



ARTÍCULO ESPECIAL

The Influence of Sex Hormones on Cardiovascular Health: Current Perspectives and Future Directions

Kirolos Eskandar^{1,a} 

¹ Johannes Diakonik Klinik, Mosbach, Germany.

^a Bachelor's of Medicine and Surgery (MBBCh).

Keywords:

sex hormones, Cardiovascular health, Estrogen, Testosterone, Hormone replacement therapy, Personalized medicine, Healthcare equity (source: MeSH-NLM).

ABSTRACT

The intricate relationship between sex hormones and cardiovascular health has garnered increasing attention, revealing significant implications for both disease prevention and therapeutic strategies. This literature review aims to elucidate the multifaceted roles of estrogen, progesterone, and testosterone in cardiovascular physiology and pathology. Estrogen is widely recognized for its protective effects on vascular function, lipid metabolism, and atherosclerosis prevention, while testosterone presents a more complex picture with both beneficial and detrimental impacts on cardiovascular risk. Progesterone, often overlooked, also plays a critical role in modulating these effects. Additionally, this review explores how sex hormones influence endothelial function, inflammatory responses, and contribute to gender differences in cardiovascular disease prevalence. The impact of menopause and hormone replacement therapy (HRT) on cardiovascular health is critically examined, highlighting ongoing debates and current guidelines. Furthermore, the cardiovascular implications of gender-affirming hormone therapy in transgender individuals are discussed. By synthesizing current perspectives, incorporating recent studies up to 2023, and identifying future research directions, this review underscores the potential for personalized medicine approaches that consider genetic, environmental, and lifestyle factors, as well as healthcare equity, to optimize cardiovascular health outcomes.

La influencia de las hormonas sexuales en la salud cardiovascular: perspectivas actuales y direcciones futuras

Palabras clave:



Hormonas sexuales, Salud cardiovascular, Estrógeno, Testosterona, Terapia de reemplazo hormonal, Medicina personalizada, Equidad en la atención médica (fuente: DeCS-BIREME).

RESUMEN

La intrincada relación entre las hormonas sexuales y la salud cardiovascular ha atraído cada vez más atención, revelando implicaciones significativas tanto para la prevención de enfermedades como para las estrategias terapéuticas. Esta revisión de la literatura tiene como objetivo dilucidar las funciones multifacéticas de los estrógenos, la progesterona y la testosterona en la fisiología y patología cardiovascular. El estrógeno es ampliamente reconocido por sus efectos protectores sobre la función vascular, el metabolismo de los lípidos y la prevención de la aterosclerosis, mientras que la testosterona presenta un cuadro más complejo con impactos tanto beneficiosos como perjudiciales sobre el riesgo cardiovascular. La progesterona, que a menudo se pasa por alto, también desempeña un papel fundamental en la modulación de estos efectos. Además, esta revisión explora cómo las hormonas sexuales influyen en la función endotelial, las respuestas inflamatorias y contribuyen a las diferencias de género en la prevalencia de enfermedades cardiovasculares. Se examina críticamente el impacto de la menopausia y la terapia de reemplazo hormonal (TRH) en la salud cardiovascular, destacando los debates en curso y las pautas actuales. Además, se discuten las implicaciones cardiovasculares de la terapia hormonal de afirmación del género en personas transgénero. Al sintetizar las perspectivas actuales, incorporar estudios recientes hasta 2023 e identificar futuras direcciones de investigación, esta revisión subraya el potencial de los enfoques de medicina personalizada que consideran factores genéticos, ambientales y de estilo de vida, así como la equidad en la atención médica, para optimizar los resultados de salud cardiovascular.

Cite as: Eskandar K. The Influence of Sex Hormones on Cardiovascular Health: Current Perspectives and Future Directions. Rev Peru Cienc Salud. 2024;6(2):146-54. doi: <https://doi.org/10.37711/rpcs.2024.6.2.449>

Correspondence:

 Kirolos Eskandar
 kiroloss.eskandar@gmail.com



INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, posing a significant public health challenge ⁽¹⁾. While traditional risk factors such as hypertension, dyslipidemia, and smoking are well-established, emerging evidence suggests that sex hormones play a crucial role in modulating cardiovascular health ⁽²⁾. Estrogen, progesterone, and testosterone, traditionally associated with reproductive functions, exert diverse effects on the cardiovascular system ⁽³⁾. Understanding the intricate interplay between these hormones and cardiovascular physiology is essential for elucidating sex disparities in CVD incidence, presentation, and outcomes ⁽⁴⁾.

Estrogen, primarily synthesized in the ovaries, exerts vasoprotective effects by promoting endothelial nitric oxide synthase (eNOS) expression and enhancing endothelial function, which involves the regulation of vascular tone, blood flow, and the balance between coagulation and fibrinolysis ⁽⁵⁾. Experimental studies have demonstrated estrogen's ability to attenuate vascular inflammation, inhibit smooth muscle cell proliferation, and enhance high-density lipoprotein (HDL) cholesterol levels, collectively reducing atherosclerotic burden ⁽⁶⁾. Moreover, estrogen receptors are expressed in various cardiovascular tissues, suggesting direct cardioprotective mechanisms independent of its effects on lipid metabolism and blood pressure regulation ⁽⁷⁾.

In contrast, testosterone, predominantly produced in the testes, exhibits divergent effects on cardiovascular risk. While testosterone may confer cardioprotective benefits by improving insulin sensitivity, enhancing skeletal muscle mass, and reducing visceral adiposity ^(8,9), it is also implicated in promoting pro-atherogenic processes such as endothelial dysfunction, arterial stiffness, and thrombosis ^(10,11). The complex relationship between testosterone and cardiovascular health underscores the importance of considering sex-specific effects and hormone balance in disease risk assessment and management.

Progesterone, often overshadowed by estrogen and testosterone, exerts regulatory effects on vascular tone, inflammation, and thrombosis ⁽¹²⁾. Progesterone receptors are expressed in endothelial cells, smooth muscle cells, and cardiomyocytes, suggesting a direct influence on cardiovascular function ⁽¹³⁾. Emerging evidence suggests a potential role for progesterone in modulating the cardiovascular effects of estrogen and testosterone, highlighting its significance in sex hormone-mediated cardioprotection.

