Abstract
Sarcopenia is a syndrome characterized by the progressive loss of muscle mass and strength with a risk of undesirable effects such as physical disability, poor quality of life and death, and it is a major contributing factor of disability and loss of independence in the elderly. Its etiopathogenics include different mechanisms that are both intrinsic to the muscle itself and related to changes in the central nervous system, as well as hormonal and lifestyle factors. Several hormones and cytokines affect muscle function and mass. The reduction in testosterone and estrogens associated with ageing speeds up the loss of muscle mass. Growth hormone is also involved in the loss of lean body mass. Although sarcopenia does not completely revert with exercise, the absence of physical activity accelerates muscle mass loss. Diagnosing sarcopenia is hindered by a lack of reliable methods for measuring muscle mass. Different strategies have been tested for its treatment: testosterone replacement therapy/other anabolic androgens, estrogens in women, growth hormone, nutritional treatment and exercise. Of all the therapeutic options available, only resistance training with or without nutritional supplementation has shown its efficacy in increasing skeletal muscle mass.

Introduction
Malnutrition is a state of nutrition in which a deficiency, excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue and body form (body shape, size and composition), body function and clinical outcome [1].

Sarcopenia (from the Greek sark, flesh, and penia, poverty) 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 European Working Group on Sarcopenia in the Elderly recently defined the diagnostic criteria (table 1) [2].

Note that the two definitions (malnutrition and sarcopenia) do not include low weight, and both can coexist with obesity.

Muscle mass is reduced by approximately 3–8% per decade starting at the age of 30 [3], and this process speeds up from the age of 60 on. This causes the reduced muscle strength and function involved in disability among the elderly. Sarcopenia increases the risk of falls and fractures and susceptibility to injuries, and can thus be the cause of functional dependence and disability in the elderly population. Sarcopenia is a component of frailty syndrome, and one of the leading risk factors for disability and death among the elderly population. Moreover, the reduction in muscle mass is accompanied by other changes in body composition, such as a progressive increase in fatty mass (table 2). These changes have been associated with greater insulin resistance in the elderly, which is involved in the etiopathogenesis of type 2 diabetes mellitus, obesity, hyperlipidemia and hypertension in the genetically susceptible population.

Malnutrition and sarcopenia are interrelated in the cycle of frailty. The loss of muscle mass is often a consequence of senescent musculoskeletal changes.
that occur with ageing, and is worsened by diseases and enhanced by weight loss.

Sarcopenia involves a reduction in muscular strength, rest and total energy expenditure. Because of the anorexia that accompanies ageing, chronic malnutrition develops, thereby worsening sarcopenia.

One of the most important difficulties involved in detecting and monitoring sarcopenia is that there is, as yet, no gold standard examination for its measurement. Different diagnostic methods are used in both clinical and investigational settings (table 3), but the diagnostic values of sarcopenia are not clearly established. The Working Group on Sarcopenia in Older People has suggested using normal values obtained in healthy young adults and establishing the cutoff point for the diagnosis of sarcopenia at two standard deviations below the mean reference value.

Several factors affecting the muscle changes associated with ageing have been identified in the development of sarcopenia. On the one hand, genetic factors, albeit not well identified, are involved. On the other, the sexual steroid deficit that occurs with ageing has a major impact on both muscle and bone trophism [4]. The decrease in sex hormones is accompanied by activation of inflammatory mediators that can act as catabolic cytokines for muscle. Growth hormone deficit is also directly involved in the etiopathogenics of sarcopenia, in synergy with the increase in inflammatory mediators and gonad hormone deficit. IGF-I concentrations in the elderly inversely predict the presence of sarcopenia, acting as a protective factor in men. Weight loss exacerbates sarcopenia, causing a greater loss of lean mass in comparison to fatty mass. Moreover, the lost weight recovered by patients usually comprises a greater proportion of fat [5]. However, even with no weight changes, longitudinal studies show progressive loss of muscle mass with ageing [6]. Exercise is inversely and independently related to free fatty

