



# The Therapeutic Intervention of Sex Steroid Hormones for Sarcopenia

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Sarcopenia, characterized by the excessive loss of skeletal muscle mass, strength, and function, is associated with the overall poor muscle performance status of the elderly, and occurs more frequently in those with chronic diseases. The causes of sarcopenia are multifactorial due to the inherent relationship between muscles and molecular mechanisms, such as mitochondrial function, inflammatory pathways, and circulating hormones. Age-related changes in sex steroid hormone concentrations, including testosterone, estrogen, progesterone, and their precursors and derivatives, are an important aspect of the pathogenesis of sarcopenia. In this review, we provide an understanding of the treatment of sarcopenia through the regulation of sex steroid hormones. The potential benefits and future research emphasis of each sex steroid hormone therapeutic intervention (testosterone, SARMs, estrogen, SERMs, DHEA, and progesterone) for sarcopenia are discussed. Enhanced understanding of the role of sex steroid hormones in the treatment for sarcopenia could lead to the development of hormone therapeutic approaches in combination with specific exercise and nutrition regimens.

**Keywords:** sarcopenia, aging, sex steroid hormones, androgen, estrogen, progesterone, dehydroepiandrosterone, drug

## INTRODUCTION

The term “sarcopenia,” established based on the efforts of different groups, is typically defined as an age-related decline in skeletal muscle mass and muscle function (1–4). It is characterized by the progressive loss of muscle mass, strength, endurance, and reduced metabolic capacity of muscle fibers (5). The average sarcopenia incidence is 5–13% for people aged 60–70 years and 11–50% for those older than 80 years (6). It is associated with many age-related adverse events, such as an increase in the duration of hospitalization (7, 8), an impaired quality of life (9), reduced mobility (8), and a higher risk of hip or vertebral fractures (10, 11). In some instances, sarcopenia is secondary to some uncontrolled chronic diseases, such as malignant tumors, liver disease, or renal dysfunction. Moreover, progressive sarcopenia may worsen the primary disease, or even increase the rate of mortality (12, 13). Currently, the common ways to treat sarcopenia have been approved as follows: aerobic and resistance exercise, protein and energy intake, and vitamin D supplementation, but with limited therapeutic effects (14, 15). Over time, sarcopenia has become a vital public health issue and is now recognized as an independently reportable clinical disorder, and better treatments are urgently needed (16).

The pathophysiology of sarcopenia is both complex and multidirectional. Reduced muscle mass in the elderly can be ascribed to the lower rate of muscle protein synthesis when compared to the

rate of muscle proteolysis (17). Microscopically, atrophy of type II muscle fibers increases, and motor units within the muscle are lost and replaced by adipose and connective tissue (18). As a result, abnormal muscle metabolism, reduced muscle mass, and muscle strength capacity as well as increased muscle damage is observed (18).

The severity of sarcopenia can be measured using three parameters: muscle strength, muscle mass, and physical performance. Hand grip strength, leg muscle strength, and a chair stand test are applied to test muscle strength (19). Low muscle mass is estimated by the lumbar muscle cross-sectional area derived from computed tomography (CT) or magnetic resonance imaging (MRI) (20), or is assessed by clinical practice, such as the appendicular skeletal muscle mass (ASMM) (21, 22). Lean body mass (LBM) is often used to measure muscle mass, especially in the condition of sarcopenia obesity (1). Physical performance is a multidirectional concept involving muscle function and nervous system function, including the body balance (23). It can be variously measured by the timed-up and go test (TUG), the 6-min walk test, and the short physical performance battery (SPPB) (1).

Research exploring the inner mechanisms of sarcopenia is expanding and includes studies on muscle fiber composition and neuromuscular function, the potential of myo-satellite cell to proliferate and differentiate, inflammatory processes, mitochondrial dysfunction, as well as the age-related alterations of anabolic hormones in the endocrine system (24–27). Muscle mass is associated with a dynamic change in the anabolic and catabolic processes of skeletal muscle tissues (27). Anabolic hormones, such as sex steroid hormones, growth hormone, and insulin, are believed to play a major role in muscle tissue growth and remodeling (27).

