

Exploring the Role of Hormones in Skin Health and Care — A Systematic Review.

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Abstract

This systematic review aims to identify the impact of hormones on the skin and explores the dermatological consequences of hormonal abnormalities.

For the present systematic review, articles focused on the effect of hormones on acne, aging, xerosis, and hyperpigmentation are considered. Articles on the therapeutic use of hormones are excluded from the present review. 119 prominent dermatology and medical journals were scrutinized for relevant references published from January 1, 2012, to December 2022. We mitigated bias by selecting references with strong methodologies, including detailed study design, clinical parameters, and rigorous statistical analysis. High-impact factors further supported the credibility of these sources.

Among the 4628 articles identified, 123 were considered relevant; of these, 79 articles were research studies and 44 were review articles. Research suggests that elevated levels of androgens, IGFs, cortisol, prolactin, and growth hormone, alongside diminished levels of estrogen, melatonin, and PTH, contribute to acne development.

Deficiencies in estrogen, androgen, melatonin, vitamin D, MSH, and IGFs and overactivation of cortisol and leptin can result in wrinkles and fine lines.

Hyperpigmentation can be triggered by increased levels of MSH, ACTH, and thyroid hormone can be involved, and decreased melatonin and vitamin D. Reduced thyroid hormone levels, estrogen, cortisol, IGF1, and growth hormone can cause xerosis. Of note, hormones like CRH, ACTH, MSH, Growth hormone, Cortisol, Melatonin, and leptin prove to exhibit a circadian behaviour in humans.

Recognizing the intricate connections between hormones and skin, professionals can develop more effective and comprehensive skin care strategies to promote overall well-being and beauty.

Keywords: Hormonal dysregulation, Endocrinology of skin, Skin aging, Circadian rhythm, Cortisol, Estrogen deficiency, Androgens, Insulin resistance, IGF-1, Melatonin, Hyperpigmentation, Acne, Xerosis, Skin barrier dysfunction.

Introduction

In the aftermath of the pandemic, there is a notable shift towards a holistic perspective on two sectors, beauty, and health (Abdalla MA, Shahatha NM, Zahim HS), prioritizing overall well-being over mere aesthetics. This

transition underscores a crucial focus on internal and root cause factors.

Consequently, the intricate role of hormones has become a focal point in current research within the skincare and healthcare sectors Agarwal S, Mirzoeva S, Readhead B, et

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al. Understanding a complete overview of existing hormone families, their impact on skin, chronobiology, and how scientific concepts evolved over time is challenging.

The endocrine system plays a crucial role in every life process. It serves as the body's intricate messaging system Antonini D, Sibilio A, Dentice M, et al; hormones circulate through the bloodstream, maintaining homeostasis by regulating most body functions, including growth and development, metabolism, reproduction, body temperature, and hormonal actions enable the body's response to the internal and external environment [1]. Also, there are various extrinsic and intrinsic factors that cause imbalance or alter natural rhythmicity in hormone levels. The skin Ayyar VS, Sukumaran S, the body's largest organ, is a frontline defense against external stressors also called exosome factors [2] Baida G, Agarwal S, Readhead B, et al. Internally, skin layers are equipped with nerve endings and receptors, including those for hormones. Visible reflection of external and internal changes can be seen on the skin.

A plethora of hormones communicate their effect through their unique chemical structures. Like many of the biological functions of the body, several hormones like melatonin, cortisol, gonadal steroids, prolactin, and thyroid hormone, exhibit rhythmic secretion and action patterns which are influenced by day and night cycle, and hormones taking parts in metabolic functions like insulin and leptin are partly regulated by environmental factors including light-dark cycle [3,4,5,6] Baida G, Bhalla P, Yemelyanov A, et al.

Skin is the longest and most exposed part of the body, which encounters environmental stressors; skin's barrier function protects the body from exosome factors. Skin also acts as the biggest neuroendocrine organ and it is a site for complicated endocrine processes such as hormone receptor expressions, hormone/precursor synthesis, and hormone deposition. The activity of hormones in specific skin cells was observed in many research articles [7, 8, 9]. Human skin functions as both a recipient and a producer of hormones.

Skin mainly synthesizes melanocyte-stimulating hormone (MSH) from skin keratinocytes, melanocytes, fibroblasts, and endothelial cells. MSH is shown to have anti-inflammatory effects. Corticotropin-releasing hormone (CRH), also produced in the sebaceous glands increasing sebocyte activity, and adrenocorticotrophic hormone (ACTH) stimulate hair follicles and melanocytes, regulating the immune response in the skin, while cortisol, stimulated by both keratinocytes and the sebaceous gland, controls the stress response. Similarly, androgen, estrogen, and vitamin D secreted from the sebaceous gland control pigmentation and sebum production and promote barrier function [10] Bracci M, Ciarapica V, Copertaro A, et al. Skin cells in their nucleus and cytoplasm have receptors for growth hormone (GH) and IGF-1 which regulate cell proliferation and differentiation processes. Sex steroids, like estrogens and androgens, have receptors scattered on skin cells and exert their influence on sebum production, hair growth, skin pigmentation, and immune responses. Cortisol has receptors on keratinocytes

and fibroblasts regulating inflammatory responses, whereas melatonin has receptor in melanocytes and regulates melanin production Bocheva G, Slominski RM, Slominski AT [7, 11, 12] Boudon, S., Heidl, M., Vuorinen, A., et al. The impact of hormones on the skin is a critical aspect for both males and females; however, the cyclic nature of many hormones throughout women's life phases, encompassing puberty, menstruation, reproduction, and menopause, causes distinct changes in skin health. This reality adds a unique layer of complexity to women's skin health journey. In adolescence, hormonal fluctuations often give rise to skin concerns such as seborrhea and acne Chae M, Bae IH, Lim S, et al, while the menstrual cycle introduces its own dynamic changes Challet E. Pregnancy entails a unique complexion journey, characterized by heightened pigmentation and potential skin sensitivity Chen Y, Lyga J. The transformative phase of menopause is accompanied by shifts in collagen levels Christou GA, Christou MA, Žiberna L, et al, contributing to skin elasticity and dryness alterations Ciaffi J, van Leeuwen NM, Schoones JW, et al. Understanding these complexities is crucial for empathizing with and addressing women's skin health concerns D'Agata AL, Roberts MB, Ashmeade T, et al..

Skin manifestation under the influence of cortisol, androgens and estrogens has been extensively studied D'Orazio J, Jarrett S, Amaro-Ortiz A, et al, whereas less research has been published for the role of other hormones in skin health in this article Dashko MO, Syzon OO, Chaplyk-Chyzo IO, et al, efforts have been made to unify and synthesize all data published in the past ten years which explores the complex interplay between skin and hormonal functions Davoudi Z, Araghi F, Vahedi M, et al, specifically emphasizing the circadian behavior of hormones and its impact on skin and related concerns.

