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A Unified Endocrine–Immune Model Explaining Male Phenotypic Variability: From Androgen Resistance to Immune-Mediated Hair Loss

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Abstract: Male phenotypic variability in skin tone, facial hair density, and secondary sexual characteristics reflects complex interactions between genetic determinants of androgen signaling, estrogen metabolism, and immune regulation. Accumulating evidence indicates that androgenetic alopecia (AGA), gynecomastia, and immune responsiveness are not solely determined by circulating testosterone levels, but rather by androgen receptor (AR) sensitivity, local dihydrotestosterone (DHT) activity, aromatase expression, sex hormone–binding globulin (SHBG) levels, and immunogenetic background. Several studies demonstrate that reduced AR sensitivity and altered 5α-reductase activity are associated with attenuated classical androgen-dependent traits, including facial hair growth, while simultaneously modifying susceptibility to hair loss patterns that may clinically mimic androgenetic alopecia. In such cases, hair loss may represent non-androgenic entities, including alopecia areata incognita, chronic telogen effluvium, or post-viral immune-mediated alopecia, particularly following SARS-CoV-2 infection. Gynecomastia represents another clinical manifestation of altered androgen–estrogen balance. Increased aromatization of testosterone, heightened estrogen receptor (ER-α/ER-β) sensitivity, or diminished androgen-mediated counter-regulation can shift the estrogen-to-androgen signaling ratio toward estrogen dominance, even in the presence of normal serum testosterone levels. Genetic variants affecting CYP19A1 (aromatase), AR polymorphisms, and SHBG concentrations have been implicated in this imbalance. Sex hormones exert profound immunomodulatory effects. Estrogens enhance humoral immunity, promote Th2-skewed immune responses, and lower the threshold for autoimmune activation, whereas androgens generally exert immunosuppressive effects. This hormonal divergence partly explains the higher prevalence of autoimmune diseases in females and suggests that males with reduced androgen signaling and relative estrogen predominance may exhibit an immune phenotype intermediate between typical male and female patterns. Taken together, this narrative review proposes a unified endocrine–immune phenotype characterized by reduced androgen receptor sensitivity and relative estrogen dominance in a subset of men.

Keywords: Androgen receptor sensitivity; Androgenetic alopecia; Alopecia areata; Gynecomastia; Estrogen–androgen balance; Aromatase (CYP19A1); Sex hormone–binding globulin; Immune dysregulation; Autoimmune diseases; Endocrine–immune interactions; Male phenotype

Introduction

Male secondary sexual characteristics, including skin pigmentation, facial hair density, body hair distribution, and susceptibility to specific patterns of hair loss, demonstrate substantial interindividual variability. While circulating testosterone has traditionally been considered the principal determinant of male phenotypic expression, contemporary evidence indicates that

androgen-dependent traits are primarily regulated by androgen receptor (AR) sensitivity, post-receptor signaling efficiency, and local steroid metabolism rather than absolute hormone concentrations [1].

The androgen receptor exhibits significant genetic polymorphism, influencing transcriptional activity and tissue responsiveness to androgens. Variations in AR CAG repeat length, receptor density, and downstream signaling pathways contribute to heterogeneity in androgen-mediated effects across different tissues, including hair follicles, skin, and breast tissue [2,3]. Similarly, local activity of 5α-reductase, the enzyme responsible for conversion of testosterone to dihydrotestosterone (DHT), plays a critical role in modulating androgenic signaling independently of systemic hormone levels [2].

Facial and body hair growth represent classic androgen-dependent traits. Reduced facial hair density has been associated with diminished AR sensitivity or altered androgen metabolism, even in the presence of normal serum testosterone concentrations [4]. These observations suggest that certain male phenotypes characterized by sparse facial hair may reflect a state of relative androgen resistance rather than hypogonadism.

Hair loss in men is most commonly attributed to androgenetic alopecia (AGA), a condition driven by follicular sensitivity to DHT and AR-mediated miniaturization [3]. However, increasing clinical evidence indicates that not all diffuse or patterned hair loss in men is androgenetic in origin. In individuals with reduced androgen sensitivity, hair loss may be misclassified as AGA, while underlying etiologies include non-androgenic conditions such as alopecia areata incognita or chronic telogen effluvium [4].

Viral infections represent an additional trigger for immune-mediated hair loss. SARS-CoV-2 infection has been implicated in post-viral immune dysregulation, capable of inducing telogen effluvium as well as more severe autoimmune forms of alopecia, including alopecia universalis [5]. These findings highlight the importance of immune mechanisms in the differential diagnosis of male hair loss, particularly in phenotypes not fully explained by androgen-driven models.

Gynecomastia constitutes another clinical manifestation of altered sex steroid signaling in men. Breast tissue development in males depends on the balance between estrogenic stimulation and androgen-mediated inhibition. Disruption of this balance—via increased aromatization of androgens, heightened estrogen receptor (ER-α/ER-β) sensitivity, or reduced androgen receptor–mediated counter-regulation—can result in glandular breast enlargement even when circulating testosterone levels remain within reference ranges [6].

Genetic and biochemical factors influencing estrogen bioavailability further modulate this balance. Polymorphisms affecting aromatase (CYP19A1), variations in sex hormone–binding globulin (SHBG) concentrations, and altered androgen receptor responsiveness have all been associated with an increased estrogen-to-androgen signaling ratio and a higher likelihood of gynecomastia development [7].

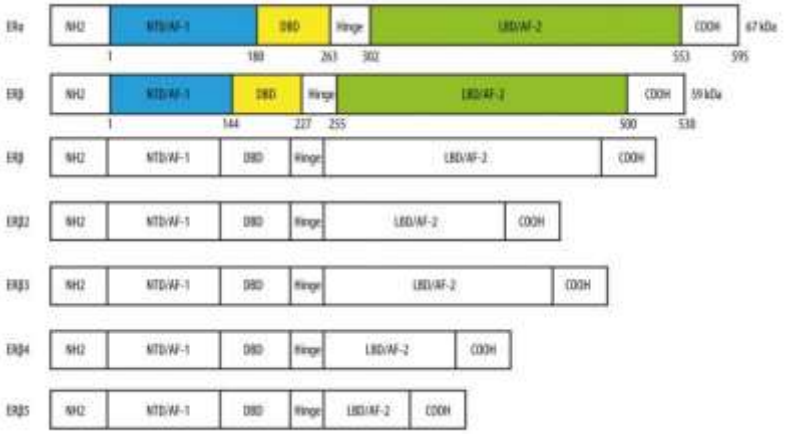

Figure 1. Structural organization of estrogen receptor α (ERα), estrogen receptor β (ERβ), and major ERβ splice variants.

