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Review Article

THE CONTROL OF SOME HORMONES RELATING TO CUTANEOUS AGING: MECHANISMS, MANIFESTATIONS, AND MANAGEMENT

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ABSTRACT: To summarize current evidence on the interaction between endocrine factors and skin aging, with a focus on the role of hormones and endocrine pathways. This review was conducted through a literature search in PubMed using the keywords "hormone," "skin aging," and "cutaneous aging." Studies addressing the role of hormones in age-related changes of skin physiology were reviewed and synthesized. Skin aging is closely associated with hormonal changes. In women, the sharp decline in estrogen during menopause is a central factor driving aging, leading to reduced collagen and elastin synthesis, dermal thinning, loss of hydration, and increased sensitivity to environmental stressors. In men, the gradual decrease in testosterone also contributes to skin aging, though typically less prominently. Overall, the evidence highlights hormones as key regulators of skin health and resilience. The changes of some hormones play an important role in the process of skin aging. These findings underscore the potential of future skin rejuvenation strategies targeting endocrine pathways.

Keywords: estrogen; progesterone; testosterone

1. INTRODUCTION

The process of skin aging is a complex biological phenomenon driven by two distinct yet interconnected pathways: intrinsic and extrinsic aging. A comprehensive understanding of their unique mechanisms and clinical presentations is fundamental to developing effective management strategies. While extrinsic factors, particularly solar radiation, are responsible for the most dramatic visible changes, the intrinsic, genetically programmed timeline of aging is profoundly governed by the body's endocrine system. The decline in hormonal signaling, therefore, represents a central pillar of the intrinsic aging process.

Within the framework of intrinsic aging, the programmed decline of the endocrine system, or hormonal senescence, stands out as a critical accelerator and modulator of the process. The age-related decrease in hormones produced by the gonads and adrenal glands—notably estrogen, testosterone, and dehydroepiandrosterone (DHEA)—directly contributes to the deterioration of skin structure and function.[1] This phenomenon, often termed "hormonal aging," is a core component of the intrinsic aging timeline. The predictable and profound changes in the endocrine environment, particularly the female menopause, provide one of the clearest examples of programmed aging, linking systemic hormonal shifts directly to visible cutaneous changes.[2]

The processes of intrinsic and extrinsic aging do not occur in isolation; rather, they are superimposed, and their effects can be synergistic.[3] The hormonal changes that drive intrinsic aging can significantly alter the skin's resilience to external damage. For instance, estrogen is known to confer a protective effect against photoaging. Consequently, the sharp decline in estrogen during menopause not only accelerates intrinsic aging processes like collagen loss but also heightens the skin's vulnerability to UV-induced damage. The clinical appearance of aged skin in chronically sun-exposed areas like the face and hands is therefore a composite phenotype, reflecting both the underlying hormonal deficiencies and the cumulative burden of photodamage. The accelerated chronological aging observed in females after menopause underscores this interplay, leading to earlier and more pronounced cutaneous changes.[4]

The clear distinction between the clinical and histological features of these two aging pathways reveals a critical principle for intervention. The underlying pathologies are fundamentally different: one is a systemic, gradual decline in biological function, while the other is a localized, severe tissue response to chronic environmental injury. This necessitates a multi-modal therapeutic approach. Strategies effective for the fine wrinkles and dryness of intrinsic aging, such as those focused on hydration and barrier repair, are likely insufficient for the deep, elastotic furrows and severe textural changes of photoaging. A comprehensive management plan must therefore address both pathways concurrently: protecting against further extrinsic damage (e.g., broad-spectrum sun protection), repairing existing photodamage (e.g., retinoids, laser resurfacing), and supporting the skin's intrinsic structural integrity against the backdrop of hormonal decline (e.g., targeted hormonal therapies, growth factors).

