Sex differences in cardiovascular-kidney-metabolic syndrome: From pathogenesis to treatment response (Review)

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Abstract. Cardiovascular-kidney-metabolic (CKM) syndrome is an emerging clinical construct that emphasizes the intertwined pathophysiology of cardiovascular disease, chronic kidney disease, and metabolic disorders. Accumulating evidence reveals profound sex-based differences in the incidence, progression, and outcomes across the spectrum of CKM syndrome. These disparities are rooted in complex interactions between sex hormones and pathophysiological processes such as inflammation, endothelial dysfunction, oxidative stress, and metabolic regulation. Premenopausal women generally exhibit protective cardiovascular and renal profiles due to estrogenic effects, whereas men, influenced by androgens, often experience more severe organ damage and faster disease progression. However, this female advantage is attenuated after menopause, and available clinical data suggest that women may experience poorer outcomes at comparable CKM stages in some cohorts. Furthermore, sex differences extend to clinical manifestations, epidemiologic patterns, and therapeutic responses, influencing the efficacy and tolerance of medications including statins, renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter 2 inhibitors, and insulin. Sex-related factors, including healthcare access, referral patterns, adherence, and trial representation, may further modify clinical outcomes. The present review synthesizes current knowledge on sex-specific mechanisms of CKM pathogenesis, clinical trajectories, and pharmacologic responses, and highlights gaps between basic and clinical research. Future directions include designing sex-stratified clinical trials, developing sex-sensitive guidelines, and leveraging translational research to inform precision medicine. Addressing sex-related differences in CKM syndrome represents a crucial step toward equitable and personalized care in cardio-renal-metabolic medicine.

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Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; ED, erectile dysfunction; ESRD, end-stage renal disease; GFR, glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; PCOS, polycystic ovary syndrome; PK/PD, pharmacokinetic/pharmacodynamic; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter 2; suPAR, soluble urokinase plasminogen activator receptor; T2D, type 2 diabetes

Key words: cardiovascular-kidney-metabolic syndrome, sex differences, chronic kidney disease, heart failure, precision medicine

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1. Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome is an emerging concept that emphasizes the interconnected pathophysiology of cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic disorders (1). The 2023 scientific statement from the American Heart Association formally defines and stages CKM syndrome, enabling a more integrated approach to these coexisting conditions (2). CKM has major public health implications: Recent data show nearly half of U.S. adults aged ≥20 years have some form of CVD, and 43.6% of deaths in patients with end-stage renal disease (ESRD) are due to cardiovascular causes (3). These statistics underscore the need for comprehensive

strategies that simultaneously target cardiac, renal, and metabolic dysfunction.

Research increasingly recognizes sex as a key factor influencing CKM syndrome. Men and women differ markedly in the incidence, progression, and outcomes of CVD, CKD, and metabolic diseases (1). These disparities stem in part from sex hormones and their effects on physiological pathways, such as the renin-angiotensin-aldosterone system (RAAS), oxidative stress, inflammation, endothelial function, and insulin sensitivity (4). For example, premenopausal women have a lower incidence of CVD than age-matched men, yet when severe cardiovascular events occur, women often experience higher mortality and worse outcomes (5). A similar pattern exists in CKD: Women have higher reported CKD prevalence, but men predominate in ESRD and dialysis (6). A large 30-year U.S. cohort (1988-2018) of 33,868 adults found that although women were less likely than men to progress to advanced CKM stages, their mortality risk was higher at each level of severity (7). These findings suggest that biological sex-related healthcare factors may jointly shape CKM trajectories. These observations highlight the urgent need to elucidate sex-specific mechanisms and translate this knowledge into interventions that reduce sex disparities in multisystem disease risk (8-10).

In summary, recognizing sex differences in CKM syndrome has important clinical significance. In the present review, current knowledge on sex-specific mechanisms of CKM pathogenesis, clinical trajectories, and pharmacologic responses are synthesized. Consistencies and gaps between basic science and clinical observations are examined, and future directions for sex-stratified prevention and treatment are outlined.

2. Sex differences in pathogenesis

Differences in endocrine regulation (sex hormone effects). Sex steroids have profound effects on cardiovascular, renal, and metabolic physiology (11-17). Estrogen generally exerts protective effects on the heart-kidney axis, whereas androgens tend to promote pathological changes (14-17). Acting through estrogen receptors ERα/ERβ, estrogen downregulates renin, angiotensin-converting enzyme (ACE), and angiotensin II receptors, thereby suppressing RAAS activity (18-20). By contrast, testosterone tends to amplify RAAS signaling, which may partly explain the higher susceptibility of men to hypertension and renal damage (21,22). Estrogen also promotes endothelial nitric oxide production and reduces oxidative stress in tissues (23-25), whereas androgens enhance vasoconstriction and oxidative injury (21,26-28). These hormone-driven effects on vasomotor tone and inflammation contribute to sex differences in vascular and renal health.

Differences in immune response and inflammation. Chronic inflammation underpins CKM pathology (29,30), and sex modulates inflammatory tone. Females generally mount stronger innate and adaptive immune responses (raising autoimmune risk) but tend toward a relatively anti-inflammatory baseline, whereas males exhibit a more pro-inflammatory profile (31,32). At the molecular level, androgens boost proinflammatory cytokines (such as TNF-α, IL-6 and IFN-γ), while estrogen suppresses inflammatory signaling and fibrosis-promoting pathways (25,33-35). For example, male animals were shown to exhibit exaggerated renal and vascular injury that was mitigated by castration and worsened by testosterone, whereas estrogen treatment was revealed to dampen fibrotic mediator release (36-42). Estrogen receptor signaling has also been shown to limit Toll-like receptor 4/NF-κB-driven cytokine release (43,44). Overall, estrogen fosters a relatively low-inflammatory, anti-fibrotic milieu, whereas androgens drive inflammation and fibrosis, contributing to plaque instability and renal scarring. These differences have significant implications for CKM disease progression and treatment strategies.

