

Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People

De Spiegeleer, Anton; Beckwée, David; Bautmans, Ivan; Petrovic, Mirko; Sarcopenia Guidelines Development group of the Belgian Society of Gerontology and Geriatrics (BSGG); Beyer, Ingo

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Pharmacological interventions to improve muscle mass, muscle strength and physical performance in older people: an umbrella review of systematic reviews and meta-analyses.

Anton De Spiegeleer^{1,6,7*}, David Beckwée^{2,3,4,5,7*}, Ivan Bautmans^{3,5} and Mirko Petrovic^{1,7} On behalf of the Sarcopenia Guidelines Development group of the Belgian Society of Gerontology and Geriatrics (BSGG)

¹ Department of Internal Medicine, section of Geriatrics, Ghent University, Ghent, Belgium.

² Rehabilitation Sciences Research Department, Vrije Universiteit Brussel, Brussels, Belgium.

³ Frailty in Ageing Research Department, Vrije Universiteit Brussel, Brussels, Belgium.

⁴ Department of Rehabilitation Sciences and Physiotherapy, University of Antwerp, Antwerp, Belgium.

⁵ Department of Geriatric Physiotherapy, SOMT University of Physiotherapy, Amersfoort, The Netherlands.

⁶ VIB Inflammation Research Center, Unit for Molecular Immunology and Inflammation, Ghent University, Ghent, Belgium.

⁷ Working group on Pharmacology of the Belgian Society of Gerontology and Geriatrics (BSGG)

Corresponding author: M. Petrovic, Tel.: +32 9 332 07 41, Fax: +32 9 332 52 51, Email: mirko.petrovic@ugent.be

* Both authors contributed equally to this work.

Abstract

Background Sarcopenia, defined as the pathological decline in muscle mass, muscle strength and physical performance with ageing, has become one of the geriatric giants because of its increasing prevalence and devastating health effects. The Belgian Society of Gerontology and Geriatrics (BSGG) is currently developing evidence based guidelines in the prevention and therapy of sarcopenia, which can be used in broad clinical practice. This systematic review summarizes the results of the working group on Pharmacology.

Objective The objective is to provide an evidence-based overview of the possible pharmacological interventions for sarcopenia with a focus on the interventions that are already studied in systematic reviews or meta-analyses.

Methods We used the method of a systematic umbrella-review. Using the electronic databases

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assessed the effect of pharmacological interventions on criteria for sarcopenia in subjects aged 65 years and over. Study selection, quality assessment and data extraction were performed by two independent reviewers.

Results A total of 7 systematic reviews or meta-analyses were identified, encompassing 10 pharmacological interventions: combined estrogen-progesterone, dehydroepiandrosterone, growth hormone, growth hormone releasing hormone, combined testosterone-growth hormone, insulin-like growth factor 1, pioglitazone and angiotensin converting enzyme inhibitors. Of important note is that very few systematic reviews or meta-analyses clearly mentioned baseline status of sarcopenia. Therefore our recommendations are generalised to older people, without specifying if the muscle effect is more effective in healthy, pre-sarcopenic or sarcopenic older people. Vitamin D had a significant effect on muscle strength and physical performance, especially in women with low baseline values (<25nmol/L). Adverse events were rare. Testosterone had a strong effect on muscle mass and a modest to minimal effect on muscle strength and physical performance respectively, when supplementing men with low serum levels (<200-300ng/dL). The adverse events were rare and mild. Insufficient evidence was available to recommend other pharmacological interventions.

Conclusion Only vitamin D, especially in older women, and testosterone in older men with clinical muscle weakness and low testosterone serum levels, can be justified in daily clinical practice to improve muscle mass, muscle strength and/or physical performance.

Key Points

- No distinct pharmacological recommendations for healthy, pre-sarcopenic and sarcopenic older people can be made, due to a lack of specific characterization of the sarcopenia status in most studies. However, recommendations can be made for older people in general.
- Vitamin D – especially in older women with low baseline levels (< 25nmol/L) - and testosterone - in older men with low baseline levels (< 200-300ng/dL) and clinical muscle weakness - can be justified in clinical practice to improve muscle mass, muscle strength and/or physical performance .
- Insufficient evidence exists to justify other pharmacological interventions in clinical practice..

1. Introduction

While a progressive and generalised loss of skeletal muscle mass and strength is inherent to ageing, in some older people there is an accelerated muscle decline with a high risk of adverse outcomes. Below a certain clinical threshold, this accelerated muscle decline is called sarcopenia. Sarcopenia has received increasing attention in both the research and public community. Different definitions and cut-offs exist for sarcopenia, but one of the more commonly used is from the European Working Group on Sarcopenia in Older People (EWGSOP) [1]. They recommend using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia. Consequently, diagnosis requires documentation of criterion 1 (low muscle mass) plus documentation of either criterion 2 (low muscle strength) or criterion 3 (low physical performance) [2]. Other definitions, e.g. from the International Working Group on Sarcopenia (IWGS), only need 1 or 2 from the 3 mentioned criteria to diagnose sarcopenia [1].

The *first* reason for this growing attention for sarcopenia derives from its increasing prevalence due to global human ageing. The EWGSOP points out that sarcopenia affects more than 50 million people today worldwide, and that this number will increase to more than 200 million people over the next 40 years [2]. *Secondly*, sarcopenia is a predictor of physical disability, poor quality of life and all-cause mortality, and is an important risk factor for falls in older people [3].

The underlying (patho)physiology of sarcopenia is complex and still insufficiently understood.