Table 1. The difference between intrinsic aging and extrinsic aging [3, 5-7]

Feature	Intrinsic (Hormonal/Chronological) Aging	Extrinsic (Photoaging) Aging
Primary Cause	Genetically programmed senescence, hormonal decline, endogenous oxidative stress	Chronic environmental exposure, primarily UV radiation; also pollution, smoking
Wrinkles	Fine, shallow, linear wrinkles	Coarse, deep furrows and wrinkles
Texture	Thin, dry, smooth, transparent	Leathery, rough, coarse, sallow
Pigmentation	Pale, even tone, few blemishes	Irregular, mottled hyperpigmentation, solar lentigines, freckles

Feature	Intrinsic (Hormonal/Chronological) Aging	Extrinsic (Photoaging) Aging
Elasticity	Gradual loss of elasticity, leading to laxity and sagging	Severe loss of elasticity, pronounced laxity
Epidermal Changes	General thinning, flattening of dermo-epidermal junction	Initial thickening (hyperplasia) followed by atrophy; cellular atypia
Dermal Changes	Gradual atrophy; organized degradation of collagen and elastin	Solar elastosis (massive accumulation of abnormal elastin); severe collagen degradation
Vascularity	Reduced number of blood vessels	Telangiectasia ("broken" blood vessels)
Associated Neoplasms	Benign lesions (e.g., cherry angiomas, sebaceous hyperplasia)	Benign, premalignant (actinic keratosis), and malignant lesions (carcinomas, melanoma)

2. MATERIALS AND METHODS

This study was conducted as a narrative review with the aim of synthesizing current evidence on the role of endocrine factors in skin aging. PubMed was selected as the primary database due to its comprehensive coverage of biomedical research. The search strategy combined keywords and MeSH terms, including "hormone," "skin aging," and "cutaneous aging." Additional terms such as "estrogen," "testosterone," "cortisol," "menopause," and "andropause" were also used. Boolean operators were applied to maximize the retrieval of relevant articles.

Publications in English were considered without restrictions on publication date. Eligible studies included clinical trials, observational research, experimental studies, and mechanistic investigations at cellular or molecular levels. Reviews and meta-analyses were also included when they provided relevant insights. Articles were excluded if they lacked a clear focus on hormonal regulation of skin or were opinion pieces without original or synthesized data.

Titles and abstracts were screened for relevance, followed by full-text review. Data were extracted narratively and organized into themes: (1) effects of sex hormones, particularly estrogen and testosterone, on skin physiology and aging; (2) influence of other endocrine factors, such as cortisol and thyroid hormones; and (3) therapeutic strategies targeting hormonal pathways, including hormone replacement therapy (HRT).

A narrative synthesis was adopted rather than a formal meta-analysis due to the heterogeneity of study designs, populations, and outcome measures. This approach enabled a broad and integrative perspective, emphasizing consistent findings, highlighting controversies, and identifying gaps in the literature.

3. RESULTS

Among the array of hormones influencing skin physiology, estrogen stands out as the most critical regulator of cutaneous health and appearance, particularly in women. The profound and rapid changes that occur in the skin following the menopausal decline in estrogen provide unequivocal evidence of its indispensable role. This "estrogen-skin axis" operates at molecular, cellular, and structural levels to maintain skin homeostasis, and its disruption is a primary catalyst for accelerated aging.

3.1. The Indispensable Role of Estrogen in Maintaining Skin Homeostasis

Estrogen is arguably the most influential hormone affecting "skinspan"—the duration of healthy, functional skin. Its deficiency, which begins in perimenopause and becomes permanent after menopause, precipitates a cascade of atrophic changes that markedly accelerate the aging process.[2] Estrogens exert pleiotropic effects, modulating the function of nearly all major skin cell types, including epidermal keratinocytes, dermal fibroblasts, and melanocytes, as well as appendages like hair follicles and sebaceous glands.[2] Beyond cellular regulation, estrogen is integral to maintaining dermal vascularity, promoting efficient wound healing, and modulating local immune responses.[2] Clinical observations affirm this connection, showing a strong positive correlation between circulating estrogen levels and perceived youthfulness, facial attractiveness, and overall skin health.[8]

3.2. Molecular Mechanisms: Estrogen Receptors (ERα, ERβ) and Signaling Pathways

The skin is a primary endocrine target organ for estrogens, with its cells expressing two main types of intracellular estrogen receptors (ERs): estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ).[9] These receptors are members of the nuclear hormone receptor superfamily and function as ligand-activated transcription factors.[2] While both receptors bind the principal estrogen, 17β-estradiol, with high affinity, they have distinct tissue distributions and can trigger different downstream effects.[2]

