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Review

Endocrine Regulation in Aging: Hormonal Decline, Compensatory Mechanisms, and Prospects for Healthy Aging Interventions

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Abstract

This study examines the processes, physiological outcomes, and novel interventions of endocrine aging through a systematic evidence-based analysis methodology. Peer-reviewed research published between 2020 and 2025 provided data collected on the basis of competitive endocrine achievements, hormonal disorderliness, and multi-organizational biological outcomes analyzed using predetermined inclusion criteria. The research also examines the modern and developing treatment methods, such as hormone modulation, lifestyle change, pharmacological agents, and precision endocrinology. The study suggest that endocrine aging is a consequence of progressive dysfunction in the production of hormones, the sensitivity of receptors, and cross-axis feedback regulation, which causes metabolic dysfunction, immune dysfunction, neurocognitive dysfunction, and frailty. New hormonal-based interventions show promise to enhance endocrine resistance and healthy lifespan. The paper identifies some major gaps in research in the areas of biomarker development, integration of multi-omics, artificial intelligence, and ethical aspects of hormone-based longevity treatment.

Keywords

Aging endocrine, Hormonal control, Metabolic impairment, Geroscience intervention, Precision endocrinology

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1. Introduction

Throughout the lifespan, the endocrine system plays a central role in regulating metabolism, growth, reproduction, and homeostasis. Aging is associated with a gradual and multifocal decline in the function of key endocrine axes, leading to reduced hormone secretion, altered feedback mechanisms, and decreased tissue responsiveness to hormonal signals [1,2]. Almost all major endocrine glands, including the pituitary, thyroid, gonads, pancreas, and adrenal glands, experience structural and functional changes over time, which compromise their ability to maintain systemic physiological stability [2,3]. These alterations impair communication between hormone-sensitive tissues, particularly those involved in muscle-liver-adipose crosstalk, resulting in less coordinated metabolic regulation. Consequently, older adults become increasingly vulnerable to chronic, age-related conditions such as metabolic syndrome, sarcopenia, osteoporosis, and impaired stress responses [4,5]. The decline in endocrine function also diminishes the body's capacity for adaptation, reducing resiliency against environmental and physiological stressors, which highlights the significance of endocrine integrity for maintaining health and functional autonomy during aging.

Sex hormones and insulin serve as prime examples of how endocrine deterioration drives aging-related pathophysiology. In women, decreased estrogen signaling during midlife and menopause has been identified as a central factor in disrupted metabolic homeostasis, increased fat deposition, and elevated susceptibility to cardiovascular and metabolic disorders. In men, testosterone gradually declines with age, contributing to muscle and bone weakening, fat accumulation, altered energy regulation, and heightened systemic inflammation [1,6]. These hormonal shifts not only impair reproductive capacity but also exacerbate risks for metabolic syndrome, insulin resistance, and related chronic diseases. Similarly, age-related insulin resistance is a key driver of metabolic dysregulation, predisposing older adults to type 2 diabetes and neurodegenerative disorders, including Alzheimer's disease, where impaired glucose metabolism compromises neuronal survival and cognitive function [7,8]. Together, these examples illustrate that endocrine decline is not merely a marker of aging but a mechanistic contributor to the development of multiple age-associated pathologies.

The body, however, exhibits compensatory mechanisms to counterbalance hormonal deficits and maintain physiological stability. Molecular crosstalk between endocrine, immune, and paracrine signaling networks enables dynamic adaptation during aging, including receptor sensitization, activation of alternative signaling pathways, and adjustments in metabolic and immune functions [9]. In men, for instance, reduced testosterone triggers shifts in fat metabolism and inflammatory signaling, reflecting a compensatory response aimed at preserving energy balance and tissue function despite hormone loss [10]. Understanding these adaptive processes is crucial for predicting age-related disease risk and developing interventions that enhance homeostasis.

Clinically, recognizing compensatory endocrine responses has important implications for healthy aging. Endocrine alterations often precede or amplify metabolic impairments, creating feedback loops that accelerate chronic disease progression [11]. Insulin resistance and dyslipidemia, for example, are primary contributors to cardiovascular disease, cognitive decline, and other age-related disorders [12]. Interventions targeting hormonal balance and tissue responsiveness, including lifestyle modifications, pharmacological therapies, and novel strategies addressing endocrine-immune-metabolic interactions, can improve physical and cognitive function, enhance resilience, and extend healthspan. Thus, research into age-related endocrine decline and compensatory mechanisms is essential for understanding how the body maintains homeostasis during aging and for informing strategies to promote longevity and functional independence.

2. Methods

This study employed a systematic evidence-synthesis approach following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Peer-reviewed articles published between 2020 and 2025 were retrieved from PubMed, Scopus, Web of Science, and Google Scholar using controlled vocabulary and Boolean operators related to endocrine aging, hormone regulation, metabolic dysfunction, and geroscience interventions.

2.1 Eligibility Criteria

Inclusion criteria:

Studies examining hormonal alterations associated with aging.

Studies assessing physiological consequences of endocrine-related interventions.

Studies evaluating interventions targeting endocrine pathways.

Exclusion criteria:

Non-peer-reviewed articles.

Animal studies lacking translational relevance.

Studies with insufficient methodological rigor.

2.2 Screening and Selection

All retrieved records were imported into reference management software, and duplicates were removed. Titles and abstracts were screened independently by two reviewers. Full texts of potentially relevant studies were assessed for eligibility, and any discrepancies were resolved through consensus.

2.3 Data Extraction

A standardized data extraction template was used to collect information on study design, population characteristics, endocrine parameters, molecular pathways, and intervention outcomes. Extracted data were categorized into four key areas: compensatory endocrine responses, physiological effects of hormonal dysregulation, current therapeutic approaches, and research gaps for future investigation.

2.4 Data Synthesis

Findings were summarized using a structured analytical model, ensuring consistency, reproducibility, and objectivity, as illustrated in Figure 1, the PRISMA flow diagram. Narrative synthesis was guided strictly by comparative analysis across studies, highlighting trends, mechanisms, and outcomes in endocrine aging.

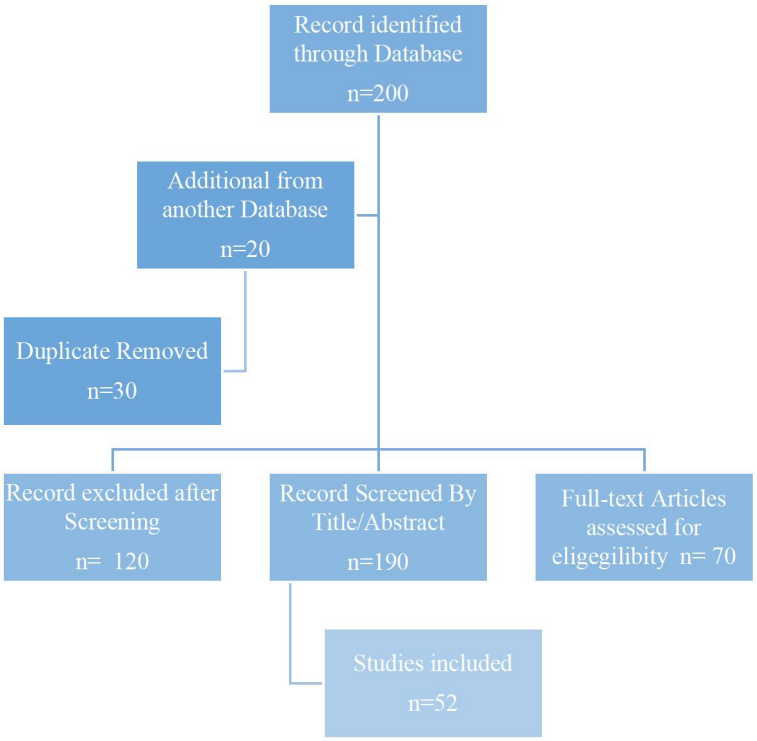

Figure 1. PRISMA flow diagram.

3. Endocrine Regulation Overview and Age-Related Hormonal Changes

The endocrine regulation is subject to accumulated changes throughout aging that affect virtually all systems of the body, leading to metabolic dysregulation, poor physiological defenses, and disease vulnerability. The underlying causes of these changes include intrinsic glandular aging, accumulating environmental factors, and crosstalk between hormonal, paracrine, and immune signaling [13-15]. The importance of comprehending these changes in the context of the major endocrine axes is in explaining processes of age-related deterioration and what approaches can be implemented to foster a healthy aging process.

