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REVIEW

Menopause and the opportunity for early cardio-renal-metabolic prevention

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ABSTRACT

The cardio-renal-metabolic syndrome is a systemic pathological entity that reflects complex interactions among obesity, diabetes, chronic kidney disease, and cardiovascular disease. In women, cardio-renal-metabolic risk increases markedly with age, and the menopausal transition functions as a key catalyst due to loss of the cardiometabolic protective effects of estrogen. The cardio-renal-metabolic syndrome is a systemic pathological entity that reflects complex interactions among obesity, diabetes, chronic kidney disease, and cardiovascular disease. In women, cardio-renal-metabolic risk increases markedly with age, and the menopausal transition functions as a key catalyst due to loss of the cardiometabolic protective effects of estrogen. This review examines the pathophysiologic mechanisms by which the menopausal transition promotes cardio-renal-metabolic and evaluates menopause as a critical window for preventive intervention. Declining estradiol levels during menopause drive redistribution of adipose tissue toward visceral depots, increased insulin resistance, endothelial dysfunction, and activation of the renin-angiotensin-aldosterone system. These changes promote progression from an absence of risk factors to more advanced clinical states. Timing-based hypotheses suggest that aggressive interventions initiated early in the menopausal transition confer maximal cardiometabolic benefit and may prevent irreversible end-organ damage. In conclusion, menopause is not merely a reproductive aging event but a crucial period for systemic risk modification that requires an integrated approach to interrupt the progression of cardio-renal-metabolic in women.

Keywords: menopause, cardio-renal-metabolic syndrome, prevention

Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality among women worldwide.[1] For decades clinical medicine has tended to evaluate cardiovascular disease, chronic kidney disease, and metabolic disorders such as obesity and type 2 diabetes in separate, fragmented silos. A fundamental conceptual shift occurred when global medical authorities formally introduced the cardio-renal-metabolic syndrome, which recognizes substantial pathophysiologic overlap and close synergistic interactions among these disorders.[2,3] The cardio-renal-metabolic syndrome emphasizes that dysfunction in one system, for example insulin resistance driven by visceral adiposity, can directly induce and worsen dysfunction in other organ systems, such as glomerular hyperfiltration in the kidney and structural hypertrophy of the left ventricle.[4,5]

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Among women, vulnerability to cardio-renal-metabolic syndrome is not linear across the lifespan but increases markedly in midlife. Menopause transition, characterized by irregular fluctuations and eventual permanent depletion of ovarian hormone production, is a critical biological inflection point that shapes vascular aging trajectories.[6–8] Historically, the menopausal transition has been viewed primarily through a reproductive-health lens or as the cause of bothersome vasomotor symptoms. However, accumulating epidemiologic evidence indicates that loss of estrogen-mediated protection initiates a cascade of pathologic cardiometabolic changes that together promote progression of cardio-renal-metabolic syndrome.[7,8] The "critical window" concept denotes the perimenopausal to early postmenopausal period when systemic adaptation to declining ovarian hormones is rapid while irreversible target-organ damage is not yet complete.[8]

This review aims to delineate the pathophysiologic connections between the menopause transition and cardio-renal-metabolic syndrome and to highlight the need to treat the menopausal phase as a critical window for prevention, early detection, and proactive management.

Method

This review used a comprehensive approach to identify and synthesize recent literature relevant to the topic. We conducted an extensive search of major international medical databases, including PubMed, Scopus, and Web of Science. The search strategy employed specific medical terms combined with Boolean operators and emphasized phrases such as cardiovascular-renal-metabolic syndrome, menopause transition, cardiovascular risk, chronic kidney disease, and the timing hypothesis. Inclusion criteria comprised original articles, randomized controlled trials, longitudinal cohort studies, and consensus statements from professional medical societies published in English. Priority was given to literature published within the past decade to ensure relevance to current clinical guidelines, with particular emphasis on articles that provided validated digital object identifiers to ensure reference integrity and accuracy.

Pathophysiologic links between menopause and cardio-renal-metabolic syndrome

The cardio-renal-metabolic syndrome is a systemic disorder rooted in interrelated pathophysiological processes linking obesity, impaired glucose tolerance, reduced renal function, and vascular injury.[9,10] The American Heart Association classifies this syndrome along a clinical severity spectrum to guide targeted interventions. In early stages, an individual may have no risk factors or may present only with dysfunctional adiposity without additional metabolic complications.[10,11] Over time, accumulation of risk factors such as hypertension, hypertriglyceridemia, and declining renal function drives progression to subclinical cardiovascular disease and ultimately to manifest cardiovascular disease, including heart failure or stroke, frequently accompanied by end-stage renal disease.[9] In women, epidemiological surveys consistently show that before age 40 most have very low risk.[12,13] However, during the fourth and fifth decades of life, coinciding with the perimenopausal and postmenopausal phases, there is a marked demographic shift toward more advanced stages of cardio-renal-metabolic syndrome. This shift cannot be attributed solely to chronological aging but reflects direct effects of dramatic changes in the endocrine profile.[7,9]

