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Selecting Potential Pharmacological Interventions in Sarcopenia

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Current Opinion Article

Title: Selecting potential pharmacological interventions in sarcopenia

Running heading: Selecting pharmacological interventions in sarcopenia

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Abstract:

Sarcopenia of age is prevalent, costly, but currently lacks proven pharmacological interventions. The pathophysiology of sarcopenia is incompletely understood, but appears to involve multiple pathways including inflammation, hormonal dysregulation, impaired regeneration, mitochondrial dysfunction and denervation. There are several ways that we might select potential pharmacological interventions for testing in clinical trials. These include a 'bottom up' approach using basic science to elucidate the molecular processes involved and identifying potential targets from this knowledge – a strategy that has led to the development of myostatin inhibitors. A 'top down' approach might use observational data to examine the association between physical function and use of certain medications, such as the association of angiotensin converting enzyme inhibitors with slower decline in physical function.

Once a pharmacological intervention has been proposed, efficacy must be demonstrated in this complex multi-morbid population. Both muscle mass and muscle function need to be measured as outcomes, but these outcomes require large sample sizes and sufficient follow-up to detect change.

Biomarkers that can predict the response of sarcopenia to intervention after a short time would greatly assist our ability to select candidate interventions in short proof of concept trials. Further development of trial methods is required to accelerate progress in this important area of medicine for older people.

Key points:

- Sarcopenia is prevalent and costly but lacks effective pharmacological treatments
- Pharmacological interventions could be selected by 'bottom up', 'top down' or combination approaches
- A tiered approach to outcomes measurement is needed, with the development of biomarkers that predict longer-term outcomes

Compliance with Ethical Standards:

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Conflicts of Interest

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Selecting potential pharmacological interventions in sarcopenia

1. Introduction

The term sarcopenia is derived from the Greek words for 'poverty' and 'flesh' and was first used in 1989 to describe age-related loss of muscle mass [1]. Sarcopenia is associated with poor current and future health [2] with increased risk of physical disability, falls, poor quality of life and admission to hospital and care homes [3] as well as ~~increasing the~~ increased risk of fragility fracture [4]. It is also costly; the estimated direct healthcare cost attributable to sarcopenia in 2000 in the USA was ~~\$US~~£18.5 billion [5] and this is only set to increase.

Sarcopenia remains largely undiagnosed and undertreated because of difficulties with a universally accepted definition, requirement for equipment to measure muscle mass and dispute regarding which outcomes would best indicate treatment efficacy [6]. However, agreement has emerged that low muscle mass alone ~~provides is of~~ insufficient clinical relevance if not combined with muscle weakness and/or functional impairment [7]. The European Working Group on Sarcopenia in Older People (EWGSOP) consensus conference in 2010 proposed a diagnosis based on low muscle mass (appendicular lean mass/height²) with either low muscle strength (grip strength) or low physical performance (gait speed) [8]. Similar guidelines have emerged from other bodies including in the USA [9], however, the diagnostic criteria for sarcopenia continue to evolve as our understanding of the epidemiology and pathophysiology continue to improve.

Sarcopenia is prevalent in older people; it occurs in at least 1 in 20 community-dwelling individuals and up to 1 in 3 frail older people living in nursing homes, and prevalence increases with age [10]. There is a clear need for intervention in sarcopenia; however, the best way to identify candidate interventions and choose which to progress into clinical trials and clinical application is less clear. This paper will review two main aspects of pharmacological intervention in sarcopenia. Firstly, we consider the ways in which candidate pharmacological interventions might be selected for testing in clinical

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trials. Secondly, we discuss what criteria might need to be met to deem a pharmacological intervention as successful and the various different outcome data that might therefore be required.

2. Pathophysiology of sarcopenia

Multiple physiological pathways contribute to the maintenance of muscle mass and function. These affect cellular function, turnover, growth, repair and the net balance of protein synthesis and degradation [11]. Loss of muscle mass can therefore occur from alterations in multiple interacting pathways. It is therefore possible that there may be several different subtypes of sarcopenia associated with different pathways. Key pathways thought to be involved in muscle tissue metabolism [12] are demonstrated in Figure 1. A comprehensive account of the pathophysiology of sarcopenia is beyond the scope of this article, but Figure 1 serves to illustrate the complex biology of the condition.

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3. Selection of Pharmacological Intervention

3.1 What does an ideal intervention look like?

An ideal pharmacological intervention would be effective in all cases of sarcopenia, no matter what the causative pathology, and would ideally be effective at treating other diseases of old age to avoid exacerbating the problem of polypharmacy. It should be inexpensive, orally administered with an acceptable frequency of administration to aid adherence, and ~~should have~~ a low risk of causing side effects.

There are various means by which pharmacological interventions could be selected for testing in trials against sarcopenia. These include 'top down' approaches through the use of observational data or reviewing the off-target effects of existing drugs, ~~a 'bottom up' approach using insights from basic biology or 'omics' techniques to select pharmacological targets~~. They also include a 'bottom up'

~~approach using insights from basic biology or 'omics' techniques to select pharmacological targets 'top down' approaches through the use of observational data or reviewing the off target effects of existing drugs.~~ These are summarised in Figure 2.

3.2 Top down approaches

Employing observational studies to examine the association between physical function and medication use in routine clinical practice is a fruitful approach to target identification. Such approaches have demonstrated that angiotensin converting enzyme (ACE) inhibitors are associated with slower decline in muscle mass, muscle strength and walking speed [13] [14]. Knowledge of the interaction of angiotensin at a cellular level in muscle (inhibition of insulin-like growth factor-1 (IGF-1) action] as well as stimulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκβ) and tumour necrosis factor α (TNFα)] has since provided supportive evidence for this interaction. Observational studies have also demonstrated that people with ~~better~~ higher level of anti-oxidants ~~status~~ have better physical function [15]. This finding accords with insights from basic biology given elevated levels of reactive oxygen species and pro-inflammatory cytokines are found in many conditions ~~when muscle wasting is present where low muscle mass is found~~ and are thought to activate ~~NFκβ~~ or the ubiquitin proteasome system via muscle RING-finger protein-1 (MuRF-1) resulting in protein degradation [12]. Allopurinol, an inhibitor of xanthine oxidase that is known to reduce oxidative stress across a range of diseases including vascular disease [16], has been associated with improved functional outcomes in patients undergoing rehabilitation [17] again suggesting that agents that reduce oxidative stress are worth testing in patients with sarcopenia.

Other agents have been noted to have positive associations with muscle function, but biological plausibility is either lacking or ~~suggests an~~ the findings suggest our incomplete understanding of biological pathways. An example here is statin use, which has been associated with greater proximal muscle strength in community dwelling individuals [18] [19]. This is despite the known phenomenon

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of statin induced myopathy. Observational studies have also revealed adverse associations with function, for example, ~~furosemide-with the use of furosemide~~ and calcium channel blockers [20]. Whilst such adverse findings might appear less useful at first glance, such data may help practitioners to avoid making sarcopenia worse, and might also suggest new avenues to explore in terms of underlying mechanisms that lead to sarcopenia.

