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REVIEW

Estrogen in skeletal muscle: metabolism, mechanisms, and exercise-induced changes

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Abstract

With the intensification of population aging, issues such as age-related skeletal muscle loss and metabolic disorders have garnered increasing attention. As the menopausal transition progresses, circulating estrogen levels decline, making locally synthesized estrogen in peripheral tissues particularly important. In addition to the ovaries, steroidogenic enzymes are present in skeletal muscle, enabling the local synthesis of myogenic estrogen. Myogenic estrogen can regulate muscle function and metabolism in an autocrine or paracrine manner within skeletal muscle tissue. Exercise, as a safe and effective non-pharmacological intervention, has been shown to regulate estrogen levels in skeletal muscle. Exercise may promote the synthesis of myogenic estrogen by enhancing the expression of estrogen precursor substances and steroidogenic enzymes in skeletal muscle, thereby improving skeletal muscle function and metabolism. This review summarizes the structure and function of estrogen receptors in skeletal muscle, the synthesis and metabolism of myogenic estrogen, the roles and mechanisms of estrogen in skeletal muscle, and the mechanisms underlying the influence of exercise on estrogen synthesis in skeletal muscle.

Article Highlights

- Skeletal muscles have the endocrine function of autonomously synthesizing myogenic estrogen.
- Myogenic estrogen can regulate muscle function and metabolism in an autocrine or paracrine manner within skeletal muscle tissue.
- Exercise may increase myogenic estrogen levels by enhancing estrogen precursor substrates and steroidogenic enzymes.
- Myogenic estrogen may mediate the benefits of exercise on muscle mass, function, metabolism, and injury repair.
- Targeted myogenic estrogen may provide intervention strategies for muscle atrophy in postmenopausal females.

Keywords Estrogen · Skeletal muscle · Exercise · Aromatase · Postmenopausal females

Introduction

With the extension of life expectancy, the global population of elderly females aged 65 and above continues to increase. Females are expected to spend more than one-third of their lives in the postmenopausal stage [1]. Due to ovarian function decline, postmenopausal females experience a significant reduction in circulating estrogen levels, entering a state of long-term estrogen deficiency [2].

It is well-established that estrogen plays a crucial role in human physiology, including the regulation of glucose and lipid metabolism, bone metabolism, reproductive function, and neural function [3, 4]. Postmenopausal females, due to aging and a lack of circulating estrogen, are more susceptible to chronic diseases, such as metabolic disorders [5], neurodegenerative diseases [6], sarcopenia [2], and osteoporosis [7]. These diseases have a significant impact on the health and quality of life of postmenopausal females [8].

Skeletal muscle is an important organ in the human body responsible for movement, metabolism, and secretion, accounting for approximately 40–50% of total body mass. It is crucial in controlling motor posture, protecting internal

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organs, and maintaining metabolic homeostasis [9]. Skeletal muscle is not only a target organ for estrogen but also a peripheral organ that synthesizes estrogen. Studies have revealed that skeletal muscle contains estrogen-metabolizing enzymes (such as aromatase) and can synthesize myogenic estrogen. Myogenic estrogen can act as an autocrine or paracrine factor in local tissues, exerting significant physiological effects [10, 11].

It is well-established that exercise benefits overall health. Research indicates that exercise training exerts beneficial effects on skeletal muscle health and estrogen levels in both menopausal females and ovariectomized rodent models [2]. Exercise may act as a "mimic" of estrogen [12], protecting skeletal muscle mass and function, and improving metabolic status. This review systematically searched PubMed, Google Scholar, Web of Science, and other databases using keywords such as "exercise," "estrogen," "ovariectomy," "skeletal muscle," "mass," "strength," "muscle injury," "satellite cells," and "mitochondria." The review focuses on three main aspects: (1) estrogen metabolism in skeletal muscle; (2) the role and mechanisms of estrogen in skeletal muscle; and (3) the impact of exercise on estrogen levels in skeletal muscle.

Estrogen metabolism in skeletal muscle

Classification of estrogens

Estrogens are primarily categorized into three types: estrone (E_1), 17β-estradiol (E_2), and estriol (E_3). Among these, 17β-estradiol (E_2) exhibits the highest physiological activity and is the predominant bioactive form [13, 14]. The affinity and reaction intensity of different estrogen types with estrogen receptors vary, with E_2 demonstrating the strongest binding affinity [14].

Aromatase and estrogen synthesis pathways

Aromatase cytochrome P450 enzyme (CYP19A1) is a key member of the cytochrome P450 family. It is the rate-limiting enzyme in estrogen synthesis, catalyzing the irreversible conversion of androgens (testosterone and androstenedione) into estrogens [15]. Aromatase is encoded by the *CYP19A1* (*P450arom*) gene. The aromatase gene (*CYP19A1*) is expressed in multiple tissues, including the brain, ovaries, blood vessels, testes, adipose tissue, liver, skeletal muscle, hair follicles, bone, and pituitary gland, with the highest expression levels observed in gonadal tissues (ovaries and testes). The expression of *CYP19A1* is regulated by tissue-specific promoters [16].

Estrogen synthesis originates from cholesterol. Through a series of enzymatic reactions, cholesterol is gradually converted into steroid precursors (such as dehydroepiandrosterone, DHEA), which ultimately generate estrogens under the action of aromatase. DHEA, primarily secreted by the adrenal glands and ovaries, is the most abundant hormone in humans and other mammals and serves as an important precursor for steroid hormones [17]. DHEA is converted into androstenedione under the catalysis of 3β-hydroxysteroid dehydrogenase (3β-HSD), which is further transformed into testosterone under the catalysis of 17β-hydroxysteroid dehydrogenase (17β-HSD). Testosterone is then irreversibly converted into estradiol by aromatase. Additionally, androstenedione can be converted into estrone by aromatase, which is further transformed into the more biologically active estradiol under the action of 17β-HSD [14].

Circulating estrogen, estrogen in skeletal muscle, and myogenic estrogen

The terms circulating estrogen, estrogen in skeletal muscle, and myogenic estrogen are interrelated yet distinct (Fig. 1). By definition and origin, estrogen in skeletal muscle is contributed by both myogenic estrogen and circulating estrogen. Myogenic estrogen is the estrogen autonomously synthesized by skeletal muscle cells [18]. Studies have shown no significant correlation between estrogen levels in skeletal muscle and circulating estrogen levels [19], and both are regulated by independent mechanisms [20]. Circulating estrogen levels cannot accurately reflect and predict estrogen levels in local tissues [21].

Circulating estrogen is primarily transported bound to sex hormone-binding globulin (SHBG) with high-affinity specificity and to albumin with low-affinity non-specificity. Bound estrogen must first dissociate from its carrier proteins and convert to its free form before it can enter cells. Due to its lipophilicity, free estrogen can diffuse across cell membranes and directly enter skeletal muscle cells to exert biological effects. Only 1%−3% of estrogen in plasma exists in the free form, which is the active form capable of directly acting on target cells [22, 23].

In vitro and in vivo studies have confirmed that skeletal muscle can autonomously synthesize myogenic estrogen from precursor substances (such as DHEA) under the catalysis of steroidogenic enzymes (including 3β-HSD, 17β-HSD, and aromatase) [19, 24, 25]. Skeletal muscle is one of the main sites of estrogen synthesis in postmenopausal females [11]. The role of myogenic estrogen cannot be ignored. In this review, myogenic estrogen specifically refers to estrogen derived from skeletal muscle. Due to space limitations, estrogen derived from other muscle tissues (such as cardiac

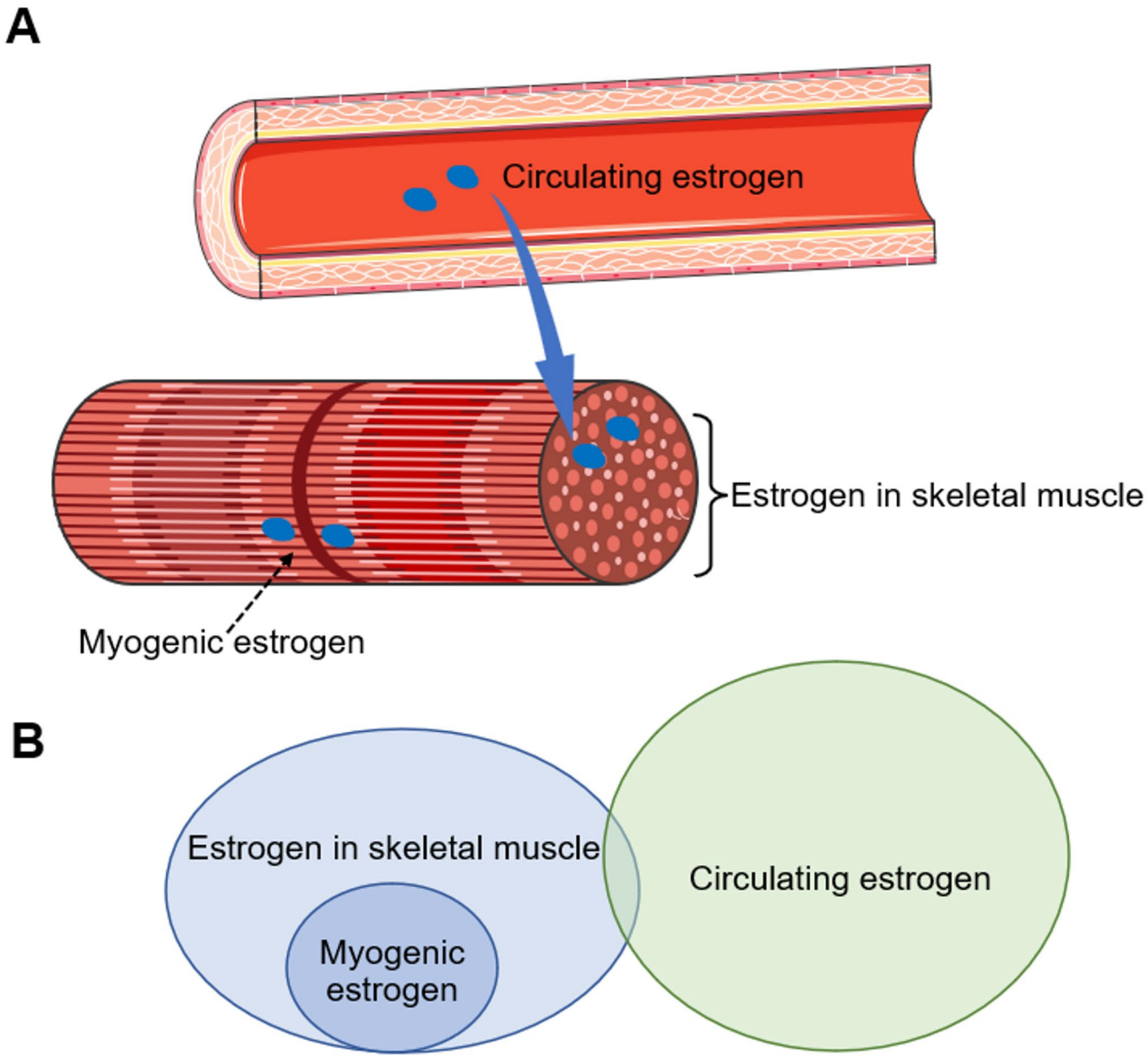

Fig. 1 Schematic diagram of the relationship between circulating estrogen, estrogen in skeletal muscle, and myogenic estrogen. (**A**) and Venn diagram (**B**) Circulating estrogen can be transported to skeletal muscle tissue via the bloodstream, becoming one of the sources of estrogen in skeletal muscle. Skeletal muscle itself can also synthesize myogenic estrogen. Myogenic estrogen is an important component of estrogen in skeletal muscle. Therefore, estrogen in skeletal muscle is contributed by both myogenic estrogen and circulating estrogen

muscle [26] and smooth muscle) is not discussed in this review.

Synthesis and catabolism of myogenic estrogen

Estrogen synthesized in extragonadal tissues (such as skeletal muscle) is chemically and functionally identical to estrogen produced by the ovaries [10, 27]. The synthetic pathway of myogenic estrogen is shown in Fig. 2. Skeletal muscle can absorb DHEA from the circulation, which is then converted to testosterone under the catalysis of 3β-HSD and 17β-HSD. Testosterone is irreversibly converted to myogenic estradiol by aromatase, which regulates the physiological functions of skeletal muscle by binding to estrogen receptors (ERs) [10, 24, 28].