Differences in endothelial function. The vascular endothelium is crucial for cardiovascular health and is strongly influenced by sex (45). Premenopausal women typically have superior endothelial function compared with men of the same age, with higher baseline nitric oxide release and vasodilatory tone (46). Estrogen contributes to this advantage by enhancing endothelial nitric oxide synthase activity and inhibiting vascular smooth muscle proliferation (27). By contrast, androgens elevate vasoconstrictors such as endothelin-1, leading to higher vascular tone in men (28). These differences change with age: After menopause, declining estrogen causes endothelium-dependent dilation to deteriorate and arterial compliance to worsen more rapidly in women (47,48). The antioxidant properties of estrogen help preserve endothelial function, whereas androgen excess exacerbates oxidative injury (49-51). The superior endothelial health of premenopausal women helps delay cardiovascular events during reproductive years, but this advantage erodes after menopause, contributing to the rising cardiovascular risk in older women.

Differences in macrovascular dysfunction and arterial stiffness. On a larger scale, arterial aging follows sex-specific patterns. Premenopausal women have more compliant large arteries and lower arterial stiffness than men, largely due to estrogen-mediated reduction of collagen deposition and enhancement of endothelial nitric oxide (52). After menopause, arterial stiffness in women accelerates rapidly and can equal or exceed that of men (48). This late-life increase in stiffness raises systolic and pulse pressures, predisposing women to isolated systolic hypertension and heart failure (HF) with preserved ejection fraction (HFpEF). A membrane estrogen receptor, G protein-coupled estrogen receptor 1 (GPER1), has been shown to promote nitric oxide release and natriuresis, effects that may contribute to female-specific cardiovascular protection and are attenuated in men (53,54). Overall, men experience greater arterial stiffening earlier in life, whereas women undergo a steeper increase after menopause. These two distinct trajectories link macrovascular dysfunction to sex-specific CKM outcomes.

Differences in renal metabolic regulation. Male and female kidneys differ anatomically and functionally. On average, men have larger kidneys and slightly higher glomerular filtration rates (GFR) in young adulthood (55). However, women appear to have some inherent protection. Despite a higher reported prevalence of early-stage CKD in women (56), men are more likely to progress to ESRD and dialysis (57). This suggests that

renal function in men may deteriorate faster, or that clinical interventions differ by sex. Biological factors likely contribute, as male kidneys appear more prone to persistent low-grade inflammation and fibrosis (39).

Sex hormones also directly influence nephron structure and function (58). In animal models, estrogen supplementation in female mice was shown to reduce markers of renal injury, including proteinuria and glomerulosclerosis, whereas elevated testosterone was associated with worsened proteinuria and nephron loss (59,60). In diabetic animal models, 17β-estradiol or selective estrogen receptor modulators were reported to attenuate glomerular hypertrophy and extracellular matrix deposition (60,61). Estrogen has also been shown to protect renal tubules: Activation of GPER1 mitigated salt-induced tubular injury and oxidative inhibition of glucose transport (62,63).

Hemodynamic sensitivity further differs by sex: Kidneys in men were shown to exhibit higher salt sensitivity and stronger RAAS activation, making hypertension more damaging (64,65). By contrast, kidneys in women were reported to be relatively shielded by estrogen-modulated RAAS, showing less salt- and pressure-induced injury (66,67). In summary, estrogen has been demonstrated to provide females with renal protection (slower fibrosis and preserved tubular function), whereas men were shown to be predisposed to accelerated nephron loss and decline. These mechanisms help explain why male patients with CKD tend to progress more rapidly and suffer worse outcomes.

Emerging biomarkers reflect these risks. For example, soluble urokinase plasminogen activator receptor (suPAR), an inflammatory marker linked to cardiorenal risk, was reported to be ~10% higher in women than men (68). Elevated suPAR was shown to predict adverse cardiovascular and renal outcomes in both sexes, but using sex-specific cutoffs may improve risk stratification (69,70).

Differences in cardiac structural and functional adaptation. Sex differences in cardiac remodeling and HF phenotypes are well documented. Men tend to develop ventricular dilation and systolic dysfunction in response to overload or injury, whereas women more often develop concentric hypertrophy and diastolic dysfunction with preserved ejection fraction (71-75). Clinically, this manifests as men more frequently presenting with HF with reduced ejection fraction (HFrEF), often due to ischemic heart disease, while women more commonly develop HFpEF linked to hypertension and obesity (74,75).

On a cellular level, pressure overload was shown to trigger different adaptations: Female hearts were reported to respond with concentric hypertrophy (wall thickening and increased stiffness) that can lead to diastolic dysfunction, whereas male hearts were shown to undergo eccentric hypertrophy (chamber dilation) and a greater decline in systolic function (76,77). Estrogen has been demonstrated to exert anti-fibrotic effects on cardiac fibroblasts, protecting premenopausal women; by contrast, men and postmenopausal women (with low estrogen) were reported to show more fibrotic remodeling (77). Female myocardium was also revealed to maintain more efficient energy metabolism under stress (78), which helps preserve function during ischemic or metabolic insults.

