

Hormonal dimorphism in sarcopenia disease

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ABSTRACT

Sarcopenia, affecting over 60% of individuals above age 80, represents a critical challenge for aging populations worldwide. Despite formal recognition as a disease by the WHO in 2016, therapeutic approaches remain limited to exercise and nutritional interventions, with no approved pharmacological treatments. Current management strategies follow a universal paradigm that assumes similar pathophysiological mechanisms across all patients, yet clinical outcomes demonstrate marked variability that may reflect fundamental sex-specific differences in muscle-aging biology. This review interrogates sexual dimorphism in muscle-aging pathophysiology through the lens of three peptide hormones, i.e., apelin, insulin, and oxytocin, and proposes sex-stratified therapeutic strategies. We analyzed pathophysiological mechanisms underlying sarcopenia, focusing on the complex hormonal regulatory network of apelin, insulin, and oxytocin and its effect on satellite-cell dysfunction, proteostasis, stress, and inflammation.

Sarcopenia manifests through fundamentally different pathways in men and women. Women experience precipitous muscle loss during menopause through rapid estrogen decline that disrupts apelin signaling, accelerates insulin resistance, and compromises oxytocin-mediated regeneration. Men demonstrate gradual deterioration paralleling testosterone reduction, with differences among individuals in hormonal dysfunction patterns. Apelin serves as a biomarker primarily in women, while myostatin functions specifically in men. Insulin sensitivity exhibits profound sexual dimorphism, with women maintaining superior muscle glucose metabolism until menopause. Current therapeutic approaches may optimize treatments for one sex while producing suboptimal outcomes for the other. Fewer than 30% of muscle aging studies report sex-disaggregated results, creating critical knowledge gaps. Effective sarcopenia management requires a deeper understanding of peptide-hormone deregulation and development of biologically informed therapeutic strategies that acknowledge distinct disease mechanisms in men and women.

INTRODUCTION

Sarcopenia, derived from the Greek words “sarx” (flesh) and “penia” (poverty), refers to the age-related loss of skeletal muscle mass, strength, and function. With the rapid aging of the global population, e.g., the number of individuals over 60 will grow from 600 million in 2000 to 1.2 billion by 2025 and is projected to double by 2050 [1, 2], sarcopenia has emerged as one of the most pressing challenges facing modern healthcare systems [3]. This progressive syndrome

affects over 60% of individuals above age 80 and represents far more than simple muscle loss; it is a complex multisystem disorder that compromises physical independence, increases fall risk and mortality, and imposes substantial economic burdens on healthcare systems worldwide [4]. Despite decades of intensive research and the formal recognition of sarcopenia as a disease by the World Health Organization in 2016, therapeutic advances have remained disappointingly limited [5]. Current approaches to impede its development rely primarily on

exercise interventions and nutritional strategies, while no approved pharmacological treatments exist [6]. Perhaps more troubling, the therapeutic responses to these interventions demonstrate marked and unpredictable variability among patients, which has long been attributed to differences among individuals in genetics, compliance, or baseline fitness, but which may instead reflect a fundamental flaw in our therapeutic paradigm [7].

Universal treatment approaches for diseases in general have historically served medicine well, particularly for acute conditions, but their limitations become apparent in the case of complex age-related disorders like sarcopenia [8]. This universal treatment paradigm assumes that pathophysiological mechanisms and therapeutic responses are fundamentally similar in all patients, and required only minor modifications for factors like age, comorbidity burden, or disease severity [9]. However, mounting evidence suggests that this assumption does not apply anymore to muscle aging, during which pathophysiological pathways and metabolic hormones regulation appear to exhibit gender-specific differences [8].

The concept of sexual dimorphism in human biology extends far beyond obvious reproductive differences to encompass fundamental differences in metabolism, hormone regulation, inflammatory responses, and cellular aging processes. In skeletal muscle, these sex differences manifest throughout the lifespan but become particularly pronounced during aging, when hormonal changes result in differences between men and women in the trajectory of muscle decline [9]. Women experience precipitous muscle loss during the menopausal transition, coinciding with rapid estrogen decline, while men demonstrate paralleling gradual testosterone reduction. These distinct patterns reflect underlying differences in muscle-fiber composition, satellite-cell biology, metabolic regulation, and hormonal sensitivity that collectively suggest that sarcopenia may be a different disease in men and women rather than a single condition with variable presentations [10–12].

Through comprehensive examination of the literature describing the pathophysiological mechanisms underlying sarcopenia in human, mouse, zebrafish, and African turquoise killifish (ATK), including a detailed review of studies of three hormonal systems (apelin, insulin, and oxytocin), we demonstrate how sexual dimorphism in muscle biology creates distinct disease trajectories that demand tailored interventions. While numerous hormones influence muscle aging, including growth hormone (GH), IGF-1, thyroid hormones, and ghrelin, most of these systems primarily exhibit

quantitative rather than qualitative sex differences [13–15]. For example, GH demonstrates sexually dimorphic secretion patterns (pulsatile in men versus continuous in women) but acts through fundamentally similar anabolic mechanisms in both sexes [15, 16]. Similarly, although ghrelin levels and thyroid-hormone sensitivity differ between sexes, these hormones regulate muscle metabolism through largely similar molecular pathways in both men and women [17]. In contrast, apelin, insulin, and oxytocin exhibit sex-specific interactions between sex hormones and metabolic regulation in muscle homeostasis. Each of these three peptides demonstrates qualitative differences in its mechanisms of action with estrogen versus testosterone, suggesting sex-specific differences in the modulation of sex-hormone levels, signaling pathways, and receptor sensitivity, and demonstrating sex-specific physiological outcomes [18–20]. In addition, these three systems do not act in isolation but participate together in a complex network influencing muscle metabolism and systemic energy balance. At the molecular level, these three peptide hormones converge on overlapping signaling cascades and share common downstream effectors that create synergistic and antagonistic interactions [21–26].

This review proposes that deregulation not only of sex hormones but also of peptide hormones contributes to the establishment of sarcopenia. Recognizing that sarcopenia manifests differently in men and women through distinct hormonal networks and cellular mechanisms will open unprecedented opportunities for targeted interventions that optimize outcomes for both sexes. Central to this endeavor will be a deeper understanding of sex-specific peptide-hormone deregulation, which emerges as a key mechanistic lever at the transition phase prior to the establishment of sarcopenia; this phase represents a potential therapeutic target for impeding or preventing sarcopenia progression in both men and women. The path forward will require coordinated research to characterize sex-specific mechanisms, develop appropriate biomarkers, and establish therapeutic protocols that harness these fundamental biological differences.

Global burden, diagnosis, and management of sarcopenia

Sarcopenia is one of the most significant age-related health challenges facing our rapidly aging global population. It is a complex syndrome that is associated with increased risk of falls and fractures and higher rates of hospitalization, disability, and mortality, and that directly impacts an individual's daily life and independence [4, 27–29]. The progressive loss of skeletal muscle mass, strength, and function typically

begins as early as age 30 and accelerates as we age [4, 30]. The substantial public health significance of sarcopenia is reflected in prevalence estimates of 10-16% in elderly individuals worldwide [2]. The formal recognition of sarcopenia as a disease by the World Health Organization and in the International Classification of Diseases (ICD-10: M62.84) in 2016 marked a pivotal moment in geriatric medicine [5, 31]. However, despite decades of research and therapy development, sarcopenia remains a pressing challenge, as to date we are able only to slow down its irreversible development, and not treat it [27, 28, 32]. As our global population continues to age and average lifespan increases, addressing sarcopenia has become critical, as longer lifespan does not necessarily translate to a longer healthy life.

A significant advancement in sarcopenia research has been the recognition of “possible sarcopenia,” defined as the reduction of skeletal-muscle strength with or without decreased muscle performance, occurring in the absence of confirmed low muscle mass [29, 33]. This pre-morbid status represents a transitional state between normal muscle health and established sarcopenia, offering an important window for early intervention. The identification of possible sarcopenia has proven to be valuable, as loss of skeletal muscle strength alone has been demonstrated to increase the risk of all-cause mortality, cardiovascular mortality, myocardial infarction, strokes, and injuries from falls [34]. In addition, the recognition of possible sarcopenia underlines the importance of understanding peptide-hormone deregulation (discussed in detail below); specifically, determining whether peptide-hormone deregulation takes place during the transitional “possible sarcopenia” state will help us to assess the potential of targeting peptide hormones as a means of impeding or preventing progression toward established sarcopenia.