Based on intracrinology, estrogen synthesized locally in peripheral tissues mainly exerts its effects at the synthesis site and is inactivated by the decomposition of steroid metabolic enzymes, avoiding entry into systemic circulation, thereby maintaining post-menopausal females' circulating estrogen at a low activity state [29]. The synthesis and decomposition of estrogen in different tissues are

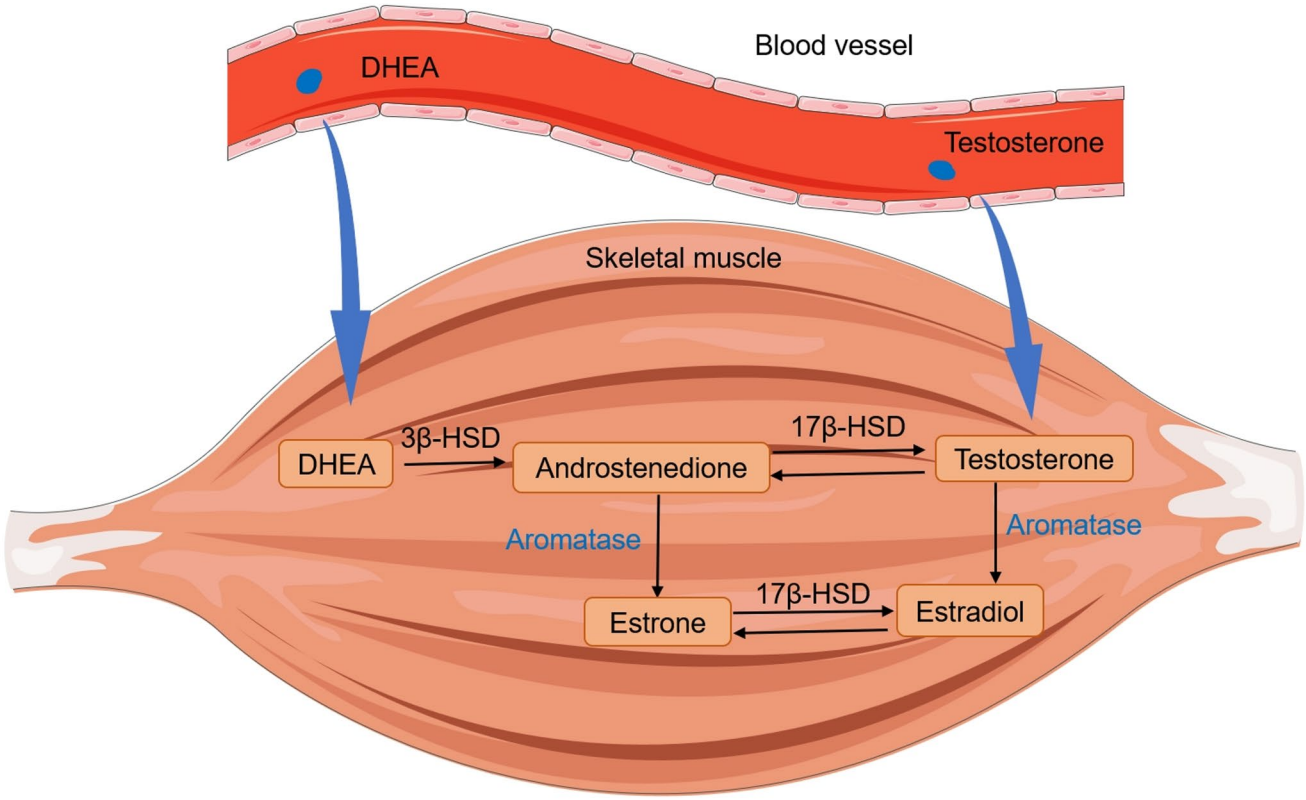

Fig. 2 Synthetic pathway of myogenic estrogen. Skeletal muscle can uptake DHEA and testosterone from the circulation. DHEA is converted to androstenedione under the catalysis of 3β-HSD. Androstenedione is then converted to estrone by aromatase and to myogenic estradiol by 17β-HSD. Additionally, androstenedione can be converted into testosterone under the catalysis of 17β-HSD, and testosterone can be transformed into myogenic estrogen under aromatase. Abbreviations: DHEA, dehydroepiandrosterone; 17β-HSD, 17β-hydroxysteroid dehydrogenase; 3β-HSD, 3β-hydroxysteroid dehydrogenase

specifically regulated by local steroid-related enzyme systems. The activity and expression levels of steroid-related enzymes are tissue-specific. Local estrogen levels are regulated by steroid-related enzymes. Each tissue synthesizes an appropriate amount of estrogen to meet local physiological needs without interfering with hormone homeostasis in other tissues [11]. Therefore, myogenic estrogen may be inactivated through decomposition and metabolism by steroid-related enzyme systems within skeletal muscle and may not enter the circulatory system.

Structure and function of estrogen receptors in skeletal muscle

Estrogen is a small lipophilic steroid hormone that can directly penetrate the cytoplasm or nucleus of target cells and bind to ERs [30]. Estrogen receptors include estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G protein-coupled estrogen receptor (GPER) [14]. ERα and ERβ are encoded by the *ESR1* and *ESR2* genes, respectively, and are members of the nuclear receptor protein family [31]. Both ERα and ERβ share the same structure, comprising a ligand-binding domain (LBD), a DNA-binding domain (DBD), and two transcriptional activation function domains (AF-1 and AF-2), with AF-2 located in the N-terminal domain. Except for the N-terminal domain (AF-2 domain), these two receptors exhibit high amino acid sequence homology [14]. GPER, initially known as GPR30 or mER, was a newly discovered membrane-bound estrogen-binding receptor in the past two or three decades. It was officially named by the International Union of Basic and Clinical Pharmacology (IUPHAR) in 2007. However, the physiological and pathological roles of GPER as a novel estrogen receptor remain largely unknown [32]. GPER is a protein encoded by the *Gper1* gene and is a seven-transmembrane G protein-coupled receptor. While GPER is mainly localized on the plasma membrane, some studies suggest that it may also be distributed in the Golgi apparatus, mitochondria, and endoplasmic reticulum [32–34].

Estrogen target tissues are widely distributed throughout the body. Estrogen receptors are present in various tissues and cell types in different quantities [35]. The distribution, expression levels, and functions of ERs vary among different tissues [36]. Both nuclear receptors (ERα and ERβ) and

membrane receptors (GPER) are expressed and localized in skeletal muscle. The relative expression abundance of the three ERs in skeletal muscle is ERα >GPER >ERβ [37, 38]. Furthermore, estrogen receptors are distributed in muscle satellite cells, myofibers (including mitochondria within myocytes), skeletal muscle cell lines, and skeletal muscle endothelial cells [10, 39].

Each estrogen receptor subtype plays an important role in skeletal muscle. Due to structural differences among estrogen receptor subtypes, the biological effects of each subtype may vary [31]. To investigate the role of estrogen receptors in skeletal muscle, researchers have employed pharmacological and genetic approaches to develop various experimental models, including ovariectomized mouse models, systemic and skeletal muscle estrogen receptor knockout animal models, and isolated skeletal muscle cell models [40].

Studies using skeletal muscle-specific ERα knockout and transgenic animal models have revealed that ERα in skeletal muscle plays a crucial role in maintaining skeletal muscle strength, insulin sensitivity, fatty acid oxidation, skeletal muscle mitochondrial function, and metabolic homeostasis, maintaining the number of muscle satellite cells, and muscle regeneration [41, 42]. Ribas et al. [43] developed skeletal muscle-specific ERα knockout mice (MERKO), which exhibited obesity, impaired systemic glucose tolerance and insulin resistance, accompanied by reduced muscle mass, accumulation of bioactive lipid intermediates in muscles, enhanced muscle inflammatory responses, impaired muscle oxidative metabolism, reduced reactive oxygen species (ROS) scavenging capacity, skeletal muscle mitochondrial dysfunction, impaired mitochondrial dynamics, and reduced mitophagy. Knockdown of *Esr1* in C2C12 myotubes reduced myotube oxygen consumption rate and increased ROS production, leading to cellular oxidative stress. Yoh et al. [44] utilized the muscle creatine kinase (Mck) gene promoter/enhancer to construct a plasmid expressing constitutively active estrogen receptor α (caERα), generating Mck-caERα transgenic (muscle-specific constitutively active ERα transgenic) mice. They found that long-term activation of muscle ERα enhanced exercise endurance in female mice. Collins et al. [45] developed female mice with muscle-specific ERα knockout (ERαKO), which showed reduced myosin regulatory light chain (RLC) phosphorylation and impaired muscle contractile force. Cabelka et al. [46] developed skeletal muscle-specific estrogen receptor α knockout (skmERαKO) mice, which exhibited increased fatigability and reduced muscle strength. This study confirmed that skeletal muscle ERα is necessary for skeletal muscle contractile function. Collins et al. [47] developed muscle satellite cells ERα knockout (scERαKO) mice and confirmed that ERα is necessary for maintaining muscle satellite cells' self-renewal and preventing apoptosis, thereby promoting muscle regeneration.

Studies using skeletal muscle-specific ERβ knockout models have shown that ERβ is a specific regulator of skeletal muscle growth and regeneration, crucial for maintaining skeletal muscle mass and strength, muscle regeneration, and muscle satellite cells expansion. Seko et al. [48] constructed female mice with muscle-specific ERβ knockout (mERβKO) and muscle satellite cells-specific ERβ knockout (scERβKO) and found that the absence of ERβ in muscle led to decreased muscle mass and strength, while the absence of ERβ in muscle satellite cells resulted in reduced muscle satellite cells proliferation and increased apoptosis, leading to impaired muscle regeneration.

At present, no reports have been published regarding muscle-specific GPER knockout or transgenic animal models. Most current understanding of GPER's physiological functions is derived from studies utilizing GPER-selective pharmacological agents (agonists and antagonists) and systemic GPER knockout animal models [49]. Within skeletal muscle, GPER plays a critical role in improving glucose homeostasis, enhancing insulin sensitivity, promoting lipid oxidation, reducing inflammation and lipogenesis, and maintaining muscle strength. Le et al. [50] demonstrated that treatment with the GPER agonist G1 in ovariectomized female mice increased muscle torque through estradiol binding to GPER in skeletal muscle. Wang et al. [51] found that activation of GPR30 with the specific agonist G1 reversed the adverse effects of ovariectomy on exercise capacity and skeletal muscle strength in rats.

Sources of estrogen in skeletal muscle across different sexes

There are significant differences in the sources of estrogen in skeletal muscle between males and premenopausal and postmenopausal females (Fig. 3). In premenopausal females, the primary source of circulating estrogen is the granulosa cells of ovarian follicles and the corpus luteum (approximately 95%), with a smaller contribution from the adrenal cortex (approximately 5%) [52]. Estradiol of ovarian origin in premenopausal females is primarily released into the bloodstream and acts on systemic target tissues, including skeletal muscle, via circulation. Therefore, estradiol in skeletal muscle of premenopausal females mainly originates from the gonads [53].

In females, menopause, characterized by the loss of ovarian function, represents an aging process. Circulating estradiol levels in postmenopausal females drop significantly and remain at a very low and constant level (1–10 pg/mL), which is below the bioactive threshold, helping to avoid excessive endometrial hyperplasia and thereby reducing the

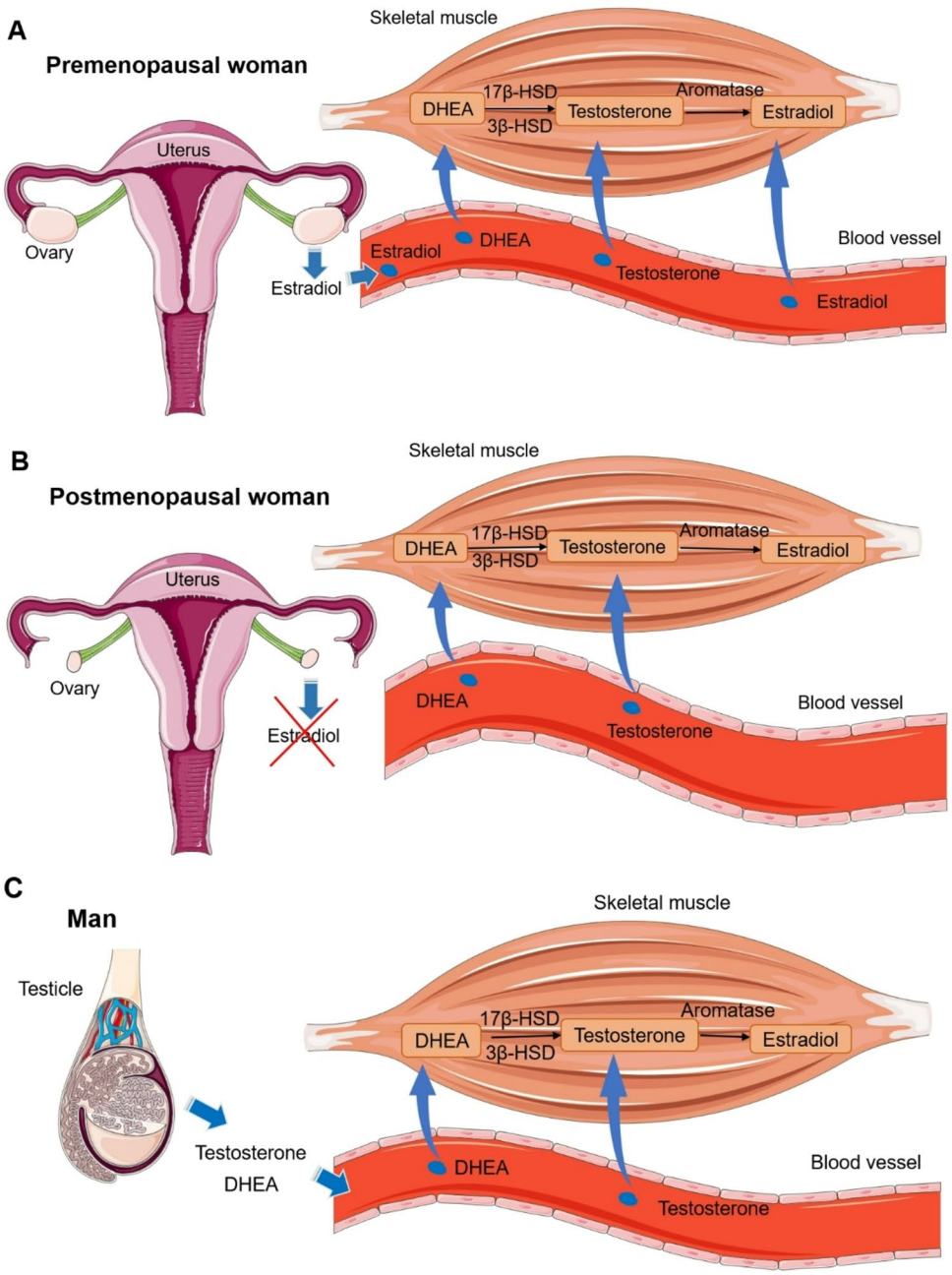

Fig. 3 Synthetic pathways of estradiol in skeletal muscle of premenopausal females. (**A**), postmenopausal females (**B**), and males (**C**) Figure **A**: In premenopausal females, estradiol synthesized in the ovaries is transported to skeletal muscle via blood circulation. Skeletal muscle can absorb DHEA and testosterone from the circulation and convert them into estradiol through the action of steroidogenic enzymes, such as aromatase. Figure **B**: In postmenopausal females, ovarian function declines, leading to a significant decrease in circulating estradiol levels. At this stage, the production of estradiol mainly relies on the conversion in peripheral tissues. Skeletal muscle absorbs DHEA and testosterone from the circulation and converts them into estradiol through local steroidogenic enzymes. Figure **C**: In males, the testes synthesize DHEA and testosterone and release them into the bloodstream. Skeletal muscle absorbs DHEA and testosterone from the circulation and converts them into estradiol through local steroidogenic enzymes. Abbreviations: DHEA, dehydroepiandrosterone; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase

risk of endometrial cancer [11]. In postmenopausal females, the estrogen locally synthesized by the skeletal muscle tissue itself (i.e., myogenic estrogen) is an important component of the estrogen in skeletal muscle [13].

