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Rehabilitative good practices in the treatment of sarcopenia. A narrative review.
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Abstract:	To date, rehabilitative good practices, which analyse all aspects of the rehabilitation management of the patient suffering from sarcopenia, are absent in literature. The purpose of our article is to carry out research and evaluation of the evidence, good practice and recommendations in the literature, relating to the rehabilitative treatment of disabilities associated with sarcopenia. Bibliographic-research was conducted on Medline, PEDro, Cochrane-Database and Google-Scholar. All the articles published in the last ten years have been analysed. The result of this research generated three guidelines, eight meta-analyses, five systematic reviews, a Cochrane review, seventeen reviews and seven consensus conferences. From the analysis of the literature, it appears that most of the work agrees in affirming that exercise and diet supplementation are the cornerstones of the rehabilitation treatment in patient suffering sarcopenia. The practice of an adequate lifestyle receives numerous high-grade recommendations in the included guidelines. Based on the data obtained, the rehabilitation management of the patient with sarcopenia must be personalized and must include exercise and nutritional supplementation. These factors are important in increasing the autonomy of the elderly essential for safe walking without neglecting stretching exercises that are important for flexibility and balance and coordination exercises.

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WALTER R. FRONTERA, MD, PHD

**Editors-in-Chief of *American Journal of
Physical Medicine & Rehabilitation***

Dear Editor,

We wish to submit our original article "*Rehabilitative good practices in the treatment of sarcopenia. A narrative review.*" (by Francesco Agostini, Andrea Bernetti, Giorgio Di Giacomo, Mattia G. Viva, Marco Paoloni, Massimiliano Mangone, Valter Santilli, Stefano Masiero) to the reviewing process for publication in journal of *American Journal of Physical Medicine & Rehabilitation*. The paper has been prepared in accordance with the instructions to authors of *American Journal of Physical Medicine & Rehabilitation* and a native speaker of English has checked the English language.

The work has not been submitted to any other publication simultaneously. This final draft of the manuscript has been approved by the listed authors, all of whom have made significant contributions to the work. We are able to declare that there are no financial or other relationships that might lead to a conflict of interests and that no part of this work has been previously published.

We look forward to receiving confirmation of receipt of this submission.

Yours faithfully,

Francesco Agostini (**Corresponding author**), Andrea Bernetti, Giorgio Di Giacomo, Mattia G. Viva, Marco Paoloni, Massimiliano Mangone, Valter Santilli, Stefano Masiero

LETTER POINT TO POINT

Reviewer Comments:

REVIEWER 1

Reviewer 1: The authors have done a great deal of revisions. However, I still have some concerns.

Authors: Dear Reviewer, thanks for the comment.

Major concerns

Reviewer 1: Referring to the search strategy, it still is not clear to me. The authors should present full electronic search strategy, including any logic syntax used, such that it could be repeated. For example, it should be read as "(sarcopenia AND guidelines) OR (sarcopenia AND rehabilitation) OR (sarcopenia AND exercise) OR (sarcopenia AND nutritional supplementation) OR (guidelines AND nutritional supplementation)".

Besides, according to the search strategy authors provided, there should be some randomized controlled trial articles been searched. However, the authors analyzed 41 guidelines or reviews only. Did the author search review article only? If yes, they should present the MESH keywords relating to review in the strategy.

Authors: Dear Reviewer, thanks for the comment. We have edited the text as follows: "*A scientific literature research (Medline, PEDro, Database Cochrane and Google Scholar) was conducted, focusing on the guidelines, from 1 October 2018 to 5 June 2019, using the Mesh terms (sarcopenia AND guidelines) OR (sarcopenia AND rehabilitation) OR (sarcopenia AND exercise) OR (sarcopenia AND nutritional supplementation) OR (guidelines AND nutritional supplementation). Specific databases for guidelines, such as guideline.gov, and the websites of the main international scientific companies, that deal with the topic, have also been consulted. Due to the few results, we decided to extend the bibliographic research to other types of articles, not excluding the articles*

that were not guidelines, using the Mesh Terms (sarcopenia AND rehabilitation) OR (sarcopenia AND exercise) OR (sarcopenia AND nutritional supplementation).

Reviewer 1: As authors have stated, exercise is the cornerstone of sarcopenia therapy, especially strength training. However, the authors did not mention anything about the intensity of strength training in line 130. The intensity is an integral part of exercise prescription, they should be included.

Authors: Dear Reviewer, thanks for the comment. We added a reference and edited the text as follows: *It is also recommended to perform 2-3 sessions per week of anaerobic / anti-resistance exercise (proper relationship between repetitions and corresponding load, for example starting with a low load, 1–2 sets of 8–15 repetitions - time under tension of 2 seconds concentric, 1 second isometric and 2 seconds eccentric / repetition - for each muscle district, and increasing progressively the load in the following weeks, decreasing the number of repetitions), which improves the cardio-metabolic status of the patients.*

Reviewer 1: As to diagnostic criteria, there are EWGSOP1, EWGSOP2, AWGS1, AWGS2, IWGA, and FNIH, at least. If possible, I suggest the authors should add diagnostic criteria for sarcopenia used in each study for clarity.

Authors: Dear Reviewer, thanks for the comment. In the limits section we have specified, when possible, the diagnostic criteria used by each article.

Reviewer 1: Since not every study has equal quality, we usually assess study quality with the Newcastle-Ottawa Scale. If possible, the authors should evaluated the studies they included with this scale.

Authors: Dear Reviewer, thanks for the comment. We added a reference and edited the text as follows: *“Only a few articles^{23,25-36,38} had been written following the appropriate rating scales and checklist.⁶²⁻⁶⁵ The quality of the included studies, when possible, were assessed by the Newcastle-*

*Ottawa Scale.*⁶⁶ *The latter two aspects were taken into consideration when evaluating the recommendations and evidence.”*

Minor issues

Reviewer 1: Line 11, there should be seven consensus conference, not nine.

Authors: Dear Reviewer, thanks for the comment. We have corrected the text as you suggested.

Reviewer 1: Line 48, "da" should be deleted.

Authors: Dear Reviewer, thanks for the comment. We have corrected the text as you suggested.

Reviewer 1: Line 144, line 151, please add the recommended amount of protein and vit D supplement.

Authors: Dear Reviewer, thanks for the comment. We have corrected the text as you suggested.

REVIEWER 2

Reviewer 2: English better but professional editor needed!

Authors: Dear Reviewer, thanks for the comment. We re-submitted the manuscript to a different editing company for the English language. We hope it is satisfactory for you.

1 **TITLE PAGE**

2 **Title:** Rehabilitative good practices in the treatment of sarcopenia. A narrative review.