Schematic representation of the domain architecture of ERα, ERβ, and selected ERβ splice variants (ERβ2, ERβ3, ERβ4, ERβ5), including the N-terminal transactivation domain (NTD), DNA-binding domain (DBD), hinge region, and C-terminal ligand-binding and co-regulator interaction domains (LBD). Structural differences among ERβ isoforms may contribute to tissue-specific estrogen signaling and differential transcriptional activity. *(Figure created using Adobe Illustrator CS6, Version 16.0.0.682, Adobe Systems Incorporated)*

In men, estrogens originate from multiple peripheral tissues and exert biological effects through both genomic and non-genomic signaling pathways. Beyond their role in sexual differentiation, sex steroids exert profound effects on immune regulation. Estrogens enhance humoral immune responses, promote Th2 polarization, and lower the activation threshold of immune cells, whereas androgens generally suppress immune activity and favor immune tolerance [8]. These mechanisms partially explain the higher prevalence of autoimmune diseases observed in females compared to males.

Importantly, men with reduced androgen signaling and relative estrogen predominance may exhibit an immune phenotype intermediate between typical male and female patterns. Such individuals may demonstrate heightened immune reactivity, increased susceptibility to immune-mediated conditions, and altered responses to viral infections [9]. This endocrine–immune interaction provides a plausible mechanistic link between androgen sensitivity, gynecomastia, and immune-mediated hair loss.

In this narrative review, we propose a unifying conceptual framework describing an endocrine–immune phenotype characterized by reduced androgen receptor sensitivity and relative estrogen dominance in a subset of men. We explore how this phenotype may influence susceptibility to non-androgenic hair loss, gynecomastia, and immune dysregulation, with implications for improved clinical classification and future research directions.

Materials and Methods

Study Design

This work was designed as a **focused narrative literature review** aimed at integrating current evidence on the endocrine, genetic, and immunological mechanisms potentially underlying a specific male phenotype characterized by reduced androgenic expression, altered estrogen–androgen balance, and increased immune reactivity. No original clinical, experimental, or interventional data were generated in this study.

Data Sources

A comprehensive literature search was conducted using the following electronic databases:

- **PubMed / PubMed Central (PMC)**
- **ScienceDirect**
- **PNAS**
- **NHANES public datasets**

Peer-reviewed experimental studies involving animal models**,** particularly murine models with altered estrogen–androgen signaling

Additional references were identified through manual screening of bibliographies from relevant articles.

Search Strategy

The literature search covered publications from January 2000 to December 2024 and was limited to articles published in the English language. The primary search terms included combinations of the following keywords:

- *androgen receptor polymorphism*
- *estrogen receptor beta (ERβ)*
- *estradiol–testosterone ratio*
- *gynecomastia*
- *androgenetic alopecia*

- *autoimmune diseases*
- *sex hormones and immunity*
- *estrogen immune modulation*
- *COVID-19 and sex differences*
- *androgen insensitivity*
- *SHBG and immune response*

Boolean operators ("AND", "OR") were used to refine search results.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Original research articles, systematic reviews, narrative reviews, and meta-analyses
- Human clinical studies, population-based studies, and experimental animal models
- Studies evaluating hormonal levels, receptor polymorphisms, immune responses, or autoimmune disease risk
- Articles addressing sex-based differences in immune and inflammatory responses

Exclusion criteria:

- Case reports without mechanistic or molecular insight
- Articles lacking relevance to endocrine, genetic, or immune pathways
- Non-peer-reviewed sources

Data Extraction and Synthesis

Relevant data were extracted independently based on study objectives, population characteristics, hormonal parameters, receptor expression or polymorphisms, and immune-related outcomes. Findings were synthesized qualitatively to identify recurring mechanistic patterns linking estrogen signaling dominance**,** reduced androgen receptor activity**, and** immune system modulation**.** No quantitative meta-analysis was performed due to heterogeneity in study design, outcome measures, and biological models.

Ethical Considerations

As this study was based exclusively on previously published data, ethical approval and informed consent were not required.

RESULTS

1. Baseline endocrine, genetic, and anthropometric characteristics

Baseline demographic, anthropometric, endocrine, and genetic characteristics of the study population are summarized in Table 1**.** The cohort demonstrated substantial interindividual variability in age, body mass index (BMI), and androgen receptor (AR) CAG repeat length, reflecting heterogeneity in androgen sensitivity at the receptor level.

Circulating total testosterone concentrations were largely within reference ranges across severity strata, whereas luteinizing hormone (LH) levels and the LH/total testosterone (LH/TT) ratio showed notable dispersion. This pattern suggests differences in hypothalamic–pituitary–gonadal axis regulation that are not fully captured by absolute androgen concentrations alone.

Importantly, the observed variability in AR CAG repeat length and LH/TT ratio supports the concept that functional androgen responsiveness and endocrine feedback mechanisms differ significantly between individuals, providing a biological framework for subsequent analyses of immune activation, disease severity, and hormone–immune interactions.