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3.3 Bottom up approaches

A 'bottom up approach' starts with the molecular processes involved in muscle atrophy and sarcopenia and identifies potential targets from this knowledge. Such an approach has revealed that myostatin (a member of the ~~transforming growth factor β (TGF β -)~~ superfamily) plays a crucial role in muscle growth via interaction with the activin receptor [6]. Myostatin negatively regulates muscle growth via inhibition of the ~~Phosphoinositide 3 Kinase/Protein kinase B (PI3K/AKT)~~ pathway and reduction of the levels of myogenic regulatory factors [12]. ~~Myostatin is inhibited by a protein called follistatin.~~

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Myostatin inhibition is required for muscle growth and development [6] and levels of myostatin have been observed to be increased in conditions with similarities to sarcopenia, such as heart failure and AIDS-related cachexia [21]. Pharmacological manipulation of myostatin has therefore become a key research target in sarcopenia [22]. ~~Several different approaches have been taken to this including myostatin blocking antibodies, myostatin propeptide, follistatin, follistatin related proteins, soluble myostatin receptors, small interfering RNA and small chemical inhibitors [22]. Several agents have now made it through to clinical trials, for example, A~~the humanised monoclonal antibody to myostatin, LY2495655. ~~A multi-centre randomised controlled trial in 2015 of LY2495655 in older people with recent falls and low muscle strength met its primary endpoint of increased appendicular lean mass at 24 weeks. It also improved fast gait speed, stair climbing time and chair rise with arms but not other functional measures, has recently been demonstrated in a multi-centre randomised~~

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controlled trial to increase appendicular lean mass and improve some measures of muscle function in older people with recent falls and low muscle strength [23].

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Ultimately a long term imbalance between rate of protein synthesis and breakdown is thought to have the potential to exacerbate age-related loss of muscle tissue [12] due to reduced total and essential amino acid intake as well as altered anabolic-catabolic balance. Branched chain amino acids, such as leucine, have been demonstrated to boost pathways leading to increased protein translation [2]. However, older skeletal muscle has been noted to have significant anabolic resistance to protein nutrition during immobilisation [24] and this has led to the suggestion that recommendations for protein intake should be increased for older people [2].

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Approaches altering downstream effects in favour of anabolism are likely therefore to need to be used in addition to nutritional supplementation. For example, the manipulation of myostatin represents an approach where a conserved signalling pathway has been reviewed [11] and manipulated. Several generic pathway points have been considered with respect to sarcopenia such as caspase inhibitors or proteasome inhibitors [6]. However, many of these would be involved in the cellular transcription pathway more generally and may have widespread effects, including the potential for promotion of cancerous changes.

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It is likely that new targets and treatment strategies will emerge as the pathways involved in sarcopenia are elucidated through reviews of gene expression patterns and more information is gained through metabolomics and proteomics [25] [26]. The Frailomic initiative is collecting urine and blood biomarkers in 75,000 participants who will be stratified as frail or not frail according to Fried's criteria [27]. Over 70% of the participants are over 65 years old [27]. The challenge of this approach will be the volume of information, and the massive task of translating this information into the development of new pharmacological agents. The clinical trials involved will be in a complex

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population with multiple diseases that contribute to physical, cognitive and functional disability. This large variability will increase the difficulty of detecting both treatment effects and adverse effects [7].

~~The fact that currently used drugs have a better known side-effect profile~~~~It is the known side effect profile that potentially provides~~~~provides another further~~ advantage to their reappropriation and may pave the way for further 'new tricks for old drugs' [2].

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The number of potential biological targets is likely to be far higher than the number of existing drugs that could be repurposed. There is therefore a limit to what observational data can tell us about target selection, and some way of refining our ability to select from the large number of targets suggested by basic biology will be needed. If a specific target or biomarker can be developed then it may be that action on these new targets could be screened for using high throughput drug screening, using both marketed drugs and those from compound libraries. Developing robust, validated preclinical models is therefore essential if we are to effectively screen large numbers of candidate molecules, but this task is made more complex by the large number of biological pathways involved in the genesis of sarcopenia.

4. Outcome measures

The history of the development of osteoporosis diagnosis and treatment reveals interesting parallels with the field of sarcopenia. Little progress was made in developing effective treatments for osteoporosis until a set of diagnostic criteria were agreed; the development of effective treatments then helped to establish these diagnostic criteria in clinical practice. One of the main issues with sarcopenia research and treatment has been the lack of an established core outcome set [28]. In health it appears that there is a relatively strong correlation between muscle mass and strength, however, the assumption that an increase in muscle mass will be associated with an increase in function does not always hold [11]. In general there is a 'hierarchy of response' to any given intervention [11]. For example, in response to resistance training in older people a large effect may be

seen in quadriceps strength but this may not translate into improved physical function [29]. Similarly, interventions might increase muscle mass, but not necessarily muscle strength; a situation seen in short-term trials of myostatin inhibitors [30]. The difficulty in selecting pharmacological interventions is therefore exacerbated by the difficulty in deciding how to declare an intervention successful.

4.1 Progression of candidate interventions through trial stages

Different outcome measures may be of use at different trial phases. For example, early phase outcomes need to be highly responsive (so as to minimise sample size) but should correlate with later trial outcomes. Such outcomes might reflect molecular and cellular changes in muscle without necessarily reflecting whole body function. Middle phase outcomes should reflect physical function and again need to correlate with later phase outcomes; a failure of such outcomes to predict late-phase trial success renders any middle-phase results of little value. Late phase outcomes need to reflect what is important to individual patients, health services and society as a whole. Again, parallels can be drawn with osteoporosis, where bone turnover markers, bone mineral density and fractures form key outcomes from early, middle and late phase trials. Potential early, mid and late phase outcomes for sarcopenia trials are suggested in Table 1.

4.2 Early Phase Outcomes

4.2.1 Biomarkers

Biomarkers are objectively measurable indicators of biological or pathological processes, and have the potential to be used as markers of response to a therapeutic intervention [31]. Measuring changes in physical function and muscle mass in sarcopenia requires sufficient time for measurable changes to occur (typically months), and because of the variability of these measures, sample sizes of typically 50-150 per arm are required. Reliable, responsive, easy to measure biomarkers for the detection and monitoring of sarcopenia could allow smaller, more rapid proof of concept trials of pharmacological interventions [26].

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Numerous biomarkers have been proposed [26] but are often not specific to sarcopenia [25]. Type III collagen is a subtype of collagen found in skeletal muscles. During its synthesis from procollagen III the N-terminal propeptide (P3NP) is cleaved and released into the circulation in direct proportion to type III synthesis and is therefore a measure of tissue remodelling [32]. In a cross-sectional study plasma concentrations of P3NP were found to be inversely related to total and appendicular lean mass in postmenopausal women but not in older men. [33].