Methodology

The PRISMA framework for systematic reviews and meta-analyses was utilized to elaborate this review article [13] De Brouwer SJ, Van Middendorp H, Stormink C, et al. In this systematic review, we focused on research articles elucidating the influence of hormones on maintaining skin health. Studies investigating skin manifestations resulting from endocrine dysfunction or imbalance were incorporated. Our review also encompasses the scientific insights shared by researchers on the circadian rhythm of hormone secretion. As the review article focuses on the non-therapeutic aspect of hormonal dysfunctions Deli T, Orosz M, Jakab A, research papers explaining hormone replacement, skin cancer El Mohtadi M, Whitehead K, Dempsey-Hibbert N, et al, and therapeutic use of hormones to treat skin diseases were excluded from the present systematic review. Extensive literature exploration was conducted across MEDLINE via PubMed, Scopus, and Google Scholar databases from January 2012 to December 2022 Franik G, Włoch S, Kowalczyk K, et al. The keywords were carefully chosen to encompass a broad range of hormones and endocrine-related terms as well as skin and dermatology-related terms Fukayama M, Asano Y, Shinozaki-Ushiku A, et al; Fukuda H, Suzuki T, Saotome A, et al this was done

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to ensure a comprehensive search that covers all potential studies related to the influence of hormones on skin health and manifestations of endocrine imbalances (Table 1) Gamble KL, Berry R, Frank SJ, et al Gasco V, Bima C, Geranzani A, et al Gnocchi D, Bruscalupi G Gowri BV, Chandravathi PL, Sindhu PS, et al.

The search strategy was used to search for relevant articles from the enlisted databases Gratton R, Del Vecchio C, Zupin L, et al. (Table 2)

Additionally, we conducted manual searches and identified cross-references to ensure a thorough exploration of pertinent literature Grymowicz M, Rudnicka E, Podfigurna A, et al, Henneicke H, Tonnus W, Hofbauer LC, Hou X, Wei Z, Zouboulis CC, et al, Jaworek AK, Jaworek M, Szafraniec K, et al.

For the present study, we incorporated research papers, case reports, and reviewed articles elucidating skin manifestations associated with various hormones 35. Kaleta K, Nikolakis G, Hossini AM, et al. Both prospective and retrospective studies were deemed eligible for inclusion. Exclusions comprised conference proceedings, non-original publications, and articles not written in English language Jiménez-Cortegana C, Ortiz-García G, Serrano A, et al.

Initial screening of articles involved evaluating titles and abstracts. Two independent reviewers conducted this primary screening with validation of results by a single expert investigator. Subsequently, a comprehensive analysis of data was undertaken to ascertain outcomes, including dysregulated hormone levels, factors influencing alterations in hormone levels, affected skin parameters, and concomitant conditions exacerbating skin manifestations Karaca Z, Taheri S, Firat ST, et al. (such as UV exposure, sleep deprivation, stress, and menstruation). Furthermore, data collection encompassed variables such as study size, participant demographics, geographic origin of research, author details, and impact factors of the articles. Methodological rigor, study findings, and conclusions were critically evaluated for each study, forming the basis of this systematic review. 4628 candidate articles were searched based on titles and abstracts 37. Kasumagic-Halilovic E, Kelly G, Sweeney CM, Fitzgerald R, et al. The investigator concentrated on non-therapeutic dimensions of hormonal dysfunctions, deliberately excluding research papers addressing hormone replacement, skin cancer, and therapeutic application of hormones in skin disease management. These topics were excluded as they fall under therapeutic dimensions, which is not the focus of this review.

Table 1: Details of keywords used for searching relevant articles on databases and for open searches.

Key words used for Hormone	Hormone, Endocrine, Corticotropin-Releasing Hormone, Adrenocorticotrophic Hormone, LH (Luteinizing Hormone), FSH (Follicle Stimulating Hormone), Growth Hormone, Prolactin, MSH (Melanocyte Stimulating Hormone), Thyroxine, Thyroid, Parathyroid Hormone (PTH), Androgen, Testosterone, Estrogen, Estradiol, Oestradiol, IGF (Insulin-Like Growth Factor), Leptin, Vitamin D, Serotonin, Epinephrine, TRH (Thyrotropin-Releasing Hormone), Vasopressin, Gonadotrophin Releasing Hormone (Gnrh), Growth Hormone-Releasing Hormone (GHRH), Prolactin-Related, PRF (Prolactin Releasing Factor)
Key Words used for skin conditions	Skin, Dermatology, Dermis, Integument, Cutis, Acne, Skin Aging, Dermatitis, Pigmentation, Skin Dryness, Xerosis, Xeroderma, Psoriasis, Blackheads, Pimples, Ageing, Photoaging, Skin Inflammation and Pigmentation

Table 2: Search strategies used for searches on PubMed (MEDLINE) and Scopus.

Sr.no	Database use	Search Strategy
1	PubMed	((Hormone[Title/Abstract] OR Endocri*[Title/Abstract]) OR Cortisol[Title/Abstract] OR Dehydroepiandrosterone[Title/Abstract] OR Melatonin[Title/Abstract] OR (corticotrophin releasing hormone[Title/Abstract]) OR CRH[Title/Abstract] OR ACTH[Title/Abstract] OR (Adrenocorticotrophic hormone [Title/Abstract]) OR LH[Title/Abstract] OR (luteinizing hormone[Title/Abstract]) OR FSH[Title/Abstract] OR (follicle stimulating hormone[Title/Abstract]) OR (growth hormone[Title/Abstract]) OR Prolactin[Title/Abstract] OR MSH[Title/Abstract] OR (melanocyte stimulating hormone[Title/Abstract]) OR Thyroid[Title/Abstract] OR Oxytocin[Title/Abstract] OR Insulin[Title/Abstract] OR (Parathyroid hormone[Title/Abstract]) OR PTH[Title/Abstract] OR Androgen[Title/Abstract] OR testosterone[Title/Abstract] OR Estrogen[Title/Abstract] OR Estradiol[Title/Abstract] OR Estrogen[Title/Abstract] OR Progesterone[Title/Abstract] OR IGF (Insulin like growth factor[Title/Abstract]) OR Leptin[Title/Abstract] OR vitamin d[Title/Abstract] OR Serotonin[Title/Abstract] OR epinephrin[Title/Abstract] OR trh[Title/Abstract] OR Vasopressin[Title/Abstract] OR (Gonadotrophin releasing hormone[Title/Abstract]) OR GnRH[Title/Abstract] OR (Growth hormone releasing hormone[Title/Abstract]) OR GHRH[Title/Abstract] OR (Prolactin relating[Title/Abstract]) OR PRF[Title/Abstract] OR (Thyroid stimulating hormone[Title/Abstract]) OR TSH[Title/Abstract] OR Calcitonin[Title/Abstract] OR Glucagon[Title/Abstract] OR (Pancreatic polypeptide[Title/Abstract]) OR Inhibin[Title/Abstract] OR (Human chorionic somatotrophin[Title/Abstract])) AND (Skin[Title/Abstract] OR Acne[Title/Abstract] OR (Skin Aging[Title/Abstract] OR dermatitis[Title/Abstract] OR Hyperpigmentation[Title/Abstract] OR *pigmentation[Title/Abstract] OR (skin[Title/Abstract] AND Deryness[Title/Abstract]) OR xerosis[Title/Abstract] OR xeroderma[Title/Abstract] OR Psoriasis[Title/Abstract]) AND ("2012/01/01"[Date - Publication] : "2022/12/31"[Date - Publication])
2	PubMed	(Blackheads OR pimples OR pustules OR rosacea OR whiteheads OR (Dry 1N skin) OR xerosis OR xeroderma OR asteatosis OR Ageing OR (skin Ageing) OR Photoaging OR (skin 1N Inf lammation) OR hyperpigmentation OR (skin 1N Dark*) OR (skin 1N redn*) OR Pigmentation) 15N (Endorin* or Hormon*) AND ("2012/01/01"[Date - Publication] : "2022/12/31"[Date - Publication])
3	PubMed	((Skin[Title/Abstract] OR derma) 2N (endo*[Title/Abstract] OR hormon*[Title/Abstract])) AND (("2012/01/01"[Date - Publication] : "2022/12/31"[Date - Publication]))
4	Scopus	TITLE-ABS-KEY (((hormone OR endocri*) OR (cortisol OR dehydroepiandrosterone OR melatonin OR (corticotrophin AND releasing AND hormone) OR crh OR acth OR (adrenocorticotrophic AND hormone) OR lh OR (luteinizing AND hormone) OR fsh OR (follicle AND stimulating AND hormone) OR (growth AND hormone) OR prolactin OR msh OR (melanocyte AND stimulating AND hormone) OR thyroid OR oxytocin OR insulin OR (parathyroid AND hormone) OR pth OR androgen OR testosterone OR estrogen OR estradiole OR estrogen OR progesterone OR igf OR (insulin AND like AND growth AND and factor) OR leptin OR vitamin AND d OR serotonin OR epinephrin OR trh OR vasopressin OR (gonadotrophin AND releasing AND hormone) OR gnrh OR (growth AND hormone AND releasing AND hormone) OR ghrh OR (prolactin AND relating) OR prf OR (thyroid AND stimulating AND hormone) OR tsh OR calcitonin OR glucagon OR (pancreatic AND polypeptide) OR inhibin OR (human AND chorionic AND somatotrophin))) W/10 (skin OR acne OR (skin AND aging) OR dermatitis OR hyperpigmentation OR *pigmentation OR (skin AND dryness) OR xerosis OR xeroderma OR (skin W/2 inf lammation))) AND PUBYEAR > 2011 AND PUBYEAR < 2023
5	Scopus	TITLE-ABS-KEY((Blackheads OR pimples OR pustules OR rosacea OR whiteheads OR (Dry W/1 skin) OR xerosis OR xeroderma OR asteatosis OR Ageing OR (skin Ageing) OR Photoaging OR (skin W/1 Inf lammation) OR hyperpigmentation OR (skin W/1 Dark*) OR (skin W/1 redn*) OR Pigmentation) W/15 (Endorin* or Hormon*)) AND PUBYEAR > 2011 AND PUBYEAR < 2023