3.1 Hypothalamic-Pituitary Axis and the Role in Aging

The hypothalamus serves as the primary integrative center of endocrine homeostasis, coordinating neural, hormonal, and environmental signals to maintain systemic equilibrium. With aging, hypothalamic regulation becomes progressively impaired, leading to dysregulation of downstream endocrine glands, including the pituitary, adrenals, gonads, and thyroid [16]. Age-related hypothalamic inflammation, oxidative stress, and altered neuroendocrine signaling disrupt circadian rhythmicity, stress responsiveness, and the secretion of essential tropic hormones [17,18]. Rather than acting as an isolated dysfunction, hypothalamic-pituitary impairment establishes a foundational disturbance that predisposes peripheral endocrine systems to maladaptive regulation across multiple physiological domains.

3.2 Sex Hormone Decline: Estrogen, Progesterone, and Testosterone

Sex hormones undergo a marked age-dependent decline with broad systemic consequences. In women, menopause-associated reductions in estrogen and progesterone alter adipose distribution, vascular function, and glucose regulation, increasing vulnerability to cardiometabolic disorders [17]. In men, gradual reductions in testosterone and its bioactive metabolites contribute to changes in body composition, musculoskeletal integrity, and energy balance [19]. Importantly, sex steroid decline exerts modulatory effects on other endocrine axes, amplifying age-related physiological vulnerability through inter-axis hormonal crosstalk rather than acting as an isolated metabolic trigger, as illustrated in Figure 2 showing the decline of estrogen, progesterone, and testosterone with aging.

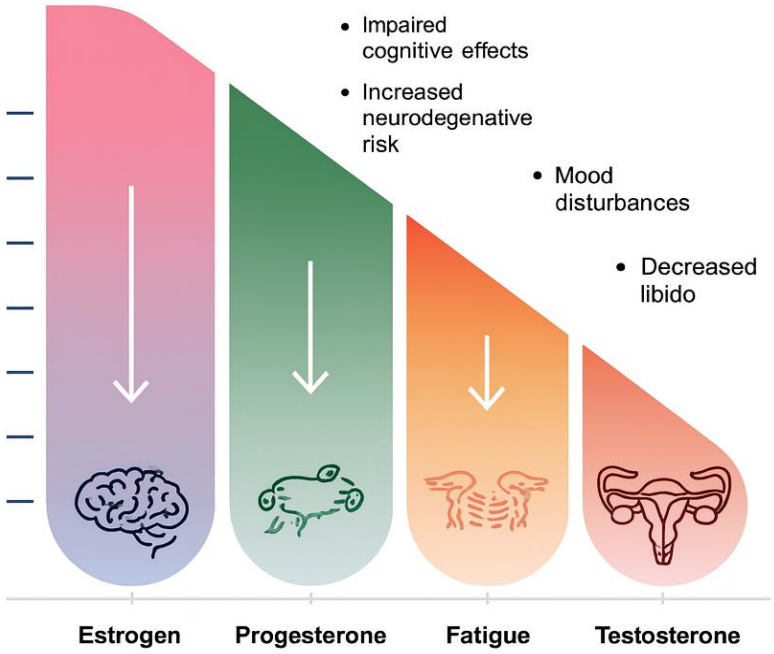

Figure 2. Sex hormone decline with aging: estrogen, progesterone, and testosterone.

In females, the abrupt postmenopausal fall in estrogen and progesterone drives visceral adiposity, insulin resistance, metabolic syndrome, osteoporosis, and cardiovascular risk, while also contributing to mood and cognitive disturbances. In males (and to a lesser extent females), the progressive age-related decline in testosterone (andropause) leads to sarcopenia, increased fat mass, reduced energy and libido, fatigue, and elevated cardiometabolic risk. Declining sex hormones interact with other endocrine axes, amplifying the systemic impact of aging.

3.3 Thyroid Hormone Regulation and Age-Related Metabolic Adaptation

Aging is associated with subtle yet functionally significant alterations in thyroid hormone regulation. Circulating levels of thyroxine (T4) and triiodothyronine (T3) decline modestly with age, accompanied by reduced responsiveness of peripheral tissues to thyroid signaling [14]. These changes modify basal metabolic rate, thermogenesis, and lipid handling, contributing to altered energy utilization [13]. In combination with reductions in sex hormones and somatotropic signaling, thyroid dysregulation participates in broader endocrine adaptations that influence systemic metabolic regulation in later life.

3.4 Growth Hormone (GH)/Insulin-Like Growth Factor-1 (IGF-1) Axis Decline and Somatic Maintenance

The age-associated decline in GH and IGF-1, commonly termed somatopause, is a defining feature of endocrine aging. Reduced GH/IGF-1 signaling impairs protein synthesis, tissue regeneration, and musculoskeletal maintenance, accelerating sarcopenia and loss of functional capacity [14,20]. Rather than acting independently, somatotropic decline interacts with thyroid, insulin, and sex hormone pathways, contributing to age-related shifts in body composition and energy utilization through coordinated endocrine regulation.

3.5 Age-Related Changes in Adrenal Hormone Secretion

Adrenal hormone secretion undergoes complex age-dependent alterations. Flattening of the circadian cortisol rhythm and elevated evening cortisol levels are associated with increased inflammatory tone and altered stress responsiveness. Concurrent declines in dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) reduce the availability of adrenal-derived sex steroid precursors [14,15]. Age-related changes in aldosterone secretion further influence fluid balance and cardiovascular regulation. Collectively, these adrenal adaptations modify systemic resilience and physiological adaptability during aging.

3.6 Insulin Regulation and Endocrine Integration in Aging

Insulin resistance in aging arises from interacting factors including increased visceral adiposity, mitochondrial dysfunction, chronic inflammation, and reduced skeletal muscle glucose uptake [21,22]. Impaired insulin signaling reflects the cumulative influence of declining sex steroids, altered thyroid function, somatotropic suppression, and adrenal hormone dysregulation rather than an isolated endocrine defect [13,22]. These interactions contribute to a coordinated endocrine metabolic feedback loop that underlies the progression of metabolaging.

3.7 Convergent Impact on Metabolic Homeostasis

Age-related alterations across multiple endocrine axes converge on a common pathophysiological outcome: progressive disruption of metabolic homeostasis. Dysregulation of the hypothalamic–pituitary axis alters circadian organization, stress responsiveness, and trophic hormone signaling, predisposing the organism to systemic metabolic imbalance. Declines in sex hormones, thyroid hormones, GH/IGF-1, adrenal hormones, and insulin signaling collectively impair glucose regulation, lipid metabolism, and energy partitioning across tissues [16].

Sex steroid deficiency promotes visceral adiposity, insulin resistance, and impaired lipid handling, increasing metabolic vulnerability during aging. Concurrent reductions in thyroid hormone availability and tissue responsiveness lower basal metabolic rate and thermogenic capacity, favoring weight gain and dyslipidemia. Decline of the GH/IGF-1 axis further limits metabolic flexibility by reducing skeletal muscle mass and regenerative capacity. Adrenal hormone alterations, including flattened cortisol rhythms and reduced DHEA levels, contribute to chronic low-grade inflammation and impaired insulin sensitivity [14-16].

Insulin resistance represents the most direct manifestation of this convergent endocrine decline. Increased visceral adiposity, mitochondrial dysfunction, inflammation, and reduced muscle glucose disposal collectively undermine insulin action, leading to hyperglycemia, dyslipidemia, and elevated risk of type 2 diabetes and cardiovascular disease. Insulin dysregulation both results from and reinforces dysfunction across other endocrine axes, forming a self-amplifying endocrine–metabolic loop characteristic of metabolaging [13,20].

At the tissue level, reduced hormonal sensitivity in adipose tissue, liver, and skeletal muscle limits metabolic adaptability, transforming adaptive endocrine changes into maladaptive outcomes. The cumulative effect is a systemic metabolic hub characterized by impaired glucose homeostasis, altered lipid handling, increased inflammatory tone, and reduced energetic efficiency, linking endocrine aging to metabolic syndrome, frailty, and age-related chronic disease.

