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Review

Endocrine Factors in Sarcopenia: Lifestyle-Based Approaches with Nutrition, Exercise, and Circadian Health

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ABSTRACT: Sarcopenia, the age-related skeletal muscle disorder characterized by declines in muscle mass, strength, and physical performance, has significant health consequences and represents a major global public health challenge. Age-related endocrine and peripheral anabolic–catabolic dysregulation plays a central role in sarcopenia development, and lifestyle factors interact with hormonal regulation to influence skeletal muscle homeostasis. In older adults, reduced hormone secretion capacity, receptor responsiveness, and peripheral metabolism impair hormonal systems, including the somatotropic, gonadal, adrenal, and thyroid axes, as well as insulin and peripheral mediators, such as adipokines, myokines, and inflammatory cytokines. These alterations promote anabolic resistance, a catabolic environment, and metabolic dysfunction, contributing to sarcopenia. Age-related changes in appetite, nutrient utilization, and food choice impair anabolic efficiency and metabolic homeostasis. Declines in physical activity and neuromuscular efficiency disrupt multiple signaling pathways required to maintain muscle mass, and psychosocial factors may increase the risk of a vicious cycle of inactivity. Alterations in the suprachiasmatic nucleus (SCN) and inconsistent behavioral zeitgebers disrupt physiological rhythms. These lifestyle domains influence skeletal muscle homeostasis independently and interact bidirectionally through shared endocrine pathways. Current pharmacological approaches remain adjunctive, limited to confirmed endocrine deficiencies. The coordinated optimization of nutrition, exercise, and circadian health, with attention to regularity and timing, may offer complementary benefits exceeding single-domain interventions. A stage-specific and individually tailored approach supported by multidimensional monitoring and digital technologies is recommended for effective sarcopenia prevention and management.

Keywords: sarcopenia, endocrine regulation, nutrition, exercise, circadian rhythm, skeletal muscle, aging

1. Introduction

By 2050, the global population aged ≥60 years is projected to double from 1 billion in 2020 to approximately 2.1 billion, whereas those aged ≥80 years are expected to triple to approximately 426 million [1]. This rapid demographic shift emphasizes the growing importance of understanding aging. Aging is a universal, intrinsic biological process that manifests even under secure, toxin-free conditions with adequate nutrition and is associated with progressive physiological dysfunction [2].

1.1. Definition and diagnosis

The term "sarcopenia," introduced in the late 20th century, describes the age-related decline in muscle mass, strength, and function. It is a major contributor to frailty, falls, disability, institutionalization, and mortality and is associated with increased risks of cancer, diabetes, and

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cardiovascular disease [3]. Beyond its direct health effects, sarcopenia also imposes a considerable socioeconomic burden, challenging healthcare sustainability in aging populations [3].

Multiple diagnostic criteria for defining sarcopenia have been proposed, which reflect evolving understanding of its clinical relevance across regions. The European Working Group on Sarcopenia in Older People 2 defines low muscle strength as the primary criterion confirmed by reduced muscle quantity or quality, with poor physical performance indicating disease severity [4]. The Asian Working Group for Sarcopenia proposes region-specific diagnostic criteria that reflect the characteristics of Asian populations, which require consideration of regional anthropometric and lifestyle characteristics, such as body size, adiposity, and habitual physical activity patterns in different social, cultural, and economic contexts [5]. More recently, the Korean Working Group on Sarcopenia has issued updated guidelines, introducing the concept of "functional sarcopenia," defined by reduced muscle strength and impaired physical performance even without measurable muscle mass loss, highlighting that functional decline may precede such reduction [6]. Incorporating these concepts into the diagnostic criteria broadens the scope beyond muscle mass, enabling earlier recognition of at-risk individuals and supporting prevention and delivery of prompt and appropriate intervention.

1.2. Prevalence

Epidemiological studies show that sarcopenia is common among older adults, although the estimated prevalence varies by the diagnostic criteria. A systematic review and meta-analysis of 109 studies reported sarcopenia prevalence of 10%–40% in community-dwelling older adults, with conservative estimates of 5%–10% [3, 7]. Additionally, prevalence is substantially higher among institutionalized and hospitalized older adults, in whom comorbidities, malnutrition, and physical inactivity accelerate muscle loss [3]. Given the projected growth of the global population aged ≥65 years by 2050 and the high prevalence and risk, sarcopenia is likely to become a major global public health challenge.

1.3. Pathophysiology

Sarcopenia has a complex etiology, which involves sociodemographic, lifestyle, and disease-related factors, of which physical inactivity and poor nutrition are identified as the strongest contributors [3]. Its pathophysiology reflects an anabolic–catabolic imbalance, resulting in progressive declines in muscle mass, strength, and function [8]. The underlying mechanisms can be broadly framed from endocrinological, physiological, nutritional, and behavioral perspectives. Age-related endocrine changes can impair muscle protein turnover [8], nutritional imbalances may exacerbate anabolic resistance and contribute to sarcopenic obesity [9], and physical inactivity and sleep disturbance can accelerate muscle atrophy and functional decline [3, 9]. These interrelated factors emphasize the multidimensional nature of sarcopenia, which is further explored in the subsequent sections, focusing on endocrinological, nutritional, physical activity, and circadian perspectives and their intersections with endocrine regulation.

2. Methods

This narrative review synthesizes current evidence on the endocrine, nutritional, physical activity, and circadian influences on sarcopenia, with a focus on their interactions and clinical implications for prevention and management. Although a systematic search was not performed, a structured literature search was conducted to reduce potential selection bias. Electronic databases, including Google Scholar, PubMed/MEDLINE, and Scopus, were searched from inception to April 2026. Search terms were applied individually and in combination across four domains: endocrine regulation (e.g., aging, sarcopenia, somatotropic axis, growth hormone, IGF-1, gonadal axis, testosterone, estrogen, adrenal axis, cortisol, thyroid axis, thyroid hormone, insulin, myokines, and adipokines); nutrition (e.g., energy balance, protein, micronutrients, and hydration); exercise and physical activity (e.g., resistance exercise, aerobic exercise, and multicomponent exercise); and circadian health (e.g., circadian regulation and sleep–wake cycle). Additional articles and book chapters were identified by manually screening the reference lists of key guidelines, consensus statements, systematic reviews, and narrative reviews.

The literature was prioritized according to the following hierarchy: (1) international and regional clinical guidelines and consensus statements; (2) systematic reviews and meta-analyses; (3) randomized controlled trials in humans; (4) prospective and cross-sectional observational studies in humans; and (5) mechanistic studies in animal or cellular models, where human evidence was limited or mechanistic context was required to interpret clinical findings. Studies were included if they addressed skeletal muscle physiology, sarcopenia pathophysiology, or lifestyle interventions relevant to aging and/or endocrine regulation. Studies were excluded if they focused on non-aging populations without clear relevance to sarcopenia or skeletal muscle physiology, or if they were published in languages other than English

without an available translation. Given the scope of this review, not all retrieved publications were cited; representative and methodologically reliable sources were selected to support each domain.

3. Endocrine factors in sarcopenia

Endocrine alterations affect muscle metabolism, regenerative potential, and functional performance, contributing to the pathogenesis and progression of sarcopenia [3]. Declines in anabolic hormones and rises in catabolic mediators reduce protein synthesis and accelerate muscle protein breakdown, compromising muscle mass preservation [3, 9]. Dysregulation of metabolic and appetite-regulating hormones promotes anabolic resistance and altered energy metabolism, leading to adverse changes in body composition [9]. Moreover, endocrine changes indirectly affect motor neurons and neuromuscular junctions, impairing physical performance [3]. Collectively, these endocrine-driven processes shift the balance toward muscle wasting, functional decline, and the overt phenotype of sarcopenia [3].

3.1. Age-related endocrine changes

Endocrine dysregulation is a central mechanism in sarcopenia development, as aging is accompanied by progressive alterations across multiple hormonal functions [8]. These changes involve impaired homeostasis of the central pituitary–hypothalamic axis and peripheral endocrine glands and can be broadly attributed to (i) reduced hormone secretion, (ii) diminished receptor responsiveness, and (iii) altered peripheral metabolism of hormones [10]. Therefore, the positive regulation of muscle homeostasis mediated by anabolic hormones progressively declines with aging [8]. Concurrently, the negative regulation by catabolic mediators, such as glucocorticoids, myostatin, and proinflammatory cytokines, becomes more prominent, shifting the balance toward proteolysis and anabolic resistance [8, 11]. These endocrine changes occur across major neuroendocrine and peripheral endocrine systems, which contribute to sarcopenia development and progression [8, 10, 12]. However, the strength of evidence linking these endocrine changes to sarcopenia differs across endocrine axes and mediators, with some mechanisms supported by human clinical or observational studies and others primarily examined in animal or cellular models. Figure 1 summarizes representative age-associated alterations in major endocrine axes, insulin, and peripheral endocrine mediators that affect skeletal muscle homeostasis and may contribute to sarcopenia.

3.1.1. Somatotropic axis

The somatotropic axis, which includes growth hormone (GH), insulin-like growth factor-1 (IGF-1), and their binding proteins and receptors, regulates growth, metabolic homeostasis, and tissue repair across the life span [12]. Pituitary GH is secreted in a pulsatile manner under hypothalamic control, stimulated by growth hormone–releasing hormone (GHRH) and ghrelin, and inhibited by somatostatin [8, 13]. Its secretion is influenced by nutritional status, physical activity, body composition, and sleep cycles [8, 13]. GH binds to hepatic receptors to stimulate IGF-1 synthesis while concurrently binding to receptors in peripheral tissues or circulating GH binding protein [13]. Through these pathways, GH exerts both indirect effects through IGF-1 and direct effects on skeletal muscle and other tissues [13]. IGF-1 is synthesized primarily in the liver under GH stimulation; however, it is also produced in peripheral tissues, mediating the anabolic effects of the somatotropic axis through endocrine and autocrine/paracrine actions [13]. Most circulating IGF-1 is bound to IGF-binding proteins (IGFBPs), primarily IGFBP-3, which is dependent on GH, and to a lesser extent IGFBP-1 and IGFBP-2, which are dependent on insulin [14]. IGF-1 stimulates muscle protein synthesis (MPS) via the protein kinase B (Akt)/mechanistic target of rapamycin (mTOR)/70-kDa ribosomal protein S6 kinase (p70S6K) pathway and suppresses proteolysis by inhibiting Forkhead box O (FoxO) signaling [8, 14]. IGF-1 also contributes to muscle repair by activating myogenic precursor cells and enhancing tissue regeneration [8, 14].

Somatopause is the progressive age-related decline in GH secretion and circulating IGF-1 concentrations, marked by the physiological reduction of somatotropic activity with aging [10]. This decline occurs in both sexes and is characterized by reduced GH pulse amplitude and frequency, resulting in lower 24-h GH secretion and diminished circulating IGF-1 levels [12]. The age-related decline in GH secretion is driven by altered hypothalamic regulation of the somatotropic axis, including reduced stimulatory actions of GHRH and ghrelin, increased somatostatin activity, and heightened sensitivity to negative feedback inhibition by IGF-1, leading to attenuated pituitary GH release [8]. Additionally, the pituitary gland becomes less responsive to hypothalamic and peripheral stimuli, such as GHRH and ghrelin, and exercise and sleep, further contributing to age-related reduced GH secretion [15]. During aging, circulating IGF-1 concentrations decline in parallel with GH secretion, which reflects reduced hepatic stimulation and impaired somatotropic signaling [16]. Although IGF-1 generally exerts negative feedback on GH release, the reduced hypothalamic drive appears to trigger an age-

related decline in GH secretion [17]. The reduced somatotropic activity leads to progressive declines in circulating IGF-1 concentrations in men and women, showing a marked decrease between the ages of 20 and 50 that plateaus beyond age 55 [12]. IGF-1 decline is accompanied by a less pronounced decline in its major carrier protein, IGFBP-3, resulting in a lower IGF-1/IGFBP-3 ratio in older adults, which may reflect reduced bioavailability [12]. This systemic decline in the GH–IGF-1 axis with reduced IGF-1 bioavailability has been consistently reported in older adults and associated with muscle atrophy and sarcopenia in human observational studies; however, the underlying intracellular signaling pathways have been primarily examined in animal and cellular models [8, 12, 15, 18].