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At the end of screening Kim EJ, Kim YK, Kim MK, et al, 40. Kim TW, Jeong JH, Hong SC., Koelemij I, Massolt ET, van Doorn R, 124 articles were considered relevant for the present review, of which 45 were review articles. The heterogeneity in study design, comprising research papers, case reports, and reviews, alongside the varied hormones and clinical and skin conditions investigated, introduces bias and poses challenges for conducting meta-analyses and quality assessments using a single tool Krutmann J, Bouloc A, Sore G, et al. However, during the paper selection process, each study's quality was rigorously evaluated through a hierarchical approach by multiple investigators Kumar N, Agarwal H. Our selection process included studies with comprehensive individual- level clinical and laboratory data, consistent diagnoses, and strong statistical analysis. Additionally, we considered the impact factor of research articles Langan EA, Hinde E, Paus R.

Results

Humans have been shown to possess over fifty hormones, and studies have been done on the precise functions these hormones play in the body Langer RD, Hodis HN, Lobo RA, et al. We carefully evaluated a wide range of hormones for their function in maintaining healthy skin Lee H, Choi EJ, Kim EJ, et al. Scientific evidence for 20 hormones directly impacting skin health, and research data supporting the circadian behaviour of seven of these hormones have been found. (Figure 1) Lephart ED, Naftolin F The ongoing increase in research activity in this field holds the promise of uncovering additional hormones that may contribute to skincare in the future.

Nevertheless, ongoing research in the forthcoming years holds the potential to enrich our understanding of the circadian regulation of hormones, offering a more comprehensive insight into this intricate physiological phenomenon. We ensured a high-quality analysis by rigorously evaluating the risk of bias in each selected article. This evaluation considered factors such as impact factor, study design, methodology,

clinical parameters, and statistical analysis. Studies were excluded if they exhibited methodological shortcomings, including inadequate study design, absence of skin-specific outcome measures, insufficient sample size, un clear role of the hormone or inadequate statistical analysis. Additionally, studies conducted to evaluate the role of hormone on life threatening diseases like cancer, sclerosis as well as the research on hormone replacement, [14-17] but during the screening process these articles were excluded as they were out of scope Lesovaya E, Agarwal S, Readhead B, et al. Hormonal action pathways are complex and vital, involving feedback loops ensuring the proper regulation and functioning of hormones in the body Liakou AI, Kontochristopoulos G, Marnelakis I, et al. Many hormones function in an axis fashion; hypothalamic hormones regulate the pituitary release of trophic hormones that, in turn, regulate the target hormones released by the target tissue or organ [18, 19]. The present section discusses the hormonal effect on the skin according to specific hormonal axes (Figure 2).

HPA Axis: Hypothalamus- Pituitary- Adrenal gland axis

The hypothalamic-pituitary-adrenal HPA axis consists of corticotrophin-releasing hormone (Hypothalamus) – ACTH (pituitary) – Cortisol (Adrenal gland). It is a complex system regulated by loops of feedback. It is the primary stress regulator mechanism of the body. The effect of stress on the skin is mainly conveyed via this axis.[20] The skin expresses many elements of the HPA axis, such as Corticotrophin releasing hormone (CRH), urocortin, proopiomelanocortin (POMC) Makrantonaki E, Jiang D, Hossini AM, et al, its derivative ACTH α -MSH, and β - endorphin [21] Lynn DD, Umari T, Dunnick CA, et al.

Corticotrophin-releasing hormone (CRH)

The hypothalamus releases this hormone in response to different number of stresses. The pituitary then secretes ACTH, which prompts the adrenal glands to release glucocorticoids [21]. Skin biopsy samples from psoriasis patients showed