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C-terminal agrin fragment (CAF) is another proposed biomarker. During neuromuscular remodeling agrin is cleaved by neurotrypsin releasing CAF which is detectable in plasma. Increases in serum CAF have been associated with neuromuscular junction disruption, muscle fibre atrophy and dysfunction [26] and have been reported to be elevated in older adults with sarcopenia compared with age

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matched controls [32]. In a trial of 23 older adults women had a higher baseline circulating CAF than men and the level increased by 10.4% after 6 weeks of resistance training. This increase was correlated with significant changes of cross sectional area of vastus lateralis (p=0.008)In men serum CAF concentrations have been reported to be inversely related to appendicular lean mass but no significant relationship was observed in women [32]. A study in 2013 looked at CAF levels in patients admitted acutely with hip fractures and found that serum levels were significantly higher(p<0.001) in all patients with sarcopenia (diagnosed using EWGSOP definition) at 172.2pM in sarcopenic patients and 93.0pM in non-sarcopenic patients [34]. This suggests that CAF levels may be of relevance in both community dwelling and hospitalised patients with sarcopenia.

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It may be that biomarkers such as P3NP and CAF have a role in helping to identify sarcopenia subtypes, but considerable work is needed to establish whether these biomarkers can predict response of muscle to interventions, and hence whether they are valid measures for use in trials. It is probable that given the multiple pathways involved in the pathogenesis of sarcopenia, a panel of biomarkers

will need to be measured, so that responses in a particular pathway affected by a candidate intervention are not missed.

4.3 Middle Phase Outcomes

4.3.1 Muscle mass

Assessment of muscle mass can be made using Dual energy X-ray ~~a~~bsorptiometry (DXA), ~~c~~omputed ~~t~~omography (CT) or ~~m~~agnetic ~~r~~esonance ~~i~~maging (MRI) [35]. CT and MRI scanning in particular have been used widely in oncology studies ~~looking at~~ assessing the impact of sarcopenia [36]. Bioelectrical impedance analysis can also be used to predict lean muscle mass; results depend on the instrument used, the conversion equation employed, and are also subject to variation depending on peripheral oedema and hydration status [37]. Bioimpedance is quick and easy to perform however and undoubtedly has a key role in screening for sarcopenia, although it is not the preferred technique for measuring muscle mass change in trials. A non-radiological method to assess skeletal muscle mass has been validated. This is based on D3-creatine dilution from an oral dose and detection of urinary creatinine enrichment by isotope ratio mass spectrometry. This has been used in longitudinal assessment of changes in skeletal muscle mass [38], and reportedly has the potential to be superior to DXA [26]. However, it requires specialist techniques that are likely to have limited availability [26].

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4.3.2 Functional measures including muscle strength

~~Because t~~he definition of sarcopenia encompasses both muscle mass and muscle function, it is therefore essential to include measurement of muscle function in any suite of sarcopenia outcomes. Isometric hand grip has been widely used as a general indicator of functional status [39], as have measures of lower limb extremity strength such as leg press strength and isokinetic leg extension strength [39]. These measures evaluate muscle function directly, and thus provide insight into physiology. They do not always reflect the way that muscle is used in daily life however, and some measures (e.g. grip strength) may not be responsive to interventions. Other measures examine muscle

function at a whole body level; for example, the time to walk 400 metres [39], six minute walking distance [40], gait speed (usually over a 3 or 4 metre course) and timed up and go test [41]. These measures better reflect how muscles are used in activities of daily living, but many are composites of muscle, nerve and cardiorespiratory function, which may dilute the impact of muscle-specific intervention effects.

4.3.3 Composite measures of function

The Short Physical Performance Battery (SPPB) is a widely used composite measure of lower extremity function [42] that has been validated and shown to be responsive to intervention [43] and associated with a clinically meaningful change [35]. It consists of measures of walking, balance and sit to stand [43] and has been shown to correlate with quality of life [44]. There are perhaps more data linking the SPPB with relevant outcomes such as death, hospitalisation, future dependency and falls than for any other functional measure; the SPPB is also easy to perform. It is therefore emerging as one of the functional measures of choice in sarcopenia trials and is under consideration as a surrogate marker of efficacy for future sarcopenia drug licensing.

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4.3.4 Activities of Daily Living and Quality of Life measures

~~Alteration in Q~~uestionnaires ~~looking at that assess~~ quality of life, functional status and psychological state are also potential outcome measures [42]. These can either be generic questionnaires or specific to sarcopenia, for examples, SarQOL is a quality of life measure that aims to be more specific to sarcopenia with seven main domains [45] and has recently been validated in English [46]. ~~It is, however, yet to be validated.~~

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4.4 Late Outcomes

These outcomes are much less specific in terms of alteration in muscular function but represent outcomes that will be of greatest importance to patients and health and social care funders. Late outcomes might include measures such as number of falls, hospital admissions, need for care assistance or risk of institutionalisation [35].

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Given the likely heterogeneity of both individuals and pathophysiological subtypes of sarcopenia, the inspection of single variables will inevitably result in a partial and incorrect picture. Multiplex analyses are gaining increasing plausibility with the development of 'omics' techniques and this approach may well be of increasing importance in an approach to biomarkers of sarcopenia. These analyses involve complex statistics but might potentially allow the early detection of subclinical syndromes as well as aiding clinical diagnosis and monitoring of response to treatment [26]. The downside of such methods is that the multivariate nature of such analyses will likely require relatively large numbers of patients. Any use of biomarkers to predict response to interventions in sarcopenia is limited by the lack of data on efficacious interventions – it is necessary to demonstrate that an intervention improves sarcopenia before one can tell if changes in a biomarker for sarcopenia predict improvements in sarcopenia itself.

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5. Conclusion

Sarcopenia is not currently routinely diagnosed in clinical practice. It is unlikely that this will become the case until a proven benefit of intervention can be established. Studies have taken place for many years looking at exercise interventions as well as nutritional supplementation in sarcopenia. Resistance training remains the key intervention proven to improve muscle function and physical performance in patients with sarcopenia. Nutritional and some pharmacological interventions may only be of benefit when combined with exercise training, however, exercise interventions may not necessarily add benefit to all pharmacological interventions.

Exercise interventions in sarcopenia are likely only to be applicable to a limited proportion of the population given their baseline functional status. Ideal agents might mimic exercise as an intervention, perhaps by acting on the same physiological pathways and thus would not need to be combined with exercise and be of benefit in those patients who can not or will not exercise. For example, a trial looking at 130 older patients with functional impairment found that the group supplemented with perindopril had an improvement in exercise capacity equivalent to that reported after six months of exercise training [47]. A further trial demonstrated that perindopril did not enhance the effect of exercise training on physical function providing further support that the effects of exercise and pharmacological intervention in this case are not additive [48].

Pharmacological intervention in sarcopenia is therefore an extremely topical and relevant avenue in sarcopenia treatment. The best way to select pharmacological interventions for trials is likely to be a combination of the top down and bottom up approaches, acting in a complementary fashion. Further work is required to define the optimum set of outcome measures used in early, middle and late-phase trials; outcomes will need to be multidimensional to ensure that success is defined not just by improvements in pathology and physiology, but in terms of patient-centred outcomes - improvement in function and increased independence. Future trials need to place these outcomes centre-stage if patients and clinicians are to be convinced of the benefits of pharmacological interventions for sarcopenia.