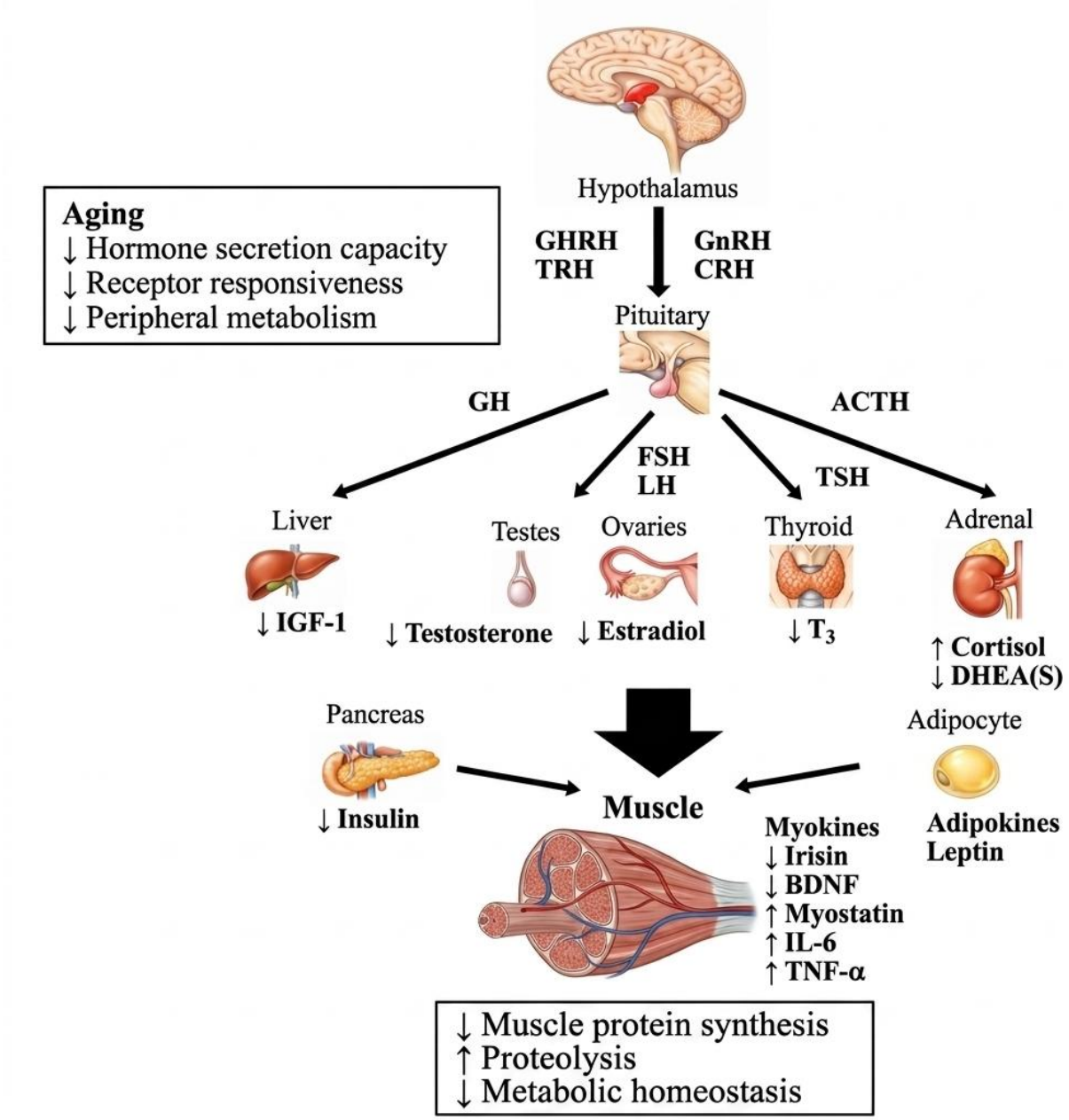

Figure 1. Representative age-associated endocrine alterations affecting skeletal muscle homeostasis and potentially contributing to sarcopenia. GHRH: Growth hormone-releasing hormone, TRH: Thyrotropin-releasing hormone, GnRH: Gonadotropin-releasing hormone, CRH: Corticotropin-releasing hormone, GH: Growth hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid-stimulating hormone, ACTH: Adrenocorticotropic hormone, IGF-1: Insulin-like growth factor-1, T_3: Triiodothyronine, DHEA(S): Dehydroepiandrosterone and dehydroepiandrosterone sulfate, BDNF: Brain-derived neurotrophic factor, IL-6: Interleukin 6, TNF-α: Tumor necrosis factor-α

3.1.2. Gonadal axis

The gonadal axis, comprising the hypothalamic–pituitary–gonadal (HPG) pathway, is crucial in regulating reproductive function and anabolic processes [19]. Gonadotropin-releasing hormone (GnRH) secreted from the hypothalamus binds to receptors on pituitary gonadotropes to stimulate the synthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn regulate sex steroid production in the testes and ovaries [20]. Testosterone promotes skeletal muscle anabolism by activating the androgen receptor (AR)-mediated Akt/mTOR signaling pathway, enhancing protein synthesis and stimulating satellite cell proliferation and differentiation [8]. Estradiol supports skeletal muscle maintenance through protective, anticatabolic, and metabolic effects; however, its direct role in the Akt/mTOR signaling–mediated MPS remains unclarified [8, 21].

Andropause and menopause refer to age-related declines in gonadal steroid production in men and women, respectively [10]. Andropause involves a subtle, gradual decline in testosterone, whereas menopause is marked by the abrupt reduction and cessation of estrogen secretion, and both reflect functional changes within the HPG axis [10]. In women, menopause is driven by the cessation of ovarian function, halting estrogen and progesterone production [10]. Ovarian dysfunction induces secondary changes in hypothalamic and pituitary regulation, following an age-related decline in the secretion of inhibin, which gradually increases FSH and LH levels [10, 12]. Women generally have lower baseline muscle mass, and the postmenopausal hormonal shifts impair muscle quality, mitochondrial function, and inflammatory regulation, while promoting visceral fat accumulation and increasing sarcopenic obesity risk [22-24]. In men, andropause is the age-related decline in testosterone levels, which is attributed to functional alterations within the hypothalamic–pituitary axis, including decreased GnRH pulsatility that attenuates LH secretion, a loss of Leydig cell count, and diminished steroidogenic function in the testes [12, 17]. Additionally, concentrations of circulating sex hormone-binding globulin progressively increase with age, which may result in a decline in bioavailable testosterone despite modest reductions in total testosterone levels [12]. Men generally have greater absolute muscle mass and strength, but age-related reductions in bioavailable testosterone progressively impair anabolic drive, satellite cell function, and type II muscle fiber maintenance, contributing to reductions in muscle mass and strength [4, 25, 26]. Collectively, age-related changes in gonadal hormones are well described; however, their associations with muscle strength, physical performance, and sarcopenia risk remain variable in human studies, and hormone-based interventions may increase muscle mass without consistent improvements in functional performance [12, 17, 27, 28]. Therefore, sex-specific differences in muscle reserve, fat distribution, estrogen decline, and testosterone bioavailability should be considered when developing strategies for sarcopenia prevention and management.

3.1.3. Adrenal axis

The adrenal axis, which comprises the hypothalamic–pituitary–adrenal (HPA) pathway, regulates stress responses, metabolism, and energy balance through the coordinated secretion of the corticotropin-releasing hormone, adrenocorticotropic hormone (ACTH), and adrenal steroids, as well as glucocorticoids such as cortisol and adrenal androgens such as dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS; collectively DHEA(S)) [29]. This pathway is activated via a hierarchical feedback loop in which circulating cortisol negatively regulates both hypothalamic and pituitary activities to maintain endocrine homeostasis [29]. Cortisol and DHEA(S) exert complementary but opposing effects on metabolism and tissue maintenance [12, 30]. Cortisol promotes energy mobilization during stress by stimulating gluconeogenesis, lipolysis, and protein catabolism, whereas DHEA(S) has been proposed to support anabolic and protective processes by enhancing insulin sensitivity, modulating immune function, and exerting anticatabolic effects on skeletal muscle; however, evidence for these effects in older adults remains limited and inconsistent [12, 30, 31].

Adrenopause is the age-associated decline in adrenal androgen production, particularly DHEA(S), whereas cortisol secretion is maintained or slightly increased, resulting in an altered cortisol/DHEA(S) ratio [10, 12]. This alteration reflects structural and functional changes within the adrenal cortex, including reduced responsiveness of the zona reticularis to ACTH and decreased steroidogenic enzyme activity [10, 12]. A precursor for androgens and estrogens, the age-related decline in DHEA(S) affects metabolic, immune, and musculoskeletal systems, potentially disrupting peripheral sex steroid availability and local tissue homeostasis [17, 32]. The rising cortisol/DHEA(S) ratio observed with aging has been associated with muscle loss and sarcopenia risk in older adults; however, the underlying mechanisms and their independent contribution to sarcopenia pathogenesis remain unclear [10, 12, 33].

3.1.4. Thyroid axis

The thyroid axis, comprising the hypothalamic–pituitary–thyroid (HPT) system, regulates basal metabolic rate, thermogenesis, protein turnover, and energy metabolism through the secretion and coordinated action of thyroid hormones: thyroxine (T_4) and triiodothyronine (T_3) [34, 35]. The hypothalamic thyrotropin-releasing hormone stimulates pituitary thyrotropes to release thyroid-stimulating hormone (TSH), which in turn promotes T_4 and T_3 secretion [34, 35]. Circulating T_3, the biologically active form, relays negative feedback to both the hypothalamus and pituitary glands to maintain systemic hormonal balance [34, 35]. Thyroid hormones play an important role in skeletal muscle metabolism, with preclinical evidence demonstrating effects on mitochondrial biogenesis, oxidative metabolism, and myofibrillar protein turnover; however, the detailed intracellular and specific fiber-type mechanisms have not been fully confirmed in human aging studies [34, 36, 37].

Aging is accompanied by gradual physiological changes in the HPT axis, which affects central regulation and peripheral hormone metabolism [10]. Centrally, mild changes in hypothalamic–pituitary feedback contribute to slightly elevated or upper-normal TSH levels, whereas peripherally, progressive reduction in T_3 concentrations, relatively stable or mildly decreased T_4 concentrations, and increased reverse T_3 (rT_3) concentrations occur [10, 17]. These peripheral hormonal changes are attributed to altered thyroid hormone metabolism with aging [38]. Specifically, age-related changes in peripheral thyroid hormone metabolism, including reduced T_4-to-T_3 conversion through altered activity of type I and type II iodothyronine deiodinases (DIO1 and DIO2), have been reported in older adults; however, tissue-specific deiodinase activity in human skeletal muscle and the contribution of type III deiodinase (DIO3) to age-related T_3 decline remain unclear, with detailed mechanisms derived primarily from animal and cellular models [36-38]. These shifts in thyroid hormone metabolism reduce peripheral T_3 availability and lower basal metabolic rates; however, while overt thyroid dysfunction clearly impairs muscle function, the direct influence of age-related T_3 decline on sarcopenia pathogenesis remains to be established [11, 36, 38].

3.1.5. Insulin

Insulin, a major anabolic hormone, regulates glucose, lipid, and protein metabolism while functioning as an essential growth factor [39]. A high blood glucose level stimulates insulin release from pancreatic β-cells through glucose metabolism–induced ATP production and subsequent calcium-dependent exocytosis, whereas glucagon, incretins, and autonomic nervous control fine-tune this process [39]. Insulin regulates glucose and energy homeostasis by promoting glucose uptake in skeletal muscle and adipose tissue, stimulating glycogen synthesis, and suppressing hepatic gluconeogenesis [39]. In skeletal muscle, insulin also enhances amino acid uptake, activates the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling pathway, and inhibits proteolytic processes, promoting MPS and cellular growth [39, 40].

Aging is accompanied by structural and functional changes in pancreatic β-cells, decreasing insulin secretion capacity and impairing glucose-stimulated insulin release [17, 39]. Additionally, age-related declines in insulin receptor sensitivity, attenuated downstream PI3K/Akt signaling, and impaired glucose transporter type 4 (GLUT4) translocation to the cell membrane contribute to peripheral insulin resistance in skeletal muscle [39, 40]. Together, these alterations in insulin secretion and action impair substrate utilization and metabolism, and chronic insulin resistance also blunts anabolic signaling through the Akt/mTOR pathway, reduces MPS, and contributes to anabolic resistance; these links between metabolic dysregulation, sarcopenia, and frailty are consistently supported by human clinical and observational evidence in older adults [32, 39, 41]. The major physiological effects, age-related changes, and evidence basis for the endocrine factors discussed above are summarized in Table 1.

3.1.6. Peripheral hormonal regulators

In older adults, peripheral regulators, including proinflammatory cytokines, myokines, and adipokines, also exhibit age-related changes that influence metabolism, inflammatory balance, and inter-organ communication with potential relevance to skeletal muscle health [42]. These mediators differ substantially in the strength of evidence supporting their clinical relevance to sarcopenia and are discussed below according to their level of evidence.

Among peripheral regulators, chronic low-grade inflammation driven by elevated proinflammatory cytokines has consistent evidence linking it to sarcopenia in older adults [43, 44]. Tumor necrosis factor-α (TNF-α) promotes a proinflammatory environment and contributes to apoptosis and metabolic dysfunction by activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated proteolytic pathways and suppressing Akt/mTOR-dependent protein synthesis [8]. Interleukin-6 (IL-6) is a pleiotropic cytokine that can act as a metabolic regulator, anti-inflammatory mediator, and promoter of myogenesis during acute elevation; however, chronically elevated IL-6 levels are consistently associated with catabolic inflammation and muscle atrophy in older adults [43-45].

Table 1. Endocrine factors: major physiological effects, age-related changes, and evidence basis [8, 10, 12, 14, 38, 39].