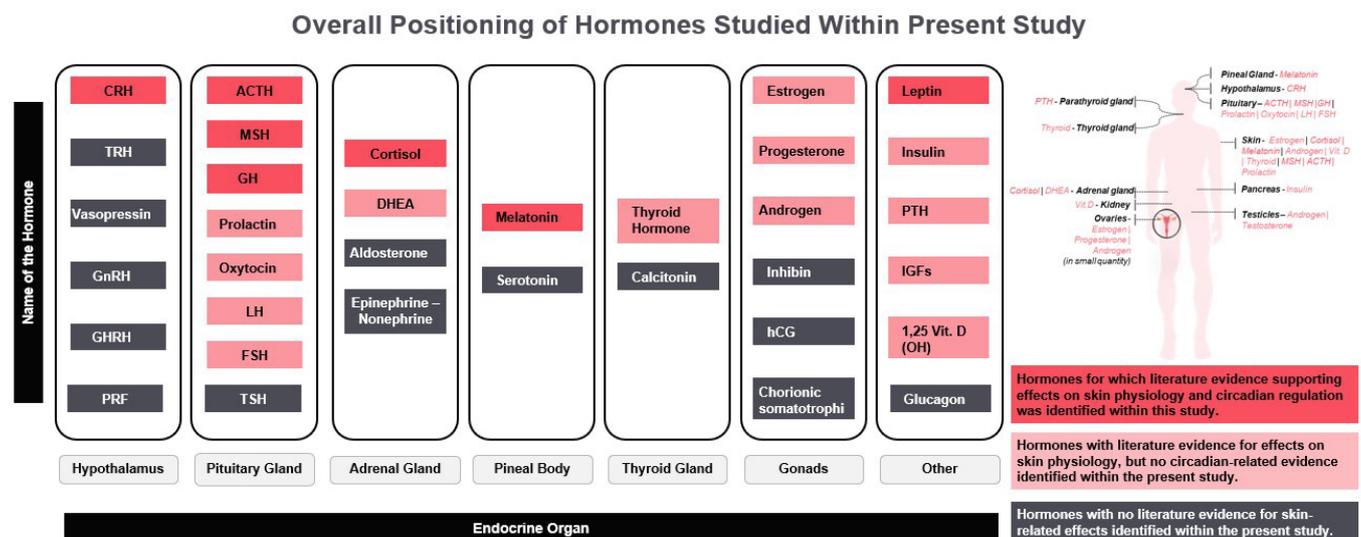


Figure 1: Axis wise hormone positioning represents hormones showing effects on skin conditions and hormones showing circadian behaviour.

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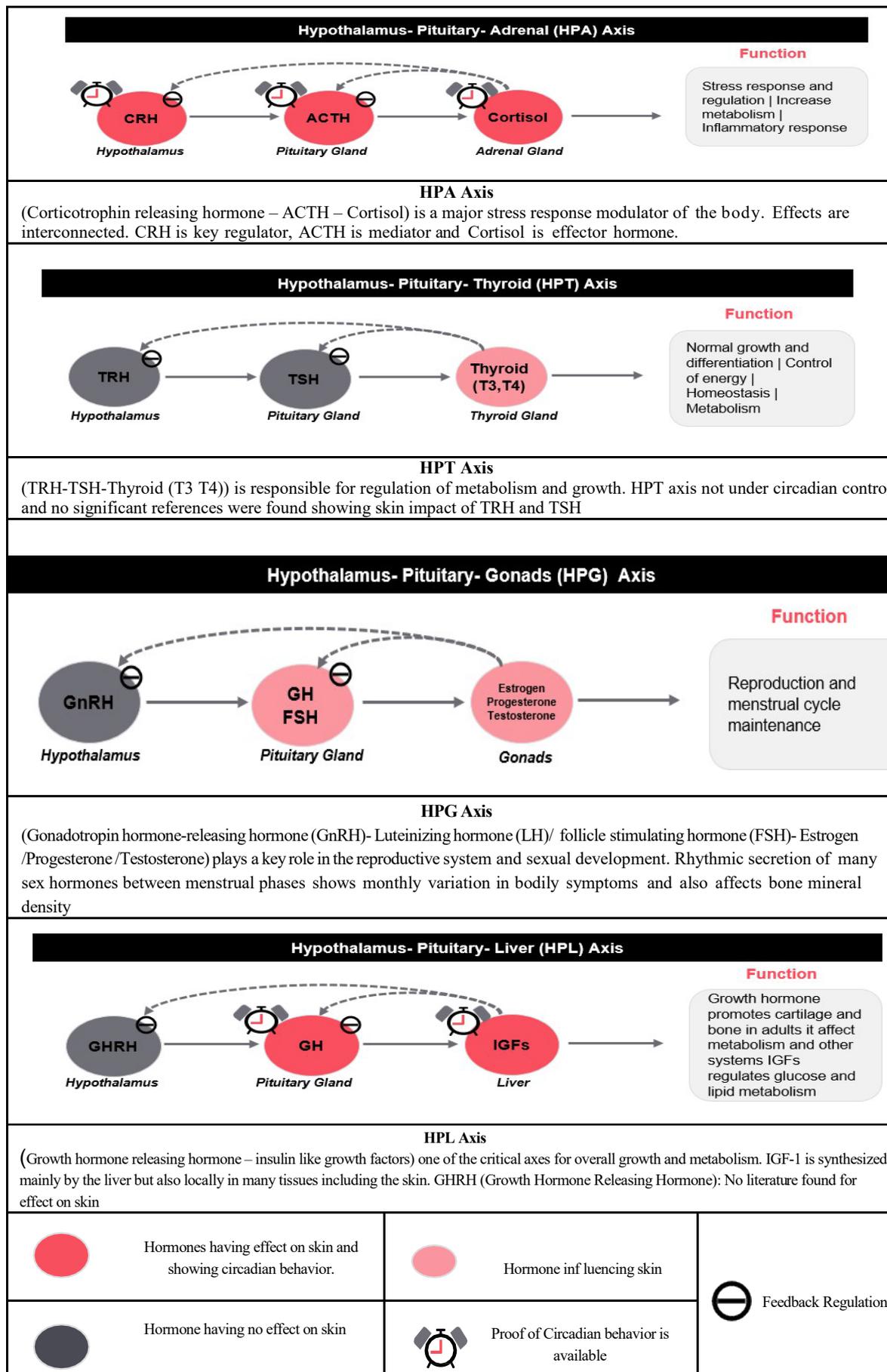


Figure 2: Working or regulation of hormone.

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reduced CRHBP (CRH binding protein) and increased levels of CRH, Interleukin 8, and Interleukin 33. [22,23] According to the case study by Theoharides et al., a 36-year-old woman with an elevated CRH level had rashes, itchy, sensitive skin, and mastocytosis [24]. Zouboulis demonstrated that CRH increases the inflammatory signalling SCD/FADS2 pathway in the sebaceous gland, which causes acne [25].

Adrenocorticotrophic hormone (ACTH)

Adrenocorticotrophic hormone, or ACTH, is a crucial HPA axis regulator and is also connected to melanogenesis. After CRH (corticotropin-releasing hormone) stimulation, POMC (proopiomelanocortin) is cleaved to produce both alpha-melanocyte stimulating hormone (MSH) and ACTH. Abnormal or inadequate ACTH synthesis results in increased Dehydroepiandrosterone sulfate (DHEAS) production, which causes hyperpigmentation [26,27]; similar results were observed in multiple studies conducted on Cushing's syndrome patients where increased levels of ACTH, cortisol, growth hormone, and IGF-1 have been linked to the development of facial acne, diffuse telogen effluvium, hirsutism, purple striae, and acanthosis nigricans, hyperkeratosis and hyperpigmentation in the area around the nape, the neck and axilla [28,29]. Multiple studies show medical disorders such as Addison's disease, bilateral adrenalectomy, and primary adrenal insufficiency reduce cortisol levels, leading to elevations in MSH and ACTH, causing diffuse hyperpigmentation in sun-exposed body areas [29-34].

Cortisol

Cortisol acts as stress biomarker of the body. Numerous studies have demonstrated that psychological stress, Cushing's disease, and polycystic ovary disease (PCOS), all raise cortisol levels, which induce acne or exacerbate pre-existing acne [35-38]. Pre-clinical research employing mice, reports skin atrophy because of elevated cortisol [39-42]. Cortisol is known to downregulate the expression of type I collagen, which results in the aging signs of fine lines, wrinkles, sagging skin, and skin barrier dysfunction in those with elevated cortisol levels [43,44]. UV B exposure, environmental dryness, and pollution are the exosomal factors that increase cortisol levels [9,45-47].