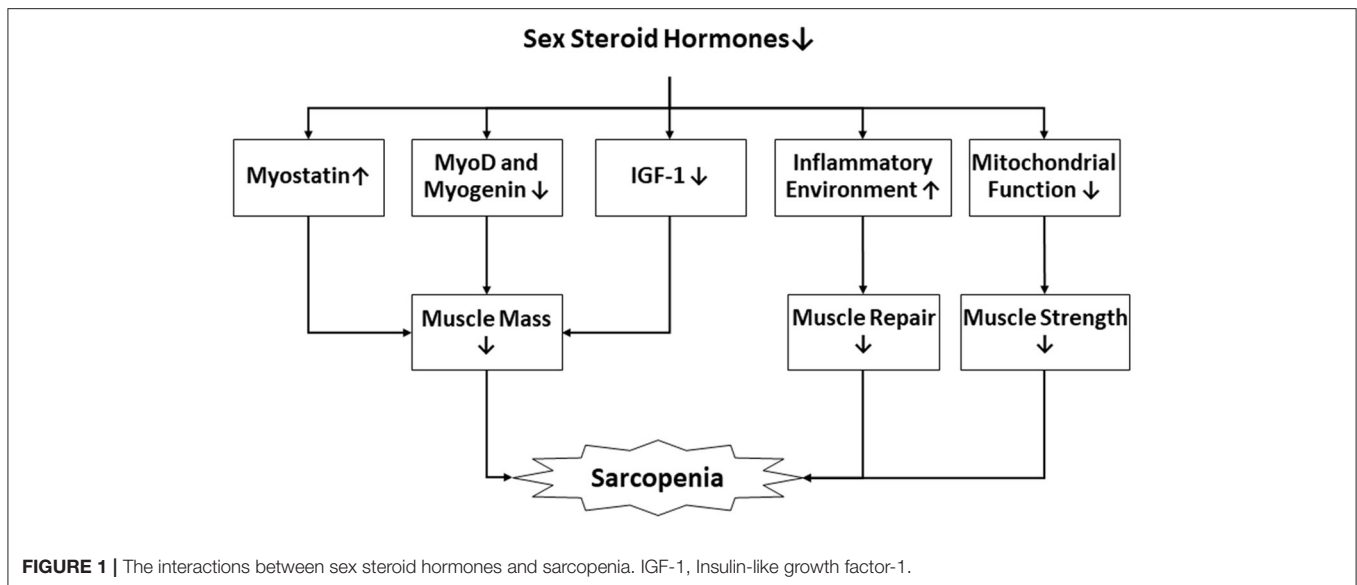
Sex steroid hormones such as testosterone, estrogen, and progesterone, are important systemic anabolic hormones involved in maintenance of skeletal muscle mass and function, including hypertrophy and the regeneration of damaged muscles (28, 29). During aging, their levels become depleted, which is consistent with decreased muscle mass (29). Myo-satellite cells, myoblasts and myocytes both express androgen receptors and estrogen receptors, while progesterone receptors are found in myocytes. It has been found that the expression of the receptors in muscle cells plays an essential role in regulating the proliferation and differentiation of these cells (30–32). Moreover, these sex steroid hormones may participate in intracellular signaling pathways such as the IGF-1/Akt/mTOR pathway, MAPK pathway, Wnt and Notch signaling, among others, either positively or negatively, although the specific mechanism is still not well-understood (33–36). In addition, suppression of myostatin mRNA expression, activation of MyoD and myogenin, improved function of mitochondrial, and counteracting inflammation play roles in the physiological effects of sex steroid hormones in the skeletal muscle cells (Table 1, Figure 1) (29, 34, 37–39).

Decreased circulating levels of the sex steroids may lead to deterioration in muscle mass and function in elderly (40). Although sex hormone-derived drugs have not been widely used, it has been demonstrated that supplemental

TABLE 1 | Physiological effects of sex steroid hormones on receptors expression, signaling pathways, and metabolic alterations in the skeletal muscles.