Table 3. Measurements of muscle mass, strength, and function in research and practice [2]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Research</th>
<th>Clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle mass</td>
<td>Computed tomography, Magnetic resonance imaging, Dual energy X-ray absorptiometry (DXA), Bioimpedance analysis (BIA), Total or partial body potassium per fat-free soft tissue</td>
<td>BIA, DXA, Anthropometry</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>Handgrip strength, Knee flexion/extension, Peak expiratory flow</td>
<td>Handgrip strength</td>
</tr>
<tr>
<td>Physical performance</td>
<td>Short Physical Performance Battery (SPPB), Usual gait speed, Timed get-up-and-go test, Stair climb power test</td>
<td>SPPB, Usual gait speed, Get-up-and-go test</td>
</tr>
</tbody>
</table>
mass, especially in women [6]. However, the relationship between spontaneous exercise and muscle mass is further complicated by additional factors such as bodyweight, excess weight and attitude towards exercise.

Different strategies have been tested in the therapeutic approach to sarcopenia [7–9], they include:
1. Replacement therapy with testosterone/other anabolic agents
2. Estrogen replacement therapy
3. Human growth hormone (HGH) replacement therapy
4. Resistance training
5. Nutritional treatment
6. Interventions on cytokines and immune function

Replacement Therapy with Testosterone/Other Anabolic Agents

Testosterone
Low testosterone concentrations are associated with lower fat-free mass, lower appendicular skeletal muscle mass and decreased knee extension strength in hypogonadal males when compared with healthy controls. These findings have been used to justify testosterone replacement treatment in hypogonadal males. Testosterone concentrations progressively decrease with age in the elderly, while SHBG levels increase, thus further decreasing bioavailable testosterone. The prevalence of hypogonadism is 20% in men over 60, and can be as high as 50% in men over 80.

In young hypogonadal males, testosterone replacement therapy is associated with increased lean mass, reduced fatty mass, and increased muscle strength and muscle protein synthesis [10]. However, there is some controversy concerning the ergogenic effect of testosterone therapy in eugonadal males, and changes in body composition have not always been followed by increased muscle strength. Furthermore, some studies using supraphysiological doses of testosterone in hypogonadal patients have obtained results similar to those obtained with resistance exercise.

In the elderly, however, there are doubts concerning the safety of testosterone therapy, especially with regard to the risk to the prostate and cardiovascular diseases. The elderly are more vulnerable to the undesirable effects of testosterone replacement therapy. Testosterone can induce and exacerbate sleep apnea, increase erythrocyte mass, and cause transient fluid retention and gynecomastia. Testosterone can also increase the size of both benign and malignant prostate tumors, and its effect on prostate carcinogenesis is unclear. It is also unclear whether replacement therapy in hypogonadal patients increases cardiovascular risk through its effect on lipid metabolism. Table 4 summarizes some of the main randomized, controlled studies that have used testosterone therapy in males aged >65 years. Most of them were conducted in hypogonadal males, and the results show some increases in lean mass and decreases in fatty mass, but these results are not always accompanied by functional benefits. In the only
study that included eugonadal patients, the benefits of the treatment on bone mass were found only in the group of patients with hypogonadism. The testosterone was administered intramuscularly by depot injection, transdermally or using a derivative suitable for oral administration (testosterone undecanoate).

The studies that showed an increase in muscle strength after testosterone replacement therapy presented methodological problems such as a lack of a control group, the use of fixed-dose hormones without titrating to maintain normal levels of circulating testosterone, or the involvement of only very small number of patients, thereby not minimizing erroneous results arising from patient learning and/or exercise training problems.