Factor	Major physiological effects	Age-related changes	Evidence basis
Somatotropic axis (GH–IGF-1)	• Promotes MPS (↑ Akt/mTOR) • Suppresses proteolysis (↓ FoxO) • Supports myogenic cell activation and regeneration • Supports metabolic homeostasis	Somatopause ↓ GH pulse amplitude/frequency → ↓ IGF-1 levels and bioavailability	• Human studies: hormonal changes and sarcopenia-related outcomes • Animal/cellular studies: signaling pathways
Gonadal axis (testosterone, estradiol)	• Promotes MPS (↑ Akt/mTOR) • Suppresses proteolysis (↓ FoxO) • Supports muscle maintenance and metabolic homeostasis • Supports anabolic drive	Andropause/menopause In men: ↓ GnRH pulsatility/LH drive and ↑ SHBG → ↓ testosterone levels and bioavailability In women: ↓ ovarian function → ↑ FSH/LH → ↓ estrogen production	• Human studies: hormonal changes and sarcopenia-related outcomes • Animal/cellular studies: signaling pathways
Adrenal axis (cortisol, DHEA(S))	Cortisol • Suppresses MPS (↓ Akt/mTOR) • Promotes proteolysis (↑ FoxO) • Gluconeogenesis, lipolysis, and protein catabolism DHEA(S) • Supports peripheral sex steroid availability • Attenuates cortisol-driven proteolysis	Adrenopause Maintained or slightly ↑ cortisol with ↓ DHEA(S) → ↑ cortisol/DHEA(S) ratio → reduced anabolic support and a chronic catabolic drive	• Human studies: cortisol/DHEA(S) ratio changes • Signaling pathways remain unclear
Thyroid axis (T_4, T_3)	• Regulates myofibrillar protein turnover and muscle function • Supports mitochondrial biogenesis and oxidative metabolism • Regulates basal metabolic rate and thermogenesis	HPT alterations → slightly ↑ TSH with ↓ T_3 and reduced thyroid hormone responsiveness	• Human studies: hormonal changes • Age-related T_3–sarcopenia association remains unclear
Insulin	• Promotes glucose utilization and amino acid uptake • Stimulates MPS • Suppresses proteolysis • Supports metabolic homeostasis	β-cell dysfunction and insulin resistance → ↓ insulin secretion capacity and sensitivity	• Human studies: insulin resistance and sarcopenia-related outcomes • Animal/cellular studies: signaling pathways

GH: Growth hormone, IGF-1: Insulin-like growth factor-1, MPS: Muscle protein synthesis, Akt: Protein kinase B, mTOR: Mechanistic target of rapamycin, FoxO: Forkhead box O, GnRH: Gonadotropin-releasing hormone, LH: Luteinizing hormone, SHBG: Sex hormone-binding globulin, FSH: Follicle-stimulating hormone, DHEA(S): Dehydroepiandrosterone and dehydroepiandrosterone sulfate, T_4: Thyroxine, T_3: Triiodothyronine, HPT: Hypothalamic–pituitary–thyroid, TSH: Thyroid-stimulating hormone.

Myostatin, a member of the transforming growth factor-β superfamily, is a negative regulator of muscle growth in preclinical models, suppressing protein synthesis through mothers against decapentaplegic homolog 2/3 (Smad2/3) signaling and promoting proteolysis through FoxO activation [46, 47]. Age-related increases in myostatin expression, driven by chronic inflammation and increased glucocorticoid exposure, have been proposed to contribute to anabolic resistance and progressive muscle loss; however, the association between circulating myostatin levels and sarcopenia in humans remains inconsistent, with conflicting results across studies differing in age, sex, physical activity level, and measurement methodology [28, 47]. Although myostatin/activin pathway inhibition has emerged as a pharmacological target in sarcopenia research, early clinical trials have not consistently demonstrated improvements in muscle strength or physical performance despite increases in lean mass [28, 48].

Among adipokines, leptin is secreted primarily by adipocytes and regulates systemic energy homeostasis by modulating appetite and energy expenditure [11, 42]. In skeletal muscle, leptin may promote myocyte proliferation and differentiation through anabolic signaling pathways; however, aging and increased fat mass are associated with reduced leptin receptor expression, elevated circulating leptin levels, and leptin resistance, which may impair leptin-mediated muscle regulation [11, 42]. Age-related leptin resistance may further exacerbate insulin resistance, as discussed in Section 3.1.5, by impairing shared peripheral signaling pathways and blunting anabolic responsiveness in skeletal muscle [42, 49].

Skeletal muscle acts as an endocrine organ, secreting myokines that mediate crosstalk with other tissues and may influence energy metabolism, inflammation, and muscle remodeling [45]. Among these, several myokines have been identified as regulators of muscle–organ communication and metabolic adaptation; however, current evidence is largely derived from animal models and small human studies, and their clinical relevance to sarcopenia in older adults remains to be established [50]. Irisin, derived from the cleavage of fibronectin type III domain-containing protein 5 during muscle contraction, may promote energy expenditure through the browning of white adipose tissue and has been associated with enhanced fatty acid oxidation in preclinical studies [45, 51]. Brain-derived neurotrophic factor (BDNF) has been suggested to support skeletal muscle fiber maintenance and regeneration, promote motoneuron function, and enhance fat oxidation through adenosine 5′-monophosphate-activated protein kinase (AMPK) signaling; however, findings from human studies remain inconsistent [52-54].

Collectively, these peripheral mediators form a dynamic network in which the balance between anabolic and catabolic signals may progressively shift toward muscle wasting with aging (Table 2) [8, 11, 50]. Understanding the varying levels of evidence for these mediators is essential for prioritizing clinically meaningful targets in sarcopenia prevention and management.

Table 2. Peripheral hormonal regulators: major physiological effects, age-related changes, and evidence basis [8, 11, 42, 45, 46, 50, 52-54].

Factor	Major physiological effects	Age-related changes	Evidence basis
TNF-α	• Promotes proteolysis (↑ NF-κB, ↑ p38/MAPK) • Suppresses MPS (↓ Akt/mTOR) • Increases insulin resistance, inflammation, and oxidative stress	Chronic low-grade inflammation, ROS accumulation, and immune dysregulation → chronic ↑ TNF-α	• Human studies: association with sarcopenia-related outcomes • Animal/cellular studies: signaling pathways
IL-6	• Acute ↑: supports glucose homeostasis, lipolysis, anti-inflammatory signaling, and myogenesis • Chronic ↑: contributes to catabolic inflammation and muscle atrophy	Chronic low-grade inflammation, altered signaling pathways, and reduced exercise responsiveness → ↑ basal IL-6 with impaired adaptive signaling	• Human studies: association with sarcopenia-related outcomes • Animal/cellular studies: signaling pathways
Myostatin	• Suppresses MPS (↓ Akt/mTOR) • Promotes proteolysis (↑ FoxO, ↑ Smad2/3) • Increases insulin resistance and adipogenesis	Chronic low-grade inflammation, anabolic resistance, and reduced growth factor signaling → ↑ myostatin expression and activity	• Human studies: inconsistent associations with sarcopenia • Animal/cellular studies: signaling pathways
Leptin	• Regulates appetite and energy expenditure • Promotes myoblast proliferation and differentiation • Modulates insulin sensitivity and metabolism	Aging and ↑ fat mass → ↑ leptin, ↓ leptin receptor expression, and ↑ leptin resistance	• Human studies: obesity/metabolic dysfunction and sarcopenia-related outcomes • Animal/cellular studies: signaling pathways
Irisin	• Promotes browning of white adipose tissue (↑ UCP1) • Enhances fat oxidation • Improves insulin sensitivity and metabolic flexibility	Reduced physical activity and impaired PGC-1α/FNDC5 signaling → ↓ irisin expression and circulating levels	• Human studies: preliminary and inconsistent findings • Animal/cellular studies: signaling pathways
BDNF	• Supports motoneuron maintenance and neuromuscular function • Skeletal muscle fiber maintenance, regeneration, and differentiation • Increases fat oxidation via AMPK-related signaling	Reduced physical activity, inflammation, and mitochondrial dysfunction → ↓ BDNF expression	• Human studies: preliminary and inconsistent findings • Animal/cellular studies: signaling pathways

TNF-α: Tumor necrosis factor-α, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, p38/MAPK: p38 mitogen-activated protein kinase, MPS: Muscle protein synthesis, Akt: Protein kinase B, mTOR: Mechanistic target of rapamycin, ROS: Reactive oxygen species, IL-6: Interleukin-6, FoxO: Forkhead box O, Smad2/3: Mothers against decapentaplegic homolog 2/3, UCP1: Uncoupling protein 1, PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator-1 alpha, FNDC5: Fibronectin type III domain-containing protein 5, BDNF: Brain-derived neurotrophic factor, AMPK: Adenosine 5′-monophosphate-activated protein kinase.

3.2. Endocrine factors in the pathophysiology of sarcopenia

The endocrine pathophysiology of sarcopenia can arise from an age-related imbalance between anabolic hormones and catabolic or proinflammatory factors, contributing to anabolic resistance and progressive muscle loss [8]. Aging disrupts the coordinated regulation among key endocrine axes, whereas peripheral regulators further amplify catabolic signaling and inflammation [17, 49]. Age-related impairments in endocrine and peripheral regulators may disrupt MPS, increase proteolysis, diminish regenerative potential, and reduce metabolic efficiency [3, 11].

3.2.1. Anabolic factors

Anabolic endocrine and peripheral factors are generally understood to stimulate protein synthesis, suppress protein degradation, and drive mitochondrial biogenesis to maintain skeletal muscle mass and metabolic homeostasis, thereby enhancing metabolic efficiency [18, 55]. Major anabolic regulators function in a coordinated manner to maintain muscle proteostasis, regenerative capacity, and metabolic homeostasis [8, 11, 42, 45]. These regulators are suggested to promote protein synthesis and myofibrillar repair through the anabolic signaling pathways previously described, while inhibiting protein degradation [18, 56]. Concurrently, anabolic regulators may indirectly influence metabolic homeostasis by enhancing mitochondrial function and biogenesis via peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α)-dependent mechanisms, thereby supporting insulin sensitivity and substrate utilization while attenuating oxidative stress and inflammatory signaling [53, 56].

In older adults, the coordinated activity of these anabolic pathways becomes progressively dysregulated, contributing to the pathophysiologic etiology of sarcopenia [10, 48, 49]. Additionally, skeletal muscle responsiveness to anabolic stimuli, such as nutrient intake and physical activity, is blunted by reduced receptor sensitivity and post-receptor signaling efficiency, contributing to deregulated nutrient sensing and loss of proteostasis, two major hallmarks of aging [3, 26, 57]. This endocrine and peripheral dysfunction may impair protein synthesis and mitochondrial turnover, reduce satellite cell activation, increase oxidative stress, and promote chronic low-grade inflammation, collectively intensifying the catabolic environment within aged muscle [11, 18, 57]. These systemic and local alterations disrupt muscle homeostasis and regenerative potential, underlying the progressive decline in muscle mass, strength, function, and metabolic homeostasis that characterizes sarcopenia [3, 56, 57].

3.2.2. Catabolic factors

Catabolic endocrine and peripheral factors have been shown to activate proteolytic systems and impair metabolic and hormonal homeostasis, thereby contributing to skeletal muscle degradation and metabolic dysregulation [8, 11]. Key catabolic regulators disrupt muscle homeostasis by activating the proteolytic signaling pathways previously described, which stimulate ubiquitin–proteasome and autophagy–lysosomal-mediated protein degradation while inhibiting MPS [49, 55, 56]. In parallel, these factors disrupt mitochondrial homeostasis, promote insulin resistance, and intensify oxidative stress and systemic inflammation, perpetuating proteolysis and metabolic inflexibility [49, 56, 57].

In older adults, persistent activation of catabolic endocrine and peripheral pathways underlies the core pathophysiology of sarcopenia [11, 18, 57]. Chronic catabolic signaling progressively shifts muscle homeostasis toward proteolysis and inflammation through mitochondrial dysfunction and oxidative stress, while blunting responsiveness to anabolic stimuli [8, 11, 42, 55, 56]. These endocrine and peripheral alterations accelerate fundamental hallmarks of aging, resulting in progressive muscle atrophy and metabolic dysregulation that characterize the clinical phenotype of sarcopenia [3, 18, 57].

Paradoxically, certain age-related endocrine alterations, such as declines in GH and IGF-1 levels, may provide systemic protection by mitigating risks of cancer and diabetes, suggesting an adaptive, longevity-oriented remodeling of the endocrine system [10]. Given these paradoxical influences of age-related endocrine alterations, behavioral factors, including nutrition, physical activity, and circadian health, can optimize the endocrine environment, mitigating sarcopenic decline while maintaining adaptive, longevity-oriented responses [32, 58].

4. Nutrition

Nutrition is a crucial and modifiable factor in maintaining skeletal muscle mass, strength, and metabolic function throughout aging [3, 32]. Adequate energy and nutrient intake provide substrates for MPS and interact with hormonal and molecular pathways that regulate anabolic–catabolic balance [9, 59]. Conversely, chronic malnutrition, poor diet quality, and age-related anorexia hasten sarcopenia development by disrupting key endocrine pathways, impairing MPS, and intensifying systemic inflammation [60-62].

The following sections will describe age-related nutritional changes and their implications for sarcopenia and present a review of key nutritional determinants and their interactions with endocrine regulation, highlighting the role of nutrition in muscle health.