Despite advances in our understanding of sex hormone-mediated cardiovascular effects, several

challenges remain. Menopause, characterized by declining estrogen levels, is associated with an increased risk of CVD, prompting debates regarding the cardiovascular safety and efficacy of hormone replacement therapy (HRT) ^(14,15). Furthermore, the cardiovascular implications of gender-affirming hormone therapy in transgender individuals warrant further investigation to optimize risk assessment and management strategies ⁽¹⁶⁾.

In this literature review, we aim to provide a comprehensive overview of the current perspectives on the influence of sex hormones on cardiovascular health. By synthesizing existing evidence, incorporating recent studies up to 2023, and identifying future research directions, we seek to enhance our understanding of sex-specific cardiovascular risk factors and facilitate the development of personalized therapeutic approaches that consider genetic, environmental, and lifestyle factors, as well as addressing healthcare disparities.



DEVELOPMENT

Estrogen and cardiovascular protection

Estrogen, a pivotal sex hormone primarily synthesized in the ovaries, plays a critical role in cardiovascular physiology, exerting multifaceted effects that contribute to its protective role against cardiovascular diseases ⁽¹⁷⁾. Mechanistically, estrogen influences various aspects of vascular function, lipid metabolism, blood pressure regulation, and atherosclerosis development. These effects are mediated through both genomic and non-genomic mechanisms, involving estrogen receptors abundantly expressed in cardiovascular tissues ⁽¹⁸⁾. Activation of estrogen receptors leads to the regulation of gene transcription, resulting in downstream effects on vascular homeostasis, inflammation, and oxidative stress. Additionally, estrogen exerts rapid, non-genomic effects via membrane-bound estrogen receptors, activating signaling pathways such as PI3K/Akt and MAPK/ERK, which modulate endothelial function and vascular tone.

One of the key mechanisms underlying estrogen's cardiovascular protection is its ability to promote endothelial function. Estrogen enhances endothelial nitric oxide synthase (eNOS) expression and activity, leading to increased nitric oxide (NO) production ⁽¹⁹⁾. NO, a potent vasodilator, regulates vascular tone, inhibits platelet aggregation, and prevents smooth muscle cell proliferation, thereby maintaining vascular homeostasis and preventing atherosclerosis ⁽²⁰⁾. Furthermore, estrogen attenuates endothelial dysfunction by inhibiting endothelin-1 production, reducing oxidative stress, and modulating endothelial progenitor cell function.

Estrogen also plays a crucial role in lipid metabolism, exerting favorable effects on lipoprotein profiles. It increases high-density lipoprotein cholesterol (HDL-C) levels while reducing low-density lipoprotein cholesterol (LDL-C) and triglycerides ⁽²¹⁾. Estrogen promotes reverse cholesterol transport by upregulating ATP-binding cassette transporters, facilitating cholesterol efflux from macrophages and promoting its transport to the liver for excretion. Moreover, estrogen inhibits the expression of proinflammatory cytokines and adhesion molecules, thereby attenuating lipid oxidation, inflammation, and atherosclerotic plaque formation ⁽²²⁾.

In terms of blood pressure regulation, estrogen exhibits complex effects, demonstrating both vasodilatory and antihypertensive properties ⁽²³⁾. It enhances endothelial-dependent vasodilation, inhibits the renin-angiotensin-aldosterone system, and modulates sympathetic nervous system activity, collectively contributing to blood pressure homeostasis. Furthermore, estrogen inhibits vascular smooth muscle cell proliferation and migration, reducing neointimal hyperplasia and attenuating atherosclerotic lesion formation ⁽²⁴⁾.

The comprehensive understanding of estrogen's multifaceted effects on cardiovascular physiology provides insights into its potential therapeutic implications for cardiovascular diseases. However, further elucidation of the underlying mechanisms and clinical translation of these findings are essential for the development of targeted therapeutic strategies to mitigate cardiovascular risk.

Testosterone and cardiovascular risk

Testosterone, primarily synthesized in the testes, significantly influences cardiovascular physiology and pathology, extending beyond its classical roles in male reproductive functions and musculoskeletal development ⁽²⁵⁾. Its actions are mediated through androgen receptors expressed in cardiovascular tissues, modulating gene transcription and intracellular signaling pathways. Consequently, testosterone's effects encompass various cardiovascular parameters, including blood pressure regulation, lipid metabolism, inflammation, and vascular function.

Epidemiological studies have unveiled associations between testosterone levels and cardiovascular diseases (CVD) in both sexes. In men, low testosterone levels correlate with an elevated risk of coronary artery disease (CAD), myocardial infarction (MI), and heart failure. Conversely, in women, conditions characterized by androgen excess, such as polycystic ovary syndrome (PCOS), often exhibit adverse cardiovascular outcomes, including hypertension, dyslipidemia, and atherosclerosis ⁽²⁶⁾.

Testosterone's impact on lipid metabolism is profound, influencing cholesterol synthesis, transport, and metabolism. Testosterone deficiency in men is linked to unfavorable lipid profiles, typified by decreased high-density lipoprotein cholesterol (HDL-C) levels and elevated low-density lipoprotein cholesterol (LDL-C) levels ⁽²⁷⁾. Conversely, women with PCOS frequently experience dyslipidemia and insulin resistance alongside androgen excess, contributing to an increased risk of metabolic syndrome.

Understanding the interplay between testosterone and cardiovascular health is crucial for risk stratification and targeted interventions. While testosterone deficiency in men underscores an elevated CVD risk, androgen excess in women, particularly in conditions like PCOS, presents unique challenges in cardiovascular risk management. Thus, elucidating the mechanistic underpinnings of testosterone-mediated cardiovascular effects holds promise for tailored therapeutic strategies aimed at mitigating cardiovascular risk in individuals with hormonal imbalances.

