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REVIEW

The Innovation Nutrition

From testosterone to 11-oxygenated androgens: Integrating endocrine biology, nutrition, and systemic health across the lifespan

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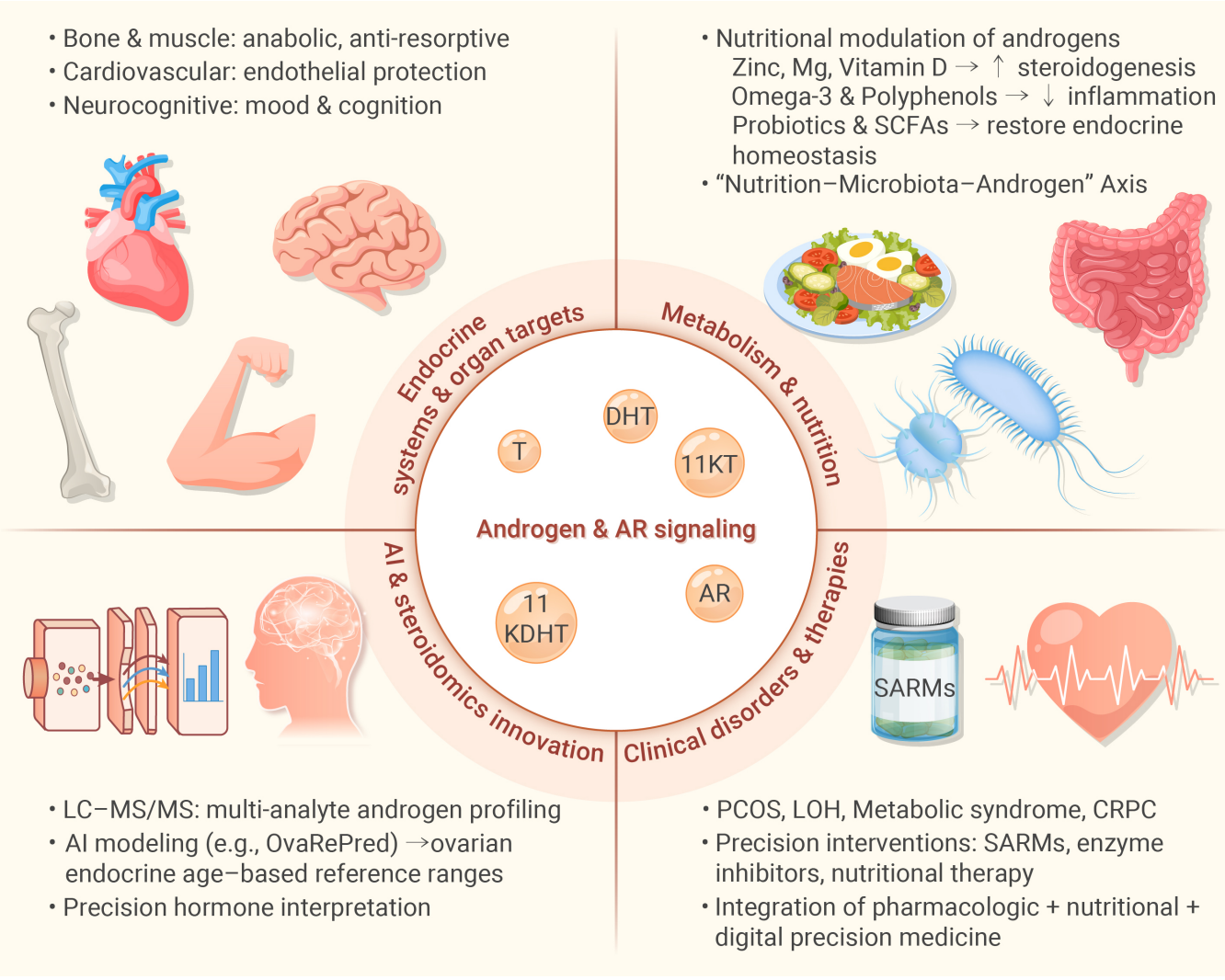
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Androgens regulate multisystem physiology via AR signaling.
- T, DHT, and 11-oxygenated androgens affect bone, muscle, and metabolism.
- Nutrition modulates steroidogenesis and the microbiota–androgen axis.
- LC-MS/MS enables accurate multi-androgen profiling.
- AI tools support precision androgen medicine.

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From testosterone to 11-oxygenated androgens: Integrating endocrine biology, nutrition, and systemic health across the lifespan

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Androgens, historically regarded as male sex hormones, are increasingly recognized as central regulators of multisystem physiology across the lifespan in both sexes. Beyond reproductive functions, classical androgens together with emerging 11-oxygenated androgens participate in the regulation of metabolic homeostasis, immune balance, cardiovascular function, musculoskeletal integrity, neurocognitive processes, and systemic aging. Advances in steroidomics, liquid chromatography–tandem mass spectrometry (LC-MS/MS), and androgen receptor biology are reshaping androgen research from a reproduction-centered perspective toward an integrated endocrine framework linking physiology, disease, nutrition, and precision medicine.This review synthesizes current understanding of androgen biosynthesis, metabolism, and receptor signaling, and summarizes their roles in reproductive disorders such as polycystic ovary syndrome, congenital adrenal hyperplasia, and late-onset hypogonadism, as well as prostate disease, metabolic and cardiovascular disorders, bone and muscle health, dermatologic conditions, and neuropsychiatric function. Therapeutic approaches-including hormone replacement therapy, selective androgen receptor modulators, enzyme-targeted interventions, and structured safety monitoring-are also discussed.An emerging frontier is the integration of nutrition and gut microbiota into androgen regulation. Micronutrients such as zinc, magnesium, and vitamin D, together with balanced macronutrient intake, anti-inflammatory dietary patterns, and probiotics, influence steroidogenesis, inflammation, insulin resistance, and androgen receptor signaling, forming a potential "nutrition–microbiota–androgen axis".Meanwhile, LC-MS/MS-based multi-androgen profiling and early integration with AI approaches-such as ovarian-endocrine-age modeling exemplified by OvaRePred-may enable individualized interpretation and predictive analytics. Collectively, the convergence of advanced analytics, nutrition science, and AI-driven modeling is redefining androgen medicine and enabling more precise diagnosis and personalized endocrine health management.

OVERVIEW OF ANDROGENS

Androgens, traditionally regarded as "male hormones," are now recognized as pivotal regulators of multisystem physiology in both sexes.[1,2] Beyond their well-known roles in reproductive differentiation and sexual function, androgens orchestrate a wide range of biological processes encompassing bone and muscle integrity, metabolic homeostasis,[3-4] immune regulation,[5-8] neurocognition,[9-10] and vascular health.[3-4] These pleiotropic effects are mediated primarily through testosterone (T), dihydrotestosterone (DHT), and a growing class of 11-oxygenated androgens, which act via the androgen receptor (AR) in nearly all major tissues.[11-14] The concept of "androgen health" has thus expanded from reproductive endocrinology to a broader framework linking endocrine balance with systemic aging and chronic disease prevention.[12,14-16]

Across the lifespan, androgen signaling maintains the equilibrium between anabolism and catabolism, modulates insulin and lipid metabolism, supports erythropoiesis, and influences inflammatory tone.[2,4,17] Physiological androgen decline contributes to osteoporosis, sarcopenia, depression, and cardiometabolic dysfunction.[18-21] In contrast, excessive androgen exposure-as observed in conditions like polycystic ovary syndrome (PCOS) or exogenous misuse—can provoke metabolic derangements, vascular stiffness, and reproductive abnormalities.[3,22-24] This bidirectional vulnerability underscores androgens as both vital homeostatic mediators and potential disease drivers when imbalanced.[12,17,25]

Recent advances in steroidomics, mass-spectrometry profiling, and artificial-intelligence–assisted analytics have enabled the precise mapping of androgen pathways, revealing complex interactions among gonadal, adrenal, and peripheral sources.[26-31] Particularly, 11-oxygenated androgens such as 11-ketotestosterone (11KT) and 11-ketodihydrotestosterone (11KDHT) have emerged as potent AR agonists that sustain androgenic activity even under gonadal suppression.[11-12] Their discovery redefines traditional models of androgen biology and opens new avenues for biomarker development and targeted intervention.

An increasingly recognized dimension of androgen physiology lies in its intimate connection with nutrition and metabolism. Adequate intake of key micronutrients—such as zinc, magnesium, and vitamin D—serves as cofactors for steroidogenic enzymes, whereas balanced protein and unsaturated-fat consumption preserves hormone transport and receptor sensitivity.[32-35] Conversely, excessive refined carbohydrates or saturated fats impair insulin signaling and favor peripheral aromatization of T to estrogens, fueling metabolic syndrome or hyperandrogenic states.[36] Energy restriction and malnutrition suppress the hypothalamic–pituitary–gonadal (HPG) axis, leading to hypoandrogenism and muscle loss, while obesity enhances aromatase activity and disrupts the androgen–estrogen balance.[37] Emerging evidence also highlights the gut microbiota as a critical intermediary, modulating androgen metabolism and systemic inflammation through diet-dependent microbial metabolites.[38-41] These insights position the androgen–nutrition axis as a new frontier in precision endocrinology and metabolic health.

In this review, we summarize current knowledge of androgen biosynthesis, metabolism, and receptor signaling; delineate their systemic physiological

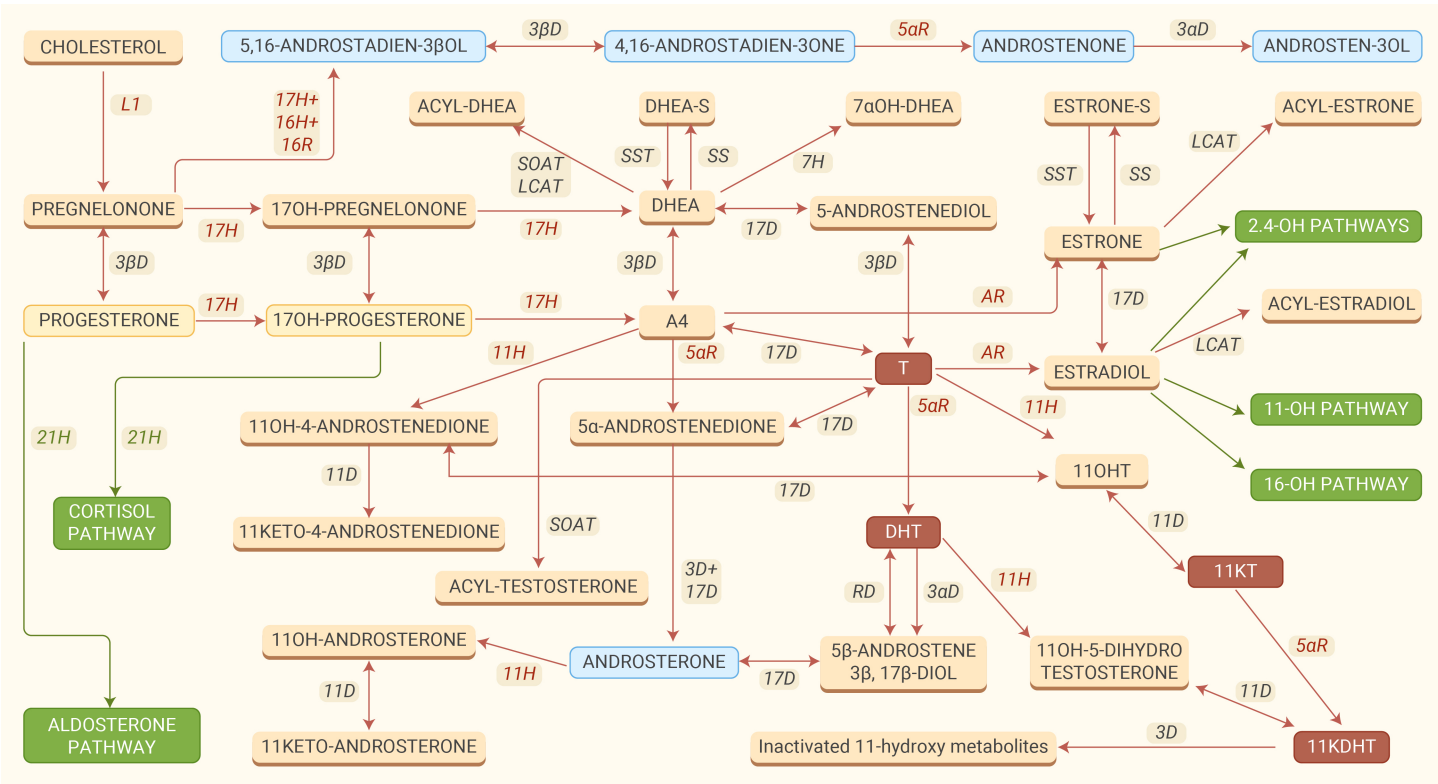

Figure 1. Overview of Classic and 11-Oxygenated Androgen Biosynthesis and Conversion Pathways. This diagram summarizes androgen synthesis from cholesterol via key intermediates to T and 11KT. The other branches of steroid hormone pathway were also indicated. Color coding: Brown = major bioactive androgens; Green = functional pathway branches. Abbreviations: L1, CYP11A1 – cholesterol side-chain cleavage enzyme (P450scc); 17H, CYP17A1 – 17α-hydroxylase / 17,20-lyase; 3βD, 3β-HSD – 3β-hydroxysteroid dehydrogenase; 4R, AKR1D1 – 5β-reductase; 7H, CYP7B1 – 25-hydroxycholesterol 7α-hydroxylase; 17D, 17β-HSD type 3/5 – 17β-hydroxysteroid dehydrogenase isoforms; 16H, CYP3A7 / CYP1A1 – 16α-hydroxylase; 16R, CYP3A_4 – 16β-hydroxylase; 11H, CYP11B1 – 11β-hydroxylase; 11D, 11β-HSD type 1/2 – 11β-hydroxysteroid dehydrogenase; 5αR, SRD5A1/2 – 5α-reductase; 3αD, 3α-HSD (AKR1C family) – 3α-hydroxysteroid dehydrogenase; RD, non-specific reductase; SST / SS, STS – steroid sulfatase; SOAT, SULT2A1 – sulfotransferase; LCAT, lecithin–cholesterol acyltransferase; AR, CYP19A1 – aromatase; 3D, 3α-HSD / 3β-HSD (AKR1C).

and pathological roles; and explore emerging intersections with nutrition, metabolism, and immune regulation. Integrating metabolomic profiling, nutritional science, and AI-driven analysis will pave the way toward precision androgen medicine—one that personalizes endocrine and nutritional interventions to optimize health across the reproductive, metabolic, and aging continuum.

ANDROGEN BIOLOGY: SOURCES, REGULATION, METABOLISM, AND MECHANISMS OF ACTION

Androgens are a class of essential steroid hormones involved in the regulation of various physiological processes, including reproductive system development, bone density maintenance, muscle growth, and the modulation of sexual drive.[2] The pathways underlying androgen biosynthesis and metabolism are highly complex and are regulated by multiple endocrine axes (Figure 1). Their synthesis depends not only on endocrine glands such as the testes, ovaries, and adrenals but also on regulation by the HPG axis, the hypothalamic-pituitary-adrenal (HPA) axis, and peripheral tissues, in addition to modulation via autocrine and paracrine signaling pathways.[42] This section will focus on the mechanisms governing androgen synthesis and regulation, as well as the metabolic pathways and biological functions of T and its principal metabolites.