4. Endocrine Adaptive Compensatory Changes in Aging

As one gets older, there is a broad range of biological alterations that disturb the highly tuned endocrine systems that keep the system on track. To address these perturbations, the body responds to these perturbations with a number of compensatory endocrine processes aimed at restoring homeostasis, moderating physiological deterioration, and maintaining metabolic stability as long as possible. The compensatory mechanisms include neuroendocrine feedback mechanisms, peripheral tissue mechanisms, metabolic re-recruitment, immune-endocrine mechanisms, and cognitive mechanisms. Although these mechanisms are originally useful in maintaining the functional integrity of the aging organism, there is the progressive weakening of these mechanisms due to the loss of sensitivity of endocrine tissues, a decrease in the ability to repair them, and a decrease in their reserves.

4.1 Feedback Adjustments in the Hypothalamic-Pituitary System

Changes occurring in the hypothalamic–pituitary axes represent some of the earliest compensatory mechanisms associated with endocrine aging. With advancing age, functional alterations occur in both central regulatory structures and peripheral endocrine glands, leading to changes in hormonal synthesis, secretion, and feedback sensitivity [23]. These alterations often arise from impairments in hormone production by peripheral glands such as the ovaries, testes, thyroid, and adrenal glands, which subsequently trigger adaptive regulatory responses aimed at maintaining endocrine homeostasis through feedback mechanisms [24].

Age-related decreases in gonadal steroid secretion reduce the inhibitory feedback exerted on the hypothalamus and anterior pituitary. As a result, the hypothalamus increases the release of gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to secrete higher levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This compensatory elevation of gonadotropins is a characteristic feature of the regulation of the hypothalamic–pituitary–gonadal (HPG) axis during endocrine aging [24]. Similar feedback adjustments may also occur in other endocrine axes, where reduced peripheral hormone output induces compensatory changes in pituitary hormone secretion in an attempt to preserve physiological balance.

This compensatory increase in LH and FSH tries to balance the lowering estrogen levels, but the effect is usually not enough to normalize the reproductive or metabolic functions [25].

These compensatory responses are actively made in the brain through redistribution of energy resources to the basic neuroendocrine activities. This is in line with the brain-body energy conservation model that opines that molecular

damage that comes with aging increases the metabolic demands of the somatic tissues, which forces the central nervous system to shift the metabolic priorities [26]. These changes are necessary to maintain neural activity at the expense of peripheral hormone production and tissue sensitivity. The female reproductive ageing is an excellent example: premature dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis results in the rupture of ovulatory cycles, loss of ovarian reserve, and more general physiological effects than just fertility [27].

Recent data also demonstrate that the pituitary directly acts on somatic organs such as bones and adipose tissue, indicating a broader systemic effect of pituitary aging than has been previously realized [28]. The compensatory alterations demonstrate the effort of the pituitary to maintain endocrine homeostasis in the entire body despite deteriorating hormone production and impaired feedback sensitivity of the peripheral glands with aging.

4.2 Peripheral Tissue Sensitivity and Receptor Level Adaptations

During aging, peripheral tissues initiate compensatory adaptations to counteract declining circulating hormone levels and preserve physiological function. These adaptations occur primarily at the receptor and post-receptor levels and include modulation of hormone receptor density, alterations in receptor affinity, and reprogramming of intracellular signaling cascades. Such mechanisms allow target tissues to transiently maintain responsiveness despite reduced endocrine input.

Tissue sensitivity refers to the capacity of peripheral organs to detect, transduce, and respond appropriately to hormonal signals. This process depends not only on hormone availability but also on receptor integrity, signal amplification efficiency, and downstream metabolic competence. Aging disrupts each of these components. Prolonged exposure to altered hormonal environments can induce receptor downregulation, impaired ligand–receptor binding, and attenuation of intracellular signaling pathways, ultimately reducing functional responsiveness even when hormone levels remain sufficient.

The skin provides a representative model of receptor-level adaptation in aging tissues. As a hormonally responsive organ influenced by insulin-like IGF-1, GH, and retinoids, aging skin exhibits changes in cellular proliferation, barrier integrity, and extracellular matrix organization [29]. In early stages, cutaneous cells partially compensate for reduced endocrine stimulation through receptor sensitization and activation of alternative signaling pathways. However, sustained hormonal imbalance, oxidative stress, and cumulative cellular damage progressively limit these adaptive responses.

With advancing age, declining cellular repair capacity and increasing oxidative burden promote receptor desensitization and signaling inefficiency. Once receptor responsiveness is compromised, peripheral tissues lose their ability to buffer endocrine fluctuations, accelerating systemic dysregulation. This decline in tissue sensitivity thus represents a critical constraint on compensatory endocrine mechanisms, marking the transition from adaptive regulation to maladaptive dysfunction.

4.3 Cellular Repair, Antioxidant Activity, and Metabolic Rehabilitation

At the cellular level, aging is accompanied by compensatory responses aimed at preserving metabolic stability, including activation of antioxidant pathways, DNA repair mechanisms, and mitochondrial bioenergetic reprogramming. The hypothalamic–pituitary–adrenal (HPA) axis plays a central role in regulating these adaptations through glucocorticoid-mediated stress and inflammatory responses [30,31]. With advancing age, altered glucocorticoid signaling and receptor sensitivity compromise tissue resilience, contributing to cumulative metabolic strain [32]. These buffering mechanisms remain effective in early and midlife but progressively weaken as cellular damage accumulates.

4.4 Immuno-Endocrine Interactions and Inflammatory Compensation

Immunosenescence and chronic low-grade inflammation (inflammaging) are linked to aging, and both are also intimately coupled with endocrine processes. Cytokines, hormones, and stress mediators are used to communicate between immune organs and endocrine glands. Compensatory changes in this immuno-endocrine system occur during aging, trying to preserve inflammatory balance and tissue integrity.

The natural immune factors, such as acute-phase proteins and cytokines, coordinate the hypothalamic and pituitary activities to adjust the systemic energy distribution and stress response [30]. Nevertheless, chronic endocrine disturbance impairs the capacity of the body to restrain inflammation, which results in adaptive compensation mechanisms, such as increased glucocorticoid secretion and adrenal hypersensitivity. These alterations are the causes of endocrine fatigue and increase the vulnerability to degenerative and metabolic illnesses.

4.5 Neural and Cognitive Compensatory Pathways

Endocrine compensation is also performed by cognitive centers in the brain modulating neural circuits that control appetite, thermoregulation, circadian rhythm, and energy expenditure. With age, the neuroendocrine communication is impaired, and the hypothalamus readjusts these signalling pathways to maintain metabolic activity, changing the outputs of the hypothalamus to do so, which affects appetite control, sympathetic tone, and neuropeptide release [31].

These neural adaptations are important in offsetting the effect of age-related metabolic inefficiencies. Nevertheless, their effectiveness is limited gradually by neuroinflammation, compromised neurotransmitter signaling, and impaired hypothalamic plasticity. Finally, cognitive and neural compensatory processes become unable to overcome and compensate for systemic endocrine decline.

4.6 Compensatory Mechanisms Limitations in Advanced Aging

In advanced aging, compensatory endocrine responses lose efficacy due to impaired feedback sensitivity, receptor dysfunction, metabolic fatigue, and accumulated cellular damage. This transition marks a shift from adaptive aging to systemic instability, described as metabolaging fatigue, wherein hormonal dysregulation and metabolic insufficiency reinforce one another. Structural and functional deterioration in adipose tissue, skeletal muscle, and liver further erodes compensatory capacity, promoting insulin resistance and inflammatory burden [33,34].

5. Endocrine Dysregulation and Its Physiological and Health Implications

Endocrine deregulation has highly extensive widespread effects on various physiological systems. The basis of reproductive, metabolic, cardiovascular, neural, and immune stability is hormonal stability. The disruption of this precarious inner environment may be due to endogenous hormonal alterations in old age and exogenous exposures like endocrine-disrupting chemicals. These disruptions undermine the functions of the endocrine system to synchronize biological functions, which leads to chronic diseases and accelerated deterioration of physiological functions. Hormonal swings, environmental shocks, and tissue sensitivity are complexly interrelated such that endocrine anomalies influence aging patterns and health consequences [35].

