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Sarcopenia in Chronic Illness and Rehabilitative Approaches

Raoul Saggini, Simona Maria Carmignano, Lucia Cosenza, Tommaso Palermo and Rosa Grazia Bellomo

Abstract

Primary sarcopenia is considered to be age-related when no other cause is evident, other than aging itself. Secondary sarcopenia should be considered when one or more other causes are evident, such as multiple chronic conditions. Previous studies have reported that low muscle strength and impaired physical performance can be found in chronic diseases, including metabolic disease (diabetes, hypertension, and obesity), arthritis, osteoporosis, cancer, chronic kidney disease, chronic obstructive pulmonary disease, neuromuscular disease, and chronic infection. The development of preventive and therapeutic strategies against secondary sarcopenia and wasting disorders in general is an epidemiological need. The planning of a complex rehabilitation program in sarcopenia associated to chronic conditions, in the context of a comprehensive treatment, is made up of a nutritional support, exercise, correction of lifestyles, and the use of advanced physical energies. Therefore, for the purposes of the optimal management, it is essential to identify the pathogenesis and clinical characteristics that can affect the different rehabilitative treatment.

Keywords: secondary sarcopenia, chronic illness, rehabilitative approaches

1. Introduction

Many definitions available on sarcopenia agree on to define it as paraphysiological phenomenon, characterized by loss of muscle mass that occurs with aging.
Some authors emphasize the histopathology defining sarcopenia as an increase of the adipose and connective component within the muscle itself, whereas others focus on the reduction of muscle strength and physical function [1, 2].

Cachexia is a composite word from the Greek words “kakos” (bad) and “hexis” (condition) and refers to the prognosis and functionality of patients suffering from cachexia. The characteristic of this complex metabolic disturbance is weight loss due to an underlying cause disease, such as heart failure, chronic pulmonary diseases, or cancer. According to the definition given by Cruz-Jentoft et al. in 2010, cachexia is found in patients with unintentional weight loss of 5% in the past year, a body mass index (BMI) lower than 20, decreased muscle mass as shown with bioimpedance analysis (BIA) or dual-energy X-ray absorptiometry (DEXA), low muscle strength, low serum albumin levels, anemia, and elevated biomarkers of inflammation [2].

Weight loss becomes a clinical sign of any progressive acute or chronic disease state. In its extreme form, it involves a significant lean body mass (including skeletal muscle) and fat loss. Skeletal muscle provides a fundamental basis for human function, enabling locomotion, and respiration. Muscle wasting is related to a poor quality of life and increased morbidity/mortality [3].

2. Sarcopenia in chronic illness

Sarcopenia can be defined as primary sarcopenia when due to the aging process and secondary when due to comorbidities, malnutrition, or immobility (Figure 1).

![Figure 1. Classification of sarcopenia.](image-url)
• Comorbidities that induce sarcopenia are organ failure (e.g. heart, kidneys, lungs, brain and liver), inflammatory diseases, cancer, and endocrine diseases.

• Malnutrition due to gastrointestinal disorders, anorexia in cases of polypharmacy, and inadequate intake due to psychosocial disorders lead to secondary sarcopenia.

• Inactivity as a result postoperative deconditioning or prolonged rehabilitation is the reason for activity-related secondary sarcopenia [4].

It has been known for millennia that muscle and fat wasting leads to poor outcomes, including deaths in chronic disease states. It is usually accompanied by physical inactivity, decreased mobility, slow gait, and poor physical endurance, which are also common features of the frailty syndrome. Although the specific contribution of each of these factors is unknown, there are more and more convincing evidence of chronic low-grade inflammation prominent role in the development of sarcopenia. According to recent studies, chronic inflammation is associated with many degenerative diseases [5]. Systemic inflammation is thus dependent on many factors that include diseases such as obesity, type 2 diabetes, dementia [5, 6], heart failure, and rheumatic diseases [7, 8], which can then be the result of this inflammatory condition and/or themselves can be the cause of the increase of inflammation. The impact of inflammation on the development of sarcopenia is supported by many studies. Animal studies show that low-grade inflammation reduction following the administration of ibuprofen in rats have determined a significant decrease in the loss of muscle mass [9]. Other studies, always conducted on animals, have shown that administration of interleukin-6 (IL-6) or tumor necrosis factor alpha (TNF-α) increases the skeletal muscle degradation, decreases protein synthesis, and reduces plasma concentrations of insulin-like growth factor (IGF) [10]. However, considering the studies of healthy elderly people living in the community, it was confirmed that one pro-inflammatory state produces, in the long-term, negative effects on sarcopenia. In the study “Longitudinal Aging Study Amsterdam,” high levels of IL-6 and C-reactive protein (CRP) were associated with a double or triple risk of losing more than 40% to the hand grip (strength of the handshake) over 3 years. TNF-α, IL-1a, IL-6, IL-18, C-reactive protein (CRP) and fibrinogen are among the cytokines and acute phase proteins, that result to be more elevated in pro-inflammatory state [11]. Moreover, high levels of muscle catabolic biomarkers, which include IL-6, are important predictors of the decline in muscle strength [12]. Other authors report that IL-6 is a multifunctional cytokine because it has both pro and anti-inflammatory effects by determining muscular growth or atrophy, and according to different conditions, its effect is anabolic or catabolic. Several different pathophysiological processes induce sarcopenia following distinct pathways: neurological diseases produce sarcopenia by loss of motor neurons. Malabsorption leads to protein deficits and muscle catabolism. Disuse of muscles due to physical inactivity is followed by muscle degeneration. Hormonal disturbances of the thyroid, hypercortisolism, and insulin resistance lead to sarcopenia resulting from protein deficiency [13, 14]. These processes are found in combination or alone in many acute and chronic diseases above all in elderly patients, for example heart failure, chronic obstructive pulmonary disease (COPD), diabetes, neurological diseases, musculoskeletal diseases, as well as post-traumatic or postoperative conditions [15].
2.1. Sarcopenia: obesity and diabetes

Although the mechanism by which the potential TNF-α and IL-6 increase and the relationship with sarcopenia is not yet well defined, they may be related to the increase of the intramuscular adipose tissue. Under the pro-inflammatory stimulus, the intramuscular contents and intra-myocellular fat deposits increase creating a vicious circle where adipocytes, which secrete IL-6 and TNF-α as well as adipocines such as leptin and adiponectin, further promote inflammation [16].

More recently, Newman et al. have shown that it is important to consider in sarcopenia the percentage of fat mass. These authors have shown that people with higher body weight is not classified as suffering from sarcopenia, though their lean mass is sufficient compared to the total body weight [17]. Both sarcopenia and obesity represent, as the individual factors, a risk for adverse events, it has been shown that if present in combination, act synergistically increasing the earlier onset of disability [18]. For example, Rolland et al. found in a cohort study of women with sarcopenia, decreased physical performance (climbing stairs) compared to a group of healthy same aged, the worse performance was related to sarcopenia associated with obesity [19].