References

- [1] Rosenberg I, Rosenberg, "Summary comments," Am J Clin Nutr, 1989;50: pp. 50-1231-1233, 1989.
- [2] A-Sayer, A, S-Robinson, S, Patel H et al., H. Patel, T. Shavlakadze, C. Cooper and M. Grounds, "New horizons in the pathogenesis, diagnosis and management of sarcopenia," Age Ageing, 2013;42:145-150, vol. 42, pp. 145-150, 2013.

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- [3] ~~C. Roberts, C. Dodds, R. Sayer, A. R. Dodds and A. Sayer, "Current Clinical Care of Older older Adults with Sarcopenia," J Clin Densitom. 2015;18:193-198, pp. 18(4): 193-198, 2015.~~
- [4] ~~M. Grossmann M., "Myostatin inhibition: A new treatment for androgen deprivation-induced sarcopenia?," J Clin Endocrinol Metab. 2014;99:3636-3628, vol. 99, pp. 3636-3628, 2014.~~
- [5] ~~I. Janssen, J. D. Shepard, D. P. Katzmarzyk P et al. and R. Roubenoff, "The healthcare costs of sarcopenia in the United States," J Am Geriatr Soc. 2004;52:80-85, pp. 52: 80-85, 2004.~~
- [6] ~~M. Brotto M., and E. Abreu E., "Sarcopenia: pharmacology of today and tomorrow," J Pharmacol Exp Ther. 2012;343:540-546, vol. 343, no. 3, pp. 540-546, 2012.~~
- [7] ~~M. Cesari, M. Fielding, R. Benichou, O et al., R. Fielding, O. Benichou, R. Bernabei, S. Bhasin, J. Guralnik, A. Jette, F. Landi, M. Pahor, L. Rodriguez-Manas, Y. Rolland, R. Roubenoff, A. Sinclair, S. Studenski and T. Traverson, "Pharmacological Interventions in Frailty and Sarcopenia: Report by the International Conference on Frailty and Sarcopenia Research Task Force," J Frailty Aging. 2015;4:114-120, pp. 4(3): 114-120, 2015.~~
- [8] ~~A. Cruz-Jentoft A., J. Baeyens, J. Bauer, J et al., J. Bauer, Y. Boirie, T. Cederholm, F. Landi, F. Martin, J. Michel, Y. Rolland, S. Schneider, E. Topinkova, M. Vandewoude and M. Zamboni, "Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People," Age Ageing. 2010;39:412-423, vol. 39, pp. 412-423, 2010.~~
- [9] ~~R. Fielding, R. B. Vellas, B. W. Evans, W et al., S. Bhasin, J. Morley, A. Newman, G. Abellan van Kan, S. Andrieu, J. Bauer, D. Breuille, T. Cederholm, J. Chandler, C. De Maynard, L. Donini, T. Harris, A. Kannt, F. Guibert, G. Onder, R. Papanicolaou, Y. Rolland, D. Rooks, C. Sieber, E. Souhami, S. Verlaan and M. Zamboni, "Sarcopenia: An Undiagnosed Condition in Older Adults. Current Consensus Definition: Prevalence, Etiology, and Consequences. International Working Group on Sarcopenia," J Am Med Dir Asso. 2011;12:249-256, vol. 12, pp. 249-256, 2011.~~
- [10] ~~A. Cruz-Jentoft A., F. Landi, F. S. Schneider, S et al., C. Zuniga, H. Arai, Y. Boirie, L. Chen, R. Fielding, F. Martin, J. Michel, C. Sieber, J. Stout, S. Studenski, B. Vellas, J. Woo, M. Zamboni and T. Cederholm, "Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS)," Age Ageing. 2014;43:748-759, vol. 43, pp. 748-759, 2014.~~
- [11] ~~J. Compston, J. Fearon, K. and K. Fearon, "Emerging therapeutic concepts for muscle and bone preservation/formation. Bone. 2015;80:157-161," Bone, vol. 80, pp. 157-161, 2015.~~
- [12] ~~S. Lecker, S. R. Jagoe, R. Gilbert, A et al., A. Gilbert, M. Gomes, V. Baracos, J. Bailey, S. Price, W. Mitch and A. Goldberg, "Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression," FASEB J. 2004;18:39-51, vol. 18, pp. 39-51, 2004.~~
- [13] ~~G. Onder, G. Penninx, B. Balkrishnan, L et al., B. Penninx, R. Balkrishnan, L. Fried, P. Chaves, J. Williamson, C. Carter, M. Di Bari, J. Guralnik and M. Pahor, "Relation between use of angiotensin converting enzyme inhibitors and muscle strength and physical function in older~~

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women: an observational study. Lancet. 2002;359:926-930, vol. 359, pp. 926-930, 2002.

Formatted: Font: Not Italic

[14] C. Carter, C. Groban, L. and L. Groban, "Role of the renin-angiotensin system in age-related sarcopenia and diastolic dysfunction," Aging Health. 2008;4:37-46, vol. 4, no. 1, pp. 37-46, 2008.

Formatted: Font: Not Italic

[15] R. Dodds, R. Sayer, A. and A. Sayer, "Sarcopenia," Arq Bras Endocrinol Metabol. 2014;58:464-469, vol. 58, no. 5, pp. 464-469, 2014.

Formatted: Font: Not Italic

[16] J. George, J. Carr, E. Davies, J et al., E. Carr, J. Davies, J. Belch and A. Struthers, "High-Dose Allopurinol Improves Endothelial Function by Profoundly Reducing Vascular Oxidative Stress and Not by Lowering Uric Acid," Circulation. 2006;114:2508-2516, vol. 114, no. 23, pp. 2508-2516, 2006.

Formatted: Font: Not Italic

Formatted: Font: Not Italic

[17] L. Beveridge, L. Ramage, L. M. McMurdo, M et al., J. George and M. Witham, "Allopurinol use is associated with greater functional gains in older rehabilitation patients," Age Ageing. 2013;42:400-404, vol. 42, no. 3, pp. 400-404, 2013.

Formatted: Font: Not Italic

[18] J. Woo, J. Leung, J. Sham, A et al., J. Leung, A. Sham and T. Kwok, "Defining sarcopenia in terms of risk of physical limitations: A 5-year follow-up study of 3,153 Chinese men and women," J Am Geriatr Soc. 2009;57:2224-2231, vol. 57, no. 12, pp. 2224-2231, 2009.

Formatted: Font: Not Italic

[19] G. Onder, G. C. Della Vedova, C. Landi, F. and F. Landi, "Validated treatments and therapeutics perspectives regarding pharmacological products for sarcopenia," J Nutr Health Aging. 2009;13:746-756, vol. 13, no. 8, pp. 746-756, 2009.

Formatted: Font: Not Italic

[20] T. Ashfield, T. H. Syddall, H. Martin, H et al., H. Martin, E. Dennison, C. C and A. Sayer, "Grip strength and cardiovascular drug use in older people: findings from the Hertfordshire Cohort Study," Age Ageing. 2010;39:185-191, vol. 39, pp. 185-191, 2010.