	Receptors expression in muscle cells	IGF-1/Akt/mTOR pathway	MAPK pathway	Wnt and notch pathway	Myostatin	MyoD and myogenin	IGF-1	Inflammatory environment	Mitochondrial function
Testosterone	+	+	+	+	+	ND	+	+	+
Estrogen	+	+	+	ND	+	+	+	+	+
Progesterone	+	ND	ND	ND	ND	+	ND	ND	+
DHEA	ND	ND	ND	ND	ND	ND	+	ND	+

DHEA, Dehydroepiandrosterone; IGF-1, Insulin-like growth factor-1; ND, No available data.



hormone intervention could be an effective approach to treat sarcopenia (41). In this review, we will outline the role of sex steroid hormones in the treatment of sarcopenia, focusing on recent findings.

## TESTOSTERONE

Testosterone, a representative sex steroid hormone, is mainly produced by male Leydig cells and female ovarian thecal cells, and partly by adrenal gland (42). As the principal physiological anabolic hormone, testosterone increases protein synthesis in skeletal muscle, promotes muscle regeneration and repair by activation of myo-satellite cells, counteracts muscle proteolysis, and increases intramuscular insulin-like growth factor-1 (IGF-1) levels, etc. (43–45). During aging, testosterone levels in healthy men fall by 1% annually from the age of 30. For women, the testosterone levels at 40 years of age are about 50% of those at 20 years of age (46, 47). In some clinical conditions, the reductions in the testosterone levels may result in poorer clinical prognosis (48, 49).

Considering the significant physiological functions of testosterone, and its consistent benefits on muscle mass and strength in hypogonadal treatment, multiple randomized controlled trials (RCTs) have been conducted to explore the effects of testosterone replacement therapy (TRT) on the elderly since the 1990s. However, the effects observed on muscle performance and physical function were inconsistent due to the different treatment methods employed (47, 48, 50, 51). For healthy older men, TRT can help increase LBM, but muscle strength does not change (50, 52). Some other clinical trials showed that testosterone substitution results in an increase of both LBM and muscle strength (53–55). Previous trials were also limited by their relatively short duration, small sample sizes, and the heterogeneity of testosterone doses, regimens, and on-treatment testosterone levels (50–54). A meta-analysis

conducted in 2018 showed that TRT may increase physical performance (measured by the Physical Activity Scale for the Elderly score and the 6-min walk test), but failed to increase muscle strength (measured by leg muscle strength and hand grip strength) (56).

The positive effects of exercise and physical training, including slowing down muscle loss and improving strength and performance in the elderly, have been substantiated (57, 58). Physical training, as the most effective intervention for sarcopenia, is often used in combination with pharmacological interventions to improve the effectiveness. Although, previous studies of TRT combined with exercise presented inconsistent results (55, 56, 59, 60), several clinical trials showed that the combination treatment can help increase the muscle mass or strength (59, 60). A prospective study demonstrated that TRT offers no benefit beyond resistance exercise alone (61). In 2021, a systematic review and meta-analysis on TRT of 21 RCTs for LBM and 15 RCTs for muscle strength concluded that both LBM and muscular strength were significantly improved by a combination regimen, which included physical exercise and testosterone-based interventions, when compared with physical exercise or testosterone-based interventions alone (62).

Several studies showed that patients with chronic diseases or injury can benefit from TRT (63, 64). Resistance training combined with TRT maximized improvements in muscle mass when compared with TRT alone for patients with spinal cord injury (63). In patients with advanced cancer, TRT improved LBM and physical activity, as well as their quality of life compared to placebo (64).

Recent studies in elderly women explored the anabolic effect of testosterone on sarcopenia (65, 66). Compared with placebo, low doses of TRT in women elevated the serum testosterone concentration and induced a significant increase in total LBM, and showed microscopic type II muscle fiber hypertrophy induced by testosterone (65). Another study showed

that short-term TRT in hysterectomized women with low circulating testosterone levels was related to increased trunk muscle area (66).

Nevertheless, TRT is still not widely recommended due to the adverse effects. TRT is associated with a higher risk of urogenital problems including benign prostatic hyperplasia and prostate cancer (67). Additionally, adverse cardiovascular events such as a significant increase in coronary artery non-calcified plaque volume (68) and menstrual changes in women and gynecomastia in men (69) are known to occur. A recent meta-analysis of testosterone did not indicate significant side effects and suggested that the adverse effects may be decreased by avoiding supraphysiological levels of plasma testosterone (62).