The menopausal transition triggers substantial metabolic dysregulation by altering adipose tissue distribution and promoting insulin resistance.[14–16] Estrogen receptors are widely expressed in adipose tissue, skeletal muscle, and liver.[17,18] In a healthy premenopausal state, adequate estrogen levels favor subcutaneous fat deposition.[14,19] When ovarian estradiol production declines, lipid metabolism shifts and fat is redistributed toward visceral depots within the abdominal cavity.[14,16] Visceral adipose tissue is not an inert energy store but an active endocrine organ that secretes proinflammatory adipokines, including tumor necrosis factor-alpha and interleukin-6, while reducing production of adiponectin, which has anti-atherogenic properties.[14,17,20] Chronic low-grade inflammation induced by visceral fat accumulation disrupts intracellular insulin signaling pathways, provoking compensatory hyperinsulinemia that culminates in insulin resistance. These rapid changes in body composition shift women's metabolic status toward persistent dysfunction.[14,16,17]

Beyond metabolic disturbance, the vasculature in postmenopausal women becomes particularly vulnerable due to endothelial dysfunction and atherogenic dyslipidemia. Blood vessels are highly responsive to estrogen, which regulates endothelial nitric oxide production to preserve vasodilation and inhibit platelet aggregation.[21–23] Estrogen deficiency shifts the vascular balance toward vasoconstriction by increasing production of molecules such as endothelin-1, contributing directly to rises in systolic blood pressure and

increased arterial stiffness.[21,22] Menopause also produces an adverse lipid profile, with low-density lipoprotein particles more prone to oxidation and high-density lipoprotein losing reverse cholesterol transport function and acquiring proinflammatory properties.[21,22] This microvascular dysfunction extends beyond the cardiovascular system and directly affects renal hemodynamics. Estrogen normally suppresses renin gene expression; when estrogen levels fall, this inhibition is released, permitting activation of the renin-angiotensin-aldosterone system. Overactivity of this system causes persistent efferent arteriolar vasoconstriction, elevating intraglomerular pressure, damaging podocytes, and precipitating microalbuminuria as an early marker of renal injury in cardio-renal-metabolic syndrome.[24,25]

Transitional menopause as a critical window for intervention

The paradigm for cardiometabolic prevention in adult women has shifted with broader acceptance of the timing hypothesis in the medical community. This critical window refers to the interval from the perimenopausal phase through the first ten years after the final menstrual period.[7,8,26] During this interval, vascular endothelium and renal epithelial structures largely remain intact and retain responsiveness to protective interventions.[22,27] Pathophysiologic abnormalities that arise during this period, such as early endothelial dysfunction or mild glucose intolerance, are often reversible and have not yet progressed to permanent atherosclerotic calcified lesions or extensive renal fibrosis. If comprehensive medical interventions are implemented promptly within this window, protective effects on cardiovascular and renal function are maximized.[28,29] Conversely, if interventions are delayed until permanent scarring of the glomerulus or complicated atherosclerotic plaque has developed in the coronary arteries, the primary effectiveness of treatment is reduced and, in some cases, clinical complication risk may increase. Therefore, early recognition that a woman has entered the menopausal transition should be treated as an urgent clinical signal to perform a comprehensive cardiometabolic risk assessment.[7,28–30]

Integrated prevention strategies and future research directions

Preventing progression of the cardio-renal-metabolic syndrome during the menopausal transition requires coordinated multidisciplinary approaches that combine intensive lifestyle modification with selective pharmacotherapy. Because basal metabolic rate declines naturally with estrogen loss, caloric restriction and transition to an anti-inflammatory dietary pattern are recommended to prevent visceral fat accumulation.[31,32] Combined exercise programs that include aerobic activity and resistance training have a central physiological role, as active skeletal muscle serves as the primary depot for glucose disposal, effectively reversing insulin resistance and preserving endothelial function.[33,34] In medical therapy, menopausal hormone therapy remains one of the most effective frontline interventions when initiated at an appropriate time.[33] Exogenous estrogen administered within the critical window has been associated with preservation of insulin sensitivity and delayed onset of type 2 diabetes.[33–35] Transdermal hormone delivery is often preferred because it bypasses first-pass hepatic metabolism and may reduce the risk of thromboembolic events compared with oral hormone therapy.[36]

For postmenopausal women who show early organ damage consistent with the cardio-renal-metabolic syndrome, contemporary therapeutics offer cardiorenal protection through novel pharmacologic agents such as sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists.[37,38] These agents provide pleiotropic benefits beyond glycemic control.[39,40] Drugs that promote natriuresis are important for lowering the elevated intraglomerular pressure often observed after menopause, while simultaneously protecting the myocardium from excessive hemodynamic load.[37,38] Agents targeting incretin receptors have demonstrated substantial reductions in persistent visceral adiposity and systemic inflammation, enabling marked improvements in metabolic risk profiles.[40,41] Future research should invest in developing highly specific biomarkers of ovarian aging to predict renal and cardiovascular trajectory before clinical manifestations appear. Integrating artificial intelligence–derived data with high-resolution adipose tissue imaging may guide clinicians in delivering treatments tailored to each woman's genetic and endocrine risk profile, thereby optimizing defenses against the cardio-renal-metabolic syndrome.

Conclusion

The cardio-renal-metabolic syndrome represents an accelerating systemic health threat in middle-aged women. This review underscores that the menopausal transition is not a passive, benign physiologic adaptation but rather a major endocrine event that promotes visceral adipose hypertrophy, vascular

endothelial dysfunction, and insulin resistance. Recognizing menopause as a decisive critical window creates an unmatched opportunity for healthcare systems to implement preventive interventions. Comprehensive lifestyle optimization, judicious early use of hormone therapy during perimenopause where indicated, and application of modern cardiorenal pharmacotherapies should be regarded as components of an integrated management strategy. With a proactive, integrated clinical approach during this critical window, morbidity from heart and kidney failure in older women can be meaningfully reduced.

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