Formatted: Font: Not Italic

[21] V. Guasconi, V. Puri, P. and P. Puri, "Epigenetic drugs in the treatment of skeletal muscle atrophy," Curr Opin Clin Nutr Metab Care. 2008;11:233-241, vol. 11, no. 3, pp. 233-241, 2008.

Formatted: Font: Not Italic

[22] K. Tsuchida, K., "Targeting myostatin for therapies against muscle-wasting disorders," Curr Opin Drug Discov Devel. 2008;11:487-494, vol. 11, no. 4, pp. 487-494, 2008.

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[23] C. Becker, C. S. Lord, S. Studenski, S et al., S. Warden, R. Fielding, C. Recknor, M. Hochberg, S. Ferrari, H. Blain, E. Binder, Y. Rollad, S. Poiraudreau, C. Benson, S. Myers, L. Hu, Q. Ahmad, K. Pacuch, E. Gomez, O. Benichou and S. group, "Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial," Lancet. 2015;3:948-957, vol. 3, no. 12, pp. 948-957, 2015.

Formatted: Font: Not Italic

[24] S. Budui, S. A. Rossi, A. Zamboni, M. and M. Zamboni, "The pathogenetic basis of sarcopenia," Clin Cases Miner Bone Metab. 2015;12:22-26, vol. 12, no. 1, pp. 22-26, 2015.

Formatted: Font: Not Italic

[25] G. Abellan van Kan, G. W. Cameron Chulmea, W. S. Gillette-Guyonnet, S et al., M. Houles, C. Dupuy, Y. Rolland and B. Vellas, "Clinical trials on sarcopenia: methodological issues regarding phase 3 trials," Clin Geriatr Med. 2011;27:471-482, vol. 27, no. 3, pp. 471-482, 2011.

Formatted: Font: Not Italic

- [26] R. Calvani, R. Marini, F. Cesari, M. et al., F. Marini, M. Cesari, M. Tosato, S. Anker, S. von Haehling, R. Miller, R. Bernabei, F. Landi, E. Marzetti and S. consortium, "Biomarkers for physical frailty and sarcopenia: state of the science and future developments." J Cachexia Sarcopenia Muscle. 2015;6:278-286, vol. 6, pp. 278-286, 2015.
- [27] J. Eruslimsky, J. J. Grillari, J. T. Grune, T. et al., P. Jansen-Duerr, G. Lippi, A. Sinclair, J. Tegnér, J. Viña, A. Durrance-Bagale, R. Miñambres, M. Viegas, L. Rodríguez-Mañas and F. Consortium., "In search of 'omics'-based biomarkers to predict risk of frailty and its consequences in older individuals: The FRAILOMIC initiative." Gerontology. 2016;62:182-190, vol. 62, no. 2, pp. 182-190, 2016.
- [28] J. Reginster, J. C. Cooper, C. R. Rozzili, R. et al., K. JA, G. Appleboom, I. Bautmans, H. Bischoff-Ferrari, M. Boers, M. Brandi, O. Bruyere, A. Cherubini, B. Flamion, R. Fielding, L. Van Loon, E. McCloskey, B. Mitlak, A. Pilotto, S. Reiter-Niesert, Y. Rolland, Y. Tsouderos, M. Visser and A. Cruz-Jentoft, "Recommendations for the registration of drugs to treat sarcopenia." Aging Clin Exp Res. 2016;28:47-58, Milan, 2015.
- [29] C. Liu, C. Latham, N. and N. Latham, "ProgProgressive resistance strength training for improving physical function in older adults: Systematic Review." Cochrane Database Systematic Rev. 2009;3:CD002759, vol. 3, 2009.
- [30] D. Padhi, D. Higano, C. Shore, N. et al., C. Higano, N. Shore, P. Sieber, E. Rasmussen and M. Smith, "Pharmacologic inhibition of myostatin and changes in lean body mass and lower extremity size in patients receiving androgen deprivation therapy for prostate cancer." J Clin Endocrinol Metab. 2014;99:E1967-1975, vol. 99, pp. E1967-E1975, 2014.
- [31] Biomarkers Definitions Working Group, "Biomarkers and surrogate endpoints: preferred definitions and conceptual framework." Clin Pharmacol Ther. 2001;69:89-95, vol. 69, pp. 89-95, 2001.
- [32] M. Fragala, M. A. Jajtner, A. K. Beyer, K. et al., J. Townsend, N. Emerson, T. Scanlon, L. Oliveira, J. Hoffman and J. Stout, "Biomarkers of muscle quality: N-terminal propeptide of type III procollagen and C-terminal agrin fragment responses to resistance exercise training in older adults." J Cachexia Sarcopenia Muscle. 2014;5:139-148, vol. 5, no. 2, pp. 139-148, 2014.
- [33] S. Berry, S. V. Ramachandran, V. P. Cawthon, P. et al., P. Gona, M. RR, L. Cupples and D. Kiel, "Procollagen type II N-terminal peptide (P3NP) and lean mass: a cross-sectional study." J Frailty Aging. 2013;2:129-134, vol. 2, pp. 129-134, 2013.
- [34] E. Marzetti, E. R. Calvani, R. Lorenzi, M. et al., M. Lorenzi, F. Marini, E. D'Angelo, A. M. Martone, M. Celi, T. Matteo, R. Bernabei and F. Landi, "Serum levels of C-terminal agrin fragment (CAF) are associated with sarcopenia in older hip fracture patients." Exp Gerontol. 2014;60:79-82, vol. 60, pp. 79-82, 2014.
- [35] G. Abellan Van Kan, G. Andre, E. Andre, H. Bischoff-Ferrari, H. et al., Y. Boirie, G. Onder, M. Pahor, P. Ritz, Y. Rolland, C. Sampaio, S. Studenski, M. Visser and B. Vellas, "Carla task force on sarcopenia: Propositions for clinical trials." J Nutr Health Aging. 2009;13:700-707, vol. 13, no. 8, pp. 700-707, 2009.