Inflammation, hormonal dysregulation, changed neuronal activity, (epi)genetics, nutritional changes and immobility have all been shown to be involved, and are highly heterogeneous between individuals [4, 5]. As a consequence of not knowing the exact pathophysiology, the ultimate (i.e. targeted and highly efficient) therapy for sarcopenia does not yet exist. However some interventions are already recognized to have a positive effectiveness/safety profile or are currently under investigation. Three groups of interventions can be differentiated at the moment: exercise, nutrition and pharmacological interventions.

This clinical review presents the results of the working group on Pharmacology within the Sarcopenia Guidelines Development group of the Belgian Society of Gerontology and Geriatrics (BSGG)

[Electronic Supplementary Material Appendix S1]. The aim is to provide an overview of the possible pharmacological interventions targeting one or more of the three sarcopenia-domains (muscle mass, muscle strength or physical performance) - with a focus on the interventions that are already studied in systematic reviews or meta-analyses. Therefore we used the method of a systematic umbrella-review.

2. Methods

2.1. Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for this review [6]. We systematically searched two databases (PubMed and Web of Science) from the earliest date available (1950s for PubMed, 1900 for Web of Science) until October 31st 2017. Keywords used corresponded to the PICOS design (Population: older adults; Intervention: pharmacological; Comparison: non-exposed control; Outcomes: sarcopenia; Study design: systematic review) (see full search strategies in Electronic Supplementary Material Appendix S2).

2.2. Study selection

Systematic reviews in English regarding the effect of pharmacological interventions on one or more of the three criteria of sarcopenia in older adults (≥ 65 y), i.e. muscle mass, muscle strength or physical performance, were eligible for inclusion in the umbrella review. Original studies, editorials, letters to the editor and animal studies were excluded. Two reviewers, blinded for each other's results, screened the titles and abstracts for eligibility by using the Rayyan web application for systematic reviews [7]. Subsequently, the same reviewers screened full-text articles of studies. They resolved mutual disagreements by discussion.

2.3. Data extraction and methodological quality assessment

Two authors completed data extraction by using a data extraction form based on a template provided by the Cochrane Collaboration. The authors extracted data regarding the key characteristics of the reviews, including: participants, pharmacological treatment, outcomes assessed. No assumptions were

made on missing or unclear data. Besides sarcopenia-related outcomes (muscle mass, muscle strength, physical performance), the authors also considered adverse effects.

Two reviewers assessed methodological quality of the studies by using the ‘Assessment of multiple systematic reviews’ (AMSTAR) [8]. This 11-item tool assesses the degree to which review methods avoided bias. The reviewers rated methodological quality as high (score 8-11), moderate (score 4-7) or low (score 0-3). However, they did not perform quality assessment of included studies within reviews.

To organise the evidence, one investigator systematically synthesized each review’s extracted data, resulting in statements for all reviews mapped to that intervention. In addition, two investigators with clinical experience then developed independently an overall synthesis, beyond a simple summary of the main results of each review. We considered these overall syntheses ‘bottom line statements’ about the main effect of interventions within each intervention. The two investigators resolved mutual disagreements by discussion or by consulting a third investigator. Finally, we assigned a rating of the quality of the evidence (1 very low - 2 low - 3 moderate - 4 high) supporting each bottom line statement by using a method that is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for primary evidence [9]. The method takes into account the ‘study design’ (meta-analysis yes/no) and the ratings of the quality of evidence of the included systematic reviews (AMSTAR) (see Figure 1).

PUT FIGURE 1 HERE

3. Results and discussion

3.1. Included studies

We screened a total of 460 studies for eligibility (Figure 2). After screening the title and abstract, we excluded 446 studies. Eventually, we included 7 systematic reviews [10-16]. AMSTAR scores varied between 1 [12] and 8 [13] (Figure 3).

PUT FIGURE 2 HERE

The reviews investigated the effect of the following pharmacological interventions: angiotensin-converting enzyme inhibitors [16], vitamin D [10, 15], beta-estradiol combined with cyclic norethisterone acetate [14], dehydroepiandrosterone (DHEA) [11], growth hormone [11], insulin-like growth factor 1 (IGF 1) [11], pioglitazone [14], testosterone [11-13], testosterone combined with growth hormone [11]. Table 1 presents an overview of all included articles.

PUT FIGURE 3 HERE

PUT TABLE 1 HERE

It was difficult for this umbrella-review to distinguish subjects with sarcopenia from healthy subjects as most systematic reviews did not characterize the sarcopenia or frailty status of the subjects. The fact that there are no universally accepted criteria for the diagnosis of sarcopenia is probably the most important reason for this. Therefore, in this umbrella-review the conclusions are focused on elderly subjects in a broader sense.

Based on the body of evidence, bottom line statements about the main effects of each intervention- including a rating of the quality of the evidence supporting each bottom line statement- are presented in Table 2. In the text below, consideration of each pharmacological intervention starts with a recommendation based on these bottom line statements, followed by the results of our umbrella review and discussion respectively.

PUT TABLE 2 HERE

3.2. Vitamin D

We recommend vitamin D supplementation to improve muscle strength and physical performance in older people, especially in older women with very low baseline levels. Monitoring of the serum calcium is needed [low quality of evidence].

Anagnostis et al. summarized the muscle effects of vitamin D supplementation in older women [10].