4.1. Age-related nutritional changes

Age-related nutritional changes vary, involving reduced appetite, impaired nutrient utilization, and specific micronutrient deficiencies that weaken anabolic potential and metabolic resilience [9, 63, 64]. A significant alteration is the anorexia of aging, an involuntary decline in appetite associated with reduced hunger, early satiety, and lower habitual food intake [9, 65]. This decline in energy intake is linked to altered hypothalamic regulation, reduced sensory perception, and changes in appetite-regulating hormones [62, 66]. Additionally, decreased digestive and absorptive efficiency, due to factors such as compromised dentition and delayed gastric emptying, can limit nutrient ingestion, whereas increased splanchnic extraction reduces the systemic bioavailability of dietary amino acids [9, 67, 68]. Collectively, these impairments increase the risk of deficiencies in essential micronutrients, such as vitamin D, antioxidant vitamins, and minerals, which can exacerbate oxidative stress and impair muscle contractile function [69, 70]. Parallel to the decline in nutrient intake, aging may also affect the quality of dietary patterns [61]. In older adults, food choices may shift toward processed, easily chewable, and convenient foods that are energy-dense but nutrient-poor, and these changes are attributed to physiological, physical, and psychosocial factors, such as taste and smell changes, dental issues, reduced mobility, social isolation, and low motivation to prepare balanced meals [24, 62, 71]. These alterations may contribute to detrimental changes in body composition, such as sarcopenic obesity, in which reduced muscle mass coexists with excess adiposity, exacerbating insulin resistance, adipose-driven inflammation, and muscle catabolism [63, 72]. This overlapping condition often results in worse health outcomes than either sarcopenia or obesity, creating a vicious cycle in which obesity-induced inflammation and insulin resistance hasten muscle catabolism, which in turn reinforces metabolic dysregulation [57, 72]. Collectively, the interrelated nutritional disturbances impair anabolic efficiency, activate proteolytic and inflammatory pathways, and create a metabolic environment that heightens susceptibility to sarcopenia [3, 9, 67].

4.2. Nutritional determinants of sarcopenia: Interactions with endocrine regulation

Nutrition influences skeletal muscle maintenance by not only providing substrates for protein synthesis but also modulating key endocrine axes that regulate anabolic and catabolic balance [59, 73]. Age-related alterations in energy balance, protein intake, micronutrient status, and hydration influence hormonal systems, modulating the metabolic environment that contributes to sarcopenia [49, 74]. The following subsections outline the major nutritional determinants of sarcopenia and highlight their mechanistic interactions with endocrine regulation.

4.2.1. Energy: regulation of the somatotropic and adrenal axes

Adequate energy balance is the fundamental metabolic requirement for skeletal muscle maintenance, as the intake–expenditure equilibrium regulates the hormonal signaling pathways that control muscle proteostasis [67, 75]. In older adults, chronic negative or positive energy imbalances can accelerate sarcopenia through different but equally detrimental endocrine mechanisms [67, 76].

Chronic negative energy balance may induce a systemic shift toward catabolism to sustain essential physiological functions rather than tissue maintenance [9, 24]. Mechanistically, energy deficiency can uncouple the somatotropic axis by inducing hepatic resistance to GH, mediated by reduced receptor density and impaired post-receptor signaling [77]. This resistance suppresses IGF-1 synthesis, thereby inhibiting the ligand required for activating the anabolic pathway and suppressing postprandial MPS [18, 26, 77]. Concurrently, this deficit increases systemic metabolic stress and activates the HPA axis to mobilize endogenous substrates via gluconeogenesis [18, 42]. The adaptive elevation in circulating cortisol exerts direct catabolic effects by binding to intracellular receptors and activating the catabolic signaling pathway to facilitate proteolysis [26, 49]. Furthermore, cortisol reinforces this catabolic state by suppressing GH–IGF-1 signaling, which subsequently blocks the anabolic signals required for muscle repair [33, 42, 78].

Conversely, a chronic positive energy balance resulting in obesity can disrupt endocrine homeostasis and augment anabolic resistance [18, 63]. Specifically, visceral adipose tissue accumulation is associated with the secretion of proinflammatory adipokines, such as TNF-α and IL-6, and induces leptin resistance [45, 49]. These alterations may increase insulin resistance, which directly impairs the anabolic signaling pathway, blunting MPS [49, 63]. Chronic low-grade inflammation driven by increased proinflammatory cytokines from adipose tissue activates catabolic cascades, resulting in muscle atrophy [18, 33]. Furthermore, leptin resistance and metabolic dysregulation disrupt mitochondrial homeostasis,

promoting reactive oxygen species (ROS) accumulation that accelerates muscle damage [24, 49]. The convergence of these anabolic blockades and catabolic drivers may create a vicious cycle that drives muscle atrophy despite the abundance of energy substrates [63, 64, 72].

Therefore, nutritional strategies for sarcopenia prevention must be tailored to optimize energy balance and attenuate specific endocrine dysregulations [9]. For individuals with age-related anorexia, which results in negative energy balance, increasing energy and nutrient density, enhancing meal palatability, and optimizing meal frequency can help regulate HPA axis activation and restore IGF-1 bioavailability [60, 77]. Conversely, in individuals with excess energy balance, nutritional interventions aim at reducing adiposity and inflammatory cytokines through moderate caloric restriction [9, 72]. However, to prevent further muscle loss during weight reduction, this restriction must be carefully calibrated and accompanied by adequate protein intake to preserve anabolic signaling and MPS [9, 63, 79].

4.2.2. Protein: activation of anabolic pathways and hormonal responsiveness

Dietary protein simultaneously serves as a substrate for myofibrillar accretion and a potent signaling molecule that directly activates anabolic pathways and modulates hormonal responsiveness [9, 59, 75]. In older adults, anabolic resistance, a blunted MPS response to dietary amino acids, can compromise the efficacy of this signaling [63, 80]. This resistance results from physiological maladaptations, including increased splanchnic extraction that limits systemic amino acid availability, impaired amino acid tissue delivery caused by reduced insulin-mediated capillary recruitment, and intracellular anabolic signaling defects that blunt muscle hypertrophy [32, 63]. Skeletal muscle exhibits low sensitivity to leucine, the primary nutritional trigger for the mTOR pathway, and altered nutrient sensing results in impaired phosphorylation of key downstream effectors, increasing the intracellular threshold required to trigger protein synthesis [9, 63, 80]. With this age-related anabolic resistance, inadequate dietary protein intake fails to exceed the intracellular leucine threshold necessary to maximize skeletal muscle responsiveness to insulin and IGF signaling [67, 80]. Reduced amino acid availability further impairs insulin- and IGF-1-mediated suppression of proteolysis, disrupting the hormonal synergy necessary for muscle maintenance [49, 69]. Consequently, insufficient dietary protein induces a net negative protein balance and glucocorticoid-driven catabolic pathways with blunted anabolic insulin and IGF-1 signaling, promoting progressive sarcopenia [10, 59, 63].

To overcome anabolic resistance and optimize hormonal regulation, nutritional guidelines for sarcopenia recommend protein intake above the standard recommended daily allowance (RDA) of 0.8 g/kg/day [9, 81, 82]. Current consensus supports a condition-specific approach, with targets of 1.0–1.2 g/kg/day for healthy older adults, 1.2–1.5 g/kg/day for those with sarcopenia or chronic diseases, and up to 2.0 g/kg/day for those with severe illness or malnutrition [63, 75]. Importantly, dietary protein intake must be distributed across main meals, providing approximately 25–30 g of high-quality protein containing 2.5–3.0 g of leucine to overcome the high leucine threshold and maximize the interaction between amino acids and anabolic hormones for MPS [9, 69, 80]. Dietary sources for leucine include dairy products, eggs, lean meats, fish, seafood, and legumes, which are recommended owing to their high essential amino acid profile and efficient digestion that rapidly increases plasma leucine levels [24, 75]. Protein supplementation, such as whey protein isolate, offers a valuable therapeutic strategy for older adults with reduced appetite or compromised dentition [24, 83]. However, supplementation is most effective when it complements rather than replaces whole foods, as natural sources, such as omega-3 fatty acids in fish and selenium in eggs, provide essential micronutrients that modulate inflammation and support the broader endocrine environment, which may be absent in isolated protein powders [9, 62].

4.2.3. Micronutrients: regulation of endocrine signaling and inflammatory balance

Specific micronutrients influence the endocrine axes by regulating hormonal synthesis, receptor sensitivity, and inflammatory signaling [9, 61].

Vitamin D, a secosteroid prohormone, supports musculoskeletal health by regulating calcium and phosphorus homeostasis [8, 59]. Vitamin D deficiency increases parathyroid hormone (PTH) activity and disinhibits the NF-κB pathway, which upregulates catabolic cytokines (TNF-α and IL-6) and blunts insulin receptor signaling, exacerbating metabolic dysfunction and anabolic resistance [41, 84]. This deficiency also reduces vitamin D receptor activity in skeletal muscle tissue, which impairs calcium homeostasis and mitochondrial function that result in muscle atrophy and impaired excitation–contraction coupling [24, 57, 85, 86]. Collectively, these systemic and local alterations may lead to progressive muscle atrophy and contractile dysfunction, accelerating muscle mass loss and functional decline [8, 62].

Magnesium influences the somatotropic axis by supporting the receptor phosphorylation cascades

required for MPS [77, 87]. Selenium regulates thyroid hormone metabolism as a component of deiodinase enzymes, which convert inactive T_4 to the biologically active T_3 necessary for mitochondrial biogenesis [34, 37]. Additionally, calcium homeostasis is essential for excitation–contraction coupling that affects neuromuscular transmission and is crucial for regulating PTH levels to prevent its catabolic effects on skeletal muscle [86, 88]. Collectively, deficiencies in these essential minerals may correlate with reduced grip strength, lower appendicular lean mass, and altered neuromuscular function, emphasizing their importance in preserving the anabolic and contractile integrity of skeletal muscle [9, 24, 62].

Adequate intake of anti-inflammatory nutrients supports a balanced inflammatory environment, attenuating the catabolic drive of sarcopenia [24, 89]. Omega-3 fatty acids may modify the composition of myocellular membranes and lipid rafts, modulating cellular signaling and suppressing the transcription of inflammatory factors [64]. Dietary antioxidant vitamins, minerals, and phytochemicals may help neutralize the excessive ROS generated by mitochondrial dysfunction, preventing the oxidative activation of proteolytic pathways [62, 90]. The RDA and supplementation strategies for micronutrients vary by age, region, and clinical situation, often resulting in heterogeneous outcomes in intervention studies of older adults. For instance, the RDA for vitamin D in the USA is 800 IU/day for adults aged >70 years, whereas the Korean RDA is 600 IU/day for those >75 years, with both guidelines aiming to maintain serum 25-hydroxyvitamin D (25(OH)D) levels >30 ng/mL [63, 91]. Although studies demonstrating anabolic benefits of omega-3 fatty acids utilize high doses (>2–4 g/day) rich in eicosapentaenoic acid and docosahexaenoic acid, the evidence remains mixed, with some intervention studies showing improvements in muscle function rather than mass and others failing to demonstrate significant anabolic effects [24, 92]. Similarly, results for antioxidant supplementation are conflicting because some research reports benefit, whereas other studies suggest that high-dose antioxidants blunt physiological ROS signaling essential for anabolic sensitivity, potentially exacerbating anabolic resistance [58, 62, 93]. Together, rather than relying on isolated high-dose supplementation, current guidelines emphasize a diverse diet rich in fruits, vegetables, fatty fish, and nuts, which maximize the synergistic effects of these protective nutrients in maintaining an anabolic microenvironment [9, 70, 74].

4.2.4. Hydration: osmotic homeostasis and endocrine regulation

Hydration status may influence muscle function and endocrine homeostasis in older adults, who experience physiological maladaptations that alter hydration status [9, 10, 94].

Impaired thirst perception results from blunted hypothalamic osmoreceptor sensitivity, reducing the voluntary drive to drink despite rising plasma osmolality in older adults [95]. Additionally, age-related nephron loss and diminished renal responsiveness to antidiuretic hormone can contribute to reduced renal function, impairing the kidney's ability to conserve water during dehydration [94, 95]. Physiologically, muscle cell dehydration may inhibit mTOR complex activity, and compensatory activation of the renin–angiotensin–aldosterone system can increase angiotensin II and arginine vasopressin, which may impair substrate availability and blunt hormonal responsiveness, reinforcing catabolic pathways [9, 42, 96]. Furthermore, altered intracellular electrolyte concentrations may disrupt excitation–contraction coupling, impairing neuromuscular efficiency [9, 64].

In older adults, altered antidiuretic hormone homeostasis, medications, comorbidities, and low solute intake (e.g., sodium restriction and low protein) can also exacerbate age-related impairment in water-excretory capacity, which may result in water retention and induce dilutional hyponatremia [97, 98]. Therefore, excessive water intake can lead to dilutional hyponatremia in older adults, which may disrupt neuromuscular integrity and cellular homeostasis, potentially contributing to muscle loss and functional decline associated with sarcopenia [57, 64, 95, 98].