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21

22

23 **ABSTRACT**

24 To date, rehabilitative good practices, which analyse all aspects of the rehabilitation management
25 of the patient suffering from sarcopenia, are absent in literature. The purpose of our article is to
26 carry out research and evaluation of the evidence, good practice and recommendations in the
27 literature, relating to the rehabilitative treatment of disabilities associated with sarcopenia.
28 Bibliographic-research was conducted on Medline, PEDro, Cochrane-Database and Google-
29 Scholar. All the articles published in the last ten years have been analysed. The result of this
30 research generated three guidelines, eight meta-analyses, five systematic reviews, a Cochrane
31 review, seventeen reviews and seven consensus conferences. From the analysis of the literature,
32 it appears that most of the work agrees in affirming that exercise and diet supplementation are
33 the cornerstones of the rehabilitation treatment in patient suffering sarcopenia. The practice of an
34 adequate lifestyle receives numerous high-grade recommendations in the included guidelines.
35 Based on the data obtained, the rehabilitation management of the patient with sarcopenia must be
36 personalized and must include exercise and nutritional supplementation. These factors are
37 important in increasing the autonomy of the elderly essential for safe walking without neglecting
38 stretching exercises that are important for flexibility and balance and coordination exercises.

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46 **Keywords:** Sarcopenia; Guidelines; Exercise; Diet supplementation; Vitamin D.

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69 INTRODUCTION

70 The term sarcopenia (from Greek sarx-penia) was introduced for the first time by Rosenberg in
71 1989¹ to describe the progressive loss of skeletal muscle mass associated with aging. The
72 definition has been furthermore extended to incorporate an alteration of the components of
73 strength and physical performance.² The age-related loss of muscle strength leads to a
74 progressive functional decrease in addition to an increase in morbidity / mortality, depression
75 and hospitalization, by reducing the quality of life.³⁻⁵ The European Working Group on
76 Sarcopenia in Older People (EWGSOP) recognized in a recent update (EWGSOP2) the
77 coexistence of a deficit of muscular strength as a primary parameter (characterizing component)
78 associated with a global reduction of muscle mass closely related to it.^{6,7} Different stages of the
79 degenerative process have also been recognized for diagnostic purposes. Sarcopenia leads to a
80 quantitative and qualitative reduction of muscle tissue (increase in protein degradation with a
81 decrease in its synthesis), with progressive replacement with not contractile fibrous tissue and,
82 subsequently, adipose tissue.⁸⁻¹² After the 40s, healthy adults lose approximately 8% of his
83 muscle mass every 10 years, therefore, between the 40s and 70s, there is an average progressive
84 decrease of 24%, which decreases further by 15% every 10 years in the subsequent years.¹³ It is
85 interesting how the loss of muscle strength appears to be lower in those patients who have
86 maintained a higher level of exercise during their lifetime.¹⁴ This underlines the importance of
87 regular exercise and how various factors, such as a sedentary lifestyle, inactivity and / or
88 immobilization, are involved in age-related changes, which should therefore not simply be
89 considered as a consequence of the biological aging process.¹⁵ As for the treatment, early
90 recognition and intervention is the cornerstone to improved outcomes in patients with
91 sarcopenia.

92 Today, the management of the patient with sarcopenia includes non-pharmacological and
93 pharmacological protocols. Among non-pharmacological ones, exercise and diet are considered
94 the most important keys in the treatment of sarcopenia. Among the countless others, for example,
95 short-term resistance exercise has been demonstrated to increase ability and capacity of skeletal
96 muscle to synthesize proteins.¹⁶ Resistance training, which positively affects the neuromuscular
97 system and increases the rate of protein synthesis, and muscle strength training have been shown
98 to be successful treatments in the prevention and management of sarcopenia.¹⁷ A recent meta-
99 analysis revealed some benefit of using a combined approach of dietary supplements (proteins
100 and vitamin D) and exercise.¹⁸ High protein intake (1.2-1.6 g/kg per day) has been suggested to
101 prevent age-related sarcopenia.¹⁹⁻²¹ To date, good clinical practices, which analyse all aspects of
102 the rehabilitation management of the patient suffering from sarcopenia, are absent in the
103 literature.

104 The purpose of this article will be to present, compare and summarize the most recent guidelines
105 and the major evidence in the literature dealing with the topic, so as to be able to determine the
106 best practices related to the rehabilitation management of the patient with this condition.

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115 **MATERIALS AND METHODS**

116 A scientific literature research (Medline, PEDro, Database Cochrane and Google Scholar) was
117 conducted, focusing on the guidelines, from 1 October 2018 to 5 June 2019, using the Mesh
118 terms (sarcopenia AND guidelines) OR (sarcopenia AND rehabilitation) OR (sarcopenia AND
119 exercise) OR (sarcopenia AND nutritional supplementation) OR (guidelines AND nutritional
120 supplementation). Specific databases for guidelines, such as guideline.gov, and the websites of
121 the main international scientific societies, that deal with the topic, have also been consulted.

122 Due to the few results, we decided to extend the bibliographic research to other types of articles,
123 not excluding the articles that were not guidelines, using the Mesh Terms (sarcopenia AND
124 rehabilitation) OR (sarcopenia AND exercise) OR (sarcopenia AND nutritional
125 supplementation). The research included articles dealing with the rehabilitative management of
126 the patient suffering from sarcopenia.

127 Three Researchers in Physical and Rehabilitation Medicine conducted data extraction
128 independently and the inconsistencies were overcome by the comparison of the data and the
129 debate.

130 Documents that have been excluded include those that have been written more than ten years
131 ago, was not possible to find the complete text, not in English, with non-rehabilitative topics as
132 well as those with a methodology not adequately described or that did not provide evidence-
133 based elements.

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138 **RESULTS**

139 The result of this research has generated three guidelines,²²⁻²⁴ eight meta-analyzes,²⁵⁻³² five
140 systematic reviews,³³⁻³⁷ a Cochrane review,³⁸ seventeen reviews³⁹⁻⁵⁵ and seven consensus
141 conferences (Figure 1).^{6,56-61} Tables 1-4 summarize the recommendations / evidence expressed in
142 the various articles included, based on the different types of articles (table 1: guidelines; table 2:
143 meta-analysis; table 3.1-3.2: systematic reviews and reviews; table 4: consensus conference). In
144 the presence of articles published by the same working group, those most recently published
145 have been taken into consideration.

146 Only a few articles^{23,25-36,38} had been realized following the appropriate rating scales and
147 checklist.⁶²⁻⁶⁵ The quality of the included studies, when possible, were assessed by the
148 Newcastle-Ottawa Scale.⁶⁶ The latter two aspects were taken into consideration during the
149 evaluation of the recommendations and evidence.

