Review

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Beyond reproduction: unraveling the impact of sex hormones on cardiometabolic health

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Abstract: This review thoroughly explores the multifaceted roles of sexual hormones, emphasizing their impact beyond reproductive functions and underscoring their significant influence on cardiometabolic regulation. It analyzes the broader physiological implications of estrogen, testosterone, and progesterone, highlighting their effects on metabolic syndrome, lipid metabolism, glucose homeostasis, and cardiovascular health. Drawing from diverse molecular, clinical, and therapeutic studies, the paper delves into the intricate interplay between these hormones and cardiometabolic processes. By presenting a comprehensive analysis that goes beyond traditional perspectives, and recognizing sexual hormones as more than reproductive agents, the review sheds light on their broader significance in health and disease management, advocating for holistic and personalized medical approaches.

Keywords: estrogens; progesterone; androgens; metabolic syndrome; cardiovascular diseases

Introduction

Sexual hormones, including estrogens, androgens, and progesterone, play crucial roles in regulating cardiometabolic functions. Generally, estrogens are associated with cardiovascular health in premenopausal women, while androgens, especially testosterone, can enhance insulin sensitivity in men, thus acknowledging individual variations. The role of progesterone in cardiometabolic health is complex and multifaceted. Epidemiologically, conditions like metabolic syndrome and cardiovascular diseases exhibit a notable sex disparity, with variations across geographical regions. For example, the prevalence of metabolic syndrome is lower in premenopausal women but increases significantly postmenopause, suggesting a substantial hormonal influence.

Despite the recognized connection between sexual hormones and cardiometabolic health, the precise molecular mechanisms and clinical implications remain insufficiently understood. The distinct impact of hormonal fluctuations across the lifespan and the specific contributions of various hormone receptor subtypes to metabolic regulation are not fully clarified. This paper explores the complex interactions between sexual hormones and cardiometabolic pathways, focusing on the divergent roles of different hormone receptors in glucose homeostasis. Addressing these knowledge gaps has the potential to improve the clinical management of related disorders and establish a groundwork for sex-specific therapies.

The clinical significance of comprehending hormonal influences on cardiometabolic health is paramount, directly influencing the prevention and treatment of metabolic and cardiovascular diseases. This paper will explore recent research findings, scrutinize the functions of various receptors, and contemplate the potential of targeted hormonal therapies. By navigating the intricacies of sexual hormones in cardiometabolic regulation, we aim to underscore the imperative for advanced and nuanced knowledge in clinical and scientific domains. By doing so, we aspire to establish a framework supporting the creation of more precise and effective interventions for cardiometabolic disorders tailored to the unique hormonal profiles of individuals.

Sexual hormones: an overview

Sexual hormones, notably estrogens, progesterone, and androgens, play crucial roles beyond reproduction, being key regulators of metabolism and cardiovascular health.

Estrogens

Estrogens are synthesized in both men and women, but at higher levels in the latter, mainly in the ovaries, adrenal

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glands, and adipose tissues. Their actions are mediated by intranuclear estrogen receptors (ERα and ERβ) which traditionally govern gene expression, and by the G protein-coupled estrogen receptor (GPER), also known as G protein-coupled estrogen receptor 1 (GPER1), which facilitates rapid, non-genomic responses [1–4]. A portion of ERα is also targeted to the cell membrane (mER), facilitating swift, non-genomic signaling [5]. In the female body, estrogen is predominantly produced in the ovaries, adrenal glands, and adipose tissues, playing a central role in regulating the menstrual cycle, reproductive system, and lipid metabolism [6]. Although in lower concentrations in men, estradiol is integral to male sexual health, harmonizing with testosterone to oversee libido, erectile function, and sperm development [7].

Progesterone

Progesterone mainly in females, acts via nuclear progesterone receptors (PGR) and a series of membrane receptors, mPRα through mPRε [8, 9] to regulate the menstrual cycle, prepare the endometrium for implantation, support fetal development, and enhance bone health by promoting osteoblast activity [10]. In males, it is also involved in spermiogenesis, sperm capacitation, and testosterone synthesis while modulating gonadotropin secretion and aiding sleep [11]. In the realm of cardiovascular health, progesterone may exert protective effects against vascular injury and atherosclerosis, influencing blood pressure regulation [12, 13].

In addition to these receptors, Progesterone Receptor Membrane Component 1 (PGRMC1) plays a significant role in progesterone signaling. PGRMC1 is a heme-binding protein that can act as an adaptor protein, transporting mPRα to the cell surface. This suggests that PGRMC1 and mPRα are components of a membrane progesterone receptor complex. However, PGRMC1's role extends beyond this, as it is involved in various cellular processes and is expressed in many tissues. It is distinct from both the classic nuclear PGR and the membrane progesterone receptors (mPRα through mPRε), contributing to the complex and multifaceted ways that progesterone influences cellular function [14–16].

For a comprehensive visualization of these pathways, refer to Figure 1, which illustrates the nuclear and membrane-associated receptors mediating the genomic and nongenomic actions of these hormones.

Androgens

Androgens including testosterone, dihydrotestosterone (DHT), and androstenedione, are synthesized in the gonads and adrenal glands and exert their biological effects through both genomic and non-genomic mechanisms. Testosterone is a principal androgen, a class of steroid hormones that plays an essential role in the development of male secondary sexual characteristics and reproductive function. The classical genomic mechanism involves nuclear androgen receptors (AR), which, upon binding testosterone, regulate gene expression that governs secondary sexual characteristics, muscle maintenance, and functions within the central nervous system. These changes are typically more gradual, with gene expression alterations unfolding over hours to days [17, 18]. Complementarily, androgens, particularly testosterone also engage non-genomic pathways through membrane receptors, rapidly altering cellular activity. These receptors, notably G Protein-Coupled Receptor class C group 6 member A (GPRC6A) and the zinc transporter ZIP9 (SLC39A9), are pivotal in initiating swift intracellular signaling cascades. GPRC6A mediates rapid signaling responses including the activation of intracellular calcium release, while ZIP9 binds testosterone and triggers pathways involving calcium mobilization and MAPK activation [19]. The molecular identity of membrane androgen receptors (mARs) is diverse, and although not fully characterized, they are known to modulate processes such as cell proliferation and apoptosis.

While nuclear receptors are classically associated with genomic effects and G Protein-Coupled Receptors (GPCRs) are classically associated with non-genomic effects, both types of receptors can mediate both genomic and non-genomic responses depending on the context and the specific signaling pathways involved [1–3].

This orchestration between nuclear and membrane receptors and their ligands represents an intricate network, which is crucial for the body homeostasis. Understanding this complex interplay is key to advancing therapeutic strategies in the realms of endocrine and metabolic health, where we can utilise dual signaling potential of these hormones through both genomic and non-genomic pathways.