Although no significant effect was seen of vitamin D supplementation on muscle mass (criterion 1) (pooled standardized mean difference or SMD=0.058, 95% confidence interval (CI)=[-0.118, 0.233]),

a small but significant effect was seen on muscle strength (criterion 2) (pooled SMD=0.25, 95%CI=[0.01, 0.48]) and physical performance (criterion 3) (e.g. pooled Timed Up and Go=-0.19, 95%CI=[-0.35, -0.02]). More prominent effects were seen in patients with deficient baseline vitamin D levels (<25nmol/L) and in co-administration with calcium. In addition, a significant decrease in mortality and fall risk was shown when supplementing with vitamin D. Adverse events of vitamin D supplementation described in this review were hypercalcaemia (risk ratio or RR 3.18, [1.17;8.68]) and nephrolithiasis (RR 1.17, [1.02;1.34]), both rare. The meta-analysis of Beudart et al., encompassing other clinical trials, also suggested a small but significant effect on physical performance (gait speed and Timed Up and Go), while not finding a significant effect on muscle mass or muscle strength [17, 18]. It is noteworthy that in both systematic reviews most studies concerned supplementation with the inactive forms of vitamin D, i.e. cholecalciferol (D3) or ergocalciferol (D2).

We hypothesize that the more pronounced effects on functional outcomes in contrast to the lack of effect on muscle mass could be explained by vitamin D causing mostly a gain in muscle quality instead of quantity. Indeed, recent studies suggest that activation of intracellular vitamin D receptors in muscle induces a decline of intramuscular lipids, enhancing the muscle quality [19, 20]. A recent systematic meta-analysis of Rosendahl-Riise et al. [21], not retrieved in our search because not focusing on the syndrome of sarcopenia, found no significant effect of vitamin D supplementation on muscle strength and physical performance in older people, measured by grip strength and Timed-Up and Go Test respectively. This contrast to our results could be explained by the large heterogeneity of the studies in the meta-analysis ($I^2 \geq 95\%$) and the focus on community-dwelling older people. The heterogeneity was both on the level of patient characteristics as well as on the level of the intervention. Concerning the side-effects of vitamin D, a Cochrane systematic review of vitamin D/calcium supplementation on preventing fractures in older people, found a small but significant increase in gastrointestinal symptoms and renal disease associated with vitamin D and calcium intake, probably related to the hypercalcaemia and nephrolithiasis, in accordance with our results [22]. Interestingly high vitamin D doses (> 1000IU daily) seem to increase the risk of falling in older people [23]. It must be pointed out that most studies so far are conducted in post-menopausal women,

and clinical trials in older men are lacking. In conclusion, it seems that vitamin D supplementation, especially in older women, can be beneficial to improve muscle strength or physical performance, mostly when supplementing those with very low baseline vitamin D levels (<25nmol/L), without ‘oversupplementing’ (< 1000IU daily). However it is clear that more subgroup analyses are needed to find the subjects with a ‘good’ genetic profile, sarcopenia -, and vitamin D baseline levels that take most advantage of a particular dose and duration of vitamin D/calcium supplementation, in line with the concept of personalized medicine. Indeed current studies are already focusing on subgroups analyses, e.g. the meta-analysis in community-dwelling older people from Rosendahl-Riise et al, and investigating genetic variants responsible for vitamin D status and dose-response [21, 24, 25].

3.3. Beta estradiol + cyclic norethisterone acetate

We do not recommend the combination of estrogen and progesterone to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

From the included systematic reviews, only the review of Poggiogalle et al. discussed the combination of an estrogen and progesterone [14]. They found a small but significant improvement of muscle mass after sex hormone replacement therapy in post-menopausal women. However, out of this systematic review we did not find results on muscle strength or physical performance, neither on adverse events [14].

A meta-analysis published in 2009, found a beneficial effect on muscle strength of estrogen-based treatments in postmenopausal women [26]. In contrast, a large randomized clinical trial in 2010, found no significant improvement in muscle strength or physical performance of hormone replacement therapy [27]. More subgroup analyses are needed in the future to elucidate this discrepancy.

3.4. Dehydroepiandrosterone (DHEA)

We do not recommend DHEA supplementation to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

Dehydroepiandrosterone, a steroid that can be transformed into estrogen or testosterone in the body, could possibly have some effect on muscle strength, but the results were inconclusive and data on muscle mass, physical performance and adverse events were lacking [11].

Although the only included systematic review (Borst et al.) dates from 2004, later trials and reviews not included in our umbrella review, remain inconclusive about the muscle effects of DHEA [28]. It needs to be pointed out that no randomized clinical trial of DHEA-supplementation that measures one of the three sarcopenia domains is published in the last five years. One of the possible reasons could be the status of relatively cheap over-the-counter product of DHEA, making it less interesting for pharmaceutical companies. To make conclusions about the muscle benefits of DHEA in older people, more studies will be needed in the future.

3.5. Growth hormone

We do not recommend growth hormone (GH) supplementation to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

Borst et al. concluded that growth hormone replacement in older subjects, although increasing muscle mass, does not univocally improve muscle strength nor physical performance and has a high incidence of adverse events, making it inappropriate as a muscle intervention in older people [11]. Adverse events described were fluid retention, gynaecomastia, orthostatic hypotension, carpal tunnel compression, hyperglycaemia, arthralgia and general malaise. Borst et al. reported a drop-out rate in some clinical trials around 40% in the supplemented group vs. 10% in the placebo group, attributed to the adverse events.

A long-term clinical trial (10 years) found a mitigation of the expected age-related decline in muscle strength when supplementing GH to older people with overt pituitary disease [29]. However, this trial was not controlled and the baseline IGF-1 levels, downstream targets of growth hormone, were much lower than expected in older people without overt pituitary disease. No long-term controlled clinical trials in older people without overt pituitary disease exist to recommend growth hormone supplementation.