In males, the main sources of circulating estrogen include extra-gonadal tissues (approximately 80%) and the testes (approximately 20%). Circulating estradiol levels in males are approximately 10–40 pg/mL [52], which exceeds that in postmenopausal females. In males, estrogen in skeletal muscle is mainly synthesized locally from testosterone, androstenedione, DHEA, and DHEA sulfate through steroidogenic enzymes [14, 54].

Effects and potential mechanisms of estrogen in skeletal muscle

Skeletal muscle is one of the target tissues of estrogen. The effects of estrogen on skeletal muscle are bidirectional. At normal physiological concentrations, estrogen plays a crucial role in improving muscle antioxidant capacity, promoting muscle protein synthesis, regulating glucose and lipid metabolism, and maintaining mitochondrial function (Fig. 4). However, supraphysiological doses of estrogen (i.e., estrogen levels higher than normal physiological concentrations) may have potential adverse effects on skeletal muscle

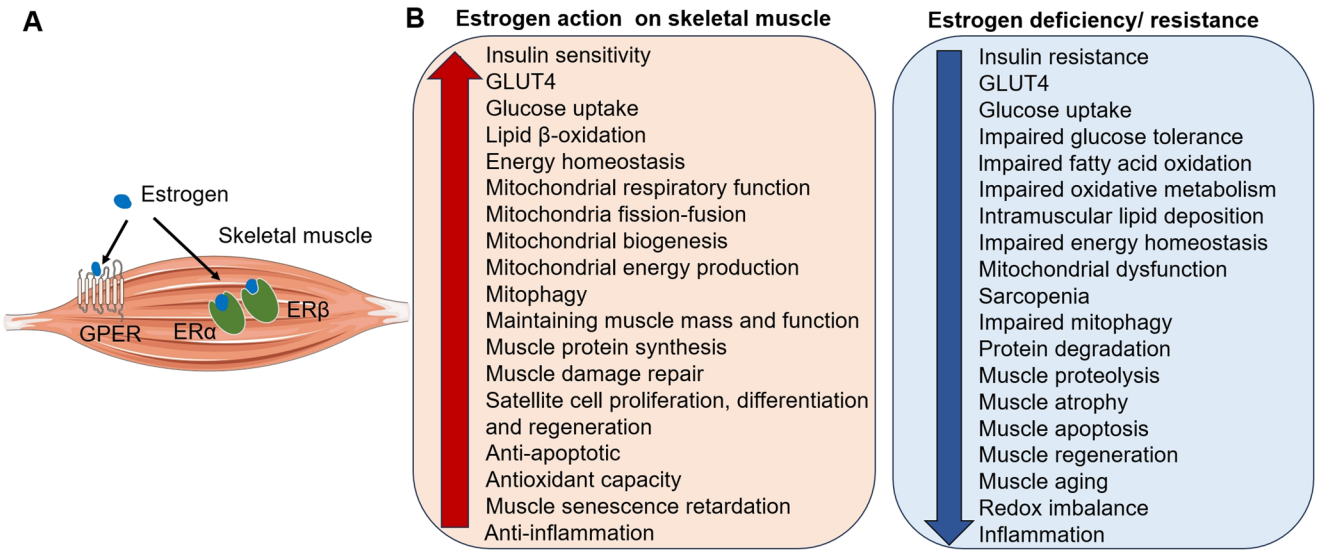

Fig. 4 Effects of estrogen on skeletal muscle. **A** Schematic diagram of estrogen binding to ERs in skeletal muscle. **B** Positive effects of estrogen on skeletal muscle at physiological concentrations, as well as the negative impacts of estrogen deficiency or estrogen resistance in skeletal muscle. Red upward arrows indicate increase, promotion, or improvement, while blue downward arrows indicate decrease, inhibition, or deterioration. Abbreviations: GLUT4, glucose transporter 4; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GPER, G protein-coupled estrogen receptor

[55]. Herein, we focus on the protective effects of estrogen on skeletal muscle at normal physiological concentrations.

Estrogen enhances skeletal muscle injury and repair

Estrogen improves anti-inflammatory and antioxidant capacity in skeletal muscle

Estrogen acts as an antioxidant and sarcolemmal stabilizer, enhancing the anti-inflammatory and antioxidant capacity of skeletal muscle and promoting muscle injury repair [56]. Specifically, estrogen is beneficial in reducing oxidative stress in skeletal muscle and slowing down the release of skeletal muscle injury markers such as creatine kinase, intramuscular lysosomal acid hydrolase, lactate dehydrogenase, and myoglobin into the circulation. In addition, estrogen can reduce the production and release of inflammatory cells (such as neutrophils and macrophages) and pro-inflammatory cytokines (such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1), alleviating the inflammatory response of skeletal muscles [56, 57].

A clinical study found that estradiol can attenuate neutrophil infiltration induced by a single bout of high-intensity eccentric exercise in men [58]. Dieli-Conwright et al. [59] discovered that estrogen therapy can alleviate skeletal muscle injury induced by a single bout of maximal eccentric resistance exercise in postmenopausal females and reduce levels of muscle injury and inflammation markers.

Bilateral ovariectomized rodents are a classic animal model for simulating the relative lack of circulating estrogen in postmenopausal females [60]. Animal experiments have shown that estrogen can enhance the antioxidant capacity of skeletal muscle and reduce skeletal muscle injury. For example, Feng et al. [61] found that exogenous estrogen supplementation can reduce serum creatine kinase activity in ovariectomized rats after acute muscle injury, increase levels of antioxidant-related indicators (such as glutathione) in the serum, thereby maintaining total antioxidant capacity in the body, enhancing the stability of the sarcolemma, and promoting regeneration after skeletal muscle injury. Additionally, the team led by Shi et al. [62] found that estradiol supplementation can inhibit oxidative stress by activating the SIRT1/PGC-1α/Nrf2 pathway, reducing skeletal muscle injury caused by contusion in ovariectomized mice.

Estrogen promotes activation and proliferation of skeletal muscle satellite cells

Muscle satellite cells are skeletal muscle stem cells located between the basement membrane of muscle fibers and the sarcolemma [47]. In adulthood, the maintenance of skeletal muscle mass and function is mediated by muscle satellite cells. Under homeostatic conditions, muscle satellite cells remain in a quiescent state, maintaining a stable number of muscle fibers [63]. In response to external stimuli such as muscle injury or physical exercise (e.g., mechanical stress), muscle satellite cells are activated and proliferate, differentiating into myoblasts. Myoblasts then fuse and further differentiate to form multinucleated myotubes and muscle

fibers, thereby promoting the repair and regeneration of muscle tissue [64].

Studies have shown that long-term estrogen deficiency reduces the number and function of muscle satellite cells [47, 65]. Estrogen supplementation can increase the number of muscle satellite cells, enhance their function and responsiveness, and promote repair and regeneration after skeletal muscle injury by promoting the activation, proliferation, and differentiation of muscle satellite cells [10, 66]. For example, Larson et al. [67] found that ovariectomy-induced loss of estradiol impairs the adaptive potential of mouse skeletal muscle after repeated injuries ($BaCl_2$-induced muscle injury) and leads to a reduction in the number of muscle satellite cells. Tanideh et al. [68] discovered that subcutaneous injection of estradiol benzoate (3 mg/kg) in ovariectomized rats promotes an increase in the number of muscle satellite cells. Similarly, Mangan et al. [69] found that estrogen supplementation (subcutaneous implantation of estrogen sustained-release tablets, 0.25 mg, for 21 days) can promote the proliferation and differentiation of satellite cells in rat soleus and gastrocnemius muscles, primarily by activating and proliferating satellite cells through the phosphatidylinositol-3-kinase (PI3K) signaling pathway.

Estrogen regulation of skeletal muscle mass and function

The decline in circulating estrogen levels during menopause in females is associated with the loss of skeletal muscle mass and function [2, 70]. Estrogen replacement therapy can partially offset or reverse the adverse changes in skeletal muscle mass and function in postmenopausal females [71].

Clinical trials have confirmed that estrogen plays an important role in maintaining the homeostasis of female skeletal muscle mass and offsetting or delaying the loss of skeletal muscle mass and function. For example, a study found that estrogen replacement therapy has a positive impact on muscle fiber contraction function and muscle nuclear tissue in postmenopausal females, and this effect may be achieved through the regulation of actin-myosin interaction and muscle nuclear domains by estrogen [72]. Dam et al. [73] found that compared with placebo, transdermal estrogen therapy enhanced the effect of increased muscle mass and strength in early postmenopausal females after resistance training.

At present, relevant meta-analyses have explored the impact of estrogen therapy on muscle mass and function in postmenopausal females. In 2009, a meta-analysis published by Greising et al. [74], which included 23 studies, showed that estrogen-based hormone therapy was beneficial for improving muscle strength in postmenopausal females. In 2019, a systematic review and meta-analysis published by Javed et al. [75] evaluated 12 randomized clinical trials involving 4,474 postmenopausal females. The results showed that compared with females who did not receive hormone therapy and those who received a placebo, females who received estrogen-based hormone therapy had less muscle mass loss, but this finding was not statistically significant. In 2020, a systematic review and meta-analysis conducted by Xu et al. [76] included 9 randomized controlled trials involving 2,476 postmenopausal females. The results showed that hormone therapy may not improve muscle strength in postmenopausal females, or the effect size was too small to determine a significant therapeutic effect. At present, there is significant heterogeneity in the conclusions of relevant studies. This heterogeneity may stem from significant differences in estrogen supplementation dosage, intervention period, administration route (such as transdermal patches, oral tablets, creams, etc.), postmenopausal therapeutic window, age of participants, years since menopause, dietary structure, physical activity level, nutritional status, and genetic background among different studies. These confounding factors are difficult to fully control in clinical studies.

Estrogen regulation of skeletal muscle protein synthesis and degradation homeostasis

The maintenance of muscle mass depends on the dynamic balance between muscle protein synthesis and degradation. In an estrogen-deficient state, muscle protein metabolism becomes imbalanced (i.e., the rate of protein synthesis is lower than the rate of protein degradation), leading to muscle fiber atrophy and ultimately causing an overall loss of skeletal muscle mass [77]. Estrogen helps maintain muscle mass and strength by promoting muscle protein synthesis and inhibiting skeletal muscle protein degradation [70].

Animal experiments have further confirmed the important role of estrogen in maintaining skeletal muscle mass homeostasis. For example, a study by Kitajima et al. [78] showed that ovariectomized mice exhibited time-dependent skeletal muscle atrophy and strength decline. Prestes et al. [79] found that ovariectomized rats had significantly decreased cross-sectional area and mass of skeletal muscle. Similarly, Moran et al. [80] reported that estradiol replacement therapy could reverse ovarian excision-induced muscle contraction and myosin dysfunction in mice.

The regulation of skeletal muscle protein metabolism by estrogen involves a complex signaling network. Specifically, estrogen can promote protein synthesis by activating protein synthesis metabolic pathways (such as the IGF-1/AKT/mTOR pathway) and inhibit protein catabolism pathways (such as the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway), thereby regulating the

synthesis and degradation of skeletal muscle protein and maintaining the stability of skeletal muscle mass [2, 81].

Estrogen inhibits skeletal muscle cell apoptosis

Circulating estrogen deficiency in postmenopausal females can induce skeletal muscle cell apoptosis, leading to skeletal muscle mass loss and strength decline [77]. For example, Karvinen et al. [71] found that ovariectomy (simulating circulating estrogen deficiency) resulted in downregulated expression of anti-apoptotic related microRNAs and activated apoptotic signaling cascades in mouse skeletal muscle, increasing skeletal muscle cell apoptosis and reducing skeletal muscle mass.

As a key regulator of skeletal muscle cell apoptosis, estrogen can protect skeletal muscle from apoptosis through various mechanisms, thereby preventing the loss of skeletal muscle mass [82]. Heat shock proteins (HSPs) are a class of endogenous protective proteins widely present in mammals and play an important anti-apoptotic role in skeletal muscle cells. Estrogen can upregulate the expression of HSPs, regulate the expression levels of various apoptosis-related proteins, and maintain the stability of mitochondrial membranes, thereby inhibiting the apoptosis of skeletal muscle cells and maintaining skeletal muscle mass and function [77]. Specifically, estrogen can upregulate the expression of HSP27, which binds to Caspase-3, preventing its cleavage and activation and maintaining it in an inactive state. HSP27 can also downregulate the expression of pro-apoptotic factors (such as Bax, Caspase-3, cytochrome C, p53) and upregulate the expression of anti-apoptotic proteins (such as Bcl-2), preventing the release of cytochrome C and thereby inhibiting the initiation of the apoptotic process and promoting cell survival [77].