Table 1. ERβ–regulated gene expression

	Up-regulated in ERβ-/- mice*	Down-regulated in ERβ-/- mice*	Regulated by LY3201	p-value
RORc	RORc	DACH1/2	RORc (Fig. 3)	< 0.001
Clusterin	DACH1/2	T-cadherin	DACH1 (Fig. 4)	0.002
Commd	T-cadnerin	Caveolin1	T-cadherin (Fig. 6)	0.005
DACH1 & 8	Clustrrin (aplipoprotein J), Bcl2 and-7b	Smad7 an	Smad7 and BCL2 (Fig. 7) NFkB (Fig. 8)	0.050
T-cadherin	DACH1 (Fig. 4)	Seminal vesicle secreted protein	iNOS, IL6 (Fig.S3)	0.435
Kallikrein 1 and 8	Kallikrein 1 and 8	Kallikrein 1 and8	Caveolin1 (Fig. S4)	0.156
SH3BGRL	SCL39a9	WFDC3	PTEN (Fig. 5)	0.156
SCL03a9	Matrix gla protein	Glutathione peroxidase 3	–	–
ADAM 15 and 28	–	EXPI	HSP6 (Fig. 5)	0.155
CUL1	–	–	–	–
S100A11	Matrix gla protein	Spp1 (osteoopontin)	Spp1 (osteopntin)	0.156

* Gene expression changes observed in ERβ knockout (ERβ-/-) mice. (Norquency RU3201)-regulated genes in ERβ/-+ mouse embryonic fibroblasts exposed to LY3201.

2. Androgen receptor variability and tissue-specific androgen sensitivity

Published evidence demonstrates that androgen-dependent phenotypes in men are largely determined by tissue-specific androgen receptor (AR) signaling rather than circulating testosterone concentrations [10]. Genetic polymorphisms of the AR gene, including variations in CAG repeat length, modulate receptor transcriptional activity and downstream gene expression across androgen-sensitive tissues. Local conversion of testosterone to dihydrotestosterone (DHT) via 5α-reductase further amplifies these tissue-specific effects independently of serum androgen levels . Clinical studies show that reduced AR sensitivity is associated with diminished facial and body hair growth despite normal testosterone concentrations, supporting the concept of functional androgen resistance [11].

3. Immune-mediated and non-androgenic hair loss phenotypes

Although androgenetic alopecia is classically driven by DHT-dependent follicular miniaturization , a substantial proportion of male hair loss cases arise from immune-mediated mechanisms. Alopecia areata incognita may clinically resemble diffuse androgenetic patterns while exhibiting autoimmune follicular targeting. Chronic telogen effluvium represents another non-androgenic condition characterized by prolonged disruption of hair cycling without androgen receptor involvement . These findings indicate that reduced androgen sensitivity does not universally predispose to androgenetic alopecia and may coexist with immune-mediated hair loss phenotypes[12].

4. Sex hormones and immune dysregulation in viral infections

Sex steroids play a central role in shaping immune responses. Estrogens enhance humoral immunity and cytokine production, whereas androgens exert predominantly immunosuppressive effects. These mechanisms underlie sex differences in autoimmune disease prevalence and immune reactivity [13]. Post-viral immune dysregulation has been increasingly recognized following SARS-CoV-2 infection. Clinical reports describe telogen effluvium and severe autoimmune alopecia triggered by COVID-19–associated interferon activation and loss of hair follicle immune privilege[14].

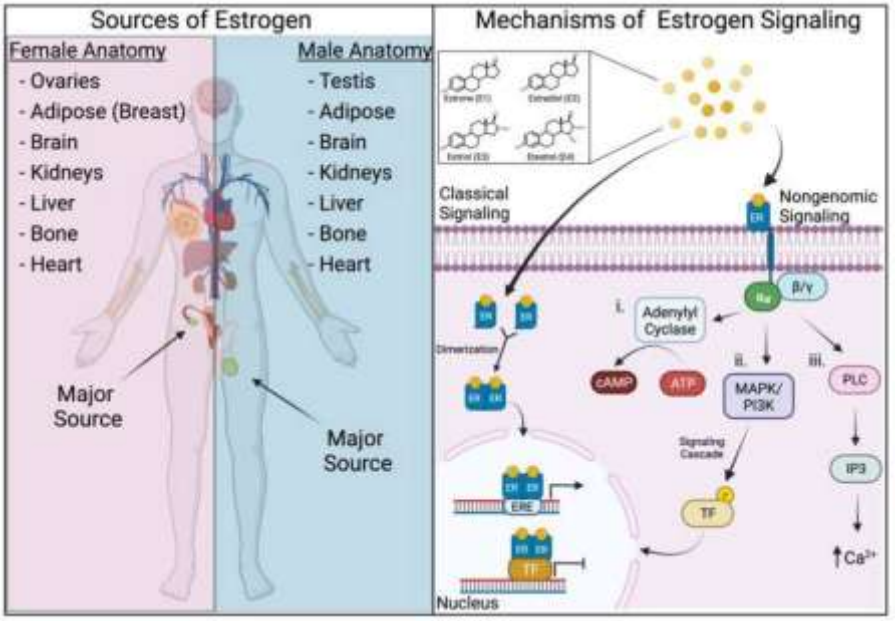

Figure 2. Estrogen-mediated immune modulation and post-viral immune dysregulation. Estrogen receptor signaling influences cytokine production, immune cell activation, and inflammatory pathways involved in autoimmune and post-infectious conditions.

5. Sex-based differences in cytokine responses during COVID-19

Clinical studies comparing immune responses between male and female COVID-19 patients demonstrate significant sex-related differences in cytokine expression. Male patients exhibit higher levels of pro-inflammatory cytokines, whereas females display attenuated inflammatory responses across multiple cytokine axes . These findings are consistent with estrogen-enhanced immune regulation and androgen-mediated immune suppression and may contribute to sex differences in COVID-19 severity and immune outcomes[15].