150 By virtue of the main evidence, we have divided the results into the following topics.

151

152 **Exercise**

153 Exercise is the cornerstone in the global lifestyle management of sarcopenia patients. All the
154 manuscripts agree in adopting a training scheme that includes moderate-intensity aerobic
155 exercise for at least 150 minutes a week, or approximately 30 minutes / day for 5 days a week. It
156 is also recommended to perform 2-3 sessions per week of anaerobic / anti-resistance exercise
157 (proper relationship between repetitions and corresponding load, for example starting with a low
158 load, 1–2 sets of 8–15 repetitions - time under tension of 2 seconds concentric, 1 second
159 isometric and 2 seconds eccentric / repetition - for each muscle district, and increasing
160 progressively the load in the following weeks, decreasing the number of repetitions), which

161 improves the cardio-metabolic status of the patients.^{21,22,29-32,34,38,49,52,67} This type of training,
162 especially if combined with aerobic exercise, increases muscle mass, improves patient balance
163 and coordination, improves glycemic control and insulin resistance and lowers blood pressure
164 values.^{21,22,38,49,52}

165 Exercise therefore represents an integral part of the rehabilitation program to be promptly
166 recommended to the patient. The resistance exercise stimulates the activation of anabolic signals
167 due to mechanical and metabolic stress, promoting protein synthesis, causing an increase in
168 muscle mass (from 3.4% to 7.5%), strength (from 6.6% to 37%) and functional capacity, as well
169 as a reduction in the risk of falls (from 4.7% to 58.1%) in the frail and elderly. This therapeutic
170 option is a key element in order to regain the muscle functions necessary for daily life
171 activities.^{21,22,29-32,34,38,49,52}

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173 **Nutritional Supplements**

174 Nutritional supplements are widely used today in clinical practice in patients with sarcopenia. In
175 particular, protein supplements (1.2-1.6 g/kg per day)^{19-21,28,31,32,36} are recommended in order to
176 compensate for the reduction of protein synthesis and reduce the deterioration of muscle mass.
177 Protein supplements are also recommended because they significantly increase the effects of a
178 muscular resistance training.^{22,28,31,32,36,40} Indeed, it is repeatedly stressed in the literature that,
179 before protein supplementation, an assessment of the patient's nutritional status must be carried
180 out, in order to obtain a complete evaluation of it.^{22,41}

181 Equally recommended, especially from the most recent manuscripts, the integration with vitamin
182 D (500-800 IU/day)⁶⁸ by virtue of the very high percentage of coexistence between sarcopenia
183 and osteoporosis. Vitamin D is able to slow down the progressive deterioration of bone tissue

184 further aggravated by the lack of activity of the muscles which, through the tendons, represent an
185 important bio-stimulus for the bone deposition of calcium. There is evidence of important
186 interactions between bones and muscles that cause a kind of negative resonance between the two
187 tissues when they are simultaneously affected by osteoporosis and sarcopenia, respectively.^{22,45,50}
188 Maintaining an appropriate intake of vitamin D would appear to be one of the ways to minimize
189 aging-related physiological and functional changes in skeletal muscles.^{22,53,69,70}
190 Also, with regard to this recommendation, the importance of a nutritional assessment and bone
191 mineral density is underlined, in order to increase the personalization of the medical
192 intervention.^{54,55} The authors stress the importance of a global approach to the osteo-muscular
193 system through the integration not only of proteins but also of the bone components such as
194 calcium, magnesium and vitamin D.^{22,28,41,50,53,55}
195 Furthermore, Aytakin et al.⁵⁶ analyzed, in their 2018 review, the possible implications of
196 hypovitaminosis B in the development of sarcopenia, comparing the nutritional
197 recommendations used in the United Kingdom and how these correlates with the decline in
198 muscle function in elderly subjects.

199

200 **Combination of Exercise and Nutritional Supplementation**

201 The approach, which today is certainly the most used and has the greatest evidence in the
202 literature, is that which includes an integration between exercise and nutritional
203 supplementation.^{22,24-27,31,32} Many authors point out that the effects of protein supplements,
204 combined with resistance exercises, compared to exercise alone, could have a greater effect in
205 preventing the reduction of muscle mass and age-related loss of strength, with important
206 implications on body composition and physical function in the elderly.^{22,31,32,35,39,44} Also, the

207 combined approach of exercise and vitamin D turned out to be more effective than the same
208 treatments taken individually.^{22,47,48,51}

209 The combination of exercise and multi-nutrient supplementation, including protein, creatine and
210 vitamin D, has recently been recommended as effective in enhancing quality of life and thus
211 promoting successful aging.^{58,60}

212

213 **Lifestyle**

214 According to all the articles that have addressed this topic, lifestyle changes are the first step in
215 the treatment of sarcopenia. Over the years, it has been understood that managing only diet and
216 exercise, through standardized and non-personalized prescriptions on the patient, did not produce
217 clinically satisfactory results. Increasing importance has been attached to psychological factors,
218 both as factors that contribute to the development of the pathology, and as comorbidities that can
219 complicate the therapeutic process and cause any relapses. In this regard, it has been shown how
220 the association of cognitive-behavioral therapy increases the rehabilitative and therapeutic
221 possibilities in these patients, in order to control the greater adherence to dietary and exercise
222 prescriptions.^{22,30,71} Patient education on the correct lifestyle, in terms of to stop smoking,
223 regimented food and regular practice of exercise, in association with information about the risks
224 related to the disease, is the starting point of the therapeutic path.

225

226 **Exercise and Pharmacological Therapies**

227 De Spiegeleer et al.,³³ in 2018 realized a meta-analysis on pharmacological treatments to
228 improve muscle mass, muscle strength and physical performance in older people. The authors
229 highlighted that only vitamin D, especially in elderly women, and testosterone, in elderly men

230 with clinical muscle weakness and low serum testosterone levels, could be justified in daily
231 clinical practice, in order to improve muscle mass, strength muscle and / or physical
232 performance.

233 In 2018, Shin et al.⁴² carried out a review with the aim of investigating the relationship between
234 testosterone and sarcopenia. The effectiveness of this treatment changes depending on the
235 subject and the exercises involved. However, the side effects (increasing cardiovascular risk) are
236 worrisome and the precise contribution in the sarcopenic treatment is not yet evident. For this
237 reason, the use of testosterone in patients with sarcopenia is not recommended.

238

239 **Complementary Therapies**

240 In 2017, Guescini et al.,⁴⁶ in a review, evaluated the combination of exercise and muscle
241 antioxidants (creatine and coenzyme Q10) to counteract sarcopenia, proposing this combination
242 as effective in slowing down the deterioration of muscle tissue.