Clinical diagnosis

The diagnostic process, all steps of which are performed by specialists, begins with muscle-strength assessment. The primary measure used for this first test is handgrip strength, because of the simplicity of the test and the strong correlation of hand strength with overall strength, although the test results may not fully reflect the strength of larger muscle groups and or overall mobility capability [35–37]. Next, specialists select one or more subsequent tests depending on the severity of muscle-strength assessment. Lower-body function is evaluated through chair-stand tests, while mobility is assessed via the Short Physical Performance Battery (SPPB) [35, 38]. Muscle mass is assessed via dual-energy X-ray absorptiometry (DXA) as the reference standard [39,

40], while CT and MRI offer superior muscle-quality assessment but are limited by cost and availability [41, 42]. More accessible alternatives for muscle-mass assessment include bioelectrical impedance analysis [43, 44], although its accuracy is affected by hydration status, and ultrasound [45, 46], which shows promise as a portable real-time option but currently lacks standardized protocols for reproducible use. Despite the value of the above diagnostic tests in assessing muscle strength, the recent recognition of “possible sarcopenia” demonstrates their limitations in diagnosing sarcopenia; hence, new diagnostic methods are needed, such as the use of biomarkers.

Biomarkers

The identification of reliable biomarkers for sarcopenia remains an active research area [47]. Key molecular markers include atrogin-1 (FBXO32) and MuRF1, which are regulated by the Akt1/FOXO1 pathway and upregulated prior to muscle-atrophy onset, linking sarcopenia to the ubiquitin proteasome system for muscle protein degradation [48–50]. Myostatin levels exhibit sex-specific differences in their association with skeletal muscle homeostasis, with myostatin acting as a homeostatic regulator in men while showing stronger association with sarcopenia development in women [51–55]. Conversely, IGF-1 is a sarcopenia biomarker in women, where serum IGF-1 levels associate with frailty and low muscle mass, but not in men [56]. Similarly, the cutoff values of serum creatinine-to-cystatin C ratio required for sarcopenia screening differ between men and women, as do the associations of this ratio with frailty outcomes [57–59]. These findings underscore that biomarker validation, while essential for characterization of early-stage sarcopenia, must account for sexual dimorphism in muscle biology. While various inflammatory markers show promise, they require further validation with sex-stratified analyses before clinical implementation [60, 61]. The challenge will be to develop biomarkers that are both clinically accessible and sufficiently accurate for sarcopenia diagnosis and monitoring across both sexes, which will require sex-informed reference ranges and diagnostic thresholds.

Sarcopenia management

Despite the absence of pharmacological treatments specifically for sarcopenia, a multimodal management approach combining exercise, nutritional, and emerging therapeutic strategies has shown efficacy in attenuating muscle loss and improving functional outcomes in both men and women [6, 62]. Resistance training remains the cornerstone of sarcopenia management, with robust evidence demonstrating efficacy in improving muscle

mass, strength, and functional performance [6, 62, 63]. Progressive resistance-training protocols consistently show significant improvements through enhanced muscle-protein synthesis, satellite-cell activation, and improved mitochondrial function [6, 64]. However, optimal parameters vary based on baseline fitness, age, comorbidities, and sex-specific physiological differences.

Nutritional strategies have been developed that address age-related protein metabolism changes through high-quality protein supplementation including leucine, creatine, vitamin D, and micronutrients (vitamins C and E, omega-3 fatty acids); such strategies show promise, although individual responses vary considerably [6, 62, 65].

While no approved pharmacological treatments exist for sarcopenia, myostatin inhibitors and activin-receptor antagonists demonstrate muscle-mass increases, although functional improvements are inconsistent and cardiovascular concerns persist [66, 67]. Hormone-replacement strategies show muscle and strength benefits but present risks (cardiovascular/prostate effects in men, virilization in women), and their complex interactions with other hormonal systems remain poorly understood, limiting therapeutic optimization until there is a better understanding of these interactions, in particular, how the interactions differ between women and men [68–71].

Pathophysiological processes in sarcopenia

The development of sarcopenia involves multiple interconnected pathophysiological processes that collectively drive progressive muscle deterioration, including mitochondrial dysfunction, chronic inflammation, hormonal decline, neuromuscular junction degradation, and impaired protein synthesis, with type II fibers (fast-twitch anaerobic) preferentially lost [72–74]. Understanding these mechanisms is essential for developing therapeutic interventions and identifying prevention targets.

Hormonal changes

Sarcopenia has been associated with age-related decline in sex hormones and the consequent inability of the hormones to support the function of satellite cells, which are the resident muscle stem cells crucial for muscle repair and regeneration [75–77]. The broader hormonal decline includes decreased levels of anabolic hormones such as growth hormone, estrogen, testosterone, ghrelin, thyroid hormones, and insulin-like growth factor-1 (IGF-1) [78–84], combined with an age-related increase in the activity of catabolic

hormones including cortisol and pro-inflammatory cytokines, creating an environment that favors muscle loss and compromises protein synthesis and cellular repair mechanisms [85–88]. However, recent studies demonstrate that testosterone supplementation can promote satellite-cell entry into the cell cycle, thereby increasing their number [89].

Muscle stem cells

Sarcopenia is intimately linked to dysfunction of satellite cells [89, 90]. Under normal physiological conditions, satellite cells remain in a reversible quiescent state, ready to activate upon muscle injury or demand for growth [91–93]. However, aging disrupts this delicate regulatory system through multiple interconnected mechanisms. The decline in satellite-cell numbers occurs in the early stages of muscle aging and is likely due to physiological changes affecting the satellite-cell niche and cell-autonomous alterations that together disturb the proper balance between cell quiescence, proliferation, and apoptosis [90, 94, 95]. As individuals age, the micro-environment within muscle tissue changes, disrupting normal quiescence [94, 95]. More importantly, geriatric satellite cells lose their normal quiescent state with age, mediated by the derepressing of p16(INK4), which results in conversion of the normally reversible activation-quiescent state to an irreversible senescent state, thereby limiting muscle-tissue repair and regeneration [95–97]. In geriatric mice, both the loss of muscle fibers and depletion of activated muscle stem cells correlate with satellite-cell entry into this senescent state [95], highlighting the interconnected nature of cellular aging and tissue deterioration.

Proteostasis

Central to sarcopenia disease is the disruption of proteostasis, the cellular process responsible for maintaining protein balance within muscle fibers [98, 99]. Age-related physiological changes create an imbalance between muscle-protein synthesis and breakdown that favors catabolism over anabolism. Specifically, declines in anabolic hormones (testosterone, growth hormone, IGF-1) have been shown to reduce muscle-protein synthesis, promote atrophy, and increase anabolic resistance [100, 101]. This shift is driven by impaired protein regulation and reduced responsiveness of the mTORC1 and MAPK signaling pathways to contraction-induced stimuli [102]. This results in net muscle-protein loss and accumulation of damaged proteins within muscle fibers, both of which compromise the structural integrity and functional capability of muscle [99, 103].

Mitochondrial biogenesis

Concurrently with muscle aging, progressive decline in mitochondrial biogenesis and oxidative function is another fundamental mechanism impairing cellular energy production and the muscle's ability to meet physiological demands prior to sarcopenia onset [104–106]. The decline in mitochondrial integrity, network organization, and ATP production occurs before sarcomere breakdown [107], linking energetic failure to the progressive loss of muscle mass, strength, and function characteristic of the disease [104, 106, 108].

Neuromuscular system

The age-related progressive loss of motor neurons and deterioration of neuromuscular junction (NMJ) integrity contributes to both muscle atrophy and reduced functional performance [109, 110]. During aging, NMJs undergo profound structural and functional changes, including endplate fragmentation, widening of synaptic clefts, and altered acetylcholine-receptor distribution [111–113]. The loss of motor neurons during aging initiates the denervation-reinnervation cycle, whereby surviving motor neurons attempt to compensate through axonal sprouting [109, 110], a mechanism that progressively fails as increasing numbers of denervated fibers are unable to be successfully reinnervated or replaced [82, 109, 110].

Inflammation

Chronic systemic low-grade inflammation, also termed “inflammaging,” further disrupts normal muscle maintenance by elevating pro-inflammatory cytokines and promoting protein breakdown while inhibiting protein synthesis [88, 114]. Sources of inflammaging include accumulation of senescent cells that secrete inflammatory factors (the senescence-associated secretory phenotype, or SASP), increased visceral adiposity, and mitochondrial dysfunction [115, 116]. Inflammaging is characterized by increased levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP), each of which can activate proteolytic pathways such as the ubiquitin-proteasome system [88, 114]. Beyond the direct effects of inflammaging on protein turnover, inflammaging profoundly impairs muscle metabolic health by contributing to insulin resistance through interference with insulin-receptor signaling cascades and disruption of glucose-transporter translocation, thereby compromising the muscle's anabolic capacity and creating a state of “anabolic resistance” whereby muscle becomes less responsive to growth-promoting stimuli such as nutrition and exercise [117–119].

