Purpose of review
Sarcopenia is a geriatric syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death. Sarcopenia is a multifactorial process involving the decline of androgens, including dehydroepiandrosterone sulphate (DHEAS) and testosterone. The aim of this review is to highlight the effects of DHEAS and testosterone treatment to counteract sarcopenia, especially in older men.

Recent findings
DHEAS and, more importantly, testosterone treatment are associated with increased muscle mass, whereas the effects on muscle function and physical performance are less clear. The results of recent randomized placebo controlled trials with DHEAS in older men and women and testosterone in men with mobility limitation are discussed. The novel current and future scenarios to attenuate the detrimental effects and to optimize the efficacy of sex hormone treatment are also addressed.

Summary
DHEAS and testosterone are important options in the armamentarium of sarcopenia treatment in older men. Future studies are needed to address new approaches by using selective compounds, targeting the correct form and dosage, tailoring the correct patient to treat, and taking into account the multifactorial origin and the new definition of sarcopenia.

Keywords
DHEAS, older men, sarcopenia, testosterone

INTRODUCTION
Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death. The recent consensus documents elaborated by the European (EWGSOP) and North-American taskforces recommend to consider low muscle mass and muscle function (strength or performance) for the diagnosis of sarcopenia [1–3].

SARCOPENIA AS MULTIFACTORIAL PROCESS: THE ROLE OF SEX HORMONES
Sarcopenia is a multifactorial process involving several possible mechanisms including physical activity, nutritional intake, oxidative stress, inflammation, and hormonal changes. However, the precise contribution of each factor is unknown. There is emerging evidence that the disruption of several positive regulators (Akt and serum response factor) of muscle hypertrophy with age is an important feature in the progression of sarcopenia. In contrast, many investigators have failed to demonstrate an age-related enhancement in levels of common negative regulators (Atrogin-1, myostatin, and calpain) in senescent mammalian muscles.

There is evidence that sex hormones [testosterone, estrogens, and dehydroepiandrosterone sulphate (DHEAS)], whose levels decrease with age, exert an important role in the age-related onset of sarcopenia [4•]. The adrenal hormones DHEA, DHEAS, and androstenedione undergo extraglandular metabolism by a complicated network of enzymes leading to physiologically active testosterone and estradiol (Fig. 1). The decline in DHEAS may also have a role in the age-related dysregulation of testosterone in men where testosterone levels decrease by 1% per year, and, bioavailable testosterone by 2% per year from age 30. In women,
testosterone levels drop rapidly from 20 to 45 years of age.

Many epidemiological studies show that combined age-associated decline of sex hormones has a strong impact on mortality and osteo-metabolic diseases [5], leading to the hypothesis that DHEAS and testosterone supplementation may induce beneficial effects in typical age-related changes in body composition and physical function.

This is not surprising because the phenotypes of hygogonadism and hypoadrenalism share many aspects with aging phenotype, especially in terms of changes in body composition, well being, and depressive status. Many of the physical and behavioral changes that occur in elderly men are similar to those observed in younger men with hypogonadism [6].

MOLECULAR MECHANISMS UNDERLYING THE BENEFICIAL EFFECTS OF DEHYDROEPANDROSTERONE SULPHATE AND TESTOSTERONE ON SARCOPENIA

DHEAS may affect muscle performance. In effect the skeletal muscle is able to convert DHEA into active androgens and estrogens, and to stimulate insulin-like growth factor-1 (IGF-1) which is important in muscle growth and recovery [7]. The maintenance of adult muscle depends on satellite cell activation, proliferation, survival, and differentiation that can also be stimulated by testosterone [8,9]. The effects of testosterone on muscle can be categorized as anabolic, anticatabolic, and potentially anti-inflammatory (Fig. 2) [10**,11]. Sex hormones can stimulate the muscle protein synthesis and improve recycling of intracellular amino acids, the breakdown rate, and promote the activity of motoneurons [10**].

Testosterone promotes commitment of pluripotent stem cells to myogenic lineage but inhibits their differentiation into adipocytes via an androgen receptor-mediated pathway, suggesting the rationale for its well known effects on the reduction in body fat mass and the increase in fat free mass and insulin sensitivity [12**].