The ability of the organism to change hormone concentrations and receptor densities as well as downstream signaling to both internal and external conditions through endocrine flexibility is necessary to preserve phenotypic stability. Nevertheless, this flexibility is lost as one grows old, and this increases their vulnerability to metabolic diseases, fragile immune systems, rapid tissue decay, and mortality [36]. The example of estrogen loss in menopause in women shows such a weakness, and the probability of developing metabolic syndromes, cardiovascular disease, osteoporosis, and mortality in general is dramatically high [37]. To make this decrease worse, xenobiotics like endocrine-disrupting chemicals can also compound this process by imitating, altering, or blocking hormone activity, thus influencing reproductive health, the immune system, and cancer vulnerability [38].

Additionally, the decreased absorption and responsiveness of the aging tissues to circulating hormones contribute to an aggravation of metabolic imbalance and the decreased response of compensatory endocrine responses. These changes highlight the importance of further research on how endocrine disruption is involved in the multisystem degradation. The dynamics between the changes in endogenous hormones and exposure to the environment are critical to the development of specific interventions that would facilitate healthier aging patterns [39].

5.1 Sarcopenia and Musculoskeletal Decay

Sarcopenia, the progressive and generalized loss of skeletal muscle mass, strength, and functional capacity, is widely recognized as a hallmark of age-related endocrine dysregulation. This condition arises from complex interactions between hormonal decline, neuromuscular degeneration, and metabolic alterations that accompany aging. In particular, reductions in anabolic hormones such as GH, IGF-1, testosterone, and estrogen contribute significantly to impaired muscle protein synthesis and reduced regenerative potential of skeletal muscle tissue [40]. In addition, aging muscles exhibit decreased responsiveness to endocrine signaling, further limiting their ability to maintain structural integrity and metabolic efficiency [41]. Together, these hormonal and cellular changes compromise muscle maintenance, repair capacity, and overall physical performance, as discussed in Section 4.2.

In women, menopause represents a critical transition in musculoskeletal aging. The sharp decline in estrogen levels during this period disrupts the balance between bone formation and bone resorption, leading to accelerated bone loss and deterioration of skeletal microarchitecture. Consequently, decreased estrogen availability contributes to increased bone fragility, reduced muscle protein synthesis, and a heightened risk of fractures and functional decline [37]. Estrogen plays a central role in regulating bone remodeling, calcium homeostasis, and muscle viability; therefore, its deficiency destabilizes the coordinated physiological mechanisms responsible for maintaining musculoskeletal health [42]. The combined effects of hormonal decline and reduced tissue responsiveness significantly increase the vulnerability of aging individuals to sarcopenia, osteoporosis, and mobility limitations.

In addition to hormonal depletion, aging muscle and bone tissues exhibit diminished receptor expression and impaired intracellular signaling efficiency. These cellular alterations limit the effectiveness of circulating hormones and progressively reduce adaptive capacity. Early ovarian aging, which may begin to affect reproductive function in the late thirties, initiates endocrine changes that predispose individuals to long-term musculoskeletal deterioration [43].

Androgens also contribute significantly to musculoskeletal health in both sexes by supporting muscle protein accretion, bone remodeling, and energy balance. Age-related reductions in androgen levels further exacerbate muscle weakness, skeletal fragility, fatigue, and reduced functional mobility, increasing susceptibility to frailty [44]. The combined effects

of declining sex hormone availability and reduced tissue-level hormonal responsiveness establish a biological milieu that favors sarcopenia, osteoporosis, and generalized musculoskeletal frailty during aging.

5.2 Metabolic Syndrome and Glucose Dysregulation

Metabolic syndrome represents a downstream manifestation of cumulative endocrine imbalance rather than the repeated outcome of individual hormonal declines. Insulin resistance, dyslipidemia, central adiposity, and impaired glucose handling emerge from the convergence of altered sex steroid signaling, disrupted insulin pathways, and reduced tissue adaptability [37]. Exposure to endocrine-disrupting chemicals may further exacerbate these vulnerabilities by interfering with hormone receptors and metabolic signaling cascades, intensifying oxidative stress and inflammatory load [38].

5.3 Cardiovascular Consequences of Hormonal Deterioration

Hormonal signals control cardiovascular health, including control of vascular tone, lipid balance, cardiac metabolism, and inflammatory pathways. Menopause disrupts vascular elasticity, advances the unhealthy lipid profiles, and intensifies the inflammatory condition, and all these factors increase the susceptibility of cardiovascular diseases among aging persons, especially in postmenopausal women [37]. Vascular homeostasis can also be disrupted by exogenous disruptors, which interact with nuclear receptors and lead to hypertension and endothelial dysfunction [39].

5.4 Cognitive Aging and Neuroendocrine Effects

The changes in hormone levels have a tremendous impact on the brain structure and functioning. Sex steroids consist of estrogens and progesterone that promote synaptic plasticity, neuroprotection, and cognitive resilience. The diminishment in these hormones has been reported as being related to increased susceptibility to mood disorders and neurodegenerative diseases, such as Alzheimer's disease [41]. The dysregulation of the endocrine system causes changes in the balance of neurotransmitters, stress reactions, and neuroinflammatory processes, which eventually determine cognitive aging patterns.

5.5 Host Defense and Vulnerability to Infections

Cross-talk of endocrine and immune systems is necessary to regulate inflammatory reactions, pathogen defenses, and tissue repair. The deterioration of hormones undermines the immune surveillance, predisposes to the infection, and worsens autoimmune behavior. Sex hormones have a strong influence on the immune system, and depletion of estrogen or androgen suppresses the immune system, both innate and adaptive [41]. At the same time, endocrine-disrupting chemicals may tune the activity of cytokines and immune cell differentiation, which may increase susceptibility to infectious and inflammatory diseases [35,39].

Table 1. Physiological and health implications of endocrine dysregulation.

Physiological System	Key Hormonal Influences	Age-Related Endocrine Changes	Consequences	Exogenous/Environmental Modulators	Ref.
Musculoskeletal (Sarcopenia, Osteoporosis)	Estrogens, Androgens, GH, IGF-1	Decline in estrogen (menopause), reduced androgen levels, decreased receptor sensitivity	Muscle loss, reduced bone density, fractures, frailty	Endocrine-disrupting chemicals, low physical activity, poor nutrition	[37,43,44]
Metabolic System (Metabolic Syndrome, Glucose Dysregulation)	Insulin, Estrogens, Thyroid Hormones, Cortisol	Impaired estrogen signaling, reduced insulin sensitivity, altered thyroid function	Obesity, type 2 diabetes, dyslipidemia, central adiposity	Xenobiotics affecting insulin pathways, high-calorie diet, sedentary lifestyle	[37,38]
Cardiovascular System	Estrogens, Androgens, Cortisol, Aldosterone	Estrogen decline, increased arterial stiffness, altered lipid metabolism	Hypertension, atherosclerosis, increased cardiovascular disease risk	Endocrine-disrupting chemicals, smoking, high-fat diet	[37,39]
Nervous System (Cognitive Aging)	Estrogens, Progesterone, Cortisol, Thyroid Hormones	Reduced sex steroids, altered stress hormone regulation	Cognitive decline, neurodegenerative disease risk, mood disorders	Neurotoxins, chronic stress, environmental pollutants	[41]
Immune System	Estrogens, Androgens, Cortisol, Thyroid Hormones	Hormonal decline reduces immune cell function, altered cytokine profiles	Increased infection susceptibility, autoimmune dysregulation, impaired tissue repair	Endocrine disruptors, chronic inflammation, pollutants	[35,39,41]
Frailty & Longevity	Multisystem hormonal integration	Cumulative hormonal decline, reduced tissue responsiveness	Decreased resilience, increased morbidity and mortality	Lifestyle factors, environmental endocrine disruptors	[37,40]

5.6 Frailty, Longevity, and Risk of Mortality

Frailty is the ultimate breakdown of multisystem physiological resilience, which is strongly dependent on endocrine deterioration. A decline in hormones is also a cause of decreased muscle activity, poor metabolic plasticity, poor immunity, and poor cognitive stability, which all increase the risk of mortality. The fact that sex differences in disease vulnerability and life expectancy also indicate that hormonal roles in the aging process should be comprehended since endocrine dysregulation can influence the disease processes differently in both men and women [37,40].

Interactions between endogenous hormonal loss, tissue insensitivity, and environmental disruptors contribute to lifespan and healthspan. Ensuring endocrine stability and minimizing environmental endocrine stressors is an effective approach to achieving healthier aging and decreasing the burden of chronic disease, as summarized in Table 1.