In the skin, ERβ is the predominantly expressed isoform, particularly in epidermal keratinocytes and dermal fibroblasts.[10] The classical, or genomic, signaling pathway involves estrogen binding to these receptors in the cytoplasm or nucleus. The hormone-receptor complex then dimerizes, translocates to the nucleus, and binds to specific DNA sequences known as Estrogen Response Elements (EREs) in the promoter regions of target genes, thereby upregulating or downregulating their transcription.[2] The cellular response to estrogen can be fine-tuned by the relative ratio of ERα to ERβ.[2] Notably, activation of ERβ is associated with protective effects, such as promoting wound healing and potentially offering chemo-protection against skin cancers.[11, 12] In addition to this classical pathway, estrogens can also initiate rapid, non-genomic signaling through membrane-associated receptors, leading to the swift activation of intracellular signaling cascades, such as the phosphorylation of ERK1/ERK2 kinases, which influence cell proliferation.[10]

3.3. The Menopausal Transition: Quantifying the Impact of Hypoestrogenism

The perimenopausal and menopausal periods represent a dramatic hormonal shift, with the precipitous decline in estrogen production leading to quantifiable and clinically significant deterioration of the skin.

Collagen Synthesis and Degradation: The most profound effect of estrogen loss is on the skin's collagen framework. Multiple studies have quantified a staggering loss of approximately 30% of the skin's collagen within the first five years following menopause.[2] After this initial rapid decline, collagen content continues to decrease at a more gradual rate of about 2.1% per year.[13] This loss, which includes both the structural Type I and the more elastic Type III collagen, is directly correlated with the duration of estrogen deficiency rather than with chronological age, highlighting the hormone's critical role in maintaining the dermal matrix.[2] Estrogen normally promotes collagen synthesis by upregulating key signaling molecules like transforming growth factor-beta (TGF−β).[10]

Elastin and Extracellular Matrix (ECM) Integrity: Estrogen deficiency accelerates the degeneration of elastin fibers, leading to a loss of skin resilience that manifests clinically as sagging, laxity, and wrinkling.[14] Mechanistic studies suggest that estrogen normally suppresses the activity of elastase, an enzyme that degrades elastin; its absence allows for unchecked degradation of the elastic fiber network.[10] The entire extracellular matrix, which provides structural support and hydration, is compromised by the loss of estrogen.[15]

Epidermal and Dermal Thickness: As a direct consequence of the degradation of its structural components, the skin becomes progressively thinner and more fragile. Skin thickness is estimated to decrease by an average of 1.13% per postmenopausal year, contributing to an atrophic appearance.[2]

Hydration, Sebum Production, and Barrier Function: Menopausal skin is characteristically dry (xerosis) and often itchy (pruritus).[13] This occurs because estrogen is crucial for maintaining skin hydration. It stimulates the production of hydrophilic glycosaminoglycans (GAGs), such as hyaluronic acid, in the dermis. These molecules are powerful humectants that bind and retain water, ensuring skin turgor and suppleness.[9] With estrogen loss, GAG levels plummet, the skin's water-holding capacity diminishes, and barrier function becomes impaired, resulting in increased transepidermal water loss (TEWL).[14]

Vascularity and Wound Healing: Postmenopausal skin exhibits reduced vascularity, which compromises nutrient delivery and the skin's overall vitality.[2] Furthermore, estrogen plays a vital role in all phases of cutaneous wound healing. Its absence leads to significantly delayed and impaired repair processes.[2] Estrogen normally accelerates healing by stimulating the deposition of new matrix proteins, promoting keratinocyte migration to cover the wound, and protecting these cells from apoptosis.[10]

The quantification of a 30% collagen loss in the first five years of menopause signifies more than just an acceleration of aging; it represents a "structural cliff." This period marks an unparalleled degradation of the skin's foundational framework, a rate of decline not observed at any other point in a woman's life or in the more linear aging process of men. This biological reality has profound therapeutic implications. The structural integrity lost during this period is far more difficult to rebuild than it is to preserve. Once the collagen architecture has collapsed and the ECM is significantly compromised, interventions are relegated to a corrective, rather than a preventative, role. This suggests that the most critical window of opportunity for intervention is not years after menopause but during the perimenopausal transition, when estrogen levels first begin to decline. Prophylactic strategies initiated during this phase—whether hormonal or non-hormonal—could serve to "cushion the fall" from this structural cliff, preserving the existing collagen matrix before it undergoes catastrophic failure. This shifts the clinical paradigm from one of repair to one of proactive preservation.