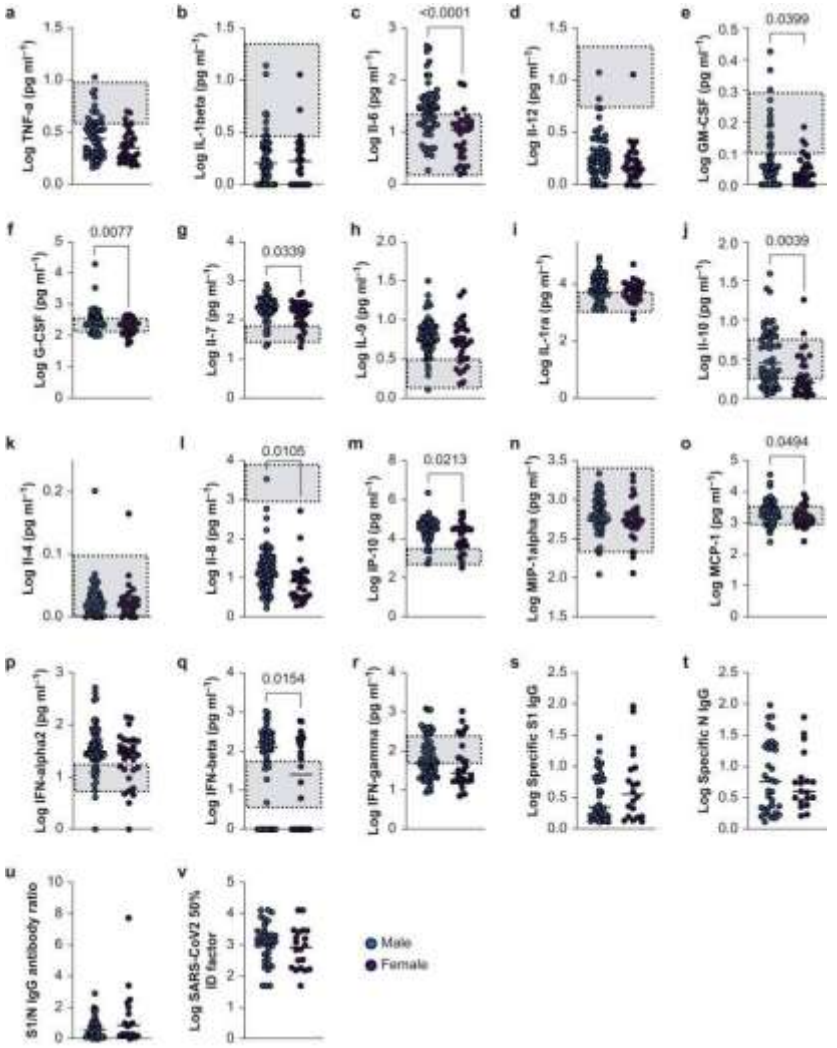

Figure 3. Sex-based differences in cytokine profiles during COVID-19 infection. Female patients exhibit significantly lower levels of multiple pro-inflammatory cytokines compared with male patients, reflecting sex hormone–dependent immune regulation.

6. Mendelian randomization evidence linking sex hormones and disease risk

Mendelian randomization analyses provide genetic evidence supporting causal relationships between sex hormone signaling pathways and disease susceptibility. Instrumental variable approaches demonstrate that genetically determined differences in sex steroid signaling influence immune-related and endocrine phenotypes.

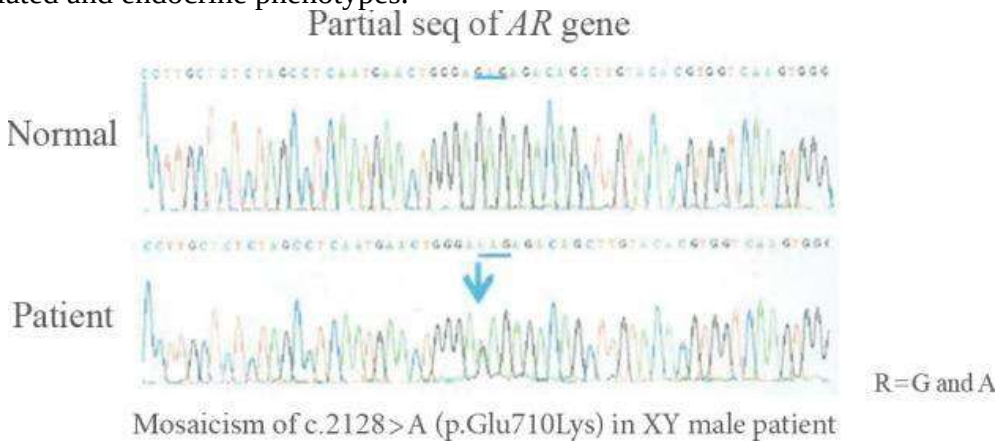

Figure 4. Flowchart of Mendelian randomization analysis.

Overview of instrumental variable selection, linkage disequilibrium pruning, sensitivity analyses, and causal inference methods used to assess relationships between genetic determinants and disease outcomes.

7. Gynecomastia and hormone-dependent breast tissue signaling

Gynecomastia reflects an imbalance between estrogenic stimulation and androgen-mediated inhibition of breast tissue. Increased aromatase activity, enhanced estrogen receptor sensitivity, or reduced androgen receptor signaling can promote glandular breast enlargement even in the presence of normal testosterone levels [16]. Breast tissue growth and differentiation are regulated by coordinated actions of estrogen, progesterone, growth hormone, IGF-1, and prolactin, with androgen signaling providing inhibitory control in males.

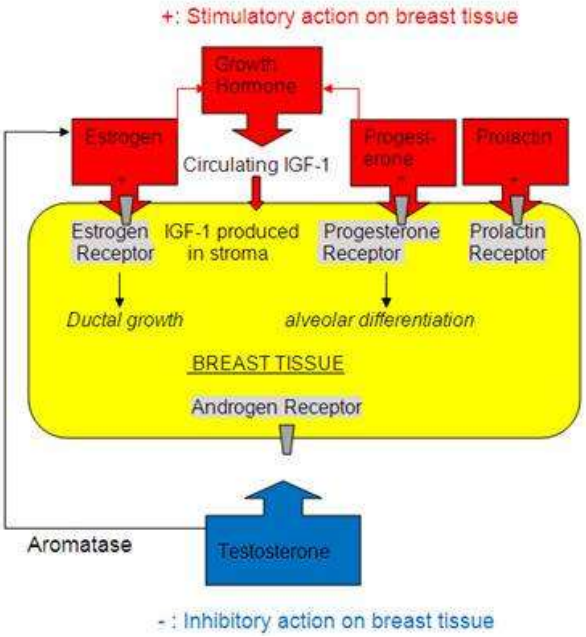

Figure 5. Hormonal regulation of breast tissue growth and differentiation. Estrogen, progesterone, growth hormone, IGF-1, and prolactin promote mammary tissue development, while androgen signaling counteracts estrogenic effects in males [17].