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253 **DISCUSSION**

254 Of the guidelines analyzed in our study,²²⁻²⁴ only one provides clear recommendations about
255 nutritional supplementation and exercise²² in the treatment of sarcopenia. The remaining,^{23,24} on
256 the other hand, deal in detail with all the aspects concerning the pathophysiology and diagnosis
257 of the disease, without providing, however, clear and targeted recommendations regarding the
258 treatment and the combined approaches, including rehabilitation.

259 It is also important to underline the lack of papers that address the topic in a transversal and
260 exhaustive way, as they are, more often than not, focused only on an individual aspect of the
261 treatment of sarcopenic pathology.

262 From the analysis of the literature, it appears that most of the work all agrees in affirming that
263 exercise and diet supplements are the cornerstones of the rehabilitation treatment in patient
264 suffering sarcopenia. Most of the included studies refer to the definition of the World Health
265 Organization (WHO) which recognizes in the regular exercise (defined as 150 minutes per week
266 of moderate intensity aerobic exercise) a protective factor against different pathologies, able not
267 only to reduce the degree of disability thanks to the maintenance of physical performance, but
268 also to reduce mortality by about 25%. It is therefore evident that, to date, exercise represents the
269 keystone to successful aging, prescribed at the most appropriate dose and at all ages. Although
270 the main programs of exercise for the elderly are more focused on a low intensity aerobic
271 exercise, in literature it is now widely accepted, as the most appropriate way to counteract the
272 progression of sarcopenia and improve performance that being resistance training with
273 progressive loads.

274 With high resistance and high-speed exercises, it is possible to obtain an increase in muscle
275 strength and power respectively. These factors are certainly important in increasing the

276 autonomy of the elderly subject, without neglecting stretching exercises, important for flexibility
277 and balance and coordination exercises, essential for safe walking. None of the included articles,
278 however, provides specifics about this training method or provides clear and evident
279 recommendations.

280 Exercise is not only used in order to maintain muscle tone and trophism, but also guarantees a
281 positive effect on bone mineralization, since muscular trophism represents the fundamental
282 stimulus for the remodeling of skeletal structures and its failure results in a qualitative
283 deterioration of bone tissue followed by an increased risk of fracture secondary to frailty. This
284 certainly represents an important point and highlights the role of regular exercise even more, in
285 accordance with the strong connection existing between sarcopenic and osteoporotic
286 pathology.⁷²⁻⁷⁶

287 The result, that can therefore be consequent to the practice of a regular exercise, is an increase in
288 performance and a reduction in the risk of developing disability.

289 As exercise, adequate nutritional supplementation seems to have positive effects on the quantity
290 and quality of muscle tissue. The most recommended macronutrients are
291 proteins,^{22,25,26,28,31,32,35,39,41,43,45,47-51,53-55,58,60} followed by vitamin D.^{22,27,28,33,35,39-41,43,45,48,51,54,59}

292 Vitamin D deficiency is very common in the elderly due to various factors (reduction of sun
293 exposure, inadequate diet and reduced intestinal absorption). Supplementing with vitamin D, in
294 addition to the already known beneficial effects on the increase in bone strength with consequent
295 reduction of the fractures' risk, would seem to significantly increase muscle strength, also
296 reducing the risk of falls by about 15-20% compared to patients with vitamin D
297 deficiency.^{22,33,35,44,48,51,59}

298 The practice of an adequate lifestyle that involves the suspension of habitual smoking, an
299 adequate and balanced diet and the abandonment of a sedentary life, receive numerous high-
300 grade recommendations in the included guidelines.^{23,24} In addition, all the articles that have
301 addressed this issue highlight its benefits in the management of the patient with
302 sarcopenia.^{24,25,35,47,49}

303 As for complementary therapies, there is a limited amount of evidence in the literature. For
304 creatine and coenzyme Q10, there is little evidence in the literature and a low level.⁴⁶

305

306 **Take Home Message**

307 Based on the evidence contained in the included documents, in the management of sarcopenic
308 patients, exercise is recommended in order to avoid or slow down the progressive deterioration
309 of the muscular system. Specifically, activities such as aerobic exercise, muscle strengthening,
310 balance, flexibility and resistance exercises and a cardiorespiratory training are strongly
311 recommended, even if no details are given on its type, duration and frequency. It is however
312 widely accepted a weight-bearing exercise, as the main way in order to oppose the progression of
313 sarcopenic pathology.

314 A nutritional supplement with proteins and vitamin D is also strongly recommended in order to
315 slow down the progressive deterioration of the osteo-muscular system.

316 Lifestyle changes such as for example to suspend smoking, regime food and promote health
317 education are also recommended.

318 To date, in the literature, there is ample evidence on the use of nutritional supplements, alone or
319 in combination, in sarcopenic patients, in order to refill the physiologically loss. Among these,
320 those with moderate-weak level of evidence are vitamins, especially those of group B, C and E,

321 creatine, coenzyme Q10, essential amino acids, HMB, while others, with less evidence, are the
322 royal jelly, quercetin, caffeine, catechin tea and traditional Japanese herbs.

323 Among the drug therapies, testosterone has evidence of efficacy.

324 Nutritional supplementation with fatty acids and pharmacotherapy with estrogens and Selective
325 androgen receptor modulators (SARM) is not recommended.

326 By virtue of the conflicting evidence in the literature, it is not possible to make recommendations
327 on the usefulness of pharmacotherapy with anabolic hormones and growth hormones.

328 **Limits**

329 A limitation of this study is the possible heterogeneity of the population used in the included
330 studies. It was not always possible to identify the diagnostic criteria used by the included
331 studies.^{22,24,31,32,34,39-41,45,46,49,54,55,59} Most of the studies^{23,25,27,29,33,35,37,38,42-44,47,48,50-53,56,58} used the
332 first version of the European Working Group on Sarcopenia in Older People criteria (2010),⁶⁹
333 while only an article used the 2019 update.⁶ The first version of the Asian Working Group for
334 Sarcopenia criteria⁷⁷ was used by 3 articles (2014),^{26,28,30} while the 2016 update was used by only
335 one article.⁵⁷ No article used the update published in 2020.⁷⁸ The Foundation for the National
336 Institutes of Health criteria⁶⁰ were used by 3 articles.^{23,44,60} The criteria of the International
337 Working Group on Sarcopenia⁶¹ were used by 5 articles.^{33,36,37,44,61}

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344 **CONCLUSIONS**

345 Nowadays, the role of an adequate multi-professional, multi-disciplinary and multi-therapeutic
346 rehabilitation program which include exercise and diet, tailored to the needs of each individual
347 sarcopenic patient, represent the *sine qua non* in the treatment of disorders related to aging, as
348 highlighted by the current evidence in the literature, in order to counteract the progressive
349 reduction of physical performance and to limit an increase in the global patient's disability.
350 Exercise, meaning 150 minutes per week of moderate intensity aerobic exercise, in addition to an
351 adequate lifestyle and a targeted dietary supplement, currently represent the main
352 recommendations in the literature, which can guide the physician in the management of the
353 patient with this pathology.