Sexual hormones and metabolic regulation

Overview of metabolic syndrome (MetS), definition and diagnostic criteria

Metabolic syndrome (MetS), also termed Syndrome X or Reaven syndrome, represents a constellation of physiological, biochemical, clinical, and metabolic conditions that

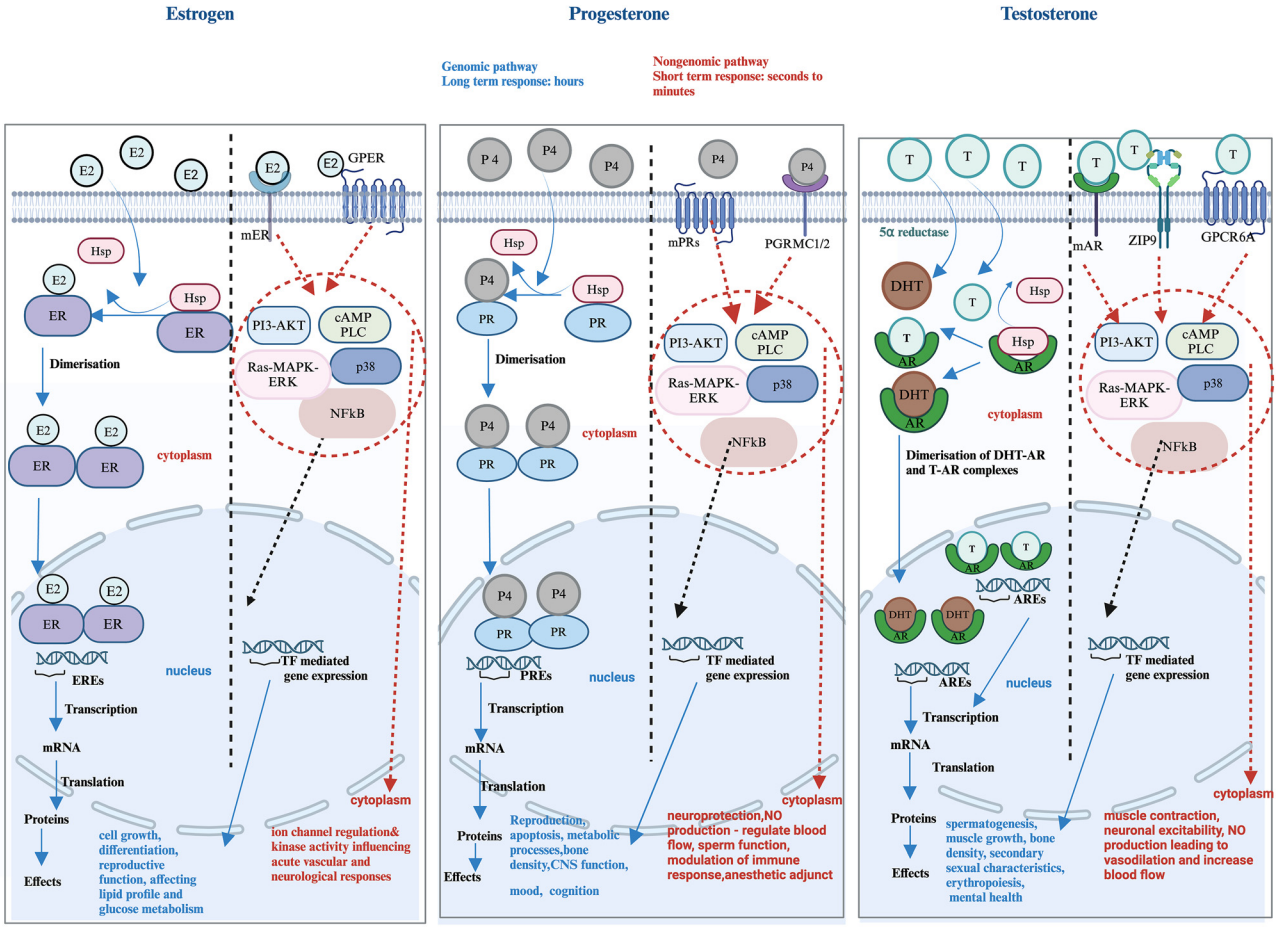

Figure 1: Diagram of sex hormone cellular pathways. This illustration elucidates the complex pathways through which sex hormones – estrogen (E2), progesterone (P4), and testosterone (T) – modulate cellular functions via genomic and nongenomic mechanisms. Genomic pathways, indicated by blue solid lines, reveal the traditional process where hormones bind their respective intracellular receptors – Estrogen Receptor (ER), Progesterone Receptor (PR), and Androgen Receptor (AR) – in the cytoplasm. Following dimerization, these complexes translocate to the nucleus, where they engage Estrogen Response Elements (EREs), Progesterone Response Elements (PREs), and Androgen Response Elements (AREs), catalyzing transcription and subsequent protein synthesis. The biological outcomes of these genomic interactions, include regulation of cell growth, differentiation, and metabolic processes. Nongenomic pathways, marked with dashed lines and red coloring, commence with hormone binding to membrane-associated receptors such as G Protein-Coupled Estrogen Receptor (GPER), membrane progesterone receptors (mPRs), and G Protein-Coupled Receptors (GPCRs). This binding initiates rapid intracellular signaling via second messengers like Phosphoinositide 3-Kinase/Protein Kinase B (PI3-AKT), cyclic Adenosine Monophosphate (cAMP), and Phospholipase C (PLC), which activate kinase pathways including Mitogen-Activated Protein Kinase/Extracellular signal-Regulated Kinase (Ras-MAPK-ERK) and p38. Subsequent modulation of Transcription Factors (TF), including Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFκB), may indirectly influence genomic pathways over a prolonged timescale. These complex nongenomic responses, govern acute physiological reactions including ion channel regulation, kinase activity, neuroprotection, and vascular function. This dual signaling delineation emphasizes the complex nature of sex hormone actions, driving both the enduring genomic impacts and the transient nongenomic cellular responses that together orchestrate the physiological landscape of hormone interaction within the body. DTH, Dehidrotestosterone; CNS, Central Nervous System; NO, Nitric Oxide; ZIP9, Zinc Transporter member 9. Created with BioRender.com.

increase an individual's risk of cardiovascular disease and type 2 diabetes (T2D). The hallmark features of this syndrome encompass visceral obesity, hypertensive states, high glucose levels, insulin resistance (IR), atherogenic dyslipidemia, as well as a prothrombotic and proinflammatory state [20–26]. A prothrombotic profile suggests impairments in procoagulant factors, anti-fibrinolytic factors, platelet abnormalities, and endothelial dysfunction.

The inflammatory state in metabolic syndrome is characterized by a chronic, low-grade inflammation driven by adipose tissue dysfunction, increased oxidative stress, endothelial dysfunction, and an altered cytokine profile, notably marked by increased levels of pro-inflammatory cytokines, and potentially compromised anti-inflammatory responses [23–25, 27]. The origin of metabolic syndrome involves a complex interaction between inherent genetic

factors and environmental lifestyle elements. Prompt detection and stratification of this syndrome are vital for tailoring precision medical strategies, aiming to thwart the trajectory toward cardiovascular morbidity and diabetes [20, 21].

Testosterone and estrogen play notable roles in the MetS context. Testosterone affects muscle composition, fat distribution, and insulin sensitivity. On the other hand, estrogen is vital for regulating body weight and energy balance. Its impact becomes especially pronounced during menopause, where fluctuations in estrogen levels are linked to a heightened risk of MetS [28–30].