Previous studies have reported that estrogen deficiency affects HSPs expression in rodents and C_2C_{12} myoblasts [83, 84]. Tiidus et al. [85] found that estrogen partially activates ERα to increase HSP70 levels in muscle tissue. La Colla et al. [86] found that physiological concentrations of estradiol (100 nmol/L) could significantly inhibit H_2O_2-induced apoptosis of C_2C_{12} myoblasts by regulating the expression of apoptotic transcription factors p53 and FoxO and their target genes. Similarly, Vasconsuelo et al. [87] found that estradiol intervention could inhibit H_2O_2-induced apoptosis of C_2C_{12} myoblasts by upregulating HSP27 and regulating caspase-3 activity.

Estrogen regulation of skeletal muscle mitochondrial function

Mitochondria are the primary source of energy required for skeletal muscle contraction and movement, playing a crucial role in the quality, function, and metabolism of skeletal muscle. Mitochondrial dysfunction is a key factor contributing to the decline in skeletal muscle mass with aging [88]. Estrogen plays an important role in regulating mitochondrial homeostasis in skeletal muscle. Estrogen can regulate multiple aspects of skeletal muscle mitochondrial function, including mitochondrial bioenergetics, mitochondrial biogenesis, mitochondrial dynamics (fusion and fission), mitophagy, mitochondrial apoptosis, calcium homeostasis, ATP production, and ROS production [35, 89]. Estrogen deficiency can induce skeletal muscle mitochondrial dysfunction, alterations in mitochondrial dynamics, abnormalities in mitophagy, and mitochondrial-mediated apoptosis, thereby accelerating the process of muscle atrophy [2].

Estrogen may improve skeletal muscle function by regulating mitochondrial function in skeletal muscle. For example, a study by Hu et al. [90] showed that estradiol supplementation can alleviate the decline in skeletal muscle strength and mitochondrial dysfunction in ovariectomized mice, thereby mitigating muscle dysfunction caused by estrogen deficiency. Silva et al. [91] found that compared to estrogen replacement therapy, endurance training can increase skeletal muscle mitochondrial content and improve redox status and inflammatory status in ovariectomized rats. Similarly, a study by Nagai et al. [92] showed that ovariectomy reduces exercise endurance in mice and upregulates the expression of mitochondrial uncoupling protein 3 (UCP3) in skeletal muscle. Estrogen administration can restore exercise endurance in ovariectomized mice and downregulate the expression of UCP3 in skeletal muscle mitochondria. This study suggests that estrogen may increase ATP production by inhibiting mitochondrial uncoupling in skeletal muscle, thereby improving exercise endurance.

Estrogen regulation of skeletal muscle glycolipid metabolism

Postmenopausal females are more prone to metabolic-related diseases such as obesity, impaired glucose tolerance, insulin resistance, and type 2 diabetes due to decreased estrogen levels [93]. As a key site for the oxidation and utilization of glucose and fatty acids, skeletal muscle is a major organ regulating glycolipid metabolism [94]. Estrogen deficiency may lead to metabolic dysfunction in skeletal muscle in postmenopausal females by affecting mitochondrial quantity, autophagic function, energy uncoupling, and membrane stability in skeletal muscle [10]. Evidence from both human and rodent studies indicates that estrogen can regulate glucose and lipid homeostasis in skeletal muscle [95].

Human trials have confirmed that estrogen deficiency can lead to abnormalities in glycolipid metabolism in skeletal muscle. For example, Gibb et al. [96] found that

oral administration of the aromatase inhibitor anastrozole (1 mg/d for 6 weeks) to healthy adult males significantly reduced plasma estradiol levels and decreased insulin sensitivity in peripheral tissues, including skeletal muscle. Studies have shown that the decline in skeletal muscle mass in postmenopausal females may be accompanied by a reduction in force production and an increase in intramuscular fat content. Hormone replacement therapy (HRT) has been shown to alleviate muscle loss, muscle dysfunction, and intramuscular fat accumulation in postmenopausal females [97]. Furthermore, Maher et al. [98] discovered that estradiol supplementation in males for 8 consecutive days increased the expression of lipid oxidation-related genes and proteins in skeletal muscle, enhancing skeletal muscle β-oxidation capacity.

In terms of estrogen and skeletal muscle glucose metabolism, animal experiments have shown that estrogen deficiency can lead to dysfunction in skeletal muscle glucose metabolism, specifically manifested as a decrease in glucose transporter 4 (GLUT4) content, reduced glucose uptake capacity, and decreased skeletal muscle glycogen content. For example, Hansen et al. [99] found that estrogen deficiency (6 weeks after rat ovariectomy) reduced contraction-stimulated glucose transport in skeletal muscle. Min et al. [100] discovered that ovariectomized rats (5 months after surgery) exhibited systemic glucose metabolism and glucose tolerance abnormalities, with significant decreases in skeletal muscle glucose metabolism-related indicators (mRNA and protein levels of p-AKT, p-38MAPK, PGC-1α, and GLUT4), accompanied by a reduction in skeletal muscle glycogen content.

Further animal studies have shown that estrogen supplementation can improve skeletal muscle glucose metabolism by promoting glucose uptake and glycogen synthesis in skeletal muscle. For instance, Puah et al. [101] found that oral estradiol administration (5 mg/kg/day for 10 weeks) in ovariectomized mice promoted insulin-mediated glucose uptake and utilization in skeletal muscle, improving skeletal muscle glucose metabolism. Narasimhan et al. [102] also discovered that ovariectomized rats showed decreased expression of insulin signaling molecules and reduced glucose oxidation capacity in skeletal muscle, while exogenous estradiol supplementation (subcutaneous injection, 6 μg/kg/d for 21 days) significantly improved skeletal muscle glycogen synthesis and glucose tolerance in ovariectomized rats. Ahmed-Sorour et al. [103] showed that exogenous estradiol supplementation (subcutaneous injection, 5 μg/kg for 15 weeks) could effectively reduce gluconeogenesis in ovariectomized mice and improve glycogen synthesis in liver and skeletal muscle tissues.

Regarding estrogen and skeletal muscle lipid metabolism, relevant animal experiments have shown that estrogen deficiency may lead to dysfunction in skeletal muscle lipid metabolism, specifically manifested as intramuscular lipid deposition, decreased fatty acid oxidation capacity in skeletal muscle, and altered expression of lipid metabolism-related genes [95]. For example, Jackson et al. [104] found that loss of ovarian function in mice (8–10 weeks after ovariectomy) led to increased storage of skeletal muscle intramyocellular lipids (IMCL), significantly increased protein content of skeletal muscle fatty acid transporters CD36/FAT and FABPpm, and decreased lipid catabolism in skeletal muscle. Zhong et al. [105] reported that compared to the sham-operated group, ovariectomized rats showed increased intermuscular fat content in the gastrocnemius muscle. Additionally, Cavalcanti-de-Albuquerque et al. [106] discovered that ovariectomy in rats led to changes in mitochondria related to lipid substrate usage in skeletal muscle and decreased muscle lipid oxidation capacity.

Further animal studies have shown that estrogen can improve skeletal muscle lipid metabolism by promoting mitochondrial fatty acid oxidation in skeletal muscle. For example, Hamilton et al. [107] showed that selective activation of ERα could improve insulin sensitivity in high-fat diet-fed ovariectomized mice, enhance systemic energy metabolism and skeletal muscle mitochondrial function, and increase mitochondrial biogenesis and fatty acid oxidation. Campbell and Febbraio [108] found that ovariectomy in rats led to decreased activity of carnitine palmitoyltransferase I (CPT-1) in skeletal muscle and reduced lipid oxidation capacity in skeletal muscle. Estradiol supplementation could improve skeletal muscle lipid metabolism by increasing the maximum activity of key enzymes in the skeletal muscle lipid oxidation pathway. Furthermore, Campbell et al. [109] found that estradiol could upregulate the expression of peroxisome proliferator-activated receptor α and lipid oxidation-related genes in skeletal muscle of ovariectomized rats.

It is worth mentioning that supplementation with physiological doses of estradiol can improve skeletal muscle glucose metabolism. However, supplementation with supraphysiological doses of estradiol may inhibit glucose metabolism. Cell experiments have found that Garrido et al. [110] discovered that primary human myotubes acutely exposed to supraphysiological doses of estradiol (10 μmol/L estradiol in cell culture medium) harmed glucose metabolism. Specifically, supraphysiological doses of estradiol may inhibit the protein kinase C (PKC) signaling pathway, thereby inhibiting glycogen synthesis from glucose and inducing insulin resistance.

Role of myogenic estrogen in skeletal muscle

After menopause, peripheral tissues in females can locally synthesize bioactive estrogens. Although the total amount of estrogen synthesized by extragonadal tissues may be small, its concentration in local tissues can be relatively high, exerting biological effects in a paracrine or autocrine manner. Estrogen derived from peripheral tissues plays distinct roles in different tissues [111]. Myogenic estrogen may act on itself and adjacent skeletal muscle cells through paracrine or autocrine mechanisms. By binding to estrogen receptors, myogenic estrogen regulates physiological processes such as proliferation, differentiation, repair, regeneration, and apoptosis of skeletal muscle cells, thereby maintaining normal physiological functions and metabolic homeostasis of skeletal muscle. This has a positive impact on the quality of life of postmenopausal females [27, 111]. A clinical study demonstrated that intramuscular estrogen levels are significant predictors of muscle performance, strength, and power [19]. Furthermore, Pöllänen et al. [18] reported that compared with premenopausal females, postmenopausal females showed significantly increased steroidogenic enzymes (3β-HSD and aromatase) and estrogen content in skeletal muscle. This suggests that postmenopausal females may experience compensatory local production of estrogen in skeletal muscle to meet physiological needs.

Methodologies for studying myogenic estrogen include the generation of skeletal muscle-specific aromatase gene overexpression [112, 113] or knockout animal models [114], and using estrogen-depleted conditioned media in C_2C_{12} myoblast models [115]. In rodent models, skeletal muscle-specific overexpression or knockout of the aromatase gene leads to corresponding increases or decreases in intramuscular estrogen levels, respectively. Aladhami et al. [113] utilized CRISPR/Cas9 technology and doxycycline induction to create a female mouse model with skeletal muscle-specific aromatase overexpression (SkM-Arom↑) for the first time. Results showed that elevated endogenous estrogen in skeletal muscle did not positively affect systemic insulin resistance, glucose tolerance, or body fat in high-fat diet-induced obese mice. Subsequently, the research team further developed a male mouse model with skeletal muscle-specific aromatase overexpression and found that it improved high-fat diet-induced systemic metabolic disorders in male mice, including hyperglycemia, hyperinsulinemia, impaired glucose tolerance, adipose tissue inflammation, and hepatic lipid accumulation, while promoting skeletal muscle hypertrophy [112]. Additionally, our team has generated skeletal muscle-specific aromatase knockout mouse models and observed that myogenic estrogens may play a critical role in maintaining mitochondrial function and antioxidant capacity in the skeletal muscle of ovariectomized mice [114]. Based on current findings, we hypothesize that the potential roles of myogenic estrogens in improving skeletal muscle health should not be overlooked, and that their effects may exhibit sexual dimorphism. However, this hypothesis requires further validation through future research.

Pathways of estrogen action in skeletal muscle

Exogenous estrogen enters skeletal muscle through blood circulation and exerts physiological effects after binding to estrogen receptors. Myogenic estrogen directly binds to estrogen receptors within skeletal muscle. Therefore, despite differing origins, both exogenous estrogen supplementation and myogenic estrogen act through the same pathway in skeletal muscle, essentially via estrogen receptors within skeletal muscle cells (Fig. 5). The response mechanism of estrogen receptors to estradiol is complex and not yet fully elucidated. Based on dependence on gene regulation, estrogen-dependent signaling mechanisms can be divided into direct genomic and indirect non-genomic pathways [52].

Direct genomic signaling pathways represent the classical mechanism of estrogen signaling, involving direct binding of estrogen nuclear receptors (ERα and ERβ) to specific DNA sequences [14]. In this process, ERα and ERβ act as ligand-activated transcription factors that undergo conformational changes upon binding to estradiol, forming dimeric complexes [116]. Subsequently, the estradiol-receptor complex (E_2-ER) translocates to the nucleus, where it binds to estrogen response elements (EREs) in the promoters of target genes or interacts with other transcription factors (such as activator protein-1 (AP-1) and specificity protein-1 (Sp-1)) to regulate gene transcription [14].

Indirect non-genomic estrogen signaling pathways, also known as membrane-initiated estrogen signaling, involve estrogen binding to G protein-coupled estrogen receptors (GPER) on the surface of skeletal muscle cell membranes. This interaction regulates the opening of ion channels or activates various protein kinases (such as PI3K, protein kinase B (AKT), and mitogen-activated protein kinases (MAPK)), initiating downstream intracellular signaling cascades that mediate non-genomic effects [10]. Non-genomic pathways are rapid, occurring within seconds to minutes, and do not depend on RNA transcription or protein synthesis. Instead, they act through membrane-based ion channels, intracellular second messengers (such as modulation of cAMP levels), and protein kinase cascades, ultimately leading to indirect changes in gene expression [117]. Additionally, estrogen can initiate both genomic and non-genomic actions mediated by mitochondrial estrogen nuclear receptors and GPER, regulating mitochondrial respiration, ATP production, and ROS formation [118].