3.6. GHRH and IGF-1

We do not recommend GHRH or IGF1 supplementation to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

The GH/IGF-1 pathway is complex, and it may be that a better efficacy/safety profile is obtained when supplementing with other pathway molecules than growth hormone. In the systematic review of Borst et al., besides growth hormone, also growth hormone releasing hormone (GHRH) and insulin-like growth factor 1 (IGF-1) were discussed, upstream and downstream molecules from GH respectively. Muscle mass and muscle strength in some studies were found to be increased when supplementing GHRH in healthy older people, while muscle strength was increased when supplementing IGF-1 in older women after hip fracture. There were no data on physical performance. Both molecules were well tolerated and had a good safety profile, with only transient hyperlipidaemia reported [11].

Recent studies seem to confirm the potency of GHRH to combat muscle ageing in older people, and also of the related growth hormone secretagogue receptor (GHSR) agonists and ghrelin analogues [30-32]. However no firm conclusions can be made today.

3.7. Pioglitazone

We do not recommend pioglitazone to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

Poggiogalle et al. discussed the effect of pioglitazone, a peroxisome proliferator-activated receptor gamma (PPAR γ) agonist, on muscle mass [14]. Although a positive significant effect was seen with pioglitazone on visceral fat loss in obese men, only a small, non-significant effect was measured on muscle mass gain in this population. Our results did not contain data on muscle strength, physical performance or adverse events.

One other randomized clinical trial, not included in the review of Poggiogalle, can be found that investigates the effects of pioglitazone on muscle outcomes in older people [33]. In accordance with

our results, this study of Marsh et al. did not show a strong, univocal effect on muscle outcome: only a potentiating effect of pioglitazone on muscle power in women, but not in men, when associated with resistance training [33]. Reasons for this sex difference are not clear. It is thought that the potential positive muscle effects of pioglitazone are mediated by an improved fatty acid metabolism, a known effect of PPAR γ agonists besides their hypolipidemic effect [34].

3.8. Testosterone

We consider testosterone supplementation a possible intervention to improve muscle mass and muscle strength in older men with low serum testosterone levels (< 200-300ng/dL) and clinical muscle weakness. Monitoring of the haematocrit, lipid profile and prostatic parameters is needed (high quality of evidence).

Based on our eligibility criteria, three systematic reviews/meta-analyses with data on testosterone supplementation targeting one or more sarcopenia domains were retained [11-13]. All of them only discussed supplementation in older men. Although a consensus exists about the clear effect on muscle mass, a less pronounced effect was seen on muscle strength and an even less effect on physical performance. The less pronounced effects on muscle strength and physical performance can be explained by insufficient treatment duration, low test sensitivity and absence of androgen deficiency at baseline. Possible adverse events of testosterone supplementation were fluid retention, gynaecomastia, worsening of sleep apnoea, polycythaemia, and acceleration of benign or malignant prostatic tumours. However physiological doses of testosterone supplementation both in healthy and older people with frailty were well tolerated: in most studies only a mild polycythaemia was actually seen, while not showing an increase in prostatic or cardiovascular events [11-13].

These results are in agreement with two recent large trials: the Testosterone's Effects on Atherosclerosis Progression in Aging Men or TEAAM trial and the Testosterone Trials or TTrials, where testosterone supplementation in community-dwelling healthy older men was associated with only modest improvements in physical performance and considered safe [35, 36]. Recent studies measuring cardiovascular endpoints in older men supplemented with testosterone, also suggest a

beneficial cardiovascular effect when supplementing those with low levels [37, 38]. Further clinical investigations, including pharmacogenomics and other new insights from personalized medicines, are needed to select individuals who benefit most from testosterone supplementation. However, pending the results of such trials, we currently recommend for each older patient with clinical muscle weakness and low serum testosterone levels, a trial phase may be worthwhile. If no clinical effects are seen after 6 months, it is advised to stop supplementation [39]. A practical guide to start testosterone supplementation can be found in the review of De Spiegeleer et al. [39].

3.9. Testosterone + growth hormone

We do not recommend the combination of testosterone and GH supplementation to improve muscle mass, muscle strength or physical performance in older people (very low quality of evidence).

Borst et al. reviewed the effects of testosterone combined with growth hormone. They found an increase in muscle mass in healthy older men, but no significant effect on muscle strength. No data were available on physical performance or on the adverse events.

More recent trials do suggest a synergistic effect [11, 40, 41]. However, long-term studies will be needed to elucidate these possible effects, as well as the adverse events.

3.10. Angiotensin Converting Enzyme (ACE)-inhibitors

We do not recommend ACE-inhibitors to improve muscle mass, muscle strength or physical performance in older people (moderate quality of evidence).

One systematic meta-analysis reported the effects of ACE-inhibitors on muscle strength and physical performance [16]. Three different ACE-inhibitors were used in the included original studies: enalapril, perindopril and fosinopril. The meta-analysis did show a modest positive effect in favour of the intervention; however no significant results were obtained. They attributed the reason for the non-significance to the short intervening times (5-9 months) and limitations of the meta-analysis (high heterogeneity, limited amount of studies, with only studies from 2000 until 2015). No data on muscle mass or possible adverse events were available.

More recent clinical trials not included in the systematic review, were also not able to find a significant effect of ACE-inhibitors on one of the three sarcopenia criteria [42, 43]. However it is speculated that subgroups of older people, e.g. with heart failure or with a severe sarcopenic status, might benefit from ACE-inhibitors in terms of muscle outcomes [1, 44]. Also it might be that some ACE-inhibitors are superior to others, contradicting the idea of a class effect. Further studies are ongoing. Today there is no evidence to use ACE-inhibitors to improve muscle mass, muscle strength or physical performance in older people.