Testosterone treatment is also associated with elevation in hemoglobin of 0.8 g/dl on average, and in old men with mild anemia, it can be considered an additional mechanism by which testosterone ameliorates muscle oxygenation and function [13]. Indirect effects on skeletal muscle include the down-modulation of myostatin and the increase in IGF-1 and polyamines (Fig. 2).

The profound link between sex hormones and sarcopenia emerging from these mechanisms has been tested in intervention studies [10**].

RANDOMIZED CONTROLLED TRIAL ON DEHYDROEPANDROSTERONE SULPHATE AND SARCOPENIA

During the past decade a number of randomized controlled clinical trials have been performed to test the effectiveness of DHEAS supplementation in older men and women and they are nicely summarized in a recent review [14*].
Table 1 depicts the characteristics of the studies selected from this review [15–19], in participants (women and men) at least 50 years and older. The studies differed in their included populations, duration of follow-up, and interventions (e.g., exercise). Study sizes ranged from 19 to 280 participants, with durations of follow-up ranging from 3 to 24 months. The dose of oral DHEA ranged from 50 [15] to 75 mg/day [18]. Three studies used concomitant interventions in addition to DHEA supplementation, two using exercise training [16,19] and the other [15] gentle exercise (endurance and resistance training).

All the studies examined measures of muscle strength. Two studies showed improvement in leg press [18,19], but in both DHEA treatment was combined with exercise. Nevertheless, similar numbers of studies had negative results for this endpoint. Four studies also examined measures of physical performance. Only one study showed improvement in a composite score measuring physical performance [15]; the rest reported no differences between DHEA and control for any. All together these trials suggest improvement in muscle strength or function especially in women but only when DHEA treatment is combined with exercise.

As previously reported, one of the mechanisms by which DHEA exerts its anabolic effects is the transformation into testosterone rather than estradiol (Fig. 1). The anabolic properties of testosterone in the skeletal muscle have been tested in a randomized controlled trial (RCT) addressing the effects of testosterone on muscle function. The findings from 11 RCTs were examined using the methods of meta-analysis to determine whether androgen treatment [testosterone/5α-dihydrotestosterone (DHT)] increased strength in men aged 65 years and older [20]. This was the first synthesis on the effect of testosterone/DHT on strength in older men using only randomized, double-blind trials. A moderate increase in muscle strength was found in patients on testosterone/DHT therapy versus placebo group. The average patient in the treatment condition receiving testosterone performed better than approximately 19.3% of the placebo group. More recent studies including periods of treatment ranging from 20 weeks to 24 months, not included in the Ottenbacher et al. study, are summarized in Table 2. Kenny et al. [21] in 2010 investigated in a double-blind RCT the effects of testosterone supplementation on body composition, muscle, physical function, and safety in 131 men (mean age 77.1) with low testosterone, history of fracture, or bone mineral density with T-score –2.0 SD or less and frailty. Participants received 5 mg/day of testosterone or placebo for 12–24 months; all received calcium (1500 mg/day diet and supplement) and cholecalciferol (1000 IU/day). Ninety-nine men (75.6%) completed 12 months, and 62 (47.3%) ended the therapy (mean 23 months; range 16–24 months for 62 who completed therapy). Study adherence was 54%, with 40% of patients maintaining 70% adherence. Total and bioavailable testosterone at 12 months was 583 and 157 ng/dl, respectively, in the treatment group. There was an increase in lean mass and a decrease in fat mass in the testosterone group, but, no differences in strength or physical performance, and safety parameters.

These findings were somewhat confirmed by Srinivas-Shankar et al. [22] who tested the effects of 6-months testosterone treatment in an intermediate...
Table 1. Randomized controlled trial intervention studies addressing the effects of DHEA on muscle strength and physical function in older patients in the period between 2005 and 2012