Androgen biosynthesis and regulatory mechanisms

Androgen production in males and females. Androgen biosynthesis in both sexes involves contributions from the gonads, adrenal glands, and peripheral tissues, differing mainly in quantitative output, hormonal regulation, and the relative balance of adrenal versus gonadal sources. In women, androgens are synthesized primarily by the ovaries and adrenal cortex, with additional interconversion occurring in peripheral tissues. Within the ovary, theca cells produce A_4 and small amounts of Dehydroepiandrosterone (DHEA) under Luteinizing Hormone (LH) stimulation, while granulosa cells convert A_4 to estrogens in the regulation of follicle-stimulating hormone (FSH), with a portion of A_4 also transformed into T.[43] The adrenal cortex further secretes DHEA, Dehydroepiandrosterone sulfate (DHEAS), and 11-oxygenated androgens such as 11KT, which contribute substantially to systemic and local androgen activity through peripheral activation pathways.[12] In men, androgen synthesis is dominated by testicular Leydig cells, which produce T under LH regulation via the hypothalamic–pituitary–testicular (HPT) axis.[44] The adrenal glands additionally secrete weaker androgens-DHEA, Androstenedione (A_4), and 11β-hydroxytestosterone (11OHT)—that can be converted peripherally into active 11KT and 11KDHT, thereby supplementing total androgenic activity, particularly under pathological or developmental conditions.[12]

In both males and females, peripheral tissues—including skin, adipose tissue, and skeletal muscle—express enzymes such as 5α-reductase and 11β-HSD, allowing in situ conversion of adrenal- and gonadal-derived precursors into biologically active androgens or estrogens.[12,45-46] In peripheral androgen excess, DHT predominates in skin and prostate-related effects, while 11KT may dominate systemic and metabolic actions, highlighting the need to consider both gonadal and adrenal sources in androgen-related pathophysiology.[12,47]

Regulation of Androgen Synthesis. Androgen production is regulated through coordinated central and peripheral pathways. Gonadal secretion is primarily controlled by the HPG axis, operating via the HPT axis in men and the hypothalamic–pituitary–ovarian (HPO) axis in women.[48] Pulsatile secretion of GnRH activates pituitary release of LH and FSH. In males, LH stimulates Leydig cells to upregulate essential steroidogenic enzymes (CYP11A1, CYP17A1, HSD3B), facilitating the conversion of cholesterol via pregnenolone and A_4 into T, whereas FSH acts on Sertoli cells to promote aromatase activity and inhibin B production, thereby supporting spermatogenesis.[49-50] In females, LH stimulates theca-cell androgen synthesis via the same cascade, and FSH induces granulosa-cell production of inhibin B and estradiol, promoting follicular growth.[51] Circulating T and its downstream metabolites provide negative feedback to the hypothalamus and pituitary, thereby modu-

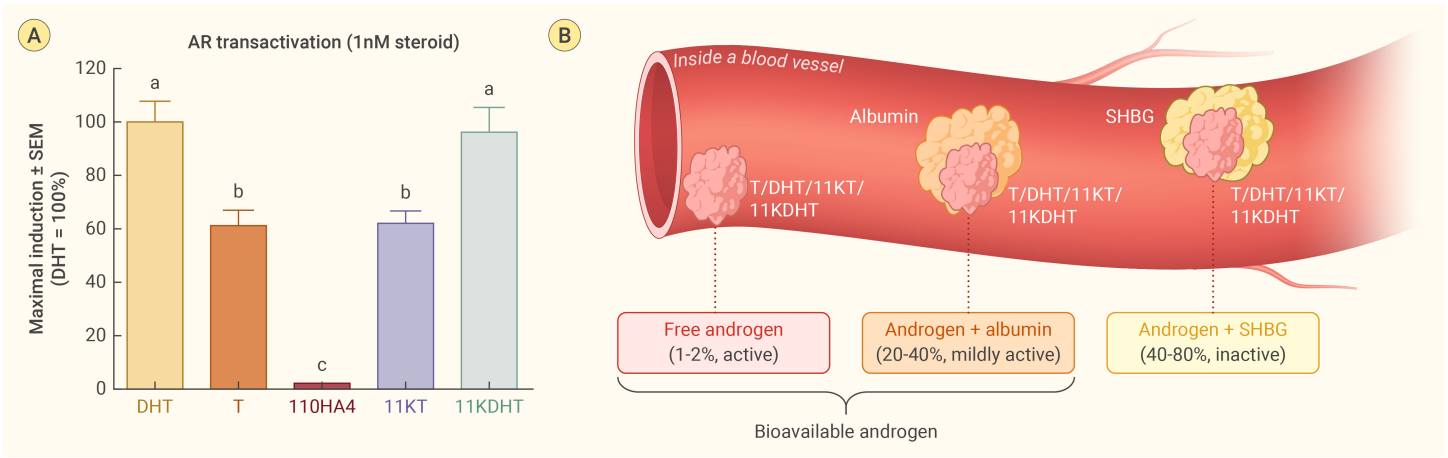

Figure 2. Androgen bioactivity and binding dynamics. Comparative androgen receptor transactivation of key steroids (1 nM), showing DHT and 11KDHT as the most potent agonists, followed by T and 11KT.[11] (B) Circulating androgens exist as free, albumin-bound, or SHBG-bound fractions, with only the free and loosely bound forms being bioavailable and biologically active.

lating and maintaining appropriate levels of GnRH and gonadotropin release.[48]

In addition to the gonads, the adrenal cortex—under the control of the HPA axis—serves as a source of weaker androgens, including DHEA, DHEAS, and 11-oxygenated C19 steroids.[12,52] ACTH pulsatility drives zona reticularis steroidogenesis, while insulin, IGF-1, and intra-adrenal modulators refine enzyme activity.[53-54] Sequential oxidation by 11β-HSD2 and reduction by AKR1C3 convert 11-hydroxy precursors to potent androgens (11KT, 11KDHT) with high androgen-receptor affinity and resistance to aromatization.[13]

Peripheral tissues—including skin, adipose, liver, and prostate—express activating enzymes such as 5α-reductase (types 1 and 2) and 11β-hydroxysteroid dehydrogenases (11β-HSD1 and HSD2), whose expression and activity are modulated by local and systemic cues.[22,55] 5α-Reductase is upregulated by androgens, insulin/IGF-1 signaling, inflammatory cytokines (e.g., TNF-α), and thyroid hormones, while estrogens and certain growth factors can downregulate its activity.[22,56] Likewise, 11β-HSD1— which regenerates active glucocorticoids and can interconvert 11-oxygenated androgens—is induced by glucocorticoids themselves, high circulating insulin, and PPARγ agonists, whereas 11β-HSD2—which inactivates glucocorticoids—is upregulated in states of mineralocorticoid excess and by factors like angiotensin II.[12,14,55] These tissue-specific modulators fine-tune local androgen and corticosteroid levels, enabling organ-level specificity of hormonal effects independent of systemic hormone concentrations.[55,57] This dynamic interplay between central hormonal control (HPG and HPA axes), gonadal and adrenal steroid output, and peripheral activation underscores the complexity and precision of androgen regulation in health and disease.

Androgen metabolism

Androgen metabolism involves a complex network of enzymatic conversions that regulate the activation, inactivation, and clearance of androgens in target tissues. The major circulating androgens include T, DHT, A_4, DHEA, and 11-oxygenated androgens such as 11KT.[12] These androgens stem from the gonads and adrenal glands and undergo extensive peripheral metabolism.[55,57]

T can be metabolized into the more potent androgen DHT via 5α-reductase (isoenzymes type 1 and 2), which is abundantly expressed in tissues such as the prostate, skin, hair follicles, and liver.[58] DHT binds the androgen receptor with greater affinity and is responsible for many classical androgen-dependent processes, including development of the external genitalia and secondary sexual traits.[58] Alternatively, T may be aromatized by aromatase (CYP19A1) to estradiol, particularly in adipose tissue and brain.[59]

Androgen inactivation proceeds through multiple metabolic routes. T and DHT are converted by 3α- and 3β-hydroxysteroid dehydrogenases into less active or inactive metabolites, including androsterone and etiocholanolone.[60] These metabolites subsequently undergo hepatic conjugation—via glucuronidation or sulfation—and are eliminated in the urine. The conjugation steps are mediated by UDP-glucuronosyltransferases and sulfotransferases.[61-62]

11-oxygenated androgens, previously thought to be inactive, are now recognized as potent androgens.[11-12] For example, $11OHA_4$ and $11KA_4$ can be converted by 11β-hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2) to 11KT and 11KDHT, which are non-aromatizable and highly active at the AR.[13,63] These pathways are particularly relevant in tissues like the adrenal gland,[12,63] liver,[55] skin,[64] and prostate.[13] Adipose tissue, through expression of 11β-HSD1, may also play a role in the local processing of 11-oxygenated androgens.[55,65-66]

Overall, androgen metabolism is tissue-specific and highly regulated, ensuring that local androgenic activity reflects not just circulating hormone levels but also the local enzymatic milieu. Dysregulation of androgen metabolism contributes to several clinical disorders, including androgen insensitivity, polycystic ovary syndrome (PCOS), congenital adrenal hyperplasia (CAH), and prostate disease.[12]

Key rate-limiting enzymes in androgen pathway

Androgen production and biotransformation are governed by a series of critical rate-limiting enzymes that shape overall hormone levels, tissue-specific actions, and physiological homeostasis. Steroidogenesis is initiated by the transport of cholesterol into mitochondria via steroidogenic acute regulatory protein (StAR), widely regarded as the first rate-limiting step in this pathway.[67] Within the mitochondria, cholesterol is subsequently converted to pregnenolone by CYP11A1 (cholesterol side-chain cleavage enzyme).[67]

A key regulatory node is CYP17A1, which exhibits both 17α-hydroxylase and 17,20-lyase activities, enabling the conversion of pregnenolone or progesterone into DHEA or A_4, the principal precursors of androgens. CYP17A1 activity represents a major rate-limiting step in androgen biosynthesis, especially within the adrenal cortex and in gonadal theca and Leydig cells.[49,67]

In peripheral tissues, 5α-reductase (types 1 and 2, encoded by SRD5A1 and SRD5A2) catalyzes the conversion of T to the more potent DHT, a critical local activator of androgen signaling in the prostate, skin, and hair follicles.[58]

For 11-oxygenated androgens, 11β-hydroxylase (CYP11B1) and 11β-hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2) regulate the formation and interconversion of $11OHA_4$, 11KT, and 11KDHT—steroids now recognized as potent androgens.[12]

Inactivation and clearance of androgens involve 3α/3β-HSDs, UGTs, and SULTs, which reduce and conjugate active androgens for excretion.[60-62] Alterations in these enzymes can lead to hyperandrogenism, androgen insensitivity, or steroidogenic deficiencies.[22]

Androgen receptor (AR) distribution and bioavailability of circulating androgens

The androgen receptor (AR) is a member of the nuclear receptor family and acts as a ligand-activated transcriptional regulator.[68] When activated by androgens such as T, DHT, 11KT, or 11KDHT, the receptor undergoes nuclear translocation, binds to androgen response elements, and modulates target

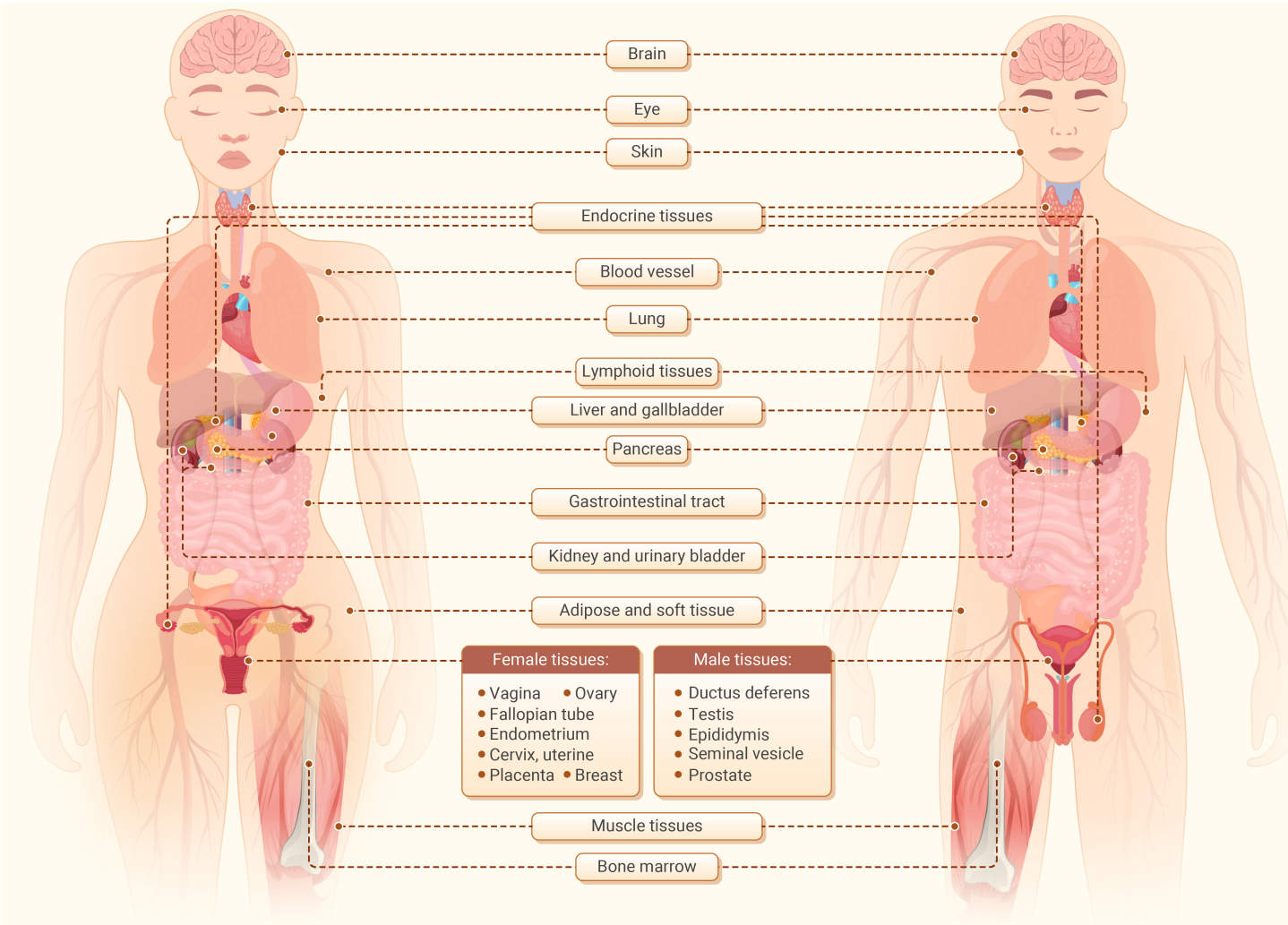

Figure 3. Distribution of androgen receptor (AR) expression. ARs are widely expressed across multiple organs and systems in both sexes, highlighting the broad physiological influence of androgens.

gene expression.[11,13] Androgens differ in AR affinity: DHT exhibits the strongest binding and transactivation, while 11KT and 11KDHT—major adrenal 11-oxygenated androgens—also display high AR activity that can equal or exceed T or DHT in certain tissues (Figure 2A).[11,13] In contrast, 11OHT has lower potency, and A_4 requires conversion to T or DHT for activation.[11]

In the circulation, androgens are distributed across three forms: unbound (free), albumin-associated, and sex hormone–binding globulin (SHBG)–bound fractions (Figure 2B).[69-71] Free androgens account for only 1–3% of total levels yet are the most biologically active because they readily diffuse into cells and activate AR (Figure 2A).[72] In contrast, 40–80% of circulating androgens are tightly bound to SHBG, forming high-affinity but inactive complexes (Figure 2B). SHBG concentrations vary with sex, age, body weight, insulin resistance, thyroid and liver function, and sex-hormone balance.[73-75] Men generally have lower SHBG,[76-77] whereas pregnancy and oral contraceptive use markedly increase levels in women.[78-79] Low SHBG is linked to obesity, insulin resistance, and PCOS.[76,80-81] Albumin-bound androgens are weakly bound and readily dissociable, contributing to the bioavailable pool together with free androgens.[82] Because albumin levels are relatively stable, SHBG variation exerts a greater influence on androgen bioavailability.[16,83]

Free androgens are also present in other biological fluids. They diffuse into saliva, making salivary assays reliable indicators of free hormone levels.[84-85] Androgens in sebaceous secretions and sweat contribute to acne vulgaris and androgenic alopecia, while low levels in breast milk may play roles in lactational endocrinology.[86] In cerebrospinal fluid, they exert neuromodulatory effects on mood, cognition, and behavior.[87-88] Collectively, androgen distribution across multiple body compartments supports their diverse systemic functions.

AR is widely expressed across human tissues, mediating diverse physiological functions (Figure 3).[89] In reproductive organs, AR regulates spermatogenesis and prostate function in males and contributes to follicular and endometrial regulation in females.[89] In muscle and bone, AR supports anabolic growth and bone mineral density.[90-91] In skin and hair follicles, it modulates sebaceous activity and hair growth.[91] AR is also expressed within the central nervous system, where it contributes to the regulation of behavior, cognitive processes, and neuroendocrine activity,[91-92] and in the cardiovascular system, where it affects cardiac function and vascular tone.[93] AR expression is further detected in the adrenal cortex, linking AR to steroidogenic regulation.[12] Beyond transcription, AR participates in proliferation, differentiation, and apoptosis,[91,94] and dysregulated AR signaling contributes to numerous physiological and pathological states.[12,94] Tissue-specific AR expression data were derived from the Human Protein Atlas.[95]

Androgens and nutrient–metabolic utilization

Androgens are key regulators of energy homeostasis. They enhance skeletal muscle protein synthesis and mitochondrial formation, increase resting metabolic rate, and limit visceral fat deposition, collectively supporting favorable body composition.[96-98] T deficiency often leads to muscle atrophy, increased adiposity, and reduced insulin sensitivity, whereas excessive or exogenous androgen exposure may induce insulin resistance and dyslipidemia.[99-100] In addition, androgens influence appetite and caloric intake via hypothalamic pathways: low T in men has been linked to diminished appetite, while hyperandrogenic conditions, such as in women with PCOS, may promote overeating and excessive energy consumption.[101-103] Overall, androgens orchestrate a multi-level regulatory network that sustains metabolic

balance and enhances nutrient utilization efficiency.

Nutrition–androgen interactions: metabolic modulation rather than direct endocrine control

Nutritional factors influence androgen biology predominantly through indirect metabolic and endocrine pathways, rather than by directly regulating gonadal or adrenal steroidogenesis.[104-105] Energy balance, macronutrient composition, and micronutrient availability modulate insulin sensitivity, adiposity, inflammation, and hepatic protein synthesis, all of which shape circulating androgen profiles and tissue-specific androgen action.[106-107]

Several micronutrients have been associated with androgen status, including zinc, magnesium, and vitamin D. Zinc participates in steroidogenic enzyme activity and androgen receptor (AR) signaling, while vitamin D has been linked to androgen levels through effects on insulin sensitivity and sex hormone–binding globulin (SHBG).[35,108-111] However, evidence from randomized controlled trials remains inconsistent, and observed associations are often confounded by body composition, metabolic health, and baseline hormonal status.[112-113] These findings underscore that nutritional influences on androgens are context-dependent and mediated by systemic metabolic effects, rather than reflecting direct nutrient–hormone causality.