6. Emerging Interventions to Healthy Endocrine Aging

It is now viewed as a priority in aging studies that optimal endocrine aging contributes significantly to metabolic well-being, cognitive ability, musculoskeletal health, and well-being as a whole. There is an emerging body of evidence that highlights the necessity of multifaceted approaches to both intrinsic hormonal loss and to the intricate mechanisms between endocrine axes that ensue with age [45]. Endocrine aging is dynamic and therefore requires therapeutic solutions that have the ability to restore or maintain hormonal balance without compromising the homeostasis of the entire system. These strategies include conventional hormone replacement therapy (HRT), innovative endocrine regulators, lifestyle-related interventions, and modern precision-medicine treatment [46].

It is important to understand the physiological changes that take place in endocrine systems such as GH, adrenal, thyroid, ovarian, and testicular axes in order to design specific interventions that can improve healthspan. These systemic changes are closely connected with the chronic diseases, including osteoporosis, cardiovascular disease, metabolic syndrome, neurodegeneration, and immunosenescence [46]. The complex processes of hormonal aging, such as genomic instability, mitochondrial dysfunction, chronic low-grade inflammation, and changes in nutrient-sensing pathways, are still being discovered through the use of molecular endocrinology [47,48].

Integrated systems biology and multi-omics studies are becoming increasingly informative of emerging interventions, allowing the identification of genetic and molecular determinants of endocrine decline and providing new therapeutic targets [49]. This part examines the most promising and dynamic approaches to supporting endocrine resilience, reducing age-associated hormonal dysfunctions, and the growth of healthy aging. They consist of hormone-replacement therapy, GH and IGF-1 therapy, thyroid therapy, adrenal therapy, lifestyle-based therapy, pharmacological therapies, nutraceutical therapy, and personalized endocrine therapy. All these strategies provide an integrated and proactive model of improving the endocrine health of older adults [50,51].

6.1 HRT and Bioidentical Hormones

The hormone replacement treatment is one of the most popular methods of reversing the hormonal changes of aging, especially among postmenopausal women. HRT is supposed to replace the decreased levels of sex hormones, which reduces the symptoms of vasomotor irregularities, bone loss, mood swings, and metabolic problems. Conventional HRT normally entails synthetic/semi-synthetic estrogens and progestogens, whereas bioidentical hormone preparations are structurally equivalent to endogenous hormones and might provide more physiologic hormonal replacement.

Current methods focus on personalized therapy that is dependent on the intensity of the symptoms, risk factors, and unique endocrine profiles in the patients. With increasing knowledge of hormonal interactions, personalized HRT could become more customized in terms of dose adjustments and biomarker-based monitoring, as well as combinations of hormones that more closely mimic natural physiological rhythms [45]. There is more progress in the system of delivery, such as transdermal patches or subcutaneous pellets, or controlled-release oral forms that improve the safety and effectiveness.

6.2 GH and IGF-1 Modulators

The GH and insulin-like IGF-1 decrease significantly with age, which has contributed to the loss of muscle mass, excessive fat build-up, loss of physical performance, and poor cell repair. This axis has to be modulated by new strategies without causing supraphysiological levels of hormones, which are at great risk.

Strategies currently being examined are GH secretagogues, peptides that can trigger endogenous GH, and lifestyle-based strategies, including resistance training, sleep optimization, and high-protein diets. It is being investigated with selective IGF-1 pathway modulators to maximize the anabolic effects and reduce the negative effects on the insulin sensitivity and risk of cancer [46]. The idea is to rejuvenate the elements of youthful GH/IGF-1 signaling without the complexities that come with the use of exogenous GH.

6.3 Optimization of Thyroid Hormone in the Elderly

Thyroid activity has a bearing on the metabolism rate, the performance of the cardiovascular system, mental well-being, and temperature regulation. As a person grows old, there is a subtle alteration of thyroid-stimulating hormone (TSH) and peripheral conversion of T4 to T3 that can cause fatigue, weight gain, mood changes, and cognitive deterioration.

New directions are concerned with more accurate and personalized optimization of thyroid hormones. They involve not only the assessment of serum TSH but also peripheral biomarkers of tissue-specific thyroid action. Older persons might require modified doses of levothyroxine, T3/T4 therapy, or intervention to facilitate effective T4-to-T3 transformation. Replacement of optimal thyroid activity will be able to increase energy expenditure, cognitive performance, and general metabolic resilience in older adults [52].

6.4 Supplementation in the DHEA and Adrenal Support

The adrenal steroid DHEA, which is the precursor of estrogens and androgens, reduces progressively with age. Lower levels of DHEA are linked to less vitality, immunological defects, metabolic imbalance, and low levels of stress resilience.

New directions involve low-dose, individual endocrine-based, profile-specific DHEA supplementation. It is aimed at sustaining adrenal activity, promoting hormonal equilibrium, and enriching well-being without provoking excessive androgenic activity. With supplementation, the measures to enhance adrenal resilience, including circadian rhythm synchronization, stress-reduction measures, and nutritional support, are gaining more and more critical importance [46]. These methods are to maximize the HPA axis, which is key in ensuring that there is endocrine stability during aging.

6.5 Lifestyle Interventions: Diet, Exercise, Sleeping, and Stress Reduction

Endocrine health is one of the pillars that consists of lifestyle modification. Hormonal pathways, as well as systemic aging, have strong influences on diet, physical activities, sleep patterns, and stress.

Diet: Abnormal diets with high nutrient densities, such as whole food, phytonutrients, and balanced macronutrients, aid in the metabolic homeostasis and normalization of insulin and cortisol levels. Sufficient protein consumption is obligatory in hormonal regulation of muscle mass and metabolism rate.

Exercise: Aerobic and resistance exercise have been shown to stimulate anabolic hormones, increase insulin sensitivity, maintain bone density, and facilitate GH and IGF-1 signaling [52].

Sleep: REM sleep controls cortisol, melatonin, GH, and reproductive hormones. Persistent sleep deprivation interferes with the endocrine cycles and paces up physiological aging.

The reduction of stress: Long-term stress activates cortisol and breaks adrenal, thyroid, and gonadal axes. Stress hormones can be normalized through mindfulness practices and relaxation techniques as well as improved social support and help strengthen endocrine resilience.

Taken together, these lifestyle interventions are one of the most convenient low-risk approaches to endocrine health throughout the lifespan.

6.6 Pharmacological Innovations Endocrine Pathways

There is a lot of success in designing pharmacological agents that inhibit certain endocrine pathways in aging. Selective hormone receptor modulators, metabolic stabilizers, and other compounds that target nutrient-sensing pathways like AMPK, mTOR, and sirtuins are novel therapeutics.

Inflammatory cytokines, mitochondrial dysfunction, and oxidative stress agents are also showing interest since these processes interrelate with the regulation of hormones [50]. Moreover, there are new types of biologics and small-molecule agents that target to control endocrine-immune crosstalk, as immune dysregulation is a cause and effect of hormone loss [48].

6.7 Nutraceuticals and Functional Foods with an Endocrine Benefit

Supplementary methods that help to maintain endocrine activity are provided by nutraceuticals and functional foods. Antioxidant effects, anti-inflammatory effects, and regulation of metabolic enzymes are bioactive compounds that can affect hormonal pathways of products of plant, marine, or fermented foods.

Polyphenols, omega-3 fatty acids, adaptogens, and phytoestrogens are under consideration in terms of their ability to support thyroid functioning, enhance insulin sensitivity, regulate cortisol release, and promote the feeling of hormonal balance in the reproductive system [49]. Such interventions are potentially promising because they are low-risk, readily available interventions, although standardization and dose-response characterization are areas of current research.

6.8 Precision Medicine and Hormone-Based Interventions to Personality

Precision medicine is a revolutionary concept of endocrine aging. Clinicians are able to develop interventions based on the endocrine landscape of an individual using genomic information, biomarkers, metabolomics, and highly developed imaging. This enables more subtle hormone optimization-based approaches, which take into consideration hormone metabolism, receptor sensitivity, and signalling networks' genetic variability.

Biological analyses of personal endocrine aging trajectories and prediction of therapeutic responses are increasingly being identified using machine-learning models and network-based biological analyses [52]. This individualized model acknowledges the heterogeneity of aging and tries to maximize endocrine well-being and reduce risks of generalized hormone replacement therapies, as outlined in Table 2.