**Dehydroepiandrosterone**

Dehydroepiandrosterone (DHEA) supplementation is being researched as sarcopenia treatment. DHEA is produced in the adrenal cortex and is a precursor of different sexual steroids. DHEA concentrations progressively decrease after the age of 30 years, giving rise to different studies using DHEA supplementation to revert the pathophysiological changes associated to age. It has been suggested

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**Table 4. Testosterone effect on body composition parameters and muscle strength in males**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Age years</th>
<th>Status</th>
<th>Dose of testosterone</th>
<th>Duration</th>
<th>Effects observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brill, 2002</td>
<td>RCT, double blinded</td>
<td>68</td>
<td>Hypogonadal</td>
<td>5 mg/day</td>
<td>4 weeks</td>
<td>→ strength → fat mass → sexual function</td>
</tr>
<tr>
<td>Kenny, 2000</td>
<td>RCT, double blinded</td>
<td>76</td>
<td>Hypogonadal</td>
<td>5 mg/day TTS</td>
<td>12 months</td>
<td>→ strength ↓ underlying loss of BMD</td>
</tr>
<tr>
<td>Clague, 1999</td>
<td>RCT, double blinded</td>
<td>68</td>
<td>Hypogonadal community</td>
<td>200 mg IM/2 weeks</td>
<td>12 weeks</td>
<td>→ hand grip strength → leg strength</td>
</tr>
<tr>
<td>Snyder, 1999</td>
<td>RCT, double blinded</td>
<td>65</td>
<td>Hypogonadal/eugonadal</td>
<td>6 mg/day</td>
<td>36 months</td>
<td>1.9 kg ↑ lean mass → leg strength ↑ lumbar but not hip BMD in hypogonadal group only</td>
</tr>
<tr>
<td>Sih, 1997</td>
<td>RCT, double blinded</td>
<td>68</td>
<td>Hypogonadal community</td>
<td>200 mg IM/2 weeks</td>
<td>12 months</td>
<td>10% ↑ hand grip strength</td>
</tr>
<tr>
<td>Wittert, 2003</td>
<td>RCT, double blinded</td>
<td>69</td>
<td>Hypogonadal community</td>
<td>80 mg/12 h oral</td>
<td>12 months</td>
<td>2% ↑ lean mass ↓ fat mass → grip and leg strength</td>
</tr>
</tbody>
</table>

RCT = Randomized controlled clinical trial; → = remains unchanged; ↑ = increases; ↓ = decreases.
that DHEA can increase muscle strength by increasing the circulating testosterone/cortisol ratio.

DHEA treatment has been tested in two studies. In the first, 100 mg of DHEA was administered for 6 months to people aged 50–65, obtaining an increase in lean mass and decrease in fatty mass. However, a moderate increase in muscle strength was found only in men, not in women, while testosterone concentrations increased considerably in the latter. The second [11], a randomized and placebo-controlled study, involved administering 50 mg/day of DHEA for one year to both men and women aged 60–80 years. The group did not achieve the results of the previous study, and no increase was found in lean mass based on the measurement of the body’s potassium content.

Oxandrolone
Oxandrolone is an androgenic steroid with a powerful anabolic effect that is suitable for oral use. Its main advantage is that it is less hepatotoxic than other oral androgens and it is resistant to hepatic metabolism. Its undesirable effects are mild and transient and include minor increases in transaminases and reduced HDL cholesterol levels.

There are no clinical studies with oxandrolone in elderly patients with sarcopenia, although there are numerous accounts on wasting conditions such as wasting syndrome associated with HIV infection, neuromuscular and other chronic diseases that involve loss of muscle mass. They show that oxandrolone increases protein synthesis in skeletal muscle, muscle function and exercise levels, protein and energy intake and reduces visceral and total fatty mass while improving nitrogen retention. Oxandrolone could therefore be a therapeutic strategy for the treatment of sarcopenia in the elderly.

Androstenedione
Androstenedione is an androgen produced by the adrenal glands and gonads in both men and women. It is synthesized from DHEA and converted into testosterone or estrone. The anticipated results are mediated by an increase in circulating testosterone, so it has been used considerably as an anabolic agent in athletes. No controlled studies have used androstenedione in the elderly, and the few studies published were conducted in young people. The results regarding its efficacy in increasing plasma testosterone levels have been inconsistent, and an increase in protein synthesis or muscle strength has not been found when comparing resistance training with or without androstenedione [12].