3.11. Strengths and limitations

The most important strength using the method of an umbrella-review is the power to efficiently extract clinical relevant information on which general consensus exists in contrast to conclusions of one research group, i.e. an umbrella review considers for inclusion the highest level of evidence. Our literature search is also systematic in nature, in accordance with the PRISMA-guidelines, which gives a higher level of evidence than a narrative review. Because our umbrella review is dependent on the quality of the systematic reviews/meta-analyses, we assessed this quality by using the AMSTAR-criteria.

A limitation, inherent to our strict search terms (see section 2.1), is the low total amount of eligible reviews (seven reviews in total). In combination with the often low quality of the systematic reviews/meta-analyses, this results in low to moderate ratings of evidence supporting most bottom line statements. Another limitation, inherent to an umbrella-review, is that we did not evaluate the quality of the individual randomized clinical trials or analysed the clinical trials to the level of the raw data. Lastly, physical activity and nutrition, two interventions with generally accepted effects against sarcopenia, and pharmacological interventions not yet discussed in systematic reviews or meta-analyses (e.g. myostatin-inhibitors, selective androgen receptor modulators or SARMs,...) were not in the scope of this review.

4. Conclusion

Based on the results of this umbrella-review we conclude that vitamin D – especially in older women with very low baseline levels (<25nmol/L) - and testosterone - in men with clinical muscle weakness and low serum testosterone levels (<200-300ng/dL) - are the only pharmacological interventions that could be justified in clinical practice to improve one or more of the three sarcopenia-domains (muscle mass, muscle strength and physical performance). For other pharmacological treatments including combined estrogen-progesteron, dehydroepiandrosterone, growth hormone, growth hormone releasing hormone, combined testosterone-growth hormone, insulin-like growth factor 1, pioglitazone and angiotensin converting enzyme inhibitors, there is insufficient scientific evidence.

Electronic Supplementary Material

Electronic Supplementary Material Appendix S1

Sarcopenia Guideline Development group of the BSGG

Ivan Bautmans
Charlotte Beudart
David Beckwée
Ingo Beyer
Sandra De Breucker
Anne-Marie De Cock
Andreas Delaere
Marie de Saint-Hubert
Anton De Spiegeleer
Evelien Gielen
Stany Perkisas
Maurits Vandewoude