Sex hormones and fat mass

The impact of sex hormones on body weight exhibits sex-specific patterns. In males, there is a tendency to accumulate more visceral fat, while females typically exhibit subcutaneous fat accumulation [31]. The android pattern in men correlates with an elevated risk of developing MetS. Conversely, the gynoid pattern in women may confer a degree of protection. The subcutaneous fat in gynoid obesity is less metabolically active than visceral fat, thereby is associated with a reduced risk of metabolic complications [32–34]. Furthermore, sex differences in metabolism are reflected in variations in energy expenditure and feeding patterns in mice [35, 36]. The patterns of body fat distribution influence cardiometabolic risk more than the total level of adiposity [37–40]. The correlation between body fat distribution and metabolic health, particularly within the context of MetS, is extensively studied.

In murine models, sex-specific metabolic differences can be partially attributed to variations in physical activity, energy expenditure, and feeding patterns between male and female mice. Notably, rodents exhibit a higher ratio of brown adipose tissue (BAT) to white adipose tissue (WAT), significantly influencing their metabolic responses. BAT, which is more metabolically active than WAT, plays a more prominent role in rodents than in adult humans, where it is relatively scarce [41, 42]. Therefore, this might cause differences in disease progression and response to metabolic challenges.

It has been recently reviewed that estrogen stimulates BAT activity and thermogenesis. This effect is mediated both directly at the tissue level and indirectly through the brain, influencing the sympathetic nervous system. Ovariectomy in animal models diminishes UCP1 gene expression in BAT, while estrogen replacement reverses this effect. Testosterone, conversely, appears to exert an inhibitory effect on UCP1. *In vitro* studies have shown that testosterone hinders mitochondrial biogenesis and brown adipocyte differentiation. The impact of progesterone on BAT is less clear, with some studies indicating inhibitory effects, especially at high concentrations, and others suggesting stimulatory effects [43]. Complementing this, Kim et al. discovered that estrogen significantly promotes the browning of WAT in female mice, indicating estrogen's pivotal role in fat distribution and energy expenditure [44]. Further, Torres Irizarry et al. highlighted the importance of hypothalamic estrogen signaling, particularly in the ventromedial area, in maintaining metabolic balance [45].

Link et al. explored the relationship between the number of X chromosomes and fat accumulation, revealing that mice with an XX chromosome configuration tend to gain more weight, mainly when fed a high-fat diet. The research highlights the *Kdm5c* gene, which does not undergo X chromosome inactivation, as a critical factor in this process. Adjusting the expression of *Kdm5c* in female mice to match that typically found in males resulted in a decrease in body fat and weight. These findings suggest that *Kdm5c* dosage is a determining factor in the biological differences in fat storage between males and females [46].

Aladhami et al. investigated the effects of increased estrogen in skeletal muscle on obesity and metabolism in female mice. The study used a skeletal muscle-specific aromatase overexpression, anticipating that this would affect high-fat diet-induced obesity. Surprisingly, the results showed that while skeletal muscle and circulating estrogen levels were increased, there was no beneficial impact on body weight, body composition, or metabolic outcomes. This suggests that simply increasing estrogen in skeletal muscle is insufficient to counteract obesity-related metabolic dysfunctions. However, a physiological concentration of circulating estrogen could improve bone mineral density and reduce adipose tissue inflammation, indicating complex and tissue-specific roles of estrogen in metabolism and body weight regulation [47].

In summary, sex hormones significantly influence body fat distribution and metabolic activity, contributing to sex-specific cardiometabolic risks. While visceral fat is linked to higher MetS risk in males, subcutaneous fat in females offers some metabolic protection. The underlying mechanism may include that estrogen increases BAT activity, which influences energy expenditure and body fat distribution.

Sex hormones and lipid metabolism

Estrogens

At the molecular level, estrogens impact lipid metabolism through estrogen receptors (ERs), especially within adipose

tissue. Upon binding to ERs, estrogens can modulate the expression and activity of critical enzymes such as lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL) [48]. Estrogens enhance LPL activity, which is responsible for the hydrolysis of triglycerides in chylomicrons and very low-density lipoproteins (VLDL), facilitating fatty acid uptake [49, 50]. This leads to increased fat deposition in subcutaneous fat depots, a pattern more commonly seen in women [51]. On the other hand, estrogens inhibit HSL, which is key to lipolysis. By inhibiting HSL, estrogen leads to the conservation of fat stores within adipose tissues. This is again more pronounced in subcutaneous fat, thus maintaining the body's energy reserves [52]. The combined effect of these estrogen-mediated actions on LPL and HSL enzymes contributes to the typical female pattern of storing more fat in subcutaneous rather than visceral tissues. Visceral fat is less prevalent in women than in men and is associated with a heightened risk of metabolic diseases. Thus, through the modulation of LPL and HSL activities, estrogen plays a significant role in determining the distribution of body fat, which in turn influences an individual's risk profile for various cardiometabolic diseases.

Clinically, the effect of estrogen on lipid profile is evident in postmenopausal women, who experience a decline in estrogen levels and often show an unfavorable lipid profile with increased low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol. This change is associated with an increased risk of cardiovascular diseases [53, 54].

Progesterone

While direct studies on progesterone and metabolic syndrome are sparse, research in related areas like menopause and polycystic ovary syndrome (PCOS) suggests that progesterone may also play a role in lipid metabolism. During menopause, a period marked by hormonal fluctuations including a decrease in progesterone levels, there is a notable shift in lipid profiles manifested as reduced levels of HDL and elevated apolipoprotein B, contributing to an increased risk of cardiovascular diseases. Still, there is no direct correlation between progesterone concentration and concentrations of lipids and lipoproteins [55]. On the contrary, the study by Liang et al. suggests that in the male population, progesterone was negatively correlated with total cholesterol (TC) and LDL cholesterol (LDL-C). However, the research did not find a significant correlation between progesterone levels and lipid profiles in females, indicating possible sex-specific effects [56].

Studies have observed alterations in lipid profiles in the context of PCOS, which is frequently characterized by hormonal imbalances, including reduced progesterone levels. According to Rashidi et al. in obese women with PCOS, there is an increase in triglycerides, while in non-obese PCOS women, there is an increase in total cholesterol [57].

Intriguingly, progesterone's influence extends beyond traditional pathways. The PGRMC1 has been identified as a key player in adipogenesis. Insulin and PPARγ agonists notably enhance PGRMC1 expression, which then interacts with low-density lipoprotein receptors (VLDL-R and LDL-R) and glucose transporter type 4 (GLUT4). This interaction facilitates the translocation of these receptors to the plasma membrane, promoting lipid uptake, accumulation, and *de novo* fatty acid synthesis in adipocytes [58]. Taken together, these studies depict a multifaceted role of progesterone in lipid metabolism, influenced by various factors such as sex, hormonal balance, and genetic predispositions. Further research is warranted to untangle these interactions and to understand the potential of progesterone-targeted therapies.