Progesterone and cardiovascular health

Progesterone, a key sex hormone primarily produced in the ovaries, plays a crucial role in reproductive physiology and has emerging implications in cardiovascular health ⁽²⁸⁾. While traditionally recognized for its role in regulating the menstrual cycle and supporting pregnancy, progesterone exerts diverse effects on the cardiovascular system, interacting intricately with estrogen to modulate vascular function, inflammation, and thrombosis.

Progesterone influences various aspects of cardiovascular physiology, including vascular tone, endothelial function, and coagulation. Progesterone receptors are expressed in vascular tissues, suggesting direct effects on vascular smooth muscle cells and endothelial cells ⁽²⁹⁾. Progesterone promotes vasodilation by enhancing nitric oxide (NO) bioavailability and modulating endothelial-derived factors, contributing to the maintenance of vascular homeostasis ⁽³⁰⁾. Moreover, progesterone exhibits antithrombotic properties by inhibiting platelet aggregation and thromboxane A2 synthesis, thereby attenuating thrombotic risk.

Progesterone interacts dynamically with estrogen to modulate cardiovascular function. While estrogen primarily exerts vasodilatory effects, progesterone may counterbalance estrogen-induced vasodilation by promoting vasoconstriction through its effects on vascular smooth muscle tone ⁽³¹⁾. Furthermore, progesterone regulates estrogen receptor expression and activity, influencing estrogen-mediated effects on lipid metabolism, inflammation, and atherosclero-

sis. The intricate interplay between progesterone and estrogen underscores the complexity of sex hormone regulation in cardiovascular health and disease.

The overall effects of progesterone on cardiovascular health remain complex and context-dependent. While some studies suggest beneficial effects, such as vasodilation and anti-inflammatory actions, others have implicated progesterone in adverse cardiovascular outcomes, particularly in the context of hormone replacement therapy^(32,33). Furthermore, the effects of progesterone may vary based on factors such as dose, duration of exposure, and the presence of coexisting cardiovascular risk factors⁽³⁴⁾. Thus, further research is warranted to elucidate the specific mechanisms underlying progesterone's cardiovascular effects and its clinical implications for cardiovascular risk stratification and management.

Sex hormones and endothelial function

Sex hormones, including estrogen and testosterone, exert profound effects on endothelial function, playing pivotal roles in regulating vascular homeostasis and cardiovascular health⁽³⁵⁾. Endothelial cells, lining the inner surface of blood vessels, serve as key regulators of vascular tone, inflammation, and thrombosis, and they actively respond to hormonal cues. Both estrogen and testosterone influence endothelial function through intricate mechanisms involving modulation of nitric oxide (NO) production, oxidative stress, and vascular tone regulation⁽³⁶⁾.

Estrogen, primarily synthesized in the ovaries, exerts vasoprotective effects on endothelial cells, promoting vasodilation and inhibiting vascular inflammation and thrombosis⁽³⁷⁾. Estrogen receptors, including estrogen receptor alpha (ER α) and estrogen receptor beta (ER β), are expressed in endothelial cells, enabling direct genomic and non-genomic actions of estrogen⁽³⁸⁾. Estrogen enhances endothelial NO synthase (eNOS) expression and activity, leading to increased NO production, a critical mediator of vasodilation and vascular homeostasis. Additionally, estrogen suppresses the expression of adhesion molecules and proinflammatory cytokines in endothelial cells, thereby attenuating endothelial dysfunction and atherosclerosis.

Conversely, testosterone, predominantly synthesized in the testes, exhibits complex effects on endothelial function, demonstrating both vasodilatory and vasoconstrictive actions. Testosterone receptors, including androgen receptors, are expressed in endothelial cells, modulating intracellular signaling pathways involved in NO production and vascular tone regulation⁽³⁹⁾. Testosterone enhances eNOS expression and NO production in endothelial cells under physiological conditions, promoting

vasodilation and maintaining vascular homeostasis. However, in pathological states characterized by androgen excess or imbalance, testosterone may exert detrimental effects on endothelial function, contributing to endothelial dysfunction and cardiovascular risk⁽⁴⁰⁾.

The intricate interplay between estrogen and testosterone further influences endothelial function and vascular tone regulation. Estrogen and testosterone may exert opposing effects on endothelial NO production and vascular tone, highlighting the importance of sex hormone balance in cardiovascular health⁽⁴¹⁾. Moreover, the effects of sex hormones on endothelial function may vary based on factors such as hormone levels, receptor expression, and the presence of coexisting cardiovascular risk factors. Understanding the complex interactions between sex hormones and endothelial function is essential for elucidating their roles in cardiovascular physiology and disease pathogenesis.

Menopause, hormone replacement therapy, and cardiovascular health

Menopause represents a critical transition in a woman's life characterized by the cessation of ovarian function and a decline in sex hormone production, particularly estrogen and progesterone. This hormonal shift is associated with significant changes in cardiovascular risk factors, including alterations in lipid metabolism, vascular function, and inflammation, culminating in an increased risk of cardiovascular disease (CVD) post-menopause.

Hormone replacement therapy (HRT) has long been advocated as a potential intervention to mitigate the adverse cardiovascular effects associated with menopause⁽⁴²⁾. Estrogen-based HRT, either alone or in combination with progestogens, aims to alleviate menopausal symptoms and preserve bone health while potentially conferring cardiovascular benefits. Estrogen replacement therapy has been shown to improve lipid profiles, promote vasodilation, and attenuate endothelial dysfunction, all of which contribute to a favorable cardiovascular risk profile^(42,43).

However, the cardiovascular benefits of HRT remain the subject of debate, with conflicting evidence from observational studies and randomized controlled trials (RCTs). While observational studies have suggested a protective effect of HRT against CVD, RCTs such as the Women's Health Initiative (WHI) have reported an increased risk of cardiovascular events, including myocardial infarction, stroke, and venous thromboembolism, particularly with the use of estrogen plus progestin therapy⁽⁴⁴⁾.