Furthermore, the observation that the decline in skin collagen post-menopause parallels the reduction in bone mineral density is not coincidental but points to a systemic, estrogen-dependent failure in maintaining structural proteins.[16] Both the dermal matrix of the skin and the organic matrix of bone are primarily composed of Type I collagen. The cells responsible for their synthesis and maintenance—fibroblasts in the skin and osteoblasts in bone—are both highly responsive to estrogen. The precipitous drop in estrogen at menopause systemically cripples the body's ability to sustain these vital collagenous tissues. Therefore, the visible deterioration of the skin—increased wrinkling, thinning, and laxity—can be viewed as an accessible and external clinical marker for a concurrent, but invisible, process of skeletal degradation. This elevates the dermatological assessment of menopausal skin aging from a purely aesthetic concern to a potential indicator of a more morbid systemic health risk, namely osteoporosis. Clinicians can thus use the state of a woman's skin as a prompt for discussions and screening regarding her bone health.

3.4. The Androgenic Influence on Male and Female Skin

While estrogen governs the landscape of female skin aging, androgens—primarily testosterone and its derivatives—are the principal architects of male skin structure and function. The differing levels and lifelong exposure to these hormones explain the fundamental and visible differences in how male and female skin ages. The gradual decline of androgens in men during andropause and the role of adrenal androgens like DHEA in both sexes further contribute to the complex hormonal narrative of skin aging

Testosterone is the primary determinant of the distinct characteristics of male skin.[17] Its lifelong influence results in skin that is thicker than female skin. This increased thickness is predominantly due to a denser dermis, which contains a higher concentration of collagen fibers.[17] Testosterone also potently stimulates the sebaceous glands, leading to significantly higher sebum production.[17] This results in men typically having larger pores and oilier skin. While this predisposes men to certain forms of acne, the elevated sebum production provides a more robust natural moisturizing factor, supporting the skin's lipid barrier and protecting against dryness for a longer period of life.

As men age, they experience a gradual decline in testosterone levels, a process sometimes referred to as "andropause".[18] This hormonal shift leads to visible changes in the skin. The reduction in androgenic stimulation results in a decrease in dermal density and elasticity, contributing to the formation of wrinkles and sagging skin. Concurrently, sebum production diminishes, causing the skin to become progressively drier.

3.5. Dehydroepiandrosterone (DHEA): The Adrenal Precursor and Its Decline

Dehydroepiandrosterone (DHEA), an androgen precursor secreted by the adrenal glands, is another key player in hormonal aging for both sexes.[2] DHEA levels peak in the third decade of life and then decline steadily and dramatically, falling to as low as 10-20% of their peak concentrations in the elderly.[2] This decline contributes to the signs of skin aging in both men and women.[1]

The role of DHEA becomes particularly critical for women after menopause. With the cessation of ovarian estrogen production, the peripheral conversion of adrenal DHEA into active estrogens and androgens becomes the primary source of these hormones.[2] However, because DHEA levels are also falling, this compensatory biosynthesis is significantly limited, exacerbating the postmenopausal hormone deficit. Some studies suggest that supplementation with DHEA may improve skin appearance in older individuals by increasing sebum production, hydration, and thickness.[19, 20]

3.6. Comparative Androgenic Effects: Why Male Skin Ages Structurally Differently

The differences in hormonal profiles create distinct aging trajectories for male and female skin.[17] Male skin begins with a significant structural advantage conferred by testosterone: it is thicker and possesses a higher collagen density from puberty onwards. The aging process in men is characterized by a slow, linear decline that mirrors the gradual reduction in testosterone levels.[21] In stark contrast, female skin generally maintains its thickness and structural integrity until menopause. At that point, the precipitous drop in estrogen triggers a period of rapid and dramatic thinning and collagen loss.

This difference in timing and tempo means that visible signs of aging often appear later in men. However, when wrinkles do form in male skin, they are typically deeper and more pronounced, often described as "fully grooved." This is attributed to the greater thickness of the skin combined with the action of stronger facial muscles. Women, on the other hand, tend to develop finer, more superficial wrinkles at an earlier age, particularly in the years immediately following menopause.