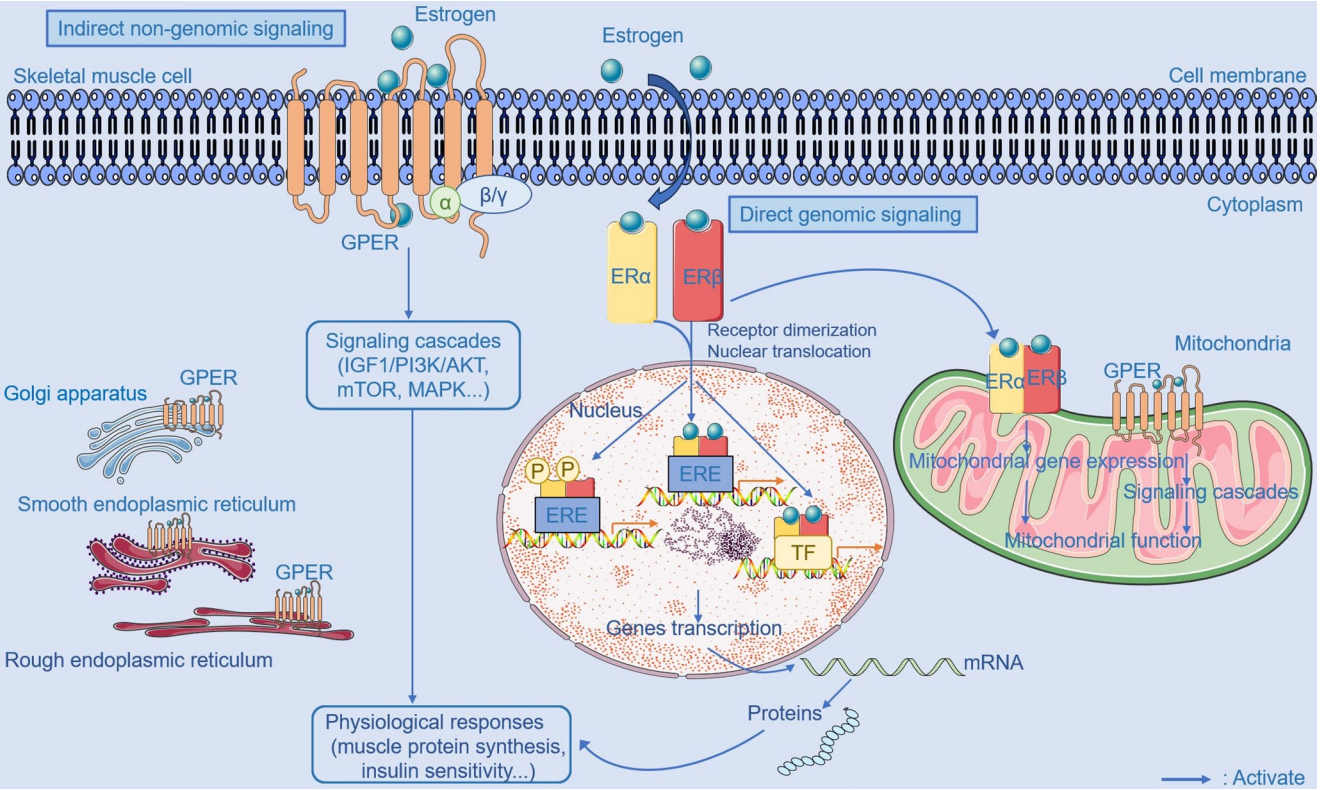

Fig. 5 Potential mechanisms of estrogen action in skeletal muscle. Estrogen exerts physiological effects through both non-genomic and genomic pathways, as well as mitochondrial effects, by binding to estrogen receptors (ERα, ERβ, and GPER) in muscle cells. (1) Non-genomic pathways: Upon binding to GPER, estrogen rapidly activates intracellular signaling molecules (e.g., PI3K/AKT and MAPK), leading to immediate cellular responses. This rapid action does not depend on gene transcription or protein synthesis but instead modulates cell function by regulating ion channel opening or activating protein kinases. (2) Genomic pathways: After binding to ERα or ERβ, the E_2/ER complex can either directly bind to estrogen response elements (EREs) in the promoters of target genes or interact with other transcription factors (e.g., AP-1 and Sp-1) to regulate gene transcription. Additionally, the E_2/ER complex can indirectly modulate gene expression by activating signal transduction pathways, resulting in phosphorylation of ER or other transcription factors. (3) Mitochondrial effects: Estrogen may localize to mitochondria and influence mitochondrial quality and function through both genomic and nongenomic pathways, although the specific mechanisms remain incompletely understood. Abbreviations: ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GPER, G protein-coupled estrogen receptor; E_2, estradiol; ERE, estrogen response element; IGF1, insulin-like growth factor 1; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; TF, transcription factor

Effects of exercise on estrogen in skeletal muscle

HRT is widely used to alleviate various symptoms in menopausal females, but this treatment may be accompanied by a range of side effects and disease risks, including cardiovascular disease, breast cancer, and endometrial cancer complications [119]. In contrast, exercise serves as a safe, economical, and effective non-pharmacological intervention that can act as an alternative to hormone therapy [2]. Furthermore, exercise helps mimic and/or enhance the positive effects of estrogen on skeletal muscle function [10]. However, current research findings on the impact of exercise on estrogen levels in skeletal muscle remain inconsistent (Table 1). A recent systematic review suggests that a single bout of resistance training does not alter intramuscular sex hormone concentrations in humans, whereas a single bout of aerobic exercise increases intramuscular sex hormone levels in rodents [120]. The estrogen levels in skeletal muscle are influenced by a combination of factors, including mode of exercise, exercise intensity, frequency, duration and period, training level, age, sex, health status, and individual metabolic characteristics.

Effects of endurance exercise on estrogen in skeletal muscle

Currently, there is limited research on the changes in estrogen levels in skeletal muscle induced by endurance exercise. Shi et al. [121] found that 8 weeks of treadmill training significantly increased the content of aromatase and estradiol in the skeletal muscle of ovariectomized rats. Furthermore,

Table 1 Summary of the effects of exercise on estrogen in skeletal muscle

Author/year/references	Subjects	Type of exercise	Intensity, frequency, and duration of exercise	Estrogen levels in skeletal muscle
Dalgaard et al., 2022 [20]	Postmenopausal females	Resistance training	12 weeks,3 times per week, according to the American College of Sports Medicine guidelines	↓
Dalgaard et al., 2022 [20]	Postmenopausal females	Acute resistance exercise	A bout of resistance exercise	↔
Haines et al., 2018 [138]	Physically active, eumenorrheic females	Eccentric exercise	10 sets of 10 repetitions with 3 min of rest between sets at an isokinetic speed of 30°/second	↔
Shi et al., 2019 [121]	Female ovariectomized rats	Treadmill training	6 d/week,1 h/d,25 m/min, 8 weeks	↑
Aizawa et al., 2008 [123]	Male and female rats	Acute treadmill training	Running on a motor-driven treadmill for 10-minute intervals at a speed of 15 m/min without incline (0% grade)	↑ (male rats); ↔ (female rats)
Aizawa et al., 2011 [124]	Male rats	Treadmill training	30 m/min,30 min/d,5 d/week,12 weeks	↔

↑: significantly increase; ↓: significantly decrease; ↔: no significant changes

the research team led by Shi et al. [122] demonstrated in cellular experiments that mechanical stretch (simulating myoblast exercise at the cellular level) increased the mRNA and protein expression levels of steroidogenic enzymes (including aromatase, 3β-HSD, and 17β-HSD) in C_2C_{12} myoblasts, thereby promoting estradiol production in these cells. Aizawa et al. [123] discovered that acute endurance exercise significantly elevated estradiol levels in the skeletal muscle of male rats but did not cause significant changes in female mice. Additionally, acute endurance exercise increased the expression levels of steroidogenic enzymes (17β-HSD and 3β-HSD) in the skeletal muscle of both male and female rats, although the expression levels of aromatase varied by sex. This suggests that acute exercise may enhance local steroidogenesis in the skeletal muscle of both sexes, but with sex differences [123]. Subsequently, Aizawa et al. [124] subjected male rats to 12 weeks of treadmill training and found that long-term endurance exercise increased the protein expression of steroidogenic enzymes (aromatase and 5α-reductase) and dihydrotestosterone (DHT) concentrations in the skeletal muscle of male rats but did not alter estradiol levels. Therefore, adaptive changes in estrogen levels in skeletal muscle in response to exercise may vary by sex. Furthermore, some animal [105] and human studies [125–127] have reported that endurance exercise can lead to elevated circulating estrogen levels, but unfortunately, these studies did not measure estrogen levels in skeletal muscle.

Based on studies related to skeletal muscle steroids, we hypothesize that both acute and long-term endurance training may promote the synthesis of myogenic estrogen in skeletal muscle, increasing estrogen levels to maintain normal skeletal muscle function [28].

Effects of resistance exercise on estrogen in skeletal muscle

Currently, the effects of resistance exercise on estrogen in skeletal muscle have not been fully investigated. Dalgaard et al. [20] found that postmenopausal females who underwent 12 weeks of resistance training experienced a significant increase in circulating estrogen levels but a significant decrease in estrogen levels in skeletal muscle. The study also revealed no significant changes in estrogen levels in skeletal muscle after acute resistance exercise in postmenopausal females. Furthermore, some studies [126, 128, 129] have shown that resistance exercise can lead to elevated circulating estrogen levels in females, but unfortunately, these studies did not measure estrogen levels in skeletal muscle.

Although resistance exercise training is more effective than endurance exercise training in increasing muscle mass and strength [130], current evidence supporting the ability of resistance exercise to increase estrogen levels in skeletal muscle is insufficient. We hypothesize that resistance exercise may lead to a transient increase in estrogen in skeletal muscle, which may be rapidly metabolized and cleared after exercise. Future research is needed to further clarify the effects of resistance exercise on estrogen in skeletal muscle.

Possible mechanisms of exercise effects on estrogen synthesis in skeletal muscle

Exercise is an effective method for inducing muscle steroidogenesis [28]. Long-term exercise training may induce adaptive changes in estrogen production in skeletal muscle. As previously mentioned, studies [114, 121, 124] have

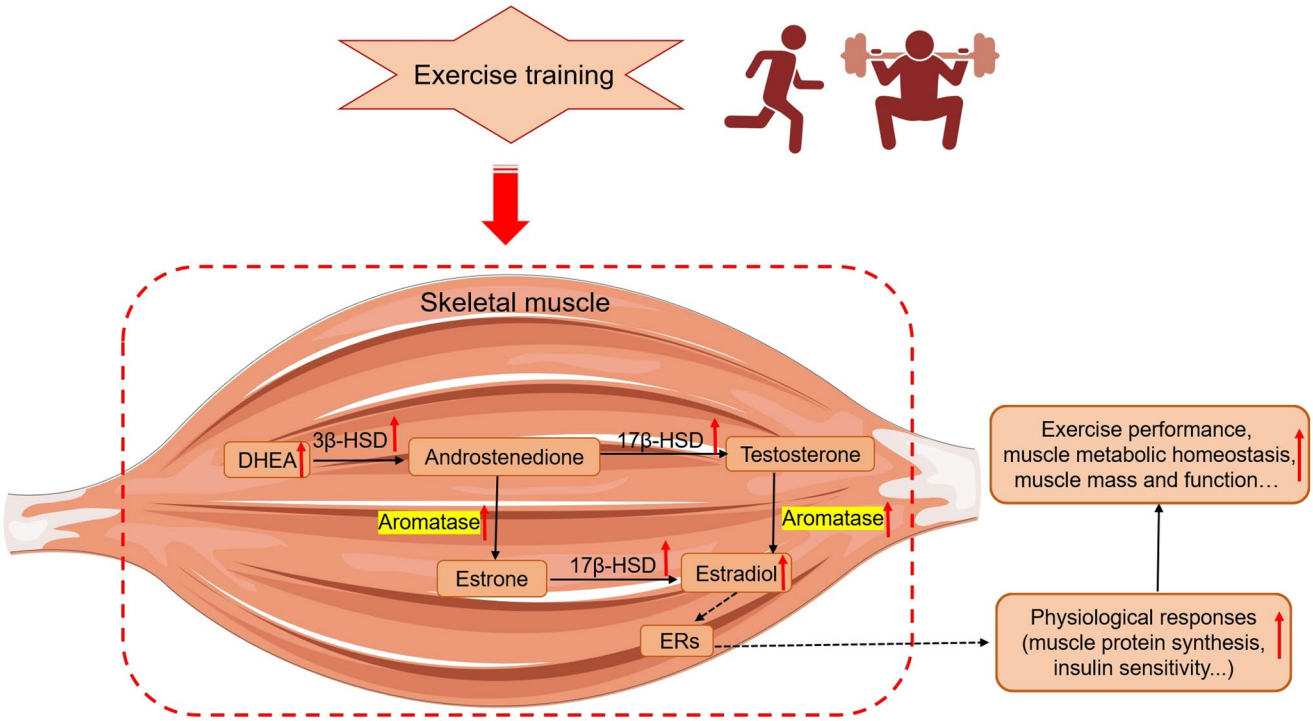

Fig. 6 Potential mechanisms of exercise training promoting estrogen synthesis in skeletal muscle. Exercise training (such as endurance training and resistance training) may promote the uptake of DHEA from the circulation into skeletal muscle, increase the expression of enzymes related to estrogen synthesis in skeletal muscle (including aromatase, 3β-HSD, and 17β-HSD), thereby enhancing the conversion and production of estrogen in skeletal muscle. By binding to ERs, estrogen in skeletal muscle further exerts its physiological functions (including promoting skeletal muscle protein synthesis and improving insulin sensitivity), contributing to improved skeletal muscle mass, function, and metabolic homeostasis. Solid arrows represent experimentally verified pathways, while dashed arrows represent potential pathways that have not yet been validated. An upward-pointing red arrow indicates upregulation. Abbreviations: DHEA, dehydroepiandrosterone; 17β-HSD, 17β-hydroxysteroid dehydrogenase; 3β-HSD, 3β-hydroxysteroid dehydrogenase; ERs, estrogen receptors

shown that exercise may increase steroidogenic enzymes and steroid levels in skeletal muscle. The increase in exercise-induced myogenic estradiol and the expression of steroidogenic enzymes in skeletal muscle may contribute to the prevention and treatment of diseases such as obesity, type 2 diabetes, osteoporosis, metabolic syndrome, and sarcopenia [28]. Our team's recent findings indicate that exercise-induced myogenic estradiol production may contribute to enhancing skeletal muscle antioxidant capacity [114]. Furthermore, we hypothesize that myogenic estrogen may function similarly to "myokines." Myogenic estrogen appears to be released in response to acute and/or chronic exercise and acts through paracrine or autocrine pathways [131]. Mechanistically, estrogen in skeletal muscle may mediate the beneficial effects of exercise on skeletal muscle mass and function. Specifically, exercise training may promote the synthesis of myogenic estrogen by increasing the levels of DHEA and aromatase in skeletal muscle, thereby enhancing estrogen levels in skeletal muscle and contributing to improved skeletal muscle mass and function (Fig. 6). Certainly, this hypothesis requires further validation through more clinical and basic research in the future.