2.2. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common cause of morbidity and mortality worldwide. The burden of disease is induced to a great extent by extrapulmonary symptoms, such as osteoporosis, heart failure, and sarcopenia. Using only BMI as a predictor of muscle mass or sarcopenia is misleading in these patients because the combination of abdominal obesity and sarcopenia is often present [20]. Sarcopenia affects 15% of patients with chronic obstructive pulmonary disease (COPD) stable and compromises the independence and the functional state of the musculoskeletal system. This loss of muscle mass does not seem to affect the outcome of pulmonary rehabilitation, which can lead to remission of the syndrome in selected patients. Pulmonary rehabilitation can improve symptoms and quality of life of patients with respiratory disease. It releases dyspnea and fatigue, as well as increasing exercise tolerance, emotional function so in indirect way it decreases frailty such as weakness, inactivity and fatigue, and then sarcopenia [21, 22].

It has been reported that patients with COPD and sarcopenia have nearly overlapping results after pulmonary rehabilitation compared to patients with COPD without sarcopenia, in terms of upper and lower limb strength, exercise capacity and health status [23].

Another important data are the absence of statistical differences about the body composition, functional performance, or health status between patients with and patients without sarcopenia undergone to pulmonary rehabilitation [24].

Musculoskeletal dysfunction is a recognized manifestation of COPD whose characteristics include the weakness of the quadriceps, the atrophy, and the change of type II fibers, all associated with a poor prognosis independent from lung function [25]. COPD determines an imbalance favoring protein breakdown over synthesis, apoptosis, sarcomere and sarcolemma...
damage, reduced myosin heavy chain-I isoform type I [slow twitch/endurance] muscle fibers, and a decreased density of capillaries and mitochondria [26–28]. This chronic disease is related to abnormalities of oxidative enzymes, mitochondrial activity, and expression of myogenin and m-cadherin—key molecules required for muscle growth and repair [29]. In chronic conditions, the poor peripheral oxygenation linked to abnormalities of gas exchange typical of COPD and anemia, as well as increased oxidation processes [30–32] associated with hypercapnia, create an acidosis condition that alters muscle proteases [33, 34], increasing catabolic activity in the muscle [35]. In addition, the effect of tobacco is associated with the [36] myopathy induced by corticosteroid use (especially systemic steroids) [37, 38], malnutrition that has a negative balance of energy [39], and reduction of physical activity leading sarcopenia [40]. The other mechanism involved in the genesis of sarcopenia is a sedentary lifestyle due not only to previous habits but also to reduced exercise tolerance. This was highlighted by disproportionate impairment of lower limb musculature in comparison to the upper limbs (that are subjected to a lesser degree of physical inactivity than the legs) [41] and by similarity in the structural changes seen in the sarcopenia of COPD and atrophy due to muscle disuse [42]. Furthermore, recovery of strength is possible with muscle training and conditioning [43, 44], and the apparent lack of correlation between the severity of airflow limitation and extent of muscle dysfunction [45]. Rehabilitation would therefore be expected to improve frailty and sarcopenia, but there are little published data on this as an intervention.

2.3. Sarcopenia: chronic renal failure

Patients with end-stage renal disease (ESRD) and chronic renal failure (CRF) receiving dialysis can have altered nutritional status and body composition due to dietary restrictions, level of physical activity, co-morbidities, metabolic alterations, and inflammation. Fatigue and immobility due to low muscle function are frequent symptoms reported by patients with chronic kidney disease. Sarcopenia is found in all stages of the disease and more distinctly in patients with high grades of renal function impairment. Pereira et al. found a significantly higher association of sarcopenia, diagnosed by BPA and hand grip strength measurements and mortality [46]. The degradation of proteins is an important energy production mechanism since the amino acids are rapidly converted to glucose. In conditions of catabolism generates an imbalance in favor of the degradation compared to the synthesis of proteins and, not existing a storage of the same, the muscle proteins are degraded and, if not additional sufficiently, develop muscle atrophy that determines a condition of sarcopenia [47, 48].

Many diseases promote protein catabolism, including the IRC; in particular, it was noted that during and after the hemodialysis session protein degradation is significantly accelerated. Several studies have shown that the ubiquitin-proteasome system (UPS) is the major proteolytic system in renal patients (Figure 2); despite prove even other hyperactive pathways (lysosomal cathepsin and calpain-gated calcium), caspase is a protease involved in cell apoptosis process that accelerates the degradation of the muscle through the reduction of complex protein structures in simple proteins, useful substrates for the UPS [49].

Several evidences have shown that patients with CRF, insulin resistance, inflammation, metabolic acidosis, and excess of angiotensin II determine high levels of caspase 3 and
Figure 2. The proteins responsible for muscle degradation are first of all ubiquitin: the enzyme activates the ubiquitin E1, activating a cascade of ATP-dependent events. The ubiquitin chain is recognized by the proteasome 19S, which catalyzes entrance of the protein substrate in the proteasome core 20S, which is cleaved to peptides of the 26S proteasome. The peptides are degraded into amino acids to build cellular proteins or are released from the cells. From: Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. The American Journal of Clinical Nutrition 2010;91(suppl):1128S-1132S.

a significant increase of catabolic processes. These conditions promote the degradation of muscle protein, itself CRF can induce and enhance insulin resistance, encouraging the development of sarcopenia [50–52]. Another consequence of CRF, even more, of the hemodialysis treatment, is the presence of a chronic inflammatory state that, through different modulators, including TNF-alpha, suppresses the action of insulin, increases blood cortisol levels, and activates caspase-3. Glucocorticoids enhance degradation of muscle proteins by upregulation of UPS system. Metabolic acidosis, that is very common, especially in the case of dialysis treatment, determines sarcopenia through multiple mechanisms: induces a negative nitrogen balance and protein synthesis, promotes protein degradation by the UPS system and caspase 3 and alteration of pathway PI3K/Akt, which is a critical transduction signal in cell proliferation and cell cycle progression, apoptosis, and cellular metabolism. It reduces blood levels of IGF-1 and increases those of glucocorticoids. It is probably the main cause of the high prevalence of sarcopenia CFR [53]. The dialysis treatment, by itself, may determine, during each session, a damage to the protein metabolism, with the loss of amino acids and proteins in the dialysate, which reduces the availability of nutrients for muscle synthesis [54]. Many studies, in fact, show that the dialysis catabolic effects induce negative impact on the homeostasis of skeletal muscle protein with reduction of their synthesis and increase of their degradation [55]. Other authors noted that the increased protein lysis persists up to 2 hours after the end of hemodialysis session [56].

The mechanisms underlying this alteration of protein turnover were due not only to the reduction of circulating levels of amino acids and proteins but also to alterations of the factor and EIF2B (eukaryotic translation initiation factor 2 subunit B), which acts in the early steps of protein synthesis and activation of the inflammatory cascade [57].
2.4. Sarcopenia: chronic heart failure (CHF)

Heart dysfunction is a major factor limiting physical performance and skeletal muscle abnormalities, which often accompany CHF, may also contribute to fatigue and dyspnea (Figure 3).