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- [36] C. Yip C, C. Dinkel C, A. Mahajan A et al., M. Siddique, G. Cook and V. Goh, "Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome.", *Insights Imaging*. 2015;6:489-497, vol. 6, no. 4, pp. 489-497, 2015.
- [37] V. Baracos V, and S. Kazemi-Bajestani S., "Clinical outcomes related to muscle mass in humans with cancer and catabolic illnesses.", *Int J Biochem Cell Biol*. 2013;45:2302-2308, vol. 45, no. 10, pp. 2302-8, 2013.
- [38] G. Loncar G, D. Omersa D, N. Cvetinovic N et al., A. Arandjelovic and M. Lainscak, "Emerging biomarkers in heart failure and cardiac cachexia.", *Int J Mol Sci*. 2014;15, vol. 15, no. 12, pp. 23878-23896, 2014.
- [39] M. Pahor M., "Mobility and Functional Outcomes for Sarcopenia Trials.", *J Frailty Aging*. 2015;4:123-124, vol. 4, no. 3, pp. 123-124, 2015.
- [40] L. Burton L, D. Sumukadas D, M. Witham M et al., A. Struthers and M. McMurdo, "Does spirinolactone improve exercise capacity in functionally impaired older people without heart failure? [abstract]. In *British Geriatrics Society Autumn Meeting; 2011 12-14 Oct; Brighton Centre. Brighton: British Geriatrics Society; 2011. Abstract number 2*," Brighton, United Kingdom, 2011.
- [41] R. Dennis R, U. Ponnappan U, R. Kodell R et al., K. Garner, C. Parkes, M. Bopp, K. Padala, C. Peterson, P. Padala and D. Sullivan, "Immune function and muscle adaptations to resistance exercise in older adults: Study protocol for a randomized control trial of a nutritional supplement.", *Trials*. 2015;16:121-135, vol. 16, no. 1, p. 121, 2015.
- [42] N. LeBrasseur N, N. Lajevardi N, R. Miciek R et al., N. Mazer, T. Storer and S. Bhasin, "Effects of testosterone therapy on muscle performance and physical function in older men with mobility limitations (The TOM trial): Design and methods.", *Contemp Clin Trials*. 2009;30:133-140, vol. 30, no. 2, pp. 133-140, 2009.
- [43] M. Pahor M, Blair S, Espeland M et al., and T. L. S. Investigators, "Effects of a physical activity intervention on measures of physical performance: Results of the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) Study.", *J Gerontol A Biol Sci Med Sci*. 2006;61A:1157-1165, vol. 61A, no. 11, pp. 1157-1165, 2006.
- [44] B. Oh B, B. Cho B, Choi H et al., H. C. Choi, K. Y. Son, S. Park, S. Chun and S. Cho, "The influence of lower-extremity function in elderly individuals' quality of life (QOL): An analysis of the correlation between SPPB and EQ-5D.", *Arch Gerontol Geriatr*. 2014;58:278-282, vol. 58, no. 2, pp. 278-182, 2014.
- [45] C. Beaudart C, E. Biver E, J. Reginster J et al., R. Rizzoli, Y. Rolland, I. Bautmans, J. Petermans, S. Gillain, F. Buckinx, J. Van Beveren, M. Jacquemain, P. Italiano, N. Dardenne and O. Bruyere, "Development of a self-administrated quality of life questionnaire for sarcopenia in elderly subjects: the SarQoL.", *Age Ageing*. 2015;44:960-966, vol. 44, no. 6, pp. 960-966, 2015.
- [46] C. Beaudart C, M. Edwards M, C. Moss C et al., J. Reginster, R. Moon, C. Parsons, C. Dmoulin, R. Rizzole, E. Biver, E. Dennison, O. Bruyere and C. Cooper, "English translation and validation of the SarQoL®, a quality of life questionnaire specific for sarcopenia.", *Age Ageing*. 2016. Published online 27 Oct 2016 (doi 10.1093/ageing/afw192), vol. 0, pp. 1-7, 2016.

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[47] ~~M. W. Witham, D. Sumukadas, D. McMurdo and M. E. McMurdo, "ACE inhibitors for sarcopenia - as good as exercise training?," *Age Ageing*, 2008;37;363-365, vol. 37, pp. 363-365, 2008.~~

Formatted: Font: Not Italic

[48] ~~D. Sumukadas, D. M. Band, M. S. Miller, S. et al. and a. et., "Do ACE inhibitors improve the response to exercise training in functionally impaired older adults? A randomized controlled trial," *J Gerontol A Biol Sci Med Sci*, 2014;69;736-743, vol. 69, no. 6, pp. 736-743, 2014.~~

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Bibliography

- [1] I. Rosenberg, "Summary comments," *Am J Clin Nut*, pp. 50: 1231-1233, 1989.
- [2] A. Sayer, S. Robinson, H. Patel, T. Shavlakadze, C. Cooper and M. Grounds, "New horizons in the pathogenesis, diagnosis and management of sarcopenia," *Age and Ageing*, vol. 42, pp. 145-150, 2013.
- [3] C. Roberts, R. Dodds and A. Sayer, "Current Clinical Care of Older Adults with Sarcopenia," *J Clin Densitom*, pp. 18(4): 193-198, 2015.
- [4] M. Grossmann, "Myostatin inhibition: A new treatment for androgen deprivation-induced sarcopenia?," *Journal of Clinical Endocrinology and Metabolism*, vol. 99, pp. 3636-3628, 2014.
- [5] I. Janssen, D. Shepard, P. Katzmarzyk and R. Roubenoff, "The healthcare costs of sarcopenia in the United States," *J Am Geriatr Soc*, pp. 52: 80-85, 2004.
- [6] M. Brotto and E. Abreu, "Sarcopenia: pharmacology of today and tomorrow," *Journal of Pharmacology and Experimental Therapeutics*, vol. 343, no. 3, pp. 540-546, 2012.
- [7] M. Cesari, R. Fielding, O. Benichou, R. Bernabei, S. Bhasin, J. Guralnik, A. Jette, F. Landi, M. Pahor, L. Rodriguez-Manas, Y. Rolland, R. Roubenoff, A. Sinclair, S. Studenski and T. Trivison, "Pharmacological Interventions In Frailty and Sarcopenia: Report by the International Conference on Frailty and Sarcopenia Research Task Force," *J Frailty Aging*, pp. 4(3): 114-120, 2015.
- [8] A. Cruz-Jentoft, F. Landi, S. Schneider, C. Zuniga, H. Arai, Y. Boirie, L. Chen, R. Fielding, F. Martin, J. Michel, C. Sieber, J. Stout, S. Studenski, B. Vellas, J. Woo, M. Zamboni and T. Cederholm, "Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS)," *Age Ageing*, vol. 43, pp. 748-759, 2014.
- [9] J. Compston and K. Fearon, "Emerging therapeutic concepts for muscle and bone preservation/formation," *Bone*, vol. 80, pp. 157-161, 2015.