Estrogen Replacement Therapy

The prevalence of osteopenia and osteoporosis in women over 50 years is 42 and 17%, respectively. Menopause is associated with a reduction in lean mass and
bone mineral density, both of which are related to estrogen deficit. However, there is some controversy concerning the precise role of estrogens in the loss of bone mass, and it is not very clear whether estrogen replacement therapy can prevent or revert such a loss. Moreover, different studies have shown a significant relationship between lean mass and bone mineral density, and women with osteoporosis have less appendicular skeletal muscle mass than controls without osteoporosis. Walsh and colleagues recently showed that sarcopenia is more prevalent in women with osteopenia (25%) and osteoporosis (50%) than in women with normal mineral bone density (0.8%). Women with osteoporosis and sarcopenia are at high risk of disability and fractures, and therapeutic and preventive measures should thus be taken.

Several studies have assessed the effect of estrogen replacement therapy on muscle mass in postmenopausal women. Low doses of estradiol (0.25 mg) have not altered appendicular skeletal muscle mass after 6 months of treatment, and physical activity remained unchanged in a large group of women over 65 years of age [13]. In younger women (mean 55 years), full doses of estrogen/progestagen replacement therapy have been shown to be effective in increasing lean mass and reducing fatty mass after 6 months of treatment. In women receiving long-term estrogen replacement therapy, however, there were no significant differences with regard to lean mass between treated women and untreated controls.

**Human Growth Hormone Replacement Therapy**

HGH replacement therapy increases muscle mass and strength in young adults with hypopituitarism [14]. In middle-aged people, HGH has an anabolic effect as in adults over 50 years with adult-onset HGH deficit the treatment increases muscle strength in both men and women [15]. As HGH is required for maintaining muscle and bone, and since the elderly population is HGH deficient, it has been suggested that HGH therapy could be useful for treating sarcopenia. Table 5 summarizes some of the studies conducted with HGH in the elderly.

In summary, HGH therapy does not increase muscle mass or strength in elderly patients. Biological improvements (increased lean mass, reduced fatty mass) are achieved, but they are not accompanied by enhanced strength or activities of daily living capabilities. Studies have been conducted combining exercise and HGH administration. Addition of the growth hormone has not been shown to increase the beneficial effect of exercise.

Combined HGH and testosterone therapy has been shown to have a positive impact on muscle mass. The results for muscle strength, however, are not consistent and only small increases were obtained.

Other strategies have been tested to reproduce the effects of the natural pulsatile secretion of HGH, such as the nocturnal pulsatile administration of GHRH. Vittone and colleagues tested intramuscular nocturnal administration
of GHRH for 6 weeks in people aged 64–76 years with low levels of circulating IGF-I. The GH values measured through integrated 12-hour secretion doubled but, surprisingly, circulating IGF-I remained unaltered. The outcome was only a moderate increase in muscle strength in some exercises. Note that there were no significant undesirable effects.

Khorram conducted a randomized, placebo-controlled study to evaluate nocturnal GHRH administration for 5 months in people with a mean age of 66. The results showed an increase in nitrogen balance in both men and women and a modest increase in muscle mass and strength in men. The only striking undesirable effect was transient hyperlipidemia, which reverted when the study ended.

Treatment with IGF-I combined with IGFBP3 has been shown to be useful in a small group of patients as it increases muscle mass and preserves bone mass. The IGF-I/IGFBP3 combination enables the administration of higher doses of IGF-I without causing hypoglycemia. In general, it is a well-tolerated treatment. IGF-I therapy, however, has not been found to be better than HGH treatment in obese elderly women, in whom fat-free mass increased at the expense of numerous undesirable effects.