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390 **COMPLIANCE WITH ETHICAL STANDARDS**

391 **Disclosure of Potential Conflicts of Interest:** The authors declare that they have no conflict of
392 interest.

393 **Research involving Human Participants and/or Animals:** Not applicable.

394 **Informed Consent:** Not applicable.

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636 **FIGURE LEGEND**

637 **Figure 1. Flow chart.**

1 **TITLE:** Rehabilitative Good Practices in the Treatment of Sarcopenia – a Narrative Review.

2

3 **ABSTRACT**

4 To date, rehabilitative good practices, which analyse all aspects of the rehabilitation management
5 of the patient suffering from sarcopenia, are absent in literature. The purpose of our article is to
6 carry out research and evaluation of the evidence, good practice and recommendations in the
7 literature, relating to the rehabilitative treatment of disabilities associated with sarcopenia.
8 Bibliographic-research was conducted on Medline, PEDro, Cochrane-Database and Google-
9 Scholar. All the articles published in the last ten years have been analysed. The result of this
10 research generated three guidelines, eight meta-analyses, five systematic reviews, a Cochrane
11 review, seventeen reviews and seven consensus conferences. From the analysis of the literature, it
12 appears that most of the work agrees in affirming that exercise and diet supplementation are the
13 cornerstones of the rehabilitation treatment in patient suffering sarcopenia. The practice of an
14 adequate lifestyle receives numerous high-grade recommendations in the included guidelines.
15 Based on the data obtained, the rehabilitation management of the patient with sarcopenia must be
16 personalized and must include exercise and nutritional supplementation. These factors are
17 important in increasing the autonomy of the elderly essential for safe walking without neglecting
18 stretching exercises that are important for flexibility and balance and coordination exercises.

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24 **Keywords:** Sarcopenia; Guidelines; Exercise; Diet supplementation; Vitamin D.

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47 **INTRODUCTION**

48 The term sarcopenia (from Greek sarx-penia) was introduced for the first time by Rosenberg in
49 1989¹ to describe the progressive loss of skeletal muscle mass associated with aging. The definition
50 has been furthermore extended to incorporate an alteration of the components of strength and
51 physical performance.² The age-related loss of muscle strength leads to a progressive functional
52 decrease in addition to an increase in morbidity / mortality, depression and hospitalization, by
53 reducing the quality of life.³⁻⁵ The European Working Group on Sarcopenia in Older People
54 (EWGSOP) recognized in a recent update (EWGSOP2) the coexistence of a deficit of muscular
55 strength as a primary parameter (characterizing component) associated with a global reduction of
56 muscle mass closely related to it.^{6,7} Different stages of the degenerative process have also been
57 recognized for diagnostic purposes. Sarcopenia leads to a quantitative and qualitative reduction of
58 muscle tissue (increase in protein degradation with a decrease in its synthesis), with progressive
59 replacement with not contractile fibrous tissue and, subsequently, adipose tissue.⁸⁻¹² After the 40s,
60 healthy adults lose approximately 8% of his muscle mass every 10 years, therefore, between the
61 40s and 70s, there is an average progressive decrease of 24%, which decreases further by 15%
62 every 10 years in the subsequent years.¹³ It is interesting how the loss of muscle strength appears
63 to be lower in those patients who have maintained a higher level of exercise during their lifetime.¹⁴
64 This underlines the importance of regular exercise and how various factors, such as a sedentary
65 lifestyle, inactivity and / or immobilization, are involved in age-related changes, which should
66 therefore not simply be considered as a consequence of the biological aging process.¹⁵ As for the
67 treatment, early recognition and intervention is the cornerstone to improved outcomes in patients
68 with sarcopenia.

69 Today, the management of the patient with sarcopenia includes non-pharmacological and
70 pharmacological protocols. Among non-pharmacological ones, exercise and diet are considered
71 the most important keys in the treatment of sarcopenia. Among the countless others, for example,
72 short-term resistance exercise has been demonstrated to increase ability and capacity of skeletal
73 muscle to synthesize proteins.¹⁶ Resistance training, which positively affects the neuromuscular
74 system and increases the rate of protein synthesis, and muscle strength training have been shown
75 to be successful treatments in the prevention and management of sarcopenia.¹⁷ A recent meta-
76 analysis revealed some benefit of using a combined approach of dietary supplements (proteins and
77 vitamin D) and exercise.¹⁸ High protein intake (1.2-1.6 g/kg per day) has been suggested to prevent
78 age-related sarcopenia.¹⁹⁻²¹ To date, good clinical practices, which analyse all aspects of the
79 rehabilitation management of the patient suffering from sarcopenia, are absent in the literature.
80 The purpose of this article will be to present, compare and summarize the most recent guidelines
81 and the major evidence in the literature dealing with the topic, so as to be able to determine the
82 best practices related to the rehabilitation management of the patient with this condition.

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92 **MATERIALS AND METHODS**

93 A scientific literature research (Medline, PEDro, Database Cochrane and Google Scholar) was
94 conducted, focusing on the guidelines, from 1 October 2018 to 5 June 2019, using the Mesh terms
95 (sarcopenia AND guidelines) OR (sarcopenia AND rehabilitation) OR (sarcopenia AND exercise)
96 OR (sarcopenia AND nutritional supplementation) OR (guidelines AND nutritional
97 supplementation). Specific databases for guidelines, such as guideline.gov, and the websites of the
98 main international scientific societies, that deal with the topic, have also been consulted.

99 Due to the few results, we decided to extend the bibliographic research to other types of articles,
100 not excluding the articles that were not guidelines, using the Mesh Terms (sarcopenia AND
101 rehabilitation) OR (sarcopenia AND exercise) OR (sarcopenia AND nutritional supplementation).

102 The research included articles dealing with the rehabilitative management of the patient suffering
103 from sarcopenia.

104 Three Researchers in Physical and Rehabilitation Medicine conducted data extraction
105 independently and the inconsistencies were overcome by the comparison of the data and the
106 debate.

107 Documents that have been excluded include those that have been written more than ten years ago,
108 was not possible to find the complete text, not in English, with non-rehabilitative topics as well as
109 those with a methodology not adequately described or that did not provide evidence-based
110 elements.