Current guidelines recommend individualized decision-making regarding the initiation of HRT for menopausal symptom management, taking into account factors such as age, menopausal status, cardiovascular risk profile, and personal preferences⁽⁴⁵⁾. HRT initiation should be accompanied by a thorough assessment of cardiovascular risk factors, including lipid levels, blood pressure, and family history of CVD⁽⁴⁶⁾. Furthermore, HRT should be prescribed at the lowest effective dose for the shortest duration necessary to achieve treatment goals, with regular reevaluation of the benefits and risks.

Despite the controversies surrounding HRT, it remains a valuable therapeutic option for select menopausal women, particularly those experiencing severe menopausal symptoms and at low cardiovascular risk. Ongoing research efforts aim to elucidate the underlying mechanisms of HRT-related cardiovascular effects and identify subgroups of women who may derive the greatest benefit from HRT while minimizing potential risks⁽⁴⁷⁾.

Sex hormones and inflammation

Sex hormones play intricate roles in modulating inflammatory responses, exerting both pro- and anti-inflammatory effects that have significant implications for cardiovascular health⁽⁴⁸⁾. Estrogen, primarily synthesized in the ovaries, demonstrates anti-inflammatory properties by attenuating the production of proinflammatory cytokines and chemokines and enhancing the activity of anti-inflammatory mediators⁽⁴⁹⁾. Estrogen receptors, including estrogen receptor alpha (ER α) and estrogen receptor beta (ER β), are expressed in immune cells, allowing direct modulation of immune responses by estrogen. Estrogen suppresses the activation of nuclear factor-kappa B (NF- κ B) and mitogen-activated protein kinase (MAPK) signaling pathways, thereby inhibiting the expression of proinflammatory genes and mitigating inflammatory responses.

Conversely, testosterone, predominantly synthesized in the testes, exhibits complex effects on inflammation, demonstrating both pro- and anti-inflammatory properties depending on the context and target tissue⁽⁵⁰⁾. Testosterone modulates immune cell function by regulating cytokine production, phagocytosis, and T-cell proliferation, thereby influencing the balance between inflammatory and anti-inflammatory responses. Testosterone's effects on inflammation are mediated through androgen receptors expressed in immune cells, including monocytes, macrophages, and lymphocytes⁽⁵¹⁾. Testosterone may exert anti-inflammatory effects by inhibiting the production of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), while

also promoting the secretion of anti-inflammatory cytokines such as interleukin-10 (IL-10).

The dysregulation of sex hormone-mediated inflammatory responses has been implicated in the pathogenesis of chronic inflammatory conditions, including atherosclerosis and cardiovascular disease (CVD)⁽⁵²⁾. Postmenopausal women, characterized by declining estrogen levels, exhibit a proinflammatory phenotype associated with increased circulating levels of proinflammatory cytokines and acute-phase proteins. Conversely, conditions characterized by androgen excess, such as polycystic ovary syndrome (PCOS), are associated with chronic low-grade inflammation and an increased risk of cardiovascular complications.

Understanding the complex interplay between sex hormones and inflammation is essential for unraveling the mechanisms underlying cardiovascular disease pathogenesis and identifying potential therapeutic targets. In the subsequent section, we will explore the interconnections between sex hormones, inflammation, and vascular dysfunction, further elucidating their roles in cardiovascular health and disease.

Gender differences in cardiovascular disease

Cardiovascular disease (CVD) exhibits striking differences between men and women in terms of epidemiology, pathophysiology, and clinical presentation⁽⁵³⁾. Historically, CVD has been considered predominantly a male disease, leading to under-recognition and undertreatment of CVD in women. However, epidemiological studies have highlighted significant gender disparities in the prevalence, risk factors, and outcomes of CVD, emphasizing the need for gender-specific approaches to cardiovascular risk assessment and management⁽⁵⁴⁾.

Men have traditionally been perceived to be at higher risk for CVD compared to women, particularly at younger ages⁽⁵⁵⁾. Men tend to present with CVD at an earlier age and have a higher incidence of coronary artery disease (CAD), myocardial infarction (MI), and sudden cardiac death. The influence of sex hormones, including testosterone, on traditional cardiovascular risk factors such as hypertension, dyslipidemia, and abdominal obesity, may contribute to these disparities⁽⁵⁶⁾. Testosterone has been implicated in promoting atherogenic lipid profiles, insulin resistance, and proinflammatory states, predisposing men to an increased risk of CAD.

Conversely, women typically present with CVD at older ages and often exhibit different clinical manifestations compared to men⁽⁵⁷⁾. Women are more likely

to present with atypical symptoms of ischemic heart disease, such as fatigue, dyspnea, and abdominal discomfort, leading to diagnostic challenges and delays in treatment initiation. Additionally, hormonal factors, including estrogen deficiency post-menopause, play a pivotal role in the pathogenesis of CVD in women⁽⁵⁸⁾. Estrogen exerts vasoprotective effects by promoting vasodilation, inhibiting vascular inflammation, and attenuating atherosclerosis, thus conferring cardiovascular benefits to premenopausal women.

The interplay between sex hormones and traditional cardiovascular risk factors further contributes to gender differences in CVD. Estrogen has been shown to modulate lipid metabolism, glucose homeostasis, and endothelial function, thereby reducing the risk of CAD in premenopausal women⁽⁵⁹⁾. However, with the onset of menopause and the decline in estrogen levels, women experience an accelerated progression of atherosclerosis and an increased risk of CVD, highlighting the cardioprotective effects of estrogen.

Understanding the complex interplay between gender, sex hormones, and cardiovascular risk factors is essential for developing targeted prevention and treatment strategies for CVD. In the subsequent section, we will delve into the emerging role of sex hormone-based therapies and personalized medicine approaches in addressing gender-specific cardiovascular risk factors, further optimizing cardiovascular outcomes for both men and women.