Androgens

From a molecular perspective, androgens often exert opposite effects compared to estrogens. Specifically, testosterone has been shown to inhibit LPL activity, reducing the uptake of circulating lipids into adipose tissue, increasing HSL activity, and promoting lipolysis [59]. These actions are consistent with the observation that men typically have less subcutaneous fat and more visceral fat than women. Furthermore, both estrogens and androgens play roles in adipocyte differentiation. Estrogens promote the differentiation of preadipocytes into mature adipocytes, particularly in subcutaneous fat depots, and influence the size and number of lipid droplets [60]. Androgens, however, have been reported to decrease adipogenesis thus lipid accumulation [61].

Clinically, the impact of testosterone on lipid profiles is evident and influenced by physiological states. Among men, a reduction in testosterone is often linked to dyslipidemia, characterized by increased LDL cholesterol and triglycerides coupled with decreased HDL cholesterol [62]. This suggests a protective role of testosterone against dyslipidemia. The relationship between testosterone and lipid profiles in women, especially those diagnosed with PCOS, presents a more convoluted picture. While dyslipidemia commonly accompanies PCOS, the extent to which testosterone directly influences lipid alterations is subject to ongoing scrutiny. A study in 2001 investigating Indian women with PCOS identified a unique pattern of dyslipidemia, with increased triglycerides and suppressed HDL-cholesterol. However, it did not establish a causal link between elevated testosterone and these lipid changes, proposing instead that obesity might be a more critical

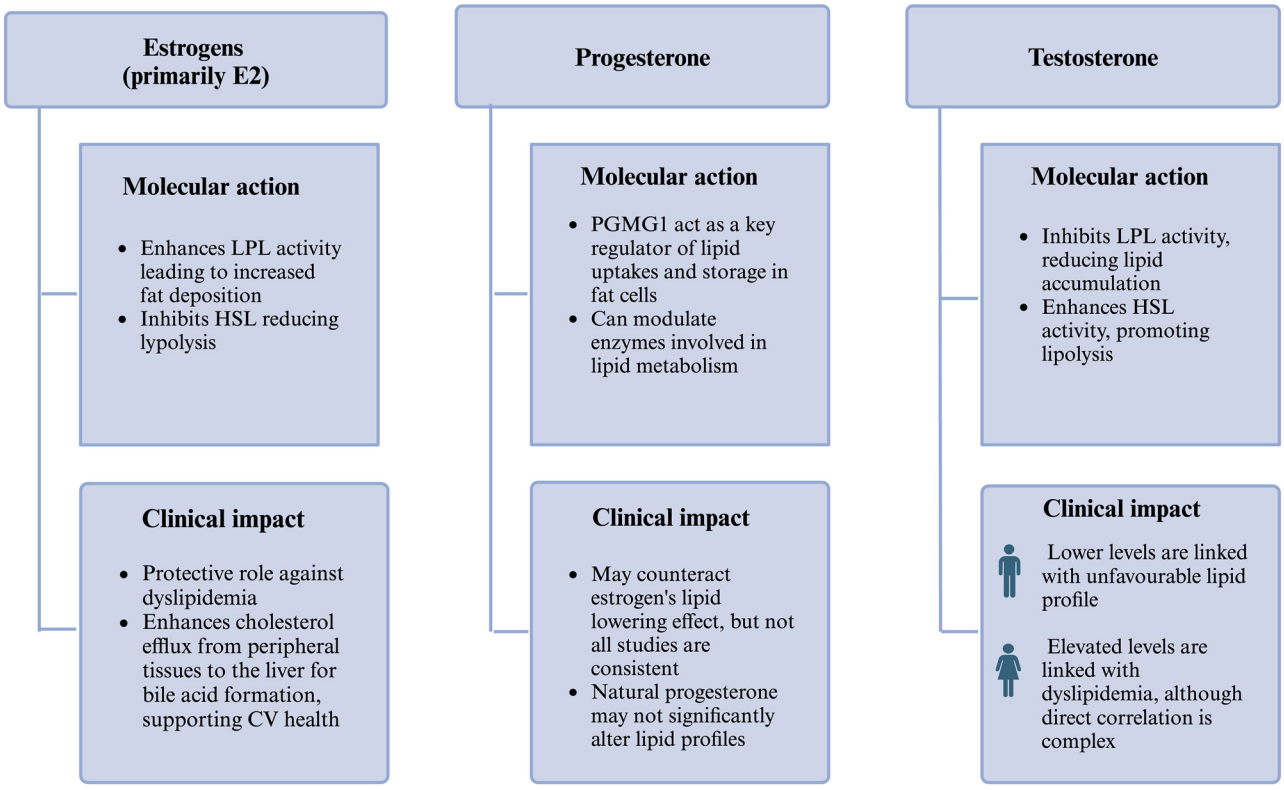

Figure 2: The role of sex hormones in lipid metabolism. This flowchart represents the molecular actions and clinical impacts of estrogen, progesterone, and testosterone on lipid metabolism. Estrogen is shown to have a protective role against dyslipidemia, enhancing cholesterol transport and promoting excretion, while progesterone's influence appears more indirect and nuanced, particularly in postmenopausal women. Testosterone influences lipid metabolism differently in males and females, reflecting its complex role in metabolic health. LPL, Lipoprotein Lipase; HSL, Hormone-Sensitive Lipase; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein. Created with BioRender.com.

determinant in the dyslipidemia profile characteristic of PCOS. In contrast, more recent research by Nazki et al. suggests that the lipid abnormalities in PCOS are pervasive, affecting women irrespective of obesity status, thus underscoring the importance of consistent monitoring of both lipid and hormone levels in the effective management of PCOS [63]. These findings delineate the intricate and significant role of testosterone in the lipid metabolic pathways of women with PCOS.

In summary, estrogens progesterone and androgens regulate lipid metabolism through complex interactions with enzymes, adipocyte differentiation, and adipogenesis. These hormones exert their effects in a sex-specific manner, contributing to the distinct patterns of fat distribution and metabolic profiles observed in men and women. The roles of estrogen, progesterone, and testosterone in lipid metabolism are summarized in Figure 2.

Sex hormone in glucose homeostasis

There are sex differences in the genetic programming of pancreatic endocrine cells. Yong et al. combined pancreas perfusion and single-cell genomic data to explore the sex differences in the human pancreas at single-cell level. The study found that female endocrine cells have a higher secretion capacity than males. Single-cell RNA-sequencing analysis suggested that endocrine cells in male controls have molecular signatures that resemble T2D. The authors also identified genomic elements associated with genome-wide association study T2D loci with differential accessibility between female and male δ-cells. These genomic elements may play a sex-specific influence in the pathogenesis of T2D [64]. Recent investigations into the sexual dimorphism of pancreatic β-cell modulation have unveiled intricate mechanisms that could elucidate disparities in metabolic disease prevalence and response to treatment between sexes. McEwan et al. provide compelling evidence that sensory inputs to pancreatic β-cells are differentially modulated by sex. Their study delineates how the interplay between hormonal milieu and sensory neuron signaling contributes to distinct β-cell functions in males and females [65]. They show how the sensory innervation of the pancreatic islets is variably modulated by testosterone and estrogen, which affects insulin