In terms of outcomes, women with chronic HF have lower mortality and fewer sudden deaths than men (79). This survival advantage may reflect later onset age in women, fewer ischemic triggers, and estrogenic protection. For instance, in ischemia-reperfusion models, estrogen was shown to improve coronary collateral circulation and reduce infarct size, whereas androgens were revealed to exacerbate cardiomyocyte apoptosis and impair repair (80-83). Certain cardiomyopathies further highlight sex effects: Stress-induced ('Takotsubo') cardiomyopathy and peripartum cardiomyopathy occur almost exclusively in women (84,85).

In summary, the female heart remodels distinctly, tending toward concentric hypertrophy and stiffness while preserving systolic function, whereas the male heart dilates and loses contractile reserve. Notably, after myocardial infarction women often exhibit higher levels of fibrotic biomarkers (such as galectin-3) than men, correlating with greater hypertrophy and HF (86,87). This suggests that when injured, female hearts may engage profibrotic pathways more readily, illustrating the complex and sometimes paradoxical nature of sex differences in cardiac adaptation.

Differences in lipid and glucose metabolism. Sex also shapes metabolic profiles relevant to CKM risk. Menopause triggers adverse lipid changes in women: Low-density lipoprotein (LDL) cholesterol rises and high-density lipoprotein cholesterol falls after estrogen loss, which may erode atherosclerosis protection in women (88). A life-course study found that the lipid-related cardiovascular risk in women is lower than that in men only during premenopausal ages; in childhood and after ~50 years of age, lipid profiles in women are more atherogenic than those in men (89). By contrast, men often have higher triglycerides, more small dense LDL particles, and greater visceral fat, all of which increase atherosclerotic risk in middle age (90,91).

Sex differences also extend to glucose and insulin metabolism. Women generally have slightly higher insulin sensitivity and stronger pancreatic β-cell insulin secretion than men (92-94). Consequently, men develop insulin resistance and type 2 diabetes (T2D) at lower body mass indices, whereas women are often diagnosed later and at higher BMI (95). Unique female stressors increase diabetes risk: A history of gestational diabetes is a major predictor of later T2D in women (96), and menopause can unmask latent insulin resistance (97). Men also tend to accumulate visceral fat, whereas premenopausal women usually store more subcutaneous fat (98). Visceral fat promotes inflammation and insulin resistance, thus men with obesity face higher metabolic risk. After menopause, fat in women redistributes toward visceral depots and risk climbs rapidly (99,100).

Sex differences persist once diabetes is established. Diabetes effectively eliminates the baseline cardiovascular advantage of women: Diabetic women suffer a disproportionately larger relative increase in coronary and stroke risk than diabetic men (101-103). For example, several studies found diabetic women have an ~27% higher stroke risk than diabetic men (102,103). Conversely, men with diabetes are more prone to microvascular complications: They have higher rates of diabetic kidney disease, retinopathy, and neuropathy than women (104). Clinically, diabetic men often have greater proteinuria, faster progression to dialysis, and more severe retinopathy or limb amputations. These disparities may reflect