In the HPA axis, scientific evidence for the circadian behaviour of ACTH and cortisol is found; both hormones have the highest activity 30 min after waking (around 6.00-8.00 am), while the lowest level is attended during night [48-52]. Increased cortisol or ACTH at nighttime due to different stressors causes sleep disturbance; researchers studied the effect of elevated cortisol on shift workers and sleep-deprived individuals [53-56] Similarly, increased cortisol in atopic dermatitis, psoriasis, and other skin inflammatory conditions contribute to loss of night sleep in patients [50,57]. In summary, the HPA axis plays a vital role in skin health, with elevated corticoids contributing to acne, inflammation, and aging. Imbalances in cortisol and ACTH are associated with hyperpigmentation. The axis responds to diverse stressors, encompassing environmental exposomes and psychological stressors, influencing skin manifestations.

HPT axis: Hypothalamus – Pituitary- Thyroid axis

Thyroid-releasing hormone (TRH) is released by hypothalamic neurons, which, in turn, stimulates the anterior pituitary to release the thyroid-stimulating hormone (TSH). TSH stimulates thyroid follicular cells, prompting the release of thyroxine (T4) at 80% and triiodothyronine (T3) at 20% [58]. The amount of current research suggests that thyroid (T3 and T4) plays a role in preserving skin health, although there is no evidence linking TRH and TSH to skin health. Current knowledge in this area does not support circadian oscillations in thyroid hormone levels. The primary cutaneous signs of hypothyroidism include xerosis, thin-scaly skin, myxedema, purpura, dry and coarse hair, telogen effluvium, and poor wound healing. Skin symptoms of hyperthyroidism include erythema, hyperpigmentation, telangiectasia, pruritus, and thin, smooth skin [59]. Wistar rats with hypothyroidism that are exposed to the sun for an extended period develop photooxidative skin damage and show indications of photoaging [60]. According to research including 700 vitiligo patients, individuals with hyperthyroidism appear to have more widespread vitiligo activity. The areas more prone to friction, like the acral and joint areas, are more affected by depigmentation [61]. Inflammatory skin conditions like urticaria are more severe in individuals with thyroid dysfunction. Hyperthyroidism is associated with warm, moist skin, elevated temperature, palmoplantar hyperhidrosis (excessive sweating in the palms), and hyperpigmentation, while hypothyroidism is related to dry skin and carotenemia pigmentation [62]. Thyroid autoimmunity was associated with urticaria in atopic dermatitis patients [63]. Some studies concluded that thyroid disease and active smoking may be associated with more severe skin inflammatory conditions like hidradenitis suppurativa and psoriasis [64-66].

HPG axis: Hypothalamus- Pituitary- Gonads (HPG) axis

The reproductive axis is regulated starting at the hypothalamus, where neurosecretory cells produce and release gonadotropin-releasing hormone (GnRH) in a pulsatile manner; this prompts the anterior pituitary's gonadotropes to synthesize and release follicle-stimulating hormone (FSH) and luteinizing hormone (LH), governing gonadal function and the release of estrogen, progesterone, and testosterone from the gonads [67]. Throughout a woman's life cycle, hormonal dynamics exert a profound influence on skin health. Puberty initiates a cascade of hormonal changes, notably heightened androgen levels, precipitating increased sebum production and consequent acne formation. Concurrently, hormonal fluctuations modulate skin oiliness, further exacerbating acne development. The menstrual cycle, intricately regulated by estrogens and progesterone, imparts fluctuations in skin hydration and oil secretion, manifesting as alterations in skin texture. Pregnancy introduces substantial hormonal shifts, prominently elevated estrogen levels, fostering a luminous by augmenting skin elasticity and moisture levels via enhanced blood flow. Conversely, menopause heralds a decline in estrogen, precipitating diminished collagen synthesis, culminating in skin dryness,

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diffuse telogen effluvium or androgenetic alopecia of female pattern, and textural alterations. Post-menopausal stages pinpoint the significance of 17-beta estradiol, for bone health and its pivotal in preserving skin resilience amidst age-related changes. This symbiotic interplay between hormones and skin health underscores their indelible impact on the dynamic canvas of a woman's life cycle [68- 70]. Numerous studies examine the skin aging effects of impaired HPG axis or estrogen in premenopausal or menopausal females. However, in the present review, we tried to explore the impact of HPG axis hormones on non-premenopausal or non- menopausal skin parameters.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

An increase in luteinizing hormone (LH), a decrease in follicle-stimulating hormone (FSH) and an increased LH:FSH ratio is observed in females with PCOS, which results in increased instances of acne, acanthosis nigricans and hirsutism; the severity of these effect increases in obese patients [71,72]

Estrogen and Progesterone

For estrogen, the skin is the second target after reproductive organs. Decreased estrogens and progesterone, and fluctuations in estrogen and progesterone ratio lead to skin aging signs like wrinkles, increased oiliness in the T-zone, increased skin pigmentation and enlarged pore size, skin eruption/urticaria (skin rash), acne, UVB-induced deterioration of the extracellular matrix (ECM), atrophy, impaired wound healing and decrease barrier function, moisture, trans epidermal water loss (TEWL), antioxidant capacity [73-78]. Increased estrogen level leads to skin eruption/urticaria (skin rash), acne, and catamenial pigmentation; it is pigmentation due to a rhythmic high wave of estrogen in the luteal phase, which increases melanocyte production [79-82]. An increase/hypersensitivity of progesterone leads to autoimmune progesterone dermatitis (APD), which causes urticaria (rash), eczema, and vesiculobullous eruptions [83-85].

Androgens

An increase in androgens, including androstenedione, testosterone, 5-alpha-dehydroepiandrosterone (DHEA), and DHEA-S, leads to acne, hirsutism, androgenetic alopecia, and skin concerns due to sebaceous gland hypertrophy [25,86,87].

HPL axis: Hypothalamus – Pituitary – Liver axis

The HPL axis significantly impacts how different animals regulate their development. Growth hormone releasing hormone (GHRH) and Somatostatin are the two main hypothalamic hormones that regulate growth hormone (GH) release from the pituitary; these hormones have stimulatory and inhibitory actions, respectively. Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are critical for supporting children's linear growth, influencing the growth plate and cartilages, and controlling protein, lipid, and carbohydrate metabolism in children and adults. Additionally, sebaceous gland growth and pilosebaceous unit formation are specifically impacted by GH and IGF-1, either directly

or through their synergistic effects with androgens and the encouragement of DNA synthesis [88]. Growth hormone secretion follows circadian and diurnal patterns; the peak level of growth hormone is between 2:00 to 4:00 am. Changes in sleep patterns that disturb the circadian rhythm result in low growth hormones released in circulation [89].

Growth hormone (GH)

Growth hormone excess results in gigantism in children, while neurofibromatosis, McCune Albright syndrome, and Carney complex are some of the severe growth hormone-related disorders; acromegaly is one of the GH excess disorders, which shows skin manifestations including skin thickening, coarsening of facial features, skin puffiness, acrochordons, lentiginous spots, acanthosis nigricans, acne, oily skin, hypertrichosis, hirsutism, hyperhidrosis. Similarly, GH deficiency leads to skin dryness, thinness, paleness, thin hair, and reduced sweating [88]. Various case studies of acromegaly patients reported increased GH and IGF-1 levels causing increase sebum, high skin pH, hyperpigmentation on toes, acanthosis with velvety brownish-dark plaques and soft, brown hyperpigmented polypoid growths on the neck, groin, and bilateral axillae, enlargement of soft tissues, oily skin, puffiness, dilated pores [26,90-92].