The strong anabolic effects of TRT, especially when combined with physical exercise, on muscle mass have been confirmed by a large body of evidence and the effects on muscle strength and function are supported by recent studies. Due to its inevitable side effects, TRT is still not recommended for wide use. Short term or intermittent TRT to maintain low serum testosterone levels in circulation may help lower incidence of adverse events. In the future, the risk-benefit balance between the adverse effects and effectiveness of TRT for sarcopenia needs to be explored. Furthermore, a specific TRT regimen (dosage for hormone therapy, in combination with exercise or nutrition) for older sarcopenic patients with different health conditions is worth exploring.

## SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS)

As an alternative to androgen replacement therapy, SARMS were created to provide a targeted therapeutic effect through the androgen receptors in different tissues. Binding of SARMS to androgen receptor in the prostate and seminal vesicles is partial agonistic, while in muscle and bone it is fully agonistic (70). Some SARMS have an anabolic/androgenic ratio of 20:1, in contrast to the ratio of 1:1 for testosterone (71).

The effects of highly selective drugs have been analyzed in several preclinical studies (72–75). Among them, one study demonstrated increased gastrocnemius muscle weight, bone biomechanical properties, and bone mineral density in ovariectomized female rats that were administered SARMS (72). On this basis, several clinical trials have found SARMS to benefit with body composition, exhibiting increased muscle mass, and decreased fat quality. However, its effects on muscle strength and function and its long-term efficacy remain inconclusive (70, 76–79). In a phase II clinical trial, Dalton JT showed that enobosarm (SARM) resulted in dose-dependent improvements in both LBM and physical performance as evaluated by the stair climbing test in healthy postmenopausal women and in aged men (80). Nevertheless, enobosarm failed to improve stair climb power in a separate phase III clinical trial, although LBM was increased significantly (81, 82).

According to various clinical trials, postmenopausal women could also take advantage of SARMS treatment. Neil D suggested that healthy postmenopausal women presented higher sensitivity

to LBM improvement when treated with GSK2881078 (SARM) than healthy elderly men. Furthermore, the female cohort presented a better response at lower doses than males (73). In addition to postmenopausal women, patients suffering from any chronic disease, such as osteoporosis, non-small-cell lung cancer, stress urinary incontinence, and hip fractures, can also benefit from SARMS treatment with increased muscle mass (70, 81). Besides, the side effects of SARMS are much milder than TRT, such as the increases in alanine transaminase and aspartate transaminase, reductions in high density lipoprotein, and suppression of sex hormone binding globulin and total testosterone levels (76–78, 80).

Although SARMS have been shown to increase muscle mass, food and drug administration (FDA) still does not approve SARMS for the treatment of sarcopenia despite the fewer side effects when compared with testosterone. This may be a result of the inconsistent results of SARMS on muscle function. However, given the potential and safety of SARM therapy, future RCTs should be continued. It is recommended that SARMS be combined with nutritional supplements or exercise training, which will contribute to increased LBM and muscle function, especially for those with chronic diseases.

## ESTROGEN

Estrogen, a common sex steroid hormone active in the reproductive organs, is also found in other organs and tissues, such as the skeletal muscle (83). In postmenopausal women or following bilateral oophorectomy, limited estrogen levels can cause osteoporosis, frailty, and sarcopenia (84–86). Estrogen deficiency is also related to decreased muscle strength (87), but the effects and function of estrogen on muscles remain unclear (88, 89). Estrogen may reduce the inflammation in the surrounding environment and thus prevent depletion of satellite cells, which help enhance skeletal muscle repair and growth if provided with necessary precursors (90).