The inflammatory milieu also disrupts satellite-cell function, by impairing their activation, proliferation, and differentiation capacity, thereby compromising the muscle's regenerative potential [120, 121]. Importantly, men and women exhibit distinct inflammatory profiles and tissue-specific responses to inflammation, both of which contribute to sex-specific sarcopenia trajectories [10, 12].

The regulatory network for apelin, insulin, and oxytocin as a sex-specific strategy for sarcopenia management

Apelin, insulin, and oxytocin are peptide hormones that are key regulators of muscle homeostasis, enhancing muscle health through complementary processes. Age-related decline in their signaling may contribute significantly to sarcopenia, yet the complex interplay of these hormonal changes during aging remains poorly characterized, particularly regarding sex-specific differences. Developing effective therapies requires comprehensive characterization of age-related hormonal networks and their sex-specific variations.

Apelin

Apelin, originally identified as the endogenous ligand for the APJ receptor (now termed APLNR), is produced through proteolytic processing of a 77-amino acid precursor protein and exists in multiple bioactive forms, including apelin-36, -17, and -13, each exhibiting distinct biological activities and tissue-specific expression patterns [122, 123]. The apelin/APLNR system is distributed widely throughout the body, with particularly high expression levels in skeletal muscle, the cardiovascular system, adipose tissue, and the central nervous and reproductive systems, positioning it as a critical regulator of energy homeostasis and metabolic function [124–127].

In skeletal muscle, apelin functions as a potent myokine that orchestrates multiple aspects of muscle physiology, including glucose uptake, fatty-acid oxidation, mitochondrial biogenesis, satellite-cell proliferation and activation, and contractile protein synthesis [124, 128, 129]. The peptide exerts its effects through binding to APLNR, a G-protein-coupled receptor that activates downstream signaling cascades involving AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) [130]. These pathways collectively enhance muscle oxidative capacity, improve insulin sensitivity, and promote anabolic processes essential for muscle maintenance and repair [130]. Apelin levels decline significantly with age but correlate positively with the

beneficial effects of exercise in older people, suggesting a mechanistic link between apelin deficiency and sarcopenia [124].

Insulin

Insulin, which is secreted by pancreatic β -cells, is the master regulator of glucose homeostasis and anabolic metabolism [131]. Insulin orchestrates these metabolic functions by binding to insulin receptors on target tissues, triggering the PI3K/Akt/mTOR signaling pathway, which simultaneously promotes nutrient uptake and storage, enhances protein synthesis, inhibits protein breakdown, and stimulates cellular growth and proliferation. In skeletal muscle, which accounts for approximately 70-80% of glucose disposal under physiological conditions, this set of insulin-initiated processes creates a net anabolic environment supporting muscle-mass maintenance and growth through inhibition of the ubiquitin-proteasome system and autophagy [132]. Insulin also directly promotes the proliferation and differentiation of muscle satellite stem cells, increasing the expression of proliferation markers (Ki67, PCNA, Pax7) and differentiation markers (MYOD, MYOG, MYH) via PI3K-Akt and MAPK signaling [133, 134], and enhancing myotube formation and creatine-kinase activity [133, 134].

Oxytocin

Oxytocin, a neuropeptide hormone synthesized in the hypothalamus and evolutionary conserved across vertebrates, was recently shown to function as an important regulator of muscle homeostasis and regeneration, beyond its classical roles in parturition, lactation, and social bonding [135, 136]. Oxytocin exerts its effects through binding to oxytocin receptors (OXTR) and to G-protein-coupled receptors, both of which activate complex intracellular signaling cascades involving calcium mobilization, protein kinase C activation, MAPK/ERK, AKT, and AMPK signaling, and downstream transcriptional factors such as MyoD, all of which are essential for muscle function, maintenance, and repair [77, 137, 138].

OXTR expression is present in both mature myofibers and satellite cells; in both sites, oxytocin signaling influences proliferation, differentiation, and fusion dynamics critical for developmental myogenesis and regenerative response to injury [77]. Oxytocin also influences metabolic processes, including glucose uptake, insulin sensitivity, and mitochondrial function [77, 139]. OXTR expression levels are modulated by mechanical loading, nutritional status, the hormonal milieu, and aging [77].

The apelin-insulin-oxytocin complex regulatory network

A key feature of this hormonal triad is their convergence on shared downstream effectors, particularly AMPK and GLUT4 translocation, through distinct upstream mechanisms, enabling complementary and potentially synergistic regulation of muscle metabolism (Figure 1).

Apelin-insulin hormonal network

Apelin regulates glucose and lipid metabolism, insulin sensitivity, and energy homeostasis through pathways such as AMPK, PI3K/AKT/mTOR, and eNOS, and also through interacting with insulin signaling [23–26]. Apelin has a complex role in glucose homeostasis, as apelin inhibits glucose-stimulated insulin secretion from pancreatic islets at lower concentrations (1-10⁴ nmol/L) but stimulates it at higher concentrations (10 μ M) [23, 140]. In addition, in insulin-resistant states, apelin enhances insulin-stimulated glucose uptake by activating AMPK and promoting GLUT4 translocation through pathways distinct from but complementary to insulin's PI3K/AKT route. Insulin drives GLUT4 to the cell surface via PI3K/AKT-mediated phosphorylation of TBC1D4, apelin acts through AMPK to phosphorylate a closely related but distinct protein, TBC1D1, achieving the same result through an independent upstream cascade. In insulin resistance, PI3K/AKT pathway is impaired, yet the AMPK/TBC1D1 route remains functional. Apelin can therefore drive GLUT4 translocation and glucose uptake even when insulin's own signaling is compromised, providing a parallel route to the same destination making this mechanism particularly relevant for combating insulin resistance in sarcopenia [141, 142].

Conversely, insulin directly regulates apelin expression in both human and mouse adipocytes through the activation of PI3K, protein kinase C, and MAPK signaling pathways [143]. In obese patients, elevated plasma apelin levels correlate with increased insulin concentrations, establishing apelin as a novel adipokine linked to obesity-associated insulin sensitivity. The dysregulation of insulin-apelin signaling may therefore affect muscle-adipose tissue crosstalk and metabolic homeostasis in insulin-resistant conditions [143].

Insulin-oxytocin hormonal network

Oxytocin is produced in the hypothalamus then released into the circulation and also by a subpopulation of sympathetic neurons that directly innervate adipose tissue [144]. Oxytocin enhances glucose uptake and lipid

utilization in muscle and adipose tissue [144, 145] positioning oxytocin as a key integrator linking central neuroendocrine control with peripheral energy homeostasis. Oxytocin stimulates glucose-induced insulin secretion through calcium-CaMKK-AMPK pathways [137, 146]. Central insulin in turn activates hypothalamic oxytocin neurons to release oxytocin into circulation, creating a feedback loop that establishes oxytocin as both regulator and downstream effector of insulin signaling [147]. This axis is particularly relevant postprandially, when rising insulin levels activate hypothalamic oxytocin neurons that promote glucose disposal and lipid oxidation. In skeletal muscle, oxytocin-receptor activation enhances insulin sensitivity through increased GLUT4 translocation, improved mitochondrial oxidative capacity, and lipid oxidation, all via AMPK-dependent and calcium-dependent signaling cascades [137, 148]. In adipose tissue, oxytocin promotes browning of white adipocytes and thermogenic activity, contributing to energy expenditure [149, 150].