Current recommendations for older adults emphasize the maintenance of optimal hydration status through adequate daily fluid intake, consumption of water-rich foods, and individualized adjustments based on renal function, medication use, and comorbidities such as hypertension or diabetes [9, 95, 97]. However, no universal consensus has been established on the optimal fluid intake volume or timing specifically for sarcopenia prevention, as individual requirements vary significantly based on metabolic rate, environmental conditions, clinical status, and physical activity levels [9, 98, 99]. Accordingly, hydration strategies should be considered a supportive component of nutritional management and individualized to maintain optimal hydration status and electrolyte balance within comprehensive sarcopenia management [24, 90].

5. Exercise and physical activity

Exercise and physical activity are among the strongest modifiable determinants of skeletal muscle mass, quality, and functional capacity across the lifespan and are

considered the primary intervention in sarcopenia prevention and treatment [3]. Exercise is not only a mechanical stimulus for muscle hypertrophy but also a potent modulator of the endocrine system that influences the secretion and sensitivity of key anabolic and catabolic hormones, myokines, and inflammatory factors [32, 100].

The following sections summarize age-related changes in physical activity patterns, explore the dynamic crosstalk between exercise and endocrine regulation in skeletal muscle, and review specific exercise modalities as prevention and treatment strategies for sarcopenia.

5.1. Age-related changes in physical activity

Physical activity is crucial for maintaining skeletal muscle homeostasis; however, aging is accompanied by a progressive decline in habitual physical activity, with a shift toward a sedentary lifestyle characterized by prolonged inactivity and reduced engagement in moderate-to-vigorous exercise [3, 56, 63]. This decline results from a complex interplay of physiological, psychological, and social factors, such as chronic disease, musculoskeletal pain, fear of falling, reduced motivation, and social isolation, which can create a cycle of disuse that hastens muscle atrophy [4, 101, 102]. Consequently, this age-related decline in physical activity disrupts the mechanical, neural, and metabolic signaling pathways required to maintain muscle mass and endocrine responsiveness, resulting in impaired proteostasis, elevated inflammation, and diminished metabolic flexibility that accelerate sarcopenia onset and progression [4, 6, 57, 63, 89, 103].

5.2. Exercise in sarcopenia: interactions with endocrine regulation

Exercise maintains skeletal muscle mass through a dual mechanism that enhances anabolic pathways and suppresses catabolic cascades to optimize the metabolic environment: by providing the mechanical load to drive protein synthesis and by modulating key endocrine pathways, including the somatotropic, gonadal, adrenal, and thyroid axes, as well as insulin and myokine signaling [26, 42, 63].

The following subsections outline the major mechanisms by which exercise counteracts sarcopenia and highlight their mechanistic and synergistic interactions with endocrine regulation.

5.2.1. Regulation of proteostasis and muscle function

The maintenance of skeletal muscle mass and functional capacity depends on proteostasis, a dynamic equilibrium between protein synthesis and breakdown progressively compromised with aging [57, 63, 67]. Mechanical loading during exercise induces mechanotransduction, in which physical stimuli are converted into intracellular biochemical signals by various mechanosensors within muscle fibers [56, 100]. These stimuli activate the mTOR complex and p70S6K signaling pathways to promote muscle growth [56, 100, 104]. Concurrently, mechanical stimuli sensed by muscle fibers activate the PI3K/Akt pathway, which converts physical stress into anticatabolic signaling through the phosphorylation of FoxO transcription factors [104]. However, aging impairs this mechanosensitivity by disrupting the initial activation of mechanosensors, blunting anabolic mTOR signaling, and enhancing catabolic pathway activity, which may contribute to anabolic resistance and muscle protein breakdown [26, 105]. In parallel, physical activity provides a neural stimulus that enhances neuromuscular efficiency by optimizing motor unit discharge rates and coordination while stimulating the secretion of neurotrophic factors, such as BDNF, which may support motoneuron maintenance and regulation [57, 63, 106]. However, aging disrupts this neural connectivity through the loss of spinal alpha motor neurons and subsequent reinnervation failure, resulting in muscle fiber denervation that accelerates functional decline [3, 26, 57].

5.2.2. Endocrine regulation and myokine signaling

Regular exercise modulates the endocrine environment by restoring somatotropic and gonadal axis activity and attenuating catabolic hormones while stimulating skeletal muscle to secrete myokines that mediate muscle–organ crosstalk [12, 106].

Although this response is typically attenuated in older adults, an adequate type and volume of exercise provides an effective physiological stimulus for enhancing hypothalamic drive via increased neurotransmitter signaling (e.g., norepinephrine and acetylcholine) [15, 107, 108]. This stimulation promotes GHRH secretion while inhibiting somatostatin, resulting in pulsatile GH secretion that triggers central (hepatic) and local (muscular) IGF-1 synthesis, which may effectively counteract somatopause by replenishing the anabolic stimulation required to maintain skeletal muscle mass [12, 14]. In parallel, the physiological stimulus provided by acute resistance exercise can elicit a transient increase in circulating testosterone levels, which is attributed to metabolic demand and hemodynamic shifts rather than central hypothalamic activation [100]. Physical activity also influences the thyroid axis, which regulates the basal metabolic rate and mitochondrial biogenesis [35, 38]. Mechanistically, exercise of sufficient intensity can upregulate the activity of thyroid-converting enzyme (DIO2) within skeletal muscle, enhancing the local

conversion of T_4 to biologically active T_3 [35, 36]. This increased intracellular T_3 bioavailability promotes mitochondrial biogenesis, which may help preserve metabolic flexibility and muscle function against the age-related decline in systemic thyroid hormones [10, 36, 38]. Additionally, physical activity can control the adrenal axis, which regulates the secretion of catabolic glucocorticoids [29]. Although acute exercise induces a transient rise in cortisol levels to facilitate substrate mobilization via gluconeogenesis and lipolysis, regular training modulates the HPA axis by enhancing negative feedback sensitivity, which is particularly beneficial for older adults who may exhibit age-associated hypercortisolemia [29, 78]. This adaptation helps optimize the cortisol/DHEA(S) ratio, which mitigates the chronic catabolic drive [26, 55]. Furthermore, physical activity can counteract metabolic dysregulation in sarcopenia by improving insulin sensitivity in the skeletal muscle [32, 76]. Muscle contraction stimulates glucose uptake through an insulin-independent pathway involving AMPK activation and calcium signaling, which can promote the translocation of GLUT4 to the sarcolemma even with defective insulin signaling [40, 109]. The improved glucose homeostasis helps restore the anabolic efficacy of insulin signaling and may facilitate amino acid delivery, thereby attenuating metabolic inflexibility and muscle wasting associated with sarcopenia [41].

The skeletal muscle is not only a target of systemic hormones but also a dynamic secretory organ that releases myokines to mediate autocrine, paracrine, and endocrine crosstalk [45, 106]. As regards anabolic and metabolic regulation, physical activity may counteract the age-related decline in beneficial myokines by stimulating the release of irisin and BDNF [3, 75, 106]. This exercise-induced upregulation of myokines can enhance fatty acid oxidation and support motoneuron maintenance, which helps restore metabolic flexibility and neuromuscular integrity compromised in sarcopenia [45, 75]. Conversely, physical activity may suppress myostatin expression via mechanical loading-dependent signaling, counteracting its typical upregulation by age-associated inflammation and glucocorticoids [45, 50, 106]. Although chronic, non-exercise-associated elevation of IL-6 levels promotes oxidative stress and proteolysis, exercise may induce a transient release of muscle-derived IL-6 via contraction-mediated metabolic signaling that stimulates the production of anti-inflammatory cytokines [45, 106]. This adaptive response can reduce TNF-α and chronic basal IL-6 levels, contributing to systemic immune homeostasis and attenuating the inflammatory progression of sarcopenia [50, 67].

5.3. Exercise modalities

Applying the aforementioned physiological insights into prevention and management of sarcopenia requires the comprehensive use of various exercise modalities, as general physical activity alone may be insufficient to counteract the physiological deficits associated with sarcopenia [3, 110, 111]. Given that no single modality can fully address the complex pathophysiology of sarcopenia, adaptations induced by various training modalities must be clarified [63, 112, 113].

The following subsections review the evidence base for resistance, aerobic, and multicomponent functional training to emphasize their effects on the endocrine system, muscle homeostasis, and functional capacity.

5.3.1. Resistance exercise: anabolic stimulation

Resistance exercise is defined as physical activity that involves muscles working against an external force or weight to increase muscle strength and mass [114, 115]. It is one of the primary nonpharmacological interventions for sarcopenia [3, 114, 115]. Common examples include the use of free weights, resistance bands, or bodyweight exercises, which generate mechanical tension to stimulate MPS and recruit high-threshold motor units [56, 67, 115-117].

Mechanical loading during resistance exercise activates the anabolic signaling pathways to drive MPS and suppress age-related catabolic signaling and proteolysis in skeletal muscle [67, 100, 104, 116]. Additionally, resistance exercise is effective in recruiting type II (fast-twitch) muscle fibers, which are susceptible to atrophy during aging and less stimulated by lower-intensity activities [80, 116]. From an endocrine perspective, resistance exercise can acutely increase anabolic hormone levels and modulate myokines and cytokines while chronically improving skeletal muscle sensitivity to anabolic signals, partially compensating for anabolic resistance through enhanced post-receptor signaling efficiency [12, 45, 56, 63, 69, 100].

Importantly, intensity determines the efficacy of resistance exercise to overcome the elevated anabolic threshold of muscle [3, 105, 118]. To elicit an effective hypertrophic response, evidence suggests that training loads need to exceed 60%–70% of the one-repetition maximum (1RM) [32, 119]. However, the implementation of high-intensity resistance exercise in older adults can be constrained by various factors, such as musculoskeletal conditions and safety concerns [111]. Although low-intensity resistance exercise fails to stimulate significant hypertrophy in the absence of fatigue, research indicates that low-intensity training (30%–40% 1RM) performed to volitional failure can stimulate MPS and hypertrophy comparable with high-intensity training [63, 80]. Additionally, low-intensity

resistance exercise (20% 1RM) combined with blood flow restriction was found to activate protein synthesis and promote muscle adaptation through metabolic stress rather than high mechanical tension alone [120].

Clinically, resistance exercise enhances functional capacity by preserving motor unit integrity and skeletal muscle mass, improving muscular strength and power, and facilitating the performance of essential activities of daily living (ADLs), such as rising from a chair, climbing stairs, and maintaining balance [3, 63, 116]. Consequently, these improvements contribute to breaking the cycle of sarcopenia associated disuse atrophy, reducing fall risk, preserving independence, and improving the quality of life in older adults [102, 111].

5.3.2. Aerobic exercise: metabolic regulation

Aerobic exercise involves rhythmic and continuous physical activity that engages large muscle groups and increases cardiorespiratory demand to enhance endurance capacity [114, 115]. Common examples include walking, running, cycling, and swimming, which primarily rely on aerobic metabolism to improve skeletal muscle quality and overall metabolic health [114, 115].

Aerobic exercise stimulates mitochondrial biogenesis through the activation of the PGC-1α pathway, counteracting age-related accumulation of mitochondrial DNA damage and oxidative stress that can accelerate muscle apoptosis and dysfunction [18, 56, 90, 116, 121]. This metabolic adaptation is further enhanced by increased capillary density, which improves oxygen delivery and nutrient exchange to support metabolic health in skeletal muscle [56, 57]. From an endocrine perspective, aerobic exercise can improve insulin sensitivity and reduce chronic elevation of cortisol levels while optimizing intracellular metabolic flexibility to regulate glucose and lipid oxidation in muscle [10, 56, 76, 116]. Additionally, aerobic exercise stimulates the release of irisin, which may promote the browning of white adipose tissue and improve glucose homeostasis [45, 51].

Despite the lack of standardized intensity guidelines for aerobic exercise in sarcopenia, previous intervention studies have utilized intensities of 50%–70% of maximum oxygen uptake (VO_2max) or a rating of perceived exertion of 13 (somewhat hard) on the Borg scale to elicit mitochondrial and metabolic adaptations [111, 119, 122]. Similar to resistance exercise, the implementation of these intensities in older adults can be constrained by various factors, such as diminished cardiorespiratory reserve, joint-related pain, and reduced exercise tolerance [111, 123, 124]. In such instances, moderate-intensity activities, such as walking, performed for extended durations (150–300 minutes per week), may be a viable alternative [32, 125].

Clinically, although resistance exercise directly influences muscle mass and strength, aerobic exercise indirectly supports sarcopenia management through systemic physiological and psychological adaptations, including improved cognitive function and mood [3, 114, 116, 126]. By improving cardiorespiratory fitness and metabolic resilience, aerobic exercise can mitigate systemic inflammation and insulin resistance that drive muscle catabolism while reducing the risk of chronic comorbidities that require hospitalization and cause immobility-induced disuse atrophy [41, 45, 63, 116]. Together, these adaptations render aerobic exercise as an important complement to resistance training in the comprehensive management of sarcopenia [3, 63].