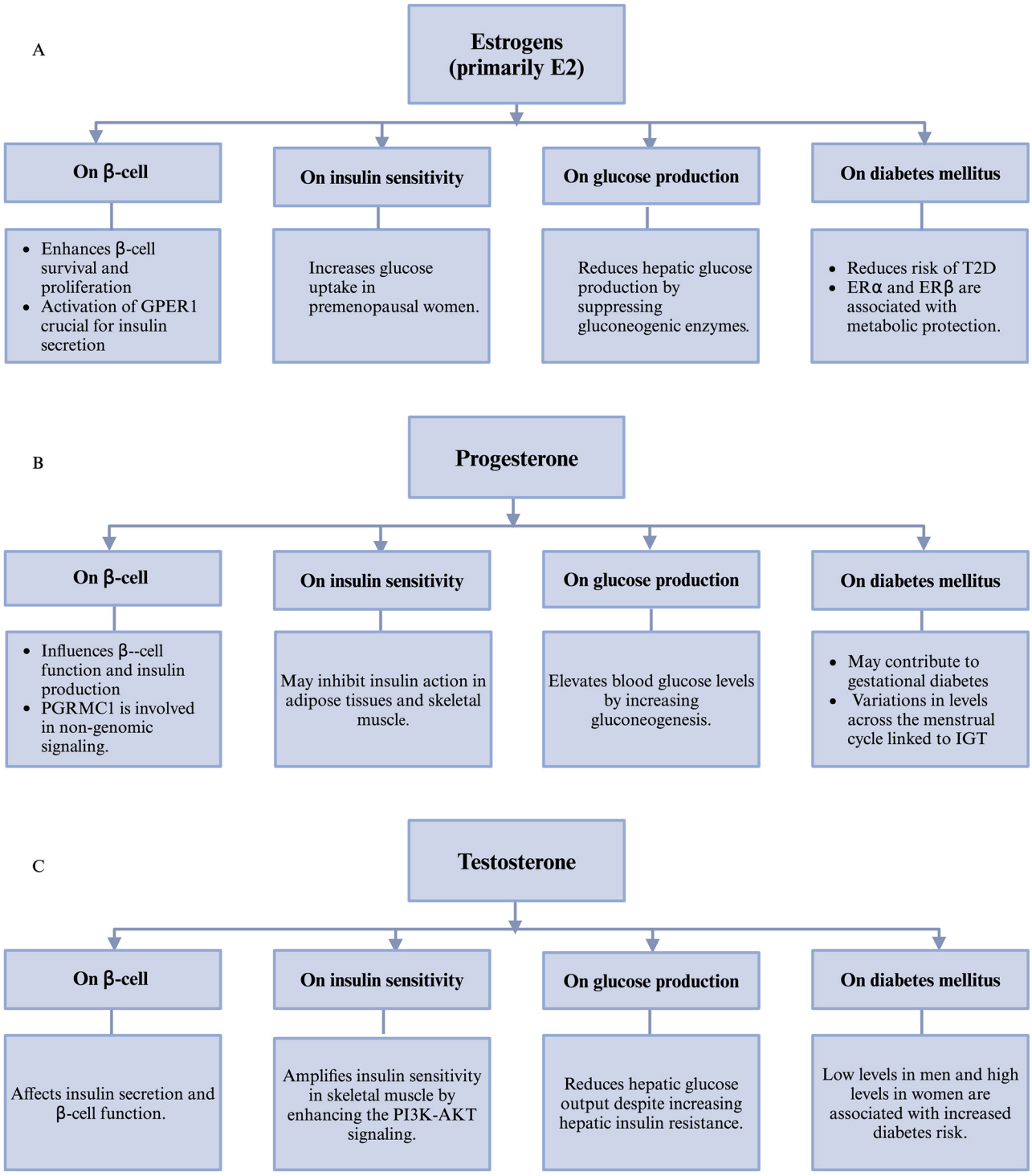

Figure 3: Comparative effects of estrogen (A), progesterone (B), and testosterone (C) on glucose metabolism and diabetes mellitus risk. Estrogen enhances β-cell proliferation and insulin sensitivity, reducing hepatic glucose production, which may lower type 2 diabetes risk. Progesterone affects insulin production and has a role in gestational diabetes and glucose tolerance. Testosterone impacts muscle insulin sensitivity and hepatic glucose output, with its levels inversely associated with diabetes risk in men and women. E2, estradiol; PGRMC1, Progesterone Receptor Membrane Component 1; PI3-AKT, Phosphoinositide 3-Kinase/Protein Kinase B signaling pathway. Created with BioRender.com.

secretion. This dimorphism suggests that the etiology of diabetes may fundamentally differ between sexes. Indeed, clinical studies have demonstrated that men are more prone to impaired fasting glucose, whereas women more commonly exhibit impaired glucose tolerance. Moreover, type 1 diabetes (T1D) represents a unique case of sexual dimorphism in autoimmunity, predominantly affecting males. This underscores the influence of sex on metabolic and autoimmune disease patterns [66]. The effects of estrogen, progesterone and testosterone in glucose metabolism are summarized in Figure 3.

Estrogens

The relationship of estrogen with insulin resistance and type T2D has been well-investigated in molecular and clinical contexts.

On a molecular level, both ERα and ERβ receptors are associated with metabolic protection. ERα knockout mice exhibit peripheral insulin resistance [67], ERβ plays a similar role in metabolic regulation. Its activation is associated with improved lipid profiles and adipocyte differentiation. ERβ knockout mice develop more severe metabolic syndrome under an HFD compared to their wild-type counterparts, suggesting a protective role in metabolic health [68]. Estradiol may reduce hepatic glucose production, mediated, at least in part, by suppression of the expression of gluconeogenic enzymes [69]. In another study, female mice lacking nuclear ERα expression exhibited insulin resistance and increased hepatic gluconeogenesis. An impairment in brain glucose sensing and glucose-stimulated insulin release was also observed, but the same effects were not seen in their male counterparts. Conversely, mice that expressed membrane-associated ERα (mER) receptors, both male and female, displayed hyperglycemia and glucose intolerance [5]. These results show that brain glucose sensing, glucose tolerance, glycemia, and glucose-stimulated insulin secretion are all significantly influenced by the central expression of nuclear ERα.

In addition to ERα and ERβ, the GPER1, also known as GPR30, plays a critical role in pancreatic β-cell function. Activation of this receptor prevented β-cell apoptosis and may be involved in the islet adaptation against insulin-resistance [70].

Activation of GPER by estradiol is also crucial for insulin secretion from the β-cells [70]. Recent studies have proposed that ERα/β heterodimers play an antiapoptotic role in β cells, and decreases in these heterodimers lead to β cell apoptosis, especially in the context of environmental estrogen mimics like bisphenol-A [71].

Acting as a metabolic modulator, fibroblast growth factor 21 (FGF21) is produced by various cell types, including hepatocytes, white and brown adipocytes, skeletal and cardiac myocytes, and pancreatic β-cells. It enhances insulin sensitivity and glucose uptake, helping to reduce serum hyperglycemia, promotes lipid oxidation, and inhibits lipogenesis. It continues to be an exciting area of research given its broad array of functions [72]. Sex hormones, including estrogen, can impact FGF21 levels and a variety of its downstream effects. In male mice, estrogen deficiency led to reduced hepatic FGF21 production; female mice also showed reduced hepatic FGF21 levels following ovariectomy. It has been found that estrogen positively regulates FGF21 expression by enhancing the binding of transcription factor 7-like 2 (TCF7L2) and RNA polymerase II to the FGF21 promoter. The GPER1 is also involved in this process [73]. Thus, estrogen plays a vital role in regulating hepatic FGF21 expression. Investigating further this estrogen–FGF21 interaction may have important implications in how sex hormones may impact metabolic health and lipid regulation.