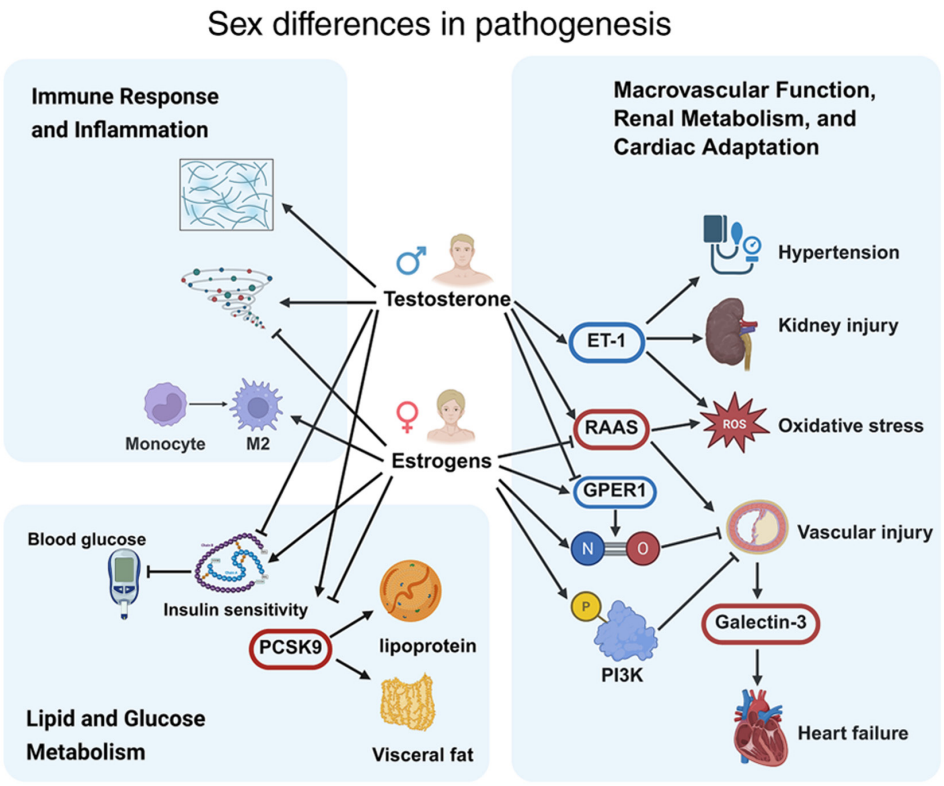

Figure 1. Sex differences in endocrine regulation, immune response, inflammation, and endothelial function. The sex-specific differences in endocrine regulation, immune response, inflammation, and endothelial function are illustrated. Female individuals exhibit protective effects predominantly mediated by estrogens, which contrast with the pro-inflammatory effects associated with testosterone in males. Dyslipidemia is more prevalent in males, contributing to cardiovascular risk. In terms of immune response and inflammation, females demonstrate greater T-cell activity along with higher levels of interferons and immunoglobulins, indicative of a more robust adaptive immune response. Conversely, males exhibit a heightened inflammatory profile. Regarding endothelial function, females maintain more preserved endothelial function, whereas males experience greater endothelial injury accompanied by elevated levels of inflammatory markers. These differences highlight the influence of sex hormones on the pathophysiology of inflammatory and vascular conditions. ET-1, endothelin-1; RAAS, renin-angiotensin-aldosterone system; GPER1, G protein-coupled estrogen receptor 1; PCSK9, proprotein convertase subtilisin/kexin type 9; ROS, reactive oxygen species.

androgen-driven inflammation and behavioral factors such as poorer glycemic control and higher smoking rates in men (93). There is also evidence that women with diabetes may receive less aggressive cardiovascular preventive care than men (102).

Underlying these outcomes, emerging mediators are being identified. For instance, circulating proprotein convertase subtilisin/kexin type 9 (PCSK9), which degrades LDL receptors, is higher in women than in men, and rises further after menopause (105). This estrogen-associated PCSK9 increase may partly explain the disproportionate LDL elevation and atherosclerotic risk women experience post-menopause (106).

In summary, baseline sex differences in lipid and glucose metabolism create distinct vulnerabilities: Men have a smaller 'metabolic reserve' and develop dyslipidemia and insulin resistance at earlier stages, while premenopausal women benefit from estrogen-mediated protection but then suffer a sharper risk rise after menopause. These metabolic factors contribute to the sex-specific patterns of CKM-related disease (Fig. 1).

3. Clinical manifestations and epidemiological differences

Cardiovascular event incidence and types. Sex differences profoundly affect clinical CKM outcomes. Men have a significantly higher risk of coronary artery disease and myocardial infarction in early and mid-adulthood than women (107,108). Cardiovascular events in premenopausal women are typically delayed by roughly a decade due to estrogen-mediated protective effects (107,108). Over the lifespan, men and women were shown to have similar overall HF risk, but the subtypes differ: Men more often develop HFrEF (usually ischemic), while women more often develop HFpEF (often linked to hypertension and obesity) (74,75).

Men were shown to have a higher incidence of acute cardiovascular events, including sudden cardiac death and life-threatening arrhythmias, and were revealed to be more likely to present in midlife with acute coronary syndromes or abrupt HF. By contrast, women more often develop chronic HF at older ages, typically on a background of long-standing hypertension and metabolic disease. When a major event such as myocardial infarction occurs, women frequently experience worse short-term outcomes with higher in-hospital mortality, likely reflecting older age, greater comorbidity burden, delays in recognition, and biological differences in response (109,110).

CKD progression differences. CKD epidemiology also shows sex patterns. Women report slightly higher CKD prevalence in the general population, likely reflecting greater longevity in women (111). However, men progress to advanced CKD and require dialysis more often than women (112). In fact, men outnumber women in dialysis programs worldwide