**Table 5. Effects of HGH supplementation in elderly subjects**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Changes in body composition</th>
<th>Changes in muscle function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudman</td>
<td>Healthy 61–81 IGF-I &lt;350 U/l</td>
<td>HGH 0.03 mg/kg 3 days per week for 3 months</td>
<td>↑ HGH 0.03 mg/kg 3 days per week for 3 months</td>
<td>↑8.8% lean mass ↓14.4% fatty mass ↑1.6% bone mass</td>
</tr>
<tr>
<td>Papadakis</td>
<td>Healthy 70–85 IGF-I low</td>
<td>HGH 0.03 mg/kg 3 days per week for 3 months</td>
<td>↑4.4% lean mass</td>
<td>No changes</td>
</tr>
<tr>
<td>Taaffe</td>
<td>Healthy 65–82 IGF-I mean 106 ±14 weeks Prior exercise</td>
<td>rHGH 0.02 mg/kg for 10 weeks + resistance exercises</td>
<td>No weight changes</td>
<td>No changes</td>
</tr>
<tr>
<td>Jorgensen</td>
<td>Adult GH deficit</td>
<td>HGH 17 μg/kg for 3 years</td>
<td>↑ weight 8.4 kg</td>
<td>↑ Quadriceps muscle strength</td>
</tr>
<tr>
<td>Thompson</td>
<td>Obese post-menopausal women</td>
<td>rHGH 0.025 mg/kg or IGF-I 0.015 mg/kg/0.6 mg/kg</td>
<td>Greater weight and fatty mass loss with GH and high doses of IGF-I</td>
<td>↑ lean mass</td>
</tr>
</tbody>
</table>

↑ = Increases; ↓ = decreases.
The undesirable effects of HGH are greater in the elderly:
- Carpal tunnel syndrome
- Gynecomastia
- Hyperglycemia. The diabetogenic effects of HGH are greater in elderly patients, in whom its administration for one week triples insulin secretion during the glucose overload
- Fluid retention; edemas in the lower extremities
- Arthralgia
- Orthostatic hypotension
- High rate of withdrawal from treatment (43% in some studies)

**Resistance Training**

Resistance strength training in the elderly [16]:
- Increases muscle mass
- Increases muscle strength
- Improves balance
- Improves resistance

Resistance training is a more effective method to increase muscle strength and mass than endurance training. In a crossover study including elderly males with different types of training, it was found that resistance exercise (weight lifting) maintained muscle mass and strength more than other types of exercise (swimming). Compared with young people, resistance training in the elderly increases muscle strength less in absolute terms but to a similar extent in relative terms. High-intensity exercises (70–80% of maximum capacity) have been found to be the most effective [17]. The mean time to achieving positive effects is 10–12 weeks, although some studies have found it to be after 2 weeks of training. Some physicians are reluctant to recommend this type of exercise to the elderly, but it has been shown that, with appropriate training, they are completely safe even for the very old [18]. Few undesirable effects have been reported, and such exercise would only have to be limited in patients with congestive heart failure.

Table 6 summarizes the main studies that have used resistance training to evaluate its effect on muscle strength in the elderly.

Exercise must be accompanied by sufficient protein intake [19, 20]. The elderly population often consumes less protein than the recommended daily intake for adults (0.8 g protein/kg of weight per day). Elderly people also have a higher protein catabolism rate, and their protein requirements are likely to be higher than those of the non-elderly adult population. Some studies have shown a synergic effect between protein supplementation and physical exercise [18], and insufficient protein intake has probably prevented better exercise outcomes.
Nutritional Therapy

There are few studies on the effect of nutritional therapy on sarcopenia. Most of them have modified the protein content in the diet [21]. In a study using labeled amino acids, Volpi showed that an increase in available amino acid