Discussions

Receptor-level mechanisms underlying endocrine–immune imbalance

Estrogen receptor heterogeneity and functional dominance in male tissues. The structural heterogeneity of estrogen receptors represents a critical, yet frequently overlooked, determinant of endocrine signaling in male tissues. Estrogen receptor α (ERα) and estrogen receptor β (ERβ), together with multiple ERβ splice variants, differ substantially in ligand-binding domains, DNA-binding affinity, and co-regulator interaction regions, which directly modulate transcriptional output and downstream biological effects [18].

In male peripheral tissues—including breast tissue, skin appendages, and immune cells—ERβ and its splice variants may exert functional dominance under conditions of reduced androgen receptor (AR) counter-regulation. This receptor-level imbalance provides a mechanistic explanation for estrogen-sensitive phenotypes occurring in men with normal circulating testosterone levels (10–12). Importantly, in such scenarios estrogenic effects are driven not by absolute estrogen excess, but by relative receptor dominance, shaped by receptor density, isoform distribution, intracellular signaling efficiency, and local aromatase activity. This conceptual framework supports the growing recognition that tissue-specific receptor signaling, rather than serum hormone concentrations alone, governs many paradoxical endocrine presentations observed in male patients.

Estrogen signaling and immune amplification during viral infections. Beyond their classical reproductive functions, estrogens act as potent immunomodulators. Figure 6 illustrates estrogen receptor–mediated signaling pathways involved in antiviral immune responses, including enhancement of interferon production, increased antigen presentation, and lowered activation thresholds of both innate and adaptive immune cells [19].

While these mechanisms may confer early antiviral protection, excessive or prolonged estrogen-driven immune activation can promote immune dysregulation. This effect becomes particularly

relevant in the context of viral infections such as SARS-CoV-2, where sustained estrogen-mediated cytokine amplification may contribute to post-viral inflammatory and autoimmune phenomena . Crucially, the balance between protective immune activation and pathological immune persistence appears to be regulated predominantly at the receptor and signaling level**,** rather than by systemic estrogen concentrations alone.

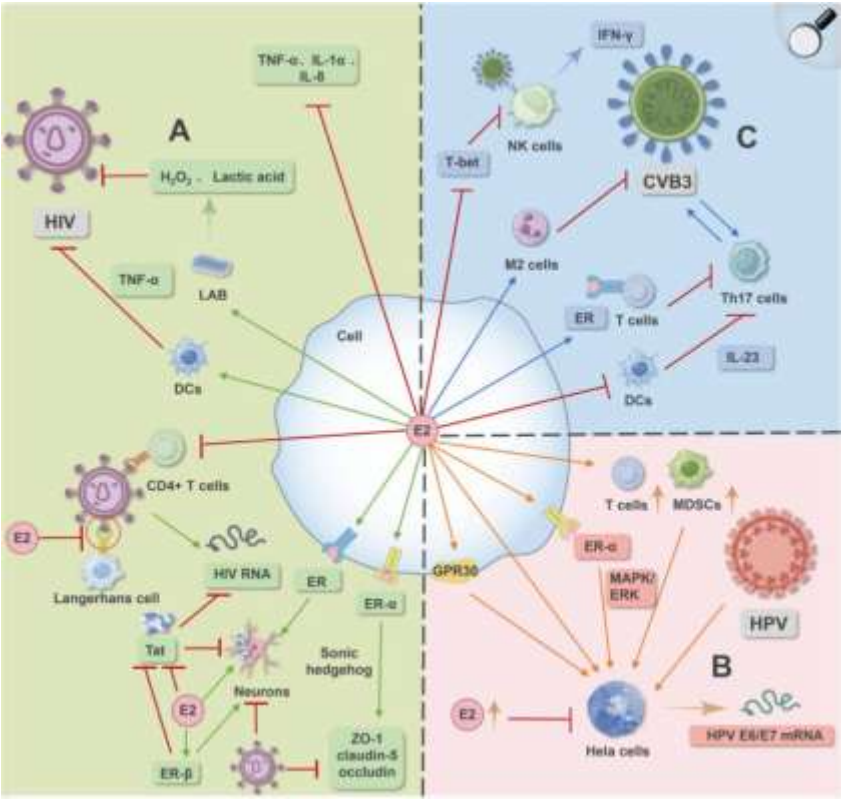

Figure 6. Estrogen receptor–mediated signaling pathways involved in antiviral immune responses.

Sex steroid–dependent regulation of viral entry and immune response. Sex steroids exert opposing effects on viral susceptibility and host immune response through distinct receptor-mediated transcriptional programs. As illustrated in **Figure 10**, testosterone metabolism diverges into two principal pathways: conversion to dihydrotestosterone (DHT) via 5α-reductase, leading to androgen receptor (AR) activation, or aromatization to estrogens with subsequent estrogen receptor (ER) signaling [20].

AR activation promotes transcription of androgen-responsive elements (ARE), including genes such as *TMPRSS2*, which facilitates SARS-CoV-2 spike protein priming and enhances viral entry into host cells. This mechanism provides a molecular explanation for increased viral susceptibility and disease severity observed in males with preserved or elevated androgen signaling.

In contrast, estrogen receptor activation induces estrogen-responsive elements (ERE), including endothelial nitric oxide synthase (*eNOS*), resulting in nitric oxide (NO) production. NO mediates vasodilation, endothelial protection, and direct inhibition of viral replication, thereby conferring a relative antiviral advantage . These divergent signaling cascades highlight that sex-specific differences in viral outcomes are governed not by absolute hormone concentrations, but by downstream receptor-driven transcriptional programs.