Clinically, estrogen has been demonstrated to enhance glucose uptake in premenopausal women, thus promoting insulin sensitivity [74]. It is hypothesized that the decline in estrogen levels after menopause is a crucial factor contributing to the reduced insulin sensitivity observed in aging women [75, 76]. In contrast, mice may not completely recapitulate this pattern due to differences in fat distribution and hormonal regulation.

Progesterone

Molecular mechanisms. Progesterone exerts a multifaceted impact on glucose homeostasis, through a combination of genomic and non-genomic actions. It binds to the PGR in the liver, adipose tissue, and skeletal muscle. This binding leads to transcriptional modulation of genes associated with insulin signaling and glucose metabolism [77]. This hormone's influence extends to direct stimulation of insulin production and hepatic glycogen synthesis. Yet, intriguingly, it may also inhibit insulin action in adipose tissues and skeletal muscle [78, 79]. PGR in rat adipocytes provide further insight into its potential in suppressing lipolysis [80]. Recent research suggests the role of progesterone in elevating blood glucose levels by upregulating genes involved in gluconeogenesis, driven by its binding to hepatic PGRMC1 (non-genomic actions), especially in insulin-resistant states [81, 82]. Additionally, progesterone's activation of glycogen phosphorylase in the liver contributes to increased glucose levels [83].

Clinically, progesterone's metabolic effects have been observed in various conditions. For instance, variations in progesterone levels across the menstrual cycle, with a peak

in the luteal phase, have been correlated with impaired glucose tolerance and insulin sensitivity [84]. During pregnancy, progesterone levels increase, playing a pivotal role in the adaptation of maternal glucose metabolism. Progesterone is reported to promote β-cell growth and proliferation, enhancing the insulin secretion capacity to meet the demands imposed by gestational changes [85]. However, the clinical relevance is unclear; increased progesterone levels also correlate with gestational diabetes onset [82, 86], a relationship often linked to increased insulin resistance and diminished GLUT4 expression in skeletal muscles [83]. In murine models, the absence of PR has been linked to improved glucose tolerance and reduced glucose levels [87], attributed to β-cell expansion due to proliferation [83].

The role of progesterone in hormone replacement therapy (HRT) has been evaluated on lipid and glucose metabolism. Studies involving postmenopausal women have indicated that natural progesterone may not significantly alter lipid profiles [88, 89], suggesting its potential utility in HRT in contrast to synthetic progestogens such as medroxyprogesterone acetate, levonorgestrel, and norgestrel, that have been associated with adverse metabolic effect.

Androgens

The influence of androgens, specifically testosterone, on glucose regulation is intricate, multi-dimensional, and subject to subtle variations.

From a molecular perspective, testosterone amplifies insulin sensitivity in skeletal muscle by enhancing the PI3K-AKT signaling cascade. Pal et al. demonstrated that testosterone supplementation ameliorated insulin sensitivity in male mice subjected to HFD, a model mimicking T2D. Additionally, testosterone up regulates the *p85 gene*, an integral part of the PI3K complex, thereby improving insulin sensitivity [90]. Intriguingly, testosterone also appears to reduce hepatic glucose production while simultaneously elevating hepatic insulin resistance, a paradox that may serve as a compensatory mechanism to sustain glucose equilibrium [91].

Clinically, hypogonadism, marked by diminished testosterone levels, is frequently correlated with compromised glucose tolerance and increased insulin resistance in men, thereby increasing the risk of T2D [28, 92, 93], suggesting a protective role of testosterone against MetS.

Testosterone replacement therapy in men has been shown to mitigate insulin resistance, underscoring its role in glucose metabolism [94, 95]. However, the relationship between testosterone and metabolic syndrome is far from straightforward. Some studies indicate that elevated testosterone levels could also exacerbate metabolic syndrome, particularly in women with conditions like PCOS [96]. Thus, testosterone's effects on insulin sensitivity manifest differently in men and women: while elevated testosterone levels in men may confer protection against diabetes; in women, they are associated with an increased risk. Numerous factors, including general health, body composition, and hormonal equilibrium also modulate the interplay between testosterone and glucose regulation. Further investigations are imperative to decode the intricate relationships.

In conclusion, testosterone, estradiol, and progesterone all play specific and significant roles in regulating β-cell function, glucose levels, and insulin sensitivity. However, the relationships between these hormones and various metabolic processes are complex and influenced by various factors.

The role of sexual hormones in cardiovascular diseases

Sex hormones may have a role in the observed differences in the occurrence of cardiovascular diseases (CVD) between males and females [97]. These hormones orchestrate a complex physiological responses that influence the cardiovascular system's integrity and functionality.

Adiposity, regulated in part by sex hormones, is a recognized variable in the gender disparity observed in CVD risk [98]. Hormonal fluctuations exert multifaceted influences on CVD, both through modulation of risk factors such as obesity and metabolic syndrome and via direct effects on cardiovascular function [99].

The role of estrogen and androgen receptors in vascular endothelium and smooth muscle cells is crucial. These receptors modulate vascular tone and are instrumental in the regulation of blood pressure and the process of vascular aging [100, 101]. Evidence suggests that the mechanisms underpinning sex hormone influences are significant contributors to cardiovascular risk factors, particularly in men [102]. Additionally, the sex-dependent variation in heme oxygenase activity may elucidate the protective effects against cardiovascular ischemia observed in females during their reproductive period [103]. The interplay between GPCRs, such as estrogen and endothelin receptors, and oxidative stress in hypertension and vascular aging further exemplifies the complexity of these pathways [104]. Additionally, oxidative stress has a role in the pathogenesis of hypertension and vascular aging [100]. For an in-depth analysis of the roles of sex and gender in hypertension, Reckelhoff provides a critical review of the current literature [105].

The role of sex hormones in hypertension and vascular aging

Men are far more likely than women to have hypertension and have it earlier. This discrepancy can be partially explained by the differing effects of sex hormones and the genetically determined the renin–angiotensin system. This system is essential in the pathophysiology of hypertension and testosterone and estrogen, modulating it in diverse ways [106–108]. Additionally, research has shown that the impact of ERα polymorphisms on arterial stiffness varies between genders, indicating the possibility of an extra genetic component [109].

Estrogens

A complex molecular interplay characterizes the role of estrogen in modulating hypertension. Consider the ERs, particularly ERα, as complex regulatory networks within the vascular system, in response to estrogens. These receptors are not merely passive entities, e.g. the AF2 domain of ERα is essential for blood pressure regulation. Animal studies have shown that a deficiency or dysfunction in this domain increases susceptibility to hypertension, particularly in response to angiotensin II [110].