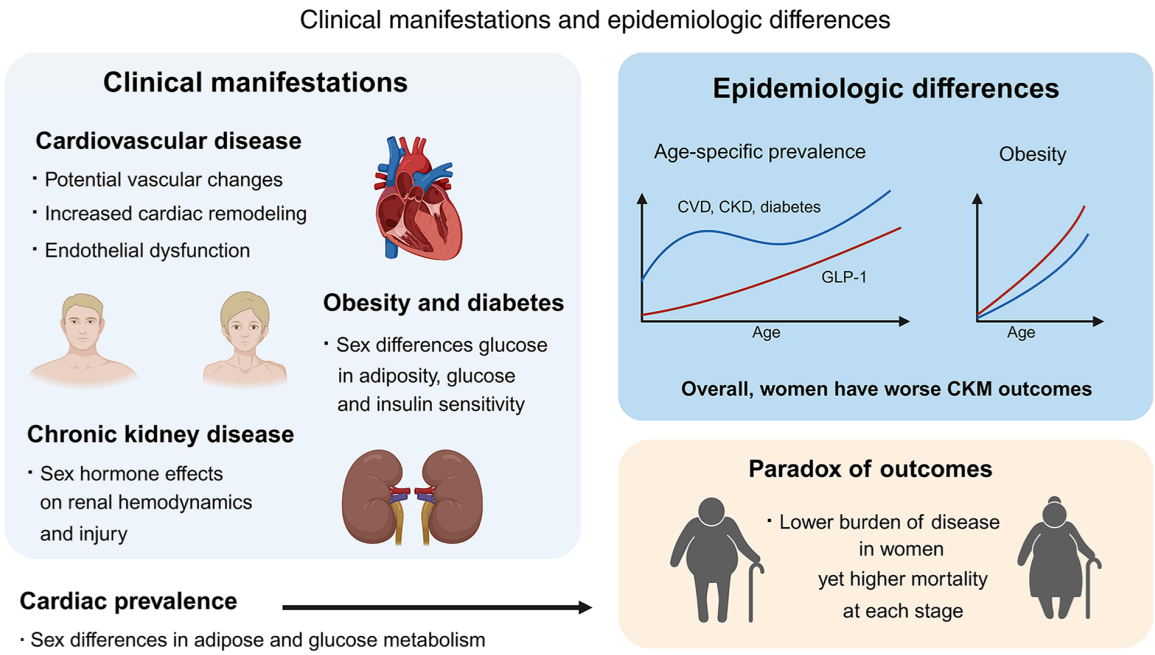

Figure 2. Sex differences in cardiovascular and metabolic disease prevalence and outcomes. The sex-specific differences in the prevalence and clinical manifestations of cardiovascular and metabolic diseases are highlighted, focusing on cardiac, renal and metabolic outcomes. Men tend to develop earlier coronary artery disease, more visceral adiposity, and greater microvascular diabetic complications, whereas women more commonly develop heart failure with preserved ejection fraction, postmenopausal metabolic deterioration, and disproportionate cardiovascular risk once diabetes is established. These patterns should be interpreted together with sex-related factors such as access to prevention, referral timing, and treatment intensity. Overall, these findings illustrate how biological sex and healthcare-related factors jointly shape CKM outcomes across the life course. CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CKD, chronic kidney disease.

despite similar overall CKD burden (113). Possible explanations include faster biological progression in men (greater fibrosis/inflammation) (39), lower competing mortality in men, and healthcare factors such as differences in referral timing and access to kidney replacement therapy. Because these access-related issues are influenced by sex, they should be interpreted as sex-related disparities rather than purely biological differences. Notably, even after adjusting for age and comorbidities, female patients with ESRD were reported to have lower access to dialysis than male patients (114, 115), suggesting sex disparities in CKD management.

Clinically, male patients with CKD often present with higher proteinuria and faster GFR decline, whereas women may linger at moderate CKD stages. Nonetheless, clinicians should be vigilant about risk in women after menopause, when protective factors in women decline (111). In practice, this means applying aggressive CKD monitoring and intervention in men to delay progression, while ensuring timely nephrology referral in women to avoid sex-based treatment delays (116).

Sex distribution of T2D and complications. Globally, slightly more men than women have T2D (93). Men are typically diagnosed at younger ages and lower BMI, whereas women are often older at diagnosis with higher BMI and more cardiovascular risk factors (117). Women also experience unique physiological stressors: Gestational diabetes is a strong predictor of future diabetes in women (96), and menopause was shown to unmask latent insulin resistance (97).

Sex differences are amplified in diabetes outcomes and have practical implications for CKM management. In women, diabetes substantially attenuates the premenopausal cardiovascular advantage and is associated with a higher relative burden of cardiovascular complications. Therefore, cardiovascular risk assessment, lipid-lowering therapy, blood pressure control and early screening for coronary and cerebrovascular disease should be emphasized in women with diabetes. In men, diabetes is more frequently accompanied by microvascular complications, including diabetic kidney disease, retinopathy and neuropathy, supporting closer surveillance of albuminuria, renal function, retinal disease and peripheral vascular complications. These clinical patterns indicate that diabetes care in CKM syndrome should incorporate sex-sensitive risk assessment rather than applying a uniform monitoring strategy to all patients (Fig. 2) (93,102).

Sexual dysfunction as a prognostic factor. Sexual dysfunction is an underrecognized marker of CKM risk. In men, erectile dysfunction (ED) reflects systemic endothelial dysfunction and strongly predicts cardiovascular events and mortality (men with ED have roughly 40% higher CVD risk) (118). In women, sexual dysfunction (reduced arousal, lubrication, orgasm) was reported to be associated with hypertension, diabetes, and metabolic syndrome, suggesting genital and systemic vascular impairment (119). Clinically, the presence of ED should prompt aggressive cardiovascular risk management, and healthcare providers should inquire about sexual health in women as it may identify high-risk patients (120). Treating sexual dysfunction was shown to improve quality of life and may enhance adherence to cardiometabolic therapies (121). In summary, sexual dysfunction signals underlying vascular disease and warrants a comprehensive, sex-sensitive prevention and care approach.