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115 **RESULTS**

116 The result of this research has generated three guidelines,²²⁻²⁴ eight meta-analyzes,²⁵⁻³² five
117 systematic reviews,³³⁻³⁷ a Cochrane review,³⁸ seventeen reviews³⁹⁻⁵⁵ and seven consensus
118 conferences (Figure 1).^{6,56-61} Tables 1-4 summarize the recommendations / evidence expressed in
119 the various articles included, based on the different types of articles (table 1: guidelines; table 2:
120 meta-analysis; table 3.1-3.2: systematic reviews and reviews; table 4: consensus conference). In
121 the presence of articles published by the same working group, those most recently published have
122 been taken into consideration.

123 Only a few articles^{23,25-36,38} had been realized following the appropriate rating scales and
124 checklist.⁶²⁻⁶⁵ The quality of the included studies, when possible, were assessed by the Newcastle-
125 Ottawa Scale.⁶⁶ The latter two aspects were taken into consideration during the evaluation of the
126 recommendations and evidence.

127 By virtue of the main evidence, we have divided the results into the following topics.

128

129 **Exercise**

130 Exercise is the cornerstone in the global lifestyle management of sarcopenia patients. All the
131 manuscripts agree in adopting a training scheme that includes moderate-intensity aerobic exercise
132 for at least 150 minutes a week, or approximately 30 minutes / day for 5 days a week. It is also
133 recommended to perform 2-3 sessions per week of anaerobic / anti-resistance exercise (proper
134 relationship between repetitions and corresponding load, for example starting with a low load, 1–
135 2 sets of 8–15 repetitions - time under tension of 2 seconds concentric, 1 second isometric and 2
136 seconds eccentric / repetition - for each muscle district, and increasing progressively the load in
137 the following weeks, decreasing the number of repetitions), which improves the cardio-metabolic

138 status of the patients.^{21,22,29-32,34,38,49,52,67} This type of training, especially if combined with aerobic
139 exercise, increases muscle mass, improves patient balance and coordination, improves glycemic
140 control and insulin resistance and lowers blood pressure values.^{21,22,38,49,52}
141 Exercise therefore represents an integral part of the rehabilitation program to be promptly
142 recommended to the patient. The resistance exercise stimulates the activation of anabolic signals
143 due to mechanical and metabolic stress, promoting protein synthesis, causing an increase in muscle
144 mass (from 3.4% to 7.5%), strength (from 6.6% to 37%) and functional capacity, as well as a
145 reduction in the risk of falls (from 4.7% to 58.1%) in the frail and elderly. This therapeutic option
146 is a key element in order to regain the muscle functions necessary for daily life activities.<sup>21,22,29-
147 32,34,38,49,52</sup>

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149 **Nutritional Supplements**

150 Nutritional supplements are widely used today in clinical practice in patients with sarcopenia. In
151 particular, protein supplements (1.2-1.6 g/kg per day)^{19-21,28,31,32,36} are recommended in order to
152 compensate for the reduction of protein synthesis and reduce the deterioration of muscle mass.
153 Protein supplements are also recommended because they significantly increase the effects of a
154 muscular resistance training.^{22,28,31,32,36,40} Indeed, it is repeatedly stressed in the literature that,
155 before protein supplementation, an assessment of the patient's nutritional status must be carried
156 out, in order to obtain a complete evaluation of it.^{22,41}

157 Equally recommended, especially from the most recent manuscripts, the integration with vitamin
158 D (500-800 IU/day)⁶⁸ by virtue of the very high percentage of coexistence between sarcopenia and
159 osteoporosis. Vitamin D is able to slow down the progressive deterioration of bone tissue further
160 aggravated by the lack of activity of the muscles which, through the tendons, represent an

161 important bio-stimulus for the bone deposition of calcium. There is evidence of important
162 interactions between bones and muscles that cause a kind of negative resonance between the two
163 tissues when they are simultaneously affected by osteoporosis and sarcopenia, respectively.^{22,45,50}
164 Maintaining an appropriate intake of vitamin D would appear to be one of the ways to minimize
165 aging-related physiological and functional changes in skeletal muscles.^{22,53,69,70}
166 Also, with regard to this recommendation, the importance of a nutritional assessment and bone
167 mineral density is underlined, in order to increase the personalization of the medical
168 intervention.^{54,55} The authors stress the importance of a global approach to the osteo-muscular
169 system through the integration not only of proteins but also of the bone components such as
170 calcium, magnesium and vitamin D.^{22,28,41,50,53,55}
171 Furthermore, Aytakin et al.⁵⁶ analyzed, in their 2018 review, the possible implications of
172 hypovitaminosis B in the development of sarcopenia, comparing the nutritional recommendations
173 used in the United Kingdom and how these correlates with the decline in muscle function in elderly
174 subjects.

175

176 **Combination of Exercise and Nutritional Supplementation**

177 The approach, which today is certainly the most used and has the greatest evidence in the literature,
178 is that which includes an integration between exercise and nutritional supplementation.^{22,24-27,31,32}
179 Many authors point out that the effects of protein supplements, combined with resistance exercises,
180 compared to exercise alone, could have a greater effect in preventing the reduction of muscle mass
181 and age-related loss of strength, with important implications on body composition and physical
182 function in the elderly.^{22,31,32,35,39,44} Also, the combined approach of exercise and vitamin D turned
183 out to be more effective than the same treatments taken individually.^{22,47,48,51}

184 The combination of exercise and multi-nutrient supplementation, including protein, creatine and
185 vitamin D, has recently been recommended as effective in enhancing quality of life and thus
186 promoting successful aging.^{58,60}

187

188 **Lifestyle**

189 According to all the articles that have addressed this topic, lifestyle changes are the first step in the
190 treatment of sarcopenia. Over the years, it has been understood that managing only diet and
191 exercise, through standardized and non-personalized prescriptions on the patient, did not produce
192 clinically satisfactory results. Increasing importance has been attached to psychological factors,
193 both as factors that contribute to the development of the pathology, and as comorbidities that can
194 complicate the therapeutic process and cause any relapses. In this regard, it has been shown how
195 the association of cognitive-behavioral therapy increases the rehabilitative and therapeutic
196 possibilities in these patients, in order to control the greater adherence to dietary and exercise
197 prescriptions.^{22,30,71} Patient education on the correct lifestyle, in terms of to stop smoking,
198 regimented food and regular practice of exercise, in association with information about the risks
199 related to the disease, is the starting point of the therapeutic path.

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201 **Exercise and Pharmacological Therapies**

202 De Spiegeleer et al.,³³ in 2018 realized a meta-analysis on pharmacological treatments to improve
203 muscle mass, muscle strength and physical performance in older people. The authors highlighted
204 that only vitamin D, especially in elderly women, and testosterone, in elderly men with clinical
205 muscle weakness and low serum testosterone levels, could be justified in daily clinical practice, in
206 order to improve muscle mass, strength muscle and / or physical performance.