- [10] S. Lecker, R. Jagoe, A. Gilbert, M. Gomes, V. Baracos, J. Bailey, S. Price, W. Mitch and A. Goldberg, "Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression," *FASEB J.*, vol. 18, pp. 39-51, 2004.
- [11] A. Cruz-Jentoft, J. Baeyens, J. Bauer, Y. Boirie, T. Cederholm, F. Landi, F. Martin, J. Michel, Y. Rolland, S. Schneider, E. Topinkova, M. Vandewoude and M. Zamboni, "Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People," *Age Ageing*, vol. 39, pp. 412-423, 2010.
- [12] R. Fielding, B. Vellas, W. Evans, S. Bhasin, J. Morley, A. Newman, G. Abellan van Kan, S. Andrieu, J. Bauer, D. Breuille, T. Cederholm, J. Chandler, C. De Maynard, L. Donini, T. Harris, A. Kannt, F. Guibert, G. Onder, R. Papanicolaou, Y. Rolland, D. Rooks, C. Sieber, E. Souhami, S. Verlaan and M. Zamboni, "Sarcopenia: An Undiagnosed Condition in Older Adults. Current Consensus Definition: Prevalence, Etiology, and Consequences. International Working Group on Sarcopenia," *J Am Med Dir Assoc*, vol. 12, pp. 249-256, 2011.
- [13] G. Onder, B. Penninx, R. Balkrishnan, L. Fried, P. Chaves, J. Williamson, C. Carter, M. Di Bari, J. Guralnik and M. Pahor, "Relation between use of angiotensin converting enzyme inhibitors and muscle strength and physical function in older women: an observational study," *Lancet*, vol. 359, pp. 926-930, 2002.
- [14] C. Carter and L. Groban, "Role of the renin-angiotensin system in age-related sarcopenia and diastolic dysfunction," *Aging Health*, vol. 4, no. 1, pp. 37-46, 2008.
- [15] R. Dodds and A. Sayer, "Sarcopenia," *Arch Bras Endocrinol Metabol*, vol. 58, no. 5, pp. 464-469, 2014.
- [16] J. George, E. Carr, J. Davies, J. Belch and A. Struthers, "High-Dose Allopurinol Improves Endothelial Function by Profoundly Reducing Vascular Oxidative Stress and Not by Lowering Uric Acid," *Circulation*, vol. 114, no. 23, pp. 2508-2516, 2006.
- [17] L. Beveridge, L. Ramage, M. McMurdo, J. George and M. Witham, "Allopurinol use is associated with greater functional gains in older rehabilitation patients," *Age Ageing*, vol. 42, no. 3, pp. 400-404, 2013.
- [18] J. Woo, J. Leung, A. Sham and T. Kwok, "Defining sarcopenia in terms of risk of physical limitations: A 5-year follow-up study of 3,153 Chinese men and women," *Journal of American Geriatrics Society*, vol. 57, no. 12, pp. 2224-2231, 2009.
- [19] G. Onder, C. Della Vedova and F. Landi, "Validated treatments and therapeutics perspectives regarding pharmacological products for sarcopenia," *Journal of Nutrition, Health and Aging*, vol. 13, no. 8, pp. 746-756, 2009.
- [20] T. Ashfield, H. Syddall, H. Martin, E. Dennison, C. C and A. Sayer, "Grip strength and cardiovascular drug use in older people: findings from the Hertfordshire Cohort Study," *Age and Ageing*, vol. 39, pp. 185-191, 2010.
- [21] V. Guasconi and P. Puri, "Epigenetic drugs in the treatment of skeletal muscle atrophy," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 11, no. 3, pp. 233-241, 2008.

- [22] K. Tsuchida, "Targeting myostatin for therapies against muscle-wasting disorders," *Current Opinion in Drug Discovery and Development*, vol. 11, no. 4, pp. 487-494, 2008.
- [23] C. Becker, S. Lord, S. Studenski, S. Warden, R. Fielding, C. Recknor, M. Hochberg, S. Ferrari, H. Blain, E. Binder, Y. Rollad, S. Poiraudeau, C. Benson, S. Myers, L. Hu, Q. Ahmad, K. Pacuch, E. Gomez, O. Benichou and S. group, "Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial," *The Lancet*, vol. 3, no. 12, pp. 948-957, 2015.
- [24] S. Budui, A. Rossi and M. Zamboni, "The pathogenetic basis of sarcopenia," *Clinical cases in mineral and bone metabolism*, vol. 12, no. 1, pp. 22-26, 2015.
- [25] G. Abellan van Kan, W. Cameron Chulmea, S. Gillette-Guyonnet, M. Houles, C. Dupuy, Y. Rolland and B. Vellas, "Clinical trials on sarcopenia: methodological issues regarding phase 3 trials," *Clin Geriatr Med*, vol. 27, no. 3, pp. 471-482, 2011.
- [26] R. Calvani, F. Marini, M. Cesari, M. Tosato, S. Anker, S. von Haehling, R. Miller, R. Bernabei, F. Landi, E. Marzetti and S. consortium, "Biomarkers for physical frailty and sarcopenia: state of the science and future developments," *Journal of Cachexia, Sarcopenia and Muscle*, vol. 6, pp. 278-286, 2015.
- [27] J. Erusalimsky, J. Grillari, T. Grune, P. Jansen Duerr, G. Lippi, A. Sinclair, J. Tegnér, J. Viña, A. Durrance-Bagale, R. Miñambres, M. Viegas, L. Rodríguez-Mañas and F. Consortium., "In Search of 'Omics' Based Biomarkers to Predict Risk of Frailty and Its Consequences in Older Individuals: The FRAILOMIC Initiative," *Gerontology*, vol. 62, no. 2, pp. 182-190, 2016.
- [28] J. Reginster, C. Cooper, R. Rozzili, K. JA, G. Appleboom, I. Bautmans, H. Bischoff-Ferrari, M. Boers, M. Brandi, O. Bruyere, A. Cherubini, B. Flamion, R. Fielding, L. Van Loon, E. McCloskey, B. Mitlak, A. Pilotto, S. Reiter-Niesert, Y. Rolland, Y. Tsouderos, M. Visser and A. Cruz-Jentoft, "Recommendations for the registration of drugs to treat sarcopenia," Milan, 2015.
- [29] C. Liu and N. Latham, "Progressive resistance-strength training for improving physical function in older adults: Systematic Review," *Cochrane Database Systematic Rev*, vol. 3, 2009.
- [30] D. Padhi, C. Higano, N. Shore, P. Sieber, E. Rasmussen and M. Smith, "Pharmacologic inhibition of myostatin and changes in lean body mass and lower extremity size in patients receiving androgen deprivation therapy for prostate cancer," *J Clin Endocrinol Metab*, vol. 99, pp. E1967-E1975, 2014.
- [31] Biomarkers Definitions Working Group, "Biomarkers and surrogate endpoints: preferred definitions and conceptual framework," *Clin Pharmacol Ther*, vol. 69, pp. 89-95, 2001.
- [32] M. Fragala, A. Jajtner, K. Beyer, J. Townsend, N. Emerson, T. Scanlon, L. Oliveira, J. Hoffman and J. Stout, "Biomarkers of muscle quality: N-terminal propeptide of type III procollagen and C-terminal agrin-fragment responses to resistance-exercise training in older adults," *Journal of Cachexia, Sarcopenia and Muscle*, vol. 5, no. 2, pp. 139-148, 2014.
- [33] S. Berry, V. Ramachandran, P. Cawthon, P. Gona, M. RR, L. Cupples and D. Kiel, "Procollagen type II N-terminal peptide (P3NP) and lean mass: a cross-sectional study," *J Frailty Aging*, vol. 2, pp. 129-134, 2013.