Dietary patterns also modulate androgen profiles through their effects on insulin resistance and adipose tissue distribution.[114-115] Caloric excess, high glycemic load diets, and central obesity are consistently associated with hyperandrogenic phenotypes, particularly in women with polycystic ovary syndrome (PCOS).[114-115] Conversely, weight reduction and improved insulin sensitivity are often accompanied by reductions in circulating androgens.[116-117] Notably, these effects are not limited to classic androgens such as testosterone, but extend to 11-oxygenated androgens, which are increasingly recognized as metabolically sensitive components of the androgen pool.[12,14]

Importantly, 11-oxygenated androgens appear to reflect adrenal–metabolic crosstalk rather than reproductive axis activity.[12,14,23,65] Their associations with insulin resistance, adiposity, and metabolic inflammation suggest that they may serve as metabolic readouts of nutritional state. From a nutritional research perspective, this distinction is critical: rather than replacing testosterone measurements, 11-oxygenated androgens may provide complementary information in studies focusing on metabolic outcomes, long-term dietary exposure, or insulin-related phenotypes.

Nevertheless, current evidence does not support individual nutrients or dietary components as direct or targeted modulators of androgen synthesis. A major limitation of the existing literature lies in nutritional exposure assessment, as many studies rely on imprecise or semi-quantitative approaches, with self-reported dietary questionnaires remaining the predominant assessment tool. Such methods often fail to adequately capture inter-individual variability in nutrient intake and bioavailability.[118-120] Consequently, associations between specific nutrients and androgen status are frequently inconsistent across studies and difficult to interpret mechanistically.

With the expanding clinical adoption of mass spectrometry-based platforms, high-precision profiling of nutritional biomarkers-including amino acids, vitamins, fatty acids, and trace elements-is becoming increasingly feasible and clinically integrated. When coupled with AI-enabled analytical frameworks that explicitly account for inter-individual metabolic heterogeneity, these technologies provide a critical opportunity to re-evaluate nutrient-hormone relationships with substantially improved biological resolution. Accordingly, future nutrition-focused research should prioritize rigorously designed clinical trials or well-curated real-world studies that incorporate quantitative nutrient measurements, explicitly adjust for adiposity and insulin sensitivity, and clearly predefine androgens as outcomes, mediators, or stratification variables. Such approaches are essential for delineating the physiological roles of specific nutrients within integrated metabolic–endocrine networks, rather than inferring direct nutrient–hormone causality from observational associations.

Gut microbiota and androgen metabolism: a biologically plausible, metabolically mediated axis

The gut microbiota has increasingly been recognized as a potential modulator of androgen metabolism, giving rise to the concept of a nutrition–microbiota–endocrine axis. From a biological standpoint, this framework is highly plausible, as microbial activity interfaces with multiple metabolic and signaling pathways known to influence androgen production, clearance, and tissue action.[121-122] However, despite its conceptual appeal, current human evidence remains heterogeneous and largely associative, and its role in androgen regulation should therefore be interpreted with appropriate caution. Importantly, this limitation reflects not only biological complexity but, to a substantial extent, fundamental constraints in hormonal and nutritional measurement.

A critical barrier in this field is the lack of comprehensive and precise endocrine phenotyping. In many human studies, androgen status is inferred from a limited set of immunoassay-based measurements—often restricted to total testosterone—while broader androgen panels, including adrenal-derived and metabolically sensitive androgens such as 11-oxygenated species, are rarely assessed.[123] Likewise, key nutritional exposures and metabolic intermediates that plausibly link the microbiota to endocrine outcomes—such as amino acids, fatty acids, bile acid profiles, micronutrients, and inflammatory mediators—are frequently unavailable or inadequately quantified. Without accurate, high-resolution measurement of these components, mechanistic interpretation of microbiota–androgen associations remains inherently constrained.

Mechanistically, the gut microbiota is unlikely to exert direct control over gonadal or adrenal steroidogenesis. Instead, its influence on androgen biology appears to be predominantly mediated through systemic metabolic pathways. Microbial metabolites such as short-chain fatty acids (SCFAs) modulate insulin sensitivity, low-grade inflammation, and hepatic energy metabolism, thereby shaping the endocrine milieu that governs androgen synthesis and clearance.[124] In parallel, microbiota-derived secondary bile acids regulate nuclear receptors involved in steroid metabolism and metabolic homeostasis, indirectly affecting androgen turnover.[124] In addition, microbial β-glucuronidase activity may contribute to enterohepatic recycling of steroid hormones, potentially altering circulating androgen availability without directly modifying steroidogenic pathways.[125]

At present, however, direct causal links between specific bacterial taxa, microbial metabolites, or defined microbial signatures and androgen biosynthesis remain limited. Much of the available mechanistic evidence derives from animal models or small observational studies.[38,40,126] In human nutrition and microbiome research, disentangling microbiota-related effects from major confounders—including dietary composition, adiposity, medication use, and host genetic background—remains challenging. These difficulties are further compounded by incomplete endocrine and nutritional profiling, which precludes reliable stratification of androgen phenotypes across populations. Consequently, no reproducible microbial profile can yet be robustly linked to androgen excess or deficiency.

In this context, integrating comprehensive androgen panels with microbiome profiling represents a methodological necessity rather than a technical refinement. Rather than assuming direct microbial regulation of steroidogenesis, androgens—particularly 11-oxygenated species—should be interpreted as endocrine readouts of microbiota-associated metabolic states. Given their predominantly adrenal origin and strong associations with insulin resistance, adiposity, and inflammation, 11-oxygenated androgens better reflect adrenal–metabolic crosstalk than reproductive axis activity and provide information not captured by testosterone alone.[12,23] Clinically, the microbiota–androgen axis should be viewed as an emerging, metabolically mediated framework rather than an established therapeutic target, as androgen changes accompanying microbiota modulation are more likely secondary to metabolic or inflammatory improvement than to direct microbial control.

Looking ahead, progress in this field will depend critically on advances in measurement infrastructure. As high-precision mass spectrometry–based platforms for androgen panels, nutritional biomarkers, and metabolic intermediates become more widely available—and as standardized microbiome monitoring and longitudinal profiling are increasingly implemented—targeted modulation of specific microbial functions or taxa may become a rational strategy in selected metabolic contexts. Without such measurement precision, however, neither mechanistic inference nor therapeutic translation is feasible.

Overall, while the nutrition–microbiota–androgen axis represents a

compelling biological model, its clinical relevance will hinge on future studies employing integrated designs that combine dietary assessment, microbiome profiling, metabolic characterization, and comprehensive, high-quality endocrine measurements. Until these methodological foundations are in place, claims regarding microbiota-driven androgen modulation should remain conservative, with primary emphasis placed on metabolic context, functional readouts, and analytical rigor.

DISORDERS ASSOCIATED WITH ANDROGEN ABNORMALITIES AND THERAPEUTIC STRATEGIES

Androgens exert systemic regulatory effects across immune, reproductive, metabolic, cardiovascular, musculoskeletal, dermatologic, and neuropsychiatric systems. Dysregulation of androgen production, metabolism, or receptor signaling may manifest as androgen excess, androgen deficiency, or tissue-specific androgen imbalance. Importantly, emerging recognition of adrenal-derived 11-oxygenated androgens has substantially expanded the mechanistic landscape of androgen-related disorders.

Androgen excess disorders

Androgen excess represents a central pathophysiological feature in several endocrine and metabolic disorders. While clinical phenotypes differ between sexes, shared mechanisms frequently involve dysregulated steroidogenesis, altered peripheral metabolism, and metabolic–endocrine coupling.

Polycystic Ovary Syndrome (PCOS). PCOS is the most prevalent endocrine disorder in reproductive-age women and is defined by hyperandrogenism and metabolic dysfunction.[22] Excess androgen production arises predominantly from ovarian theca cells and adrenal pathways. Beyond classical androgens such as T and A_4, adrenal-derived 11-oxygenated androgens—including 11OHA4, 11OHT, 11KA4, and 11KT—are now recognized as major bioactive contributors.[12,23] Notably, these androgens demonstrate stronger associations with insulin resistance and cardiometabolic risk than T alone.[12,23]

Hyperinsulinemia plays a pivotal mechanistic role by stimulating ovarian steroidogenesis and suppressing SHBG, thereby increasing circulating bioavailable androgens.[12,127] Clinically, PCOS manifests as menstrual irregularity, hirsutism, acne vulgaris, and subfertility.[128] Therapeutic strategies primarily target metabolic correction and AR signaling modulation. Antiandrogens (spironolactone, flutamide, finasteride) mitigate androgenic symptoms, while oral contraceptives suppress ovarian androgen production.[129]Lifestyle modification and insulin sensitizers (metformin) improve insulin sensitivity and reduce androgen excess.[130] Mass spectrometry–based androgen panels offer superior specificity for characterizing androgen origin and metabolic signatures.[131-134] Dietary interventions, particularly Mediterranean dietary patterns and probiotic supplementation, further improve insulin sensitivity and indirectly attenuate hyperandrogenism.[135-140]

Congenital Adrenal Hyperplasia (CAH). CAH comprises inherited disorders of adrenal steroidogenesis, most commonly due to 21-hydroxylase deficiency.[141,142] Impaired cortisol synthesis leads to ACTH-driven adrenal androgen excess. Clinical manifestations vary by severity and sex but reflect shared endocrine disruption. Emerging data suggest that abnormalities in enzymes involved in 11-oxygenated androgen metabolism may contribute to non-classic hyperandrogenic phenotypes.[12] Glucocorticoid replacement suppresses ACTH and reduces androgen overproduction.[143-144] Novel therapeutic approaches targeting specific androgen metabolic pathways are under investigation.[12,145-146] Further research into the molecular and enzymatic basis of non-classic CAH—especially the role of 11-oxygenated androgen metabolism—may refine disease classification and open new avenues for targeted therapy.

Metabolic Hyperandrogenic Phenotypes in Males. Hyperandrogenic metabolic phenotypes analogous to PCOS have been described in men.[24] It is characterized by insulin resistance and elevated androgen precursors such as DHEA, occurring in both lean and non-lean phenotypes.[24] Clinical features include central obesity, acne vulgaris, early-onset androgenetic alopecia, reduced sperm quality, and an increased risk of erectile dysfunction (ED).[24,147] Mechanistically, metabolic dysregulation appears to drive altered androgen metabolism rather than primary gonadal overproduction.[24] This reinforces the concept that androgen excess may arise from systemic metabolic disturbances across sexes.

Androgen deficiency disorders

Androgen deficiency arises from impaired gonadal steroidogenesis, hypothalamic–pituitary dysfunction, or age-related endocrine decline. Although clinical consequences differ between sexes, shared mechanisms involve diminished AR signaling, altered anabolic balance, and metabolic perturbation.

Late-onset hypogonadism (LOH). LOH reflects progressive decline in T production associated with aging.[148-149] Symptoms include reduced sexual function, loss of muscle mass, bone loss, fatigue, and mood changes.[148] Testosterone replacement therapy (TRT) restores physiological concentrations and improves functional outcomes.[148-149]

Premature ovarian insufficiency (POI). POI is characterized by early depletion of ovarian follicles and reduced estrogen and androgen production.[150-151] Hypoandrogenism contributes to decreased libido, vaginal atrophy, bone loss, and impaired quality of life.[150-151] The cornerstone of therapy remains hormone replacement with estrogen and progestogen to relieve menopausal symptoms and mitigate long-term risks. In selected cases, low-dose T or DHEA may be added for women with persistent hypoandrogenic symptoms or impaired bone health, provided that treatment is individualized and closely monitored for androgen-related side effects.[150-151]

Systemic Consequences of Hypoandrogenism. Across both sexes, androgen deficiency exerts widespread systemic effects that extend well beyond reproductive function. Reduced androgen signaling disrupts skeletal homeostasis by diminishing osteoblast activity and bone formation, thereby predisposing individuals to progressive bone loss and osteoporosis. In parallel, impaired androgen-mediated anabolic pathways compromise muscle protein synthesis, contributing to sarcopenia, reduced strength, and functional decline. At the vascular level, insufficient androgen activity is associated with impaired endothelial nitric oxide (NO) signaling, which may promote endothelial dysfunction, adverse metabolic profiles, and increased cardiovascular risk. Moreover, accumulating evidence links hypoandrogenism to neuropsychiatric vulnerability, including fatigue, mood disturbances, and cognitive changes, reflecting the neuromodulatory and neuroprotective roles of androgens. Collectively, these alterations highlight the systemic regulatory importance of physiological androgen levels. In appropriately selected individuals with confirmed androgen deficiency, testosterone replacement therapy (TRT) and selective androgen receptor modulators (SARMs) represent the principal therapeutic strategies aimed at restoring anabolic balance, improving metabolic and vascular function, and mitigating long-term complications.[15,148,152]

Tissue-specific androgen dysregulation

Certain androgen-related disorders predominantly arise from tissue-specific dysregulation of androgen signaling, rather than from overt systemic androgen excess or deficiency. These conditions underscore the importance of local steroid metabolism, receptor sensitivity, and intracrine androgen activation.

Prostate Diseases The dihydrotestosterone–androgen receptor (DHT–AR) signaling axis represents the central molecular driver of benign prostatic hyperplasia (BPH) and prostate cancer.[153-156] Within prostatic tissue, local conversion of testosterone to DHT amplifies AR activation, promoting stromal and epithelial proliferation. Emerging evidence further implicates adrenal-derived 11-oxygenated androgens, particularly 11KT, as potent AR agonists capable of sustaining AR signaling.[11,13,157] These findings suggest that AR activation in prostate pathology is not exclusively dependent on classical androgens.

Clinically, BPH management primarily targets local androgen action through 5α-reductase inhibitors, which reduce DHT synthesis, and α-adrenergic antagonists, which alleviate lower urinary tract symptoms.[158-162] In prostate cancer, androgen deprivation therapy (ADT) remains foundational.[163] However, therapeutic resistance frequently emerges via AR amplification, constitutively active splice variants, and alternative steroidogenic pathways.[164-165] Notably, 11KT has been proposed as a potential contributor to persistent AR activation despite conventional androgen suppression.[11,13,166-167] Novel therapeutic strategies—including PROTAC-mediated AR degradation,

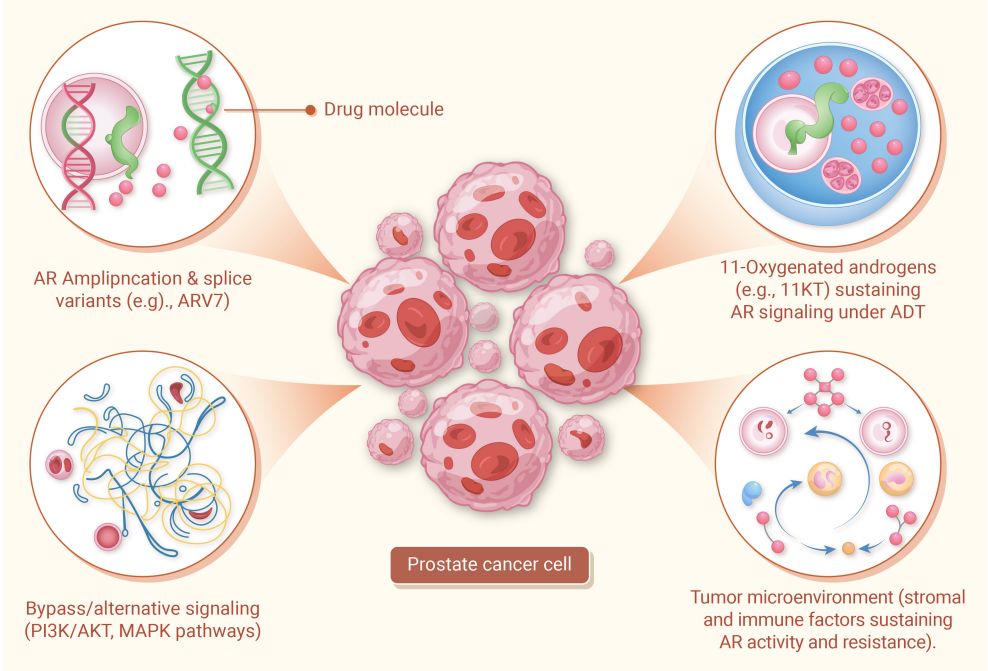

Figure 4. Mechanisms of prostate cancer drug resistance. Prostate cancer cells develop resistance through multiple mechanisms.

PSMA-targeted radioligand therapy, and PARP inhibitors—aim to overcome these resistance mechanisms.[168-172] Targeting both classical and 11-oxygenated androgen pathways may offer a new strategy to overcome resistance and improve long-term outcomes (Figure 4).

Skin and Appendages. In cutaneous tissues, excess androgen signaling stimulates sebaceous gland activity and follicular miniaturization, contributing to acne vulgaris, hirsutism, and androgenic alopecia (Figure 5).[173-175] Conversely, androgen deficiency reduces sebaceous secretion and impairs hair growth, resulting in dry, fragile skin and decreased pilosebaceous function.[175] Thus, balanced androgen signaling is essential for maintaining skin integrity, optimal sebum production, and healthy hair follicle cycling, highlighting key therapeutic targets for anti-androgen or replacement interventions.