Table 2. Emerging interventions for healthy endocrine aging.

Intervention	Target Hormonal/Endocrine Axis	Mechanism of Action	Potential Benefits	Ref.
HRT & Bioidentical Hormones	Estrogens, Progestogens, Androgens	Restores declining hormone levels; tailored dosing; bioidentical formulations mimic endogenous hormones	Reduces vasomotor symptoms, bone loss, mood disturbances, metabolic dysregulation	[45]
GH & IGF-1 Modulation	GH/IGF-1 axis	GH secretagogues, peptides, lifestyle enhancers (resistance training, sleep, protein intake)	Improved muscle mass, reduced fat deposition, enhanced physical performance, better cellular repair	[46]
Thyroid Hormone Optimization	Thyroid (TSH, T4, T3)	Individualized dosing, combination T4/T3 therapy, tissue-specific biomarkers	Enhanced energy metabolism, cognitive function, cardiovascular and thermoregulatory balance	[52]
DHEA Supplementation & Adrenal Support	Adrenal hormones (DHEA, cortisol precursors)	Low-dose supplementation, circadian rhythm alignment, stress reduction, nutrition	Improved vitality, immune function, metabolic balance, stress resilience	[46]
Lifestyle Interventions	Multisystem (GH, insulin, cortisol, sex steroids)	Diet (nutrient-dense, protein-rich), exercise (aerobic + resistance), restorative sleep, stress management	Stabilized insulin and cortisol, preserved muscle and bone, improved metabolic and endocrine function	[52]
Pharmacological Innovations	Sex hormones, GH/IGF-1, nutrient-sensing pathways (AMPK, mTOR, sirtuins)	Selective hormone receptor modulators, metabolic stabilizers, anti-inflammatory/antioxidant agents	Modulation of endocrine-immune crosstalk, improved metabolic homeostasis, slowed cellular aging	[48,50]
Nutraceuticals & Functional Foods	Multiple endocrine pathways	Bioactive compounds (polyphenols, omega-3s, adaptogens, phytoestrogens) modulate hormonal enzymes and receptors	Improved thyroid activity, insulin sensitivity, cortisol regulation, reproductive hormone balance	[49]
Precision/Personalized Endocrine Medicine	Individual endocrine landscape	Genomic, biomarker, metabolomics-guided interventions; machine learning for prediction	Optimized hormone therapy, tailored interventions, reduced risk of adverse effects, personalized healthspan enhancement	[52]

7. Future Directions

Future studies of endocrine aging need to be more integrative, technologically sophisticated, and concerned with ethics. Even though available evidence draws attention to the essential mechanisms of the hormonal decline and possible therapeutic interventions, the most significant gaps in the context of early detection, individualized treatment, and extended safety assessment have been identified. Endocrine aging is a multifaceted process with many interactions among diverse pathways, including inflammation, mitochondrial dysfunction, genomic instability, nutrient sensing, and others, and needs multidimensional approaches to achieve a more comprehensive understanding and control age-dependent hormonal decline [50,51]. With the emergent scientific efforts bridging the gap between endocrinology and systems biology, artificial intelligence, and sophisticated clinical trial design, solutions have a continued proliferation of ways to enhance healthspan by means of targeted endocrine maximization. The subsequent subsections identify the major future perspectives that must be crucial in the development of the field.

7.1 Moving Endocrine Biomarkers Towards Early Signs of Deterioration

One of the most important aspects of the endocrine aging studies is that there should be a sensitive and selective biomarker that can identify the early loss of hormones before the clinical presentation. Existing biomarkers tend to be based on the serum hormone levels, and this may not necessarily be a true reflection of receptor sensitivity, tissue-

specific hormone activity, or even compensatory responses that occur within the endocrine axes [45]. The alterations in conversion pathways with age, e.g., the conversion of T4 to T3, the alteration of the bioavailability of IGF-1, or the alteration in adrenal precursors, are more accurately assessed by more sophisticated indicators that reflect functional hormonal action as opposed to isolated hormone concentrations.

Next-generation biomarkers may also incorporate molecular signals of inflammation, oxidative stress, mitochondrial activity, and epigenetic drift that, taken together, have an effect on endocrine signalling [50]. MicroRNA signature, metabolomic, and cytokine clusters may provide extra clarity to identify early endocrine disruption. Multi-dimensional biomarkers, which contain metabolic, genomic, and immunologic readouts, can give more precise forecasts of endocrine deterioration and permit prior actions to be carried out with the aim of preserving endocrine robustness [45,51].

7.2 Multi-omics Solutions Endocrinology and Aging Biology

Multi-omics techniques, which include genomics, transcriptomics, proteomics, metabolomics, and epigenomics, have the potential to revolutionize the study of endocrine aging. Isolated hormonal alterations do not cause endocrine decline but rather are integrated into all of the molecular networks that are mediated by stress response systems, nutrient-sensing pathways, the health of mitochondria, and systemic inflammation [51].

Using multi-omics data, scientists can visualize endocrine aging pathways with unprecedented accuracy. These methods will help us understand how genetic variations affect hormone metabolism, how environmental exposures alter endocrine sensitivity, and how cellular signaling undergoes changes as people age [52]. Network biology specifically can be used to determine central regulatory nodes, the malfunction of which speeds up hormonal depreciation. These nodes can be used as emerging therapeutic targets to prevent and reverse endocrine aging.

Furthermore, by enhancing the division of people into risks, multi-omics studies will enable more specific therapeutic decisions in HRT, optimization of thyroid therapy, or metabolic treatments. These insights will contribute to addressing the weaknesses of universal endocrine approaches to care and contribute to creating individualized models of care [46,52].

7.3 Artificial Intelligence and Hormonal Aging Predictive Models

The field of artificial intelligence (AI) is among the most promising to predict hormonal aging and direct individual therapeutic interventions. AI algorithms have the ability to process extensive datasets based on hormone, genetic, imaging, metabolomic, and lifestyle trends to crunch predictions of endocrine degradation [52]. Such models can be used to predict the risks in the future, like osteoporosis, metabolic syndrome, or cognitive impairment, by detecting slight hormonal maladaptations many years before they have an adverse clinical effect.

The machine-learning systems can also aid the treatment decision by modeling the effect that other hormone replacement regimens, thyroid treatment, or lifestyle changes would have on the long-term outcomes of a particular person. With this predictive analytics, a significant step forward in precise endocrinology would occur, as clinicians would be able to base interventions on the dynamic endocrine modeling instead of the fixed laboratory values [47].

Eventually, AI-driven endocrine health monitors may combine wearable data, circadian hormone variability, and the use of continuous metabolic indicators to generate real-time hormonal health data in real time. Such systems would enable the earlier identification and more accurate modifications of the treatment plans, thus enhancing healthspan and resilience in old age.

7.4 Clinical Tests Requirement to Confirm New Treatment Plans

The biggest obstacle in the research on endocrine aging is the lack of long-term, strong clinical trials comparing new interventions. Most of the therapies, including GH modulators, bioidentical hormone preparations, nutraceutical agents, and adrenal support compounds, are promising but not widely clinically validated [45,48,50]. Moreover, both sex-specific and age-specific variations are not studied properly, which restricts the relevance of the results to different populations.

Clinical trials to be conducted in the future should include:

Longitudinal study designs to identify the data movement of endocrine alterations.

Various populations of participants, including underrepresented sexes and ages.

Multi-modal outcomes, including metabolic functioning, cognitive functioning, immune functioning, and musculoskeletal functioning.

Combined biomarkers, which indicate endocrine networks as opposed to single hormone levels.

It should also be tested in trials whether interventions that seek to modulate endocrine axes are safe in the long run, especially those that act on GH, IGF-1 signaling, and sex steroid pathways, which can be dangerous when not tightly

regulated [45,50]. Also, an assessment of multi-component interventions, including combined lifestyle, hormonal, and nutraceutical interventions, may give information on the synergistic effects that may be more favorable in the aging of endocrine health.

7.5 Ethical Concerns of Hormonal Enhancement of Longevity

With a shift in hormonal interventions, as the treatment of the disease turns into a possible manner to expand the healthspan, the ethical issues become even more significant. Enhancement using hormones creates issues on the availability, equity, and difference between therapeutic necessity and elective enhancement. Records of the possible abuse of hormones like GH, testosterone, or thyroid substances indicate that there is a need to have well-delineated ethical guidelines and regulatory controls.