Heart dysfunction is associated by metabolic changes that implicate inflammatory and endocrine disorders that determine muscle atrophy and weakness [58].

Cardiac myopathy is defined as muscle fiber atrophy, decreased capillary density, and a low number of type I fibers (fast) compared to type 2, with alteration of the normal ratio between type 1 fibers and type 2 fibers, changes that are responsible for intolerance to physical exercise [59]. Mechanism involved is the ubiquitin-mediated proteolysis and anorexia that exacerbate the weight loss process.

The UPS involves a multi-subunit protease that specifically degrades ubiquitin-conjugated proteins through the action of three enzymes, the ubiquitin-activating enzyme, the ubiquitin-conjugating enzyme, and ubiquitin ligases (atrogin-1 and MuRF-1). A higher frequency of myonuclear apoptosis has also been found in the muscle of patients with CHF relative to age-matched healthy controls [60].

In fact, patients develop anorexia that is secondary to intestinal edema with symptoms like dysgeusia, nausea, and gastroenteropathy and it is also mediated by several drugs such as digoxin, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and diuretics that favor a loss of nutrients. So, an insufficient intake or absorption of primary nutritional elements, or their loss, determines a malnutrition condition and muscle depletion.

Figure 3. Pathophysiology of secondary sarcopenia.
Furthermore, elevation of angiotensin II levels aggravates these mechanisms. High levels of angiotensin II increase cytokines, such as TNF-alpha, interleukin 6, and glucocorticoids, which induce muscle protein degradation. TNF-α and its soluble receptors have been associated with declines in muscle mass and strength [61]. Another pathophysiological process is related to the decrease of expression of growth hormone (GH) and IGF-1 (anabolic hormones) in muscle, possibly contributing to muscle mass loss [62].

2.5. Sarcopenia: cancer

Within neoplastic sarcopenia definition (often described as cachexia), are included both the real cases of primary cachexia and the cases of nutritional deterioration secondary to obstruction of the digestive tract, chemo-radiotherapy toxicity, and post-surgical intestinal malabsorption syndromes (secondary cachexia). Cachexia is, regardless of the histology and location of the primary tumor, the most common paraneoplastic syndrome in patients with advanced cancer. Over 70% of cancer patients, especially in advanced stages, develop signs and symptoms of cachexia, and about 20% die because of its consequences [63].

Cachexia is characterized by alterations of all metabolic systems, production of circulating factors in part produced by the tumor, in part by the host cells, mainly macrophages, in response to the tumor, and reduced caloric intake.

Some of these alterations appear early in the natural history of neoplastic disease:

a. Glucose metabolism: Increased gluconeogenesis from lactate, amino acids, and free fatty acids with loss of protein and lipid reserves.

b. Protein metabolism: Increased turnover with decreased muscle and hepatic protein synthesis, increased hepatic synthesis of acute phase proteins, increased serum levels of proteolysis-inducing factor (PIF), and increased protein degradation from muscle tissue. The activation of muscle proteolytic systems, such as that of the ubiquitin-proteasome, is present even before there has been weight loss, suggesting that biomolecular alterations responsible for muscular loss are highlighted early in the natural history of neoplastic disease. Other proteolytic mechanisms provide the activation of calcium-dependent systems, such as that of calpain (regulated by a kinase ATP-dependent and an inhibitor, calpastatin).

c. Lipid metabolism: Increased beta-oxidation of fatty acids and the turnover of free fatty acids, increased serum lipoprotein, triglycerides, and production of lipid mobilizing factor (LMF), which induces lipolysis [64].

Some systemic effects of cancer cachexia, such as anorexia, “fatigue,” and increased resting energy expenditure, are the result of circulating factors’ action in part produced by the tumor and in part by the host cells, mainly macrophages, in response to the tumor. Among them, a central role is given by the pro-inflammatory cytokines (IL-1, IL-6, TNF-α, IFN-γ), which trigger the acute phase response with reduced synthesis of proteins (albumin, prealbumin, and transferrin) [65]. Cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) have been suggested as involved in cancer-related anorexia, possibly by increasing the levels of corticotropin-releasing hormone (CRH), a central nervous system neurotransmitter that suppresses food intake, and the firing of glucose-sensitive neurons, which would also decrease food intake [66].
2.6. Secondary sarcopenia: assessment

The variability of weight, even when expressed as body mass index (BMI), is very wide in patients with chronic conditions. There is a correlation between the amount of weight loss and survival. The weight loss cannot be explained only by the decreased supply of food. In fact, it may be related to the size of the increase in basal metabolic rate (resting energy consumption). It is important at the same time in particular for patients suffering from metabolic syndrome and respiratory problems to assess the degree of overweight and obesity.

Therefore, it is necessary to investigate:

- Weight and height (BMI body mass index), and weight loss percentage in the previous period (2 weeks, 1 month, or 6 months).
- Assessment of the quantity and quality of food intake (presence or not of dysphagia). The term sarcopenic dysphagia means a condition characterized by the presence of dysphagia due to sarcopenia of swallowing muscles associated with secondary sarcopenia. Unlike in the elderly dysphagia in stroke outcome, the sarcopenic dysphagia is rarely acknowledged, probably due to the fact that the definition and diagnostic criteria of this condition have not yet been clearly established. According to Butler et al., muscle strength, measured with handgrip, correlates directly with the isometric strength of posterior tongue. This observation indicates that the muscle strength of tongue can be reduced with the generalized deficit in skeletal muscle force, like in sarcopenia [67].

The 10-item Eating Assessment Tool (EAT-10) and a water test (e.g. Toronto Bedside Swallowing Screening Test) or different viscosities (e.g. Volume-Viscosity Swallowing Test) combined with pulse oximetry are useful for dysphagia screening, and if it is confirmed, it requires further secondary clinical evaluations (speech therapist) and possibly instrumental study (Videofluoroscopic Swallowing Study) [68].

The Mini Nutritional Assessment (MNA) [68] is a multidimensional assessment tool, which is easy to complete and allow an easy and feasible large-scale use. The MNA includes 18 items divided into three main sectors (anthropometry and variations in weight, measuring quantitative and qualitative food intake, and disability status and cognitive status); the maximum score is 30. A score below 17 is indicative of malnutrition, a score between 17 and 23.5 is indicative of risk of malnutrition, and a score greater than 24 indicates a normal nutritional status. The questionnaire allows to classify the nutritional state in an univoque way and has high interpersonal reliability and clearly defined thresholds. It has been validated in several ethnicities and ethnic-specific anthropometric cut-off has been set up [69].