Oxytocin-apelin hormonal network

The apelin-oxytocin relationship exhibits anatomical and functional connections within the hypothalamus, where the two peptides co-localize in magnocellular neurons of the supraoptic and paraventricular nuclei [151, 152]. Apelin regulates hypothalamic oxytocin neurons through receptor binding, with intracerebroventricular apelin administration in rats suppressing both magnocellular and parvocellular oxytocin neuron function [153–155]. However, apelin expression is not exclusive to oxytocinergic neurons [151]; some apelin-positive cells are vasopressinergic [153–155]. Because oxytocin neurons express apelin receptors, oxytocin may influence apelin expression through autocrine or paracrine signaling, although direct experimental evidence is lacking. Apelin's regulatory influence appears context-specific, with distinct inhibitory effects during lactation [153] and variable effects in other

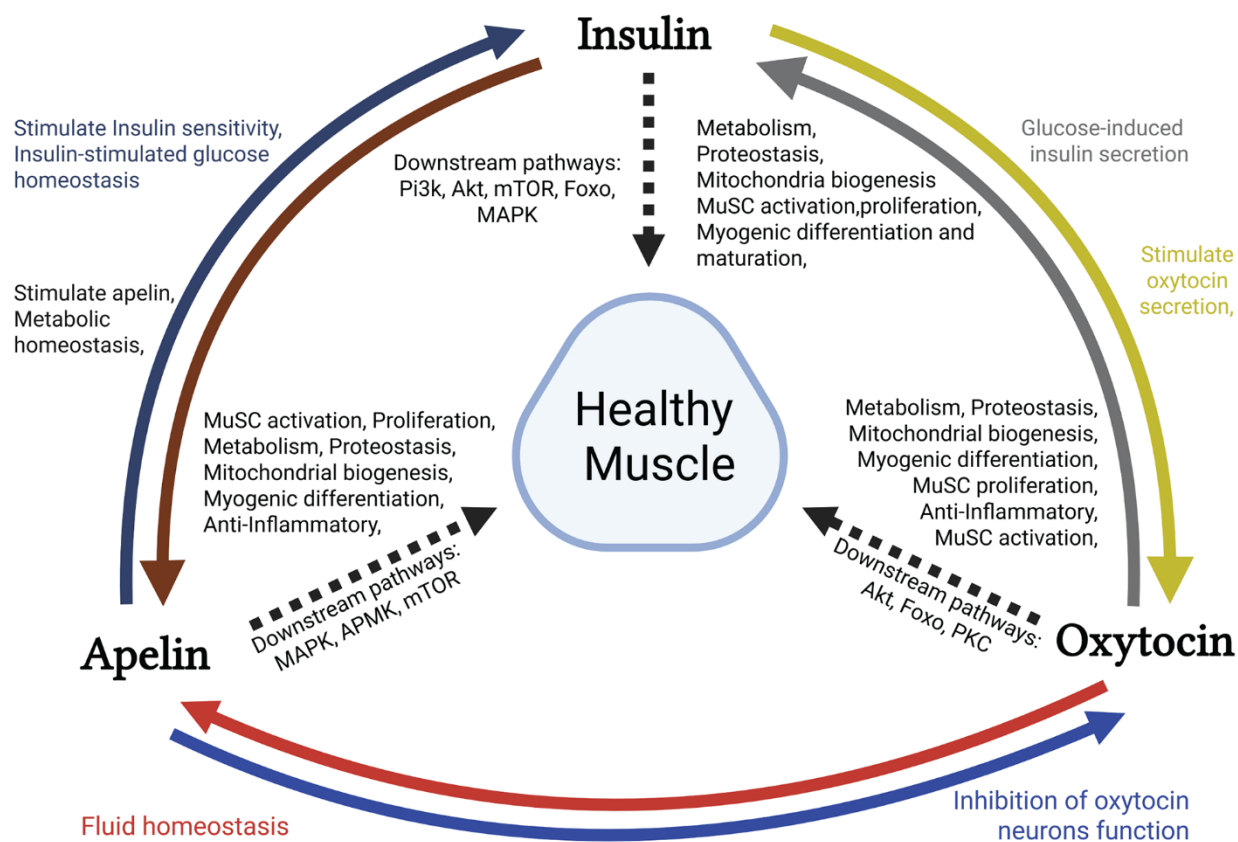


Figure 1. The apelin-insulin-oxytocin axis: a multi-hormonal network for muscle health. Schematic representation of the coordinated effects of insulin, oxytocin, and apelin on muscle health and systemic homeostasis. The colored arrows illustrate how these hormones are influenced by one another. Dashed black arrows denote downstream signaling pathways and indicate pathway-mediated effects on healthy muscle tissue. Key downstream pathways include MAPK/AMPK/mTOR (apelin), PI3K/AKT/mTOR/Foxo/MAPK (insulin), and Akt/Foxo/PKC (oxytocin). All three hormones promote muscle satellite cell (MuSC) activation, proliferation, metabolism, proteostasis, mitochondrial biogenesis, and myogenic differentiation, ultimately contributing to overall metabolic homeostasis. The diagram illustrates the synergistic and overlapping mechanisms by which these hormones maintain healthy muscle tissue and anabolic-catabolic balance.

physiological states [154]. During water deprivation, apelin and vasopressin are reciprocally regulated in a coordinated negative feedback loop to conserve fluid. Vasopressin rises and promotes renal water retention, directly counteracting the dehydration stimulus. Simultaneously, apelin falls in the plasma and accumulates within the hypothalamic neurons rather than being released [151, 155, 156]. The withdrawal of apelin removes its inhibitory brake on vasopressin neurons, allowing them to fire in optimized phasic bursts and sustain maximal vasopressin release [155]. The two peptides thus act in concert: rising vasopressin retains water at the kidney, while falling apelin amplifies that response, and together constitutes the negative feedback that resists further fluid loss [155, 156].

The sexual dimorphism of apelin, insulin, and oxytocin

The apelin/sex hormone axis

Apelin and its receptor (APLNR) are expressed throughout the hypothalamic-pituitary-gonadal axis, where apelin directly modulates sex-hormone secretion (estrogen, progesterone, testosterone) (Figure 2) while inhibiting gonadotropin (LH, FSH) release at the pituitary and hypothalamic levels [157, 158].

In females, estrogen upregulates apelin and APLNR expression in reproductive tissues while progesterone downregulates them [157, 159, 160]. In ovarian cancer cells, APLNR and estrogen receptor- α (ER α) engage in