Bone and Muscle System. Androgens exert essential anabolic effects by regulating osteoblast and myocyte function.[176-177] Tissue-level androgen insufficiency or impaired receptor signaling contributes to osteoporosis and sarcopenia.[18,19,178] TRT and SARMs improve musculoskeletal outcomes by restoring anabolic balance while minimizing off-target effects.[15,152,179-181]

Metabolic and cardiovascular systems

Androgen abnormalities are closely intertwined with systemic metabolic homeostasis, reflecting a bidirectional relationship between endocrine regulation and metabolic function. Reduced androgen levels are consistently associated with increased visceral adiposity, impaired glucose metabolism, and the development of insulin resistance.[24,99,182-184] These alterations contribute to a self-reinforcing cycle in which adiposity further exacerbates endocrine dysregulation. Conversely, elevations in androgen precursors, particularly in metabolically dysregulated states, may also disrupt metabolic balance, highlighting that both androgen deficiency and excess can adversely influence metabolic pathways.

Notably, adrenal-derived 11-oxygenated androgens have emerged as metabolically sensitive components of the androgen pool, demonstrating particularly strong associations with insulin resistance, adverse lipid profiles, and cardiometabolic risk.[12,23] These findings suggest that androgen-related metabolic effects extend beyond classical testosterone-centered paradigms.

At the vascular level, physiological androgen signaling supports endothelial integrity, partly through modulation of nitric oxide pathways.[4,185-187] Androgen deficiency accelerates endothelial dysfunction and atherosclerotic progression, whereas androgen excess may increase thrombotic and cardiovascular risk.[3-4]

Neuropsychiatric manifestations

Androgens play a significant neuromodulatory role, influencing mood regulation, cognitive performance, and neuroprotective processes within the central nervous system.[9-10,21,188] Through androgen receptor–mediated mechanisms, these hormones contribute to synaptic plasticity, neuronal survival, and modulation of neurotransmitter systems involved in emotional and cognitive function. Declining androgen levels have been associated with increased vulnerability to neuropsychiatric disturbances, including depressive symptoms, reduced vitality, and cognitive decline.[189-190] Such observations support the concept that hypoandrogenism may contribute to alterations in brain function beyond reproductive aging. Therapeutic strategies like TRT, delivered via injections, gels, or patches, have shown efficacy in improving mood and cognition,[21,191] while SARMs are being developed to maximize neural benefits with fewer side effects.[15,192]

Immune and inflammatory regulation

Androgens are pivotal in maintaining immune tolerance through coordinated regulation of central and peripheral mechanisms.[5] Within the thymus, physiological androgen signaling accelerates thymic involution and shapes negative selection of autoreactive T cells, influencing central tolerance and TCR diversity.[193-195] Peripherally, androgens suppress NF-κB and STAT pathways, promote Treg and anti-inflammatory macrophage phenotypes, and restrain cytokine-driven inflammation (Figure 6).[6-7] Deficiency weakens tolerance, increasing pro-inflammatory cytokines and autoimmune risk, whereas excess may induce low-grade inflammation and metabolic dysfunction.[196] Androgen receptor expression across immune cells highlights their systemic immunoregulatory role.[197] Therapeutically, androgen replacement or selective AR modulators (SARMs) can restore Treg balance and suppress autoimmunity, while androgen blockade may transiently enhance thymic output and antitumor immunity.[194,198] Nutritional cofactors such as zinc, vitamin D, omega-3 fatty acids, and polyphenols synergize by supporting steroidogenesis and reducing NF-κB–mediated inflammation, thereby sustaining immune tolerance and endocrine homeostasis.[35,108-110,136-137,199]

The systemic impact of androgen imbalance extends beyond reproductive function, influencing metabolic, cardiovascular, skeletal, and neuropsychological health. Table 1 summarizes the major organ-specific effects associated with androgen excess and deficiency, providing a framework for understanding subsequent therapeutic interventions.[6,12,18,129,148,194,200-201]

Therapeutic strategies

Modern therapeutic strategies targeting androgen abnormalities encompass a spectrum of pharmacologic approaches designed to restore hormonal balance, attenuate pathological androgen signaling, or selectively modulate AR activity. TRT remains the principal intervention for individuals with confirmed androgen deficiency, aiming to re-establish physiological androgen concentrations and improve musculoskeletal, metabolic, and neuropsychiatric outcomes.[18,148,152]

Conversely, conditions characterized by androgen excess or heightened AR signaling frequently require androgen-lowering or receptor-blocking strategies. Anti-androgens primarily act through competitive inhibition of AR activation, whereas 5α-reductase inhibitors suppress the local conversion of testosterone to the more potent DHT, thereby attenuating tissue-specific androgen effects.[202-203]

In oncology and selected hyperandrogenic states, inhibitors targeting the critical steroidogenic enzyme CYP17A1 represent a key therapeutic class that reduces adrenal and gonadal androgen biosynthesis.[204-205] More recently,

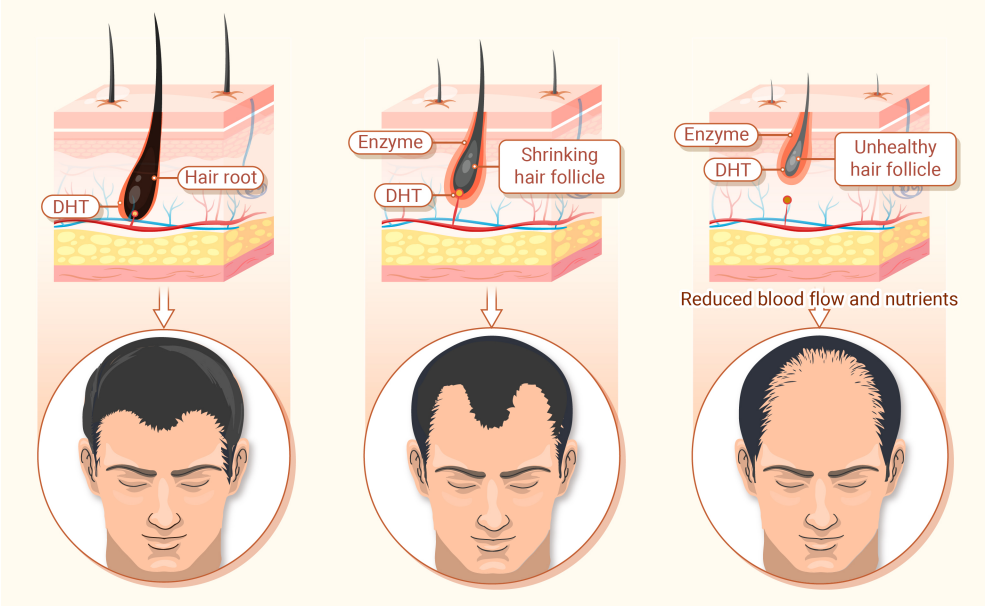

Figure 5. Role of dihydrotestosterone (DHT) in androgenic alopecia. Excessive DHT binds to receptors in hair follicles, triggering follicular miniaturization and reduced blood supply. Over time, this leads to progressive hair thinning and loss, particularly in genetically susceptible individuals, illustrating the hormonal mechanism underlying male pattern baldness.

SARMs have emerged as a promising therapeutic paradigm, offering tissue-selective anabolic benefits while minimizing off-target effects.[15,206] Collectively, these therapies reflect a shift toward mechanism-based androgen modulation, emphasizing individualized treatment selection guided by endocrine, metabolic, and tissue-specific considerations.

Nutritional and metabolic modulation

Nutritional modulation influences androgen biology predominantly through indirect metabolic and regulatory pathways, rather than by directly altering steroidogenic processes.[105] Diet-derived effects are largely mediated via changes in insulin sensitivity, adiposity, mitochondrial function, and systemic inflammatory tone, all of which are well-established determinants of androgen synthesis, metabolism, and receptor signaling. Within this framework, adequate micronutrient status represents a critical permissive factor for physiological steroidogenesis. Essential trace elements and vitamins, including zinc, vitamin D, and magnesium, participate in enzymatic reactions, receptor signaling, and mitochondrial bioenergetics that collectively support androgen production and action.[35]

Equally important, anti-inflammatory nutrients modulate androgen biology by attenuating chronic low-grade inflammation, a condition known to disrupt endocrine signaling.[207-210] Bioactive dietary components such as omega-3 fatty acids and polyphenols suppress pro-inflammatory pathways, including NF-κB activation, thereby mitigating inflammation-induced impairment of steroidogenic enzyme activity and AR function.[207-210] Through these mechanisms, nutritional factors help preserve endocrine stability by improving the systemic metabolic environment rather than acting as direct hormonal regulators. Thus, integrating these dietary strategies with pharmacologic or hormonal therapies may enhance therapeutic efficacy, reduce side effects, and promote systemic metabolic resilience (Figure 7).

Taken together, these observations position nutrition not as a direct regulator of androgen production, but as a critical determinant of the metabolic milieu within which androgen physiology operates. This perspective underscores the necessity of integrating metabolic and endocrine frameworks when interpreting nutrient–hormone interactions, designing mechanistic studies, and developing clinically meaningful intervention strategies.

Safety and clinical monitoring

Safe androgen therapy requires comprehensive baseline assessment and ongoing monitoring to balance efficacy and safety. Baseline measurement of total and free T confirms deficiency, guiding dose selection, while regular testing ensures hormone levels remain within physiological range.[148,211] Evaluation of target organ function is essential, with liver and kidney tests used to monitor potential toxicity, and prostate assessment in men performed through digital rectal examination and prostate-specific antigen (PSA) measurement to detect early adverse changes.[18,212] Common adverse effects—primarily resulting from androgen excess—include erythrocytosis, necessitating hematocrit monitoring to prevent thrombotic complications, as well as occasional cases of hepatic or renal dysfunction.[212-213] In men, prostate volume and PSA should be closely monitored to identify progression of benign prostatic hyperplasia or malignancy.[212] Risk mitigation strategies include dose reduction, treatment interruption, or phlebotomy. Clinical guidelines from the Endocrine Society and European Association of Urology emphasize individualized therapy, contraindication screening, and structured follow-up to optimize therapeutic benefit and minimize adverse.[148,214-215]

MEASUREMENT OF ANDROGENS

Accurate and reliable analytical methods are essential for measurement of androgens. However, existing immunoassay-based methods have several well-recognized limitations, including cross-reactivity, poor accuracy at low concentrations, and poor comparability of results among different manufacturers. These shortcomings have led to a large number of false-positive results for hyperandrogenemia.[216] In contrast, LC-MS/MS offers multiple advantages such as higher sensitivity, higher specificity, a broader linear range, and the ability to simultaneously quantify multiple target analytes, and inter-laboratory comparability, especially at low hormone concentrations, thereby providing a superior method for measuring androgens.[217-219] In recent years, with continuous advancements in instrumentation, improvements in sample preparation techniques, and the incorporation of stable isotope-labeled internal standards, the performance of LC-MS/MS for determining androgen levels has been greatly enhanced.[220]

At present, the Journal of Clinical Endocrinology and Metabolism stipulates that key findings in androgen measurement should be generated using mass spectrometry–based techniques.[26] Similarly, the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS endorses LC–MS/MS as the preferred methodology for assessing total and free testosterone.[200] Worldwide, an increasing number of clinical laboratories have adopted LC–MS/MS for androgen analysis, recognizing it as the analytical reference standard and the "gold standard" for steroid hormone quantification.[221] Notably, LC–MS/MS typically yields lower absolute concentrations than immunoassays yet identifies a greater number of hyperandrogenemic cases, reflecting the limited analytical specificity of immunoassay-based testosterone measurements, particularly in women.[222] Beyond analytical accuracy, LC-MS/MS provides a critical clinical advantage through multiplex steroid profiling. Accumulating evidence indicates that reliance on T alone may lead to a substantial proportion of false-negative classifications of androgen excess.[131,223] Without significant incremental cost, LC–MS/MS platforms enable the simultaneous quantification of multiple clinically relevant androgens, including testosterone, androstenedione (A4), dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), and adrenal-derived 11-oxygenated androgens such as 11-ketotestosterone (11KT), thereby offering a more comprehensive characterization of androgen sources and metabolic pathways.[131,223] Importantly, recent advances in assay development have led to the availability of standardized, commercially developed LC–MS/MS reagent kits enabling integrated androgen panel measurements, including validated detection of 11-oxygenated androgens, thereby improving the feasibility of multidimensional steroid profiling in clinical practice. However, important challenges remain, including the need for harmonized reference

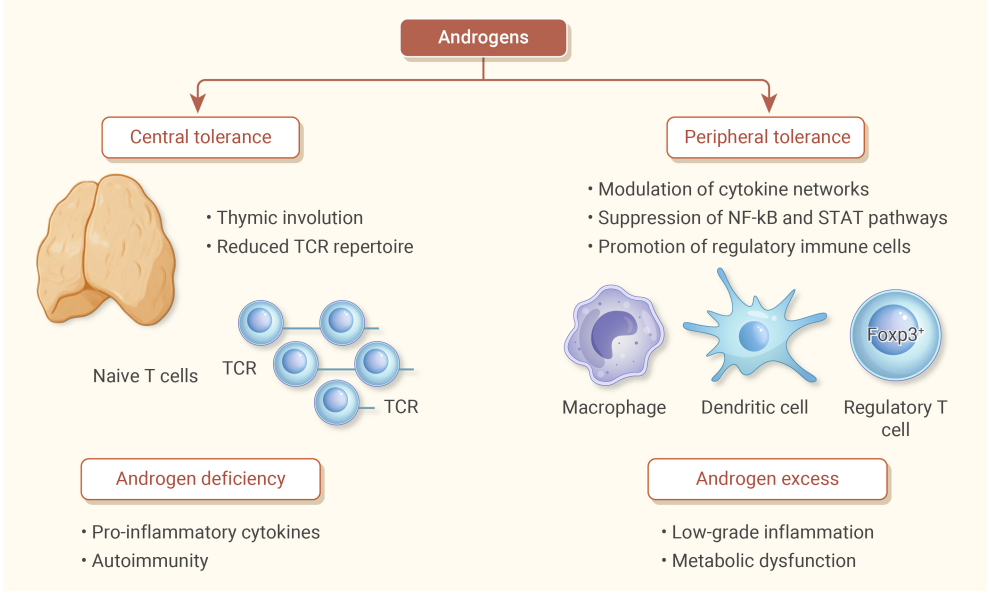

Figure 6. Androgen regulation of central and peripheral immune tolerance. Androgens maintain immune homeostasis by shaping both central and peripheral tolerance. Physiological signaling limits thymic output and modulates cytokine pathways to promote regulatory immune phenotypes, while androgen deficiency favors autoimmune diseases and androgen excess induces low-grade inflammation and metabolic dysfunction.

intervals, outcome-based clinical decision thresholds, and further validation of their clinical utility across diverse populations and disease contexts.

In circulation, T—representative of most androgens—exists in multiple binding states: a free fraction, a loosely albumin-bound fraction, and a tightly bound fraction complexed with SHBG.[224] The sum of the free and albumin-bound fractions is defined as bioavailable T, reflecting the hormonally active pool accessible to tissues.[225] This binding pattern also applies to other androgens such as A_4 and 11-oxygenated derivatives, which similarly distribute between free and protein-bound forms in plasma.[12,224]

Free or bioavailable T correlates more strongly with clinical manifestations than total T.[123] Free T can be determined using equilibrium dialysis, while bioavailable T is commonly assessed by ammonium sulfate precipitation, a method in which 50% ammonium sulfate selectively removes the SHBG-bound fraction.[225] Given the labor-intensive nature of these techniques, most laboratories measure total T, SHBG, and albumin concentrations and then estimate free or bioavailable T using validated calculation formulas.[225] Although the calculated values correlate reasonably with precipitation results, substantial deviations are common.[225] Hence, when resources permit, direct measurement by ammonium sulfate precipitation remains the reference approach for accurately quantifying bioavailable T. The American Association of Clinical Endocrinologists (AACE), along with other professional organizations, noted in their 2015 PCOS clinical guidelines that free T is a more sensitive marker of androgen excess than total T and recommended its measurement using the equilibrium dialysis technique.[226] Therefore, when laboratories perform T testing, total T should be measured first, followed, where possible, by measurement of free or bioavailable T, preferably using equilibrium dialysis or ammonium sulfate precipitation. If direct measurement is not feasible, potential biases should be carefully considered, and calculation formulas and constants should be optimized to minimize deviation between calculated and measured values. Table 2 lists a comparison between direct measurement methods and indirect calculation methods for T determination.

CRITICAL PERSPECTIVES, METHODOLOGICAL LIMITATIONS, AND FUTURE DIRECTIONS

The evolving understanding of androgen biology has underscored the complexity and heterogeneity of androgen metabolism and signaling across individuals. Despite significant advances in androgen-related diagnostics and therapeutics, several critical challenges and promising research avenues remain. Addressing these will be pivotal for refining precision medicine approaches and optimizing clinical outcomes in androgen-related disorders.