The hormonal aging process in men is less a discrete event and more a gradual erosion of a pre-existing structural advantage. Unlike the "structural cliff" of menopause, andropause in the skin is a slow, steady decline from a higher baseline. This implies that the strategic imperatives for managing skin aging should differ by gender. For men, the focus should be on consistent, long-term maintenance and protection to slow the rate of this gradual erosion. For women, a more acute and targeted intervention strategy during the perimenopausal transition is critical to mitigate the effects of the rapid structural collapse. This nuanced view moves beyond simplistic notions of who "ages better" to a more sophisticated understanding of the different temporal dynamics of hormonal aging and the corresponding therapeutic approaches required.

3.7. Emerging treatments: SERMs and Phytoestrogens

Selective Estrogen Receptor Modulators (SERMs): SERMs are a class of compounds that can act as estrogen agonists in some tissues while acting as antagonists or having neutral effects in others.[2] The therapeutic goal is to develop a SERM that delivers the desired estrogenic benefits to the skin, bone, and central nervous system, while simultaneously blocking estrogenic activity in the breast and uterus, thereby providing a much safer long-term risk profile.[22]

Phytoestrogens: These are naturally occurring plant-derived compounds that possess a structural similarity to 17β-estradiol, allowing them to bind to and modulate estrogen receptors.[23] They tend to have a higher binding affinity for ERβ, the predominant estrogen receptor in the skin, which is associated with protective effects.[24] Phytoestrogens, particularly isoflavones like genistein from soy, represent a promising alternative for managing skin aging, especially when applied topically.[23]

Mechanisms and Evidence: Research has shown that topical phytoestrogens can increase the production of collagen and hyaluronic acid, improve skin hydration and elasticity, and provide potent antioxidant effects to protect against oxidative stress.[24] They achieve this by modulating key signaling pathways, upregulating antioxidant defenses, and inhibiting the matrix metalloproteinases (MMPs) that degrade collagen.[24] Clinical trials using topical genistein formulations have demonstrated significant improvements in facial wrinkles and skin hydration in postmenopausal women, with the benefit of localized action and a lack of systemic side effects.[23]

The limitations and risks of systemic HRT have catalyzed a paradigm shift in the management of hormonal skin aging. The future lies not in broad, systemic interventions but in localized, tissue-selective, and biomimetic approaches. The research into SERMs, topical phytoestrogens, and novel concepts like "soft estrogens"—molecules designed for potent local effects in the skin followed by rapid metabolic inactivation before entering systemic circulation [25]—all point toward a more sophisticated strategy. This new frontier can be described as "Receptor-Targeted Cosmeceuticals." The goal is to precisely modulate estrogen receptor activity within the skin's microenvironment to harness the hormone's benefits while completely avoiding systemic exposure and its associated risks. This represents a convergence of endocrinology, pharmacology, and dermatology, moving from the "blunt instrument" of traditional HRT to the "scalpel" of targeted, skin-specific therapies.

3.8. Future directions

3.8.1. Development of Local/Intradermal Estrogen Therapy

Small trials report improved elasticity, firmness and wrinkle depth with topical estradiol/estriol.[26] Yet systemic absorption from facial skin is insufficiently quantified; clinicians remain wary, especially for patients with hormone sensitive conditions. Photoaged facial sites may show "estrogen resistance," with procollagen increases seen in sun protected but not sun exposed skin.[27] Thus current guidelines do not endorse HRT (systemic or topical) solely for "estrogen deficient skin".[28] Safer surrogates include weaker estrogens (estriol) and "soft drug" designs such as methyl estradiolpropanoate (MEP), which are metabolized to inactive forms upon systemic entry; a 14 week RCT showed improvements in dryness, laxity and atrophy.[29] Priority research needs are long term RCTs on efficacy in photoaged facial skin, standardized formulations/doses, and rigorous PK to define systemic exposure during local facial use.

3.8.2. Exploitation of Endogenous (Intracrine) Steroidogenesis of the Skin

Beyond endocrine signaling, skin synthesizes its own steroids ("intracrinology") from precursors such as DHEA/DHEAS using local enzymes (CYP11A1/P450scc, 3β HSD, 17β HSD, etc.).[30] After menopause, tissue conversion of adrenal DHEA becomes a primary source of estrogens.[30, 31] Circulating DHEA/DHEAS falls to ~10–20% of youthful levels with age.[2] Cutaneous steroidogenesis also wanes: reduced StAR expression impairs cholesterol transport to mitochondria—the rate limiting entry step for steroid synthesis—driving local hypoestrogenism, oxidative stress, atrophy and delayed healing.[31, 32] Intracrine decline is one of three pillars of menopausal skin aging, alongside systemic estrogen loss and lower ER expression.[14]

Therapeutic strategies:

- Topical DHEA (pro hormone): supplies substrate for local, self regulated conversion to androgens/estrogens; a 1% DHEA cream improved sebum, brightness and epidermal atrophy over 4 months in postmenopausal women (pilot, placebo controlled).[20] Safety requires vigilance for androgenic effects (acne, hirsutism).