The MNA is also a nutrition guide. Timely intervention blocks the weight loss in people who are at risk of malnutrition or undernourished. It takes in regard anthropometric, global, dietary, and subjective assessment, and it gives to this tool high sensitivity (96%) and specificity (98%) [70].

The scale allows to global assessment of patient as the prevalence of malnutrition increases significantly among hospitalized and institutionalized patients and those with cognitive impairment. The connection is simple enough to guess, the inability to feed on their own, the choice of foods, and the long-lasting immobility.
Perhaps less intuitive, chronic protein energy malnutrition affects the ongoing development of higher cognitive processes rather than simply showing a generalized cognitive and motor impairment.

Deficits of cognitive, emotional, and behavioral functioning are linked to structural abnormalities of different regions of the brain. Brain structures and brain circuits calculate different components of cognitive processes. Malnutrition has long-lasting effects in the processes of cognition and behavior [71].

According to the consensus conference of EWGSOP of 2009, the main parameters to be evaluated in the course of sarcopenia relate to muscle mass, muscle strength, and physical performance of the subject. Based on these three parameters, sarcopenia can be classified into three stages: pre-sarcopenia, sarcopenia, and its severe form [72].

Muscle mass can be assessed by magnetic resonance imaging (MRI) and computed tomography (CT); their use is limited in primary care settings by difficulties in access, costs, the lack of portable equipment, and the requirement of highly specialized personnel [73].

Dual-energy X-ray absorptiometry (DXA) is used to assess body composition and provides reproducible estimates of appendicular skeletal lean mass but it is known that the accuracy of DXA for assessing muscle mass in people of different ages and different pathological conditions may vary [74]. Bio-electrical impedance analysis (BIA) estimates the volume of fat and lean body mass based on the relationship between the volume of a conductor and its electrical resistance. It is not expensive, it can be used easily in clinical practice, both on ambulatory subjects and on hospitalized patients [75, 76]. A still not widely used method, but of extreme interest for the estimation muscular mass, it is represented by the ultrasounds.

Ultrasound allows to explore parenchymas and soft tissue of the human body, responding to all the ideal requirements of a diagnostic method: the almost absolute harmlessness, practicability, rapidity of implementation, and cost contents. According to Fanelli and Kuczmarski, ultrasound application represents a prediction system of body fat that is valid at least as far as plicometry [77], but there are still many limitations related to the application of the method: there is no conventional choice of best frequency to apply, body position, and probe pressure on the surface to be evaluated (Table 1).

This method, by measuring thickness of the muscular layers, visceral and subcutaneous fat, was useful in evaluating the regional body composition and where the plicometry is limited [78]. In 2012, Leahy et al. [79] took ultrasound and DXA measurements with good predictive accuracy. In addition, others have used ultrasound to predict the body density of lean men [77], lean women [80], obese adult, Japanese men and women [81], sumo wrestlers [82], the body fat percentage of physically active British and Chinese men [83], and the fat mass of pre-pubertal Japanese children. A new technology, a small, portable, hand-held 2.5 MHz A-mode ultrasound transducer designed specifically for the purpose of body composition assessment; it is connected to a laptop computer using a USB cable, the software assumes the acoustic reflections of the fat-muscle and muscle bone interfaces (Body View, IntelaMetrix, Inc., Livermore, CA) [84].
Studies reported qualitative changes in muscle related to sarcopenia (e.g. atrophy of type II muscle fibers, increase of intramuscular fat, increase of extracellular water relative to muscle volume) and that these abnormalities can be linked to differences in echo intensity obtained from ultrasonography images.

Enhanced echo intensity (EI) represents changes caused by increase of intramuscular fat and fibrous tissue: an increase of echogenicity indicates greater fibrous tissue and fat between muscular fibers (Figure 4) [85]. The simplicity of execution, the low cost, and wide availability make them ideal in the evaluation also for bedridden patients.

Muscle strength was assessed by functional tests: handgrip strength, the walking speed, flexion/extension of the thigh muscles, and forced expiratory flow. Handgrip strength appears to be the most widely used method for the measurement of muscle strength. Isometric handgrip strength shows a good correlation with leg strength and also with lower extremity power, knee extension torque, and calf cross-sectional muscle area [86, 87]. Standardized conditions for the test [88] include seating the subject in a standard chair with their forearms resting flat on the armchairs. Six measures should be taken, three with each arm. Ideally, the patients should be encouraged to squeeze as hard and as tightly as possible for 3–5 seconds for each of the six trials; usually, the highest reading of the six measurements is reported as the final result [89].

The most widely used tool in clinical practice for the assessment of physical performance is measured by gait speed alone or as part of a test battery such as short physical performance battery (SPPB). The SPPB is a test scored to a maximum of 12 points comprising an assessment of gait speed (over 3–4 m), a balance test, and a repeated chair stand test. These tests focus on lower extremity function, as the latter has been shown to correlate with mobility, disability, and patient outcomes, including hospitalization, institutionalization, and mortality. The SPPB takes about 10 min to complete. Participants presenting a score ≤8 points have been described as having a poor physical performance [90]. Other standalone tests can be performed to assess

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<td>Lower cost than laboratory methods</td>
<td>Higher cost than field methods</td>
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<td>High accuracy and precision in the hands of an experienced technician</td>
<td>Requires experienced technician, considerable skill is necessary</td>
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<td>Capable of regional and segmental measurements</td>
<td>Measurement procedures and techniques are not yet standardized</td>
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<td>Minimal tissue compression</td>
<td>Inherent artifacts (fascia etc.)</td>
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<td>Noninvasive and no ionizing radiation</td>
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<td>Applicable for testing in the field</td>
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<td>Can measure other tissue thicknesses (muscle and bone)</td>
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<td>Short testing time, rapid procedure</td>
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Table 1. Advantages and limitations of ultrasound application.
physical performance. In the Timed Up and Go (TUG) test, individuals are asked to rise from a standard armchair, walk to a marker 3 m away, turn, walk back, and sit down again. The 6-min walk distance or 400 m walk time can be used to measure aerobic capacity. The stair climb power test also shows good correlation with other measures of leg power and physical performance but is mostly restricted to use in research settings [91].

They have been proposed numerous biomarkers to evaluate the catabolic/anabolic balance of skeletal muscle: inflammation biomarkers, such as C-reactive protein, interleukin-6, and tumor necrosis factor-α, and other clinical parameters that express the general state of health like hemoglobin, serum albumin, and urinary creatinine. In the overall evaluation, it is important to measure, also, hormones: dehydroepiandrosterone sulfate, testosterone, insulin-like growth factor-1, and vitamin D, products of oxidative damage like advanced glycation end-products, protein carbonyls, and oxidized low-density lipoproteins, or antioxidants and finally α-tocopherol [92].

3. Rehabilitative approach

3.1. Nutritional-supplementary-integrative—intervention

Malnutrition and peripheral insulin resistance, which increases glucose levels in peripheral blood, are frequent alterations in pathologies that may cause sarcopenia.