Mice with low estrogen levels showed a decline in skeletal muscle strength, and this effect could be reversed by estrogen replacement therapy (ERT) (91, 92). Nevertheless, results concerning ERT in humans are conflicting (42). Although postmenopausal estrogen therapy is not as potent as testosterone, some studies revealed that it had a positive effect on muscle strength or muscle function (42, 93–97). However, other studies didn't support the hypothesis that ERT could work against sarcopenia (98–100). A meta-analysis of 24 studies showed that postmenopausal women treated with ERT had a significant impact on muscle strength compared with placebo (94). A subsequent meta-analysis in 2019, which included 12 studies, looked at the effects of hormones on muscle mass. No significant differences between an estrogen-based or an estrogen-progesterone-based hormone therapy and placebo were observed (101). Although the type and dosage of estrogen replacement administered varied among different trials, there were still no definitive conclusions.

Similar to TRT, ERT has been shown to enhance muscle function when combined with resistance training (94). In

a randomized placebo-controlled study in postmenopausal women, estrogen-progesterone-based hormone therapy combined with high-impact physical exercise showed significant increases in muscle strength as evaluated by knee extension torque and vertical jumping height when compared with the control group (99); more research is necessary to assess these findings.

Some severe complications have been reported when ERT is used in postmenopausal women with sarcopenia, including a higher risk of cardiovascular disease, breast cancer, endometrial cancer, and deep vein thrombosis (42, 102, 103). In a large-scale clinical trial (16,608 postmenopausal women aged 50–79 years), estrogen plus progestin increased total and invasive breast cancers compared with placebo during 5 years (104). Since ERT does not translate into improved physical function, and has potential risks, ERT is not recommended for healthy postmenopausal women to prevent or treat sarcopenia. Future clinical trials of estrogen as a therapeutic intervention for sarcopenia need to be conducted cautiously.

## SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

SERMs are similar to estrogen in the observed drug effects but with fewer side effects. The highly selective drugs have estrogenic effects on the bone composition, blood vessels, and lipid metabolism but show anti-estrogenic effects on the breast and genital system (105, 106), leading to fewer side effects compared to estrogen. In a preclinical study, estradiol and SERMs influenced ER- $\alpha$  function in hSkM cells to promote muscle growth in postmenopausal women (107). Studies in ovariectomized rats have shown that raloxifene (SERM) modifies body composition by reducing body fat accumulation (108).

A RCT demonstrated that a 1-year raloxifene treatment could significantly increase the fat-free mass compared to placebo for postmenopausal women, without providing any significant advantage in muscle strength (109). In another randomized placebo-controlled trial, 1-year raloxifene treatment prevented enhanced body weight and abdominal adiposity (110). A study in 2016 consisting of 4,383 patients suggested that 5-year raloxifene treatment had significant effects on body composition achieved through maintaining body weight and increasing body mass index, with only minor side effects (111). Although it did not directly assess the roles of SERM on muscle mass or muscle strength, the 5-year trial revealed a preferential effect of SERM on the maintenance of muscle mass with fewer adverse effects. The side effects of SERMs were not significant compared with those of control groups, notably leg cramps and hot flashes (111).

Although there is still insufficient evidence on the effect of SERM on muscle mass and strength, it has been shown to maintain weight and increase fat-free mass over a long period of time in older postmenopausal women, with minor side effects. For this group, further research to explore the long-term effects of SERM on muscle mass and/or mass function may be useful, with consideration given to combining SERM with exercises, or for patients with chronic diseases who overtime, lose weight.

## DEHYDROEPIANDROSTERONE (DHEA)

DHEA is mainly produced by the adrenal glands and can be converted to active androgens or estrogens in other tissues (112, 113). As a natural precursor to steroid hormone, DHEA exerts its anabolic effects when metabolized to active androgens or estrogens. DHEA also stimulates the production of IGF-1, which helps in muscle growth and repair, and increases its bioavailability in muscles by lowering the levels of IGF-1 binding protein-1 (114–116). In addition, DHEA improved insulin sensitivity, which directly affects the anabolic efficacy, by increasing the absorption rate of amino acids in the skeletal muscle (117). DHEA levels decline with age (118), and men in their 70–80s only have ~20% of their peak value of DHEA, while similarly aged women have 30% of their peak value of DHEA (119). The decline in the level of DHEA is related to the loss of age-related muscle mass and strength (112, 113, 120, 121).