Environmental endocrine disruptors like bisphenol A (BPA), which can mimic or impede the actions of estrogen, further complicate this situation. This interference may disrupt the balance that ERs are responsible for maintaining, and lead to hypertension. This behavior is comparable to adding a mistaken component to a well-tuned system [111]. Furthermore, a 2021 study revealed the sex-specific influences of ERβ agonists and suggest that ERβ activation may offer distinct advantages in managing hypertension, especially in female, peri-menopausal mice [112].

From a clinical perspective, the role of estrogen in hypertension is complex. This is best illustrated using transdermal estrogen treatment in postmenopausal women. This treatment avoids hepatic processing, and may offer a more effective means of managing hypertension [113]. Current research is refining it, focusing on optimizing hormone therapy in dosage and duration. Achieving the right balance is crucial, as deviations can diminish the therapeutic benefits. This is particularly important in estrogen-only hormone therapy, where the equilibrium between efficacy and safety is paramount [114]. In conclusion, the complex and ever-changing link between estrogen and hypertension presents opportunities as well as obstacles for us. The potential for creating focused and efficient hypertension treatments, especially for postmenopausal women, is growing.

Androgens

At molecular level, understanding testosterone's influence on vascular health requires delving into its intricate interactions with blood vessels. The role of testosterone in vascular tone is a delicate balance between two opposing forces: vasodilation and vasoconstriction. This balance is not just a simple on-off switch but a sophisticated cellular mechanism [115].

On one hand, testosterone's ability to promote vasodilation is closely tied to its interaction with nitric oxide (NO) production, a key player in relaxing the blood vessels. Imagine NO as a messenger sent by the endothelial cells lining the blood vessels, instructing the surrounding smooth muscle cells to relax. Testosterone enhances this message, boosting NO production and thus encouraging the vessels to relax. This action is akin to a gentle nudge, coaxing the vessels to open and facilitate smoother blood flow [115, 116].

On the other hand, testosterone also has a less discussed but equally important role in vasoconstriction. This effect operates independently of the endothelium, delving deeper into the muscle layer of the blood vessels. Here, testosterone influences ion channels within the smooth muscle cells. These channels control the flow of ions in and out of the cells, which can lead to vasoconstriction [115].

Genomic effects involve changes in gene expression, while non-genomic effects lead to rapid changes in cellular function [117–120]. Mishra et Kumar revealed how the angiotensin two receptor activation can mitigate the hypertensive effects induced by testosterone, particularly in pregnant rats. This discovery is significant because it illuminates prospective treatments for hypertension in pregnancy, a condition that is complicated for both the mother and the fetus. It deserves more attention in hypertension research [121]. Another study underscored the role of testosterone in mitigating hypoxia-induced hypertension by modulating the transcriptional activity of Nuclear Respiratory Factor 1 (NRF1). Under hypoxic conditions, NRF1 is activated, leading to increased expression of endothelin-1 (ET-1) and angiotensin-converting enzyme (ACE), which contribute to elevated blood pressure through vasoconstriction and sodium retention. Testosterone intervenes by attenuating NRF1's stimulation on these genes. It reduces ET-1-mediated vasoconstriction and moderates the renin–angiotensin system by influencing ACE expression. This regulatory effect of testosterone on NRF1 under hypoxic conditions underscores its potential therapeutic value in managing hypertension associated with low-oxygen conditions [122].

The role of testosterone in arterial stiffness is inversely related, where lower levels of this hormone are associated

with increased stiffness in arteries. This suggests testosterone's protective role in maintaining vascular elasticity and reducing the risk of hypertension. Testosterone's influence is multifaceted: it directly affects the contractility of vascular smooth muscle cells. It indirectly alters the composition of the extracellular matrix, which is crucial for the structural integrity and elasticity of arterial walls [123, 124]. By promoting cell senescence and vascular remodeling via the Gas6/Axl pathway, testosterone may have a preventive effect on vascular aging [125]. Although testosterone is mainly a male hormone, there is evidence that it may also play a role in postmenopausal arterial stiffness in women. Elevated levels of serum testosterone and free androgen index have been associated with subclinical atherosclerosis in recently menopausal women. Free androgen index was also a significant predictor of arterial stiffness, as measured by carotid-femoral pulse wave velocity – PWV [126, 127].

From a clinical point of view, Wei et al. discerns a complex interplay among testosterone levels, obesity, and hypertension. Their findings underscore a noteworthy correlation between elevated serum testosterone levels and a diminished prevalence of hypertension in men. This correlation manifests as a discernible reduction in both systolic and diastolic blood pressure as testosterone levels ascend. It is crucial to note, however, that this association predominantly manifests in non-obese individuals. The protective influence of testosterone against hypertension appears to lose its efficacy in obesity. In fact, in obese individuals, heightened testosterone levels correlate with elevated blood pressure, suggesting a paradoxical relationship. Hence, while testosterone generally exerts a mitigating effect on hypertension and reduces blood pressure in males, the efficacy of these beneficial effects is notably contingent upon the individual's obesity status [128].

The research conducted by Park et al. delves into the complex interplay between testosterone deficiency (TD) and the emergence of diabetes and hypertension, two pivotal cardiovascular risk factors. The study, which tracks a group of middle-aged and older men, finds that the risk of diabetes is almost twice as high for those with TD as it is for those with normal testosterone levels. For the elderly, the presence of TD correlates with an increased likelihood of both hypertension and diabetes. These findings highlight the critical role of TD in men's cardiovascular health, suggesting that testosterone levels could be a key focus in mitigating the risk of these chronic conditions [129].

In the intricate world of cardiovascular health, hormones like testosterone are not just supporting characters but key protagonists, influencing everything from the behavior of blood vessels to overall heart health.

The role of sex hormones in coronary artery disease

Sexual hormones have a notable impact on cardiovascular calcification, a process linked to the advancement of cardiovascular disease. Woodward et al. explored the differential effects of estrogens and androgens. Estrogens emerged as protective agents, potentially inhibiting the pathways leading to vascular calcification. In contrast, androgens displayed a more complex behavior, with their effects hinging on receptor interactions and hormonal balance. This study underscores the importance of understanding the complex roles of sex hormones in cardiovascular health, paving the way for more personalized approaches to treating cardiovascular diseases [130]. In another dimension, Harris et al. conducted a comprehensive analysis within the UK Biobank cohort to examine the association of sex hormones with myocardial infarction (MI) risk. Their findings revealed no direct correlation between estrogen or testosterone levels and MI risk in both genders. However, a notable observation was that in men, a higher estrogen-to-testosterone ratio correlated with a reduced MI risk, suggesting a complex interplay of these hormones [131]. Albrektsen et al. further delved into the gender disparities, finding that men had approximately double the risk of women, even after adjusting for traditional risk factors like lipid levels, blood pressure, smoking, diabetes, body mass index, and physical activity. This gender gap, although persistent, appeared to diminish with age, highlighting the evolving nature of cardiovascular risk across the lifespan [132]. Further, Le et al. discovered that sex steroids regulate autophagy during MI. Their study revealed that androgens, during ischemia-reperfusion, downregulate the anti-apoptotic protein Bcl-xL, tipping the balance towards apoptosis and exacerbating cardiac damage. This finding opens new avenues in understanding the molecular mechanisms at play during cardiac events [133]. Lastly, Faresjö et al. provided a fascinating insight into the hormonal changes preceding MI. Their study observed a significant decrease in testosterone levels in both men and women about a month before an AMI, paralleling elevated cortisol levels. This pattern, echoing a biological mechanism observed in stress responses, suggests an underlying mechanism in the hormonal dynamics [134].

