Spine BMD improved, no change in hip BMD.
Ishani 2008 ^[49]	Posthoc RCT (placebo)	CKDG3–4, post-menopausal + low BMD	7316 (4973)	Raloxifene	3 yrs	BMD, fracture	Spine and hip BMD improved. Vertebral fracture risk reduced; no effect on non-vertebral fracture risk.
Tanaka 2011 ^[50]	Controlled clinical trial	CKDG5D post-menopausal + low BMD	27	Raloxifene	1 yr	BMD, bone turnover markers	Spine BMD improved, no change in bone turnover markers.
Saito 2011 ^[51] + 2012 ^[52]	RCT (control)	CKDG5D (HD), peri- or post-menopausal	60	Raloxifene	1 yr	BMD, bone turnover markers	Heel ultrasound BMD improved, bone turnover markers decreased.
Adami 2013 ^[53]	Posthoc RCT (placebo)	CKDG3, post-menopausal + low BMD	8737 (723)	Bazedoxifene	2–3 yrs	BMD, fracture	Spine and hip BMD improved, bone turnover markers decreased. Fracture risk reduced.
Nagatoya 2015 ^[54]	Non-controlled clinical trial	CKDG5D (HD), >50 yrs	30	Raloxifene	16 wks	Bone turnover markers	Transient decrease in bone turnover markers.

Abbreviations: BMD=bone mineral density; CKDG3–5D=chronic kidney disease grades 3 to 5D; HD=hemodialysis; HDL=high-density lipoprotein; HRT=hormone replacement therapy; LDL=low-density lipoprotein; RCT=randomized controlled trial

ver, which is particularly relevant in CKD [57]. Taken together, SERMs may represent an underappreciated treatment option for postmenopausal women with CKD who have contraindications to bisphosphonates, provided thromboembolic risk is carefully assessed.

Conclusions

CKD disrupts the gonadal axis, and amenorrhea and hypogonadism are common in affected women. Preserved gonadal function is associated with better skeletal health in CKD, suggesting that sex hormone deficiency contributes to bone fragility. Although robust interventional evidence is limited, HRT and SERMs may represent viable, but underexplored, treatment options for CKD-associated osteoporosis in women, warranting further investigation.

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