Electronic Supplementary Material Appendix S2

Search string PubMed

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(((((("Review"[Publication Type]) OR "systematic review"[Title/Abstract]))) AND  
((((((((("Pharmacology"[Mesh]) OR "Testosterone"[Mesh]) OR "Hormones"[Pharmacological  
Action]) OR "Angiotensin-Converting Enzyme Inhibitors"[Pharmacological Action]) OR "Anti-  
Inflammatory Agents"[Pharmacological Action]) OR "Immunologic Factors"[Pharmacological Action])  
OR "Myostatin"[Mesh]) OR "Activin Receptors, Type II"[Mesh]) OR "Creatine"[Mesh])) OR  
(((("Hormones"[Mesh]) OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR "Anti-  
Inflammatory Agents"[Mesh]) OR "Immunologic Factors"[Mesh]))) AND ((sarcopenia) OR  
"Sarcopenia"[Mesh])
```

Search string Web of Science

1. DOCUMENT TYPES: (Review) OR TITLE: ("systematic review")
2. TOPIC: sarcopen*
3. TOPIC: Pharmaco* OR Testosteron* OR Hormon* OR "Angiotensin-Converting Enzyme Inhibitors" OR "Anti-Inflammatory Agents" OR "Immunologic Factor" OR Myostatin OR "Activin Receptor" OR "Creatine"
4. #1 AND #2
5. #3 AND #4

Compliance with Ethical Standards

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Conflicts of Interest

Anton De Spiegeleer, David Beckwée, Ivan Bautmans and Mirko Petrovic declare that they have no conflicts of interest relevant to the content of this review.

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Figures

Figure 1: Method used to rate the quality of the evidence supporting each 'bottom line' statement.

AMSTAR: Assessment of multiple systematic reviews [8].

Figure 2: PRISMA flow-chart.

Figure 3: AMSTAR scores. Legend: *Red: no; yellow: can't answer/not applicable; green: yes;*

AMSTAR: Assessment of multiple systematic reviews [8].

Tables

Table 1: Results of individual Reviews

Reference	Outcome					N° of Studies included (participants)	Results/findings (outcomes are underlined)	Comments
	S	MM	MS	FP	AE			
Angiotensin converting enzyme inhibitors								
Zhou et al. [16]			x			3 St (499)	- "Grip strength was not significantly different (-0.67, 95 % CI: -1.53 to 0.19; P = 0.12) between ACEIs and placebo or other antihypertensives"	- "Sumukadas2014 had also exercise in the intervention and control associated, but they did not show a significant effect from ACEIs; the reasons for the non-significant results may relate to the short intervening time and limitations of this meta-analysis."
Zhou et al. [16]				x		3 St (337)	- "ACEIs could not significantly improve 6-min walk distance (13.45%, 95 % CI: -16.71 to 43.61; P = 0.38) versus placebo or other antihypertensives"	- "Sumukadas2014 had also exercise in the intervention and control associated, but they did not show a significant effect from ACEIs; the reasons for the non-significant results may relate to the short intervening time and limitations of this meta-analysis."
Beta-estradiol + cyclic norethisterone acetate								
Poggiogalle et al. [14]		x				1 St (16)	<p><u>Lean Body Mass:</u> Before intervention: I vs. C: 38.8 kg vs. 39.0 kg (P=0.27)</p> <p>After intervention I vs. C: +0.347 ± 0.858 kg vs. -0.996 ± 1.58 kg (p<0.05)</p> <p>I= "Beta-estradiol (4 mg for 22 days and 1 mg for 6 days) + cyclic norethisterone acetate (1 mg for 10 days); Two 12-week periods separated by a 3-month washout "</p>	Beta-estradiol (4 mg for 22 days and 1 mg for 6 days) + cyclic norethisterone acetate (1 mg for 10 days); Two 12-week periods separated by a 3-month washout
Dehydroepiandrosterone								
Borst [11]			x			G+6:12growth hormone	"No changes were found in a variety of measures of muscle strength." "Small increases in strength were observed in men, but not women."	
Growth hormone								
Borst [11]		x				2 St (?)	- "increase in <u>fat-free mass</u> " - "GH administration improved body composition: 2.4 kg loss of fat mass and a 3.7 kg increase in <u>non-fat mass</u> ."	
Borst [11]				x		2 St (?)	- "was not accompanied by an increase in <u>strength</u> ." - "...the addition of GH to the training regimen produced no greater <u>strength</u> gains." - "elderly men participating in a 12-week resistance exercise training programme achieved similar <u>strength</u> gains with or without GH replacement" - "the addition of GH to the training regimen produced no greater <u>strength</u> gains."	

Borst [11]					x	6 St (?)	- "Researchers have reported high incidences of adverse effects from GH administration in elderly subjects, including <u>fluid retention</u> , <u>gynaecomastia</u> , <u>orthostatic hypotension</u> , <u>carpal tunnel compression</u> , <u>lower body oedema</u> and <u>general malaise</u> ."- "... a drop-out rate of 43%, compared with only 9% in the placebo group. The most common symptoms were <u>carpal tunnel syndrome</u> , <u>gynaecomastia</u> and <u>hyperglycaemia</u> ."- "High incidences of <u>carpal tunnel compression</u> , <u>fluid retention</u> and <u>arthralgia</u> ."- "Insulin secretion during glucose tolerance testing was increased three-fold" - "Authors also noted that GH causes <u>fluid retention</u> "- "Adverse events were no more common in the treatment group than in controls; however, the lack of serious side-effects may have been due to the short 2-week duration of the study"
Growth hormone releasing hormone							
Borst [11]		x				1 St (?)	- "They found improved nitrogen balance in both sexes and increased <u>muscle mass</u> in men only."
Borst [11]			x			1 St (?)	- " <u>Strength</u> was moderately increased in some exercises, but not in others in a longitudinal study without a control group"
Borst [11]					x	2 St (?)	- "No significant <u>adverse effects</u> were observed." - "The only adverse effect noted was <u>transient hyperlipidaemia</u> , which was resolved by the end of the study."
IGF 1							
Borst [11]			x			1 St (?)	"Compared to placebo, <u>grip strength</u> was increased and generally, IGF-I/IGFBP-3 was well tolerated."
Pioglitazone							
Poggiogalle et al. [14]		x				1 St (81)	<u>Lean Body Mass</u> (I vs. C) Before intervention - women: 48.8±1.6 kg vs. 47.8±1.6 kg - men: 68.0±1.3 kg vs. 66.9±1.5 kg After intervention - Women: -1.9±0.3 kg vs.-2.1±0.4 kg - Men: -2.0±0.4 kg vs.-2.5±0.4 kg (P<0.05)
Testosterone							
Borst [11]		x				9 St (?)	7 out of 9 studies showed increased <u>lean mass</u> and/or decreased fat mass. "However, the changes in body composition have been small"