207 In 2018, Shin et al.⁴² carried out a review with the aim of investigating the relationship between
208 testosterone and sarcopenia. The effectiveness of this treatment changes depending on the subject
209 and the exercises involved. However, the side effects (increasing cardiovascular risk) are
210 worrisome and the precise contribution in the sarcopenic treatment is not yet evident. For this
211 reason, the use of testosterone in patients with sarcopenia is not recommended.

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213 **Complementary Therapies**

214 In 2017, Guescini et al.,⁴⁶ in a review, evaluated the combination of exercise and muscle
215 antioxidants (creatine and coenzyme Q10) to counteract sarcopenia, proposing this combination
216 as effective in slowing down the deterioration of muscle tissue.

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230 **DISCUSSION**

231 Of the guidelines analyzed in our study,²²⁻²⁴ only one provides clear recommendations about
232 nutritional supplementation and exercise²² in the treatment of sarcopenia. The remaining,^{23,24} on
233 the other hand, deal in detail with all the aspects concerning the pathophysiology and diagnosis of
234 the disease, without providing, however, clear and targeted recommendations regarding the
235 treatment and the combined approaches, including rehabilitation.

236 It is also important to underline the lack of papers that address the topic in a transversal and
237 exhaustive way, as they are, more often than not, focused only on an individual aspect of the
238 treatment of sarcopenic pathology.

239 From the analysis of the literature, it appears that most of the work all agrees in affirming that
240 exercise and diet supplements are the cornerstones of the rehabilitation treatment in patient
241 suffering sarcopenia. Most of the included studies refer to the definition of the World Health
242 Organization (WHO) which recognizes in the regular exercise (defined as 150 minutes per week
243 of moderate intensity aerobic exercise) a protective factor against different pathologies, able not
244 only to reduce the degree of disability thanks to the maintenance of physical performance, but also
245 to reduce mortality by about 25%. It is therefore evident that, to date, exercise represents the
246 keystone to successful aging, prescribed at the most appropriate dose and at all ages. Although the
247 main programs of exercise for the elderly are more focused on a low intensity aerobic exercise, in
248 literature it is now widely accepted, as the most appropriate way to counteract the progression of
249 sarcopenia and improve performance that being resistance training with progressive loads.

250 With high resistance and high-speed exercises, it is possible to obtain an increase in muscle
251 strength and power respectively. These factors are certainly important in increasing the autonomy
252 of the elderly subject, without neglecting stretching exercises, important for flexibility and balance

253 and coordination exercises, essential for safe walking. None of the included articles, however,
254 provides specifics about this training method or provides clear and evident recommendations.

255 Exercise is not only used in order to maintain muscle tone and trophism, but also guarantees a
256 positive effect on bone mineralization, since muscular trophism represents the fundamental
257 stimulus for the remodeling of skeletal structures and its failure results in a qualitative deterioration
258 of bone tissue followed by an increased risk of fracture secondary to frailty. This certainly
259 represents an important point and highlights the role of regular exercise even more, in accordance
260 with the strong connection existing between sarcopenic and osteoporotic pathology.⁷²⁻⁷⁶

261 The result, that can therefore be consequent to the practice of a regular exercise, is an increase in
262 performance and a reduction in the risk of developing disability.

263 As exercise, adequate nutritional supplementation seems to have positive effects on the quantity
264 and quality of muscle tissue. The most recommended macronutrients are
265 proteins,^{22,25,26,28,31,32,35,39,41,43,45,47-51,53-55,58,60} followed by vitamin D.^{22,27,28,33,35,39-41,43,45,48,51,54,59}

266 Vitamin D deficiency is very common in the elderly due to various factors (reduction of sun
267 exposure, inadequate diet and reduced intestinal absorption). Supplementing with vitamin D, in
268 addition to the already known beneficial effects on the increase in bone strength with consequent
269 reduction of the fractures' risk, would seem to significantly increase muscle strength, also reducing
270 the risk of falls by about 15-20% compared to patients with vitamin D deficiency.^{22,33,35,44,48,51,59}

271 The practice of an adequate lifestyle that involves the suspension of habitual smoking, an adequate
272 and balanced diet and the abandonment of a sedentary life, receive numerous high-grade
273 recommendations in the included guidelines.^{23,24} In addition, all the articles that have addressed
274 this issue highlight its benefits in the management of the patient with sarcopenia.^{24,25,35,47,49}

275 As for complementary therapies, there is a limited amount of evidence in the literature. For creatine
276 and coenzyme Q10, there is little evidence in the literature and a low level.⁴⁶

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278 **Take Home Message**

279 Based on the evidence contained in the included documents, in the management of sarcopenic
280 patients, exercise is recommended in order to avoid or slow down the progressive deterioration of
281 the muscular system. Specifically, activities such as aerobic exercise, muscle strengthening,
282 balance, flexibility and resistance exercises and a cardiorespiratory training are strongly
283 recommended, even if no details are given on its type, duration and frequency. It is however widely
284 accepted a weight-bearing exercise, as the main way in order to oppose the progression of
285 sarcopenic pathology.

286 A nutritional supplement with proteins and vitamin D is also strongly recommended in order to
287 slow down the progressive deterioration of the osteo-muscular system.

288 Lifestyle changes such as for example to suspend smoking, regime food and promote health
289 education are also recommended.

290 To date, in the literature, there is ample evidence on the use of nutritional supplements, alone or
291 in combination, in sarcopenic patients, in order to refill the physiologically loss. Among these,
292 those with moderate-weak level of evidence are vitamins, especially those of group B, C and E,
293 creatine, coenzyme Q10, essential amino acids, HMB, while others, with less evidence, are the
294 royal jelly, quercetin, caffeine, catechin tea and traditional Japanese herbs.

295 Among the drug therapies, testosterone has evidence of efficacy.

296 Nutritional supplementation with fatty acids and pharmacotherapy with estrogens and Selective
297 androgen receptor modulators (SARM) is not recommended.

298 By virtue of the conflicting evidence in the literature, it is not possible to make recommendations
299 on the usefulness of pharmacotherapy with anabolic hormones and growth hormones.