Table 6. Effects of resistance training on muscle strength in elderly subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Gender</th>
<th>Mean age</th>
<th>Type of training</th>
<th>Duration weeks</th>
<th>Effects found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brose</td>
<td>RCT, community</td>
<td>M/F</td>
<td>69</td>
<td>3 × week 80% MC</td>
<td>14</td>
<td>36% ↑ thigh strength</td>
</tr>
<tr>
<td>Carmeli</td>
<td>RCT, nursing home</td>
<td>M/F</td>
<td>82</td>
<td>3 × week 2–5 kg weight</td>
<td>12</td>
<td>10–15% ↑ thigh strength</td>
</tr>
<tr>
<td>Charette</td>
<td>RCT, community</td>
<td>F</td>
<td>69</td>
<td>3 × week 65–75% MC</td>
<td>12</td>
<td>28–115% ↑ thigh strength, 7% ↑ type 1 fiber surface area, 20% ↑ type 2 fiber surface area</td>
</tr>
<tr>
<td>Bamman</td>
<td>RCT, healthy</td>
<td>M/F</td>
<td>69</td>
<td>3 × week 80% MC</td>
<td>25</td>
<td>82% ↑ thigh strength</td>
</tr>
<tr>
<td>Connelly</td>
<td>RCT, community</td>
<td>M/F</td>
<td>76</td>
<td>3 × week, 100% ankle dorsiflexion MC</td>
<td>2</td>
<td>15% ↑ ankle strength</td>
</tr>
<tr>
<td>Vincent</td>
<td>RCT, community, sedentary</td>
<td>M/F</td>
<td>68</td>
<td>3 × week, 50% MC</td>
<td>24</td>
<td>16% ↑ thigh strength</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 × week, 80% MC</td>
<td>24</td>
<td>20% ↑ thigh strength</td>
</tr>
<tr>
<td>Ferry</td>
<td>No control group</td>
<td>M</td>
<td>68</td>
<td>3 × week, 80% MC</td>
<td>16</td>
<td>27% ↑ thigh strength</td>
</tr>
<tr>
<td>Frontera</td>
<td>No control group</td>
<td>M</td>
<td>60–72</td>
<td>3 × week, 80% MC</td>
<td>12</td>
<td>107% ↑ thigh strength</td>
</tr>
<tr>
<td>Frontera</td>
<td>RCT, sedentary</td>
<td>F</td>
<td>74</td>
<td>3 × week, 85% MC</td>
<td>12</td>
<td>39% ↑ thigh strength</td>
</tr>
<tr>
<td>Fiatarone</td>
<td>No control group</td>
<td>M/F</td>
<td>90</td>
<td>3 × week, 80% MC</td>
<td>8</td>
<td>174% ↑ thigh strength</td>
</tr>
<tr>
<td>Fiatarone</td>
<td>RCT, nursing home</td>
<td>M/F</td>
<td>87</td>
<td>3 × week, 80% MC</td>
<td>10</td>
<td>37–178% ↑ thigh strength</td>
</tr>
<tr>
<td>Lexell</td>
<td>RCT, community</td>
<td>M/F</td>
<td>70–77</td>
<td>3 × week, 85% MC</td>
<td>11</td>
<td>163% ↑ thigh strength</td>
</tr>
<tr>
<td>Roth</td>
<td>RCT, community, sedentary</td>
<td>M/F</td>
<td>69</td>
<td>3 × week, 100% MC</td>
<td>13</td>
<td>5% ↑ thigh muscle volume</td>
</tr>
</tbody>
</table>

MC = Maximum capacity; ↑ = increase.
levels increases protein anabolism in muscle, as measured by thigh muscle biopsies. This shows that protein bioavailability is important for maintaining muscle mass, but it does not clarify the doubts regarding the efficacy of a high-protein diet in elderly patients.

Some evidence suggests that current daily protein intake recommendations (0.8 g/kg weight per day) are not sufficient enough to preserve muscle mass in the elderly. In 14 weeks, it has been shown that thigh muscle surface area decreased with this intake, as measured by CAT scan, suggesting that protein consumption should be greater.

Optimal protein intake for the elderly was recently reviewed [22]. In this review, the experts question the recommended dietary allowance for protein, 0.8 g of protein/kg per day, regardless of age. With the current evidence, we know that intake greater than the RDA can improve muscle mass, strength and function in the elderly. Therefore, in the absence of contraindications, protein intake should be about 1.5 g/kg per day.