Beyond measurement precision: mass spectrometry, biological age frameworks, and AI-driven endocrine interpretation

Accurate and standardized measurement of androgen biomarkers is fundamental to both mechanistic understanding and clinical translation. Although immunochemiluminescence assays remain widely adopted because of their operational convenience and scalability, intrinsic analytical limitations — including cross-reactivity, restricted specificity, and suboptimal sensitivity at low concentrations — constrain reliable quantification of structurally related or low-abundance steroids.[227-228] These constraints are particularly relevant for emerging biomarkers such as 11-oxygenated androgens (e.g., 11KT), for which robust immunoassay platforms remain limited. In contrast, LC-MS/MS offers superior analytical specificity, sensitivity, and multiplex capability, enabling simultaneous profiling of classical and newly recognized adrenal-derived androgens.[26-27] Beyond improved accuracy, a critical advantage of mass spectrometry lies in its capacity to quantify expanding panels of steroidal, metabolic, and nutritional biomarkers within a unified analytical framework. Nonetheless, practical challenges related to throughput, standardization, and inter-platform comparability underscore the necessity for methodological harmonization and clinically meaningful interpretive strategies.[26,229]

However, analytical precision alone does not resolve the central challenge of biomarker interpretation. In women, substantial interindividual heterogeneity in ovarian reserve limits the physiological relevance of conventional chronological age-based reference intervals.[230] To address this limitation, we applied the OvaRePred (HerTempo) framework, integrating AMH with age to derive an individualized ovarian endocrine age.[28] This physiology-anchored metric provides an alternative biological axis for biomarker interpretation. Ovariane-endocrine-age–stratified analyses reveal that ovarian aging–related markers, including AMH, testosterone, and androstenedione, exhibit coherent endocrine-age–dependent trajectories, whereas predominantly adrenal-derived 11-oxygenated androgens (e.g., 11KA4) remain comparatively stable and are less influenced by ovarian aging dynamics. These findings suggest that physiology-specific age models may improve biological resolution and reduce variability inherent to population-averaged reference systems.

Importantly, the broader conceptual implication extends beyond ovarian biology. As LC-MS/MS increasingly enables quantification of novel biomarkers linked to diverse physiological aging processes, interpretation frameworks anchored to domain-specific biological age metrics may offer enhanced clinical coherence. In principle, biomarkers associated with ovarian, thymic, or metabolic aging may benefit from integration with corresponding AI-derived physiological age models, rather than reliance on chronological age alone. We acknowledge that this integrative paradigm remains largely hypothesis-driven. The present work therefore represents an exploratory attempt focused on ovarian aging, where preliminary observations indicate that ovarian endocrine age-based reference stratification may enhance diagnostic resolution within precision endocrinology.

The integration of high-precision mass spectrometry profiling with artificial intelligence further expands the translational potential of multidimensional biomarker assessment. AI-based models can incorporate complex biochemical panels alongside physiological age metrics, metabolic context, receptor variability, comorbidities, and therapeutic exposures to generate individualized interpretive insights.[28-31,231-236] Looking forward, the convergence of multiplex biochemical measurement, physiology-anchored AI frameworks, and longitudinal monitoring strategies may form the methodological foundation of next-generation precision endocrine diagnostics and

Table 1. Systemic effects of androgen excess and deficiencys.

System / Organ	Androgen Excess	Androgen Deficiency
Reproductive system	Women: Polycystic ovary syndrome (PCOS), anovulation, infertility; Men: Feedback suppression of the HPG axis leading to testicular atrophy, oligozoospermia, and erectile dysfunction (ED) due to vascular, endothelial, and neurogenic imbalance; may also contribute to prostate hyperplasia and inflammation	Women: Decreased libido, or ovarian insufficiency; Men: Late-onset hypogonadism, reduced libido, ED, infertility, and prostatic atrophy or chronic prostatitis
Metabolic system	Insulin resistance, central obesity, dyslipidemia, increased risk of metabolic syndrome	Reduced lean mass(Sarcopenia), increased adiposity, insulin resistance, metabolic syndrome risk
Cardiovascular system	Hypertension, endothelial dysfunction, pro-atherogenic lipid profile	Decreased vascular tone, endothelial dysfunction, increased atherosclerosis risk
Skeletal system	Early increase in bone mass but potential imbalance in remodeling	Decreased bone mineral density, osteoporosis, fracture risk
Skin and appendages	Acne, seborrhea, hirsutism, androgenic alopecia	Dry skin, decreased sebum, reduced hair growth
Neuropsychological system	Irritability, aggression, anxiety	Fatigue, depression, cognitive decline
Hepatic / hematologic system	Erythrocytosis, hepatic enzyme elevation (esp. with exogenous androgens)	Anemia, reduced erythropoiesis
Immune / inflammatory system	Low-grade inflammation, oxidative stress increase	Reduced immune resilience, pro-inflammatory shift with aging

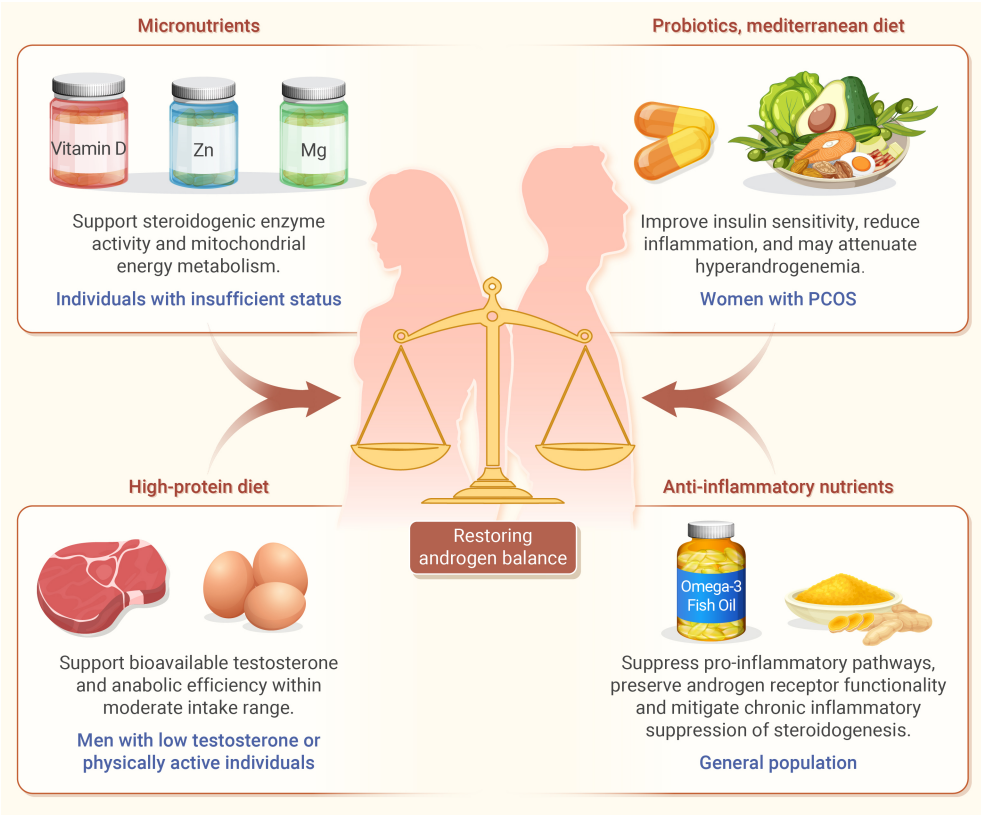

Figure 7. Nutritional strategies for restoring androgen balance across diverse populations. This figure highlights key dietary approaches that influence androgen synthesis and signaling. Micronutrients (vitamin D, zinc, magnesium) enhance steroidogenic activity, while probiotics and Mediterranean-style diets improve insulin sensitivity and reduce hyperandrogenemia in women with PCOS. High-protein intake supports bioavailable testosterone in men with low levels, and anti-inflammatory nutrients such as omega-3 fatty acids help preserve androgen receptor function. Together, these interventions contribute to maintaining androgen homeostasis.

personalized androgen management.

Toward precision nutrition in androgen regulation: from association to actionable biology

Future advances in nutrition-based modulation of androgen biology will require a transition from association-driven hypotheses to measurement-centered, biologically grounded frameworks. Nutritional and microbiota-related effects on androgens are predominantly indirect, mediated through systemic metabolic processes and strongly influenced by individual context. Under these conditions, precision nutrition cannot be meaningfully built on self-reported dietary data, isolated nutrient supplementation, or testosterone-centered assessment alone.

The feasibility of precision nutritional endocrinology depends on high-resolution phenotyping. Comprehensive androgen panels—particularly those including adrenal-derived, metabolically sensitive androgens such as 11-oxygenated species—should be integrated with quantitative nutritional biomarkers, metabolomic profiling, and microbiome-derived functional outputs. Within this framework, androgens are better conceptualized as endocrine readouts of metabolic state, insulin sensitivity, and inflammatory burden, rather than as direct targets of dietary manipulation.

Accordingly, future research should move away from the search for universal "androgen-modulating nutrients" and toward defining endocrine–metabolic response patterns under controlled nutritional perturbations. When combined with AI-enabled modeling, such approaches enable stratification based on biological response rather than dietary exposure alone. Only through the convergence of precise measurement, metabolic context, and computational integration can personalized nutritional strategies be rationally designed to optimize androgen-related outcomes across reproductive, metabolic, and musculoskeletal health.

Methodological limitations

Despite growing interest in androgen–nutrition interactions, several conceptual and methodological limitations continue to constrain progress. A central issue is the historical over-reliance on simplified endocrine paradigms, particularly the use of total testosterone as a proxy for global

Table 2. Comparison Between Direct Measurement and Indirect Calculation Methods for Testosterone Determination.

Analyte	Form in Circulation	Direct Measurement Method	Indirect Calculation	Advantages / Disadvantages of Direct Measurement	Advantages / Disadvantages of Indirect Calculation
Total Androgens	Free androgens + protein-bound Androgens	Direct measurement, preferably by LC-MS/MS	None	LC-MS/MS provides high specificity and accuracy	None
Free Androgens	Completely unbound Androgens	Equilibrium dialysis method	Requires measurement of total androgens and SHBG, then calculated using formulas	High accuracy but complex procedure and costly	Simple and inexpensive, but may show large bias in specific populations
Bioavailable Androgens	Free + albumin-bound androgens (non–SHBG-bound fraction)	50% ammonium sulfate precipitation method	Requires measurement of total androgens, albumin, and SHBG, then calculated using formulas	High accuracy but labor-intensive and technically demanding	Easy to perform but sometimes shows large deviation; formulas and constants must be carefully optimized

androgen status. This approach fails to capture the complexity of androgen biosynthesis, peripheral metabolism, and tissue-specific action, especially in women and metabolically heterogeneous populations. Although 11-oxygenated androgens are increasingly recognized as clinically relevant, they remain underrepresented in most human studies, limiting mechanistic resolution and cross-study comparability.

Measurement infrastructure represents an additional bottleneck. Much of the existing literature relies on immunoassay-based hormone data, which are vulnerable to cross-reactivity, poor sensitivity at low concentrations, and inter-platform variability. While LC-MS/MS offers superior analytical performance and multiplex capability, its adoption in large-scale clinical and nutritional studies remains incomplete. Similarly, nutritional and metabolic phenotyping is often limited by semi-quantitative dietary questionnaires and incomplete metabolite assessment, rendering causal inference highly susceptible to confounding by adiposity, insulin resistance, medication use, and genetic background.

Finally, most available evidence is cross-sectional or derived from small observational cohorts, precluding robust causal inference or temporal modeling. Future progress will require integrated, longitudinal designs combining precise endocrine measurement, quantitative nutritional and metabolic profiling, and advanced analytical frameworks. Without such methodological rigor, the promise of precision androgen medicine and nutrition will remain conceptually compelling but empirically fragile.

CONCLUSION

Androgens and their metabolites are central regulators of reproductive, metabolic, skeletal, cardiovascular, and neural health. Dysregulated androgen signaling contributes to conditions spanning infertility, metabolic syndrome, sarcopenia, and neurodegenerative diseases. Recent advances in androgen metabolism and receptor biology, along with the early integration of AI-based endocrine-age modeling tools such as OvaRePred, are opening new possibilities for individualized androgen reference ranges and diagnostic interpretation. Although still at an initial stage, these AI frameworks complement mass spectrometric precision and hold promise for next-generation androgen profiling and personalized endocrine medicine.

Beyond pharmacologic modulation, emerging evidence underscores the synergistic role of clinical nutrition in androgen regulation. Micronutrients such as vitamin D, zinc, and magnesium support steroidogenesis and receptor function, while omega-3 fatty acids, polyphenols, and probiotics mitigate inflammation and restore endocrine–metabolic homeostasis. Integrating nutritional precision with pharmacologic, behavioral, and digital health strategies represents a multidimensional approach to maintaining androgen balance across the lifespan. Ultimately, harmonizing endocrine, metabolic, and nutritional pathways through precision medicine will be key to transforming androgen-related disease management and promoting systemic health resilience.

REFERENCES

1. Gerald T. and Raj G. (2022). Testosterone and the androgen receptor. *Urol. Clin. North Am.* **49**:603–614. DOI:10.1016/j.ucl.2022.07.004
2. Mooradian A.D., Morley J.E. and Korenman S.G. (1987). Biological actions of androgens. *Endocr. Rev.* **8**:1–28. DOI:10.1210/edrv-8-1-1
3. Pepene C.E.G. (2011). Androgen excess as a major determinant of cardiovascular risk in women: Evidence from the polycystic ovary syndrome. *Acta Endocrinol-Buch.* **7**:529–533. DOI:10.4183/aeb.2011.529
4. Lopes R.A.M., Neves K.B., Carneiro F.S., et al. (2012). Testosterone and vascular function in aging. *Front. Physiol.* **3**:89. DOI:10.3389/fphys.2012.00089
5. Ben-Batalla I., Vargas-Delgado M.E., von Amsberg G., et al. (2020). Influence of androgens on immunity to self and foreign: Effects on immunity and cancer. *Front. Immunol.* **11**:1184. DOI:10.3389/fimmu.2020.01184
6. Becerra-Diaz M., Song M. and Heller N. (2020). Androgen and androgen receptors as regulators of monocyte and macrophage biology in the healthy and diseased lung. *Front. Immunol.* **11**:1698. DOI:10.3389/fimmu.2020.01698
7. Basilio J., Hochreiter B., Hoesel B., et al. (2022). Antagonistic functions of androgen receptor and NF-κB in prostate cancer-experimental and computational analyses. *Cancers* **14**:6164. DOI:10.3390/cancers14246164
8. Rupp M.R.G. and Jorgensen T.N. (2018). Androgen-induced immunosuppression. *Front. Immunol.* **9**:794. DOI:10.3389/fimmu.2018.00794
9. Walther A. and Seuffert J. (2020). Testosterone and dehydroepiandrosterone treatment in ageing men: Are we all set. *World J. Mens Health* **38**:178–190. DOI:10.5534/wjmh.190006
10. Pan X.F., Wu X.Y., Kaminga A.C., et al. (2019). Dehydroepiandrosterone and dehydroepiandrosterone sulfate in Alzheimer's disease: A systematic review and meta-analysis. *Front. Aging Neurosci.* **11**:61. DOI:10.3389/fnagi.2019.00061
11. Storbeck K.H., Bloem L.M., Africander D., et al. (2013). 11β-hydroxydihydrotestosterone and 11-ketodihydrotestosterone, novel C19 steroids with androgenic activity: A putative role in castration resistant prostate cancer. *Mol. Cell. Endocrinol.* **377**:135–146. DOI:10.1016/j.mce.2013.07.006
12. Turcu A.F., Rege J., Auchus R.J., et al. (2020). 11-oxygenated androgens in health and disease. *Nat. Rev. Endocrinol.* **16**:284–296. DOI:10.1038/s41574-020-0336-x
13. Pretorius E., Africander D.J., Vlok M., et al. (2016). 11-ketotestosterone and 11-ketodihydrotestosterone in castration resistant prostate cancer: Potent androgens which can no longer be ignored. *PLoS One* **11**:e0159867. DOI:10.1371/journal.pone.0159867
14. Storbeck K.H. and O'Reilly M.W. (2023). The clinical and biochemical significance of 11-oxygenated androgens in human health and disease. *Eur. J. Endocrinol.* **188**:R98–R109. DOI:10.1093/ejendo/lvad047
15. Solomon Z.J., Mirabal J.R., Mazur D.J., et al. (2019). Selective androgen receptor modulators: Current knowledge and clinical applications. *Sex. Med. Rev.* **7**:84–94. DOI:10.1016/j.sxmr.2018.09.006
16. Chen J.G., Sowers M.R., Moran F.M., et al. (2006). Circulating bioactive androgens in midlife women. *J. Clin. Endocrinol. Metab.* **91**:4387–4394. DOI:10.1210/jc.2006-0284
17. Christiansen A.R., Lipshultz L.I., Hotaling J.M., et al. (2020). Selective androgen receptor modulators: The future of androgen therapy. *Transl. Androl. Urol.* **9**:S135–S148. DOI:10.21037/tau.2019.11.02
18. Bhasin S., Cunningham G.R., Hayes F.J., et al. (2021). Testosterone therapy in adult men with androgen deficiency syndromes: An endocrine society clinical practice guideline (vol 91, pg 1995, 2006). *J. Clin. Endocrinol. Metab.* **106**:E2843–E2843. DOI:10.1210/clinem/dgab306
19. Chen J.F., Lin P.W., Tsai Y.R., et al. (2019). Androgens and androgen receptor actions on bone health and disease: From androgen deficiency to androgen therapy. *Cells* **8**:1318. DOI:10.3390/cells8111318
20. Bhasin S., Woodhouse L., Casaburi R., et al. (2001). Testosterone dose-response relationships in healthy young men. *Am. J. Physiol. Endocrinol. Metab.* **281**:E1172–E1181. DOI:10.1152/ajpendo.2001.281.6.E1172
21. Wang B.L., Liu X.Q., Chen W.X., et al. (2025). Effects of androgen replacement therapy on cognitive function in patients with hypogonadism: A systematic review