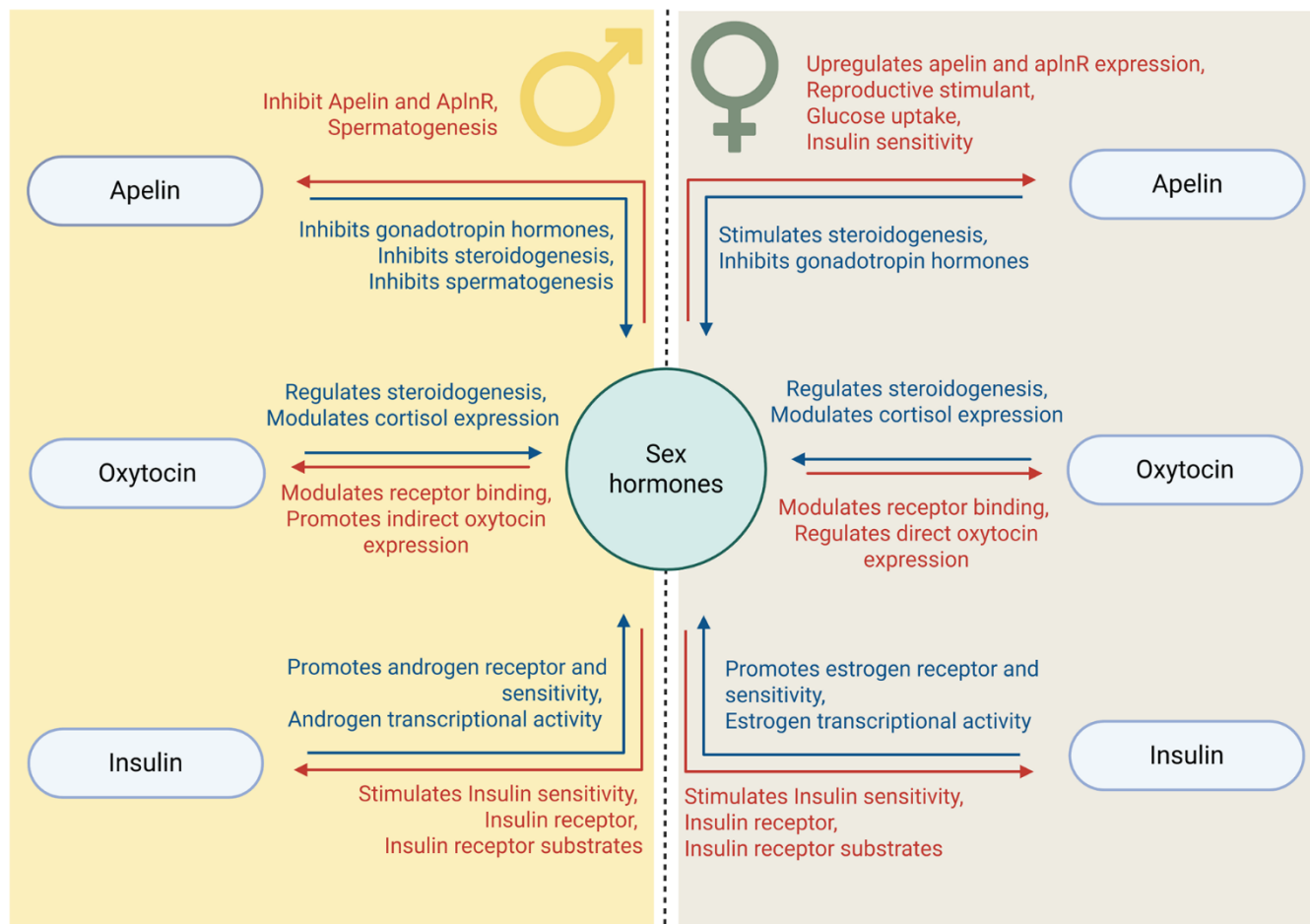


Figure 2. Crosstalk between apelin, oxytocin, or insulin and sex-hormone pathways: a sex-dimorphic perspective. Schematic illustration of the sex-specific bidirectional interactions between metabolic hormones (apelin, insulin, and oxytocin) and sex hormones. The central horizontal dashed line separates the male (left) and female (right) regulatory patterns. Blue text indicates effects on sex-hormone production and signaling, while red text shows the reciprocal effects of sex hormones on metabolic-hormone expression and function. Bidirectional arrows represent mutual regulatory relationships, demonstrating that metabolic hormones influence sex-hormone synthesis and receptor activity, and sex hormones modulate the expression and sensitivity of metabolic-hormone systems.

direct crosstalk [161, 162]. The levels of circulating apelin are higher during women's reproductive years, with menstrual cycle variations [163, 164]. In ovarian tissues, apelin stimulates estradiol and progesterone production through the MAPK/ERK, PI3K/Akt, and AMPK signaling pathways, enhancing follicular development, promoting cell proliferation, and amplifying IGF-1 and FSH effects on steroid synthesis [20, 165, 166]. Concurrent postmenopausal declines in estrogen and apelin contribute to muscle loss [167, 168], coinciding with decreased muscle-glucose uptake and mitochondrial dysfunction [169, 170].

In males, the apelin-APLNR system tends to suppress testosterone production rather than be stimulated by it [171]. Apelin and APLNR are expressed in testicular Leydig cells and seminiferous tubules [172]. In diabetic mice, elevated apelin and APLNR are associated with reduced testosterone production and impaired spermatogenesis [172]. In diabetic mice and human testicular tissue, central apelin-13 administration suppresses LH and testosterone levels while reducing Leydig cell numbers, whereas blocking the apelin receptor (with ML221 antagonist) restores testosterone production and improves spermatogenesis [172–174].

The insulin/sex hormone axis

Insulin and sex hormones engage in complex bidirectional regulation that shapes metabolic homeostasis (Figure 2). For example, estrogen enhances insulin sensitivity by upregulating insulin-receptor expression, GLUT4, and insulin receptor substrate (IRS) signaling while reducing inflammatory cytokines (TNF- α , IL-6) [175–177]. Estrogen receptor- α (ER α) activation promotes mitochondrial biogenesis and oxidative metabolism, collectively protecting insulin signaling [178, 179].

Testosterone similarly enhance insulin sensitivity through insulin-receptor expression, IRS/PI3K/Akt phosphorylation, GLUT4 upregulation, and improved mitochondrial function and muscle-fiber composition [180–182]. Testosterone also directly activates the Akt, ERK, and mTOR pathways [183, 184], although these effects differ by muscle-fiber type, metabolic state, and hormonal context [182, 185, 186].

In the reverse direction, insulin-activated pathways (PI3k, Akt, MAPK/ERK) promote ER α phosphorylation [187, 188] can activate ER α in a ligand-independent manner [188, 189]. Insulin also increases androgen receptor (AR) expression, sensitivity, and transcriptional activity. Chronic hyperinsulinemia amplifies AR signaling, while insulin deficiency impairs androgen action [190, 191].

Additionally, insulin modulates local sex-hormone bioavailability by regulating steroidogenic enzymes (CYP19A1, 5 α -reductase) and suppressing synthesis of hepatic SHBG (sex hormone binding globulin) via hepatic nuclear factor 4 α (HNF-4 α) inhibition [192, 193], such that hyperinsulinemia increases the bioavailable concentrations of both androgens and estrogens.

Compared to men, women generally maintain superior skeletal-muscle insulin sensitivity throughout most of the lifespan, attributable to estrogen's multifaceted protective effects [194–196]. Following menopause, however, rapid estrogen decline leads to accelerated muscle-insulin resistance development over 2-5 years [197, 198] with decreased muscle-glucose uptake, impaired insulin-stimulated protein synthesis, increased intramuscular lipid accumulation, and heightened inflammatory-mediated insulin resistance [197–199], creating a pathological cascade whereby insulin resistance and muscle loss reinforce one another [200–203].

The trajectory of testosterone in men is fundamentally different from the estrogen trajectory in women [204–206]. Testosterone decline occurs gradually, which contributes to a slower development of muscle-insulin resistance [184, 207, 208] and allows for compensatory mechanisms and metabolic adaptation that together may partially impede rapid muscle deterioration [208]. Men's greater baseline muscle mass provides a glucose disposal capacity that is greater than that in women and that may mask early metabolic consequences, potentially delaying clinical sarcopenia recognition [209–212].

The oxytocin/sex hormone axis

Age-related decline in circulating oxytocin and muscle OXTR expression in women and men is implicated in sarcopenia pathogenesis, with sex hormones fundamentally shaping these declines [77, 213, 214].

Oxytocin and sex hormones form a bidirectional regulatory network influencing reproductive function and muscle homeostasis (Figure 2). Estrogen directly upregulates OXTR gene expression through estrogen-response elements in the OXTR promoter and enhances hypothalamic oxytocin synthesis [152, 215, 216]; consequently, women maintain higher levels of circulating oxytocin throughout the lifespan compared to men, with concentrations peaking during ovulation [217, 218].

Testosterone's effects are mediated largely through aromatization to estradiol rather than through direct

androgenic action [219, 220]. Estrogen treatment fully restores oxytocin responsiveness in male reproductive tissues, while testosterone alone is ineffective, demonstrating that androgens regulate oxytocin-receptor expression only after conversion to estrogen [221–223].

Progesterone inhibits OXTR binding and downstream signaling, providing cycle-dependent modulation that is particularly important in maintaining uterine quiescence during pregnancy [224, 225]. Oxytocin reciprocally influences sex hormones through direct modulation of gonadal steroidogenesis (stimulating testosterone and DHT in Leydig cells and progesterone in granulosa cells), and through indirect suppression of the cortisol-driven HPA axis [226, 227]. Oxytocin inhibits pituitary ACTH secretion and adrenal cortisol responsiveness [228, 229], thereby reducing the cortisol-mediated antagonism of sex-hormone action, gonadal steroidogenesis suppression, and muscle-protein degradation, all of which contributes to sarcopenia.

In muscle, oxytocin-estrogen interactions support anti-inflammatory cytokines [230], growth-factor activation [231], satellite-cell activation and proliferation [232], muscle repair, and protein synthesis through AKT/FoxO1 and PKC pathway activation [11, 233], with estrogen amplifying both oxytocin production and muscle responsiveness [223]. This creates a positive feedback with estrogen stimulating OXT and its receptor while oxytocin contributes to muscle maintenance and regeneration [77]. The menopausal transition sharply disrupts this positive feedback loop: estrogen decline reduces OXTR expression and sensitivity, impairs regenerative capacity, compromises satellite-cell function [11, 232, 234], and prolongs post-exercise inflammatory responses [235–238], deficits that are partially restored by oxytocin administration in preclinical models [239].

Compared to women, men show lower baseline oxytocin levels and more gradual changes in muscle function with age [238, 240, 241]. For example, in contrast to women, men maintain the capacity for explosive muscle contraction throughout much of aging, which may be the result of a testosterone-OXTR interactions [241–243], i.e., testosterone modulates OXTR expression preferentially in type II (fast-twitch) fibers, altering muscle-fiber-type composition and myonuclear organization [139, 242–244]. When testosterone levels fall below critical thresholds, as in clinical hypogonadism, the oxytocin system's muscle-protective functions become significantly compromised, potentially accelerating sarcopenia [71, 245, 246].