5.3.3. Multicomponent exercise program

Multicomponent exercise combines resistance, aerobic, balance, flexibility, and functional training within a single session or program [3, 111, 126, 127]. Balance exercise involves static and dynamic activities aimed at improving postural control and stability, and flexibility exercise focuses on maintaining the range of motion for joint health [114, 115]. Functional training is a task-oriented exercise designed to mimic and enhance ADL performance through multi-joint movements and task-specific patterns [114, 115, 128]. Common examples of multicomponent exercise programs include circuit-based training, which integrates various exercise modalities and static and dynamic movements to translate isolated physiological gains into functional capacity for daily living [114, 126, 127].

By combining the anabolic stimulation of resistance exercise with the metabolic regulation of aerobic exercise, multicomponent exercise further improves proprioceptive feedback and neuromuscular coordination by incorporating balance, flexibility, and functional training [3, 57, 67, 114, 115]. This integrated neuromuscular–endocrine interaction network enhances neural control, mitochondrial efficiency, and anabolic–catabolic balance, improving motor unit recruitment for functional tasks while maintaining systemic physiological homeostasis [10, 45, 106, 114, 129].

In older adults, multicomponent exercise programs can address functional decline by reducing fall and frailty risk and improving walking ability and stability [111, 114, 115]. By targeting these deficits, the program offers an effective option for individuals with low baseline exercise capacity who may not initially tolerate higher-intensity single-modality training [1, 111, 126]. To ensure safety and efficacy, individualized prescriptions based on structured functional capacity assessments are essential and typically involve 2–3 weekly sessions of 45–60 min at light-to-moderate intensity, integrating resistance,

aerobic, balance, and flexibility training within each session [117, 122, 126-128, 130, 131].

Taken together, the multicomponent exercise approach enhances the synergistic effects of various exercise modalities across physiological, physical, and psychological domains, which helps preserve functional capacity, autonomy, and independence and supports long-term quality of life and sarcopenia management [3, 111, 114, 115, 119].

6. Circadian rhythm

Circadian rhythms are endogenous biological oscillations with a period of approximately 24 h coordinated by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus and peripheral clocks to synchronize physiological processes with the light–dark cycle [132]. The sleep–wake cycle is a principal circadian-regulated behavior that results from the interaction between circadian signals from the SCN and sleep homeostatic drive, which together regulate sleep pressure and arousal for 24-h [132]. Sleep architecture consists of non–rapid eye movement (NREM) and rapid eye movement stages, with slow-wave sleep (N3) identified as the deepest NREM stage and an important period for nocturnal neuroendocrine activity [133]. Circadian rhythms and sleep may influence skeletal muscle homeostasis by supporting recovery and modulating endocrine rhythmicity, metabolic regulation, and tissue-specific molecular clocks [132, 134]. Thus, they have been proposed as adjunct targets for the prevention and management of sarcopenia [9, 132, 134, 135]. However, clinical evidence directly linking circadian health to sarcopenia outcomes remains limited; therefore, circadian health should be considered a supportive strategy that complements established sarcopenia management.

The following sections focus on age-related alterations in the circadian rhythm, evidence linking sleep–circadian disruption to sarcopenia, and practical strategies to improve circadian alignment as complementary approaches to exercise and nutritional support for sarcopenia prevention and management.

6.1. Age-related alterations in the circadian rhythm

Aging involves progressive circadian alterations, including a tendency toward a phase advance (earlier timing of daily rhythms), reduced amplitude, and diminished stability of day–night oscillations across multiple physiological systems [132, 134]. These changes can reflect age-associated changes in SCN function and output signaling, coupled with diminished sensitivity to external signals (e.g., light–dark cycle) and reduced consistency of behavioral synchronizers that stabilize circadian phase and amplitude [135]. Circadian disruptions in older adults may alter the rhythmicity of core body temperature and melatonin secretion, as well as autonomic and cardiometabolic patterning, which together can weaken physiological signals that consolidate sleep and support daytime activity [95, 136-138]. These changes can be compounded by clinical and lifestyle-related factors, such as multimorbidity, pain, nocturia, sleep-disordered breathing, polypharmacy, depression and cognitive decline, and irregularity of social and behavioral zeitgebers (e.g., outdoor light exposure, meal timing, and physical activity), which further reduce circadian amplitude and stability [1, 134, 136-138]. Collectively, these age-related changes may blunt normal diurnal hormonal rhythms, disrupt the circadian regulation of neuroendocrine axes, and increase the risk of sarcopenia [134, 135, 137, 139].

6.2. Circadian regulation of neuroendocrine axes

SCN-generated circadian signals drive neuroendocrine rhythms through hypothalamic–pituitary pathways, organizing daily oscillations in anabolic and catabolic hormone levels [132, 137]. These neuroendocrine rhythms reflect not only the intrinsic circadian clockwork but also interactions with behavioral and environmental synchronizers, particularly sleep–wake timing, light exposure, eating patterns, and physical activity [137, 140, 141].

Within the HPA axis, SCN-driven hypothalamic–pituitary signaling and autonomic control of adrenal sensitivity regulate cortisol rhythmicity [137, 142]. Under normal conditions, cortisol typically peaks in the morning for substrate mobilization and reaches a nocturnal nadir for recovery [78, 132]. Circadian disruption and sleep fragmentation can increase nadir cortisol levels and reduce day–night amplitude through arousal-related activation and diminished sleep-associated inhibition of the HPA axis [10, 78]. Owing to the catabolic effects of cortisol on skeletal muscle, dysregulated cortisol rhythmicity may alter anabolic–catabolic signaling and skeletal muscle homeostasis [42, 138].

SCN-linked hypothalamic signaling and sleep-state modulation of GHRH and somatostatin modulate somatotropic regulation, resulting in pulsatile GH secretion [132, 143]. In the normal state, dominant GH pulses occur soon after sleep onset and are closely aligned with slow-wave sleep, resulting in a marked nocturnal rise in GH and somatotropic signaling [133, 134]. Age-related sleep and circadian disruptions can affect GH pulsatility by blunting the sleep-associated increase in GH secretion and altering the normal timing of somatotropic signaling [10, 134]. Given the role of GH–IGF-1 signaling in

protein anabolism, disruption of its temporal patterning may adversely affect MPS [15, 137].

SCN-linked signals and the sleep–wake state also regulate the HPG axis, which influences pulsatile secretion of hypothalamic GnRH and pituitary gonadotropin [10, 137]. In women, the menstrual cycle phase and menopausal status are major determinants of gonadotropin and ovarian steroid profiles, exerting a greater influence than day–night circadian variation [137, 144]. In men, testosterone peaks in the morning and rises overnight, with the nocturnal increase associated with sleep timing and continuity [132, 138]. In older men, circadian misalignment and chronic sleep restriction may attenuate the morning peak and overnight increase in testosterone levels, disrupting the diurnal testosterone rhythm [134, 138]. Attenuation and disorganization of testosterone rhythms may reduce sleep-associated androgen exposure, compromise recovery-related processes, and affect muscle maintenance and anabolic signaling [132, 138].

6.3. Circadian regulation of peripheral tissues

Beyond neuroendocrine control, peripheral circadian clocks control time-of-day variations in gene expression and tissue function through transcriptional–translational feedback loops involving core clock components (e.g., the brain and muscle ARNT-like 1 [BMAL1]–circadian locomotor output cycles kaput [CLOCK] heterodimer) [137, 140]. These clocks coordinate tissue-specific substrate metabolism, endocrine responsiveness, inflammatory signaling, and repair [132, 137, 140, 145].

Peripheral clocks in metabolic tissues regulate circadian patterns of glucose and lipid utilization by modulating pancreatic islet secretory capacity, hepatic substrate production, and adipose tissue lipolysis in alignment with feeding–fasting cycles and neuroendocrine signals [132, 137, 140]. Insulin sensitivity and glucose tolerance peak earlier in the day and decline by evening, with coordinated hepatic glucose handling and lipid mobilization [132, 146]. Sleep disruption and circadian misalignment, particularly with irregular food intake, can impair insulin sensitivity and alter pancreatic, hepatic, and adipose metabolic dynamics, desynchronizing normal postprandial metabolism and substrate availability [137, 138, 146].

Appetite-related endocrine signals follow circadian patterns regulated by SCN-linked neuroendocrine signals integrated with peripheral clocks in adipose and gastrointestinal tissues, together with autonomic nervous system activity and feeding–fasting timing [132, 137, 142]. Normally, leptin, a satiety-related hormone, rises at night, whereas ghrelin, an orexigenic hormone, exhibits meal-anticipatory fluctuations with preprandial increases that align with habitual meal timing [137, 146, 147]. However, circadian misalignment and irregular eating patterns can disrupt leptin and ghrelin rhythmicity, altering appetite and meal timing [132, 137, 146].

The interaction of intrinsic circadian clocks in immune cells with SCN-linked systemic signals regulates immune–inflammatory rhythmicity, which coordinates immune cell and mediator rhythms and inflammatory responsiveness in 24-h [132]. The rest–activity phase, which differs between diurnal and nocturnal patterns, is associated with circadian variations in circulating immune parameters, resulting in increased hematopoietic cells and leukocytes during the rest phase and higher proinflammatory cytokines (e.g., TNF and IL-1β) during the active phase [132, 148]. Circadian disruption caused by inappropriate exposure to light or sleep–wake misalignment can attenuate this rhythmic immune regulation and impair inflammatory homeostasis [132, 146].

Skeletal muscle contains a self-sustaining peripheral clock in which transcriptional–translational feedback loops (e.g., BMAL1–CLOCK and Period [Per]–Cryptochrome [Cry] proteins) regulate circadian programs crucial to myogenesis, muscle function, and metabolism [135, 136, 138]. Normally, peripheral clocks in skeletal muscle coordinate 24-h oscillations in clock-controlled gene (CCG) expression, with metabolic and functional processes peaking during the active period and repair and proteostasis activities increasing during the rest period [135, 136, 138]. Circadian misalignment, sleep disruption, and age-related attenuation of rhythmicity may dampen or desynchronize the expression of these CCGs, which reduces the temporal coordination of metabolic and repair processes in skeletal muscle [135, 136, 138].

These peripheral clocks and systemic regulators are synchronized by SCN-linked central signals and behavioral influences, such as meal timing, sleep–wake cycle, and light exposure [136, 137]. However, misalignment may cause internal desynchrony across organs and tissues and contribute to physiological alterations in sarcopenia [132, 134, 136-138].

6.4. Circadian rhythm and sarcopenia

Accumulating evidence associates circadian and sleep disturbances with sarcopenia-related declines in muscle mass and function, consistent with the effects on endocrine timing, metabolic control, and inflammatory signaling [136, 138]. Observational studies have demonstrated associations between sleep duration and sarcopenia-related outcomes, with evidence showing a U-shaped pattern in which short and long sleep are related to lower muscle mass and poorer physical performance

[149-151]. Short and long sleep may contribute to muscle loss and functional decline through different pathways, such as reduced sleep-dependent recovery and adverse endocrine, metabolic, and inflammatory profiles in short sleep and underlying morbidity, low physical activity, and inflammatory burden in long sleep [134, 138, 150]. Sleep quality and timing may also help maintain functional capacity, as poor sleep quality, including increased fragmentation, prolonged sleep latency, and reduced sleep efficiency, are associated with lower grip strength and slower gait speed in older adults [95, 134, 150, 152]. Considering the limited clinical evidence, optimizing circadian alignment through regular sleep–wake schedules, appropriate light exposure, and consistent meal and physical activity timing may be applied as an adjunctive strategy that supports exercise and nutritional interventions within a comprehensive behavioral approach [136, 138, 139].

7. Clinical implications and integrative management

Translating mechanistic understanding into clinical utility is complicated by the heterogeneity of sarcopenia and bidirectional interactions between physiological alterations and lifestyle behaviors [57, 90]. Age-related alterations in key neuroendocrine systems do not occur in isolation and are modulated by nutritional inadequacy, physical inactivity, and circadian misalignment [12, 76]. Nutrition, physical activity, and sleep–circadian behaviors are interconnected, and disruptions in one can influence the others and exacerbate anabolic resistance, highlighting the need for integrated clinical management rather than single-domain interventions [32, 63, 67, 75, 80, 138].

The following subsections examine the efficacy and risks of pharmacological and hormonal interventions, bidirectional crosstalk among nutrition, exercise, and sleep–circadian behaviors, and a stage-specific framework for sarcopenia prevention and management. They further address multidimensional monitoring and adaptive management strategies with the emerging role of digital and artificial intelligence (AI)-assisted technologies in personalized care for older adults.

7.1. Pharmacological and hormonal interventions: efficacy and risks

Despite advances in understanding age-related muscle loss, no drugs are currently approved for sarcopenia, as the heterogeneity of sarcopenia and limited translation of muscle mass gains into clinically meaningful improvements in strength and physical performance hinder drug development [3, 153, 154]. Consequently, pharmacological and hormonal interventions are used as indication-based adjunctive therapies for confirmed endocrine deficiency rather than as primary treatments for sarcopenia [32, 103, 128, 153]. In this context, pharmacological support aims to optimize the physiological environment for muscle maintenance and function, not to replace lifestyle-based interventions, with careful monitoring for systemic adverse effects [8, 9, 103, 128].