and meta-analysis. *Biomed. Rep.* **22**:105. DOI:10.3892/br.2025.1983
22. Azziz R., Carmina E., Dewailly D., et al. (2009). The androgen excess and PCOS society criteria for the polycystic ovary syndrome: The complete task force report. *Fertil. Steril.* **91**:456–488. DOI:10.1016/j.fertnstert.2008.06.035
23. O'Reilly M.W., Kempegowda P., Jenkinson C., et al. (2017). 11-oxygenated C19 steroids are the predominant androgens in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **102**:840–848. DOI:10.1210/jc.2016-3285
24. Di Guardo F., Cerana M.C., D'urso G., et al. (2019). Male PCOS equivalent and nutritional restriction: Are we stepping forward. *Med. Hypotheses* **126**:1–3. DOI:10.1016/j.mehy.2019.03.003
25. Sharma A. and Welt C.K. (2021). Practical approach to hyperandrogenism in women. *Med. Clin. North Am.* **105**:1099–1116. DOI:10.1016/j.mcna.2021.06.008
26. Handelsman D.J. and Wartofsky L. (2013). Requirement for mass spectrometry sex steroid assays in the journal of clinical endocrinology and metabolism. *J. Clin. Endocrinol. Metab.* **98**:3971–3973. DOI:10.1210/jc.2013-3375
27. Karashima S. and Osaka I. (2022). Rapidity and precision of steroid hormone measurement. *J. Clin. Med.* **11**:956. DOI:10.3390/jcm11040956
28. Xu H.Y., Feng G.S., Yang R., et al. (2025). OvaRePred (HerTempo): An enhanced ovarian aging clock for personalized reserve assessment, endocrine age modeling, and predicting reproductive milestones across the female lifecycle. *Front. Endocrinol.* **16**:1658068. DOI:10.3389/fendo.2025.1658068
29. Dai J., Xu H., Chen T., et al. (2025). Artificial intelligence for medicine 2025: Navigating the endless frontier. *Innov. Med.* **3**:100120. DOI:10.59717/j.xinn-med.2025.100120
30. Huang T., Xu H., Wang H., et al. (2023). Artificial intelligence for medicine: Progress, challenges, and perspectives. *Innov. Med.* **1**:100030. DOI:10.59717/j.xinn-med.2023.100030
31. Feng G., Xu H., Wan S., et al. (2024). Twelve practical recommendations for developing and applying clinical predictive models. *Innov. Med.* **2**:100105. DOI:10.59717/j.xinn-med.2024.100105
32. Whittaker J. and Wu K.X. (2021). Low-fat diets and testosterone in men: Systematic review and meta-analysis of intervention studies. *J. Steroid Biochem.* **210**:105878. DOI:10.1016/j.jsbmb.2021.105878
33. Pilz S., Trummer C., Pandis M., et al. (2018). Vitamin D: Current guidelines and future outlook. *Anticancer Res.* **38**:1145–1151. DOI:10.21873/anticanres.12333
34. Maggio M., De Vita F., Lauretani F., et al. (2014). The interplay between magnesium and testosterone in modulating physical function in men. *Int. J. Endocrinol.* **2014**:525249. DOI:10.1155/2014/525249
35. Te L.G., Liu J.S., Ma J., et al. (2023). Correlation between serum zinc and testosterone: A systematic review. *J. Trace Elem. Med. Biol.* **76**:127124. DOI:10.1016/j.jtemb.2022.127124
36. Pearce K.L. and Tremellen K. (2019). The effect of macronutrients on reproductive hormones in overweight and obese men: A pilot study. *Nutrients* **11**:3390. DOI:10.3390/nu11123059
37. Fricke C. and Voderholzer U. (2023). Endocrinology of underweight and anorexia nervosa. *Nutrients* **15**:3059. DOI:10.3390/nu15163509
38. Colldén H., Landin A., Wallenius V., et al. (2019). The gut microbiota is a major regulator of androgen metabolism in intestinal contents. *Am. J. Physiol. Endocrinol. Metab.* **317**:E1182–E1192. DOI:10.1152/ajpendo.00338.2019
39. Matsushita M., Fujita K., Motooka D., et al. (2022). Firmicutes in gut microbiota correlate with blood testosterone levels in elderly men. *World J. Mens Health* **40**:517–525. DOI:10.5534/wjmh.210190
40. Santos-Marcos J.A., Mora-Ortiz M., Tena-Sempere M., et al. (2023). Interaction between gut microbiota and sex hormones and their relation to sexual dimorphism in metabolic diseases. *Biol. Sex Differ.* **14**:4. DOI:10.1186/s13293-023-00490-2
41. Cai H., Cao X.H., Qin D.Z., et al. (2022). Gut microbiota supports male reproduction nutrition, immunity, and signaling. *Front. Microbiol.* **13**:977574. DOI:10.3389/fmicb.2022.977574
42. Penning T.M. (2010). New frontiers in androgen biosynthesis and metabolism. *Curr. Opin. Endocrinol.* **17**:233–239. DOI:10.1097/MED.0b013e3283381a31
43. Erickson G.F., Magoffin D.A., Dyer C.A., et al. (1985). The ovarian androgen producing cells - a review of structure-function relationships. *Endocr. Rev.* **6**:371–399. DOI:10.1210/edrv-6-3-371
44. Zirkin B.R. and Papadopoulos V. (2018). Leydig cells: Formation, function, and regulation. *Biol. Reprod.* **99**:101–111. DOI:10.1093/biolre/ioy059
45. Blouin K., Richard C., Brochu G., et al. (2006). Androgen inactivation and steroid-converting enzyme expression in abdominal adipose tissue in men. *J. Endocrinol.* **191**:637–649. DOI:10.1677/joe.1.06365
46. Marchetti P.M. and Barth J.H. (2013). Clinical biochemistry of dihydrotestosterone. *Ann. Clin. Biochem.* **50**:95–107. DOI:10.1258/acb.2012.012159
47. Paulukinas R.D., Mesaros C.A. and Penning T.M. (2022). Conversion of classical and 11-oxygenated androgens by insulin-induced AKR1C3 in a model of human PCOS adipocytes. *Endocrinology* **163**:bqac068. DOI:10.1210/endocr/bqac068
48. Acevedo-Rodriguez A., Kauffman A.S., Cherrington B.D., et al. (2018). Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling. *J. Neuroendocrinol.* **30**:e12590. DOI:10.1111/jne.12590
49. Payne A.H. and Hales D.B. (2004). Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. *Endocr. Rev.* **25**:947–970. DOI:10.1210/er.2003-0030
50. Santi D., Crépieux P., Reiter E., et al. (2020). Follicle-stimulating hormone (FSH) action on spermatogenesis: A focus on physiological and therapeutic roles. *J. Clin. Med.* **9**:1014. DOI:10.3390/jcm9041014
51. Muttukrishna S., Suharjono H., McGarrigle H., et al. (2004). Inhibin B and anti-Mullerian hormone: Markers of ovarian response in IVF/ICSI patients. *Bjog-Int. J. Obstet. Gy.* **111**:1248–1253. DOI:10.1111/j.1471-0528.2004.00452.x
52. Handa R.J. and Weiser M.J. (2014). Gonadal steroid hormones and the hypothalamo-pituitary-adrenal axis. *Front. Neuroendocrin.* **35**:197–220. DOI:10.1016/j.yfrne.2013.11.001
53. Pignatelli D., Xiao F., Gouveia A.M., et al. (2006). Adrenarche in the rat. *J. Endocrinol.* **191**:301–308. DOI:10.1677/joe.1.06972
54. Auchus R.J. and Rainey W.E. (2004). Adrenarche - physiology, biochemistry and human disease. *Clin. Endocrinol.* **60**:288–296. DOI:10.1046/j.1365-2265.2003.01858.x
55. Tomlinson J.W., Walker E.A., Bujalska I.J., et al. (2004). 11β-hydroxysteroid dehydrogenase type 1: A tissue-specific regulator of glucocorticoid response. *Endocr. Rev.* **25**:831–866. DOI:10.1210/er.2003-0031
56. Makridakis N.M., di Salle E. and Reichardt J.K.V. (2000). Biochemical and pharmacogenetic dissection of human steroid 5α-reductase type II. *Pharmacogenetics* **10**:407–413. DOI:10.1097/00008571-200007000-00004
57. Labrie F., Luu-The V., Bélanger A., et al. (2005). Is dehydroepiandrosterone a hormone. *J. Endocrinol.* **187**:169–196. DOI:10.1677/joe.1.06264
58. Wilson J.D., Griffin J.E. and Russell D.W. (1993). Steroid 5-alpha-reductase-2 deficiency. *Endocr. Rev.* **14**:577–593. DOI:10.1210/er.14.5.577
59. Simpson E.R., Mahendroo M.S., Means G.D., et al. (1994). Aromatase cytochrome-P450, the enzyme responsible for estrogen biosynthesis. *Endocr. Rev.* **15**:342–355. DOI:10.1210/er.15.3.342
60. Penning T.M. and Drury J.E. (2007). Human aldo-keto reductases: Function, gene regulation, and single nucleotide polymorphisms. *Arch. Biochem. Biophys.* **464**:241–250. DOI:10.1016/j.abb.2007.04.024
61. Tukey R.H. and Strassburg C.P. (2000). Human UDP-glucuronosyltransferases: Metabolism, expression, and disease. *Annu. Rev. Pharmacol.* **40**:581–616. DOI:10.1146/annurev.pharmtox.40.1.581
62. Isoherranen N. and Thummel K.E. (2013). Drug metabolism and transport during pregnancy: How does drug disposition change during pregnancy and what are the mechanisms that cause such changes. *Drug Metab. Dispos.* **41**:256–262. DOI:10.1124/dmd.112.050245
63. Rege J. and Rainey W.E. (2012). The steroid metabolome of adrenarche. *J. Endocrinol.* **214**:133–143. DOI:10.1530/Joe-12-0183
64. Slominski A.T., Manna P.R. and Tuckey R.C. (2015). On the role of skin in the regulation of local and systemic steroidogenic activities. *Steroids* **103**:72–88. DOI:10.1016/j.steroids.2015.04.006
65. O'Reilly M.W., House P.J. and Tomlinson J.W. (2014). Understanding androgen action in adipose tissue. *J. Steroid Biochem.* **143**:277–284. DOI:10.1016/j.jsbmb.2014.04.008
66. Bujalska I.J., Kumar S. and Stewart P.M. (1997). Does central obesity reflect "Cushing's disease of the omentum". *Lancet* **349**:1210–1213. DOI:10.1016/S0140-6736(96)11222-8
67. Miller W.L. and Auchus R.J. (2011). The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocr. Rev.* **32**:81–151. DOI:10.1210/er.2010-0013
68. Brinkmann A.O., Faber P.W., Vanrooij H.C.J., et al. (1989). The human androgen receptor - domain-structure, genomic organization and regulation of expression. *J. Steroid Biochem.* **34**:307–310. DOI:10.1016/0022-4731(89)90098-8
69. Swerdloff R.S. and Wang C. (2008). Free testosterone measurement by the analog displacement direct assay: Old concerns and new evidence. *Clin. Chem.* **54**:458–460. DOI:10.1373/clinchem.2007.101303
70. Cumming D.C. and Wall S.R. (1985). Non-sex hormone-binding globulin-bound testosterone as a marker for hyperandrogenism. *J. Clin. Endocrinol. Metab.* **61**:873–876. DOI:10.1210/jcem-61-5-873
71. Hammond G.L. (2016). Plasma steroid-binding proteins: Primary gatekeepers of steroid hormone action. *J. Endocrinol.* **230**:R13–R25. DOI:10.1530/Joe-16-0070
72. Gilliland J.M., Kirk J. and Smeaton T.C. (1981). Normalized androgen ratio - its application to clinical dermatology. *Clin. Exp. Dermatol.* **6**:349–353. DOI:10.1111/j.1365-2230.1981.tb02317.x
73. Gyawali P., Martin S.A., Heilbronn L.K., et al. (2018). Cross-sectional and longitudinal determinants of serum sex hormone binding globulin (SHBG) in a cohort of community-dwelling men. *PLoS One* **13**:e0200078. DOI:10.1371/journal.pone.0200078
74. Cooper L.A., Page S.T., Amory J.K., et al. (2015). The association of obesity with sex hormone-binding globulin is stronger than the association with ageing - implications for the interpretation of total testosterone measurements. *Clin. Endocrinol.* **83**:828–833. DOI:10.1111/cen.12768
75. Plymate S.R., Moore D.E., Cheng C.Y., et al. (1985). Sex hormone-binding globulin changes during the menstrual-cycle. *J. Clin. Endocrinol. Metab.* **61**:993–996. DOI:10.1210/jcem-61-5-993
76. Muka T., Nano J., Jaspers L., et al. (2017). Associations of steroid sex hormones and