<table>
<thead>
<tr>
<th>Author et al., 2010 [15]</th>
<th>Populations</th>
<th>Baseline DHEA</th>
<th>Oral DHEA dose</th>
<th>Duration of treatment</th>
<th>Effects of DHEA supplementation</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Kenny et al., 2010 [15] | 87 women, aged ≥65 | 0.30–0.32 μg/ml | DHEA 50 mg/day (N = 43) vs. placebo (N = 44) | 6 months | Markers of muscle strength:  
  - Handgrip (Jamar dynamometer): no difference from baseline with DHEA vs. placebo  
  - Leg press: significantly greater improvement in DHEA group vs. placebo group, when combined with gentle exercise  
  Physical function and performance:  
  - Composite scores (ability to rise from chair, standing balance, walking speed and the get up and go test): no difference from baseline with vs. placebo  
 | Gentle exercise: chair aerobics or yoga held during two 90-min session per week |
| Igwebuibe et al., 2008 [16] | 31 sedentary women, aged 54–72 years | 0.39–0.43 μg/ml | DHEA 50 mg/day (N = 17) vs. placebo (N = 14) | 3 months | Markers of muscle strength:  
  - Chest press: no significant effect  
  - Leg press: no significant changes in peak aerobic activity  
  Physical function and performance:  
  - Peak of oxygen uptake (marker of peak aerobic activity): no significant improvement in VO2peak  
 | Exercise training: endurance training (cycle ergometry) 4 days per week and resistance training 3 days per week |
| Muller et al., 2006 [17] | 49 men, with low strength scores aged ≥70 years | 0.66 μg/ml | DHEA 50 mg/day (N = 25) vs. placebo (N = 24) | 9 months | Markers of muscle strength:  
  - Handgrip (Jamar dynamometer): no difference from baseline with vs. placebo  
  - Knee extensor and flexor: no significant effect of DHEA on isometric knee extension or flexion when compared with placebo  
  Physical function and performance:  
  - Composite scores (ability to rise from chair, standing balance, walking speed and the get up and go test): no significant improvement between DHEA and placebo groups |
<table>
<thead>
<tr>
<th>Author</th>
<th>Populations</th>
<th>Baseline DHEA</th>
<th>Oral DHEA dose</th>
<th>Duration of treatment</th>
<th>Effects of DHEA supplementation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nair et al.</td>
<td>30 men and 87 women, aged ≥60 years</td>
<td>Men with DHEA-S &lt; 1.57 μg/ml and Women with DHEA-S &lt; 0.95 μg/ml</td>
<td>DHEA 75 mg/day (N = 56; men 24.7%) vs. placebo (N = 61; men 26.5%)</td>
<td>24 months</td>
<td>Markers of muscle strength: Chest press: no significant effect on isometric strength. Leg press: no significant effect. Knee extension and flexion when compared with placebo. No significant effect of DHEA on peak aerobic activity. No significant differences in physical function and performance: Peak of oxygen uptake (marker of peak aerobic activity): no significant differences in improvement between DHEA and placebo.</td>
<td></td>
</tr>
<tr>
<td>Villareal and Holloszy</td>
<td>28 men and 28 women, aged 65–78 years</td>
<td>Men with DHEA-S &lt; 0.33 μg/ml and Women with DHEA-S &lt; 0.95 μg/ml</td>
<td>DHEA 50 mg/day (N = 29; men 51.7%) vs. placebo (N = 27; men 48.1%)</td>
<td>10 months</td>
<td>Markers of muscle strength: All patients participated in a supervised weight training program 3 day per week. Chest press: significant increasing from baseline when combined with resistance training at 10 months, both in men and women. Leg press: significantly greater improvement with DHEA than with placebo, when combined with resistance training than with training alone. Knee extensor and flexor: greater improvement only in knee extension with DHEA and resistance training than with training alone.</td>
<td></td>
</tr>
</tbody>
</table>

DHEA, dehydroepiandrosterone.