O'Connell et al. [12]	x		16 St	- 12 out of 16 studies showed an increase in <u>lean mass</u> . "Testosterone treatment increases lean body mass in elderly men; in the minority of studies that failed to report a change, this can be explained by insufficient treatment duration, relative inaccuracy of the method to assess body composition and absence of androgen deficiency at baseline"- "Increase in lean body mass varies between 1 and 4kg over the course of testosterone treatment"	Because of the very real risks of side effects in the use of supraphysiological doses of testosterone, especially in the elderly (Bhasin et al., 2005), physiological dosages remain currently the most viable treatment option.- Most impressive gains in lean body mass are seen with injectable testosterone (+4kg), in contrast to other preparations, e.g. transdermal or oral (+1-2kg).
Borst [11]	x		10 St (?)	4 out of 10 studies showed an increase in strength	
O'Connell et al. [12]	x		19 St	- 9 out of 19 studies showed an increase in <u>strength</u> - "A number of studies have reported improvement in <u>grip strength</u> of 3–5 kg following androgen treatment. Others have shown no effect of treatment on this parameter"	- "This discrepancy between studies is not adequately explained by the different gains in muscle mass and may simply reflect the variability in the performance and poor repeatability of this measurement." - there is a smaller size of effect in studies using isokinetic dynamometry techniques
Ottensbacher et al. [13]	x		11 St (474)	- <u>overall strength</u> : ES=0.53, 95% CI=[.21, .86] - <u>upper extremity strength</u> : ES=.47, 95% CI=[.12, .84] - <u>lower extremity strength</u> : ES=.63, 95% CI=[.03, 1.28]	Sensitivity analyses revealed the elimination of one study reduced the mean g-index from 0.53 to 0.23.
O'Connell et al. [12]	x		7 St	- "Studies have failed to show an improvement in a range of functional tasks including tests of <u>balance</u> , <u>gait speed</u> , <u>chair rising</u> , <u>step height</u> and <u>functional reach</u> in response to a variety of androgen treatments." - 3 out of 7 studies showed an improvement in complex functional tasks (e.g. SF36 physical function scale)	"The combination of low test sensitivity and small changes in strength may largely explain the lack of effect of testosterone treatment on physical function."
Borst [11]	x	?		- "Risks of testosterone replacement in older men include <u>fluid retention</u> , <u>gynaecomastia</u> , worsening of <u>sleep apnoea</u> , <u>polycythaemia</u> and acceleration of benign or malignant <u>prostatic tumours</u> [14]. Amongst these risks, the potential effects of testosterone on the prostate are of the greatest concern. - "A retrospective, case-controlled study examined 45 hypogonadal men (mean age=70 years) receiving a replacement dose of testosterone over a 2-year period. Compared to controls, treated individuals had a higher incidence of <u>polycythaemia</u> , but no increase in prostate cancer."	
O'Connell et al. [12]	x		1 M.A. (?)	- <u>prostate events</u> : OR=1.78, 95%CI [1.07, 2.95] - "Testosterone is not considered to cause development of de novo <u>prostate cancer</u> " - "Testosterone treatment was also associated with increased rates of <u>haematocrit</u> ≥50% (dose-dependently in shorter-acting injectable preparations), but not with <u>cardiovascular events</u> , <u>sleep apnoea</u> or <u>death</u> " - "Testosterone treatment was not associated with significant changes in <u>blood pressure</u> , <u>glycaemia</u> or major <u>lipid fractions</u> " - "physiological testosterone replacement is well <u>tolerated</u> in elderly frail"	"Testosterone is not considered to cause development of de novo prostate cancer " - "the available safety data are largely based on studies in younger hypogonadal patients. However, the recent studies in elderly frail men suggest that physiological testosterone replacement is well tolerated in this group" (Srinivas-Shankar et al., 2010).

Ottensbacher et al. [13]				x	11 St (474)	- "Elevated <u>PSA</u> levels or <u>prostate disease</u> were reported in threestudies out of eleven."- "Four investigations stated that <u>no adverse events</u> were observed in older men receiving testosterone/DHT therapy or placebo."- Other investigations included broad statements such as worsened <u>knee arthritis</u> ." (1 study)	
Testosterone + growth hormone							
Borst [11]		x			2 St (?)	- "Combined testosterone and GH produced a 2.7kg increase in lean mass, in healthy elderly men (mean age=68 years). - "GH reduced fat mass and increased lean mass in men and women."	- 1-month duration of treatment and no placebo group. - randomized, double-blind, placebo-controlled study lasting 26 weeks: GH and/or testosterone for men and hormone replacement therapy for women.
Borst [11]			x		2 St (?)	- "Combined testosterone and GH produced no increase in strength in healthy elderly men (mean age=68 years). - "Little if any increase in strength was observed (6% increase in men receiving GH plus testosterone only)."	- 1-month duration of treatment and no placebo group. - randomized, double-blind, placebo-controlled study lasting 26 weeks
Vitamin D							
Anagnostis et al. [10]		x			-1 M.A. (555) -1 St (21)	- <u>Muscle mass</u> : SMD=.058, 95%CI=[-.118, .233],p=.52 - <u>Muscle Fibre size</u> : 'On a molecular level, vitamin D-supplementation with 4000 IU daily for 4 months increased muscle fibre size by 10%.'	umbrella review
Beaudart et al. [15]		x			- 1 St (96)	- <u>lean mass</u> : "No effects of exercise alone or of exercise combined with vitamin D supplementation were observed."	Vitamin D combined with exercise (mainly resistance-type exercise)
Anagnostis et al. [10]			x		- 1 M.A. (626)	- <u>Knee extension</u> : SMD=.05, 95% CI=[.11, .20], P=.04	umbrella review Effect seems absent if baseline 25(OH)D concentrations > 25 nmol/L
					- 1 M.A. (2302)	- 1) <u>Global muscle strength</u> : SMD=.25, 95%CI=[.01, .48] -- institutionalised & hospitalised vs community dwelling: SMD 0.45 vs 0.05;P< .01 2) <u>Grip strength</u> : SMD=.01, 95%CI=[- 0.06, 0.07], P=.87 3) <u>Lower limb muscle strength</u> : SMD=.19, 95%CI=[.05 to .34], P=.01	
					- 1 R (?)	- "no significant effect of vitamin D overall, but significant improvement in <u>strength</u> when starting 25(OH)D≤25nmol/l"	