300 **Limits**

301 A limitation of this study is the possible heterogeneity of the population used in the included
302 studies. It was not always possible to identify the diagnostic criteria used by the included
303 studies.^{22,24,31,32,34,39-41,45,46,49,54,55,59} Most of the studies^{23,25,27,29,33,35,37,38,42-44,47,48,50-53,56,58} used the
304 first version of the European Working Group on Sarcopenia in Older People criteria (2010),⁶⁹ while
305 only an article used the 2019 update.⁶ The first version of the Asian Working Group for Sarcopenia
306 criteria⁷⁷ was used by 3 articles (2014),^{26,28,30} while the 2016 update was used by only one article.⁵⁷
307 No article used the update published in 2020.⁷⁸ The Foundation for the National Institutes of Health
308 criteria⁶⁰ were used by 3 articles.^{23,44,60} The criteria of the International Working Group on
309 Sarcopenia⁶¹ were used by 5 articles.^{33,36,37,44,61}

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321 **CONCLUSIONS**

322 Nowadays, the role of an adequate multi-professional, multi-disciplinary and multi-therapeutic
323 rehabilitation program which include exercise and diet, tailored to the needs of each individual
324 sarcopenic patient, represent the *sine qua non* in the treatment of disorders related to aging, as
325 highlighted by the current evidence in the literature, in order to counteract the progressive
326 reduction of physical performance and to limit an increase in the global patient's disability.
327 Exercise, meaning 150 minutes per week of moderate intensity aerobic exercise, in addition to an
328 adequate lifestyle and a targeted dietary supplement, currently represent the main
329 recommendations in the literature, which can guide the physician in the management of the patient
330 with this pathology.

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367 **COMPLIANCE WITH ETHICAL STANDARDS**

368 **Disclosure of Potential Conflicts of Interest:** The authors declare that they have no conflict of
369 interest.

370 **Research involving Human Participants and/or Animals:** Not applicable.

371 **Informed Consent:** Not applicable.

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617 **FIGURE LEGEND**

618 **Figure 1. Flow chart.**

Guidelines recommendations.			
	Suominen et al. ²²	Dent et al. ²³	ESPEN ²⁴
EXERCISE			
Exercise	R	R	
NUTRITIONAL INTEGRATION			
Proteins	R	R	
Vitamin D	R	NR	
PHARMACOLOGICAL TREATMENT			
Anabolic hormones		NR	
Pharmacological treatment not specified		NR	

Table 1. Guidelines recommendations. R: recommended; NR: not recommended; (u): Uncertain.

Evidences expressed in meta-analysis.								
	Hita-Con. et al. ²⁵	Liao et al. ²⁶	Anton. et al. ²⁷	Yosh. et al. ²⁸	Ste. et al. ²⁹	Chang et al. ³⁰	Morton et al. ³¹	Finger et al. ³²
EXERCISE								
Exercise	E	E				E	E	E
Resistance training	E		E				E	E
Aerobic exercise	E			E	E			
NUTRITIONAL INTEGRATION								
Proteins	E	E		E			E	E
Vitamin D			E	E				
Creatine				E				
Essential AA	E	E		E				
Multi-nutrient supplementation				E				
Catechin tea				E				
PHARMACOLOGICAL TREATMENT								
SARM				NE				
OTHERS								
Health education				E				

Table 2. Evidences expressed in meta-analysis. E: evidence; NE: Not evidence; (u): Uncertain.

Evidences expressed in systematic reviews and reviews. Part 1.

	De Spieg. et al. ³³	Papa et al. ³⁴	Beaudart et al. ³⁵	Thomas et al. ³⁶	EWGSOP ³⁷	Mangione et al. ³⁸	Petroni et al. ³⁹	Garcia et al. ⁴⁰	De Rui et al. ⁴¹	Shin et al. ⁴²	Scott et al. ⁴³	Agostini et al. ⁴⁴
EXERCISE												
Exercise		E	E		E	E	E				E	E
Resistance training		E			E	E	E					
NUTRITIONAL INTEGRATION												
Proteins			E	NE	NE		E		E			E
Vitamin D	E		E				E	E	E			E
Creatine			E									
Essential AA					(u)							
HMB					E							
Fatty acids					NE							
Calcium and magnesium									E			E
PHARMACOLOGICAL TREATMENT												
Estrogens (TOS)	NE											NE
Testosterone	E				E					NE		
Dheas	NE											
Growth Hormone	NE				E							
Anabolic Hormones					E							
OTHERS												
Assistive technologies												E

Table 3 (part 1). Evidences expressed in systematic reviews and reviews. E: Evidence; NE: Not evidence; (u): Uncertain.

Evidences expressed in systematic reviews and reviews. Part 2.

	Robinson et al. ⁴⁵	Guescini et al. ⁴⁶	Martone et al. ⁴⁷	De Spi. et al. ⁴⁸	Makanae et al. ⁴⁹	Hickson et al. ⁵⁰	Deni. et al. ⁵¹	Montero-Fernandez et al. ⁵²	Barillaro et al. ⁵³	Mor. et al. ⁵⁴	Padd. et al. ⁵⁵
EXERCISE											
Exercise	E	E	E	E	E	E		E		E	
Resistance training								E		E	
Aerobic exercise							E	E		E	
NUTRITIONAL INTEGRATION											
Proteins	E		E	E	E	E	E		E	E	E
Vitamin D	E			E			E			E	
Creatine		E		E			E			E	
Coenzyme Q10		E									
Essential AA					E		E		E	E	E
Fatty acids	E										
Multi-nutrient supplementation	E						E				
PHARMACOLOGICAL TREATMENT											
Estrogens (TOS)				NE					E		
Testosterone				E						E	
Dheas				NE							
Growth hormone				NE						E	
Anabolic hormones										E	
OTHERS											
Alcohol and smoking suspension				E							

Table 3 (part 2). Evidences expressed in systematic reviews and reviews. E: evidence; NE: no evidence; (u): Uncertain.

Consensus conference evidences.							
	EWGSOP2 6	Ayt. et al. ⁵⁶	AWGS 57	Deu. et al. ⁵⁸	EUGMS 59	Stud. et al. ⁶⁰	Field. et al. ⁶¹
EXERCISE							
Exercise	E		E	E	E		
Resistance training	E		E		E		
Muscle strengthening					E		
Balance					E		
Cardio-respiratory fitness					E		
Flexibility					E		
NUTRITIONAL INTEGRATION							
Proteins	NE			E	E		
Vitamin B	E	E					
Vitamin C			E				
Vitamin D			E				
Vitamin E			E				
Creatine					E		
Essential AA	(u)		E		E		
BCAA					(u)		
HMB	E				E		
Fatty acids	NE						
Royal jelly			E				
Quercetin			E				
Caffeine			E				
KAMPO			E				
PHARMACOLOGICAL TREATMENT							
Testosterone							
Growth hormone							
Anabolic hormones							

Table 4. Consensus evidences. E: Evidence; NE: No evidence; (u): Uncertain.

Figure 1