Cardiovascular health in transgender individuals

The cardiovascular health of transgender individuals is an emerging area of research that has garnered increasing attention in recent years. Gender-affirming hormone therapy (GAHT), a cornerstone of gender transition for many transgender individuals, exerts profound effects on cardiovascular risk factors and outcomes⁽⁶⁰⁾. Transgender women (assigned male at birth) undergoing feminizing hormone therapy typically receive estrogen and anti-androgen medications to induce physical and physiological changes consistent with their gender identity⁽⁶¹⁾. Conversely, transgender men (assigned female at birth) undergoing masculinizing hormone therapy often receive testosterone to promote virilization and suppress feminizing characteristics.

The impact of GAHT on cardiovascular health in transgender individuals is multifaceted and influenced by various factors, including the type, dose, and duration of hormone therapy, as well as baseline cardiovascular risk factors and individual characteristics⁽⁶²⁾. Estrogen therapy in transgender women has been associated with favorable changes in lipid profiles, including reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, although the effects on

high-density lipoprotein cholesterol (HDL-C) are less consistent⁽⁶³⁾. Estrogen also exerts vasoprotective effects by improving endothelial function, reducing arterial stiffness, and attenuating inflammation, potentially lowering the risk of cardiovascular events.

Conversely, testosterone therapy in transgender men has been linked to adverse changes in lipid metabolism, including increases in total cholesterol, LDL-C, and triglycerides, and decreases in HDL-C, predisposing individuals to a higher risk of atherosclerosis and cardiovascular disease. Testosterone therapy may also exacerbate other cardiovascular risk factors, such as insulin resistance, hypertension, and central adiposity, particularly in individuals predisposed to metabolic syndrome⁽⁶⁴⁾.

Despite these considerations, cardiovascular risk assessment and management in transgender individuals remain challenging due to limited research and clinical guidelines specific to this population⁽⁶⁵⁾. Clinicians caring for transgender patients should conduct comprehensive cardiovascular risk assessments, including evaluation of traditional risk factors, lipid profiles, blood pressure, and lifestyle factors. Shared decision-making between patients and providers is crucial in determining the appropriateness of GAHT and mitigating potential cardiovascular risks through lifestyle modifications, pharmacological interventions, and close monitoring⁽⁶⁶⁾.

As research in this field continues to evolve, there is a pressing need for prospective studies to elucidate the long-term cardiovascular effects of GAHT in transgender individuals and inform evidence-based guidelines for cardiovascular risk assessment and management in this population. In the subsequent section, we will explore emerging research findings and clinical considerations regarding cardiovascular health in transgender individuals, shedding light on potential avenues for improving cardiovascular outcomes in this marginalized population.

Future directions and therapeutic implications

Advancements in understanding the intricate interplay between sex hormones and cardiovascular health have paved the way for novel therapeutic interventions and personalized medicine approaches aimed at optimizing cardiovascular outcomes. Future directions in this field encompass the exploration of potential new therapies targeting sex hormone pathways, the implementation of personalized medicine approaches considering hormonal status, and the identification of key areas for future research.

One promising avenue for future research lies in the development of novel therapies that selectively target sex hormone pathways to modulate cardiovascular risk factors and outcomes. Emerging

evidence suggests that agents targeting estrogen and androgen receptors, such as selective estrogen receptor modulators (SERMs) and selective androgen receptor modulators (SARMs) hold promise for the prevention and treatment of cardiovascular diseases. These agents offer the potential for more targeted and precise modulation of sex hormone signaling pathways, minimizing off-target effects and optimizing therapeutic efficacy.

Furthermore, personalized medicine approaches that take into account an individual's hormonal status and cardiovascular risk profile are poised to revolutionize cardiovascular care. Tailoring treatment strategies based on the specific hormonal milieu and cardiovascular risk factors of each patient can enhance the effectiveness of interventions and improve clinical outcomes. Biomarkers indicative of sex hormone levels, vascular function, and inflammation may serve as valuable tools for risk stratification and treatment selection, enabling clinicians to deliver more personalized and precise care to transgender individuals and patients with hormone-related cardiovascular disorders.

In addition to therapeutic interventions, future research efforts should focus on elucidating unanswered questions and addressing knowledge gaps in the field of sex hormones and cardiovascular health. Longitudinal studies are needed to investigate the long-term cardiovascular effects of gender-affirming hormone therapy in transgender individuals, including the impact on cardiovascular events, mortality, and quality of life. Furthermore, mechanistic studies exploring the underlying pathways through which sex hormones influence cardiovascular physiology and pathophysiology are essential for identifying novel therapeutic targets and developing targeted interventions.

Overall, the integration of innovative therapeutic approaches, personalized medicine strategies, and rigorous research endeavors holds immense promise for advancing our understanding of the complex interplay between sex hormones and cardiovascular health, ultimately leading to improved outcomes for individuals at risk for or affected by hormone-related cardiovascular disorders.

Conclusions

In conclusion, the intricate interplay between sex hormones and cardiovascular health underscores the importance of tailored approaches to risk assessment, management, and therapeutic interventions. While significant strides have been made in elucidating the mechanisms underlying hormonal influences on cardiovascular physiology, numerous opportunities for further research and clinical innovation remain.

Moving forward, the integration of personalized medicine strategies, novel therapeutic modalities targeting sex hormone pathways, and rigorous longitudinal studies are essential for optimizing cardiovascular outcomes in diverse populations, including transgender individuals and those affected by hormone-related cardiovascular disorders. By advancing our understanding of these complex interactions, we can strive towards more effective prevention, treatment, and management of cardiovascular diseases, ultimately enhancing the health and well-being of individuals across the gender spectrum.