The relevance of the extension of endocrine-mediated vitality to society, including effects on productivity, allocation of healthcare resources, and intergenerational equity, should also be the subject of ethical debates. In addition, because precision medicine enables highly individual hormonal therapeutic actions, the challenge of genetic privacy, data security, and algorithmic bias takes center stage [52].

A middle way should be followed so that the endocrine therapies do not cause excessive risks and inequalities to life quality. Combining patient values, open risk communication, and evidence-based regulatory systems will play a critical role in guiding the ethical practice of endocrine interventions in the aging populations [47].

8. Conclusion

Endocrine aging is a core, highly orchestrated phenomenon that involves physiological systems that become progressively dysfunctional with age due to impaired production of hormones, dysfunctional receptor sensitivity, and impaired feedback regulation, as well as inter-axis crosstalk. All the major endocrine axes, including hypothalamic-pituitary, gonadal, thyroid, somatotropic (GH/IGF-1), adrenal, and pancreatic, deteriorate simultaneously (in interdependence) and lead to metabolic dysregulation, chronic low-grade inflammation, immunosenescence, sarcopenia, frailty, and augmented vulnerability to age-associated conditions, such as type 2 diabetes, heart illness, osteoporosis, and neurodegenerative diseases. Though the aging body initially implements elaborate compensatory mechanisms, such as gonadotropin oversecretion and receptor sensitization, metabolic rerouting, and immuno-endocrine adaptations, they eventually diminish with age and develop to become maladaptive metabolizing and functional deterioration.

The new data of 2020-2025 highlights that endocrine aging is not something that happens and is a uniform process but a changeable characteristic of aging. The ability to maintain endocrine resilience, enhance tissue sensitivity to hormones, and increase healthspan is shown by lifestyle measures (optimized nutrition, resistance and aerobic exercise, sleep hygiene, and stress reduction); careful hormone optimization measures (bioidentical HRT, GH secretagogues, thyroid optimization, and low-dose DHEA); pharmacological adjudicators of nutrient-sensing and inflammatory cascades; and nutraceutical support. With the emergence of precision endocrinology, based on multi-omics profiling, artificial intelligence-based predictive models, and personalized biomarker panels, the paradigm of age-related disease treatment for proactive protection of hormonal homeostasis is bound to be changed.

Nonetheless, there is still a serious lack of knowledge: powerful, prolonged clinical trials on the safety and effectiveness of multi-modal endocrine therapies are absent; sensitive, functional indicators of early endocrine senescence are not well-developed; and ethical frameworks of hormone-based longevity enhancement still need to be elaborated so that there would be fair access and to avoid abuse. The endocrine dysregulation is at the intersection of the biology of aging and the pathology of aging. Direct manipulation of hormonal signaling networks will provide one of the most translational and actionable immediate morbidity compressions and healthier longevity. The field of geroscience can only advance in the future by incorporating stringent mechanistic studies, technology, and ethical standards to help turn the ever-increasing knowledge of endocrine aging into safe, individualized, and transformational procedures that enable individuals to age with physiological vitality instead of deteriorating hormonal decadence.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this article.

Generative AI Statement

The author declares that no Gen AI was used in the creation of this manuscript.

References

[1] Cappola AR, Auchus RJ, Fuleihan GE, Handelsman DJ, Kalyani RR, McClung MR, et al. Hormones and aging: An endocrine society scientific statement. The Journal of Clinical Endocrinology and Metabolism, 2023, 108(8), 1835-1874. DOI: 10.1210/clinem/dgad225

[2] van den Beld AW, Kaufman JM, Zillikens MC, Lamberts SW, Egan JM, van der Lely AJ. The physiology of endocrine systems with ageing. The Lancet Diabetes & Endocrinology, 2018, 6(8), 647-658. DOI: 10.1016/S2213-8587(18)30026-3
[3] Sellegounder D, Ferrucci L, Anbazhagan R, Basisty N. Molecular crosstalk between endocrine factors, paracrine signals, and the immune system during aging. Frontiers in Endocrinology, 2023, 14, 1203755. DOI: 10.3389/fendo.2023.1203755
[4] Harper J. Editorial: Insights in endocrinology of aging: 2021. Frontiers in Endocrinology, 2022, 13, 1066216. DOI: 10.3389/fendo.2022.1066216
[5] Camon C, Garratt M, Correa SM. Exploring the effects of estrogen deficiency and aging on organismal homeostasis during menopause. Nature Aging, 2024, 4(12), 1731-1744. DOI: 10.1038/s43587-024-00767-0
[6] Ezkurdia A, Ramírez MJ, Solas M. Metabolic syndrome as a risk factor for Alzheimer's disease: A focus on insulin resistance. International Journal of Molecular Sciences, 2023, 24(5), 4354. DOI: 10.3390/ijms24054354
[7] Wang SL, Shi YQ, Xin R, Kang HL, Xiong HZ, Ren JX. Exploring the role of insulin resistance in bridging the metabolic syndrome and Alzheimer's disease-a review of mechanistic studies. Frontiers in Endocrinology, 2025, 16, 1614006. DOI: 10.3389/fendo.2025.1614006
[8] Li MH, Ji R, Liu X, Wu YJ. Associations of metabolic syndrome and its components with sarcopenia, and the mediating role of insulin resistance: Findings from NHANES database. BMC Endocrine Disorders, 2024, 24(1), 203. DOI: 10.1186/s12902-024-01736-9
[9] Khalaf F, Barayan D, Saldanha S, Jeschke MG. Metabolaging: A new geroscience perspective linking aging pathologies and metabolic dysfunction. Metabolism, 2025, 166, 156158. DOI: 10.1016/j.metabol.2025.156158
[10] Cheng HY, Zhang XY, Li YH, Cao DZ, Luo CL, Zhang Q, et al. Age-related testosterone decline: Mechanisms and intervention strategies. Reproductive Biology and Endocrinology, 2024, 22(1), 144. DOI: 10.1186/s12958-024-01316-5
[11] Tsutsumi T, Tsuchiya K. Testosterone and obesity in an aging society. Biomolecules, 2025, 15(11), 1521. DOI: 10.3390/biom15111521
[12] Cao X, Thyfault JP. Exercise drives metabolic integration between muscle, adipose and liver metabolism and protects against aging-related diseases. Experimental Gerontology, 2023, 176, 112178. DOI: 10.1016/j.exger.2023.112178
[13] Basisty N, Kale A, Jeon OH, Kuehnemann C, Payne T, Rao C, et al. A proteomic atlas of senescence-associated secretomes for aging biomarker development. PLoS Biology, 2020, 18(1), e3000599. DOI: 10.1371/journal.pbio.3000599
[14] Xing YT, Xuan F, Wang KX, Zhang HF. Aging under endocrine hormone regulation. Frontiers in Endocrinology, 2023, 14, 1223529. DOI:10.3389/fendo.2023.1223529
[15] Wei R, Du ZH, Wang J, Bi JL, Lyu W, Wang HC, et al. A single-cell transcriptomic landscape characterizes the endocrine system aging in the mouse. Protein & Cell, 2025, 17(1), 27-45. DOI: 10.1093/procel/pwaf074
[16] Kolb H, Kempf K, Martin S. Insulin and aging - a disappointing relationship. Frontiers in endocrinology, 2023, 14, 1261298. DOI: 10.3389/fendo.2023.1261298
[17] Mahboobifard F, Pourgholami MH, Jorjani M, Dargahi L, Amiri M, Sadeghi S, et al. Estrogen as a key regulator of energy homeostasis and metabolic health. Biomedicine & Pharmacotherapy, 2022, 156, 113808. DOI: 10.1016/j.biopha.2022.113808
[18] Mantovani A, Garlanda C. Humoral innate immunity and acute-phase proteins. The New England Journal of Medicine, 2023, 388(5), 439-452. DOI: 10.1056/nejmra2206346
[19] Pöllänen PM, Härkönen T, Ilonen J, Toppari J, Veijola R, Siljander H, et al. Autoantibodies to N-terminally truncated GAD65 (96-585): HLA associations and predictive value for type 1 diabetes. The Journal of Clinical Endocrinology & Metabolism, 2022, 107(3), e935-e946. DOI: 10.1210/clinem/dgab816
[20] Spindler M, Palombo M, Zhang H, Thiel CM. Dysfunction of the hypothalamic-pituitary-adrenal axis and its influence on aging: The role of the hypothalamus. Scientific Reports, 2023, 13(1), 33922. DOI: 10.1038/s41598-023-33922-5
[21] Carrascosa MJ, Andres A, Ros M, Bogonez E, Arribas C, Fernandez-Agullo T, et al. Development of insulin resistance during aging: Involvement of central processes and role of adipokines. Current Protein and Peptide Science, 2011, 12(4), 305-315. DOI: 10.2174/138920311795906655
[22] Xu FZ, Dou L, Yu DN, Wu X, Liu LT, Man Y, et al. A novel "endocrine hormone": The diverse role of extracellular vesicles in multiorgan insulin resistance. International Journal of Medical Sciences, 2024, 21(11), 2081. DOI: 10.7150/ijms.97217
[23] Anawalt BD, Matsumoto AM. Aging and androgens: Physiology and clinical implications. Reviews in Endocrine & Metabolic Disorders, 2022, 23, 1123-1137. DOI: 10.1007/s11154-022-09765-2
[24] Brown ED, Obeng-Gyasi B, Hall JE, Shekhar S. The thyroid hormone axis and female reproduction. International journal of molecular sciences, 2023, 24(12), 9815. DOI: 10.3390/ijms24129815
[25] Zhu J, Zhou YE, Jin BH, Shu J. Role of estrogen in the regulation of central and peripheral energy homeostasis: From a menopausal perspective. Therapeutic Advances in Endocrinology and Metabolism, 2023, 14, 20420188231199359. DOI: 10.1177/20420188231199359
[26] Shaulson ED, Cohen AA, Picard M. The brain-body energy conservation model of aging. Nature Aging, 2024, 4, 1354. DOI: 10.1038/s43587-024-00716-x
[27] Balough JL, Dipali SS, Velez KM, Kumar TR, Duncan FE. Hallmarks of female reproductive aging in physiologic aging mice. Nature Aging, 2024, 4, 1711-1730. DOI: 10.1038/s43587-024-00769-y
[28] Zaidi M, Yuen T, Kim S. Pituitary crosstalk with bone, adipose tissue and brain. Nature Reviews Endocrinology, 2023, 19, 708-721. DOI: 10.1038/s41574-023-00894-5
[29] Bohm M, Stegemann A, Paus R, Kleszczynski K, Maity P, Wlaschek M, et al. Endocrine controls of skin aging. Endocrine Reviews, 2024, 46(3), 349-375. DOI: 10.1210/endrev/bnae034
[30] Powanda MC, Moyer ED. A brief, highly selective history of acute phase proteins as indicators of infection, inflammation and injury. Inflammopharmacology, 2021, 29(3), 897-901. DOI: 10.1007/s10787-021-00820-z.
[31] Yoo ES, Yu J, Sohn J. Neuroendocrine control of appetite and metabolism. Experimental & Molecular Medicine, 2021, 53, 505-516. DOI: 10.1038/s12276-021-00597-9
[32] Skorka-Majewicz M, Goschorska M, Zwierello W, Baranowska-Bosiacka I, Styburski D, Kapczuk P, et al. Effect of fluoride on endocrine tissues and their secretory functions--review. Chemosphere, 2020, 260, 127565. DOI: 10.1016/j.chemosphere.2020.127565
[33] Shou J, Chen PJ, Xiao WH. Mechanism of increased risk of insulin resistance in aging skeletal muscle. Diabetology & Metabolic Syndrome, 2020, 12(1), 14. DOI: 10.1186/s13098-020-0523-x