Figure 4. Echo intensity of the rectus femoris muscle. Left: High echo intensity; Right: low echo intensity. EI, echo intensity; FT, subcutaneous fat thickness; MT, muscle thickness; RF, rectus femoris muscle; VI, vastus intermedius muscle. From Watanabe et al. [85].
The feeding of patients suffering from sarcopenia is essential, mostly the intake of essential amino acids. It should be reminded the importance of 3 protein meals intake and/or supplementation, better if it is given immediately after exercise. The reduced response to the protein synthesis after ingestion of small amounts of essential amino acids can be increased by the ingestion of a mixture with a greater amount of leucine (essential branched-chain amino acid) or a supplementation with hydroxy-methyl butyrate (HMB), a metabolite of leucine; it promotes protein synthesis by preventing protein breakdown. Hormone replacement therapy, if there are no contraindications can be used. According to the recommendations of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), it must be associated to physical exercise, a high protein diet (1–1.2 g/kg per day with at least 20–25 g of high quality protein, such as those derived from milk) [93]. Rizzoli et al. reported that the recommendations for optimal dietary protein intake are daily 1.0–1.2 g/kg (body weight) with an optimal repartition over each daily meal to prevent sarcopenia [94]. Paddon-Jones et al. proposed a dietary plan that includes 25–30 g of high quality protein per meal as dietary protein recommendations for the prevention of sarcopenia [95]. A protein-enriched diet equivalent to 1.3 g/kg/day achieved through lean red meat is safe and effective for enhancing the effects of progressive resistance training. Carnitine plays a decisive role in the metabolism of long-chain free fatty acids, thus affecting lipid metabolism and energy reserves within the cells. Carnitine is a necessary cofactor for the transport of long-chain fatty acids within the mitochondrial matrix, where they are subjected to oxidation for the production of cellular energy. A clinical study has shown that administration of 6 g/day of L-carnitine for the duration of 30 days was able to significantly improve the symptom “fatigue,” appetite, and lean body mass of patients. Therefore, the administration of L-carnitine should be recommended in cachectic patients at a dose of 4–6 g/day orally for a period of time of 3-4 months being usually well tolerated by the patient. Occasional side effects of L-carnitine include epigastralgia and, more rarely, diarrhea [96].

In addition to the now well-known beneficial effects on bone, the vitamin D has positive extraskeletal effects; it acts on the muscle directly (receptor have been identified in skeletal muscle) and indirectly, through increasing of calcium that is essential for muscle contraction; and finally, it promotes the synthesis of contractile proteins [94]. Even supplements, such as omega-3 and carnitine, are widely recommended in this area [96, 97].

Creatine is a molecule produced in the body, and it is a natural amine endogenously synthesized by the liver, kidney, and pancreas from the amino acids arginine, glycine, and methionine. It stores high-energy phosphate groups in the form of phosphocreatine that releases energy to aid cellular function in brain, bones, muscles, and liver. It can be found in some foods, mostly meat, eggs, and fish [98]. Creatine supplementation became popular in the 1990s for enhancing athletic performance and building lean body mass [99]. It has also been used in the treatment of chronic heart failure and mitochondrial disorders. Recent findings have confirmed the potential therapeutic effects of creatine supplementation and have demonstrated that in the elderly, it improves the quality of life by increasing muscle strength and resistance to fatigue, improving performance in daily activities, and preventing bone loss [100, 101]. As a supplement, it is most commonly available as a monohydrate in powder, candy, gum, and liquid. Many synthetic derivatives are available, including creatine malate, creatine pyruvate,
creatine citrate, creatine-magnesium chelate, and creatine ethyl ester. Studies with older people have used this regimen 2–5 g per day to ensure the saturation of muscle compound [102], and when it is associated with resistance training, training volume is increased, thereby enhancing strength and muscle mass [103].

The quality of proteins is paramount. A major stimulus in muscle anabolism has been reported as a result of an increase in circulating leucine levels. This was inferred from the observation that the ingestion of whey protein causes even more postprandial muscle protein synthesis rates relative to the ingestion of the intact or hydrolyzed casein and the difference is in the leucine content that has a key role in increasing muscle protein synthesis [104].

Whey protein can be considered a high quality protein, due to the anabolic properties attributed to the faster digestion and absorption of essential amino acids, such as leucine [105].

The mechanism of action of whey proteins is linked to the phosphorylation of p70S6K, which targets the ribosomal subunit S6 and thus promotes protein synthesis. It has been seen that its levels remain elevated even 2 hours after ingestion of whey proteins [106]. In association with amino acid supplementation, it is helpful to administer omega-3 fatty acid because these affect the membrane fluidity, endocytosis, exocytosis, absorption, and release of neurotransmitters such as acetylcholine involved in muscle contraction. They also stimulate the pathway of protein kinase C, enhancing muscle protein synthesis [107].

A recent integrative approach is the use of melatonin. Melatonin, also known as N-acetyl-5-methoxytryptamine, is a derivative of tryptophan, an essential amino acid [108]. It is well known for its role in synchronization of circadian rhythms such as sleep timing, blood pressure, and seasonal reproduction [109, 110], but it is also an antioxidant molecule since it seems to be essential regulator of homeostasis.

Lee et al. found an inverse association between urine melatonin and sarcopenia, suggesting that melatonin may have a protective role in the pathophysiology of sarcopenia. Aging and age-related conditions show an association with low melatonin level. Considering that melatonin has anti-apoptotic effects and attenuates autophagic pathways, its decrease may have a role in the pathogenesis of sarcopenia. Muscle is one of the systems that requires more oxygen and consequently generates more reactive species. Melatonin is a protective factor against this damage, scavenging free radicals, enhancement of antioxidant enzymes, and inhibition of pro-oxidant enzymes [111, 112].

Its antioxidant function is expressed by protection of the electron transport chain and mitochondrial DNA from oxidative damage more efficiently than other conventional antioxidants. So, it increases ATP production in mitochondria [113]. For example, melatonin induces autophagy in myoblast cells collaborating in myogenic differentiation degradation [88], but it inhibits autophagy in muscles from carbon tetrachloride-treated mice by reducing oxidative stress-induced damage. Melatonin reduces endoplasmic reticulum stress in skeletal muscle by increasing the expression of several proteins as well as mRNA levels [114]; this improves protein synthesis. It reduces inflammation in muscle cells, acting specifically against these cytokines in rats [115] and also in humans [116].
Melatonin is more than a regulator of circadian rhythm, it is an antioxidant molecule, and it seems to be essential as a physiological regulator of homeostasis. So, its supplementation may be useful to prevent or treat sarcopenia-associated diseases, including osteoporosis and neuromuscular dysfunction [117].