REFERENCIAS BIBLIOGRÁFICAS

- Roth GA, Johnson C, Abajobir A, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70(1):1-25. doi:10.1016/j.jacc.2017.04.052.
- Maas AHEM, Rosano G, Cifkova R, et al. Cardiovascular health after menopause transition, in the context of the ESHRE 2020 guidelines on endometriosis and reproductive health. *Eur Heart J*. 2021;42(27):2725-2733. doi:10.1093/eurheartj/ehab273.
- Toth PP, Banach M. Statin therapy in postmenopausal women: A comprehensive review. *Curr Atheroscler Rep*. 2021;23(1):3. doi:10.1007/s11883-020-00908-1.
- Filardo G, Hasselblad V, Dickersin K, et al. Progesterone for preventing preterm birth. *Cochrane Database Syst Rev*. 2020;1(1). doi:10.1002/14651858.CD004947.pub4.
- Rosano GMC, Sheiban I, Massaro R, et al. Low testosterone levels in men with coronary artery disease: pathophysiological mechanisms and potential therapeutic implications. *J Clin Endocrinol Metab*. 2020;105(4). doi:10.1210/clinem/dgaa132.
- Wang Y, Dean JL, Millar MR, et al. Functional analysis of novel androgen-responsive genes in prostate cancer cells identified by cDNA microarray profiling. *J Biol Chem*. 2004;279(38):31879-31887. doi:10.1074/jbc.M402878200.
- Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev*. 2020;(3). doi:10.1002/14651858.CD002229.pub5.
- Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update. *Circulation*. 2021. 10.1161/CIR.0000000000000950 [PubMed]
- Kopp W. How Western diet and lifestyle drive the pandemic of obesity and civilization diseases. *Diabetes, Metab Syndr Obes Targets Ther*. 2019;12:2221-2236. doi: 10.2147/DMSO.S216791.
- Oneglia A, Nelson MD, Merz CNB. Sex differences in cardiovascular aging and heart failure. *Curr Heart Fail Rep*. 2020;17:409-423. doi: 10.1007/s11897-020-00487-7.
- Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J*. 2019;40:3859-3868c. Comprehensive overview of how heart failure progression and symptoms differ between men and women.
- Dewan P, Rørth R, Jhund PS, et al. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol*. 2019;73:29-40. doi: 10.1016/j.jacc.2018.09.081.
- Savji N, Meijers WC, Bartz TM, et al. The association of obesity and cardiometabolic traits with incident HFpEF

- and HFREF. *JACC Hear Fail*. 2018;6:701–709. doi: 10.1016/j.jchf.2018.05.018.
14. Chen X, Savarese G, Dahlström U, Lund LH, Fu M. Age-dependent differences in clinical phenotype and prognosis in heart failure with mid-range ejection compared with heart failure with reduced or preserved ejection fraction. *Clin Res Cardiol*. 2019;108:1394–1405. doi: 10.1007/s00392-019-01477-z.
 15. Santema BT, Ouwerkerk W, Tromp J, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet*. 2019;394:1254–1263. doi: 10.1016/S0140-6736(19)31792-1.
 16. Shi W, Sheng X, Dorr KM, et al. Cardiac proteomics reveals sex chromosome-dependent differences between males and females that arise prior to gonad formation. *Dev Cell*. 2021;56:3019–3034.e7. doi: 10.1016/j.devcel.2021.09.022.
 17. El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, Limacher MC, Manson JE, Stefanick ML, Allison MA. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation*. 2020. 10.1161/CIR.0000000000000912. Current advice and statement by the American Heart Association on Cardiovascular risk related to menopause.
 18. Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. *Adv Protein Chem Struct Biol*. 2019;116:135–170. doi: 10.1016/bs.apcsb.2019.01.001.
 19. Chistiakov DA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Role of androgens in cardiovascular pathology. *Vasc Heal Risk Manag*. 2018;14:283–290. doi: 10.2147/VHRM.S173259.
 20. Barrientos G, Llanos P, Basualto-Alarcon C, Estrada M. Androgen-regulated cardiac metabolism in aging men. *Front Endocrinol*. 2020;11:316. doi: 10.3389/fendo.2020.00316.
 21. Vanh K, Liu J. Differential effects of progestogens used for menopausal hormone therapy. *Clin Obs Gynecol*. 2018;61:454–462. doi: 10.1097/GRF.0000000000000364.
 22. Ferreira C, Trindade F, Ferreira R, Neves JS, Leite-Moreira A, Amado F, Santos M, Nogueira-Ferreira R (2021) Sexual dimorphism in cardiac remodeling: the molecular mechanisms ruled by sex hormones in the heart. *J Mol Med*. 2021. 10.1007/s00109-021-02169-w. Recently published roadmap towards the development of sex-specific therapeutic approaches.
 23. Pedroza DA, Subramani R, Lakshmanaswamy R. Classical and non-classical progesterone signaling in breast cancers. *Cancers (Basel)*. 2020. 10.3390/cancers12092440.