Some studies have supplemented the diet with specific amino acids such as glutamine, leucine and other branched-chain amino acids. Branched-chain amino acids (leucine, isoleucine and valine) appear to have a significant anti-anorectic and anti-wasting effect, as they interfere with serotonin synthesis in the brain, particularly hypothalamic serotonergic activity. Through this mechanism, they could have an anti-catabolic effect, thereby promoting protein synthesis and inhibiting intracellular proteolytic pathways. The outcome of leucine administration in young adults is beneficial, increasing fat-free mass when combined with exercise. However, fat-free mass has increased in the elderly using β-hydroxy-β-methyl butyrate (a leucine metabolite) supplementation combined with high-resistance training, but the increase in muscle strength was minimal, and not the same in all the analyzed muscle groups.

Essential amino acids have been shown to be capable of stimulating muscle protein anabolism. Positive results have been obtained by supplementing with 18 g of a combination of 10 essential amino acids, while the addition of 22 g of non-essential amino acids has not had additional impact on protein synthesis [23]. Supplementation with 8 g of a mixture of amino acids in a group of elderly patients with sarcopenia recently resulted in a significant increase in lean mass after 6 and 18 months of treatment, while also causing a reduction in plasma glucose, insulinemia and the HOMA. There was also a significant reduction in TNF-α and an increase in IGF-I levels.

Studies combining protein supplements with exercise have obtained the best outcomes when supplementation is administered immediately after exercise. The use of protein supplements without exercise, however, has not had any effect on muscle mass [18].

It is not clear whether creatine supplementation increases muscle strength in the elderly. Brose showed a substantial increase in muscle strength in a group of healthy elderly patients after 14 weeks of training with a resistance program.
Creatine administration only marginally increased the lean mass growth obtained with exercise, and muscle strength only increased with some exercises. Other longer-term studies (>4 months) show that creatine supplementation has a positive effect on muscle strength and resistance associated with resistance training programs. It is not known whether these changes last. A study was recently conducted to evaluate the effect of creatine (5 g/day) and conjugated linoleic acid (6 g/day) in a group of elderly patients subject to resistance training. Creatine supplementation increased fat-free mass and muscle strength, while the addition of conjugated linoleic acid reduced fatty mass more after 6 months of resistance training. No differences were found in isometric muscle strength.

Some studies have attempted to identify the optimal source of protein for the elderly. When comparing different isoprotein diets, the nitrogen balance is the same with either vegetable or animal proteins. However, post-absorptive protein catabolism is less inhibited with vegetable protein, resulting in less net protein synthesis. Moreover, there do appear to be differences in efficiency when ‘fast’ or ‘slow’ proteins are used, referring to the rate at which they are digested and amino acids are absorbed in the intestine. Serum protein is a rapidly absorbed soluble protein which produces a rapid, high and transient pattern of plasma amino acids, while casein is a slowly absorbed protein with a slow, more reduced and longer amino acid pattern. Protein efficiency in muscle is greater with serum protein than with casein.

Carbohydrate intake with a high glycemic index together with a mixture of proteins and amino acids just after resistance training has a positive impact on muscle protein synthesis. Other studies, however, have found a negative effect when mixing carbohydrates and amino acids in the elderly, probably due to the deregulation of the muscle protein response to insulin.

Nutritional supplementation in the elderly can have negative effects on conventional diet intake, and the final outcome can be negative [18]. It is therefore advisable to use nutrient-dense supplements that are fractioned so as not to compromise the natural diet.

Although functional improvements have been obtained with nutritional supplementation in the elderly, there are only modest increases in weight.

A relationship has recently been established between low vitamin D concentrations and high parathormone levels as risk factors for the development of sarcopenia in both male and female elderly patients. Skeletal muscle has vitamin D receptors, and a vitamin D deficiency in muscle is expressed in the form of myofibrillar degradation, a reduction in protein turnover and a hypocalcemia-induced decrease in insulin secretion. In fact, the osteomalacic myopathy described in patients with rickets improves after several weeks of vitamin D supplementation. Parathormone also has trophic effects on muscle, increasing protein metabolism.