Gonadal hormone replacement therapy is indicated for symptomatic endocrine deficiencies rather than for age-related skeletal muscle loss [8, 10, 95]. Testosterone therapy in men with hypogonadism increases lean mass and reduces fat mass but shows inconsistent evidence for improvements in muscle strength and physical performance [8, 128, 155]. In postmenopausal women, hormone therapy may preserve muscle quality by attenuating impairments in mitochondrial function and satellite cell activity associated with estrogen deficiency; however, its use requires individualized assessment for cardiovascular and breast cancer-related risks [17, 23, 95, 156].

Interventions targeting the somatotropic and adrenal axes have limited roles in sarcopenia management owing to safety concerns and inconsistent functional benefits [3, 8, 15, 32]. GH and IGF-1 administration may improve body composition; however, functional benefits in muscle strength and physical performance remain inconsistent [8, 15, 49]. Additionally, these interventions have adverse effects, such as insulin resistance, edema, and carpal tunnel syndrome [8, 15, 49]. Similarly, DHEA replacement for age-related adrenal decline exerts limited and inconsistent effects on muscle strength and physical performance and is therefore not considered a primary therapeutic option [8, 31, 32, 157].

Recent pharmacological research has evaluated more tissue-selective agents, such as selective androgen receptor modulators (SARMs) and myostatin/activin pathway inhibitors [3, 8, 48, 154]. Although SARMs exert androgen-like anabolic effects and myostatin/activin pathway inhibitors can increase muscle mass, early-phase studies have not revealed that these gains translate into meaningful improvements in muscle function and physical performance [3, 5, 48, 128].

In brief, current pharmacological approaches in sarcopenia are largely limited to managing clinically confirmed endocrine deficiencies and serve as adjuncts rather than primary treatments [8, 32, 48, 95, 103]. Accordingly, the inconsistent translation of muscle mass gains into functional improvements emphasizes the need for multimodal lifestyle interventions as the primary management approach to sarcopenia [9, 32, 110, 113, 154].

7.2. Crosstalk between nutrition, exercise, and sleep

Nutrition, exercise/physical activity, and sleep–circadian behaviors are closely interconnected, and disruptions in one domain can affect the others and exacerbate anabolic resistance [63, 67, 80, 138]. These interactions are mediated through endocrine pathways regulating muscle metabolism and recovery, and clinical management should emphasize an integrated approach rather than monotherapies [9, 12, 32, 49, 119, 136, 138]. The age-related changes, physiological influences, and evidence basis across these three domains are summarized in Table 3.

Table 3. Nutrition, exercise, and circadian health in sarcopenia: age-related changes, physiological influences, and evidence basis [3, 9, 63, 115, 134, 138].

Factor	Age-related changes	Physiological influences	Evidence basis
Nutrition	• Anorexia of aging • ↓ Digestive and absorptive efficiency • ↓ Diet quality • ↑ Obesity risk (e.g., sarcopenic obesity)	• ↓ Nutrient availability (e.g., ↓ proteostasis, ↑ proteolysis) • ↑ Anabolic resistance (e.g., ↓ IGF-1, ↑ insulin resistance) • ↑ Catabolic drive (e.g., cortisol, TNF-α, IL-6) • Metabolic dysregulation	• Human studies: nutritional status associated with sarcopenia-related outcomes • Guideline/intervention evidence: adequate nutrition/protein support with exercise
Exercise	• ↓ Habitual physical activity; ↑ sedentary time, ↓ moderate-to-vigorous activity • ↓ Mechanosensitivity • Type II fiber atrophy • ↓ Neuromuscular efficiency • Cycle of disuse atrophy (e.g., pain, fear of falling, ↓ motivation)	• ↓ Mechanical load and ↓ neural stimuli; ↓ proteostasis • ↓ Anabolic hormones and myokines (e.g., GH–IGF-1, testosterone, T_3, irisin, BDNF) • ↑ Catabolic mediators (e.g., cortisol, myostatin, TNF-α, IL-6) • ↑ Oxidative stress and ROS accumulation • ↓ Metabolic flexibility	• Human studies: physical activity levels strongly associated with sarcopenia-related outcomes • Guideline/intervention evidence: resistance-based multicomponent exercise as the primary intervention
Circadian health	• ↓ Circadian amplitude and stability • Sleep fragmentation and ↓ sleep efficiency • ↓ SCN responsiveness • ↓ Consistency of behavioral zeitgebers (e.g., food intake, physical activity, light exposure) • Multimorbidity, polypharmacy, and social isolation	• Endocrine–metabolic instability • ↓ Anabolic signaling (e.g., GH, testosterone) • ↑ Catabolic drive (e.g., cortisol) • ↑ Immune–inflammatory rhythm disruption • ↓ BMAL1–CLOCK activity	• Human studies: observational associations with sleep–circadian factors and sarcopenia-related outcomes • Guideline/intervention evidence: limited and emerging; adjunctive to nutrition and exercise interventions

IGF-1: Insulin-like growth factor-1, TNF-α: Tumor necrosis factor-α, IL-6: Interleukin-6, GH: Growth hormone, T_3: Triiodothyronine, BDNF: Brain-derived neurotrophic factor, ROS: Reactive oxygen species, SCN: Suprachiasmatic nucleus, BMAL1–CLOCK: Brain and muscle ARNT-like 1–circadian locomotor output cycles and kaput.

The synergy between exercise and nutrition is central to sarcopenia management, as physical activity enhances the skeletal muscle's anabolic sensitivity to nutrient availability, whereas adequate nutrition supports training adaptation and recovery [69, 80, 119]. Specifically, resistance exercise mechanically stimulates amino acid transport capacity and sensitizes anabolic signaling, whereas leucine-rich protein intake provides both substrate and nutrient-sensing signals that attenuate anabolic resistance and enhance postexercise MPS in skeletal muscle [67, 80, 105]. Nutritional adequacy modulates the anabolic endocrine environment through insulin and GH–IGF-1 signaling, with adequate protein intake supporting insulin-mediated suppression of proteolysis, whereas resistance exercise of sufficient intensity improves insulin sensitivity and modulates IGF-1 signaling, diurnal HPA axis activity, and myokine signaling [32, 67, 68, 75]. Regular exercise may help counteract dysregulation of appetite hormones, such as cholecystokinin, leptin, and ghrelin, by reducing circulating leptin levels and improving satiety sensitivity, which can support adequate food intake and energy balance in older adults with anorexia of aging [60, 65, 158]. The integration of nutritional interventions, such as

adequate energy, micronutrients, hydration, and appropriately timed protein intake, with structured exercise offers synergistic benefits for training adaptation and tissue remodeling, thereby enhancing muscle mass, quality, and physical performance beyond what either intervention achieves alone [64, 67, 70, 119, 159, 160].

Nutrition and sleep–circadian behaviors interact bidirectionally, in which sleep–circadian alignment modulates endocrine–metabolic regulation and dietary patterns, and meal timing and composition influences the sleep–wake cycle and circadian stability [133, 137, 138, 161]. Sleep-related glucose dysregulation and impaired nocturnal GH pulsatility may reduce the anabolic response to nutrient intake in skeletal muscle, partly through disrupted insulin–amino acid handling and attenuated anabolic signaling responsiveness [63, 134, 138]. In parallel, sleep restriction and fragmentation dysregulate appetite-related hormones and metabolic signaling (e.g., leptin–ghrelin balance, insulin sensitivity, and HPA axis activity), altering appetite and glycemic control that can exacerbate anabolic resistance [133, 134, 146]. Conversely, meal timing and composition can influence sleep–circadian regulation by acting as behavioral zeitgebers and altering metabolic homeostasis, and specific dietary behaviors such as late-night eating, caffeine, and alcohol consumption disrupt the sleep–wake cycle [136, 137, 150, 161]. These bidirectional interactions indicate that coordinating sleep–circadian regulation with adequate nutrition and meal timing may attenuate anabolic resistance and support muscle maintenance in older adults [63, 136, 138].

Sleep–circadian regulation influences exercise readiness and postexercise recovery, whereas habitual exercise acts as a behavioral zeitgeber that can reinforce circadian rhythmicity and stabilize the sleep–wake cycle [132, 134, 135, 138]. Sleep disruption and circadian misalignment impair neuromuscular activation, attenuate anabolic responses to exercise, disrupt nocturnal GH pulsatility, and shift diurnal HPA axis activity toward a catabolic profile, compromising training quality and recovery [132, 135, 138]. Regular physical activity can in turn reinforce circadian regularity and sleep homeostasis as behavioral zeitgebers, with exercise timing and intensity influencing melatonin rhythms and sleep regulation, supporting the nocturnal hormonal environment for muscle maintenance [134, 138, 141]. Collectively, aligning exercise timing with a stable sleep–wake cycle and optimizing sleep quality promotes recovery and enhances functional benefits of exercise-based interventions in older adults [9, 134, 138].

In older adults, anabolic resistance can limit the benefit of isolated interventions, reflecting reduced skeletal muscle responsiveness to nutritional and mechanical stimuli [63, 80, 105, 119]. With adequate dose and quality, coordinating meal patterns, physical activity, and sleep–wake cycles with consistent timing and regularity can stabilize systemic endocrine–metabolic regulation and attenuate chronic inflammation, thereby improving the physiological environment for muscle maintenance in older adults (Fig. 2) [9, 45, 69, 135, 138].

7.3. Integrated prevention and management strategy

Once established, sarcopenia is challenging to reverse because of progressive neuromuscular decline and anabolic resistance [4, 56, 162]. Accordingly, preventing sarcopenia is a clinical priority, which requires a stage-specific strategy tailored to an individual's functional trajectory and interventions scaled to baseline vulnerability, functional status, and modifiable lifestyle barriers [3, 9, 101, 163].

Based on the prevention framework outlined by Seals, et al. [58], sarcopenia prevention and management can be organized into three stages, namely, prevention, early intervention, and management and rehabilitation, each defined by objectives and intervention intensities influenced by the endocrine and lifestyle determinants outlined above [4, 12, 76, 94]. The primary prevention stage targets community-dwelling older adults at risk of sarcopenia, in whom age-related endocrine decline has begun but has not yet translated into muscle loss or functional impairment [8, 58, 103, 164]. At this stage, modifiable risk factors, such as physical inactivity, inadequate diet and protein intake, and sleep–circadian misalignment, that interact with endocrine alterations to accelerate anabolic resistance must be addressed and modified [71, 115, 138, 162]. The early intervention stage targets individuals exhibiting early functional decline or possible sarcopenia, and the objective shifts from risk-factor modification to prompt intervention before the condition becomes more severe [5, 6, 58, 162]. At this stage, early functional decline may precede measurable muscle loss, creating a critical window for interventions such as structured resistance exercise, optimized protein intake, and sleep–circadian regulation [4, 6, 162, 165]. The management and rehabilitation stage addresses individuals with sarcopenia, for whom clinical management minimizes further functional decline, reduces fall risk, and preserves independence in ADLs [3, 4, 111, 115, 166]. The intervention approach is most intensive, incorporating structured multicomponent exercise, individualized nutritional support, and sleep–circadian regulation alongside pharmacological adjuncts for confirmed endocrine deficiencies [3, 24, 111, 134, 157]. Translating this stage-specific framework into clinical practice requires appropriate assessment, multidimensional monitoring, and adaptive management [4, 9, 111, 154, 163].

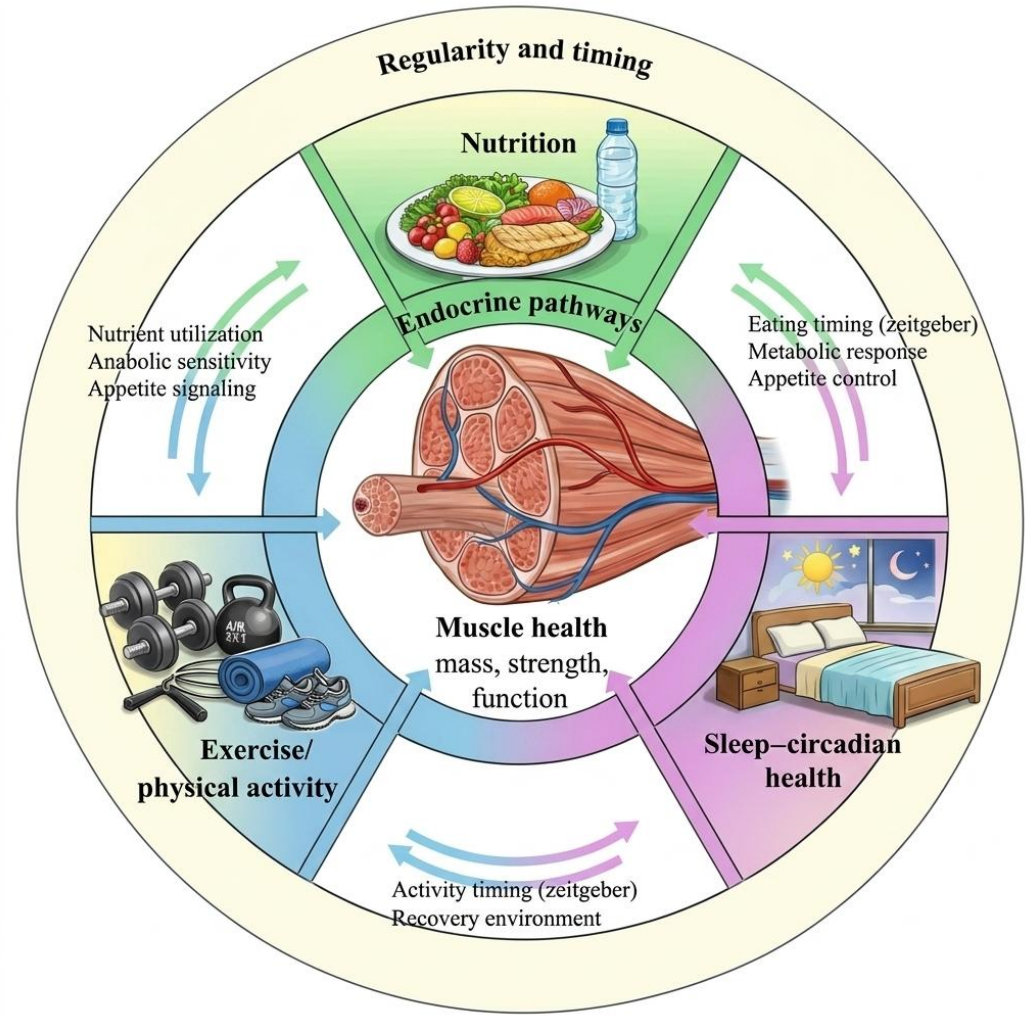

Figure 2. Interactions among nutrition, exercise/physical activity, and sleep–circadian health and their endocrine-mediated influences on skeletal muscle health.