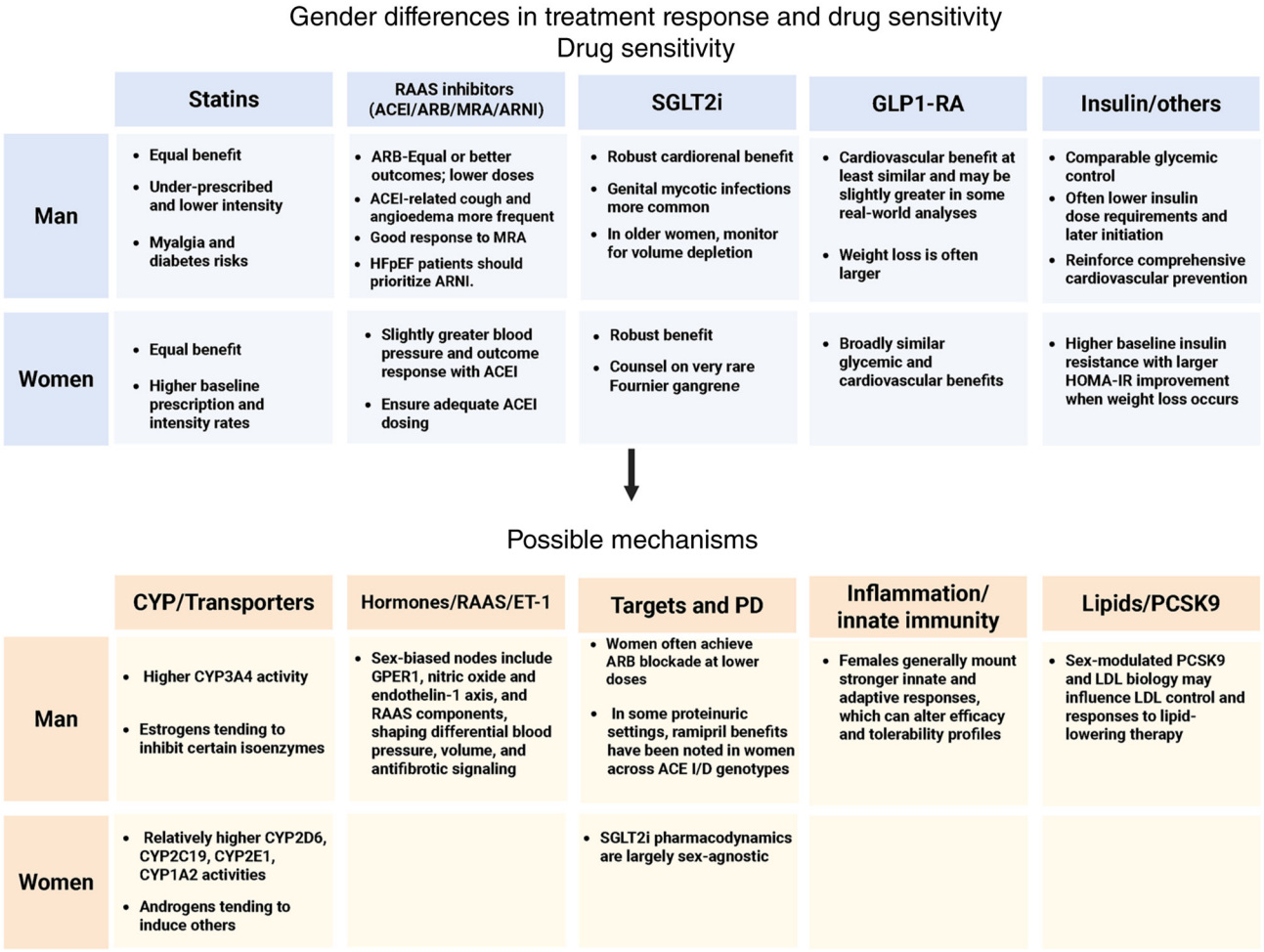

Figure 3. Sex differences in pharmacological treatment response and drug sensitivity. Sex-related differences in pharmacological treatment response and drug sensitivity in CKM syndrome are summarized. Current evidence supports the effectiveness of statins, RAAS inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and insulin-based therapies in eligible patients of both sexes. However, sex-related differences in prescribing patterns, tolerability, pharmacokinetics, and adverse-event profiles have been reported, including ACEI-related cough, SGLT2 inhibitor-associated genital mycotic infection, and treatment-initiation barriers for insulin. Because robust sex interactions have not been consistently demonstrated for several drug classes, these observations should be viewed as signals for individualized monitoring rather than as grounds for withholding guideline-directed therapy. CKM, cardiovascular-kidney-metabolic; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide-1; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor agonist; ARNI, angiotensin receptor-neprilysin inhibitor; HFpEF, heart failure with preserved ejection fraction; SGLT2i, SGLT2 inhibitor; GLP-1RA, GLP-1 receptor agonist; HOMA-IR, homeostatic model assessment of insulin resistance; CYP, cytochrome 450 enzymes; GPER1, G protein-coupled estrogen receptor 1; ET-1, endothelin-1; PD, pharmacodynamic; ACE I/D, ACE insertion/deletion; PCSK9, proprotein convertase subtilisin/kexin type 9; LDL, low-density lipoprotein.

4. Sex differences in treatment response and drug sensitivity

Sex differences influence not only disease mechanisms but also treatment responses and side effects. In CKM syndrome, therapies such as lipid-lowering agents, antihypertensives, and glucose-lowering drugs may have sex-specific nuances (Fig. 3 and Table I). Therefore, the following section emphasizes reported trends, limitations of subgroup analyses, and the need to avoid overinterpreting sex-specific treatment effects when robust interaction testing is unavailable.

Statin therapy. Statins are the cornerstone of atherosclerotic cardiovascular disease prevention, lowering LDL cholesterol and reducing events in both sexes (122). Yet a treatment gap exists: Eligible women are less likely than men to be prescribed statins (especially high-intensity regimens), receive adequate counseling, or continue therapy (often discontinuing due to side-effect concerns) (123). LDL lowering efficacy is substantial in both sexes, but women often receive lower doses and achieve target LDL less frequently (124). Notably, pooled trials show no significant sex interaction in statin benefit for primary or secondary prevention (125,126). Women may report myalgia, fatigue or concerns about adverse effects slightly more often in some studies, and statin-associated new-onset diabetes has also been reported, but these findings do not negate the overall cardiovascular benefit. Closing the gap in statin initiation, dosing, and adherence for women is essential to ensure they receive equal preventable benefit (124-126).

RAAS inhibitors. RAAS inhibitors [ACE inhibitors (ACEI), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists] are foundational for hypertension, HF, and proteinuric CKD (127). Both men and women benefit from blood pressure (BP) reduction and improved outcomes with

Table I. Summary of reported sex-related differences in major CKM therapies.