Vitamin D deficiency is very common in the elderly and could be related to loss of muscle mass and strength. Studies with vitamin D supplementation,
however, have focused more on its effect on bone mass. Some studies evaluating the fall rate in elderly patients taking vitamin D supplements found that it was lower than in non-supplemented patients, implying its positive impact on muscle mass. It therefore appears that vitamin D could help to prevent falls by improving balance. Muscle strength, walking speed and new falls were evaluated in the Frailty Intervention Trial in Elderly Subjects. After 6 months of supplementation with vitamin D or placebo, there were no differences between the two groups with regard to any of the analyzed variables. A systematic review of controlled trials to evaluate the efficacy of vitamin D supplementation on muscle strength, exercise and falls in elderly patients did not find sufficient evidence to support the use of this vitamin for these indications. Nonetheless, vitamin D supplementation has been shown to be effective in increasing bone mass and reducing falls in the elderly.

**Interventions on Cytokines and Immune Function**

Different strategies have been used to control the production of cytokines, which are responsible for lean mass loss in sarcopenia:

- Pentoxifylline: it reduces TNF-α messenger RNA transcription. It has helped to increase weight in other wasting models. However, there are no studies in elderly subjects.
- Thalidomide: it increases TNF-α mRNA degradation. There are no studies in the geriatric population.
- Megestrol acetate: it reduces IL-1, IL-6 and TNF-α production. Weight increases have been achieved in elderly patients with 12 weeks of treatment, together with increased intake, albumin and prealbumin levels and lymphocyte count. It has not been possible, however, to show an increase in lean mass or muscle strength.
- Omega-3 fatty acids: in animal models, they increase intake in cytokine-induced wasting processes. However, there are no studies in the elderly population.
- One new promising approach that is being investigated is the use of molecules known as angiotensin-converting enzyme inhibitors, commonly used for the treatment of hypertension. The rationale is that angiotensin II has a catabolic effect on skeletal muscle, so ACE inhibitors can delay age-related decline in muscle strength [24]. ACE inhibitors can increase the blood flow to the muscles, reducing inflammatory cytokine secretion and increasing insulin sensitivity and myocyte uptake of glucose. An increase has also been described in IGF-I and IGFBP3 levels in elderly patients with heart failure being treated with ACE inhibitors.

Possible mechanisms of action of ACE inhibitors affecting skeletal muscle include:
– Effects on cardiac function (in patients without left ventricle dysfunction):
  • Increased ejection fraction
  • Reduced left ventricle muscle mass
  • Preserved left ventricle function
– Effects on muscular blood flow, endothelium and metabolism:
  • Enhanced vascular function
  • Enhanced endothelial function
• Metabolic effects:
  ° Increased serum potassium
  ° Increased IGF-I levels
  ° Increased insulin sensitivity and glucose uptake by skeletal muscle
  ° Enhanced nitric oxide production, which could increase number of sarcomeres
• Changes in type of fiber:
  ° Increase in type I figures
  ° Changes in number of mitochondria and their function
  ° Changes in skeletal muscle calcium levels
  ° Improved respiratory muscle strength
  ° Effect of ACE genotype
Recent studies suggest a close relationship between muscle strength and angiotensin-converting enzyme genotypes. Genotype II is associated with greater anabolic response to exercise, with increasingly efficient type 1 muscle fibers.

The results of intervention studies with ACE inhibitors have been contradictory thus far.
• β-Adrenergic agonists. β-Adrenergic agonists promote muscle growth by acting on the β2 receptors that are predominant in skeletal muscle, thereby increasing protein synthesis and reducing catabolism. Treatment with β-adrenergic agonists, however, is limited by common (nausea, headache, insomnia) and undesirable cardiovascular effects (palpitations, increased risk of ischemia, heart failure, arrhythmia and sudden death). New agonists have been tested, including formoterol, which can induce an anabolic response in skeletal muscle at low doses, with few effects on the heart and cardiovascular system when compared with classic β-adrenergic agents (fenoterol, clenbuterol).

References
20 Campbell WW, Leidy HJ: Dietary protein and resistance training effects on muscle and body composition in older persons.