Insulin-like growth factor-1 (IGF-1)

IGF-1 is crucial for forming pilosebaceous units. IGF-1 increases the adrenal's sensitivity to ACTH and stimulates the expression and activity of essential enzymes involved in adrenal androgen production, such as dehydroepiandrosterone sulfate (DHEAS). Excess DHEAS/androgens are also responsible for the development of acne, as is the hyperactive pilosebaceous unit [93]. It has been demonstrated through experimentation that IGF-1 was overexpressed in both the epidermis and the pilosebaceous unit of acne vulgaris lesions compared to normal skin; the study also suggests the role of IGF-1 and high BMI in acne patients [94]. Additionally, studies on the relationship between nutrition and IGF-1 functioning have revealed that high-glycemic foods, cow milk, whey, and simple carbohydrates raise IGF1 levels, which causes acne to develop or worsen [94-98].

Cutaneous manifestations of hormones which function in non-axis manner

Melatonin

Melatonin, a crucial indolic hormone from the pineal gland, regulates circadian rhythms and promotes sleep. The skin, equipped with a fully operational melatonergic system, contributes to local rhythmicity, and influences various skin functions. Melatonin and its protective metabolites, N1-acetyl-5-methoxykynuramine (AMK) and antioxidant metabolite of melatonin (AFMK), exhibit photoprotective effects, with skin metabolism susceptible to environmental factors like ultraviolet radiation (UVR) and free radicals. Notably, African Americans' epidermis displays the highest melatonin concentration, suggesting potential ethnic variations in skin melatonin levels[11, 97,99]. Melatonin secretion begins after the onset of darkness, peaking between 2 and 4 a.m., followed

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by a gradual decline until morning [100]. Multiple case studies with statistically significant sample sizes suggest that decreased melatonin results in aging signs, pigmentation, and increased inflammation in atopic dermatitis [33,101,102].

α-melanocyte stimulating hormone (α-MSH)

α-MSH plays a crucial role in skin pigmentation by binding to the melanocortin-1 receptor (MC1R) on the cell membrane of melanocytes. This hormone is part of the melanocortin system, which includes α, β, and γ-MSH, and adrenocorticotropic hormone (ACTH), derived from the proteolytic cleavage of pro-opiomelanocortin (POMC) [61]. Polymorphisms of the melanocortin 1 receptor (MC1R) gene correlate with skin fairness and UV sensitivity. Loss-of-signaling MC1R is common among fair-skinned, sun-sensitive, and skin cancer-prone populations. The highest activity of MSH is observed in the daytime. UV B stress is the physical condition that affects MSH secretion. Normal levels of MSH have anti-inflammatory and antimicrobial properties. Increased concentration results in hyperpigmentation. Studies also suggest that vitiligo patients had significantly lower levels of α MSH and vitamin D than control individuals [61,103–105].

Leptin

Leptin is categorized as an adipokine hormone produced by both fibroblasts and keratinocytes. It actively participates in the pro-inflammatory regulation of sebaceous lipid metabolism. Obesity and diabetes/insulin resistance are physiological factors contributing to leptin imbalance. It is synthesized more in females as they have more adipocytes. Leptin activates the STAT-3 and NF-κB pathways and induces pro-inflammatory enzyme and cytokine (IL-6 and IL-8) secretion in sebocyte, causing acne and skin aging [106]. Highest activity of leptin is observed at nighttime [19], increased leptin concentration leads to skin tags, acne, Acanthosis nigricans, and aging, while decreased levels represent dry skin and aging signs [4,94].

1,25 D-dihydroxy vitamin D

Vitamin D's active metabolite, 1,25(OH)₂D, is pivotal in regulating skin processes such as cellular proliferation, differentiation, apoptosis, barrier maintenance, and immune functions. Exclusive to keratinocytes, the synthesis of vitamin D from its precursor 7-DHC is a unique capability. The vitamin D receptor's interaction with 1,25-(OH)₂D also influences long-chain glucosylceramides. Maintaining optimal vitamin D levels contributes to UV protection, cellular proliferation, and inflammation control in the skin. 104, Vitamin D3 levels tend to decrease during winter due to inadequate sun exposure, especially in high-latitude locations, sun avoidance practices, and insufficient exposure to UVB radiation. Factors like ozone and particulate matter, air pollutants (including persistent organic pollutants and heavy metals acting as endocrine-disrupting chemicals), age, body mass index (BMI), skin type, pregnancy, exclusive breastfeeding, genetic polymorphisms, and smoking can also contribute to the decline in Vitamin D3 levels. A decline in Vitamin D3 levels is associated with inflammatory skin conditions like atopic dermatitis, psoriasis,

and acne (hidradenitis suppurativa), reduced photoprotection, and impaired barrier function [95].

Insulin

Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans and performs a critical function of maintaining normal blood glucose levels. Diabetes mellitus (DM) is an insulin deficiency disorder. Overweight, high glycemic index diet, and other conditions like polycystic ovary syndrome (PCOS) are associated with increased insulin resistance. Type 1 DM is associated with conditions like alopecia areata, vitiligo, and necrobiosis lipoidica, while type 2 DM is linked to acanthosis nigricans, facial erythrosis, acne, itching, pigmentation, photoaging signs, and xerosis [93]. Type 1 Diabetic associated with depigmentation was observed in the study conducted on 792 Japanese women.

Prolactin

Prolactin mainly concerns mammary glands and lactation. Prolactin targets and stimulates sebocyte proliferation. Dermal fibroblasts and keratinocytes show prolactin expression. Prolactin levels increase with age, during pregnancy, and exclusively during breastfeeding. Stress, anxiety, and disturbed sleep are other environmental factors responsible for prolactin imbalance. Medical conditions like hypothyroidism, PCOS, menopause, lactation, and vitiligo are responsible for increased prolactin levels. Prolactin increases the sebaceous gland area and stimulates lipid production [71] (Table 3).

Hormonal influence on common skin concerns

The investigation into the regulatory influence of hormone upregulation or downregulation in the occurrence of skin conditions such as acne, aging, xerosis, and pigmentation is essential for a comprehensive understanding and effective management of these common skin concerns across the population. Figure 2 depicts the list of hormones that increase or decrease, which results in specific skin conditions.

Acne is a chronic, inflammatory skin condition of the pilosebaceous unit, estimated to affect 95% of adolescents in the population. Increased levels of androgens in adolescence, IGFs, prolactin, luteinizing hormone, and leptin cause acne, and increased cortisol levels also contribute to increasing severity of acne. Decreased estrogen in pre- and post-menopause and medical conditions like PSOS also contribute to acne outbreaks. Dietary imbalance and stress are contributing factors, along with hormonal imbalance.

Hormones significantly contribute to intrinsic aging. A natural reduction in estrogen and androgen decreases sebum production and sebaceous gland atrophy, leading to dry skin and wrinkles [10]. Decline of estrogens decreases the tensile strength of the skin. Premature aging, associated with reduced melatonin and Vitamin D levels, can be triggered by ultraviolet radiation, tobacco smoking, and exposure to other pollutants and toxins [11]. Additionally, increased cortisol and leptin levels, especially when coupled with stress, can accelerate the signs of aging [94].