Drug class	Reported sex-related differences	Strength of evidence	Major sex-related adverse events/ tolerability issues	Clinical implication
Statins	Women are less likely to receive high-intensity statins or achieve LDL targets; pooled trials generally show no robust sex interaction in benefit.	Moderate for treatment gap; strong for overall benefit in both sexes; limited for true efficacy interaction.	Myalgia or fatigue may be reported more frequently by women in some cohorts; small diabetes risk should be balanced against cardiovascular benefit.	Ensure equitable initiation, intensity and adherence support rather than withholding statins by sex.
RAAS inhibitors	ACEI/ARB responses may vary across studies; ARBs may be better tolerated in women when ACEI cough occurs.	Mixed; numerous findings are subgroup or obser-vational signals.	ACEI cough and angioedema occur more often in women; hyperkalemia and renal function changes require monitoring in both sexes.	Individualize according to indication, BP, kidney function and tolerability; consider ARB switch when ACEI intolerance occurs.
SGLT2 inhibitors	Large HF and CKD trials generally show comparable relative benefits in men and women; MACE results by sex are inconsistent across analyses.	Strong for benefit in both sexes; mixed for sex interaction.	Genital mycotic infections are more frequent in women; volume depletion may be more relevant in older or frail women; Fournier's gangrene is very rare.	Use in eligible patients of both sexes; provide sex-aware counseling on infection symptoms, hygiene and hydration.
GLP-1 receptor agonists	Some studies suggest greater weight loss or cardiovascular benefit in women, but evidence is inconsistent and may be confounded by body weight or baseline risk.	Moderate for overall benefit; limited for clinically actionable sex-specific differences.	Gastrointestinal intolerance is common in both sexes; no consistent sex-specific safety signal.	Do not use sex alone to determine eligibility or dosing; consider body weight, tolerability and cardio-metabolic indication.
Insulin and other glycemic therapies	Men often have greater baseline insulin resistance; women may delay insulin initiation and may require lower absolute insulin doses due to lower body weight.	Moderate for biological insulin-resistance differences; limited for sex-specific drug algorithms.	Hypoglycemia concern and weight gain may affect adherence, especially in women; metformin gastrointestinal intolerance may be more frequent in women.	Use individualized titration and counseling; address barriers to treat ment intensification and hypo-glycemia prevention.

CKM, cardiovascular-kidney-metabolic; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SGLT2, sodium-glucose cotransporter 2; HF, heart failure; CKD, chronic kidney disease; MACE, major adverse cardiovascular events; GLP-1, glucagon-like peptide-1.

these drugs, but some sex differences emerge. Some studies suggest that men may achieve slightly greater BP reduction or outcome improvement with ACEI, whereas women may have at least comparable responses to ARBs; however, the evidence is heterogeneous and does not support a universal sex-based hierarchy of RAAS inhibitor choice (128-131). Women also appear to be more sensitive to mineralocorticoid antagonists, seeing larger BP and left ventricular mass reductions with these agents (65). ACEI cause cough and angioedema more often in women, so early switch to an ARB is reasonable when intolerance arises (128). Pharmacologically, women reach effective RAAS blockade at lower ARB doses and may have greater BP lowering with combinations (such as valsartan plus amlodipine) (132-135). Long-term outcome data are mixed: Some evidence suggests stronger mortality reduction with ACEI in men, while ARBs and angiotensin receptor-neprilysin inhibitors may provide relatively greater benefit in women (especially with HFpEF) (136-138). In practice, RAAS blockade should be individualized according to indication, renal function, potassium level, BP, tolerability and comorbidity profile; sex may inform monitoring and adverse-effect vigilance but should not replace guideline-directed indications.

SGLT2 inhibitors. SGLT2 inhibitors deliver robust cardiorenal protection across diabetes, HF, and CKD, significantly reducing major adverse cardiovascular events (MACE), HF hospitalizations, and CKD progression in large trials (139-141). Analyses of sex differences have been mixed: One meta-analysis found significant MACE reduction in men but only borderline in women (likely reflecting fewer women in trials and lower baseline risk), while other analyses reported no sex interaction for cardiovascular death or HF outcomes (142-144). Dedicated HF and CKD trials show similar relative risk reductions for men and women (145,146). Adverse events do show sex patterns: Genital mycotic infections are more common in women (usually mild and treatable), men should be counseled about the very rare risk of Fournier's gangrene, and older women may be more prone to volume depletion (147-149). Overall, current evidence supports the use of SGLT2 inhibitors in eligible patients of both sexes, while emphasizing sex-aware counseling on genital infections, hydration and early symptom management. Ongoing research with greater female representation will further clarify any residual sex-specific effects (150).

Glucagon-like peptide-1 receptor agonists (GLP-1RAs). GLP-1RAs (such as liraglutide and semaglutide) improve glycemia, promote weight loss, and reduce cardiovascular and renal risk in CKM syndrome (151). Major outcome trials (LEADER and SUSTAIN-6) and meta-analyses show substantial benefits in both sexes with no consistent sex-related differences in efficacy (152). Some real-world research suggests that women may derive slightly greater cardiovascular or weight-loss benefit from GLP-1RAs, but these observations remain exploratory and may reflect differences in body weight, adherence, baseline risk or treatment selection. In practice, sex-based differences in GLP-1RA effects are not sufficiently robust to mandate different prescribing; these drugs should be used in all eligible patients while further research explores hormonal, genetic and pharmacokinetic modifiers (153).