sex hormone-binding globulin with the risk of type 2 diabetes in women: A population-based cohort study and meta-analysis. *Diabetes* **66**:577–586. DOI:10.2337/db16-0473
77. Ciarambino T., Crispino P., Leto G., et al. (2022). Influence of gender in diabetes mellitus and its complication. *Int. J. Mol. Sci.* **23**:8850. DOI:10.3390/ijms23168850
78. Kerlan V., Nahoul K., Lemartelot M.T., et al. (1994). Longitudinal-study of maternal plasma bioavailable testosterone and androstanediol glucuronide levels during pregnancy. *Clin. Endocrinol.* **40**:263–267. DOI:10.1111/j.1365-2265.1994.tb02478.x
79. Panzer C., Wise S., Fantini G., et al. (2006). Impact of oral contraceptives on sex hormone-binding globulin and androgen levels: A retrospective study in women with sexual dysfunction. *J. Sex. Med.* **3**:104–113. DOI:10.1111/j.1743-6109.2005.00198.x
80. Tchernof A. and Després J.P. (2000). Sex steroid hormones, sex hormone-binding globulin, and obesity in men and women. *Horm. Metab. Res.* **32**:526–536. DOI:10.1055/s-2007-978681
81. Zhu J.L., Chen Z., Feng W.J., et al. (2019). Sex hormone-binding globulin and polycystic ovary syndrome. *Clin. Chim. Acta* **499**:142–148. DOI:10.1016/j.cca.2019.09.010
82. Manni A., Pardridge W.M., Cefalu W., et al. (1985). Bioavailability of albumin-bound testosterone. *J. Clin. Endocrinol. Metab.* **61**:705–710. DOI:10.1210/jcem-61-4-705
83. Raivio T., Palvimo J.J., Dunkel L., et al. (2001). Novel assay for determination of androgen bioactivity in human serum. *J. Clin. Endocrinol. Metab.* **86**:1539–1544. DOI:10.1210/jc.86.4.1539
84. Riadfahmy D., Read G.F., Walker R.F., et al. (1982). Steroids in saliva for assessing endocrine function. *Endocr. Rev.* **3**:367–395. DOI:10.1210/edrv-3-4-367
85. Del Rosso J.Q. and Kircik L. (2024). The cutaneous effects of androgens and androgen-mediated sebum production and their pathophysiologic and therapeutic importance in acne vulgaris. *J. Dermatol. Treat.* **35**:2298878. DOI:10.1080/09546634.2023.2298878
86. Vass R.A., Bell E.F., Roghair R.D., et al. (2023). Insulin, testosterone, and albumin in term and preterm breast milk, donor milk, and infant formula. *Nutrients* **15**:1476. DOI:10.3390/nu15061476
87. Celec P., Ostatníková D. and Hodosy J. (2015). On the effects of testosterone on brain behavioral functions. *Front. Neurosci.* **9**:12. DOI:10.3389/fnins.2015.00012
88. Ryberg H., Norlén A.K., Landin A., et al. (2024). Sex steroid levels in corresponding cerebrospinal fluid and serum samples quantified by mass spectrometry in men. *Endocr. Connect.* **13**:e230250. DOI:10.1530/EC-23-0250
89. Quigley C.A. (1995). Androgen receptor defects - historical, clinical, and molecular perspectives (vol 16, pg 271, 1995). *Endocr. Rev.* **16**:546–546. DOI:10.1210/edrv-16-3-271
90. Bhasin S., Storer T.W., Berman N., et al. (1996). The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N. Engl. J. Med.* **335**:1–7. DOI:10.1056/nejm199607043350101
91. Heemers H.V. and Tindall D.J. (2007). Androgen receptor (AR) coregulators: A diversity of functions converging on and regulating the AR transcriptional complex. *Endocr. Rev.* **28**:778–808. DOI:10.1210/er.2007-0019
92. Forger N.G. (2009). Control of cell number in the sexually dimorphic brain and spinal cord. *J. Neuroendocrinol.* **21**:393–399. DOI:10.1111/j.1365-2826.2009.01825.x
93. Regitz-Zagrosek V., Lehmkuhl E. and Mahmoodzadeh S. (2007). Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gender Med.* **4**:S162–S177. DOI:10.1016/S1550-8579(07)80056-8
94. Bennett N.C., Gardiner R.A., Hooper J.D., et al. (2010). Molecular cell biology of androgen receptor signalling. *Int. J. Biochem. Cell Biol.* **42**:813–827. DOI:10.1016/j.biocel.2009.11.013
95. Uhlen M., Fagerberg L., Hallström B.M., et al. (2015). Tissue-based map of the human proteome. *Science* **347**:1260419. DOI:10.1126/science.1260419
96. Ahmad I. and Newell-Fugate A.E. (2022). Role of androgens and androgen receptor in control of mitochondrial function. *Am. J. Physiol. Cell. Physiol.* **323**:C835–C846. DOI:10.1152/ajpcell.00205.2022
97. Yin L.J., Luo M., Wang R., et al. (2021). Mitochondria in sex hormone-induced disorder of energy metabolism in males and females. *Front. Endocrinol.* **12**:749451. DOI:10.3389/fendo.2021.749451
98. Alemany M. (2022). The roles of androgens in humans: Biology, metabolic regulation and health. *Int. J. Mol. Sci.* **23**:11952. DOI:10.3390/ijms231911952
99. Kelly D.M. and Jones T.H. (2015). Testosterone and obesity. *Obes. Rev.* **16**:581–606. DOI:10.1111/obr.12282
100. Traish A.M. (2014). Adverse health effects of testosterone deficiency (TD) in men. *Steroids* **88**:106–116. DOI:10.1016/j.steroids.2014.05.010
101. Kelly D.M. and Jones T.H. (2013). Testosterone: A metabolic hormone in health and disease. *J. Endocrinol.* **217**:R25–R45. DOI:10.1530/Joe-12-0455
102. Hirschberg A.L. (2012). Sex hormones, appetite and eating behaviour in women. *Maturitas* **71**:248–256. DOI:10.1016/j.maturitas.2011.12.016
103. Góral A., Zywot K., Zalewski W., et al. (2025). Polycystic ovary syndrome and eating disorders-a literature review. *J. Clin. Med.* **14**:27. DOI:10.3390/jcm14010027
104. Allen N.E. and Key T.J. (2000). The effects of diet on circulating sex hormone levels in men. *Nutr. Res. Rev.* **13**:159–184. DOI:10.1079/095442200108729052
105. Zamir A., Ben-Zeev T. and Hoffman J.R. (2021). Manipulation of dietary intake on changes in circulating testosterone concentrations. *Nutrients* **13**:3375. DOI:10.3390/nu13103375
106. Mazza E., Troiano E., Ferro Y., et al. (2024). Obesity, dietary patterns, and hormonal balance modulation: Gender-specific impacts. *Nutrients* **16**:1629. DOI:10.3390/nu16111629
107. Calcaterra V., Verduci E., Stagi S., et al. (2024). How the intricate relationship between nutrition and hormonal equilibrium significantly influences endocrine and reproductive health in adolescent girls. *Front. Nutr.* **11**:1337328. DOI:10.3389/fnut.2024.1337328
108. Stiles L.I., Ferrao K., Mehta K.J. (2024). Role of zinc in health and disease. *Clin. Exp. Med.* **24**:38. DOI:10.1007/s10238-024-01302-6
109. Lin M.W. and Wu M.H. (2015). The role of vitamin D in polycystic ovary syndrome. *Indian J. Med. Res.* **142**:238–240. DOI:10.4103/0971-5916.166527
110. Trummer C., Pilz S., Schwetz V., et al. (2018). Vitamin D, PCOS and androgens in men: A systematic review. *Endocr. Connect.* **7**:R95–R113. DOI:10.1530/Ec-18-0009
111. Excoffon L., Guillaume Y.C., Woronoff-Lemsi M.C., et al. (2009). Magnesium effect on testosterone-SHBG association studied by a novel molecular chromatography approach. *J. Pharmaceut. Biomed.* **49**:175–180. DOI:10.1016/j.jpba.2008.10.041
112. Janjuha R., Bunn D., Hayhoe R., et al. (2020). Effects of dietary or supplementary micronutrients on sex hormones and IGF-1 in middle and older age: A systematic review and meta-analysis. *Nutrients* **12**:1457. DOI:10.3390/nu12051457
113. Monson N.R., Klair N., Patel U., et al. (2023). Association between vitamin D deficiency and testosterone levels in adult males: A systematic review. *Cureus J. Med. Science* **15**:e45856. DOI:10.7759/cureus.45856
114. Kowalczyk K., Kadlubek S., Kruzel A., et al. (2025). Dietary patterns and metabolic and hormonal parameters in women with suspected PCOS. *J. Clin. Med.* **14**:2708. DOI:10.3390/jcm14082708
115. Choi Y., Kang K., Je M., et al. (2025). The influence of dietary patterns on polycystic ovary syndrome management in women: A review of randomized controlled trials with and without an isocaloric dietary design. *Nutrients* **17**:674. DOI:10.3390/nu17040674
116. Dokras A., Sarwer D.B., Allison K.C., et al. (2016). Weight loss and lowering androgens predict improvements in health-related quality of life in women with PCOS. *J. Clin. Endocrinol. Metab.* **101**:2966–2974. DOI:10.1210/jc.2016-1896
117. Ni M.C., Lei H.Y., Ye T., et al. (2025). Adipose-androgen crosstalk in polycystic ovary syndrome: Mechanisms and therapeutic implications. *Front. Endocrinol.* **16**:1731179. DOI:10.3389/fendo.2025.1731179
118. Brown A.W., Aslibekyan S., Bier D., et al. (2023). Toward more rigorous and informative nutritional epidemiology: The rational space between dismissal and defense of the status quo. *Crit. Rev. Food Sci.* **63**:3150–3167. DOI:10.1080/10408398.2021.1985427
119. Bailey R.L. (2021). Overview of dietary assessment methods for measuring intakes of foods, beverages, and dietary supplements in research studies. *Curr. Opin. Biotech.* **70**:91–96. DOI:10.1016/j.copbio.2021.02.007
120. Windus J.L., Stewart S.J., Adam M.T.P., et al. (2025). Exploring dietary assessment methods used to measure individual dietary intakes in low- and middle-income countries and under-served populations in high-income countries. *Nutrients* **17**:360. DOI:10.3390/nu17020360
121. Tremaroli V. and Bäckhed F. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature* **489**:242–249. DOI:10.1038/nature11552
122. Nicholson J.K., Holmes E., Kinross J., et al. (2012). Host-gut microbiota metabolic interactions. *Science* **336**:1262–1267. DOI:10.1126/science.1223813
123. Rosner W., Auchus R.J., Azziz R., et al. (2007). Position statement: Utility, limitations, and pitfalls in measuring testosterone: An endocrine society position statement. *J. Clin. Endocrinol. Metab.* **92**:405–413. DOI:10.1210/jc.2006-1864
124. Rowland I., Gibson G., Heinken A., et al. (2018). Gut microbiota functions: Metabolism of nutrients and other food components. *Eur. J. Nutr.* **57**:1–24. DOI:10.1007/s00394-017-1445-8
125. Hu S.W., Ding Q.Y., Zhang W., et al. (2023). Gut microbial beta-glucuronidase: A vital regulator in female estrogen metabolism. *Gut Microbes* **15**:2236749. DOI:10.1080/19490976.2023.2236749
126. Hanna A., Abbas H., Yassine F., et al. (2025). Systematic review of gut microbiota composition, metabolic alterations, and the effects of treatments on PCOS and gut microbiota across human and animal studies. *Front. Microbiol.* **16**:1549499. DOI:10.3389/fmicb.2025.1549499
127. Wang K.X., Li Y.H. and Chen Y. (2023). Androgen excess: A hallmark of polycystic ovary syndrome. *Front. Endocrinol.* **14**:1273542. DOI:10.3389/fendo.2023.1273542
128. Diamanti-Kandarakis E. and Dunaif A. (2012). Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr. Rev.* **33**:981–1030. DOI:10.1210/er.2011-1034
129. Azziz R., Carmina E., Chen Z.J., et al. (2016). Polycystic ovary syndrome. *Nat. Rev. Dis. Primers* **2**:16057. DOI:10.1038/nrdp.2016.57
130. Legro R.S., Arslanian S.A., Ehrmann D.A., et al. (2021). Diagnosis and treatment of polycystic ovary syndrome: An endocrine society clinical practice guideline (vol 98, pg 4565, 2013). *J. Clin. Endocrinol. Metab.* **106**:E2462–E2462. DOI:10.1210/clinem/dgab248

131. Zhang X.H., Xu H.Y., Sun Y., et al. (2025). Simultaneous profiling of classic and 11-oxygenated androgens via a novel derivatization method coupled with HPLC-MS/MS: a game-changer for endocrine disorders. *Talanta Open* **11**:100459. DOI:10.1016/j.talo.2025.100459
132. Zhang X., Xu H., Feng G., et al. (2022). Sensitive HPLC-DMS/MS/MS method coupled with dispersive magnetic solid phase extraction followed by in situ derivatization for the simultaneous determination of multiplexing androgens and 17-hydroxyprogesterone in human serum and its application to patients with polycystic ovarian syndrome. *Clin. Chim. Acta* **538**:221–230. DOI:10.1016/j.cca.2022.11.025
133. Zhang X., Xu H., Zhou C., et al. (2022). Magnetic solid phase extraction followed by in-situ derivatization with core-shell structured magnetic graphene oxide nanocomposite for the accurate quantification of free testosterone and free androstenedione in human serum. *J. Chromatogr. B* **1196**:123188. DOI:10.1016/j.jchromb.2022.123188
134. Zhang X., Zhou C., Xu H., et al. (2021). A sensitive HPLC-DMS/MS/MS method for multiplex analysis of androgens in human serum without derivatization and its application to PCOS patients. *J. Pharm. Biomed. Anal.* **192**:113680. DOI:10.1016/j.jpba.2020.113680
135. Lim S.S., Hutchison S.K., Van Ryswyk E., et al. (2019). Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst. Rev.* **2019**:CD007506. DOI:10.1002/14651858.CD007506.pub4
136. González F., Considine R.V., Abdelhadi O.A., et al. (2020). Inflammation triggered by saturated fat ingestion is linked to insulin resistance and hyperandrogenism in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **105**:E2152–E2167. DOI:10.1210/clinem/dgaa108
137. Barrea L., Verde L., Annunziata G., et al. (2024). Role of Mediterranean diet in endocrine diseases: A joint overview by the endocrinologist and the nutritionist. *J. Endocrinol. Invest.* **47**:17–33. DOI:10.1007/s40618-023-02169-2
138. Calcaterra V., Rossi V., Massini G., et al. (2023). Probiotics and polycystic ovary syndrome: A perspective for management in adolescents with obesity. *Nutrients* **15**:3144. DOI:10.3390/nu15143144
139. Guevara D.M., Cañas S.V., Palacios I., et al. (2024). Effectiveness of probiotics, prebiotics, and synbiotics in managing insulin resistance and hormonal imbalance in women with polycystic ovary syndrome (PCOS): A systematic review of randomized clinical trials. *Nutrients* **16**:3916. DOI:10.3390/nu16223916
140. Oliveira L.C.S.D., Costa E.C., Martins F.D.G., et al. (2024). Probiotics supplementation in the treatment of male infertility: A systematic review. *J. Bras. Reprod. Assist.* **28**:341–348. DOI:10.5935/1518-0557.20240013
141. Speiser P.W. and White P.C. (2003). Congenital adrenal hyperplasia. *N. Engl. J. Med.* **349**:776–788. DOI:10.1056/NEJMra021561
142. Auchus R.J. and Arlt W. (2013). Approach to the patient: The adult with congenital adrenal hyperplasia. *J. Clin. Endocrinol. Metab.* **98**:2645–2655. DOI:10.1210/jc.2013-1440
143. Speiser P.W., Azziz R., Baskin L.S., et al. (2021). Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline (vol 95, pg 4133, 2010). *J. Clin. Endocrinol. Metab.* **106**:E2853–E2853. DOI:10.1210/clinem/dgab316
144. Mallappa A. and Merke D.P. (2022). Management challenges and therapeutic advances in congenital adrenal hyperplasia. *Nat. Rev. Endocrinol.* **18**:337–352. DOI:10.1038/s41574-022-00655-w
145. Turcu A.F. and Auchus R.J. (2015). The next 150 years of congenital adrenal hyperplasia. *J. Steroid Biochem.* **153**:63–71. DOI:10.1016/j.jsbmb.2015.05.013
146. Turcu A.F., Nanba A.T. and Auchus R.J. (2018). The rise, fall, and resurrection of 11-oxygenated androgens in human physiology and disease. *Horm. Res. Paediat.* **89**:284–291. DOI:10.1159/000486036
147. Lin H.C., Zheng Z.J., Chen Q.X., et al. (2025). Male reproductive metabolic syndrome: Redefining the "male PCOS equivalent" and its link to erectile dysfunction. *Innov. Med.* **3**:100144. DOI:10.59717/j.xinn-med.2025.100144
148. Bhasin S., Brito J.P., Cunningham G.R., et al. (2018). Testosterone therapy in men with hypogonadism: An endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **103**:1715–1744. DOI:10.1210/jc.2018-00229
149. Corona G., Vignozzi L., Sforza A., et al. (2015). Obesity and late-onset hypogonadism. *Mol. Cell. Endocrinol.* **418**:120–133. DOI:10.1016/j.mce.2015.06.031
150. Webber L., Davies M., Anderson R., et al. (2016). ESHRE guideline: Management of women with premature ovarian insufficiency. *Hum. Reprod.* **31**:926–937. DOI:10.1093/humrep/dew027
151. Wierman M.E., Arlt W., Basson R., et al. (2014). Androgen therapy in women: A reappraisal: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **99**:3489–3510. DOI:10.1210/jc.2014-2260
152. Snyder P.J., Peachey H., Hannoush P., et al. (1999). Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J. Clin. Endocrinol. Metab.* **84**:1966–1972. DOI:10.1210/jc.84.6.1966
153. Bauman D.R., Steckelbroeck S., Williams M.V., et al. (2006). Identification of the major oxidative 3α-hydroxysteroid dehydrogenase in human prostate that converts 5α-androstane-3α,17β-diol to 5α-dihydrotestosterone: A potential therapeutic target for androgen-dependent disease. *Mol. Endocrinol.* **20**:444–458. DOI:10.1210/me.2005-0287
154. Hoke G.P., McWilliams G.W. (2008). Epidemiology of benign prostatic hyperplasia and comorbidities in racial and ethnic minority populations. *Am. J. Med.* **121**:s3–s10. DOI:10.1016/j.amjmed.2008.05.021
155. Carson C. and Rittmaster R. (2003). The role of dihydrotestosterone in benign prostatic hyperplasia. *Urology* **61**:2–7. DOI:10.1016/S0090-4295(03)00045-1
156. Andriole G., Bruchovsky N., Chung L.W.K., et al. (2004). Dihydrotestosterone and the prostate: The scientific rationale for 5α-reductase inhibitors in the treatment of benign prostatic hyperplasia. *J. Urol.* **172**:1399–1403. DOI:10.1097/01.ju.0000139539.94828.29
157. du Toit T. and Swart A.C. (2020). The 11β-hydroxyandrostenedione pathway and C11-oxy C21 backdoor pathway are active in benign prostatic hyperplasia yielding 11-ketotestosterone and 11keto-progesterone. *J. Steroid Biochem.* **196**:105497. DOI:10.1016/j.jsbmb.2019.105497
158. Andriole G.L., Bostwick D.G., Brawley O.W., et al. (2010). Effect of dutasteride on the risk of prostate cancer. *N. Engl. J. Med.* **362**:1192–1202. DOI:10.1056/NEJMoa0908127
159. Bartsch G., Rittmaster R.S. and Klocker H. (2000). Dihydrotestosterone and the concept of 5α-reductase inhibition in human benign prostatic hyperplasia. *Eur. Urol.* **37**:367–380. DOI:10.1159/000020181
160. Lepor H. (2016). Alpha-blockers for the treatment of benign prostatic hyperplasia. *Urol. Clin. N. Am.* **43**:311–323. DOI:10.1016/j.ucl.2016.04.009
161. Gacci M., Corona G., Salvi M., et al. (2012). A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur. Urol.* **61**:994–1003. DOI:10.1016/j.eururo.2012.02.033
162. Liu Q.Z., Zhang X.F., Zhou F.H., et al. (2020). Efficacy and tolerability of combination therapy with alpha-blockers and phosphodiesterase-5 inhibitors compared with monotherapy for lower urinary tract symptoms: Protocol for a systematic review and network meta-analysis. *Medicine* **99**:e22834. DOI:10.1097/MD.0000000000022834
163. Schröder F., Crawford E.D., Axcrona K., et al. (2012). Androgen deprivation therapy: Past, present and future. *BJU Int.* **109**:1–12. DOI:10.1111/j.1464-410X.2012.11215.x
164. Watson P.A., Arora V.K. and Sawyers C.L. (2015). Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat. Rev. Cancer* **15**:701–711. DOI:10.1038/nrc4016
165. Scher H.I., Fizazi K., Saad F., et al. (2012). Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* **367**:1187–1197. DOI:10.1056/NEJMoa1207506
166. Snaterse G., van Dessel L.F., van Riet J., et al. (2021). 11-ketotestosterone is the predominant active androgen in prostate cancer patients after castration. *JCI Insight* **6**:148507. DOI:10.1172/jci.insight.148507
167. Barnard M., Quanson J.L., Mostaghel E., et al. (2018). 11-oxygenated androgen precursors are the preferred substrates for aldo-keto reductase 1C3 (AKR1C3): implications for castration resistant prostate cancer. *J. Steroid Biochem.* **183**:192–201. DOI:10.1016/j.jsbmb.2018.06.013
168. Kelm J.M., Pandey D.S., Malin E., et al. (2023). PROTAC'ing oncoproteins: targeted protein degradation for cancer therapy. *Mol. Cancer* **22**:62. DOI:10.1186/s12943-022-01707-5
169. Zhang Y.L., Ming A.N., Wang J.Y., et al. (2024). PROTACs targeting androgen receptor signaling: Potential therapeutic agents for castration-resistant prostate cancer. *Pharmacol. Res.* **205**:107234. DOI:10.1016/j.phrs.2024.107234
170. de Bono J., Kang J.Y. and Hussain M. (2020). Olaparib for metastatic castration-resistant prostate cancer reply. *N. Engl. J. Med.* **383**:891–891. DOI:10.1056/NEJMc2023199
171. Kostos L., Tran B. and Azad A.A. (2024). Combination of PARP inhibitors and androgen receptor pathway inhibitors in metastatic castration-resistant prostate cancer. *Drugs* **84**:1093–1109. DOI:10.1007/s40265-024-02071-y
172. Sartor A.O., Morris M.J., Chi K.N., et al. (2022). PSMAfore: A phase 3 study to compare 177Lu-PSMA-617 treatment with a change in androgen receptor pathway inhibitor in taxane-naïve patients with metastatic castration-resistant prostate cancer. *J. Clin. Oncol.* **40**:TPS211. DOI:10.1200/JCO.2022.40.6_suppl.TPS211
173. Bienenfeld A., Azarchi S., Lo Sicco K., et al. (2019). Androgens in women: Androgen-mediated skin disease and patient evaluation. *J. Am. Acad. Dermatol.* **80**:1497–1506. DOI:10.1016/j.jaad.2018.08.062
174. Ceruti J.M., Leirós G.J. and Balañá M.E. (2018). Androgens and androgen receptor action in skin and hair follicles. *Mol. Cell. Endocrinol.* **465**:122–133. DOI:10.1016/j.mce.2017.09.009
175. Zouboulis C.C., Blume-Peytavi U., Kosmadaki M., et al. (2022). Skin, hair and beyond: The impact of menopause. *Climacteric* **25**:434–442. DOI:10.1080/13697137.2022.2050206
176. Rizk J., Sahu R, Delphine Duteil D. (2023). An overview on androgen-mediated actions in skeletal muscle and adipose tissue. *Steroids* **199**:109306. DOI:10.1016/j.steroids.2023.109306