The management of weight loss in secondary sarcopenia must be evaluated with extreme care since it is known that any treatment of obesity is diet therapy which affects the loss of fat mass and lean mass. This loss of muscle mass is greater when they are prescribed diets with a very low calorie intake or less than 1000 kcal/day, which should be strongly discouraged in chronic diseases. In the management, it is necessary to ensure a moderate caloric restriction ensuring a gradual weight loss, from 0.5 to 1 kg per week, or a decline of 8–10% compared to the initial weight in 6 months. It is also necessary to ensure proper protein intake. Metabolic and epidemiological studies suggest that the current intake recommendations for protein in elderly may not be sufficient.

### 3.2. Reduction of chronic inflammation

Despite the different chronic conditions can lead to secondary sarcopenia, one of the factors underlying the development and progression is the state of chronic inflammation. The pronounced anti-inflammatory effects of extremely low frequency (ELF) magnetic fields may improve the well-being of patients suffering from illnesses of different etiology. Human studies regarding ultralow frequency magnetic field effects have been carried out in several clinical settings over the past 20 years for treating bone and joint diseases, neuropathies, spinal cord injury, diabetic neuropathy, immune disorders, and cardiomyopathy. Properly configured signals have been demonstrated to regulate major cellular functions, including cell proliferation, differentiation, apoptosis, cell cycle, DNA replication, and cytokine/chemokine expression [118, 119].

The anti-inflammatory effects have demonstrated a decrease in pro-inflammatory cytokines and increase in anti-inflammatory cytokines after traumatic brain injury. Several metabolic parameters change in consequence of exposure to electromagnetic field, as observed in injured rats [120], stroke, decreased pain in osteoarthritis [121], wound healing [122] and postsurgical recovery [123].

Saggini et al. show inflammatory effects of external pulsed electromagnetic fields in the treatment of low back pain with a decrease of pro-inflammatory cytokines (IL-6) after 40 minutes to a sequence of electromagnetic fields of low intensity with inferior frequencies at 100 KHz for a number of 10 sessions in 3 weeks [124]. Furthermore, they allow, as a consequence, a ionic flow capable of optimizing the intrinsic capacity of maintaining the intra and extracellular potential difference essential for the cellular metabolism and homeostasis [125].

The frequency of the field was such to “stimulate” several ions in the sense of the cyclotron frequency. These ions may be involved in the enzymatic chains experimentally affected. This issue needs to be analyzed in detail in the future through well-designed experiments [125].
The term cyclotron frequency points to the form of resonance, which is established at the level of cell membranes, using electromagnetic fields at a very low intensity and at a specific frequency (cyclotron), able to influence and stimulate the metabolism of human cells. It acts to adjust the ordered traffic of selected ions between the internal and external environments of the cell; it stimulates the activity of those ion-dependent enzymes allowing the occurrence of several biological reactions [126].

The bioresonance cyclotron technology (Figure 5) (Quantum Electrodynamic Catalysis) is able to provide magnetic fields that respond to the laws of quantum electrodynamics consistency (QUEC), i.e. fields that interact with the “Domains of Consistency” of water, contained in every living being, animal, and plant. The advantage of quanto-elettrodinamica (QUEC) technology is to be able to influence the movement of different ion species to the cell membranes and stimulate the formation of coherent structures by strengthening the metabolism and cell cooperation (homeostasis) [125, 126].

Exposure to bio-cyclotron resonance technology determines: a change of configuration of the water; the normalization of the ion concentration in intracellular and extracellular fluid; the biocatalytic stimulation of intracellular enzymatic functions [127, 128].

With ion cyclotron resonance, we have the possibility to intervene in noninvasive, natural and precise way, on body’s homeostasis adjustment mechanisms, where the only pharmacological support can be incomplete.

Figure 5. Ion cyclotron resonance with QUEC PHISIS QPSI.
Therefore, it is possible to:

1. Rebalance subjective metabolism
2. Adjust the enzyme functions, the ion channels, and the body pH
3. Strengthen the immune system
4. Encourage the bioavailability and absorption of nutrients for cell metabolism
5. Treat neuralgia, headaches, and migraines
6. Stimulate healing in all kinds of wounds, even after surgery
7. Balance the water retention
8. Enhance the effect of drugs and supplements
9. Detoxify and to allow antioxidant function against free radicals, metabolites, and toxins
10. Stimulate a painkiller function (acute and chronic)
11. Get muscle relaxation, from anxiety and stress
12. Improve the homeostasis recovery under stress (physiological microtrauma and muscle protein catabolism).

3.3. Physical exercise

In patients with secondary sarcopenia, both aerobic exercise (endurance) and the anaerobic exercise (resistance) are able to reduce sarcopenia and increase muscular strength and muscle power. Habitual physical inactivity of these patients is due to a number of barriers: socio-economic, psychological, and clinics.

From a clinical point of view, these patients are fragile and sedentary with significant comorbid conditions, such as osteoporosis, anemia, and heart failure, which often limit their access to physical exercise. Theoretically, a physical exercise could be harmful as it may increase temporarily the risk of fatal and nonfatal cardiovascular events, especially if in the presence of other cardiovascular risk factors.

The recommends pre-participation of exercise protocols, provide cardiovascular evaluation by means of history (personal and family history) and physical examination alone, although this screening protocol has a recognized limited power (<10%) to detect potentially lethal cardiovascular event. ECG enhances the sensitivity of the screening process by allowing early detection of cardiovascular conditions distinctively manifesting with ECG abnormalities. If in the course of screening emerge, cardiovascular abnormalities should be assessed the need for further investigation, focusing initially noninvasive, such as echocardiography, Holter monitoring, ECG-averaging, tilt testing, the ECO-stress, myocardial scintigraphy, MRI, and cardiac CT (Table 2).

It is well known that aerobic exercise induces an increase in skeletal muscle mitochondria. In fact, adaptations to aerobic training appear to be the result of exercise-induced increases in the transcription of mitochondrial genes.
Many studies have shown an improvement of muscle function even with aerobic or combined aerobic and anaerobic exercises. Aerobic training can include multiple sporting activities, such as stretching, walking, jogging, bicycle ergometer, and aerobic exercises. The latter often based on different tools: weights, elastic bands, rubber balls, rollers, and treadmill. A typical aerobic workout session could last about 90 minutes and be divided as follows: 15–20 minutes of stretching exercises, 20–50 minutes pedaling bicycle ergometer, and 20 minutes of recovery phase [129]. It should start with a lower intensity of training, with the shortest duration and for a few days a week [130]. Several authors showed a significant improvement in aerobic exercise capacity and muscle strength; an improvement in insulin resistance and anorexia; and an increase in ejection fraction, cardiac output, and stroke volume after 6 months of training. Aerobic exercise is related to significant reduction of systolic and diastolic pressure values [108] and an improvement in strength and muscle power [131]. It is well established that traditional, slow-velocity resistance exercise (RE) performing the concentric and eccentric phase of each muscle contraction in 2–3 s is a safe, feasible, and effective intervention to induce muscle hypertrophy and increase strength. It seems to increase muscle protein synthesis [132], satellite cell activation and proliferation [133], anabolic hormone production, and decrease in catabolic cytokine activity [134]. RE has been shown to increase both type I and II muscle fiber cross-sectional areas and whole body leading to an increase in muscle strength. Resistance training needs to use a progressively increasing load to maintain the desired range of repetitions per set of exercise (Table 3).