This fundamental dimorphism has direct consequences for therapy. Treatment efficacy in sarcopenia differs significantly between sexes [183]. For example, ACE inhibitors and statins show stronger cardiovascular benefits in men, while calcium-channel blockers are more effective in women and statins carry greater muscle-related adverse effects in women at equivalent doses [247, 248]. In addition, resistance-training protocols optimized for male physiology may yield suboptimal results in postmenopausal women, who require different loading parameters and recovery periods due to altered collagen synthesis [64, 249]. Further, testosterone replacement dramatically improves muscle mass and strength in hypogonadal men [250], while similar androgen interventions in women may cause virilization without proportional muscle benefit [251]; conversely, selective estrogen-receptor modulators show promise for muscle quality in postmenopausal women but lack equivalent efficacy in aging men [170, 252]. This variability, often attributed to genetic differences or compliance, may more accurately reflect a failure to account for the sex-specific mechanisms underlying muscle aging and regeneration.

Apelin, insulin, and oxytocin in muscle pathophysiology

Apelin

Under physiological conditions, apelin supports the perivascular stem-cell niche, enhancing satellite-cell function and muscle regeneration, and promotes mitochondrial function, metabolism, and adaptive responses to exercise stress [124, 253]. It stimulates muscle stem cells (MuSCs) to enhance endogenous repair in muscular dystrophy and sarcopenia models, promotes proteostasis through autophagy induction, and is essential for metabolic adaptation during high-intensity exercise [124, 254, 255]. In parallel, apelin-APLNR signaling independently enhances muscle glucose utilization and systemic insulin sensitivity via endothelial pathways [26]. In skeletal muscle, apelin also promotes mitochondrial biogenesis by increasing mitochondrial-protein expression, which in turn enhances respiratory-chain activity, ATP production, and coupling efficiency [124, 256]. At the same time, by inhibiting NF- κ B-linked inflammatory pathways and oxidative stress, apelin supports a more anti-inflammatory, metabolically efficient muscle phenotype [257].

Under pathological conditions, deficiency of either apelin or APLNR causes dramatic age-related muscle-function alteration (Figure 3), including a shift toward smaller slow-twitch type fibers and defective IGF-1

signaling [253]. Mice deficient in apelin or APLNR present dramatic muscle-function alterations with age, while apelin restoration triggers mitochondriogenesis, autophagy, anti-inflammatory pathways in myofibers, and regenerative capacity in MuSCs [124]. Apelin associated with serine protease HtrA1 is useful for sarcopenia diagnosis, particularly in men [258]. Chronic inflammatory conditions and cancer-associated cachexia show suppressed apelin expression, potentially accelerating muscle wasting [259].

Insulin

Age-related decline in muscle-insulin sensitivity is a critical factor in sarcopenia development, as impaired insulin signaling directly compromises glucose utilization and protein anabolism [260–262]. Insulin maintains muscle mass by suppressing protein degradation via FoxO inhibition, and enhancing protein synthesis when amino acids are available [262, 263];

notably, insulin-receptor signaling is more critical than IGF-1 signaling for muscle proteostasis, as combined receptor deletion in mice cause severe wasting [263]. Diabetic individuals show impaired insulin-stimulated muscle-protein synthesis even with sufficient amino acids [262]. Insulin infusion enhances mitochondrial biogenesis, mitochondrial protein synthesis, and ATP production in skeletal muscle, these benefits are recapitulated physiologically by normal post-meal insulin levels [264]; insulin deprivation leads to mitochondrial dysfunction, while insulin treatment restores mitochondrial content and function [264]. Insulin exhibits complex inflammatory effects, suppressing certain inflammatory pathways in healthy tissue through immune-signaling modulation. These anti-inflammatory effects of insulin are lost in diabetes or obesity, where chronic inflammation impairs insulin signaling, which further reduces insulin's ability to suppress inflammation and worsen insulin resistance, establishing a harmful cycle [260–262].

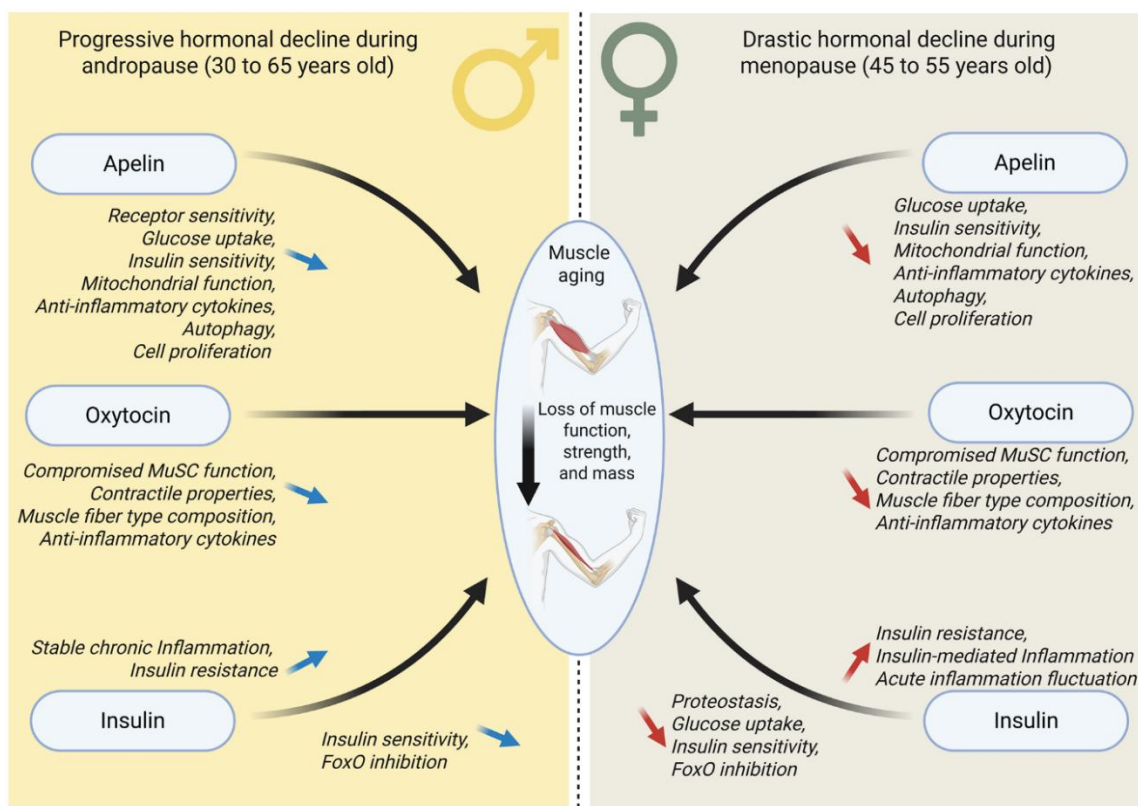


Figure 3. Sexual dimorphism in age-related hormonal changes and muscle aging. Sex-specific effects of age-related hormonal decline on muscle aging. The diagram contrasts the progressive hormonal decline during male andropause (30-65 years of age, left) with the rapid hormonal decline during female menopause (45-55 years of age, right). Black arrows indicate the declining hormone levels converging on muscle aging, and consequent loss of muscle function, strength, and mass. Blue arrows indicate progressive decline in hormone levels and their effects, while red arrows indicate rapid decline. Black italic text describes the compromised beneficial effects of each hormone in males (progressive loss), and the compromised effects in females (rapid loss). Both sexes experience reduced apelin, insulin, and signaling, leading to impaired muscle satellite cell (MuSC) function, altered muscle-fiber composition, decreased mitochondrial function, and increased inflammation, although the timeline and rate of decline differ between males and females.

Aging-associated insulin resistance compromises the metabolic environment necessary for muscle maintenance and impairs contraction. At pathophysiologically high concentrations, estradiol binds directly to insulin and insulin receptors, potentially contributing to insulin resistance in hyperestrogenemic conditions (Figure 3).

Oxytocin

Oxytocin activates Ca²⁺-CaMKK-AMPK signaling and glucose uptake in C2C12 mouse myoblast culture [137], and promotes myogenic differentiation and myoblast fusion while stimulating satellite-cell activation and proliferation in both mice and humans [11, 77]. Systemic oxytocin administration restores muscle regenerative capacity in aged mice [77].

Oxytocin simultaneously blocks catabolic programs through OXTR-mediated suppression of lysosomal, proteasomal, and autophagy pathways (reducing MuRF1, atrogin1, and LC3 expression) while activating anabolic processes that increase protein synthesis and muscle mass *in vivo* [136, 138]. The premature sarcopenia observed in oxytocin-knockout mice, combined with evidence that oxytocin restores muscle mass and protein synthesis in cachexia models and increases lean mass in humans, suggests that this loss reflects the combined failure of both proteolysis suppression and anabolic support, rather than either mechanism alone [77].