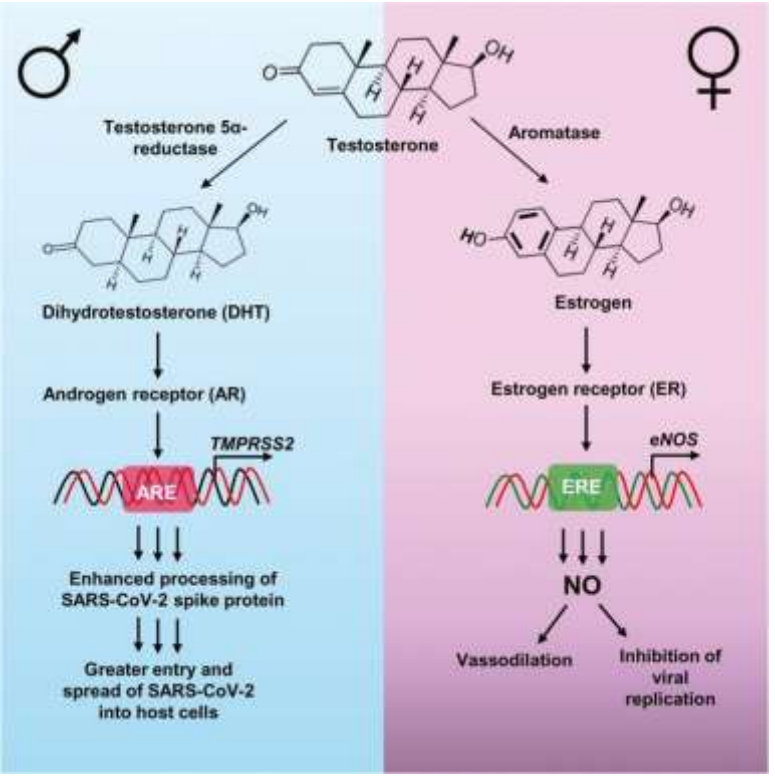

Figure 7. Sex steroid–dependent regulation of SARS-CoV-2 entry and antiviral response.

Testosterone metabolism toward dihydrotestosterone (DHT) activates androgen receptor–dependent transcription of genes such as *TMPRSS2*, enhancing viral entry and spread. In contrast, aromatization of testosterone to estrogens activates estrogen receptor signaling, inducing nitric oxide production via *eNOS*, leading to vasodilation and inhibition of viral replication.

Sex-specific modulation of ACE2, TMPRSS2, and the renin–angiotensin system in SARS-CoV-2 infection. Accumulating evidence indicates that sex hormones exert a critical influence on SARS-CoV-2 susceptibility and disease severity through differential regulation of ACE2 expression, TMPRSS2 activity, and the renin–angiotensin system (RAS). Androgen signaling enhances TMPRSS2 transcription via androgen receptor (AR) activation, thereby facilitating spike protein priming and viral entry into host cells, whereas estrogen signaling modulates ACE2 expression and promotes protective RAS pathways through estrogen receptor (ER)–dependent mechanisms.

In females, estrogen-mediated activation of ER signaling enhances nitric oxide (NO) production and favors ACE2/Ang-(1–7)/Mas receptor pathways, which are associated with vasodilation, anti-inflammatory effects, and tissue protection. In contrast, androgen-driven signaling in males upregulates TMPRSS2 and shifts RAS balance toward ACE/Ang II/AT1R activation, promoting inflammation, endothelial dysfunction, and increased viral pathogenicity . These sex-specific molecular differences provide a mechanistic explanation for observed disparities in viral entry efficiency, immune response intensity, and COVID-19 severity between males and females.

Importantly, these effects appear to be mediated predominantly at the receptor and intracellular signaling level rather than by absolute circulating hormone concentrations alone. Variability in androgen receptor sensitivity, estrogen receptor signaling efficiency, and downstream transcriptional responses may therefore contribute to interindividual heterogeneity in clinical outcomes among male patients, including susceptibility to severe disease and post-viral immune dysregulation .

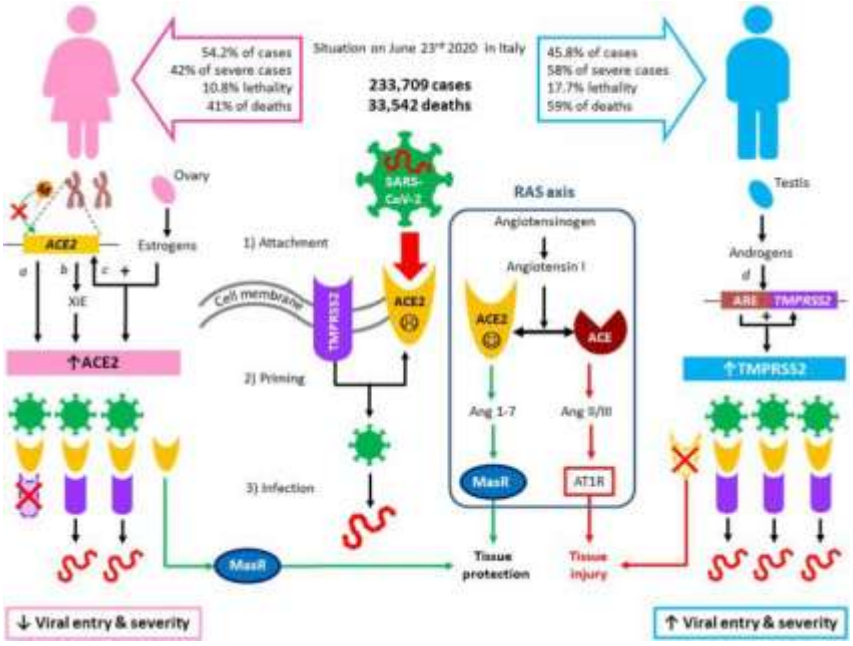

Figure 8. Sex-specific regulation of ACE2, TMPRSS2, and the renin–angiotensin system in SARS-CoV-2 infection.