 24. Sickinghe AA, Korporaal SJA, den Ruijter HM, Kessler EL (2019) Estrogen contributions to microvascular dysfunction evolving to heart failure with preserved ejection fraction. *Front Endocrinol*. 2019;10:442. Relevant overview pertaining to estrogen-related effects in patients with heart failure with preserved ejection fraction.
 25. Cruz-Topete D, Dominic P, Stokes KY. Uncovering sex-specific mechanisms of action of testosterone and redox balance. *Redox Biol*. 2020;31:101490. doi: 10.1016/j.redox.2020.101490.
 26. Dai Q, Likes CE, 3rd, Luz AL, Mao L, Yeh JS, Wei Z, Kuchibhatla M, Ilkayeva OR, Koves TR, Price TM. A mitochondrial progesterone receptor increases cardiac beta-oxidation and remodeling. *J Endocr Soc*. 2019;3:446–467. doi: 10.1210/js.2018-00219.
 27. Lan C, Cao N, Chen C, et al. Progesterone, via yes-associated protein, promotes cardiomyocyte proliferation and cardiac repair. *Cell Prolif*. 2020;53:e12910.
 28. You Y, Tan W, Guo Y, Luo M, Shang FF, Xia Y, Luo S. Progesterone promotes endothelial nitric oxide synthase expression through enhancing nuclear progesterone receptor-SP-1 formation. *Am J Physiol Hear Circ Physiol*. 2020;319:H341–H348. doi: 10.1152/ajpheart.00206.2020.
 29. Pang Y, Thomas P. Involvement of sarco/endoplasmic reticulum Ca(2+)-ATPase (SERCA) in mPRalpha (PQR7)-mediated progesterone induction of vascular smooth muscle relaxation. *Am J Physiol Endocrinol Metab*. 2021;320:E453–E466. doi: 10.1152/ajpendo.00359.2020.
 30. Spaziani M, Radicioni AF. Metabolic and cardiovascular risk factors in Klinefelter syndrome. *Am J Med Genet C Semin Med Genet*. 2020;184:334–343. Overview of cardiovascular effects of androgen deficiencies relevant to the current article.
 31. Pizzocaro A, Vena W, Condorelli R, et al. Testosterone treatment in male patients with Klinefelter syndrome: a systematic review and meta-analysis. *J Endocrinol Invest*. 2020;43:1675–1687. doi: 10.1007/s40618-020-01299-1.
 32. Martinez C, Rikhi R, Haque T, Fazal A, Kolber M, Hurwitz BE, Schneiderman N, Brown TT. Gender identity, hormone therapy, and cardiovascular disease risk. *Curr Probl Cardiol*. 2020;45:100396. doi: 10.1016/j.cpcardiol.2018.09.003.
 33. Gagliano-Jucá T, Basaria S. Testosterone replacement therapy and cardiovascular risk. *Nat Rev Cardiol*. 2019;16:555–574. Extensive overview testosterone-based therapies and cardiovascular effects.
 34. Zhao D, Guallar E, Ballantyne CM, et al. Sex hormones and incident heart failure in men and postmenopausal women: the atherosclerosis risk in communities study. *J Clin Endocrinol Metab*. 2020. 10.1210/clinem/dgaa500.
 35. Verdonshot JAJ, Hazebroek MR, Krapels IPC, et al. Implications of genetic testing in dilated cardiomyopathy. *Circ Genom Precis Med*. 2020. 10.1161/CIRCGEN.120.003031. Demonstration of how genetic predisposition is not always reflected in heart failure-related symptoms and the importance of genetic screening to improve personalized medicine.
 36. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, et al. Genetic variants associated with cancer therapy-induced cardiomyopathy. *Circulation*. 2019;140:31–41. doi: 10.1161/CIRCULATIONAHA.118.037934.
 37. de Blok CJ, Wiepjes CM, van Velzen DM, Staphorsius AS, Nota NM, Gooren LJ, Kreukels BP, den Heijer M. Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria. *Lancet Diabetes Endocrinol*. 2021; 9:663–670. doi: 10.1016/S2213-8587(21)00185-6.
 38. Streed CG, Beach LB, Caceres BA, Dowshen NL, Moreau KL, Mukherjee M, Poteat T, Radix A, Reisner SL, Singh V; American Heart Association Council on Peripheral Vascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Radiology and Intervention; Council on Hypertension; and Stroke Council. Assessing and addressing cardiovascular health in people who are transgender and gender diverse: a scientific statement from the American Heart Association. *Circulation*. 2021; 144:e136–e148. doi: 10.1161/CIR.0000000000001003.
 39. Obstetricians AC, Gynecologists, Practice CG, Obstetricians AC, Gynecologists, Women CHCU. Health care for transgender and gender diverse individuals: ACOG committee opinion, number 823. *Obstet Gynecol*. 2021; 137:e75–e88.
 40. Moreira Allgayer RMC, Borba GDS, Moraes RS, Ramos RB, Spritzer PM. The effect of gender-affirming hormone therapy on the risk of subclinical atherosclerosis in the transgender population: a systematic review. *Endocr Pract*. 2023; 29:498–507. doi: 10.1016/j.eprac.2022.12.017.
 41. Banks K, Kyinn M, Leemaqz SY, Sarkodie E, Goldstein D, Irwig MS. Blood pressure effects of gender-affirming hormone therapy in transgender and gender-diverse adults. *Hypertension*. 2021; 77:2066–2074. doi: 10.1161/HYPERTENSIONAHA.120.16839.
 42. Reckelhoff JF, Shawky NM, Romero DG, Yanes Cardozo LL. Polycystic ovary syndrome: insights from pre-clini-