**Sex hormones and sarcopenia Maggio et al.**

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<table>
<thead>
<tr>
<th>Author</th>
<th>Populations</th>
<th>Baseline total testosterone</th>
<th>Form of testosterone</th>
<th>Duration of treatment</th>
<th>Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenny et al., 2010 [21]</td>
<td>131 men (mean age 77.1 ± 7.6)</td>
<td>&lt;350 ng/dl</td>
<td>Transdermal</td>
<td>12–24 months</td>
<td>Lean mass; fat mass in testosterone group but no differences in strength or physical performance</td>
<td>Calcium and vitamin D treatment was also performed</td>
</tr>
<tr>
<td>Srinivas-Shankar et al., 2010 [22]</td>
<td>24 healthy, community-dwelling older men (60–85 years)</td>
<td>&lt;350 ng/dl</td>
<td>Transdermal hydro-alcoholic T gel (Testogel 1%) at a dose of 50 mg/day</td>
<td>6 months</td>
<td>Improved lower limb muscle strength and improve body composition, quality of life, and physical function</td>
<td>Intermediate frail population</td>
</tr>
<tr>
<td>Travison et al., 2011 [23**]</td>
<td>209 randomized participants, 165 had follow-up efficacy measures. Mean (SD) age was 74 (5.4) years</td>
<td>100–350 ng/dl</td>
<td>10g testosterone gel daily</td>
<td>6 months</td>
<td>Muscle strength and stair-climbing power</td>
<td>Participants with mobility limitation: stopped because of higher prevalence of CVD</td>
</tr>
<tr>
<td>Bhasin et al., 2012 [33**]</td>
<td>8 treatment groups received (4 groups) or 2.5 mg/day of dutasteride (4 groups)</td>
<td>300–1200 ng/dl</td>
<td>Testosterone enanthate 50, 125, 300, or 600 mg/week of for and placebo</td>
<td>20 weeks</td>
<td>Changes in fat-free mass in response to graded testosterone doses did not differ in men in whom DHT was suppressed by dutasteride</td>
<td>With and without a dual 5α-reductase inhibitor</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; DHT, 5α-dihydrotestosterone.
frail population of 24 healthy, community-dwelling older men (60–85 years) of testosterone 12 nmol/l or less or free testosterone 250 pmol/l or less. Transdermal hydro-alcoholic testosterone gel (Testogel 1%) at a dose of 50 mg/day for 6 months improved lower limb muscle strength, body composition, quality of life, and physical function. More convincing data come from the Testosterone in Older Men with Mobility Limitations (TOM) Trial [23**,24]. The aim of this placebo-controlled randomized trial was to determine whether testosterone therapy in 209 community-dwelling men affected by severe limitation in mobility with a mean age of 74 years and low testosterone level [100–350 ng/dl (3.5–12.1 nmol/l)] improves lower extremity muscle strength and physical function. Participants were randomized to placebo or 10 g testosterone gel daily for 6 months. Primary outcome was leg-press strength. Secondary outcomes included chest-press strength, stair-climb, 40-m walk, muscle mass, and physical activity. Of the 209 randomized participants, 165 had follow-up efficacy measures. Mean (SD) age was 74 (5.4) years and Short Physical Performance Battery Score 7.7 (1.4). Testosterone arm exhibited greater improvements in leg-press strength, chest-press strength and power, and loaded stair-climb than placebo. Compared with placebo, a significantly greater proportion of men receiving testosterone improved their leg-press and chest-press strengths (43 versus 18%; \( P = 0.01 \)) and stair-climbing power (28 versus 10%; \( P = 0.03 \)) more than a minimally important difference. Increases in leg-press strength and stair-climbing power were associated with changes in testosterone levels. Physical activity, walking speed, self-reported function, and fatigue did not change. Despite the significant increases in the muscle strength among elderly men, given the high doses of testosterone, the risks outweighed the benefits [23**]. Adverse cardiovascular events, categorized according to The Medical Dictionary of Regulatory Activities (MedDRA), occurred in 11 of the 106 men receiving testosterone, compared to 1 of 103 men receiving placebo. The excess of cardiovascular events in the testosterone group led the data and safety monitoring board to recommend early termination of the study [24].

These results were surprising because meta-analysis of previous trials of testosterone therapy have not shown significant increases in cardiovascular risk with testosterone therapy [25]. These and other potential complications (thrombotic and risk of prostate cancer) along with data from RCT showing only small effects on strength and physical function in older men underline the need for safer and more effective compounds [26].

**STRATEGIES TO ATTENUATE THE DETRIMENTAL EFFECTS ASSOCIATED WITH TESTOSTERONE TREATMENT OF SARCOPENIA**

To deal with the potential failure of sex hormone replacement treatment, a number of interesting strategies have been advocated in the current literature. These approaches are summarized in Figure 3. They include the correct selection of route of administration and the dosage, the ideal population to target, the intermittent interventions and the use of selective androgen receptor modulators (SARMS), and finally the combination with nutritional supplementation and exercise.