- Retinoids as intracrine enhancers: beyond collagen and turnover effects, atRA up regulates StAR and restores steroidogenesis in aged keratinocytes, potentially "priming" tissue to utilize precursors.[33] This reframes retinoids as synergists with intracrine targeted therapy.
- Other modulators: melatonin, non calcemic vitamin D derivatives, lumisterol analogs may support local neurohormonal balance with favorable safety profiles.[32]

In sum, evidence is early stage; larger, longer trials should quantify efficacy, local hormone profiles and adverse events. Nonetheless, shifting from "replacement" (potent final hormones) to "restoration" (precursors + enzymatic support) may offer a safer, physiology tuned path to rejuvenation, especially when combined with retinoids.

3.8.3. Advanced Delivery Hormone Technologies: Microneedles, Nanoparticles, Hydrogels & Micro Implants

The stratum corneum blocks most hormones (>500 Da; hydrophilic peptides) and systemic leakage risks constrain dosing—creating an "efficacy–safety paradox." Advanced delivery seeks precise dermal access with controlled exposure.[34]

Microneedles (MNs). Arrays (≈2000 μm) breach the stratum corneum to create transient microchannels with minimal pain/bleeding.[35, 36] Modalities are solid ("poke and patch"), coated ("coat and poke") for rapid micro doses, hollow ("poke and infuse) for controllable liquid delivery, dissolving (biodegradable polymer needles that release cargo), and hydrogel forming (swell to create diffusion conduits from a reservoir).[34]

Nanoparticles (NPs). Lipid (liposomes, SLNs) and polymeric carriers (e.g., PLGA) enhance stability, penetration (including follicular route), and controlled release; surfaces can be tuned (PEGylation, ligands).[37, 38] Nanoemulsions/micellar systems improve estradiol delivery with low plasma fluctuation and good cosmesis—commercial validation exists via micellar nanoparticle estradiol emulsions.[39] Platforms extend to other hormone modulators (e.g., raloxifene, 2 methoxyestradiol).[38-40]

Hydrogels. Highly hydrated, biocompatible polymer networks enable high loading and sustained, diffusion-controlled release while hydrating and softening stratum corneum; "smart" hydrogels respond to pH/temperature/enzymes for on demand dosing. They can serve as MN reservoirs or embed NPs for multi layer control.[41, 42]

Subcutaneous micro implants. Bioidentical E2/T pellets provide steady systemic exposure for 6–8 months, benefiting skin thickness, collagen and hydration as part of global HRT.[28, 43] Caveats are irreversibility until dissolved, need for 6 monthly monitoring, and risk of tachyphylaxis/supraphysiologic levels in repeat cycles. They are best reserved for selected patients unresponsive to other routes.

3.8.4. Combination of Hormones and Molecular Anti Aging Therapy (Senolytics, nicotinamide adenine dinucleotide (NAD+) Boosters, Antioxidants)

Skin aging arises from convergent pathways: hormonal decline (reduced anabolic signaling), cellular senescence and Senescence-Associated Secretory Phenotype (SASP) driven matrix degradation, mitochondrial/NAD+ decline, and oxidative stress. Combining modalities targets complementary failure points for additive or synergistic benefit.

Senotherapeutics. Senolytics selectively clear senescent cells; senomorphics suppress SASP without killing cells.[44] Removing SASP rich fibroblasts may reduce chronic inflammation and collagen breakdown, potentially amplifying the anabolic effects of HRT or estrogen mimetics while enabling lower hormone doses.[44, 45]

NAD+ boosters. NAD+ falls with age (~midlife), impairing mitochondrial function, DNA repair and sirtuins.[46] Precursors (nicotinamide mononucleotide, nicotinamide riboside) raise NAD+ in preclinical/early clinical work, with signals for improved DNA repair, collagen regeneration, and UV resilience.[46] In theory, hormones provide the "instructions," NAD+ restores cellular "capacity," yielding complementary gains.[47]

Antioxidants (topical/systemic). Reactive oxygen species (ROS) drive intrinsic and photoaging; endogenous defenses wane with age. Topical vitamins C/E, ferulic acid, polyphenols neutralize ROS.[48] Some hormones (melatonin; possibly estrogen) exert intrinsic antioxidant actions and upregulate defense enzymes, linking endocrine and redox axes.[49] Combining hormonal approaches with antioxidants supplies both internal and external ROS control.