Thus far, the efficacy of DHEA replacement therapy for sarcopenia has not been consistently demonstrated. A randomized placebo-controlled trial showed that a daily oral dose of 100 mg was effective in maintaining body fat and muscle strength in elderly men, but not in elderly women (122). A decrease in body fat was observed in some studies (123, 124), while, other studies showed slight positive effects on muscle mass, strength, or function (125, 126). In 2011, a systematic review involving eight studies failed to confirm any efficacy of DHEA administration on muscle strength or physical performance (127). A meta-analysis in 2018, comprising four RCTs showed no positive effects of DHEA on muscles (128).

It is worth noting that some research found that when combined with exercise training, DHEA may play a better role in increasing muscle mass and strength in both rats and humans (129, 130). Elderly people in a RCT benefitted from a regimen with 50 mg DHEA daily and weightlifting exercise. This study showed a significant increase in muscular strength and mass in the combination group compared with individuals in the non-combination group (130). However, such a synergistic effect of DHEA was not confirmed by another combination trial (126). The differences between the results may be associated with the diversity of research designs, particularly the treatment time and dose, and the size of the sample population.

DHEA, which has fewer side effects than testosterone, is generally well-tolerated. Minor side effects including edema, facial hair growth, acne, and seborrhea have been observed in both men and women (131, 132). Unlike testosterone, no significant prostatic adverse events of DHEA were observed in elderly men. Most of these studies revealed no positive effects from DHEA supplementation alone. This was supported by a recent high quality meta-analysis (128). When DHEA was combined with exercises, muscle mass, and strength of elderly people was enhanced in some instances. As DHEA was observed to decrease the body fat in several trials, future RCT studies should explore an optimal formulation combining an exercise regimen with DHEA supplementation for senior patients with high body weight.

**TABLE 2** | Summary of the main effects of sex steroid hormones.

	<b>Muscle mass</b>	<b>Muscle strength</b>	<b>Physical performance</b>	<b>Adverse events</b>	<b>Effects when combined with exercises</b>	<b>Patients who may benefit</b>	<b>Future directions</b>
Testosterone	Sufficient evidence in favor	Some evidence in favor	Some evidence in favor	Gynecomastia and prostatic diseases in men; menstrual changes in women; cardiovascular events	Sufficient evidence in favor	Hypogonadal men; short term or intermittent TRT for elderly men and postmenopausal women, including patients with chronic diseases or injury	Specific TRT formulation (dosage for hormone therapy, in combination with exercise or nutrition) for older sarcopenic people with different health conditions
SARMs	Sufficient evidence in favor	Insufficient evidence	Insufficient evidence	Increase in alanine transaminase and aspartate transaminase	No evidence	Elderly men and postmenopausal women, especially with chronic diseases	The long-term effects of SARMs combined with exercise training on muscle mass and/or mass function of elderly with chronic diseases
Estrogen	Insufficient evidence	Insufficient evidence	Insufficient evidence	Breast cancer, endometrial cancer, cardiovascular events, deep vein thrombosis	Some evidence in favor	Not recommended	Need to be conducted cautiously
SERMs	Some evidence in favor	Insufficient evidence	Insufficient evidence	Leg cramps, hot flashes	No evidence	Postmenopausal women who need long time administration to maintain their body weight and muscle mass	The long-term effects of SERMs on muscle mass and/or mass function of elderly with chronic diseases who are under normal weight over time
DHEA	Insufficient evidence	Insufficient evidence	Insufficient evidence	Edema, facial hair growth, acne, and seborrhea	Insufficient evidence	Not recommended	The optimal formulation of exercise and DHEA for specific high body weight seniors
Progesterone	Insufficient evidence	Insufficient evidence	Insufficient evidence	Venous thromboembolism, breast cancer	Insufficient evidence	Not recommended	The effects of bioidentical progesterone on postmenopausal women, especially with poor appetite or low body weight

*DHEA, Dehydroepiandrosterone; SARMs, Selective androgen receptor modulators; SERM, Selective estrogen receptor modulators; TRT, testosterone replacement therapy.*

## PROGESTERONE

Progesterone, commonly produced by the adrenal gland as well as the ovaries or testes, has important functions in the female reproductive system and mammary gland. It also has functions involving several other tissues, including the cardiovascular system, the central nervous system, bones, and muscles (133). Progesterone receptors and estrogen receptors which are located and expressed in skeletal muscle tissue exert their direct effects on muscle tissue (134–136).