Fast-velocity RE (performing the concentric phase as quickly as possible and taking 2 sec to perform the eccentric phase of each muscle contraction) appears to be a novel intervention for older adults to enhance muscle power. With the subsequent atrophy of type II fibers with aging, fast-velocity movements are important for preserving aging muscle health. Several studies have shown a significant increase in muscle power with fast velocity RE in older adults, because of greater motor unit recruitment of type II fibers [135].

Physical training can improve balance and stability and thus has been recommended as part of rehabilitative exercise protocols. Studies demonstrate significant flexibility improvements (some joints show range of motion improvements of greater than 40%) with supervised exercise programs, including static stretching or a combination of stretching and movements.

### Table 2. Contraindications to exercise training.

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable coronary heart disease</td>
<td>Major risk factors for coronary heart disease</td>
</tr>
<tr>
<td>Decompensated heart failure</td>
<td>Decompensated diabetes</td>
</tr>
<tr>
<td>Severe pulmonary arterial hypertension (mean arterial pressure &gt;55 mmHg)</td>
<td>Hypertension above 160/100 mmHg</td>
</tr>
<tr>
<td>Uncontrolled arrhythmias</td>
<td>Patients with pacemakers or defibrillators</td>
</tr>
<tr>
<td>Uncontrolled high blood pressure (&gt;180/110 mmHg)</td>
<td></td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td></td>
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<tr>
<td>Severe symptomatic aortic stenosis, aortic dissection</td>
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</tbody>
</table>
through a full range of motion [136]. The recovery of proprioception is an essential part of the recovery of sarcopenia for the recovery the motor task is to be made through advanced systems for muscle strength and balance. I-Moove (Figure 6) has a balancing platform with helispheric movement and continuous realignment of spatial plans and subsystems of the body in order to maintain an optimal posture in open chain or to exert a tensile force. It also provides a real-time visual feedback that allows to monitor corrections [137].

It is possible to use whole body vibration and focal vibration system that is an effective method to activate the proprioceptive sensory system. It consists of the excitation of the afferents coming from the neuromuscular spindle. This causes the activation of a large number

<table>
<thead>
<tr>
<th>Type of training</th>
<th>Frequency</th>
<th>Intensity</th>
<th>Duration/set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic exercise</td>
<td>A minimum of 5 days/week for moderate intensity or 3 days/week for vigorous intensity</td>
<td>Moderate intensity 40–60% VO₂ max 40–60% VO₂ max 40–60% VO₂ max</td>
<td>3–6 METS Accumulate at least 30 min/day of moderate-intensity activity, in bouts of at least 10 min each; continuous vigorous activity for at least 20 min/day</td>
</tr>
<tr>
<td>Resistance exercise</td>
<td>At least 2 days/week</td>
<td>Slow-to-moderate lifting velocity 60–80% of 1 RM</td>
<td>8–10 exercises 1–3 sets per exercise 8–12 repetitions (1–3 min of rest among set)</td>
</tr>
<tr>
<td>involving the major muscle groups (free weights and machines)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power training</td>
<td>2 days/week</td>
<td>Light-to-moderate loading (30–60% of 1 RM) High repetition velocity</td>
<td>1–3 sets per exercise, 6–10 repetitions</td>
</tr>
<tr>
<td>to practice only after the resistance training</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR, heart rate; RM, repetition maximum; and METS, metabolic equivalents.

Table 3. Physical exercise indications.

Figure 6. I-Moove and rehabilitative gym at University Centre of Physical Medicine and Rehabilitation University G. d’Annunzio- Chief R. Saggini.
of alpha-motor neurons, leading to the recruitment of muscle fibers, previously inactive, to contribute to muscle contraction. It has been demonstrated that mechanical vibration on a single muscle is able to activate Ia and II afferent nerve fibers of the muscle spindle, and hence the alpha motor neurons: this elicits the so-called Tonic Vibration Reflex (TVR), consisting in sustained contraction of the muscle vibrated and simultaneous relaxation of its prime antagonists. Neuromuscular electrical stimulation (NMES) is an alternative and potentially more effective mean than exercise alone of increasing the force of muscles. These alternative approaches to exercise offered a safe addition to a traditional, high-intensity volitional strengthening program with the aim to implement muscular mass and strength (as described in chapter *Rehabilitation in sarcopenic elderly*).

4. Dynamic antigravity postural system (SPAD)

SPAD®, a device for body weight relief, consisting of a machinery designed to reduce, modify, and condition the force of gravity acting on the body structures of movement during the act of rectilinear motion (Figure 7). The system is based on the rational that gait training can be made combining the motor task to sensory feedback, in line with the multisensory approach to postural balance. The system consists of a treadmill on which the patient carries out training in body weight support and of a structure to which the patient is harnessed by means of a pneumatic belt placed between the iliac crests and the costal arches, connected to lifting system with four tie rods attached to the body and to the pelvic girdle. Equipment is completed by four front pads (two on the humeral heads for the shoulder girdle and two on the anterior superior iliac spine for the pelvis), which act as stabilizers (as they prevent possible twisting of the pelvis or shoulder during movement on the treadmill), and at the same time as informants proprioceptive. Two rear pads can be placed on the interscapular region and on the sacral area; according to the characteristics of

![Figure 7. Dynamic antigravity postural system (SPAD).](image)
the patient, an inflatable collar can also be used. Each session of SPAD® provides a 30–50% mean body weight relief and a training on the treadmill with adjustable speed (down to 0.01 km/h during the first session, allowing to become familiar with the machine and thus obtaining a higher compliance). The harnessing in body weight support allows the vertical excursion of the center of gravity of the subject, facilitating the execution of longer steps, according to the possibilities of the individual patient; the step performing is corrected continuously by the operator, inviting the patient to get an ordered cadence with sequential placement of heel-plant-toe. In this way, session after session, SPAD® allows to change asymmetrical gait adaptations, working with a dual action: a mechanical one, which allows a neuromotor retraining with cortical-subcortical learning aimed to the reacquisition of a balanced body schema that minimizes the energy consumption needed to maintain the posture, and a proprioceptive one, which acts on the maintenance of automatic and induced over time walking adaptations. The last part of the session provides for the reduction of body weight relief gradually to 0% and the reduction of the speed of the treadmill until the stop; in this way, in the last part of the session, the patient continuing to maintain the proprioceptive stimulus [138–140].