Insulin and glycemic therapies. Lifestyle changes and glucose-lowering therapies are essential for both sexes, but sex differences shape insulin resistance and treatment patterns (154-156). Men display significantly higher baseline insulin resistance and experience greater improvements in fasting insulin and homeostatic model assessment of insulin resistance for a given weight loss compared with women (154,157). Most oral glycemic agents are equally effective in men and women, and GLP-1 agonists have been shown to reduce cardiovascular events similarly across sexes (158,159). Insulin therapy itself achieves comparable glycemic control, but women often delay its initiation due to concerns about weight gain and hypoglycemia (160). Women generally have lower body weight and thus require lower insulin doses; some data suggest women may experience hypoglycemia slightly more often. In addition, younger women have been shown to receive statins and other cardioprotective therapies less frequently than men, indicating gaps in comprehensive care (93). Polycystic ovary syndrome (PCOS), a hyperandrogenic condition in women, exemplifies these sex hormone effects: Women with PCOS have pronounced insulin resistance and metabolic syndrome, with concurrent dyslipidemia and early vascular dysfunction (161). This confers markedly higher cardiovascular risk. A recent systematic review and meta-analysis reported significantly elevated rates of myocardial infarction and stroke in PCOS (162). PCOS pathophysiology (androgen-driven insulin resistance) parallels male metabolic profiles, making it a human model to study sex differences in CKM outcomes. PCOS may also increase chronic kidney disease risk through systemic inflammation and metabolic stress (163). Clinically, these insights suggest a tailored approach: Men may benefit from early and intensive weight-loss strategies to reduce insulin resistance, whereas women may require proactive counseling to avoid unnecessary delay in insulin or combination therapy and to support hypoglycemia prevention. In women, cardiovascular risk management should also be intensified and education regarding self-monitoring and hypoglycemia prevention should be emphasized, especially in older age (164).

Pharmacogenomic and drug metabolism differences. Sex shapes pharmacokinetic/pharmacodynamic (PK/PD) profiles through coordinated effects on drug-metabolizing enzymes, transporters, targets, and immune tone (165-168). In aggregate, women exhibit higher hepatic CYP3A4 activity, whereas men tend to show higher CYP2D6, CYP2C19, CYP2E1, and CYP1A2 activity (166,167). Sex steroids further modulate these pathways and this regulation extends to transporters and receptors (167). Genetic polymorphisms in key enzymes such as CYP3A5 and CYP2C9 intersect with sex effects, and sex-linked expression of drug targets may shape treatment response (168). Females generally mount stronger innate and adaptive immune responses (169), which can influence efficacy and tolerability.

ACEI-induced cough was reported to occur more often in women (170). Some women were shown to achieve full RAAS blockade at lower ARB doses (171). Telmisartan exposure was revealed to be higher in females (172). Losartan exposure was demonstrated to be driven primarily by CYP2C9 genotype rather than sex (173). In proteinuric nephropathy, ramipril

was observed to reduce end-stage kidney disease risk more in women and was shown to be beneficial across ACE insertion/deletion genotypes in women (174).

Population-PK showed no clinically meaningful sex effect for dapagliflozin exposure (175). Genital mycotic infections were reported to be more frequent in women (176). Cardio-renal outcome benefits were shown to be comparable in women and men and PDs appeared to be similar when normalized to urinary creatinine (177,178).

Liraglutide exposure was shown to be 30-32% higher in females at similar body weight and this finding was replicated in population-PK meta-analyses (179-181). However, exposure-response analyses do not currently support routine sex-specific liraglutide dose adjustment. Trials and real-world data often show similar or greater weight loss in women and possibly greater cardiovascular protection in women, without a sex-specific safety signal (182-184).

Women were reported to experience metformin-related gastrointestinal intolerance more often (185,186). Insulin sensitivity has been shown to vary across the menstrual cycle and is typically lower in the luteal phase, supporting individualized titration in some women (187,188).

Collectively, current data rarely mandate routine sex-specific dosing. They do support explicit consideration of sex, genotype, and hormonal status when selecting and titrating therapy. Future trials should prespecify sex-stratified PK/PD and clinical outcome analyses to determine when observed sex differences are actionable rather than merely associative.

5. Future directions

To advance precise and equitable care in CKM syndrome, future efforts should systematically treat sex as a biological variable across research and practice. Large clinical trials need balanced enrollment of men and women, prespecified sex and menopausal status, and routine reporting of outcomes by sex to generate evidence for guidelines. At the same time, sex-related determinants such as access to care, referral timing, adherence, socioeconomic status, and underrepresentation in clinical trials should be evaluated separately from biological sex. Professional societies should codify sex specific recommendations such as prioritizing intensive cardiovascular risk management for diabetic women, ensuring closer CKD surveillance for men, and substituting ARBs when ACEI cause cough in women. Precision prescribing should evaluate sex appropriate dosing and therapy choices, including whether women benefit from lower doses of RAAS inhibitors or require different glucose lowering strategies, and targeted interventions such as early low dose estrogen at menopause should be tested in sex specific trials to assess safety and efficacy. Translational research should leverage single cell and other omics to identify sex biased molecular targets and should test interventions in both sexes under physiological hormone conditions, enabling development of selective receptor modulators or tissue specific therapies. Finally, greater awareness among clinicians and patients about sex specific risks and responses can improve prevention and adherence and support personalized management. Together these strategies aim to narrow outcome disparities and move the field toward sex-informed precision medicine in cardiorenal metabolic health.

6. Conclusion

Sex differences in CKM syndrome are complex but critically important. They span from fundamental biological mechanisms to clinical outcomes and therapeutic responses. Ongoing interdisciplinary research and collaboration are essential to realize sex-stratified precision medicine in CKM disease. By tailoring prevention and treatment to the unique needs of men and women, outcomes can be improved and truly personalized, equitable healthcare can be advanced.

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Authors' contributions

HH and JC designed the scope and structure of the review. HH, JC and YF performed structured literature searches. HH and JC critically synthesized and interpreted the findings. HH and JC wrote the original draft. YF and HH revised major sections of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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