**SELECTION OF THE OLDER POPULATION TO TREAT AND NEED FOR INDIVIDUALIZED DOSAGE**

In our opinion, the critical aspect for testosterone therapy is the appropriate identification of the population suitable for the replacement therapy. In a recent analysis performed in the InCHIANTI population, which is a representative sample of older Italian men, participants were grouped according to testosterone levels in severely hypogonadal, moderately hypogonadal and eugonadal as suggested by the most recent recommendations of Late-Onset Hypogonadism (LOH) in older men [27*,28]. According to these guidelines testosterone levels below 230 ng/dl identified patients to be treated. We found a significant difference in hemoglobin levels and muscle strengths between individuals with different testosterone status [28]. Zitzmann et al. [29] tried to identify a threshold linking testosterone levels and specific symptoms of testosterone deficiency. The urgent need for specific cut-off to be used for replacement therapy is also suggested by Emmelot-Vonk et al. [30]. These authors found that 6-months testosterone in older men with low-normal testosterone concentration did not affect functional status or cognition but increased lean body mass and had mixed metabolic effects. However, the cut-off of the testosterone used in this study to identify hypogonadal patients is questionable as the dosage to reach the anabolic or anticasabolic action without undesirable effects is still debated. The baseline characteristics of the population to treat are also of interest. The testosterone group of TOM study had a higher prevalence of hyperlipidemia, hypertension, and statin use before interventions, suggesting that coexisting illnesses should be taken into account during participant recruitment, and the definition of LOH proposed by Wu et al. [31] as a detached testosterone deficiency syndrome related to...
sexuality alone does not appear to reflect accurately the complexity of the aging male patient.

Another important critical point is the dosage and the route of administration of testosterone that should be chosen in older individuals. In TOM study the authors started with transdermal administration (which is the recommended way of administration) at the highest recommended level of 10 g of testosterone per day, titrating up to 15 g/day in some patients [to achieve testosterone levels of 500–1000 ng/dl (1.74–34.7 nmol/l)]. However, the usual procedure for testosterone substitution by gel would be to start at 5 g and titrate up to 10 g/day, which is consistent with the official international guidelines for the use of this preparation [28,32].

Caution is necessary, especially in older men who have a history of cardiovascular disease and immobility and in all men (young and old), when using higher testosterone doses than recommended.

Meanwhile, many attempts have been performed to attenuate the side-effects associated with testosterone treatment and in order to verify what mechanisms mediate the sex hormone action on muscle level.

An important issue concerns the higher potential risk of prostate dysfunction associated with testosterone treatment. Steroid 5α-reductase inhibitors are used to treat benign prostatic hyperplasia and androgenic alopecia, but the role of DHT in mediating testosterone’s effects on muscle, sexual function, erythropoiesis, and other androgen-dependent processes remains poorly understood. These authors determined whether testosterone’s effects on muscle mass, strength, and prostate volume are attenuated when its conversion to DHT is blocked by dutasteride (an inhibitor of 5α-reductase type 1 and 2). The 5α-Reductase Trial was a RCT of healthy men aged 18–50 years, comparing placebo and testosterone enanthate with dutasteride and testosterone enanthate. Eight treatment groups received 50, 125, 300, or 600 mg/week of testosterone enanthate for 20 weeks and placebo (four groups) or 2.5 mg/day of dutasteride (four groups). The 5α-Reductase Trial was a RCT of healthy men aged 18–50 years, comparing placebo and testosterone enanthate with dutasteride and testosterone enanthate. Eight treatment groups received 50, 125, 300, or 600 mg/week of testosterone enanthate for 20 weeks and placebo (four groups) or 2.5 mg/day of dutasteride (four groups). The primary outcome was change in fat-free mass, secondary outcomes among others, changes in fat mass, muscle strength, and prostate volume. A total of 139 men were randomized; 102 completed the 20-week intervention. The mean fat-free mass gained by the dutasteride group was 0.6 kg when

![Figure 3](image-url)
receiving 50 mg/week of testosterone enanthate, 2.6 kg for 125 mg/week, 5.8 kg for 300 mg/week, and 7.1 kg for 600 mg/week. The mean fat-free mass gained by the placebo groups was 0.8 kg when receiving 50 mg/week of testosterone enanthate, 3.5 kg for 125 mg/week, 5.7 kg for 300 mg/week, and 8.1 kg for 600 mg/week. Changes in fat mass, muscle strength, and prostate volume did not differ between the groups. Changes in fat-free mass in response to graded testosterone doses did not differ in men in whom DHT (which is the main determinant of prostate dysfunction) was suppressed by dutasteride from those treated with placebo, indicating that conversion of testosterone to DHT is not essential for mediating its anabolic effects on muscle.