Exercise promotes estrogen production in skeletal muscle by increasing levels of estrogen precursors

Endurance exercise can increase levels of estrogen precursors (such as DHEA, androstenedione, and testosterone) in skeletal muscle. Studies have shown that long-term endurance training (25 m/min, 1 h, 5 d/week, for 8 weeks) can increase skeletal muscle steroid hormone (such as DHEA) levels in male type 2 diabetic rats, enhancing skeletal muscle glucose utilization and insulin sensitivity [132]. Additionally, Aizawa et al. [133] found that acute treadmill exercise increases the expression of 5α-reductase in the skeletal muscle of male and female rats, enhancing levels of DHEA, free testosterone, and dihydrotestosterone in skeletal muscle.

Resistance exercise may have a promoting effect on the production of estrogen precursors in skeletal muscle. For example, Sato et al. [134] reported that 12 weeks of resistance training increased the levels of steroidogenic enzymes (including 3β-HSD, 17β-HSD, and 5α-reductase) and muscle steroid hormones (including DHEA, testosterone, and dihydrotestosterone) in the muscles of elderly men. The increase in steroidogenic enzyme content in muscles may

contribute to the improvement in muscle mass and strength after resistance training. Horii et al. [135] found that 8 weeks of resistance training (3 d/week) increased DHEA levels in the skeletal muscle of male type 2 diabetic rats, inducing muscle hypertrophy and improving hyperglycemia and insulin sensitivity by activating GLUT4-regulated signaling in skeletal muscle.

In summary, we hypothesize that exercise may promote estrogen production in skeletal muscle by increasing levels of estrogen precursors.

Exercise promotes estrogen production in skeletal muscle by increasing steroidogenic enzyme content

Endurance exercise may enhance estrogen levels in skeletal muscle by promoting the expression of steroidogenic enzymes such as aromatase, 3β-HSD, and 17β-HSD in skeletal muscle. Aizawa et al. [24] found that steroidogenic enzymes can be detected in myoblasts extracted from rat skeletal muscle and that supplementing with DHEA increases estradiol concentrations in muscle cells. Research by Aizawa et al. [124] showed that long-term endurance exercise significantly enhances mRNA and protein levels of aromatase in the gastrocnemius muscle of male rats, but no significant change in estradiol levels in the gastrocnemius muscle was observed. Shi et al. [121] found that after long-term aerobic exercise, levels of aromatase and estradiol in the skeletal muscle of ovariectomized rats were significantly increased, which may be an adaptive phenomenon to long-term exercise. Studies have shown that long-term aerobic exercise training increases the expression of steroidogenic enzymes and steroid hormones in the skeletal muscle of high-sugar-induced obese rats, while serum steroid hormone levels are also elevated [28].

In addition, resistance exercise may increase the expression of steroidogenic enzymes in skeletal muscle, thereby promoting estrogen production in skeletal muscle. Although Vingren et al. [136] found no significant differences in skeletal muscle steroid and steroidogenic enzyme concentrations in young men and females who had undergone resistance training after a single resistance exercise session, Sato et al. [134] showed that progressive resistance training can restore steroidogenic enzyme and steroid hormone levels in the skeletal muscle of elderly men.

Conclusions

Estrogen plays a crucial role in maintaining skeletal muscle mass and strength, promoting skeletal muscle repair after injury, and regulating protein and glycolipid metabolic homeostasis in skeletal muscle. As a vital organ for movement, metabolism, and secretion in the human body, skeletal muscle contains the enzymatic systems necessary for estrogen synthesis and can locally produce myogenic estrogen. Myogenic estrogen can regulate the physiological functions and metabolic homeostasis of skeletal muscle cells through paracrine or autocrine mechanisms.

Exercise is an important factor in regulating steroidogenic changes in skeletal muscle and can modulate estrogen levels in skeletal muscle. Myogenic estrogen may mediate the beneficial effects of exercise on skeletal muscle health and athletic performance. Exercise may promote the synthesis of myogenic estrogen by increasing levels of estrogen precursors and steroidogenic enzymes in skeletal muscle, thereby improving skeletal muscle mass and function.

Future perspectives

In the future, many aspects of research on exercise, estrogen, and skeletal muscle warrant further exploration. For example: (1) At present, systematic studies on metabolic differences of myogenic estrogen among individuals of different sexes and ages are lacking. Clinical evidence supporting the use of estrogen therapy for skeletal muscle diseases such as sarcopenia and Duchenne muscular dystrophy remains insufficient. The specific mechanisms of estrogen's effects on skeletal muscle and its optimal application dosage require further investigation. As a non-pharmacological means of improving estrogen levels in skeletal muscle, exercise is gradually gaining attention for its potential in alleviating muscle dysfunction caused by estrogen deficiency. More research is needed to explore the impacts of different exercise types, cycles, and intensities on myogenic estrogen and its receptors.

(2) Current research mainly focuses on postmenopausal females or ovariectomized animal models, investigating the ameliorative effects of exogenous estrogen supplementation on skeletal muscle function and metabolic degeneration caused by estrogen deficiency [10]. However, studies on myogenic estrogen are relatively scarce, and the role of estrogen produced locally in skeletal muscle appears to be underestimated. As an endocrine organ, the physiological and pathophysiological roles of myogenic estrogen in skeletal muscle remain unclear. With the establishment of models with specific knockout or overexpression of aromatase in skeletal muscle, the biological functions of myogenic estrogen are expected to be further elucidated. In addition, under the influence of exercise, myogenic estrogen may play a role in regulating skeletal muscle mass, function, and metabolism. Research on exercise and myogenic estrogen is expected to become an emerging area of focus in the fields of muscle endocrinology and exercise science. Understanding

the interplay between exercise, myogenic estrogen, and muscle physiology will provide valuable insights for developing targeted exercise interventions to mitigate age- and hormone-related muscle decline.

(3) Research on estrogen receptors is one of the most active areas in estrogen studies. The physiological and pathological roles of estrogen receptors and their signaling pathways require continuous exploration and updating. In the future, with the development of conditional knockout animal models of estrogen receptors in skeletal muscle (such as ERαKO, ERβKO, ERαβKO, AromKO, GPERKO, etc.) and conditional overexpression models (such as ERαOE, ERβOE, ERαβOE, AromOE, GPEROE, etc.) [137], as well as the application of pharmacological drugs such as selective agonists or antagonists of estrogen receptors, researchers' understanding of estrogen receptors in skeletal muscle will continue to deepen.

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Declarations

Conflict of interest The authors declare no competing interests.

References

1. Seifarth JE, McGowan CL, Milne KJ (2012) Sex and life expectancy. Gend Med 9:390–401. https://doi.org/10.1016/j.genm.2012.10.001
2. Cho E-J, Choi Y, Jung S-J, Kwak H-B (2022) Role of exercise in estrogen deficiency-induced sarcopenia. J Exerc Rehabil 18:2–9. https://doi.org/10.12965/jer.2244004.002
3. Carson JA, Manolagas SC (2015) Effects of sex steroids on bones and muscles: similarities, parallels, and putative interactions in health and disease. Bone 80:67–78. https://doi.org/10.1016/j.bone.2015.04.015
4. Alemany M (2021) Estrogens and the regulation of glucose metabolism. World J Diabetes 12:1622–1654. https://doi.org/10.4239/wjd.v12.i10.1622
5. Vogel H, Mirhashemi F, Liehl B et al (2013) Estrogen deficiency aggravates insulin resistance and induces β-cell loss and diabetes in female new Zealand obese mice. Horm Metab Res 45:430–435. https://doi.org/10.1055/s-0032-1331700
6. Gillies GE, McArthur S (2010) Estrogen actions in the brain and the basis for differential action in men and women: a case for sex-specific medicines. Pharmacol Rev 62:155–198. https://doi.org/10.1124/pr.109.002071
7. Klein-Nulend J, van Oers RFM, Bakker AD, Bacabac RG (2015) Bone cell mechanosensitivity, estrogen deficiency, and osteoporosis. J Biomech 48(5):855–865. https://doi.org/10.1016/j.jbiomech.2014.12.007
8. Sriramaneni N, Selvan C, Kumar SN et al (2024) Quality of life in postmenopausal women and its association with sarcopenia. Menopause 31:679–685. https://doi.org/10.1097/GME.0000000000002378
9. Romagnoli C, Zonefrati R, Sharma P et al (2020) Characterization of skeletal muscle endocrine control in an in vitro model of myogenesis. Calcif Tissue Int 107:18–30. https://doi.org/10.1007/s00223-020-00678-3
10. Pellegrino A, Tiidus PM, Vandenboom R (2022) Mechanisms of estrogen influence on skeletal muscle: mass, regeneration, and mitochondrial function. Sports Med 52:2853–2869. https://doi.org/10.1007/s40279-022-01733-9
11. Labrie F (2015) All sex steroids are made intracellularly in peripheral tissues by the mechanisms of intracrinology after menopause. J Steroid Biochem Mol Biol 145:133–138. https://doi.org/10.1016/j.jsbmb.2014.06.001
12. Vieira-Potter VJ, Zidon TM, Padilla J (2015) Exercise (and estrogen) make fat cells fit. Exerc Sport Sci Rev 43:172–178. https://doi.org/10.1249/JES.0000000000000046
13. Samavat H, Kurzer MS (2015) Estrogen metabolism and breast cancer. Cancer Lett 356:231–243. https://doi.org/10.1016/j.canlet.2014.04.018
14. Fuentes N, Silveyra P (2019) Estrogen receptor signaling mechanisms. Adv Protein Chem Struct Biol 116:135–170. https://doi.org/10.1016/bs.apcsb.2019.01.001
15. Azcoitia I, Mendez P, Garcia-Segura LM (2021) Aromatase in the human brain. Androgens: Clinical Research and Therapeutics 2:189–202. https://doi.org/10.1089/andro.2021.0007
16. Santen RJ, Brodie H, Simpson ER, Siiteri PK (2009) History of aromatase: saga of an important biological mediator and therapeutic target. Endocr Rev 30:343–375. https://doi.org/10.1210/er.2008-0016
17. Sato K, Iemitsu M (2018) The role of dehydroepiandrosterone (DHEA) in skeletal muscle. Vitamins and hormones. 108:205–221. https://doi.org/10.1016/bs.vh.2018.03.002
18. Pöllänen E, Sipilä S, Alen M (2011) Differential influence of peripheral and systemic sex steroids on skeletal muscle quality in pre- and postmenopausal women. Aging Cell 10:650–660. https://doi.org/10.1111/j.1474-9726.2011.00701.x
19. Pöllänen E, Kangas R, Horttanainen M et al (2015) Intramuscular sex steroid hormones are associated with skeletal muscle strength and power in women with different hormonal status. Aging Cell 14:236–248. https://doi.org/10.1111/acel.12309
20. Dalgaard LB, Oxfeldt M, Dam TV, Hansen M (2022) Intramuscular sex steroid hormones are reduced after resistance training in postmenopausal women, but not affected by estrogen therapy. Steroids 186:109087. https://doi.org/10.1016/j.steroids.2022.109087
21. Alexander SE, Pollock AC, Lamon S (2022) The effect of sex hormones on skeletal muscle adaptation in females. Eur J Sport Sci 22:1035–1045. https://doi.org/10.1080/17461391.2021.1921854
22. Laurent MR, Hammond GL, Blokland M et al (2016) Sex hormone-binding globulin regulation of androgen bioactivity *in vivo*: validation of the free hormone hypothesis. Sci Rep 6:35539. https://doi.org/10.1038/srep35539
23. Bikle DD (2020) The free hormone hypothesis: when, why, and how to measure the free hormone levels to assess vitamin D, thyroid, sex hormone, and cortisol status. JBMR Plus 5:e10418. https://doi.org/10.1002/jbm4.10418