Progestogens have not been approved for use for sarcopenia, because of insufficient research on their direct therapeutic effect on muscle mass or function. In postmenopausal women, similar to testosterone, progesterone administration improved muscle protein fractional synthesis rate by ~50% (33). The study also showed that progesterone has potent stimulatory impacts on myogenic differentiation 1 (MYOD1) mRNA expression, which is involved in muscle protein synthesis (33).

Megestrol is a synthetic progestin, which improves appetites and weight gain in patients with cancer, immunodeficiency syndrome, or other disabilities (137, 138). However, a RCT focusing on the elderly who do not have severe chronic illnesses, cancer, or immunodeficiency, showed negative results. The addition of megestrol did not seem to enhance the beneficial effects of resistance muscle training, leading to less muscle strength and function gains (139).

When combined with training and estrogen therapy, synthetic progesterone exerted a synergistic effect in increasing leg muscle cross-sectional area compared with the non-combination therapy group (140). Oral contraceptives (OC), which consists of synthetic estradiol and synthetic progesterone, are widely used by young females. A 2-year RCT indicated that young female runners receiving OC and resistance training increased LBM significantly compared to non-users (141). In contrast, another clinical study showed that OC impaired LBM gains in young women after resistant training, and this was connected to lower levels of anabolic hormones, such as DHEA and IGF-1, but higher catabolic hormone, like cortisol (142).

Adverse events including venous thromboembolism and breast cancer were observed during synthetic progesterone treatment. Compared with synthetic progestin, bioidentical progesterone is safer and more efficient. It has been shown that bioidentical progesterone can lower risk of breast cancer from estrogen (143), however, few studies have explored the effects of bioidentical progesterone on muscles.

The roles of progesterone on muscle mass or muscle function are controversial, even when combined with exercises. Based on this, we do not recommend progesterone supplementation for patients with muscle loss. Future research could focus on the use of bioidentical progesterone, especially in elderly patients with a poor appetite or low body weight.

## OUTLOOK

Both positive and negative effects are observed in treatments using sex steroid supplementation for sarcopenia, namely testosterone, SARMs, estrogen, SERMs, DHEA, and progesterone. The main effects and our suggestions are shown in **Table 2**. It can be inferred that elderly with sarcopenia with different health conditions may benefit from different hormone treatments and future trials are needed to explore.

## CONCLUSION

The decline of sex steroid hormones during aging influences the maintenance and development of skeletal muscles, resulting in sarcopenia. However, no sex steroid supplementation, including testosterone, estrogen, and progesterone, has been approved by the FDA for the management of sarcopenia, due to insufficient current evidence or low safety and effectiveness. In recent years, studies have explored better formulations of sex steroid hormones for sarcopenia, revealing more possibilities to treat this age-related disease. TRT is a promising treatment for sarcopenia, and we suggest that short term or intermittent TRT to maintain low serum testosterone levels may assist in optimizing its safety and effectiveness. Therefore, a specific TRT formulation for older sarcopenic patients with different health conditions is worth exploring. It is recommended that SARMs be combined with exercise training, especially for those with chronic diseases. Given the potential and safety of SARM therapy, future RCTs should be continued. SERMs can be used to maintain weight and increase fat-free mass over a long period of time in postmenopausal women with minor side effects. Estrogen is not recommended to treat sarcopenia or for further exploration due to its severe adverse effects. The role of progesterone and DHEA in the treatment of sarcopenia is still unclear. Large-scale clinical studies are necessary to investigate the promising drugs: testosterone, SARM and SERM. Considering the individual patient characteristics (sex, age, and chronic diseases), trials of different specific sex steroid interventions (combined with physical exercises or nutrition) for management of sarcopenia are urgently needed to determine their effectiveness and safety. Enhanced understanding of the role of sex steroid hormones in the treatment for sarcopenia could lead to the development of hormone therapeutic approaches, which could benefit patients with sarcopenia.

## AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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