**CONTINUOUS VERSUS INTERMITTENT ANDROGEN INTERVENTIONS**

Cycling androgens is another interesting option to obtaining the anabolic effects without significant side-effects. This strategy is based on the option chosen by athletes to improve physical performance by enhancing muscle mass and strength. This paradigm has been recently studied in older men being treated with testosterone. Sheffield-Moore and Dillon [34] investigated the efficacy of a monthly cycled testosterone regimen that uses half the testosterone dose as the current standard of care of continuous therapy on body composition and muscle strength in older men. Twenty-four community-dwelling older men 70 ± 2 years of age with total testosterone levels below 500 ng/dl were randomized into a 5-month double-blind placebo-controlled trial. Patients were dosed weekly for 5 months, receiving continuous testosterone (n = 8; 100 mg testosterone enanthate, i.m. injection); monthly cycled testosterone (n = 8; alternating months of testosterone and placebo); or placebo (n = 8). The main outcomes of the study included the evaluation of body composition by Dual-Energy X-Ray Absorptiometry and upper and lower body muscle strength. Secondary outcomes included body weight, serum hormones, and mixed-muscle protein fractional synthesis rate (FSR). Total lean body mass was increased and percentage fat was reduced after 5 months in continuous testosterone and monthly cycled testosterone (P < 0.05). Upper body muscle strength increased in continuous testosterone, and lower body muscle strength increased in continuous testosterone and monthly cycled testosterone (P < 0.05). FSR increased in continuous testosterone and monthly cycled testosterone (P < 0.05), but not in placebo. Cycled testosterone improved body composition and increased muscle strength compared with placebo and increased FSR similarly to continuous testosterone.

These results are extremely interesting because they help us to understand the timing of the anabolic and anticatabolic response of testosterone and provide new insight into the novel strategies to improve safety of testosterone treatment. In particular, skeletal muscle protein synthesis accounted for the anabolic effects of testosterone at 1 month, but at 6 months, net anabolism resulted from inhibition of skeletal muscle breakdown. In addition, in the presence of testosterone concentrations from the lower half to the upper half of the normal range in a monthly cycled paradigm, skeletal muscle FSR remained consistently elevated in healthy older men. Thus, if monthly on/off cycles of testosterone can consistently increase muscle protein synthesis and lean body mass without an increase in side-effects, then this paradigm would offer a significant treatment for preventing sarcopenia in older men.

The concerns about potential adverse effects of testosterone on prostate and, recently, at cardiovascular level, have also motivated the development of selective androgen receptor modulators that display tissue-selective activation of androgenic signaling.

**SELECTIVE ANDROGEN RECEPTOR MODULATORS AND MUSCLE FUNCTION**

These nonsteroidal compounds, called selective androgen receptor modulators (SARMS), have shown tissue-selective activity and improved pharmacokinetic properties. Many SARMS are currently under investigation in both men and women [26]. Of particular interest is the recent study conducted by Basaria et al. [35] from Boston University who tested the safety, tolerability, pharmacokinetics, and effects of ascending doses of a novel nonsteroidal, oral selective androgen receptor modulator (LGD-4033) on lean body mass, muscle strength, stair-climbing power, and sex hormones of healthy young-adult men. LGD-4033 binds the androgen receptor with high affinity and selectivity. In this placebo-controlled study, 76 healthy men (21–50 years) were randomized to placebo or 0.1, 0.3, or 1.0 mg LGD-4033 daily for 21 days. Hormones, lean and fat mass and muscle strength were measured during and for 5 weeks after intervention. LGD-4033 was well tolerated without serious adverse events that were not different between active and placebo groups. Hemoglobin, prostate-specific antigen, aspartate aminotransferase, alanine aminotransferase, or QT intervals did not change significantly at any dose. Lean body mass increased dose-dependently, but fat mass did not
change significantly. Hormone levels and lipids returned to baseline after treatment discontinuation. LGD-4033 was well tolerated, had favorable pharmacokinetic profile, and increased lean body mass even during this short period without change in prostate-specific antigen. However, how these preliminary interesting results obtained in young-adult men can be translated in older patients with comorbidities and concurrent medications is still unclear. Longer randomized trials should evaluate its efficacy in improving physical function and health.