Oxytocin also promotes mitochondrial biogenesis and function, increasing NRF1 and TFAM expression, improving oxidative capacity, and reducing oxidative stress and ROS production [265, 266]. In addition, oxytocin robustly reduces inflammation by down-regulating pro-inflammatory cytokines (IL-6, TNF α , IL-1 β), inhibiting NF- κ B signaling, and attenuating immune-cell activation in muscle and macrophages [267] (Figure 3).

Inflammatory and catabolic environments in cancer cachexia, inflammatory myopathies, and diabetes-related muscle loss likely impair oxytocin signaling, with women showing greater susceptibility to inflammation suppression of OXTR function and more severe associated muscle loss compared to men [268].

Modes and models of aging

Modes of aging

Mechanistically, aging represents a complex interplay between programmed processes and stochastic damage accumulation [269]. Programmed processes include

genetically encoded limits such as telomere attrition (each cell division erodes chromosome caps until triggering growth arrest or apoptosis) and hormonal decline (growth hormone, sex steroids, and peptide hormones follow predetermined timelines) [269, 270]. Simultaneously, stochastic damage accumulates through reactive oxygen species, DNA lesions, protein misfolding, and lipid peroxidation, modulated by environmental factors such as sedentary lifestyles [271, 272].

Sarcopenia exemplifies this interplay. While genetic factors account for only 25% of overall lifespan, they account for 30-85% of muscle-strength variation among individuals and 50-80% of lean mass [273]. Eight-year follow-up of active older adults showed declines in muscle strength (10.2%), muscle mass (5.4%), and gait speed (28.6%), yet these individuals far outperformed sedentary controls [274], demonstrating that inactivity accelerates muscle-strength decline and that programmed aging continues despite optimal lifestyle.

The following primary hallmarks of aging initiate muscle damage: genomic instability, epigenetic alterations, and proteostatic collapse [275]. Antagonistic hallmarks, including satellite cell dysfunction, mitochondrial failure, and cellular senescence, represent processes that are initially protective but become harmful with age, accumulating SASP-secreting cells and impairing regenerative capacity [275]. These two categories of responses converge on integrative phenotypes: stem-cell exhaustion, chronic inflammation promoting protein breakdown, and NMJ damage causing denervation that collectively drive the functional decline characteristic of sarcopenia [87, 276].

Models of aging

A spectrum of model systems, from invertebrates to clinical cohorts, has been deployed to dissect the mechanisms of sarcopenia, each offering distinct trade-offs between experimental tractability and physiological relevance [277].

Invertebrate models, *C. elegans* (*Caenorhabditis elegans*) and *Drosophila* (*Drosophila melanogaster*), provide genetic tractability and short lifespans [277] and have been instrumental in identifying conserved aging pathways such as insulin/IGF-1, TOR, sirtuins, and FOXO [278, 279]. However, these organisms lack vertebrate-specific features such as adaptive immunity and complex endocrine regulation. On the other hand, both organisms are largely post-mitotic in muscle tissue, enabling study of contractile-apparatus maintenance in isolation from the confounding effects of regeneration present in vertebrate models [280–282].

Non-mammalian vertebrates combine the advantages of invertebrate and vertebrate models. Zebrafish (*Danio rerio*) recapitulate histological and molecular hallmarks of human muscle aging including satellite cells and anatomically distinct fiber types; zebrafish and humans have a high level of genetic orthology; and a broad range of tractable transgenic tools are available for zebrafish, allowing rapid mechanistic dissection [87, 277, 283]. The African turquoise killifish (*Nothobranchius furzeri*, ATK), the shortest-lived captive vertebrate (4–6 months) [284, 285], compresses the full aging trajectory into an experimentally accessible window. Notably, research using ATK has revealed sexual dimorphism in the response to dietary restriction [286–289], with females deriving greater lifespan and muscle-aging benefit than males.

Rodent models remain the preclinical standard because of their close physiological and metabolic similarity to humans [10, 290]. Mice and rats have proven to be valuable for sarcopenia research. Natural aging studies in these organisms (18–24 months in mice; 24–30 months in rats) consistently show sex-dimorphic sarcopenia progression, often earlier and more severe in males, with this difference attributable to hormonal, metabolic, and inflammatory differences between females and males [10, 291]. The availability of genetically modified mouse strains, including an accelerated aging mouse model (SAMP8) [292] and muscle-specific knockout mice (Klotho) [293], enables mechanistic dissection of pathways implicated in muscle wasting. Of all the widely used animal models, the mouse is the closest to human physiologically, and with its extensively characterized muscle biology, it is an essential model for validating therapeutic candidates in a mammalian context before transitioning to clinical trials [294].

Human-derived models, which include primary myoblast cultures from aged donors [94, 295], 3D myobundles engineered from induced pluripotent stem cells (iPSCs) [296, 297], and patient-derived iPSC lines [298], bridge preclinical findings and clinical application [299]. Cultures of satellite cells and myoblasts from young and old donors have demonstrated that intrinsic cellular aging (reduced proliferative capacity, increased senescence) and extrinsic niche factors both contribute to muscle decline [299–301], and that female- and male-derived myoblasts differ in responses to oxidative stress and hormonal signals [302]. A limitation of human-derived *in vitro* models is that standard culture conditions do not faithfully reflect the aged muscle environment, as they strip away systemic factors: such as circulating inflammatory mediators, hormonal decline, and neuromuscular interactions, that drive aging *in vivo* [303,

304]. This becomes apparent when myogenic precursor cells from young and old donors are cultured under optimal conditions, as they display similar proliferative and differentiation profiles, suggesting that the age-related dysfunction observed *in vivo* is largely context-dependent rather than intrinsic to the cells themselves [295, 305]. However, *in vitro* models can better approximate aged muscle when deliberately modified, for example through prolonged culture or exposure to senescence-inducing factors, which introduces age-associated cellular changes and makes these systems more suitable for mechanistic studies and therapeutic screening [306].

Clinical trials remain the ultimate validation platform, yet fewer than 30% of sarcopenia clinical intervention report sex-disaggregated outcomes, a critical gap given the fundamentally dimorphic nature of the condition. Hormone-targeted therapies (e.g., apelin-receptor agonists) have faced translational setbacks due to on-target off-tissue effects [307–310], and because hormonal profiles differ fundamentally between men and women, tissue-selective or biased agonist approaches may be essential to achieving sex-appropriate therapeutic outcomes. Next-generation biased agonists such as WN561 show promise by selectively activating the G-protein pathway of APLNR while eliminating β -arrestin signaling thereby preserving cardioprotective benefits with a reduced off-target side effect profile, pending further clinical validation [311].

Optimal intervention timing and modality differ by sex: in women, initiating resistance and aerobic training with optimized protein intake during the perimenopausal transition appears most effective, while men benefit from sustained protocols that address gradual insulin resistance in the context of declining androgens. Current research increasingly focuses on individualized, multimodal combination therapies tailored to sex-specific hormonal regulation. The demonstrated ability of individuals to recover from sarcopenic states with appropriate interventions offers hope for maintaining functional independence and quality of life in aging populations.

The availability of multiple models for the study of muscle aging establishes a powerful translational pipeline: discover fundamental mechanisms in invertebrates → validate in a vertebrate with a short lifespan (African turquoise killifish) and a versatile regenerative model (zebrafish) → translate to mammalian physiology (rodents) → ensure translational fidelity in human-derived systems → validate in clinical trials (Figure 4). Each model is valuable for investigating sexual dimorphism in neuromuscular

aging and identifying sex-specific hormonal alterations that drive accelerated muscle degeneration, together advancing progress towards targeted interventions for sarcopenia that will be effective in both sexes. Together, these models form a complementary testing platform where cross-species-validated findings are far more likely to translate successfully to human interventions than use of a single model organism.