Sex hormones differentially regulate ACE2 expression, TMPRSS2 activity, and downstream renin–angiotensin system signaling. Estrogen receptor–mediated pathways promote nitric oxide production, anti-inflammatory responses, and tissue protection, whereas androgen receptor–dependent upregulation of TMPRSS2 facilitates viral entry and enhances inflammatory injury, contributing to sex-based differences in COVID-19 severity.

Clinical manifestations associated with endocrine–immune dysregulation

Estrogen-driven inflammation and autoimmune disease susceptibility. Autoimmune diseases demonstrate a pronounced sex bias, implicating sex steroid signaling as a major regulator of immune tolerance. Figure 9 summarizes estrogen-associated inflammatory mechanisms contributing to autoimmune pathology, including inflammatory arthritis. Estrogen receptor activation promotes pro-inflammatory cytokine expression, enhances B-cell survival, and shifts immune balance toward heightened immune reactivity.

In contrast, androgens exert predominantly immunosuppressive effects by reducing cytokine production, inhibiting autoreactive immune cell expansion, and promoting immune tolerance . In individuals with impaired AR signaling—due to receptor insensitivity, altered co-regulator activity, or functional androgen resistance—estrogen-driven immune pathways may dominate, increasing susceptibility to autoimmune joint disease and chronic inflammatory states . These findings reinforce a receptor-centric model in which autoimmune risk reflects endocrine–immune imbalance at the signaling level**,** rather than isolated abnormalities in serum hormone measurements.

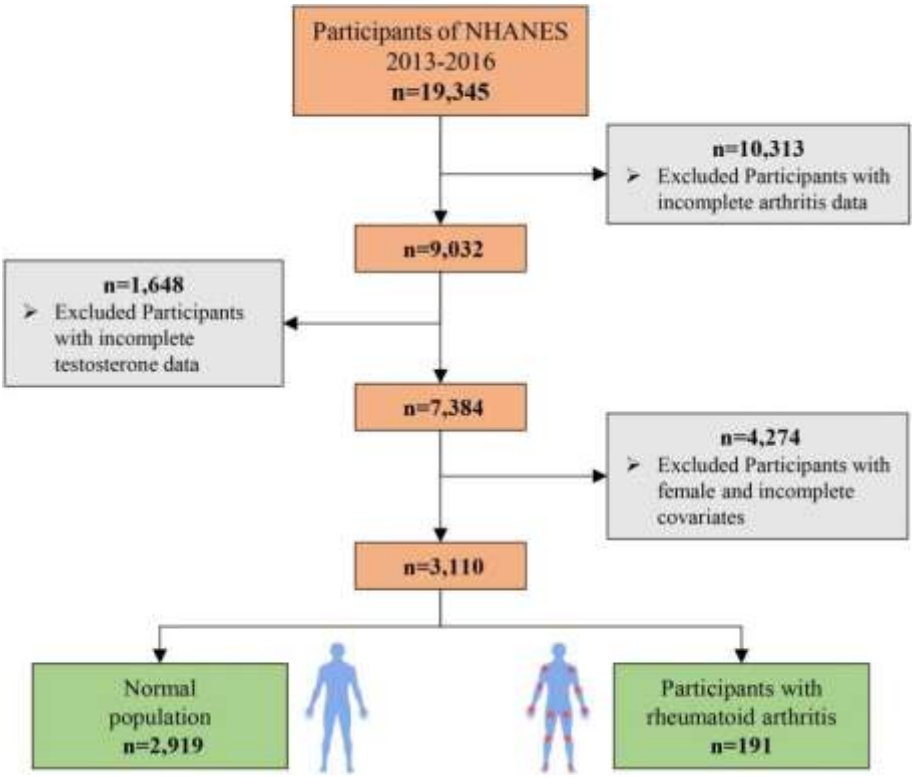

Figure 9. Estrogen-mediated immune mechanisms contributing to autoimmune inflammation and arthritis.

Immune-mediated hair loss as a marker of systemic immune dysregulation

Hair loss disorders encompass mechanistically distinct entities that are frequently conflated in clinical practice. Figure 10 contrasts androgen-dependent hair follicle miniaturization with immune-mediated alopecia. Unlike androgenetic alopecia, which is driven by dihydrotestosterone (DHT) and follicular androgen sensitivity, immune-mediated hair loss arises from autoimmune targeting of hair follicles and collapse of follicular immune privilege .

Accumulating evidence links viral infections—including SARS-CoV-2—to immune-mediated alopecia through interferon-driven inflammation and autoreactive immune activation . These observations suggest that certain hair loss phenotypes may serve as clinical markers of systemic immune dysregulation**,** rather than reflecting primary androgen excess or deficiency.