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Table 3: Skin manifestation of hormone imbalance and circadian behavior of hormones.

Name of the axis	Name of the hormone	Skin manifestation of change in level		Normal circadian nature	
		Increase level	Decrease level		
HPA axis Hypothalamus- Pituitary- Adrenal axis	CRH	Acne		Low in night and highest when wakes up	
		Skin itching			
		Sensitive skin			
		Rashes			
	ACTH	Hyperpigmentation, Acanthosis nigricans	Depigmentation	Highest 6:00 and 8:00 am and low in midnight	
		Purple striae (stretch marks)	Vitiligo		
		Acne			
	Cortisol	Aging signs Wrinkles, fine lines and sagging	Hyperpigmentation	Low in night and Highest when wakes up	
		Acne	High skin temperature		
		Stretch marks	Itchy dry skin	(6:00 to 8:00am) (ultradian- in stress response)	
Skin barrier dysfunction,					
Depigmentation					
HPT axis Hypothalamus – Pituitary- Thyroid axis	Thyroid* (*no reference for skin manifestation of TSH and TRH hormone were found)	Pruritus (Itchy skin)	Cold, mottled scaly skin, Carotenemia (type of pigmentation),		
		Urticaria (skin rash)	Pretibial myxedema		
		Thin skin	Depigmentation / Vitiligo		
		Hyperpigmentation	Photo-ageing		
		Erythema,	Xerosis		
		Telangiectasia (small, widened blood vessels on the skin)			
		Hyperhidrosis (excess sweating)			
HPG axis Hypothalamus- Pituitary- Gonads axis	LH	Acne	Aging signs- Wrinkle, Barrier function, Dry skin, Skin Thinning, UVB- induced deterioration of the ECM, Reduction in tensile strength of skin	Rhythmic variation with age (Decreases with increasing age), Puberty and menopause, menstrual phase	
		Hirsutism			
	FSH	Acanthosis nigricans			
		Seborrhea			
	Estrogen	Skin eruption / urticaria (skin rash)			
		Acne			
		Nevi hyperpigmentation			
	Progesterone	Eczema			Skin aging: decreased moisture, increased oiliness in pigmentation and enlarged pore size
		Increased sebum			
		Increased vascularity, Urticaria (rash)			
		Hyperpigmentation			
	Androgen DHEA	Acne			Melasma- Hyperpigmentation
Hirsutism					
Acanthosis nigricans					
Acrochordons/skin tags,					
Seborrhoea					
Sebaceous gland hypertrophy					

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HPL axis Hypothalamus- Pituitary- Liver axis	Growth Hormone	Skin thickening,	1. Skin Dryness, Thinness, 2. Pale skin	High in midnight between 2:00 to 4:00 am	
		Hyperpigmentation			
		-Melanocytic naevi (dark skin patches),			
		Acanthosis nigricans (Dark skin patches in folds)			
		Acne			
	Oily skin				
	Insulin-like growth factor-1 (IGF-1)	Higher- sebum content and pH of skin			Age (level decreases with increasing age)
		Lower skin temp., Hyper pigmentation,			
		Acne			
		Blackheads			
		Oily skin			
Early aging signs					
Hormonal Mechanism Without axis	Melatonin	Vitiligo	Aging signs: Skin thickness, higher sebum production, High pH Hyperpigmentation (melisma)	High in nighttime	
	α -melanocyte stimulating hormone (α - MSH)	Hyperpigmentation	Vitiligo / de- pigmentation	Highest day time	
	Leptin	Skin tags	Dry skin	High in night	
		Acne	Aging signs		
		Pigmentation - Acanthosis nigricans			
		Aging			
	1,25 D- dihydroxy vitamin D	-	Acne (Hidradenitis suppurativa)	Age (level decreases with increasing age), pregnancy, and exclusive breastfeeding	
			Decrease Photo protection		
			Decrease barrier function		
	Insulin	Acanthosis nigricans			
		Dry skin			
		Seborrhoea,			
		Acne			
Itching,					
Pigmentation,					
Photo aging signs					
Diabetic dermopathy (skin lesions and pigmentation), Thick and waxy skin, xerosis					

Variation in melanin secretion by the action of hormones such as melanocyte- stimulating hormone (MSH) and adrenocorticotrophic hormone (ACTH) is caused by genetic factors, sunlight exposure, and medications for liver and kidney disease treatments. The negative feedback to the hypothalamic-pituitary-adrenal axis (HPA) in Addison's disease causes a high concentration of adrenocorticotrophic hormone (ACTH), and low cortisol causes hyperpigmentation [33,34]. Catamenial pigmentation due to fluctuation in estrogen and progesterone in the luteal phase is also one of the reasons for hyperpigmentation in women [81]. Acanthosis nigricans, a smooth, velvety pigmentation in the area of the

nape of the neck, axillary folds, and armpits, is associated with insulin resistance in type II diabetes.

Skin dryness, or xerosis, is due to decreased sebaceous secretion and age- dependent disturbed skin barrier function. The main reasons include loss of skin elasticity, reduced stratum corneum hydration, and altered permeability, along with hormone-related dry skin issues, which are more common in females than males. Sebum secretion is affected by androgens, testosterone, 5-alpha- dehydroepiandrosterone, and estrogen. Dry palms and soles and coarse and scaly skin are typical skin manifestations of hypothyroidism [59] **Figure 3.**

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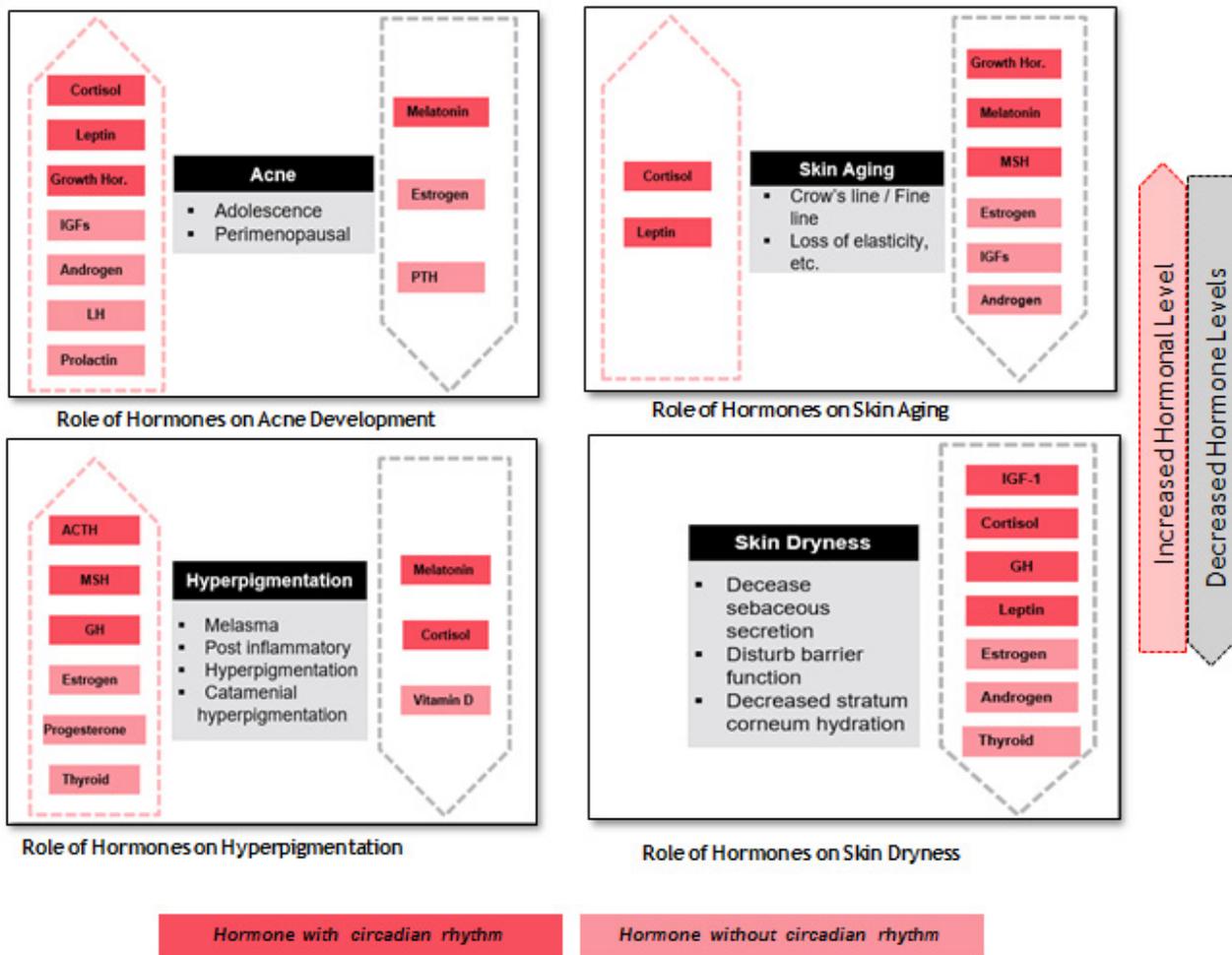