**PERSPECTIVE**

Alternative approaches aimed at improving the effectiveness of sex hormone treatment in sarcopenia in older men are the object of current studies and include the combination of testosterone, exercise and nutritional supplementation. This is of particular concern especially in older people with malnutrition and polypharmacotherapy. Epidemiological studies showed that micronutrients such as magnesium are determinants of muscle strength and function, and the use of nutritional supplement is very well known among young-adult athletes to improve physical performance [36]. Moreover, in older men of the InCHIANTI population magnesium serum levels have been positively associated with anabolic hormones including testosterone [37] supporting its potential clinical use of adjuvant anabolic support in an older population. Preliminary intervention studies provide evidence to this concept. Chapman *et al.* [38] nicely showed in a small group of undernourished older men and women that combined treatment with testosterone and nutritional supplementation reduces the number of people hospitalized and the duration of hospital admissions [39*]. These preliminary data suggest that targeting muscle and function should be one of the main goals of daily pharmacological approach in older patients with multimorbidity. One example is offered by older patients affected by prostate cancer, where long-term Androgen Deprivation Therapy (ADT) is associated with sarcopenia, insulin resistance, and increased risk of fractures [40]. In these patients continuous monitoring by a multiprofessional team of geriatricians, endocrinologists, and oncologists is needed to balance risks and benefits of ADT. These concepts also apply to older patients undergoing major surgery, especially cardiac surgery with extracorporeal circulation, where assessment of body composition and muscle function [41] should become a cornerstone for future strategies, including sex hormones, to improve the recovery and length of stay [42*].

**CONCLUSION**

As reported some years ago by The Institute of Medicine (IOM) report Testosterone and Aging there is a profound need for additional, large, carefully carried out trials of testosterone administration in well characterized groups of older men to more clearly outline benefits (muscle strength, avoidance of falls) and risk (prostate, cardiovascular) of treatment. Since sarcopenia is a multifactorial process, new clinical trials in older men should adopt multi-intervention including, in addition to testosterone and/or selective modulators, exercise and nutritional supplementation and targeting the new criteria of sarcopenia.

**Acknowledgements**

*We thank Dr Chiara Cattabiani, Dr Alessandro Vignali, Francesca De Vita, Professor Elisabetta Dall’Aglio, and Dr Valeria Buttò for their strong support in the review of the literature and their help in editing this manuscript. We also acknowledge the relevant technical support of Pietro Schianchi and Maurizio Conca. The figures and tables presented in this manuscript are original and not published elsewhere.*

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:* • of special interest **••** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 109).


This review summarizes the contribution of catabolic and anabolic mediators to sarcopenia with particular emphasis on endocrine function.


10. This is the first RCT on testosterone treatment performed in older men with mobility limitation using the gold standard measures of muscle function and physical performance. The study showed significant improvement in these outcomes but was stopped because of higher rates of cardiovascular events in testosterone group.


13. The author in this review addresses the vicious cycle between low testosterone levels and diabetes showing also recent and ongoing intervention trials testing the effect of testosterone on insulin sensitivity and diabetes.


24. Preliminary but interesting RCT using 21-day treatment of ascending doses of a novel selective androgen receptor modulator showing significant increase in lean body mass even during this short period without change in fat mass and prostate-specific antigen.


35. Original pilot study that shows an interesting option to improve the safety of testosterone treatment in older men and highlights the timing of intervention and the onset of anabolic and anticatabolic mechanisms.


38. Observational cross-sectional study showing a strong independent association between magnesium levels and anabolic hormones including testosterone. These results suggest the need of nutritional supplementation with magnesium to modulate anabolic status in older individuals and create the basis for multi-intervention in older individuals with sarcopenia.


41. Pilot study showing that combined treatment with an oral testosterone and a supplement drink was well tolerated and safe, and reduced the number of people hospitalized and duration of hospital admissions in undernourished, community dwelling older people.


44. Ongoing clinical trials testing the effect of testosterone on physical function and recovery in older men undergoing cardiac surgery.