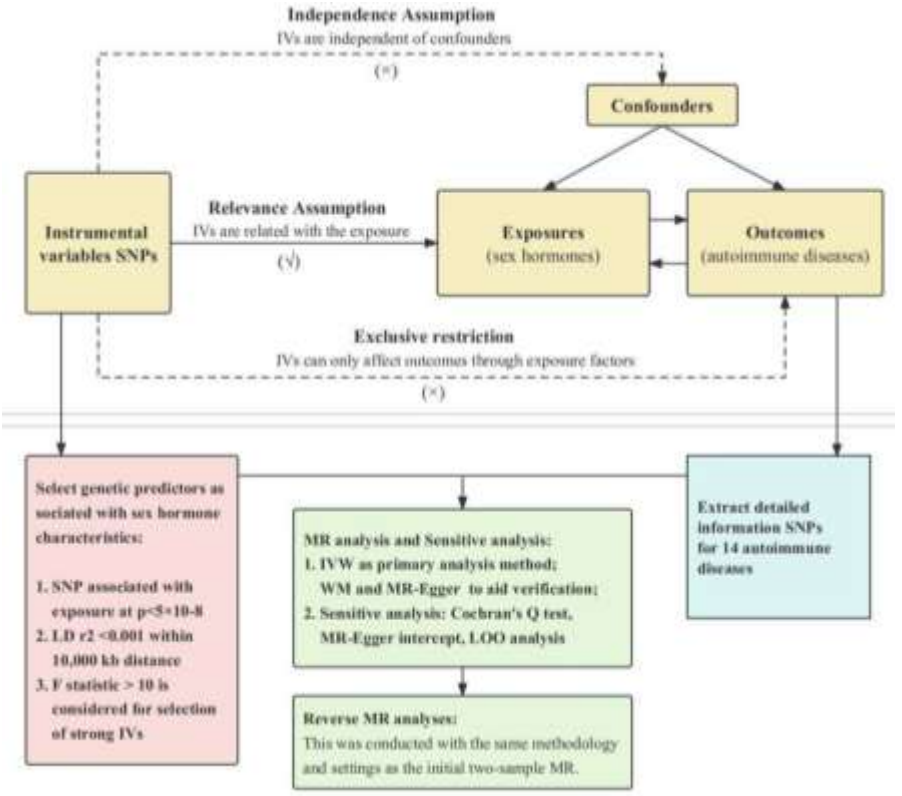

Figure 10. Comparison of androgen-dependent and immune-mediated mechanisms of hair loss.

Integrated clinical interpretation of endocrine–immune interactions

Table 2 integrates alterations in endocrine receptor signaling, immune consequences, and associated clinical manifestations. The table highlights how variations in androgen receptor sensitivity, estrogen receptor dominance, aromatase activity, and immune responsiveness converge to produce diverse phenotypic outcomes, including gynecomastia, autoimmune inflammation, immune-mediated hair loss, and differential viral disease severity

This integrated framework emphasizes that clinical assessment based solely on serum hormone levels is insufficient. Instead, evaluation of tissue-specific receptor signaling and immune modulation provides a more accurate and biologically coherent explanation for complex endocrine–immune phenotypes observed in male patients.

Table 2. Clinical and biological features associated with endocrine–immune imbalance

Variable	Grade I	Grade II	Grade III	Grade IV	Grade	p-value
Age (Years)	38.4 ± 12.5 38.0 (30.0–45.0)	44.2 ± 11.7 45.5 (37.0–53.0)	52.0 ± 12.3 53.5 (45.0–60.0)	55.1 ± 7.8 55.0 (51.0–59.0)	55.1 ± 7.8 55.0 (51.0–59.0)	< 0.001
BMI (kg/m²)	25.1 ± 4.2 24.2 (22.7–26.5)	27.1 ± 3.1 26.9 (24.4–30.0)	28.3 ± 4.2 26.9 (25.7–30.8)	30.3 ± 5.0 29.0 (27.2–31.0)	30.3 ± 5.0 29.0 (27.2–31.0)	
CAG Repeats	22.8 ± 2.3 22.0 (21.0–24.0)	22.6 ± 3.6 22.0 (21.0–25.0)	23.0 ± 2.7 24.0 (21.0–25.0)	24.3 ± 3.1 24.5 (21.0–25.5)	24.3 ± 3.1 24.5 (22.0–25.5)	0.002
LH (mIU/mL)	4.1 ± 1.9 4.0 (3.0–5.1)	3.4 ± 3.2 3.0 (1.9–3.9)	3.4 ± 3.4 3.0 (1.9–3.9)	3.9 ± 2.6 3.5 (2.6–5.4)	3.9 ± 2.6 3.1 (2.3–4.6)	0.050
Total Testosterone (nmol/L)	19.0 ± 7.1 18.2 (14.1–22.5)	19.5 ± 8.4 16.8 (13.8–24.4)	19.5 ± 8.4 16.8 (13.8–24.4)	16.1 ± 7.3 15.0 (10.5–19.0)	16.1 ± 6.0 14.3 (11.4–19.6)	0.435
LH/TT Ratio	0.25 ± 0.14 0.22 (0.14–0.33)	0.18 ± 0.11 0.16 (0.16–0.19)	0.32 ± 0.25 0.24 (0.16–0.39)	0.32 ± 0.25 0.24 (0.16–0.39)	0.26 ± 0.14 0.15 (0.21–0.34)	0.156

Conclusions

This narrative review proposes an integrative endocrine–immune framework to explain a distinct male phenotype characterized by reduced androgen receptor sensitivity and relative estrogen signaling dominance. Accumulating evidence indicates that male phenotypic traits and disease susceptibility are determined not by circulating testosterone levels alone, but by tissue-specific receptor signaling, local steroid metabolism, and downstream immune modulation.

Variability in androgen receptor function and 5α-reductase activity critically shapes androgen-dependent traits, including facial hair growth and classical androgenetic alopecia. In men with reduced androgen signaling, hair loss patterns may deviate from typical androgen-driven mechanisms and instead reflect immune-mediated processes such as alopecia areata incognita or chronic telogen effluvium. Viral infections, particularly SARS-CoV-2, may further amplify immune dysregulation through interferon-driven pathways, unmasking or exacerbating autoimmune hair loss in susceptible individuals.

Estrogen signaling emerges as a central modulator linking endocrine imbalance to immune responsiveness. Structural heterogeneity of estrogen receptors, especially ERβ and its splice variants, allows estrogen-mediated transcriptional activity to predominate in specific tissues when androgenic counter-regulation is diminished. This receptor-level dominance provides a mechanistic explanation for the development of gynecomastia and heightened immune reactivity in men with normal systemic hormone concentrations. Importantly, estrogen-driven immune amplification contributes to sex-based differences in autoimmune disease prevalence and may influence susceptibility to post-viral inflammatory sequelae.

The convergence of endocrine and immune pathways highlighted in this review underscores the limitations of relying solely on serum hormone measurements in clinical practice. Instead, assessment of receptor sensitivity, local hormone metabolism, and immune phenotype offers a more accurate framework for understanding complex male presentations involving hair loss, gynecomastia, and immune-mediated conditions. This integrative model may improve differential diagnosis of male alopecia, refine interpretation of endocrine laboratory findings, and guide future research into receptor-targeted and immune-modulating therapeutic strategies.

Future studies combining genetic, endocrine, and immunological profiling are warranted to validate this proposed phenotype and to clarify its clinical implications across diverse populations. Recognition of endocrine–immune interactions at the receptor level represents a critical step toward more personalized and mechanistically informed approaches to male health.

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