5. Exercises in virtual reality

Virtual reality exercises in the proposed protocol are based on the most recent findings about the neurophysiology of learning processes and movement memorization. The virtual reality system Riablo® is based on the use of sensors connected to a screen, which in real time sent the exact awareness of the carried out motor task to the patient, with the possibility to focus attention only on the fundamental elements of the movement reducing distracting stimuli from the surrounding real environment. It is possible to set a series of exercises: stand up from the chair; displacement of the load with bending knees; displacement of the load on the sagittal plane; displacement of the load on the sagittal and frontal planes; and bilateral squats with back support. The resulting motor performances and the collected kinematic data are entirely analyzed and recorded in the system, which calculate a score. This motivational input rewards the patient’s efforts, ensuring faster progress [141].

6. Microgravity aquatic therapy

Aquatic therapy is based upon several important bioengineering properties. The basic forces acting upon the patient while in the water consist of buoyancy, drag, and inertial forces. Additional factors affecting the patient include hydrostatic pressure and specific heat. Various properties of water contribute to therapeutic effects, including the ability to use water for resistance in place of gravity or weights. Thermal stability that permits maintenance of near-constant temperature; hydrostatic pressure that supports, stabilizes and influences heart and lung function; buoyancy that permits flotation and reduces the effects of gravity; and
turbulence and wave propagation that allow gentle manipulation and movement. In our clinical experience, microgravity aquatic therapy can restore active range of motion. In the water, where resistance of water changes depending on walking speed, it is possible to adjust the exercise intensity. Compared to slow movements, such as walking, the body is subjected to greater levels of water resistance with movements that require use of great muscle strength in a short period of time. Previous studies have found that by exercising in the water, where buoyancy makes it difficult to support the body, people can experience postural instability and improve dynamic balance and muscle strength [142]. As far as exercise safety was concerned, in the water buoyancy and viscosity, lower forces applied to body mass-bearing joints, such as the knee, and as a result, the aquatic exercise did not damage muscles and joints. Moreover, in the present aquatic exercise training, the level of intensity can be defined as “moderately strong.”

7. Resistance exercise with Kineo system

Changes related to sarcopenia have negative implications on metabolism, cardiovascular, and muscular function. Physical exercise is the most effective intervention to improve quality of life, physical, and psychological health [143].

Physical exercise acts on all the physiopathological mechanisms of sarcopenia: increases mTOR expression that controls protein synthesis in the muscle in response to exercise and nutrition; decreases fat infiltration and prevents lipotoxicity; and regulates oxidative stress through activation of mitochondrial genes and optimization of energy production, increase of capillary density, and muscle perfusion.

A training program that includes endurance and resistance exercises has more positive effects on sarcopenic muscle: resistance exercises are more effective in increasing muscle mass and strength, whereas endurance exercises are more effective for improving maximum aerobic power [144].

Increase of muscle strength and mass can be achieved with an innovative system, such as the KINEO system: a multitasking ergonomic robotic platform that will give you the opportunity to differentiate the activities of muscular work in a highly efficient and accurate way. It is the only robotic platform that allows to differentiate the workload in the two movement phases: concentric and eccentric. This allows to optimize the training of strength and also to work with maximum loads in the concentric phase, as it reduces the load in the return movement.

Kineo (Figure 8) is the only robotic platform that allows to differentiate the workload in the two movement phases: concentric and eccentric. This allows to optimize the training of strength and also to work with maximum loads in the concentric phase, as it reduces the load in the return movement.

The Kineo system makes it possible to perform the movement with or without inertia: in the latter case, the displacement of the load requires an application of muscle strength
throughout the movement, even in gestures characterized by great explosiveness. The set load remains constant in all angles and is not modified by inertia, as is the case with a traditional isotonic work. It is possible to differentiate the load between the concentric phase and the eccentric phase. It is possible to work in different conditions, such as elastic and “water viscous method.” The elastic method uses resistance bands or springs as external resistance. The elongation of an elastic element depends on the strength applied to it by the subject and the nature of the elastic material (elastic constant). The advantage of the traditional elastic method is constituted by the gradual increase in the muscular effort while varying the workload is laborious.

Kineo elastic method is its ability to use differentiated loads between the concentric and eccentric phase to generate specific muscle adaptations and to use different methods in the concentric and eccentric phase.
Water workout is, universally, recognized as the most appropriate method for prevention and functional rehabilitation, because the load adapts exactly to the real strength of the subject. The “water viscous method,” which can be considered as the most innovative, uses the principle of water workout and makes it available in a classic workout station. Kineo offers the possibility to use six levels (Figure 9) of viscosity simulating a workout in various fluids, such as water, oil, honey, and so on, which correspond to different levels of muscular effort. One of the most important applications of the water viscous method is the work for the stabilization of the joints, especially the knee joint, because the progressive increase in the viscous load involves the individual muscle groups according to physiologically correct models.

The water viscous method is characterized by the following features: the load increases or decreases depending on the speed of movement and level of viscosity; the speed is not constant but it depends on the level of applied force; and there is no inertia. When the movement stops, the load is immediately set to zero (maximum safety for the subject). Biphasic load: you can independently configure the level of viscosity in the concentric and eccentric phases (Figure 10). Unlike other methods, the progressive increase in the load according to the speed allows the subject to use a load that always respects his/her neuromuscular condition and prevents pain.

The training schedule with Kineo should involve two or three sessions a week in nonconsecutive days. The workload is related to the potentialities of the individual subject, which is analyzed with specific tests that evaluate strength, equilibrium, speed, and power. (see http://www.kineosystem.com/)

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**Figure 9.** Kineo system, concentric vs. eccentric phase.
8. Quality of life improvement

The inclusive approach to improve the quality of life includes music therapy relaxation training, diaphragmatic breathing, guided imagery, self-hypnosis, mindfulness meditation, and distracting thoughts and activities. Outdoor exercises are perceived as energizing, while indoor exercises are perceived as relaxing. Using methods derived from cognitive therapy, patients are taught how to identify and change unhelpful or negative thoughts (cognitive restructuring) that contribute to psychological distress, while facilitating coping thoughts that reduce distress and enhance other coping efforts. Occupational therapists can help patients maintain or resume their previous social role.

9. Conclusion

Sarcopenia is a disabling condition related to various adverse health outcomes such as mental disorders, poor quality of life, and mortality. Acting with rehabilitation goals is important for promoting positive functional (strength and power) and structural (hypertrophy and phenotypic changes) adaptive responses. The planning of a complex rehabilitation program in sarcopenia associated with chronic conditions, in the context of a comprehensive treatment, is made up of nutritional support, exercise, correction of lifestyles, and use of advanced physical energies. Therefore, for the purposes of the optimal management, it is essential to identify the pathogenesis aspects and clinical characteristics, which can affect the different treatment choices in rehabilitation. A specialist in the identification, evaluation, and rehabilitation of neuromuscular, musculoskeletal, and functional disorders associated with chronic conditions and its treatment emphasizing the restoration and maintenance of function and quality of life. Future research should focus on better understanding the role of rehabilitation and on defining appropriate interventions for sarcopenia in chronic illness.
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