7.4. Monitoring, screening, and adaptive management

The heterogeneity of sarcopenia and dynamic interactions between age-related physiological changes and lifestyle behaviors require multidimensional screening and monitoring approaches for adaptive management [6, 9, 115]. Given that endocrine factors mediate the effects of nutrition, physical activity, and sleep–circadian health on skeletal muscle homeostasis, these lifestyle domains can serve as indirect indicators of the endocrine environment, complementing established diagnostic measures for sarcopenia [11, 32, 138, 153].

The following subsections review current diagnostic tools and their limitations, multidimensional monitoring approaches, and adaptive management strategies for personalized sarcopenia care.

7.4.1. Current diagnostic tools and their limitations

The clinical assessment of sarcopenia relies primarily on the evaluation of muscle mass, muscle strength, and physical performance [3, 11]. Additionally, endocrine and nutritional markers provide complementary information on the physiological environment underlying muscle loss [3, 11, 32, 164].

Muscle mass is assessed by computed tomography (CT), magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA) [3, 6]. DXA and BIA are the most commonly used in clinical and research settings [3-6]. CT and MRI are considered the gold standards for assessing body composition; however, their routine use is limited by cost, accessibility, and technical requirements [3, 164]. Although DXA is more commonly used, it is also limited by cost and the need for trained personnel [3, 5]. BIA is more practical and accessible; however, its accuracy is influenced by hydration status, device-specific factors, and prediction equations employed [3-5].

Muscle strength is evaluated by handgrip strength, which is a simple, reproducible, and widely validated indicator of overall muscle strength [3, 6]. However, no uniform handgrip strength assessment has been implemented in practice, as dynamometer type, testing position, and protocol can affect measurements, and cutoff values may depend on population-specific reference data [4, 5, 128, 167].

Physical performance is assessed using different validated tools, such as gait speed, the five-times chair stand test, the short physical performance battery, and the timed up-and-go test, which evaluate broader aspects of muscle function, balance, and mobility [3, 165]. In this context, physical performance can help identify the severity and functional outcomes of sarcopenia; however, the specific tests adopted differ across guidelines and clinical settings [3-5, 165].

Endocrine and nutritional markers, such as IGF-1, testosterone, DHEA(S), vitamin D, and inflammatory cytokines, may provide complementary information on anabolic and catabolic status [8, 11, 153]. However, their routine clinical application is limited by cost, accessibility, and the absence of universally agreed reference ranges for older adults [8, 10, 11, 153, 164].

Current diagnostic tools provide a practical framework for identifying sarcopenia. However, important limitations remain, which emphasize the need for multidimensional screening and monitoring approaches that extend beyond conventional diagnostic tools [3-5, 163, 168].

7.4.2. Screening and multidimensional monitoring

Screening and monitoring that integrate behavioral and lifestyle markers can support risk stratification and evaluation of intervention response for sarcopenia prevention and management [11, 164, 169].

Nutritional monitoring for sarcopenia should encompass the assessment of energy balance, dietary protein intake and distribution, key micronutrient status, and indicators of nutritional risk, as these factors influence the endocrine and anabolic milieu underlying muscle homeostasis [9, 24, 60, 63]. Physical activity monitoring should include habitual activity levels, exercise type and frequency, and sedentary time, as these factors can indicate mechanical and endocrine signals that support MPS and neuromuscular adaptation [32, 63, 67]. Sleep–circadian health monitoring should address sleep duration, quality, and timing, as well as rest–activity rhythms; these factors can affect the nocturnal neuroendocrine milieu that supports muscle recovery and maintenance [134, 136, 139].

Repeated monitoring across these domains is crucial for the early detection of decline and stage reclassification for sarcopenia prevention and management [4, 163, 164]. However, repeated multidimensional monitoring can be a burden on participants and clinicians, potentially affecting data accuracy and consistency, whereas digital health technologies and AI-assisted tools may support continuous, passive, and scalable data collection [125, 164, 169, 170]. Smartphone-based applications, wearable sensors, and machine-learning algorithms have demonstrated potential for objective monitoring of nutritional behaviors, physical activity, and sleep–wake patterns in free-living conditions, as well as for improving sarcopenia risk stratification [9, 125, 152, 171, 172]. However, these technologies have limited validity, feasibility, interpretability, cost, and acceptability in older adults, and their integration with clinical assessments and monitoring can support personalized sarcopenia management [9, 115, 173, 174].

7.4.3. Adaptive and precision management

Translating multidimensional monitoring data into individualized intervention strategies requires risk stratification that considers a person's risk profile across domains and their interactions while accounting for adherence barriers such as comorbidity burden, accessibility, and social environment [6, 25, 115, 164, 175-177]. The World Health Organization [1] recently proposed a practical management framework for older adults, which consists of assessment, personalized planning, implementation, and monitoring, followed by reassessment and adjustment. Within this model, interventions can be refined according to an individual's clinical trajectory, adherence, and responsiveness, thereby linking multidimensional monitoring to precise sarcopenia care [1, 9, 115, 117]. Building on this framework, Figure 3 presents a personalized sarcopenia care model that integrates the endocrine, nutritional, physical, and circadian factors discussed throughout this review. It begins with screening and diagnostic classification, followed by comprehensive assessment across the four domains. This model emphasizes personalized planning, including nutritional optimization and resistance-based multicomponent exercise, while considering endocrine interventions as diagnosis-based approaches and circadian health strategies as supportive components with emerging evidence. Implementation and monitoring focus on clinically meaningful outcomes, supported by domain-specific follow-up and digital health technologies, while scheduled reassessment enables individualized modification based on response and tolerability. This model provides a practical framework for translating the endocrine and lifestyle evidence reviewed in this article into individualized, clinically actionable sarcopenia care.

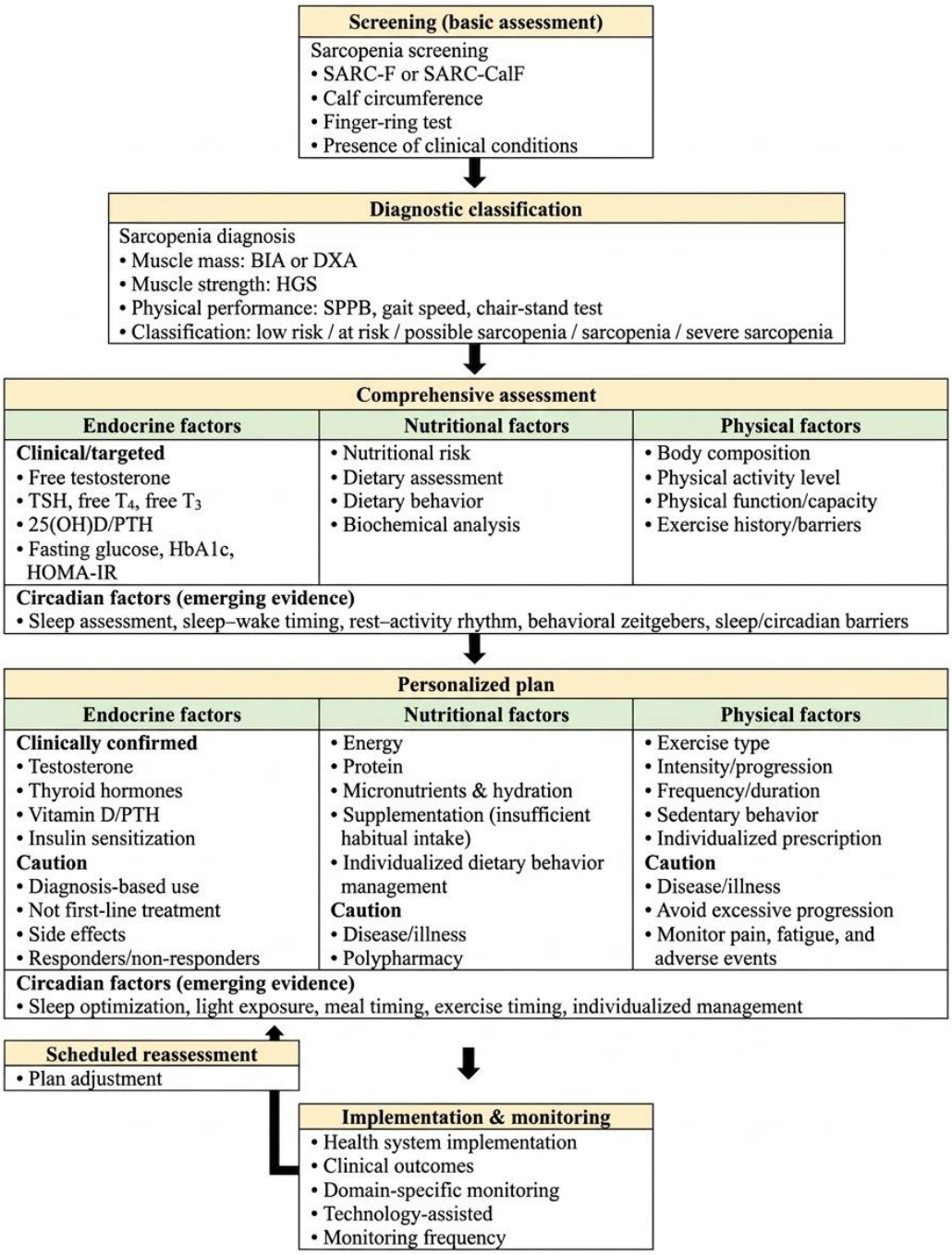

Figure 3. Multidimensional management model for personalized sarcopenia care [1, 3-6, 9, 32, 115, 117, 139, 163, 165]. A detailed version is provided in Supplementary Fig. S1. SARC-F: Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls, SARC-CalF: SARC-F with calf circumference, BIA: Bioelectrical impedance analysis, DXA: Dual-energy X-ray absorptiometry, HGS: Handgrip strength, SPPB: Short Physical Performance Battery, TSH: Thyroid-stimulating hormone, T_4: Thyroxine, T_3: Triiodothyronine, 25(OH)D: 25-hydroxyvitamin D, Ca: Calcium, PTH: Parathyroid hormone, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment of insulin resistance.

8. Conclusion and future directions

With the global population aging rapidly, sarcopenia is a major public health challenge with substantial burdens on individual functional independence and healthcare system sustainability [1, 3]. This review outlined how age-related endocrine alterations, such as changes in the somatotropic, gonadal, adrenal, and thyroid axes,

alongside insulin and peripheral regulators, influence anabolic–catabolic balance, exacerbating declines in muscle mass, strength, and function. These alterations are closely related to lifestyle behaviors, with nutrition, physical activity, and sleep–circadian health, each exerting independent and interrelated influences on the endocrine environment that regulates muscle homeostasis [32, 136, 138]. When these domains are optimized independently and coordinated in timing and regularity, their combined effects can offer a comprehensive strategy for preserving skeletal muscle health in older adults [9, 69, 136, 138]. In practice, this understanding can be applied through an adaptive and precision framework that considers individual differences in sarcopenia-related risk factors, supported by multidimensional monitoring and emerging digital health technologies [3, 9, 115, 125, 170].

Future studies should focus on hormonal responses to integrated lifestyle interventions, longitudinal studies across diverse population groups, establishment of population-specific diagnostic cutoff values, and development of precision medicine approaches incorporating endocrine profiling and behavioral phenotyping [3, 153, 154].

In conclusion, understanding how nutrition, physical activity, and sleep–circadian health interact and influence endocrine regulation provides a foundation for integrated and personalized precision approaches to sarcopenia prevention and management.

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Author contributions

SL and CYK conceptualized the study; SL prepared the original manuscript, tables, and figures; SL and CYK edited and revised the manuscript.

Competing interests

The authors declare no conflict of interest.

Supplementary data

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2026.0483.

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