An integrated model. A pragmatic stack might include: (i) a local hormonal base (e.g., DHEA or soft estrogen like MEP) or systemic HRT when indicated; (ii) daily NAD+ precursors for energy/repair capacity; (iii) high potency antioxidant photoprotection; and (iv) time limited senolytic courses to reduce senescent burden. Key research gaps are human trials testing combinations, dose finding to minimize hormonal risk, standardized cutaneous endpoints (collagen, biomechanics, imaging), and mechanistic biomarkers (SASP panels, NAD+ flux).

4. DISCUSSION

The aging of human skin is an intricate process orchestrated by a complex interplay of genetic programming, environmental insults, and, pivotally, the dynamic fluctuations of the endocrine system. Hormones, particularly sex steroids, act as master regulators of cutaneous structure and function. Their decline with age, especially the precipitous drop in estrogen during the female menopause, serves as a primary catalyst for the visible signs of intrinsic aging, including thinning, dryness, wrinkling, and loss of elasticity.

A Holistic Model of Hormonal Skin Aging

A comprehensive model of skin aging must view the clinical outcome as the net result of a shifting balance between a declining hormonal "support system" and a cumulative "damage load." The support system is comprised of anabolic and regenerative hormones like estrogen, testosterone, DHEA, and thyroid hormone, which maintain collagen synthesis, hydration, and metabolic activity. The damage load arises from both internal sources, such as the catabolic effects of the stress hormone cortisol and endogenous oxidative stress, and external environmental factors, dominated by UV radiation.

This balance is further modulated by an individual's unique physiology, including gender-specific hormonal profiles and baseline skin structure, as well as by lifestyle choices encompassing diet, stress management, and sun protection. The aging trajectory of any individual's skin is therefore a unique multifactorial equation, where hormonal senescence is a key variable that not only drives intrinsic changes but also modifies the skin's susceptibility to extrinsic damage.

Unmet Needs and Future Research Directions

Despite significant advances in our understanding, several key areas require further investigation to optimize the management of hormonally aged skin.

Skin-Specific Hormonal Therapies: While the dermatological benefits of estrogen are clear, the risks of systemic HRT preclude its use solely for skin health. There is a critical need for more robust, large-scale clinical trials focused on developing and validating skin-specific therapies. This includes low-dose topical estrogen formulations, novel SERMs with favorable skin-to-systemic activity ratios, and phytoestrogen-based cosmeceuticals. Such studies are essential to establish definitive efficacy, long-term safety profiles, and clear clinical guidelines.[14]

Elucidation of Molecular Mechanisms: While we know that compounds like phytoestrogens can improve skin health, the precise molecular mechanisms underlying their effects are not fully understood.[50] Deeper research into how these molecules interact with different estrogen receptor subtypes, modulate signaling cascades, and influence gene expression in skin cells will enable the development of more targeted and effective second-generation compounds.

Understanding Hormonal Interactions: The skin is simultaneously exposed to multiple hormones. Research is needed to better understand the complex interplay between different endocrine axes, such as the interaction between stress hormones like cortisol and sex hormones like estrogen, and their combined impact on skin aging.[51]

Personalized Medicine: The future of anti-aging dermatology lies in personalization. Developing treatment protocols that are tailored to an individual's specific hormonal status, genetic predispositions (e.g., to photoaging), microbiome profile, and lifestyle represents the next frontier. This could involve hormonal testing to guide therapy or genetic screening to identify those at highest risk who would benefit most from early preventative interventions.

5. CONCLUSION

In conclusion, the aging process of the skin is a multifaceted phenomenon with some hormones acting as a central and influential force. By understanding the profound impact of these chemical messengers, we can better appreciate the intricate biology of our skin and make informed choices to support its health and vitality throughout our lives.

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