177. Fohr B., Schulz A. and Battmann A. (2000). Sex steroids and bone metabolism: comparison of in vitro effects of 17β-estradiol and testosterone on human osteosarcoma cell lines of various gender and differentiation. *Exp. Clin. Endocr. Diab.* **108**:414–423. DOI:10.1055/s-2000-8400
178. Notelovitz M. (2002). Androgen effects on bone and muscle. *Fertil. Steril.* **77**:S34–S41. DOI:10.1016/s0015-0282(02)02968-0
179. Labrie F., Luu-The V., Labrie C., et al. (2001). DHEA and its transformation into androgens and estrogens in peripheral target tissues: intracrinology. *Front. Neuroendocrin.* **22**:185–212. DOI:10.1006/frne.2001.0216
180. Watts N.B. and Diab D.L. (2010). Long-term use of bisphosphonates in osteoporosis. *J. Clin. Endocrinol. Metab.* **95**:1555–1565. DOI:10.1210/jc.2009-1947
181. Mohler M.L., Bohl C.E., Jones A., et al. (2009). Nonsteroidal selective androgen receptor modulators (SARMs): Dissociating the anabolic and androgenic activities of the androgen receptor for therapeutic benefit. *J. Med. Chem.* **52**:3597–3617. DOI:10.1021/jm900280m
182. Corona G., Monami M., Rastrelli G., et al. (2011). Testosterone and metabolic syndrome: A meta-analysis study. *J. Sex. Med.* **8**:272–283. DOI:10.1111/j.1743-6109.2010.01991.x
183. Alberti K.G.M.M., Zimmet P. and Shaw J. (2005). The metabolic syndrome - a new worldwide definition. *Lancet* **366**:1059–1062. DOI:10.1016/S0140-6736(05)67402-8
184. Su L.H. and Chen T.H.H. (2010). Association of androgenetic alopecia with metabolic syndrome in men: A community-based survey. *Brit. J. Dermatol.* **163**:371–377. DOI:10.1111/j.1365-2133.2010.09816.x
185. Cai J.J., Wen J., Jiang W.H., et al. (2016). Androgen actions on endothelium functions and cardiovascular diseases. *J. Geriatr. Cardiol.* **13**:183–196. DOI:10.11909/j.issn.1671-5411.2016.02.003
186. Grandys M., Majerczak J., Zapart-Bukowska J., et al. (2021). Lowered serum testosterone concentration is associated with enhanced inflammation and worsened lipid profile in men. *Front. Endocrinol.* **12**:735638. DOI:10.3389/fendo.2021.735638
187. Kapoor D., Goodwin E., Channer K.S., et al. (2006). Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur. J. Endocrinol.* **154**:899–906. DOI:10.1530/eje.1.02166
188. Powrie Y.S.L. and Smith C. (2018). Central intracrine DHEA synthesis in ageing-related neuroinflammation and neurodegeneration: Therapeutic potential. *J. Neuroinflamm.* **15**:289. DOI:10.1186/s12974-018-1324-0
189. Traish A., Bolanos J., Nair S., et al. (2018). Do androgens modulate the pathophysiological pathways of inflammation. *Appraising the contemporary evidence. J. Clin. Med.* **7**:549. DOI:10.3390/jcm7120549
190. Jayaraman A., Lent-Schochet D. and Pike C.J. (2014). Diet-induced obesity and low testosterone increase neuroinflammation and impair neural function. *J. Neuroinflamm.* **11**:162. DOI:10.1186/s12974-014-0162-y
191. Glynne S., Kamal A., Kamel A.M., et al. (2025). Effect of transdermal testosterone therapy on mood and cognitive symptoms in peri- and postmenopausal women: a pilot study. *Arch. Womens Ment. Health* **28**:541–550. DOI:10.1007/s00737-024-01513-6
192. Jayaraman A., Christensen A., Moser V.A., et al. (2014). Selective androgen receptor modulator RAD140 is neuroprotective in cultured neurons and kainate-lesioned male rats. *Endocrinology* **155**:1398–1406. DOI:10.1210/en.2013-1725
193. Rode I. and Boehm T. (2012). Regenerative capacity of adult cortical thymic epithelial cells. *P. Natl. Acad. Sci. USA* **109**:3463–3468. DOI:10.1073/pnas.1118823109
194. Polesso F., Caruso B., Hammond S.A., et al. (2023). Restored thymic output after androgen blockade participates in antitumor immunity. *J. Immunol.* **210**:496–503. DOI:10.4049/jimmunol.2200696
195. Wilhelmson A.S., Rodriguez M.L., Johansson I., et al. (2020). Androgen receptors in epithelial cells regulate thymopoiesis and recent thymic emigrants in male mice. *Front. Immunol.* **11**:1342. DOI:10.3389/fimmu.2020.01342
196. Shabbir S., Khurram E., Moorthi V.S., et al. (2023). The interplay between androgens and the immune response in polycystic ovary syndrome. *J. Transl. Med.* **21**:259. DOI:10.1186/s12967-023-04116-4
197. Lai J.J., Lai K.P., Zeng W.P., et al. (2012). Androgen receptor influences on body defense system via modulation of innate and adaptive immune systems. *Am. J. Pathol.* **181**:1504–1512. DOI:10.1016/j.ajpath.2012.07.008
198. Duah M., Li L.L., Shen J.Y., et al. (2021). Thymus degeneration and regeneration. *Front. Immunol.* **12**:706244. DOI:10.3389/fimmu.2021.706244
199. Hoffmann J.P., Liu J.A., Seddu K., et al. (2023). Sex hormone signaling and regulation of immune function. *Immunity* **56**:2472–2491. DOI:10.1016/j.immuni.2023.10.008
200. Teede H.J., Misso M.L., Costello M.F., et al. (2018). Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Hum. Reprod.* **33**:1602–1618. DOI:10.1093/humrep/dey256
201. Hartgens F. and Kuipers H. (2004). Effects of androgenic-anabolic steroids in athletes. *Sports Med.* **34**:513–554. DOI:10.2165/00007256-200434080-00003
202. Dhurat R., Sharma A., Rudnicka L., et al. (2020). 5-alpha reductase inhibitors in androgenetic alopecia: Shifting paradigms, current concepts, comparative efficacy, and safety. *Dermatol. Ther.* **33**:e13379. DOI:10.1111/dth.13379
203. Nikolaou N., Hodson L. and Tomlinson J.W. (2021). The role of 5-reduction in physiology and metabolic disease: Evidence from cellular, pre-clinical and human studies. *J. Steroid Biochem.* **207**:105808. DOI:10.1016/j.jsbmb.2021.105808
204. De Bono J.S., Logothetis C.J., Molina A., et al. (2011). Abiraterone and increased survival in metastatic prostate cancer. *N. Engl. J. Med.* **364**:1995–2005. DOI:10.1056/NEJMoa1014618
205. Escamilla-Cruz M., Magaña M., Escandón-Perez S., et al. (2023). Use of 5-alpha reductase inhibitors in dermatology: A narrative review. *Dermatol. Ther.* **13**:1721–1731. DOI:10.1007/s13555-023-00974-4
206. Kango G., Malek R., Mannuel H., et al. (2024). Targeting androgen biosynthesis in prostate cancer: Implications on endocrine physiology. *Curr. Opin. Oncol.* **36**:195–201. DOI:10.1097/Cco.0000000000001032
207. Tingö L., Hutchinson A.N., Bergh C., et al. (2022). Potential modulation of inflammation by probiotic and omega-3 supplementation in elderly with chronic low-grade inflammation-a randomized, placebo-controlled trial. *Nutrients* **14**:3998. DOI:10.3390/nu14193998
208. Jamilian M., Mansury S., Bahmani F., et al. (2018). The effects of probiotic and selenium co-supplementation on parameters of mental health, hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. *J. Ovarian Res.* **11**:457. DOI:10.1186/s13048-018-0457-1
209. Bron P.A., Kleerebezem M., Brummer R.J., et al. (2017). Can probiotics modulate human disease by impacting intestinal barrier function. *Brit. J. Nutr.* **117**:93–107. DOI:10.1017/S0007114516004037
210. Ríos-Covián D., Ruas-Madiedo P., Margolles A., et al. (2016). Intestinal short chain fatty acids and their link with diet and human health. *Front. Microbiol.* **7**:185. DOI:10.3389/fmicb.2016.00185
211. Wang C., Nieschlag E., Swerdloff R., et al. (2009). ISA, ISSAM, EAU, EAA and ASA recommendations: Investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male* **12**:5–12. DOI:10.1080/13685530802389628
212. Rhoden E.L. and Morgentaler A. (2004). Risks of testosterone-replacement therapy and recommendations for monitoring. *N. Engl. J. Med.* **350**:482–492. DOI:10.1056/NEJMra022251
213. Ohlander S.J., Varghese B. and Pastuszak A.W. (2018). Erythrocytosis following testosterone therapy. *Sex. Med. Rev.* **6**:77–85. DOI:10.1016/j.sxmr.2017.04.001
214. Cornford P., van den Bergh R.C.N., Briers E., et al. (2021). EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: Treatment of relapsing and metastatic prostate cancer. *Eur. Urol.* **79**:263-282. DOI:10.1016/j.eururo.2020.09.046.
215. Mulhall J.P., Trost L.W., Brannigan R.E., et al. (2018). Evaluation and management of testosterone deficiency: AUA guideline. *J. Urol.* **200**:423–432. DOI:10.1016/j.juro.2018.03.115
216. Tosi F., Fiers T., Kaufman J.M., et al. (2016). Implications of androgen assay accuracy in the phenotyping of women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **101**:610–618. DOI:10.1210/jc.2015-2807
217. Keevil B.G. (2016). LC-MS/MS analysis of steroids in the clinical laboratory. *Clin. Biochem.* **49**:989–997. DOI:10.1016/j.clinbiochem.2016.04.009
218. Frederiksen H., Johannsen T.H., Andersen S.E., et al. (2024). Sex- and age-specific reference intervals of 16 steroid metabolites quantified simultaneously by LC-MS/MS in sera from 2458 healthy subjects aged 0 to 77 years. *Clin. Chim. Acta* **562**:119852. DOI:10.1016/j.cca.2024.119852
219. Braun V., Ceglarek U., Gaudl A., et al. (2024). Evaluation of five multisteroid LC-MS/MS methods used for routine clinical analysis: Comparable performance was obtained for nine analytes. *Clin. Chem. Lab. Med.* **62**:900–910. DOI:10.1515/cclm-2023-0847
220. Wang Q.Q. and Mesaros C. (2025). Advances and challenges in liquid chromatography-spectrometry (LC-MS) methodology for quantifying androgens and estrogens in human serum and plasma. *J. Steroid Biochem.* **245**:106618. DOI:10.1016/j.jsbmb.2024.106618
221. Vesper H.W. and Botelho J.C. (2010). Standardization of testosterone measurements in humans. *J. Steroid Biochem.* **121**:513–519. DOI:10.1016/j.jsbmb.2010.03.032
222. Shi J.Y., Bird R., Schmeling M.W., et al. (2021). Using mass spectrometry to overcome the longstanding inaccuracy of a commercially-available clinical testosterone immunoassay. *J. Chromatogr. B* **1183**:122969. DOI:10.1016/j.jchromb.2021.122969
223. Ambroziak U., Kepczynska-Nyk A., Kurylowicz A., et al. (2015). LC-MS/MS improves screening towards 21-hydroxylase deficiency. *Gynecol. Endocrinol.* **31**:296–300. DOI:10.3109/09513590.2014.994599
224. Dunn J.F., Nisula B.C. and Rodbard D. (1981). Transport of steroid-hormones - binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human-plasma. *J. Clin. Endocrinol. Metab.* **53**:58–68. DOI:10.1210/jcem-53-1-58
225. Vermeulen A., Verdonck L. and Kaufman J.M. (1999). A critical evaluation of simple methods for the estimation of free testosterone in serum. *J. Clin. Endocrinol. Metab.* **84**:3666–3672. DOI:10.1210/jc.84.10.3666

226. Goodman N.F., Cobin R.H., Futterweit W., et al. (2015). American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome. *Endocr. Pract.* **21**:1415–1426. DOI:10.4158/Ep15748.Dscpt2
227. Taieb J., Mathian B., Millot F., et al. (2003). Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clin. Chem.* **49**:1381–1395. DOI:10.1373/49.8.1381
228. Heijboer A.C. and Hannema S.E. (2023). Androgen excess and deficiency: analytical and diagnostic approaches. *Clin. Chem.* **69**:1361–1373. DOI:10.1093/clinchem/hvad146
229. French D., Drees J., Stone J.A., et al. (2019). Comparison of four clinically validated testosterone LC-MS/MS assays: Harmonization is an attainable goal. *Clin. Mass Spectrom.* **11**:12–20. DOI:10.1016/j.clinms.2018.11.005
230. Wallace W.H. and Kelsey T.W. (2010). Human ovarian reserve from conception to the menopause. *PLoS One* **5**:e8772. DOI:10.1371/journal.pone.0008772
231. Yu J.Y., Ma X.M., Wang X.Y., et al. (2022). Application and mechanism of probiotics in skin care: A review. *J. Cosmet. Dermatol.* **21**:886–894. DOI:10.1111/jocd.14734
232. Xu H., Feng G., Shi L., et al. (2023). PCOSt: A non-invasive and cost-effective screening tool for polycystic ovary syndrome. *Innovation* **4**:100407. DOI:10.1016/j.xinn.2023.100407
233. Xu H., Zhang X., Yang R., et al. (2023). Can androgens be replaced by AMH in initial screening of polycystic ovary syndrome. *Innov. Med.* **1**:100010. DOI:10.59717/j.xinn-med.2023.100010
234. Xu H., Wang W., Han Y., et al. (2024). OvaRePred: Redefing ovarian aging and pioneering the journey towards women's health management. *Innov. Med.* **2**:100068. DOI:10.59717/j.xinn-med.2024.100068
235. The Innovation Editorial Team (2024). Innovation focus in 2023. *Innovation* **5**:100560. DOI:10.1016/j.xinn.2023.100560.
236. Xu H., Feng G., Li R., et al. (2023). ADpred: A non-invasive model for three different types of dementia, and mild cognitive impairment. *Innov. Med.* **1**:100026. DOI:10.59717/j.xinn-med.2023.100026

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AUTHOR CONTRIBUTIONS

H.X., H.Z., and R.Y. conceived the study and designed the overall framework. H.X. coordinated the project and led the conceptual development of the manuscript. H.Z., R.Y., X.X., Z.C., and Y.Z. performed literature collection, data interpretation, and initial drafting. H.L., D.L., and F.B. contributed to thematic development, figure design, and manuscript revision. X.Z. and S.Y. provided critical scientific input and contributed to interpretation of key concepts and clinical perspectives.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data or code were generated in this study.