The role of sex hormone-binding globulin (SHBG) in metabolic syndrome and CVD

Sex Hormone-Binding Globulin (SHBG) is a critical glycoprotein found in the blood, synthesized predominantly in the liver, playing a vital role in modulating the bioavailability of sex hormones, particularly testosterone, DHT and estradiol. While SHBG can also bind progesterone, this interaction is comparatively weak and is not considered a major regulatory mechanism for progesterone's bioavailability [135]. Progesterone is primarily bound by corticosteroid-binding globulin (CBG), also known as transcortin, which, while having a higher affinity for glucocorticoids, still plays a significant role in transporting and regulating the bioavailability of progesterone in the bloodstream [136]. By binding to these hormones, SHBG regulates the balance between their active (free) and inactive (bound) forms, thus influencing their physiological effects on the body, including metabolism and cardiovascular health [135, 137–139].

SHBG has been shown to mitigate endoplasmic reticulum (ER) stress in hepatocytes, both *in vitro* and *ex vivo*. This action is crucial because ER stress is implicated in the pathogenesis of metabolic disorders, including obesity, MetS, and diabetes. By alleviating ER stress, SHBG contributes to maintaining cellular homeostasis and metabolic health [140]. The protective effects of SHBG against MetS, are underscored by its anti-inflammatory and lipolytic effects on adipocytes and macrophages. SHBG treatment suppresses inflammatory cytokine production and promotes lipid degradation, mechanisms that are pivotal in reducing the incidence of MetS [141]. Furthermore, SHBG's influence extends to lipid metabolism. It has been observed that SHBG overexpression in mouse models of non-alcoholic fatty liver disease (NAFLD) significantly reduces liver fat accumulation by downregulating key lipogenic enzymes. This suggests that SHBG plays a role in modulating hepatic lipogenesis, highlighting its potential in preventing or arresting the development of NAFLD [142]. Further, resveratrol, a polyphenol found in red wine, has been identified to increase hepatic SHBG production through the human Constitutive Androstane Receptor (CAR). This interaction not only elucidates a novel regulatory pathway for SHBG expression but also suggests dietary components can influence SHBG levels and, consequently, metabolic health [142].

Previous studies indicates that diminished levels of SHBG could increase the risk of MetS and T2D [143–145], even more than low testosterone levels [146–148]. A recommended threshold level of SHBG below 42 nmol/L indicates an increased risk for fatty liver and prediabetes, emphasizing the importance of early intervention strategies [149]. A study by Ding et al. further corroborated the protective effects of elevated SHBG levels [143]. However, the intricate interplay between SHBG, sexual hormones, and metabolic disorders necessitates ongoing research for a comprehensive understanding [137, 143, 144].

Regarding its predictive value, studies have shown that SHBG levels can serve as a biomarker for cardiovascular events. A study from the UK Biobank brought to light an intriguing association in men: higher SHBG levels seemed to be linked with a lower risk of MI. This association highlights the potential of SHBG as a therapeutic target in managing cardiovascular risks, especially in men [131]. However, the relationship in women is more complex; the same study by Harris et al. did not find a clear link between SHBG levels and MI risk in women. This discrepancy points to the influence of factors like menopause on SHBG's role in women's cardiovascular health. Menopausal status significantly alters hormonal balance, which in turn affects SHBG and free androgen index (FAI) levels and their impact on cardiovascular risk [131]. FAI estimates the level of androgens that are biologically active in the body. It is helpful in assessing androgen status in situations where alterations in SHBG levels (e.g., hyper/hypothyroidism, obesity, etc.) may affect the total testosterone level.

Additional findings revealed a complex relationship between SHBG concentrations and various cardiovascular events. Firstly, lower levels of SHBG are linked with an increased incidence of MI, suggesting that reduced SHBG may be a risk factor for heart attacks. In the meantime, these lower SHBG levels are associated with a decreased incidence of ischemic stroke (IS) and heart failure (HF), indicating a rather protective aspect of lower SHBG levels against those conditions. The influence of SHBG on cardiovascular health may vary depending on the type of cardiovascular event [150].

The association between SHBG levels and cardiovascular risks is also evident in studies focusing on oxidative stress. For example, a survey of premenopausal Korean women found that lower SHBG levels were intertwined with heightened cardiovascular risks and oxidative stress [145]. Similarly, diminished SHBG levels in men have been linked to atherogenic risk factors, while elevated levels seem to enhance endothelial function among young, sedentary males [151].

These findings propose SHBG as a key player in cardiovascular health, enhancing its value above that of a simple biomarker. They highlight the complex roles that SHBG may play in cardiovascular health and emphasize how its impact alters based on menopausal status, sex, and the

nature of the cardiovascular disorders. Understanding the genetic, epigenetic, and environmental determinants of SHBG levels will be crucial in developing targeted interventions for cardiometabolic disorders. Additionally, the discovery of specific receptors for SHBG on various cell types opens new avenues for investigating its direct effects on metabolic pathways.

Summary and perspective

Sex hormones, encompassing androgen, estrogen, and progesterone, play vital roles in regulating energy metabolism and cardiovascular function. This review elucidates the extensive impact of sexual hormones beyond their conventional reproductive functions, providing a detailed analysis of how testosterone, estrogen, and progesterone uniquely contribute to cardiometabolic health. It becomes clear that testosterone influences muscle mass, body fat, insulin sensitivity, and metabolic rate. Estrogen exhibits favorable effects on lipid metabolism, contributing to vascular health and cardio protection. Progesterone, frequently examined alongside estrogen, exhibits unique effects on glucose metabolism and may also exert an influence on vascular response. Acknowledging the dual role of sexual hormones in both metabolic and cardiovascular systems underscore the need for a more integrated approach in research and medical treatment. This provides novel perspectives for managing these conditions medically.

The insights into the roles of estrogen, testosterone, and progesterone in cardiometabolic health could lead to novel diagnostic markers for metabolic syndrome or cardiovascular diseases. For example, considering SHBG levels as a predictor for cardiovascular events could shift how we evaluate risk and manage patient care. Moreover, the distinction understanding of how these hormones influence inflammation and lipid metabolism might help the development of personalized hormone replacement therapies, which could be tailored to mitigate the risk of metabolic syndrome, diabetes, or atherosclerosis in patients with hormone deficiencies. Furthermore, the significant roles of sex hormones in metabolic processes and cardiovascular health could lead to the development of personalized treatment strategies based on an individual's sex hormone profile. For instance, individuals with certain hormonal imbalances could be treated with specific hormone therapies to improve their metabolic health.

Collaborative efforts between endocrinologists, cardiologists, and researchers could foster new interdisciplinary treatment protocols and potentially lead to the development of new pharmaceutical treatments that modulate hormone levels or their activity to improve cardiometabolic health outcomes.

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