24. Aizawa K, Iemitsu M, Maeda S (2007) Expression of steroidogenic enzymes and synthesis of sex steroid hormones from DHEA in skeletal muscle of rats. American Journal of Physiology-Endocrinology and Metabolism 292:E577–E584. https://doi.org/10.1152/ajpendo.00367.2006
25. Iresjö B-M, Landin A, Ohlsson C, Lundholm K (2019) Estrogen biosynthesis in cultured skeletal muscle cells (L6) induced by amino acids. Genes Nutr 14:29. https://doi.org/10.1186/s12263-019-0652-8
26. Mahmoodzadeh S, Dworatzek E (2019) The role of 17β-estradiol and estrogen receptors in regulation of Ca2+channels and mitochondrial function in cardiomyocytes. Front Endocrinol. https://doi.org/10.3389/fendo.2019.00310
27. Labrie F, Labrie C (2013) DHEA and intracrinology at menopause, a positive choice for evolution of the human species. Climacteric 16:205–213. https://doi.org/10.3109/13697137.2012.733983
28. Sato K, Iemitsu M (2015) Exercise and sex steroid hormones in skeletal muscle. J Steroid Biochem Mol Biol 145:200–205. https://doi.org/10.1016/j.jsbmb.2014.03.009
29. Pines A (2015) Climacteric commentaries. Climacteric 18:101–106. https://doi.org/10.3109/13697137.2015.993530
30. Ikeda K, Horie-Inoue K, Inoue S (2019) Functions of estrogen and estrogen receptor signaling on skeletal muscle. J Steroid Biochem Mol Biol 191:105375. https://doi.org/10.1016/j.jsbmb.2019.105375
31. Faltas CL, LeBron KA, Holz MK (2020) Unconventional estrogen signaling in health and disease. Endocrinology 161:bqaa030
32. J L, D L (2020) Does GPER really function as a G Protein-Coupled Estrogen receptor in vivo? Frontiers in endocrinology 11:. https://doi.org/10.3389/fendo.2020.00148
33. Arterburn JB, Prossnitz ER (2023) G protein–coupled estrogen receptor GPER: molecular pharmacology and therapeutic applications. Annu Rev Pharmacol Toxicol 63:295–320. https://doi.org/10.1146/annurev-pharmtox-031122-121944
34. Barton M (2012) Position paper: the membrane estrogen receptor GPER – clues and questions. Steroids 77:935–942. https://doi.org/10.1016/j.steroids.2012.04.001
35. Ventura-Clapier R, Piquereau J, Veksler V, Garnier A (2019) Estrogens, estrogen receptors effects on cardiac and skeletal muscle mitochondria. Front Endocrinol (Lausanne) 10:557. https://doi.org/10.3389/fendo.2019.00557
36. Barros RPA, Gabbi C, Morani A et al (2009) Participation of ERα and ERβ in glucose homeostasis in skeletal muscle and white adipose tissue. American Journal of Physiology-Endocrinology and Metabolism 297:E124–E133. https://doi.org/10.1152/ajpendo.00189.2009
37. Ekenros L, Papoutsi Z, Fridén C et al (2017) Expression of sex steroid hormone receptors in human skeletal muscle during the menstrual cycle. Acta Physiol (Oxf) 219:486–493. https://doi.org/10.1111/apha.12757
38. Baltgalvis KA, Greising SM, Warren GL, Lowe DA (2010) Estrogen regulates estrogen receptors and antioxidant gene expression in mouse skeletal muscle. PLoS ONE 5:e10164. https://doi.org/10.1371/journal.pone.0010164
39. Hansen M (2018) Female hormones: do they influence muscle and tendon protein metabolism? Proc Nutr Soc 77:32–41. https://doi.org/10.1017/S0029665117001951
40. Yoh K, Ikeda K, Horie K, Inoue S (2023) Roles of estrogen, estrogen receptors, and estrogen-related receptors in skeletal muscle: regulation of mitochondrial function. Int J Mol Sci 24:1853. https://doi.org/10.3390/ijms24031853
41. Al H, Z Z, Bg D, V R (2017) The role of skeletal muscle Estrogen receptors in metabolic homeostasis and insulin Sensitivity. Advances in experimental medicine and biology 1043. https://doi.org/10.1007/978-3-319-70178-3_13
42. Hevener AL, Zhou Z, Moore TM (2018) The impact of ERα action on muscle metabolism and insulin sensitivity – strong enough for a man, made for a woman. Mol Metab 15:20–34. https://doi.org/10.1016/j.molmet.2018.06.013
43. Ribas V, Drew BG, Zhou Z (2016) Skeletal muscle action of Estrogen receptor α is critical for the maintenance of mitochondrial function and metabolic homeostasis in females. Sci Transl Med 8:334ra54. https://doi.org/10.1126/scitranslmed.aad3815
44. Yoh K, Ikeda K, Nagai S et al (2022) Constitutive activation of Estrogen receptor α signaling in muscle prolongs exercise endurance in mice. Biochem Biophys Res Commun 628:11–17. https://doi.org/10.1016/j.bbrc.2022.08.064
45. Collins BC, Mader TL, Cabelka CA et al (2018) Deletion of estrogen receptor α in skeletal muscle results in impaired contractility in female mice. J Appl Physiol 124:980. https://doi.org/10.1152/japplphysiol.00864.2017
46. Cabelka CA, Baumann CW, Collins BC (2019) Effects of ovarian hormones and estrogen receptor α on physical activity and skeletal muscle fatigue in female mice. Exp Gerontol 115:155. https://doi.org/10.1016/j.exger.2018.11.003
47. Collins BC, Arpke RW, Larson AA et al (2019) Estrogen regulates the satellite cell compartment in females. Cell Rep 28:368-381e6. https://doi.org/10.1016/j.celrep.2019.06.025
48. Seko D, Fujita R, Kitajima Y et al (2020) Estrogen receptor β controls muscle growth and regeneration in young female mice. Stem Cell Reports 15:577–586. https://doi.org/10.1016/j.stemcr.2020.07.017
49. Sharma G, Prossnitz ER (2021) Targeting the G protein-coupled estrogen receptor (GPER) in obesity and diabetes. Endocrine and Metabolic Science 2:100080. https://doi.org/10.1016/j.endmts.2021.100080
50. Le G, Baumann CW, Warren GL, Lowe DA (2023) In vivo potentiation of muscle torque is enhanced in female mice through estradiol-estrogen receptor signaling. J Appl Physiol 134:722–730. https://doi.org/10.1152/japplphysiol.00731.2022
51. Wang H, Alencar A, Lin M et al (2016) Activation of GPR30 improves exercise capacity and skeletal muscle strength in senescent female Fischer344×Brown Norway rats. Biochem Biophys Res Commun 475:81–86. https://doi.org/10.1016/j.bbrc.2016.05.040
52. Vrtačnik P, Ostanek B, Mencej-Bedrač S, Marc J (2014) The many faces of estrogen signaling. Biochem Med (Zagreb) 24:329–342. https://doi.org/10.11613/BM.2014.035
53. Gharahdaghi N, Phillips BE, Szewczyk NJ (2021) Links between testosterone, oestrogen, and the growth hormone/insulin-like growth factor axis and resistance exercise muscle adaptations. Front Physiol 11:621226. https://doi.org/10.3389/fphys.2020.621226
54. Ra H, Ps C (2018) Estrogen in the male: a historical perspective. Biol Reprod 99. https://doi.org/10.1093/biolre/ioy043
55. Lobo RA (2017) Hormone-replacement therapy: current thinking. Nat Rev Endocrinol 13:220–231. https://doi.org/10.1038/nrendo.2016.164
56. Enns DL, Tiidus PM (2010) The influence of Estrogen on skeletal muscle: sex matters. Sports Med 40:41–58. https://doi.org/10.2165/11319760-000000000-00000
57. Jomard C, Gondin J (2023) Influence of sexual dimorphism on satellite cell regulation and inflammatory response during skeletal muscle regeneration. Physiol Rep 11:e15798. https://doi.org/10.14814/phy2.15798
58. MacNeil LG, Baker SK, Stevic I, Tarnopolsky MA (2011) 17β-estradiol attenuates exercise-induced neutrophil infiltration in men. Am J Physiol Regul Integr Comp Physiol 300:R1443–1451. https://doi.org/10.1152/ajpregu.00689.2009
59. Dieli-Conwright CM, Spektor TM, Rice JC et al (2009) Hormone therapy attenuates exercise-induced skeletal muscle damage in

postmenopausal women. J Appl Physiol 107(3):853–858. https://doi.org/10.1152/japplphysiol.00404.2009
60. Tiidus PM, Lowe DA, Brown M (2013) Estrogen replacement and skeletal muscle: mechanisms and population health. J Appl Physiol 115(5):569–578. https://doi.org/10.1152/japplphysiol.00629.2013
61. Feng X, Li G, Wang S (2004) Effects of Estrogen on gastrocnemius muscle strain injury and regeneration in female rats. Acta Pharmacol Sin
62. Tian X, Gao Z, Yin D et al (2023) 17beta-estradiol alleviates contusion-induced skeletal muscle injury by decreasing oxidative stress via SIRT1/PGC-1α/Nrf2 pathway. Steroids 191:109160. https://doi.org/10.1016/j.steroids.2022.109160
63. Geraci A, Calvani R, Ferri E et al (2021) Sarcopenia and menopause: the role of estradiol. Front Endocrinol (Lausanne) 12:682012. https://doi.org/10.3389/fendo.2021.682012
64. Mandelli A, Tacconi E, Levinger I (2022) The role of estrogens in osteosarcopenia: from biology to potential dual therapeutic effects. Climacteric 25:81–87. https://doi.org/10.1080/13697137.2021.1965118
65. Oxfeldt M, Dalgaard LB, Farup J, Hansen M (2022) Sex hormones and satellite cell regulation in women. Transl Sports Med 2022:9065923. https://doi.org/10.1155/2022/9065923
66. Velders M, Diel P (2013) How sex hormones promote skeletal muscle regeneration. Sports Med 43:1089–1100. https://doi.org/10.1007/s40279-013-0081-6
67. Larson AA, Baumann CW, Kyba M, Lowe DA (2020) Oestradiol affects skeletal muscle mass, strength and satellite cells following repeated injuries. Exp Physiol 105:1700–1707. https://doi.org/10.1113/EP088827
68. Tanideh N, Shahin Sheikhani H, Salesi M et al (2014) Effects of endurance exercise and Estrogen supplementation on the proliferation of satellite cells. Comp Clin Pathol 23:1645–1649. https://doi.org/10.1007/s00580-013-1839-9
69. Mangan G, Bombardier E, Mitchell AS (2014) Oestrogen-dependent satellite cell activation and proliferation following a running exercise occurs via the PI3K signalling pathway and not IGF-1. Acta Physiol (Oxf) 212:75–85. https://doi.org/10.1111/apha.12317
70. Buckinx F, Aubertin-Leheudre M (2022) Sarcopenia in menopausal women: current perspectives. Int J Womens Health 14:805–819. https://doi.org/10.2147/IJWH.S340537
71. Karvinen S, Juppi H-K, Le G (2021) Estradiol deficiency and skeletal muscle apoptosis: possible contribution of MicroRNAs. Exp Gerontol 147:111267. https://doi.org/10.1016/j.exger.2021.111267
72. Qaisar R, Renaud G, Hedstrom Y et al (2013) Hormone replacement therapy improves contractile function and myonuclear organization of single muscle fibres from postmenopausal monozygotic female twin pairs. J Physiol 591:2333–2344. https://doi.org/10.1113/jphysiol.2012.250092
73. Dam TV, Dalgaard LB, Ringgaard S (2021) Transdermal estrogen therapy improves gains in skeletal muscle mass after 12 weeks of resistance training in early postmenopausal women. Front Physiol 11:596130. https://doi.org/10.3389/fphys.2020.596130
74. Greising SM, Baltgalvis KA, Lowe DA, Warren GL (2009) Hormone therapy and skeletal muscle strength: a meta-analysis. J Gerontol Biol Sci Med Sci 64:1071–1081. https://doi.org/10.1093/gerona/glp082
75. Javed AA, Mayhew AJ, Shea AK, Raina P (2019) Association between hormone therapy and muscle mass in postmenopausal women: a systematic review and meta-analysis. JAMA Netw Open 2:e1910154. https://doi.org/10.1001/jamanetworkopen.2019.10154
76. Xu Y, Deng K-L, Xing T-F et al (2020) Effect of hormone therapy on muscle strength in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Menopause 27:827. https://doi.org/10.1097/GME.0000000000001538
77. Collins BC, Laakkonen EK, Lowe DA (2019) Aging of the musculoskeletal system: how the loss of estrogen impacts muscle strength. Bone 123:137–144. https://doi.org/10.1016/j.bone.2019.03.033
78. Kitajima Y, Ono Y (2016) Estrogens maintain skeletal muscle and satellite cell functions. J Endocrinol 229:267–275. https://doi.org/10.1530/JOE-15-0476
79. Prestes J, Leite RD, Pereira GB et al (2012) Resistance training and glycogen content in ovariectomized rats. Int J Sports Med 33:550–554. https://doi.org/10.1055/s-0032-1304646
80. Moran AL, Nelson SA, Landisch RM (2007) Estradiol replacement reverses ovariectomy-induced muscle contractile and myosin dysfunction in mature female mice. J Appl Physiol 102:1387–1393. https://doi.org/10.1152/japplphysiol.01305.2006
81. Bilodeau PA, Coyne ES, Wing SS (2016) The ubiquitin proteasome system in atrophying skeletal muscle: roles and regulation. American Journal of Physiology-Cell Physiology 311:C392–C403. https://doi.org/10.1152/ajpcell.00125.2016
82. Vasconsuelo A, Pronsato L, Ronda AC et al (2011) Role of 17β-estradiol and testosterone in apoptosis. Steroids 76:1223–1231. https://doi.org/10.1016/j.steroids.2011.08.001
83. Bombardier E, Vigna C, Bloemberg D et al (2013) The role of Estrogen receptor-α in Estrogen-mediated regulation of basal and exercise-induced Hsp70 and Hsp27 expression in rat soleus. Can J Physiol Pharmacol 91:823–829. https://doi.org/10.1139/cjpp-2013-0037
84. Locke M, Salerno SA (2020) Ovariectomy alters lengthening contraction induced heat shock protein expression. Appl Physiol Nutr Metab. https://doi.org/10.1139/apnm-2019-0212
85. Tiidus P, Bombardier E, Bloemberg D (2011) Estrogen receptor-α partially mediates estrogen effect on muscle Hsp70 levels. FASEB J 25(S1):1060.2. https://doi.org/10.1096/fasebj.25.1_supplement.1060.2
86. La Colla A, Vasconsuelo A, Milanesi L, Pronsato L (2017) 17β-Estradiol protects skeletal myoblasts from apoptosis through p53, Bcl-2, and FoxO families. J Cell Biochem 118:104–115. https://doi.org/10.1002/jcb.25616
87. Vasconsuelo A, Milanesi L, Boland R (2010) Participation of HSP27 in the antiapoptotic action of 17β-estradiol in skeletal muscle cells. Cell Stress Chaperones 15:183–192. https://doi.org/10.1007/s12192-009-0132-y
88. Wiedmer P, Jung T, Castro JP et al (2021) Sarcopenia – molecular mechanisms and open questions. Ageing Res Rev 65:101200. https://doi.org/10.1016/j.arr.2020.101200
89. Tian X, Lou S, Shi R (2023) From mitochondria to sarcopenia: role of 17β-estradiol and testosterone. Front Endocrinol 14:1156583. https://doi.org/10.3389/fendo.2023.1156583
90. Hu Y, Fang B, Tian X et al (2024) Passive exercise is an effective alternative to HRT for restoring OVX induced mitochondrial dysfunction in skeletal muscle. Front Endocrinol (Lausanne) 15:1356312. https://doi.org/10.3389/fendo.2024.1356312
91. Silva SB, Honorato-Sampaio K, Costa SP et al (2022) The superior beneficial effects of exercise training versus hormone replacement therapy on skeletal muscle of ovariectomized rats. Sci Rep 12:8764. https://doi.org/10.1038/s41598-022-12739-8
92. Nagai S, Ikeda K, Horie-Inoue K et al (2016) Estrogen modulates exercise endurance along with mitochondrial uncoupling protein 3 downregulation in skeletal muscle of female mice. Biochem Biophys Res Commun 480:758–764. https://doi.org/10.1016/j.bbrc.2016.10.129
93. Ko SH, Jung Y (2021) Energy metabolism changes and dysregulated lipid metabolism in postmenopausal women. Nutrients 13:4556. https://doi.org/10.3390/nu13124556