Figure 3: Role of hormones on general skin concerns.

Discussion

To the best of our knowledge, this is a comprehensive overview of the hormonal effects on skin health and parameters. The strength of this work relies on the assessment of all hormones of the body in the same analysis of a comprehensive search of well-known databases. By targeting systematic reviews, we have covered a higher-order summary of findings as compared to the individual original studies and, by synthesizing findings across all types of included studies, we offer a clear, detailed and unique summary of the current state of evidence about how skin parameters are affected by hormonal dysregulation. The diverse methodologies used across the included systematic reviews and other studies limited our ability to conduct a meta-analysis of findings.

Human life processes are highly coordinated, and intercellular communication maintains homeostasis, reproduction, metabolism, and environmental changes. Hormones and endocrine system play a key role in intracellular communication systems. Hormones are crucial to skin health. An imbalance in the hormone levels affects skin health and, in many cases, worsens pre-existing skin disorders when combined with additional factors such as exposomes or other physiological issues. Skin can be considered as a mirror that reflects hormone functioning.

The HPA (Hypothalamus-Pituitary-Adrenal gland) axis plays a vital role in skin health, and elevated corticoids contribute to acne, skin inflammation, and aging. Imbalances in cortisol and ACTH are associated with hyperpigmentation. The axis responds to diverse stressors, encompassing environmental exposomes and psychological stressors, influencing skin manifestations. Cortisol is a significant stress marker of the body, and factors affecting the quality of life contribute to cortisol increases.

Lack of sleep due to stress, screen time, or any other occupational reasons causes skin manifestations like skin dryness, breaks in skin barrier function [56], and also results in a disturbed circadian rhythm of cortisol and melatonin; increased levels of cortisol and decreased level of melatonin along with lack of sleep show effects on the skin and worsen pre-existing acne [54]. Additionally, the rising trend in oral steroid consumption results in effects like stretch marks and acne.

The skin manifestations of hypothyroidism and hyperthyroidism are increasing concerns in the upcoming days, as recent data shows twenty million Americans already suffer from some form of thyroid disorder. The frequency of thyroid diseases rises with age, according to the American Thyroid Association, which estimates that over 12% of US residents

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may experience a thyroid problem at some time in their lives. A sizable portion of the population, particularly those of older age who already struggle with skin dryness, aging, and other skin-related problems, may have skin manifestations of hypo- or hyperthyroidism. Skin health issues might become more serious when thyroid dysfunction is present.

Estrogens are a widely studied hormone group that plays essential roles in skin physiology, including delaying or preventing skin aging manifestations. They maintain skin thickness and hydration, reduce epidermal thinning, and increase hydroxyproline content, accelerate cutaneous wound healing, and may improve inflammatory skin disorders such as psoriasis, particularly during pregnancy. The role of skin-stored estrogen, which helps to prevent skin-aging signs ten years after menopause, makes estrogen an essential hormone for skin-aging signs in female [7]. Natural progesterone has no known influence on human skin other than this effect at normal luteal phase levels. Synthetic progestins increase body core temperature by raising the thermoregulatory set-point at which sweating occurs. Increased estrogen and progesterone levels in the premenstrual period result in flares of Hidradenitis suppurativa. In atopic dermatitis, increased estrogen and progesterone raise IgE production and inflammation. Progesterone hypersensitivity decreases estrogen and progesterone levels, especially during the luteal phase, resulting in increased skin permeability, which impacts cutaneous barrier functions.

The cyclic nature of estrogen, progesterone, LH, and FSH in menstrual phases causes various physiological and psychological effects and further impacts the quality of life. Deviations in the concentration of estrogen and progesterone during the menstrual phases influence conditions like catamenial pigmentation and progesterone dermatitis.

Increased estrogen and progesterone levels in the premenstrual period result in flares of Hidradenitis suppurativa. Androgens are obligatory in acne pathophysiology, evidenced by various clinical and experimental observations. Androgen influences perspiration, resulting in males sweating at a higher rate than females during puberty. Differentiation of apocrine sweat glands, influenced by androgens, contributes to higher secretion rates during puberty. Androgen suppression benefits female patients with mild to moderate acne by reducing sebum production [7,12], the details of these effects is essential as research can benefit a broader population facing challenges monthly.

Growth hormone is very crucial to life, and an imbalance in its levels can lead to life-threatening conditions, including malignant skin conditions; hence, manipulating GH levels for dermatological purposes is not a feasible option; the role of IGF-1 in acne formation is vital, understanding its mechanism is essential as acne is one of the significant concerns in teenagers. Melatonin is an increasingly researched topic. Sleep quality is critical for skin health. Melatonin's dermatological effects are attributable to two features: the first is sleep-promoting property, and the second is an antioxidant property; both properties result in stress reduction, skin

moisture enhancement, anti-aging, anti-wrinkle, and barrier function improvement. A recent study suggests that type 2 diabetes mellitus affects around 0.5 billion people worldwide, with projections indicating a 25% increase by 2030 and a 51% rise by 2045. Therefore, diabetic dermatopathy is an increasingly studied topic, given the significant number of people experiencing the dermatological effects of diabetes.

Conclusion

The present review explores critical insights to enhance skincare and address common skin issues. Factors such as heightened UV exposure, environmental pollutants, early-onset metabolic diseases, stressful lifestyles, and poor sleep significantly impact overall well-being. Within the realm of holistic beauty, hormones act as internal messengers influenced by all these elements. Discerning their connection to skin health establishes a foundation for skincare stakeholders to explore comprehensive solutions, promoting enhanced well-being and aesthetic vitality.

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