CONCLUSION

The apelin, insulin, and oxytocin systems exemplify how hormonal regulation of muscle metabolism, energy homeostasis, and glucose disposal operates through interconnected, sex-specific mechanisms that undergo dramatic transformation with aging. In women, estrogen acts as a central orchestrator, simultaneously enhancing apelin signaling, maintaining insulin sensitivity, and amplifying oxytocin responsiveness to preserve muscle mass throughout reproductive years. Estrogen increases expression of apelin and its receptor, enhances receptor sensitivity, and supports integrated metabolic control. The abrupt withdrawal of estrogen at menopause triggers coordinated deterioration across all three systems, producing rapid, synchronized collapse in muscle homeostasis with declining apelin levels, accelerated insulin resistance, and compromised oxytocin signaling. This cascading dysfunction contributes to the characteristic pattern of rapid muscle loss in postmenopausal women. Men experience a

fundamentally different trajectory, where gradual testosterone decline produces slower, more variable changes in these regulatory networks. Testosterone supports apelin signaling while modulating receptor sensitivity, maintains muscle insulin sensitivity through effects on fiber composition and mitochondrial function, and influences oxytocin-receptor expression in a fiber-type-specific manner. The slow testosterone decline creates a trajectory of hormonal-network dysfunction different from that in women, paralleling the more gradual sarcopenia progression in aging men. With women showing greater susceptibility to inflammation-mediated disruption but also greater responsiveness to anti-inflammatory interventions, these sex-specific responses to inflammatory stress highlight the necessity of tailoring therapeutic approaches based on biological sex and hormonal status.

Each peptide hormone in the apelin-insulin-oxytocin triad demonstrates bidirectional regulatory relationships with the others, creating a sophisticated feedback system where disruption at any node throughout the cascades network can compromise muscle homeostasis and metabolic function. Apelin and oxytocin converge on shared signaling mechanisms (AMPK activation, GLUT4 translocation, and mitochondrial biogenesis), suggesting coordinated rather than redundant actions in maintaining insulin sensitivity and muscle metabolic health. Hypothalamic co-localization of apelin and oxytocin neurons enables rapid coordination of

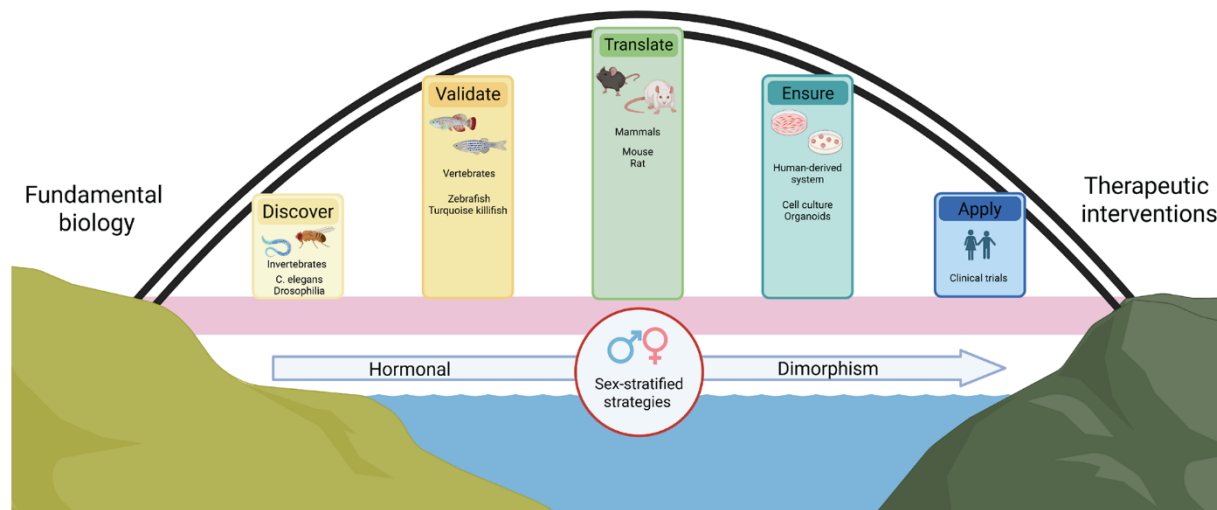


Figure 4. Bridging models from fundamental biology to sex-stratified therapeutic interventions. Schematic representation of the translational-research pipeline for developing sex-stratified therapeutic interventions. The arch illustrates the bridging progression from fundamental biology (left) to therapeutic interventions (right), encompassing five key stages: Discover (invertebrate models: *C. elegans*, *Drosophila*), Validate (vertebrate models: zebrafish, African turquoise killifish), Translate to preclinical (mammalian models: mouse, rat), Ensure (human-derived systems: cell culture, organoids), and Apply (clinical trials in humans). The foundational layers emphasize the importance of considering hormonal sexual dimorphism throughout all stages of research, converging in sex-stratified therapeutic strategies that account for biological differences between males and females.

peripheral metabolic responses to feeding, fasting, and energy demands. Insulin serves as both regulator and regulated target, modulating apelin expression in adipose tissue while activating central oxytocin release, which subsequently feeds back to enhance peripheral insulin sensitivity. In aging muscle, deterioration of this hormonal network (through reduced peptide production, diminished receptor sensitivity, or impaired central-peripheral communication) contributes to the characteristic metabolic dysfunction and insulin resistance that accelerate sarcopenia progression. The synergistic actions of apelin and oxytocin on mitochondrial function suggest therapeutic potential in targeting multiple nodes simultaneously.

The convergence of apelin, insulin, and oxytocin on AMPK represents an important metabolic integration where multiple hormonal signals are transduced into coordinated cellular responses governing energy homeostasis, protein turnover, and mitochondrial function. Each hormone contributes to distinct yet complementary mechanisms: apelin uniquely supports the perivascular stem-cell niche and exercise adaptation, insulin serves as the primary regulator of protein synthesis and degradation balance, while oxytocin provides dual action that simultaneously suppresses catabolic programs and activates anabolic pathways. The profound sexual dimorphism in these systems (estrogen amplifying all three pathways in women and testosterone modulating them more gradually in men) explains why sarcopenia manifests as abrupt postmenopausal acceleration in women versus slower, progressive decline in aging men. Pathological disruption of the hormonal network, impairing satellite-cell function, compromising mitochondrial biogenesis, and exacerbating inflammation, accelerates muscle wasting. The shared effects on mitochondrial biogenesis, oxidative capacity, and anti-inflammatory signaling suggest potential synergistic therapeutic strategies targeting multiple nodes simultaneously rather than single-hormone replacement.

Understanding sarcopenia's complex, sexually dimorphic nature requires strategic integration of complementary experimental systems. Invertebrate models provide unparalleled genetic tractability for discovering conserved molecular pathways, but their lack of satellite cells limits their regenerative capacities. Zebrafish and African turquoise killifish bridge the evolutionary gap, offering vertebrate-specific features such as satellite cells and complex neuroendocrine systems within experimentally tractable timeframes while permitting the study of extensive regenerative processes. Rodent models

remain indispensable for validating biological mechanisms in mammalian physiology and testing therapeutic interventions in systems that closely recapitulate human hormonal networks. All three model organisms reveal sexual dimorphism mirroring the difference in human sarcopenia development. Human-derived models, from primary myoblast cultures to three-dimensional organoids, provide essential translational validation, demonstrating that while intrinsic cellular aging contributes to muscle decline, the aged extracellular microenvironment and systemic factors play an equally significant role. Finally, clinical trials represent the ultimate validation platform to treat sarcopenia. Cross-species validation through this translational pipeline substantially increases the probability of successful clinical translation, filtering out species-specific artifacts while identifying conserved, therapeutically actionable mechanisms. The failure of single-target hormone therapies underscores the multifactorial complexity of sarcopenia. The gender differences observed in sarcopenia onset, trajectory, severity, and response to intervention demonstrate the sexually dimorphic nature of the disease and the need for multimodal interventions that account for the biology of both females and males.

This review aims to inspire scientific community in its efforts to develop effective next-generation anti-sarcopenia therapeutics by highlighting the central role of hormonal network dysregulation in disease progression. By mapping the sex-specific patterns of apelin, insulin, and oxytocin disruption, we hope to help lay the foundation for the design of interventions tailored to biological sex and hormonal status. Targeting age-related hormonal imbalances early, for example, during "possible sarcopenia," may offer an opportunity to intercept sarcopenia at its nascent stage, before muscle loss is established, shifting the therapeutic paradigm from treatment to prevention. It is now essential to collect and integrate data on age-related changes in apelin, insulin, and oxytocin, and the networks with which they interact, to enable design of therapies that are effective for both women and men with sarcopenia or at risk of developing it.

AUTHOR CONTRIBUTIONS

Conceptualization: Romain Menard, Romain Madelaine; Literature analysis: Romain Menard; Writing original draft: Romain Menard; Writing, Review and Editing: Romain Menard, Romain Madelaine; Funding acquisition: Romain Madelaine; Supervision: Romain Madelaine; All authors have read and agreed to the published version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL STATEMENT AND CONSENT

This review article synthesizes previously published research and does not involve primary data collection, human subjects, or animal experiments. All studies cited in this review obtained the necessary ethical approvals as reported in their original publications.

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