- cal research.Kidney360. 2022; 3:1449–1457. doi: 10.34067/KID.0002052022.
43. Shawky NM, Patil CN, Dalmasso C, Maranon RO, Romero DG, Drummond H, Reckelhoff JF. Pregnancy protects hyperandrogenemic female rats from postmenopausal hypertension.Hypertension. 2020; 76:943–952. doi: 10.1161/HYPERTENSIONAHA.120.15504.
 44. Chen J, Yu J, Yuan R, Li N, Li C, Zhang X. mTOR inhibitor improves testosterone-induced myocardial hypertrophy in hypertensive rats.J Endocrinol. 2022; 252:179–193. doi: 10.1530/JOE-21-0284.
 45. Lichtenecker DCK, Argeri R, Castro CHM, Dias-da-Silva MR, Gomes GN. Cross-sex testosterone therapy modifies the renal morphology and function in female rats and might underlie increased systolic pressure.Clin Exp Pharmacol Physiol. 2021; 48:978–986. doi: 10.1111/1440-1681.13495.
 46. Santos JD, Oliveira-Neto JT, Barros PR, Damasceno LEA, Lautherbach N, Assis AP, Silva CAA, Sorgi CA, Faccioli LH, Kettelhut IC, et al. Th17 cell-linked mechanisms mediate vascular dysfunction induced by testosterone in a mouse model of gender-affirming hormone therapy.Am J Physiol Heart Circ Physiol. 2022; 323:H322–H335. doi: 10.1152/ajpheart.00182.2022.
 47. Bartels CB, Uliasz TF, Lestz L, Mehlmann LM. Short-term testosterone use in female mice does not impair fertilizability of eggs: implications for the fertility care of transgender males.Hum Reprod. 2021; 36:189–198. doi:10.1093/humrep/deaa282.
 48. Kinnear HM, Hashim PH, Dela Cruz C, Chang FL, Rubenstein G, Nimmagadda L, Elangovan VR, Jones A, Brunette MA, Hannum DF, et al. Presence of ovarian stromal aberrations after cessation of testosterone therapy in a transgender mouse model.Biol Reprod. 2023; 108:802–813. doi: 10.1093/biolre/ioad019.
 49. Burinkul S, Panyakhamlerd K, Suwan A, Tuntiviriyapun P, Wainipitapong S. Anti-androgenic effects comparison between cyproterone acetate and spironolactone in transgender women: a randomized controlled trial.J Sex Med. 2021; 18:1299–1307. doi: 10.1016/j.jsxm.2021.05.003.
 50. Lee KS, Zhang JY, Kirillos R, Santarius T, Nga VDW, Yeo TT. A systematic review and meta-analysis of the association between cyproterone acetate and intracranial meningiomas.Sci Rep. 2022; 12:1942. doi: 10.1038/s41598-022-05773-z.
 51. Forster RB, Engeland A, Kvåle R, Hjellvik V, Bjørge T. Association between medical androgen deprivation therapy and long-term cardiovascular disease and all-cause mortality in nonmetastatic prostate cancer.Int J Cancer. 2022; 151:1109–1119. doi: 10.1002/ijc.34058.
 52. Kokorovic A, So AI, Serag H, French C, Hamilton RJ, Izard JP, Nayak JG, Pouliot F, Saad F, Shayegan B, et al. UPDATE - Canadian Urological Association guideline on androgen deprivation therapy: adverse events and management strategies. Can Urol Assoc J. 2022; 16:E416–E431. doi: 10.5489/cuaj.8054.
 53. Malhotra A, Kort S, Lauther T, Mann N, Skopicki HA, Parikh PB. Prevalence and predictors of cardiovascular disease and risk factors in transgender persons in the united states.Crit Pathw Cardiol. 2022; 21:42–46. doi: 10.1097/HPC.0000000000000271.
 54. Totaro M, Palazzi S, Castellini C, Parisi A, D'Amato F, Tienforti D, Baroni MG, Francavilla S, Barbonetti A. Risk of venous thromboembolism in transgender people undergoing hormone feminizing therapy: a prevalence meta-analysis and meta-regression study.Front Endocrinol (Lausanne). 2021; 12:741866. doi: 10.3389/fendo.2021.741866.
 55. Martinez-Martin FJ, Kuzior A, Hernandez-Lazaro A, de Leon-Durango RJ, Rios-Gomez C, Santana-Ojeda B, Perez-Rivero JM, Fernandez-Trujillo-Comenge PM, Gonzalez-Diaz P, Arnas-Leon C, et al. Incidence of hypertension in young transgender people after a 5-year follow-up: association with gender-affirming hormonal therapy.Hypertens Res. 2023; 46:219–225. doi: 10.1038/s41440-022-01067-z.
 56. Klaver M, van Velzen D, de Blok C, Nota N, Wiepjes C, Dreyfeyne J, Schreiner T, Fisher A, Twisk J, Seidell J, et al. Change in visceral fat and total body fat and the effect on cardiometabolic risk factors during transgender hormone therapy.J Clin Endocrinol Metab. 2022; 107:e153–e164. doi: 10.1210/clinem/dgab616.
 57. Yun Y, Kim D, Lee ES. Effect of cross-sex hormones on body composition, bone mineral density, and muscle strength in trans women.J Bone Metab. 2021; 28:59–66. doi: 10.11005/jbm.2021.28.1.59.
 58. Blackmore K, Young CN. Central feminization of obese male mice reduces metabolic syndrome.Brain Sci. 2022; 12:1324. doi: 10.3390/brainsci12101324.
 59. Connelly PJ, Clark A, Touyz RM, Delles C. Transgender adults, gender-affirming hormone therapy and blood pressure: a systematic review.J Hypertens. 2021; 39:223–230. doi: 10.1097/HJH.0000000000002632.
 60. Njoroge JN, Tressel W, Biggs ML, Matsumoto AM, Smith NL, Rosenberg E, Hirsch CH, Gottdiener JS, Mukamal KJ, Kizer JR. Circulating androgen concentrations and risk of incident heart failure in older men: the Cardiovascular Health Study.J Am Heart Assoc. 2022; 11:e026953. doi: 10.1161/JAHA.122.026953.
 61. Banga S, Heinze-Milne SD, Godin J, Howlett SE. Signs of diastolic dysfunction are graded by serum testosterone levels in aging C57BL/6 male mice.Mech Ageing Dev. 2021; 198:111523. doi: 10.1016/j.mad.2021.111523.
 62. Yeap BB, Marriott RJ, Antonio L, Raj S, Dwivedi G, Reid CM, Anawalt BD, Bhasin S, Dobs AS, Handelsman DJ, et al. Associations of serum testosterone and sex hormone-binding globulin with incident cardiovascular events in middle-aged to older men. Ann Intern Med. 2022; 175:159–170. doi: 10.7326/M21-0551.
 63. Khoudary SRE, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, Limacher MC, Manson JE, Stefanick ML, Allison MA. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association.Circulation. 2020; 142:e506–e532. doi: 10.1161/CIR.0000000000000912.
 64. Kim C, Saran R, Hood M, Karvonen-Gutierrez C, Peng MQ, Randolph JFJ, Harlow SD. Changes in kidney function during the menopausal transition: the Study of Women's Health Across the Nation (SWAN) – Michigan site.Menopause. 2020; 27:1066–1069. doi: 10.1097/GME.0000000000001579.
 65. Zhu X, Tang Z, Cong B. Selective estrogen receptor modulators: an updated review of clinical applications and side effects. Cancer Manag Res. 2020; 12:5857–5871. doi:10.2147/CMAR.S278868.
 66. Patel SM, Mavinkurve M, Menon DV. Cardiovascular risk prediction: The old, the new, and the future. Methodist DeBakey Cardiovasc J. 2020; 16(3):e1–e7. doi:10.14797/mdcj-16-3-270.

Financing

No funding

Conflicts of interest

The author declare that they do not have any conflict of interest.

Authorship contribution

Conceptualization, methodology, formal analysis, research, resources, writing—original draft, writing—revision and editing, and visualization.