Beaudart et al. [15]			x		- 2 St (121)	- "Both studies reported significant improvement in <u>muscle strength</u> with exercise but did not report any difference between the exercise-only group and the group with combined exercise and vitamin D supplementation."	Vitamin D combined with exercise (mainly resistance-type exercise)
Anagnostis et al. [10]				x	- 1 M.A. (274) - 1 M.A. (828)	- Timed Up and Go: SMD=-.19, 95%CI=[-.35, -.02],p=.03 - Gait: "an effect on gait was not found, although the studies that evaluated gait were of lower methodological quality and used low doses of vitamin D"	umbrella review

Beaudart et al. [15]			x	- 2 St (121)	- "Physical performance increased, for some of the physical performance outcomes, in 2/2 RCTs with no additional effect of vitamin D, except for TUG in 1/2 RCTs."	Vitamin D combined with exercise (mainly resistance-type exercise)
Anagnostis et al. [10]			x	- 1 R (42 876)	- <u>Nephrolithiasis</u> : RR=1.17, 95%CI [1.02, 1.34], P=.02, I ² =0%"in combination with calcium"	umbrella review- in combination with calcium- Vitamin D3 decreased mortality; a subgroup analysis of trials at high risk of bias suggested that vitamin D2 may increase mortality- Alfacalcidol and calcitriol increased the risk of hypercalcaemia (Vitamin D supplementation in elderly reduces also fall risk, more pronounced when supplementing up to >60nmol/l, in daily doses)
				- 1 R (75 927)	- <u>Mortality</u> : RR=.94 95%CI [.91 to 0.98], P=.002;I ² =0%"Vitamin D3 decreased mortality; a subgroup analysis of trials at high risk of bias suggested that vitamin D2 may increase mortality"	
				- 1 R (710)	- <u>Hypercalcaemia</u> : RR=3.18 95%CI [1.17 to 8.68], P=.002;I ² =17%"Alfacalcidol and calcitriol increased the risk of hypercalcaemia"	

ACEI: angiotensin converting enzyme inhibitors; AE: adverse events; BC: body composition; C: control; CI: confidence interval; ES: effect size; FP: functional performance; GH: growth hormone; I: intervention; IGF1: insulin-like growth factor 1; IGF1BP: insulin-like growth factor-binding protein; kg: kilogram; M.A.: meta-analysis; Mg: milligram; MM: muscle mass; MS: muscle strength; n.a.: not available; nmol: nanomol; OR: odds ratio; R: review; RCT: randomized controlled trial; RR: risk ratio; S: sarcopenia; SMD: standardized mean difference; St: study; TUG: timed up and go; Vit: vitamin; vs.: versus; x: indicates the construct that is addressed: sarcopenia (as a construct) or the sarcopenia sub dimension (muscle mass, muscle strength, physical performance) or adverse events; a question mark (?) indicates that the number was not mentioned in the systematic review/meta-analysis.

Table 2: Summarizing table about the main effects of interventions.

Intervention	Sarcopenia	Muscle Mass	Muscle Strength	Physical Performance	Adverse events	'Bottom line' statement	QoE
Vitamin D	Insufficient to determine	Insufficient evidence	Sufficient evidence in favour (women)	Some evidence in favour	Nephrolithiasis, hypercalcaemia	In addition to improve muscle strength and physical performance, also a significant decrease in mortality and fall risk is seen when supplementing with vitamin D. The effects are most pronounced when supplementing those with serum levels <10ng/mL. In conclusion we recommend vitamin D supplementation to improve muscle strength and physical performance in older people, especially women, with low baseline serum levels. Monitoring of the serum calcium is needed.	2
Testosterone	Insufficient to determine	Some evidence in favour (men)	Some evidence in favour (men)	Insufficient evidence	Fluid retention, gynaecomastia, worsening of sleep apnoea, polycythemia, acceleration of benign or malignant prostatic tumours;	Testosterone supplementation may be considered in older men with serum levels <200-300ng/dL and clinical muscle weakness, to improve muscle mass and muscle strength. Monitoring	4

					adverse events seem monitorable	of the Hct, lipid profile and prostatic parameters is needed.	
GH	Insufficient to determine	Some evidence in favour	Insufficient evidence	Insufficient to determine	Fluid retention, gynaecomastia, orthostatic hypotension, carpal tunnel compression, lower body oedema and general malaise	We do not recommend GH supplementation.	1
Testosterone+GH	Insufficient to determine	Some evidence in favour	Insufficient evidence	Insufficient to determine	Insufficient to determine	We do not recommend the combination of testosterone and GH.	1
GHRH	Insufficient to determine	Some evidence in favour (men)	Insufficient evidence	Insufficient to determine	Transient hyperlipidemia (1 study)	We do not recommend GHRH.	1
IGF-1	Insufficient to determine	Insufficient to determine	Some evidence in favour (women after hip fracture)	Insufficient to determine	Insufficient to determine	We do not recommend IGF-1.	1
DHEA	Insufficient to determine	Insufficient to determine	Insufficient evidence	Insufficient to determine	Insufficient to determine	We do not recommend DHEA.	1
Beta estradiol + cyclic norethisterone acetate	Insufficient to determine	Insufficient evidence	Insufficient to determine	Insufficient to determine	Insufficient to determine	We do not recommend the combination of estrogen and progesterone.	1
ACE-inhibitors	Insufficient to determine	Insufficient to determine	Insufficient evidence	Insufficient evidence	Insufficient to determine	We do not recommend ACE-inhibitors.	3
Pioglitazone	Insufficient to determine	Insufficient evidence	Insufficient to determine	Insufficient to determine	Insufficient to determine	We do not recommend pioglitazone.	1

Sufficient evidence: statistically significant pooled results (meta-analysis); Some evidence: narrative synthesis of review results (based on a majority of studies showing statistically significant results); Insufficient evidence: based on a majority of studies showing statistically non-significant effects (underpowered or no effect); Insufficient (evidence) to determine: not reported in reviews or meta-analyses (reporting gap in evidence); GH: growth hormone; GHRH: growth hormone releasing hormone; IGF-1: insulin-like growth factor 1; DHEA: dehydroepiandrosterone; ACE: angiotensin converting enzyme; QoE: quality of evidence supporting each bottom line statement (1 very low - 2 low - 3 moderate - 4 high); Hct: hematocrit.