94. Lundsgaard AM, Kiens B (2014) Gender differences in skeletal muscle substrate metabolism - molecular mechanisms and insulin sensitivity. Front Endocrinol 5:195. https://doi.org/10.3389/fendo.2014.00195
95. Spangenburg EE, Geiger PC, Leinwand LA, Lowe DA (2012) Regulation of physiological and metabolic function of muscle by female sex steroids. Med Sci Sports Exerc 44:1653–1662. https://doi.org/10.1249/MSS.0b013e31825871fa
96. Gibb FW, Homer NZM, Faqehi AMM et al (2016) Aromatase inhibition reduces insulin sensitivity in healthy men. J Clin Endocrinol Metab 101:2040–2046
97. Sipilä S, Narici M, Kjaer M et al (2013) Sex hormones and skeletal muscle weakness. Biogerontology 14:231–245. https://doi.org/10.1007/s10522-013-9425-8
98. Maher AC, Akhtar M, Tarnopolsky MA (2010) Men supplemented with 17β-estradiol have increased β-oxidation capacity in skeletal muscle. Physiol Genomics 42:342–347. https://doi.org/10.1152/physiolgenomics.00016.2010
99. Hansen PA, McCarthy TJ, Pasia EN et al (1996) Effects of ovariectomy and exercise training on muscle GLUT-4 content and glucose metabolism in rats. J Appl Physiol 80:1605–1611. https://doi.org/10.1152/jappl.1996.80.5.1605
100. Min W, Fang P, Huang G et al (2018) The decline of whole-body glucose metabolism in ovariectomized rats. Exp Gerontol 113:106–112. https://doi.org/10.1016/j.exger.2018.09.027
101. Puah JA, Bailey CJ (1985) Effect of ovarian hormones on glucose metabolism in mouse soleus muscle. Endocrinology 117:1336–1340. https://doi.org/10.1210/endo-117-4-1336
102. Narasimhan A, Sampath S, Jayaraman S, Karundevi B (2013) Estradiol favors glucose oxidation in gastrocnemius muscle through modulation of insulin signaling molecules in adult female rats. Endocr Res 38:251–262. https://doi.org/10.3109/07435800.2013.775148
103. Ahmed-Sorour H, Bailey CJ (1981) Role of ovarian hormones in the long-term control of glucose homeostasis, glycogen formation and gluconeogenesis. Ann Nutr Metab 25:208–212. https://doi.org/10.1159/000176496
104. Jackson KC, Wohlers LM, Lovering RM et al (2013) Ectopic lipid deposition and the metabolic profile of skeletal muscle in ovariectomized mice. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 304:R206–R217. https://doi.org/10.1152/ajpregu.00428.2012
105. Zhong W, Shi X, Yuan H et al (2019) Effects of exercise training on the autophagy-related muscular proteins expression in ovariectomized rats. Front Physiol 10:735. https://doi.org/10.3389/fphys.2019.00735
106. Cavalcanti-de-Albuquerque JPA, Salvador IC, Martins EL et al (2014) Role of estrogen on skeletal muscle mitochondrial function in ovariectomized rats: a time course study in different fiber types. J Appl Physiol 116:779–789. https://doi.org/10.1152/japplphysiol.00121.2013
107. Hamilton DJ, Minze LJ, Kumar T et al (2016) Estrogen receptor alpha activation enhances mitochondrial function and systemic metabolism in high-fat-fed ovariectomized mice. Physiol Rep 4:e12913. https://doi.org/10.14814/phy2.12913
108. Campbell SE, Febbraio MA (2001) Effect of ovarian hormones on mitochondrial enzyme activity in the fat oxidation pathway of skeletal muscle. Am J Physiol Endocrinol Metab 281:E803–808. https://doi.org/10.1152/ajpendo.2001.281.4.E803
109. Campbell SE, Mehan KA, Tunstall RJ et al (2003) 17 -Estradiol upregulates the expression of peroxisome proliferator-activated receptor and lipid oxidative genes in skeletal muscle. J Mol Endocrinol. https://doi.org/10.1677/jme.0.0310037
110. Garrido P, Salehzadeh F, Duque-Guimaraes DE, Al-Khalili L (2014) Negative regulation of glucose metabolism in human myotubes by supraphysiological doses of 17β-estradiol or testosterone. Metabolism 63:1178–1187. https://doi.org/10.1016/j.metabol.2014.06.003
111. Simpson ER, Davis SR (2001) Minireview: aromatase and the regulation of estrogen biosynthesis–some new perspectives. Endocrinology 142:4589–4594. https://doi.org/10.1210/endo.142.11.8547
112. Unger CA, Aladhami AK, Hope MC (2023) Skeletal muscle endogenous estrogen production ameliorates the metabolic consequences of a high-fat diet in male mice. Endocrinology 164:bqad105. https://doi.org/10.1210/endocr/bqad105
113. Aladhami AK, Unger CA, Hope MC (2022) Augmenting skeletal muscle estrogen does not prevent or rescue obesity-linked metabolic impairments in female mice. Endocrinology 163:bqac146
114. Tian X, Hu Y, Li T et al (2025) Exercise-induced mitochondrial protection in skeletal muscle of ovariectomized mice: a myogenic E2 synthesis-independent mechanism. Redox Biol 85:103735. https://doi.org/10.1016/j.redox.2025.103735
115. Han D, Denison MS, Tachibana H, Yamada K (2002) Effects of estrogenic compounds on immunoglobulin production by mouse splenocytes. Biol Pharm Bull 25:1263–1267. https://doi.org/10.1248/bpb.25.1263
116. F LD MB (2018) Signaling by steroid hormones in the 3D nuclear space. Int J Mol Sci 19. https://doi.org/10.3390/ijms19020306
117. Chen P, Li B, Ou-Yang L (2022) Role of estrogen receptors in health and disease. Front Endocrinol. https://doi.org/10.3389/fendo.2022.839005
118. Ramírez-de-Arellano A, Pereira-Suárez AL, Rico-Fuentes C (2022) Distribution and effects of estrogen receptors in prostate cancer: associated molecular mechanisms. Front Endocrinol. https://doi.org/10.3389/fendo.2021.811578
119. Aarshageetha P, Janci PRR, Tharani ND (2023) Role of alternate therapies to improve the quality of life in menopausal women: a systematic review. J Mid-life Health 14:153–158. https://doi.org/10.4103/jmh.jmh_222_22
120. Engman V, Critchlow AJ, Laakkonen EK et al (2025) The role and regulation of intramuscular sex hormones in skeletal muscle: a systematic review. J Clin Endocrinol Metab 110:e1732–e1746. https://doi.org/10.1210/clinem/dgaf174
121. Shi R, Tian X, Feng Y (2019) Expression of aromatase and synthesis of sex steroid hormones in skeletal muscle following exercise training in ovariectomized rats. Steroids 143:91–96. https://doi.org/10.1016/j.steroids.2019.01.003
122. Feng Y, Wu J, Cheng Z et al (2019) Mechanical stretch enhances sex steroidogenesis in C2C12 skeletal muscle cells. Steroids 150:108434. https://doi.org/10.1016/j.steroids.2019.108434
123. Aizawa K, Iemitsu M, Otsuki T et al (2008) Sex differences in steroidogenesis in skeletal muscle following a single bout of exercise in rats. J Appl Physiol 104:67–74. https://doi.org/10.1152/japplphysiol.00558.2007
124. Aizawa K, Iemitsu M, Maeda S et al (2011) Endurance exercise training enhances local sex steroidogenesis in skeletal muscle. Med Sci Sports Exerc 43:2072–2080. https://doi.org/10.1249/MSS.0b013e31821e9d74
125. Moradpour R (2019) The effects of regular aerobic exercise on primary dysmenorrhea in young girls. J Phys Act Horm 3:067–082
126. Copeland JL, Consitt LA, Tremblay MS (2002) Hormonal responses to endurance and resistance exercise in females aged 19–69 years. J Gerontol Biol Sci Med Sci 57:B158–165. https://doi.org/10.1093/gerona/57.4.b158
127. Ketabipoor S, Koushkie Jahromi M (2015) Effect of aerobic exercise in water on serum Estrogen and C - Reactive protein and body mass index level in obese and normal weight postmenopausal women. https://doi.org/10.17795/whb-25048. Women's Health Bulletin 2:

128. Moghadasi M, Siavashpour S (2013) The effect of 12 weeks of resistance training on hormones of bone formation in young sedentary women. Eur J Appl Physiol 113:25–32. https://doi.org/10.1007/s00421-012-2410-0
129. Razzak ZA, Khan AA, Farooqui SI (2019) Effect of aerobic and anaerobic exercise on Estrogen level, fat mass, and muscle mass among postmenopausal osteoporotic females. Int J Health Sci (Qassim) 13:10–16
130. Landi F, Marzetti E, Martone AM et al (2014) Exercise as a remedy for sarcopenia. Curr Opin Clin Nutr Metab Care 17:25–31. https://doi.org/10.1097/MCO.0000000000000018
131. Chow LS, Gerszten RE, Taylor JM et al (2022) Exerkines in health, resilience and disease. Nat Rev Endocrinol 18:273–289. https://doi.org/10.1038/s41574-022-00641-2
132. Sato K, Fujita S, Iemitsu M (2017) *Dioscorea esculenta*-induced increase in muscle sex steroid hormones is associated with enhanced insulin sensitivity in a type 2 diabetes rat model. FASEB J 31:793–801. https://doi.org/10.1096/fj.201600874R
133. Aizawa K, Iemitsu M, Maeda S (2010) Acute exercise activates local bioactive androgen metabolism in skeletal muscle. Steroids 75:219–223. https://doi.org/10.1016/j.steroids.2009.12.002
134. Sato K, Iemitsu M, Matsutani K et al (2014) Resistance training restores muscle sex steroid hormone steroidogenesis in older men. FASEB J 28:1891–1897. https://doi.org/10.1096/fj.13-245480
135. Horii N, Sato K, Mesaki N, Iemitsu M (2016) Increased muscular 5α-dihydrotestosterone in response to resistance training relates to skeletal muscle mass and glucose metabolism in type 2 diabetic rats. PLoS ONE 11:e0165689. https://doi.org/10.1371/journal.pone.0165689
136. Vingren JL, Kraemer WJ, Hatfield DL (2008) Effect of resistance exercise on muscle steroidogenesis. J Appl Physiol 105:1754–1760. https://doi.org/10.1152/japplphysiol.91235.2008
137. Li X, Li H, Jia L et al (2015) Oestrogen action and male fertility: experimental and clinical findings. Cell Mol Life Sci 72:3915–3930. https://doi.org/10.1007/s00018-015-1981-4
138. Haines M, McKinley-Barnard SK, Andre TL et al (2018) Skeletal muscle Estrogen receptor activation in response to eccentric exercise Up-Regulates Myogenic-Related gene expression independent of differing serum estradiol levels occurring during the human menstrual cycle. J Sports Sci Med 17:31–39. PMID: 29535576; PMCID: PMC5844207