[34] Palmer AK, Jensen MD. Metabolic changes in aging humans: Current evidence and therapeutic strategies. The Journal of Clinical Investigation, 2022, 132(16), e158451. DOI: 10.1172/jci158451
[35] Hassan S, Thacharodi A, Priya A, Meenatchi R, Hegde TA, Thangamani R, et al. Endocrine disruptors: Unravelling the link between chemical exposure and women's reproductive health. Environmental Research, 2023, 241, 117385. DOI: 10.1016/j.envres.2023.117385
[36] Little AG, Seebacher F. Endocrine responses to environmental variation. Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences, 2024, 379(1898), 20220515. DOI: 10.1098/rstb.2022.0515
[37] Yang JL, Hodara E, Sriprasert I, Shoupe D, Stanczyk FZ. Estrogen deficiency in the menopause and the role of hormone therapy: Integrating the findings of basic science research with clinical trials. Menopause, 2024, 31(10), 926-939. DOI: 10.1097/GME.0000000000002407
[38] Rahman MU, Ullah MW, Shah JA, Sethupathy S, Bilal H, Abdikakharovich SA, et al. Harnessing the power of bacterial laccases for xenobiotic degradation in water. Science of The Total Environment, 2024, 918, 170498. DOI: 10.1016/j.scitotenv.2024.170498
[39] Zhao Y, Fent K. Endogenous hormones matter in evaluation of endocrine disruptive effects mediated by nuclear receptors. Eco-Environment & Health, 2024, 3, 257. DOI: 10.1016/j.eehl.2024.04.006
[40] Shi YC, Ma JS, Li SJ, Liu C, Liu YN, Chen J, et al. Sex difference in human diseases: Mechanistic insights and clinical implications. Signal Transduction and Targeted Therapy, 2024, 9, 238. DOI: 10.1038/s41392-024-01929-7
[41] Barth C, Crestol A, Lange AG de, Galea LAM. Sex steroids and the female brain across the lifespan: Insights into risk of depression and Alzheimer's disease. The Lancet. Diabetes & Endocrinology, 2023, 11(12), 926-941. DOI: 10.1016/s2213-8587(23)00224-3
[42] Gilmer G, Hettinger ZR, Tuakli-Wosornu YA, Skidmore ER, Silver JK, Thurston RC, et al. Female aging: When translational models don't translate. Nature Aging, 2023, 3, 1500-1508. DOI: 10.1038/s43587-023-00509-8
[43] Dong L, Teh DBL, Kennedy BK, Huang Z. Unraveling female reproductive senescence to enhance healthy longevity. Cell Research, 2023, 33, 11-29. DOI: 10.1038/s41422-022-00718-7
[44] Bianchi VE, Bresciani E, Meanti R, Rizzi L, Omeljaniuk RJ, Torsello A. The role of androgens in women's health. Pharmacological Research, 2021, 171, 105758. DOI: 10.1016/j.phrs.2021.105758
[45] Biagetti B, Puig-Domingo M. Age-related hormones changes and its impact on health status and lifespan. Aging and Disease, 2023, 14(3), 605-620. DOI: 10.14336/AD.2022.1109
[46] Coggins C, Patel S, Nigam SN, Rai V. Hormonal changes during aging and their effects on quality of life. Exploration of Endocrine and Metabolic Diseases, 2025, 2, 101447. DOI: 10.37349/eemd.2025.101447
[47] Conover CA, Oxvig C. The IGF system and aging. Endocrine reviews, 2025, 46(2), 214-223. DOI: 10.1210/endrev/bnae029
[48] Latek D, Tutuncu Y. Linking the endocrine system with immunity. Frontiers in Endocrinology, 2025, 16, 1638965. DOI: 10.3389/fendo.2025.1638965
[49] Pataky MW, Young WF, Nair KS. Hormonal and metabolic changes of aging and the influence of lifestyle modifications. Mayo Clinic Proceedings, 2021, 96(3), 788-814. DOI: 10.1016/j.mayocp.2020.07.033
[50] Rosen R, Yarmush ML. Current trends in anti-aging strategies. Annual Review of Biomedical Engineering, 2023, 25, 363-385. DOI: 10.1146/annurev-bioeng-120122-123054
[51] Abdulrasak MA. Biochemistry of Aging: Decoding the complex pathways to longevity. Tropical Journal of Natural Product Research, 2024, 8(9), 8269-8274. DOI: 10.26538/tjnpr/v8i9.3
[52] Qoura LA, Churov AV, Maltseva ON, Arbatskiy MS, Tkacheva ON. The aging interactome: From cellular dysregulation to therapeutic frontiers in age-related diseases. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2025, 1872(1), 168060. DOI: 10.1016/j.bbadis.2025.168060