- [34] E. Marzetti, R. Calvani, M. Lorenzi, F. Marini, E. D'Angelo, A. M. Martone, M. Celi, T. Matteo, R. Bernabei and F. Landi, "Serum levels of C terminal agrin fragment (CAF) are associated with sarcopenia in older hip fracture patients," *Experimental Gerontology*, vol. 60, pp. 79-82, 2014.
- [35] G. Abellan Van Kan, E. Andre, H. Bischoff-Ferrari, Y. Boirie, G. Onder, M. Pahor, P. Ritz, Y. Rolland, C. Sampaio, S. Studenski, M. Visser and B. Vellas, "Carla task force on sarcopenia: Propositions for clinical trials," *Journal for Nutrition, Health and Aging*, vol. 13, no. 8, pp. 700-707, 2009.
- [36] C. Yip, C. Dinkel, A. Mahajan, M. Siddique, G. Cook and V. Goh, "Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome," *Insights Imaging*, vol. 6, no. 4, pp. 489-497, 2015.
- [37] V. Baracos and S. Kazemi-Bajestani, "Clinical outcomes related to muscle mass in humans with cancer and catabolic illnesses," *Int J Biochem Cell Biol*, vol. 45, no. 10, pp. 2302-8, 2013.
- [38] G. Loncar, D. Omersa, N. Cvetinovic, A. Arandjeleovic and M. Lainscak, "Emerging biomarkers in heart failure and cardiac cachexia," *International Journal of Molecular Sciences*, vol. 15, no. 12, pp. 23878-23896, 2014.
- [39] M. Pahor, "Mobility and Functional Outcomes for Sarcopenia Trials," *J Frailty Aging*, vol. 4, no. 3, pp. 123-124, 2015.
- [40] L. Burton, D. Sumukadas, M. Witham, A. Struthers and M. McMurdo, "Does sprinolactone improve exercise capacity in functionally impaired older people without heart failure?," Brighton, United Kingdom, 2011.
- [41] R. Dennis, U. Ponnappan, R. Kodell, K. Garner, C. Parkes, M. Bopp, K. Padala, C. Peterson, P. Padala and D. Sullivan, "Immune function and muscle adaptations to resistance exercise in older adults: Study protocol for a randomized control trial of a nutritional supplement," *Trials*, vol. 16, no. 1, p. 121, 2015.
- [42] N. LeBrasseur, N. Lajevardi, R. Miciek, N. Mazer, T. Storer and S. Bhasin, "Effects of testosterone therapy on muscle performance and physical function in older men with mobility limitations (The TOM trial): Design and methods," *Contemporary Clinical Trials*, vol. 30, no. 2, pp. 133-140, 2009.
- [43] M. Pahor and T. L. S. Investigators, "Effects of a Physical Activity Intervention on Measures of Physical Performance: Results of the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) Study," *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences*, vol. 61A, no. 11, pp. 1157-1165, 2006.
- [44] B. Oh, B. Cho, H. C. Choi, K. Y. Son, S. Park, S. Chun and S. Cho, "The influence of lower-extremity function in elderly individuals' quality of life (QOL): An analysis of the correlation between SPPB and EQ-5D," *Archives of Gerontology and Geriatrics*, vol. 58, no. 2, pp. 278-182, 2014.
- [45] C. Beaudart, E. Biver, J. Reginster, R. Rizzoli, Y. Rolland, I. Bautmans, J. Petermans, S. Gillain, F. Buckinx, J. Van Beveren, M. Jacquemain, P. Italiano, N. Dardenne and O. Bruyere,

"Development of a self-administrated quality of life questionnaire for sarcopenia in elderly subjects: the SarQoL," *Age and Ageing*, vol. 44, no. 6, pp. 960-966, 2015.

- [46] C. Beaudart, M. Edwards, C. Moss, J. Reginster, R. Moon, C. Parsons, C. Dmoulin, R. Rizzole, E. Biver, E. Dennison, O. Bruvère and C. Cooper, "English translation and validation of the SarQoL®, a quality of life questionnaire specific for sarcopenia," *Age Ageing*, vol. 0, pp. 1-7, 2016.
- [47] M. W. Witham, D. Sumukadas and M. E. McMurdo, "ACE inhibitors for sarcopenia—as good as exercise training?," *Age Ageing*, vol. 37, pp. 363-365, 2008.
- [48] Y. Wong and L. Flicker, "Hypovitaminosis D and frailty: Epiphenomenon or causal?," *Maturitas*, vol. 82, no. 4, pp. 328-335, 2015.
- [49] D. Wertz, "Ethical, social and legal issues in pharmacogenomics," *The Pharmacogenomics Journal*, vol. 3, pp. 194-196, 2003.
- [50] S. Vijverberg, T. Pieters and M. Cornel, "Chapter 13: Ethical and Social Issues in Pharmacogenomics Testing," in *Pharmacogenetics and Individualised Therapy, First Edition*, A. Maitland van der Zee and A. Daly, Eds., John Wiley & Sons, 2012.
- [51] H. Veasey-Rodrigues, H. Parsons, F. Janku, A. Naing, J. Wheler, A. Tsimberidou and R. Kurzrock, "A pilot study of temsirolimus and body composition," *Journal of Cachexia, Sarcopenia and Muscle*, vol. 4, no. 4, pp. 259-265, 2013.
- [52] D. Sumukadas, M. Witham, A. Struthers and M. McMurdo, "Effect of perindopril on physical function in elderly people with functional impairment: a randomized control trial," *Canadian Medical Association Journal*, vol. 177, no. 8, pp. 867-874, 2007.
- [53] D. Sumukadas, M. Band, S. Miller, V. Cvorc, M. Witham, A. Struthers and A. McConnachie, "Do ACE inhibitors improve the response to exercise training in functionally impaired older adults? A randomized controlled trial," *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, vol. 69, no. 6, pp. 736-743, 2014.
- [54] N. Sidiropoulos and A. H. Wu, "Clinical trials for pharmacogenomics testing for warfarin dosing: Relevance to general community practices," *Genetics in Medicine*, vol. 13, no. 6, pp. 505-508, 2011.
- [55] S. A. Scott, K. Sangkuhl, C. M. Stein, J. S. Hulot, J. L. Mega, D. M. Roden, T. E. Klein, M. S. Sabatine, J. A. Johnson and A. R. Shuldiner, "Clinical Pharmacogenetics Implementation and Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update," *Clinical Pharmacology and Therapeutics*, vol. 94, no. 3, pp. 317-323, 2013.
- [56] K. Sangkuhl, K. TE and R. Altman, "Clopidogrel pathway," *Pharmacogenetics and Genomics*, vol. 20, no. 7, pp. 463-465, 2010.
- [57] Y. Saab, R. Zeenny and W. Ramadan, "Optimizing clopidogrel dose response: a new clinical algorithm comprising CYP2C19 pharmacogenetics and drug interactions," *Therapeutics and Clinical Risk Management*, vol. 11, pp. 1421-1427, 2015.

- [58] M. Rieder, A. Reiner, B. Gage, D. Nickerson, C. Eby, H. McLeod, D. Blough, K. Thummel, V. DL and A. Rettie, "Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose," *New England Journal of Medicine*, vol. 352, no. 22, pp. 2285-2293, 2005.
- [59] M. Pirmohamed, F. Kamali, A. K. Daly and a. M. Wadelius, "Oral anticoagulation: a critique of recent advances and controversies," *Trends in Pharmacological Sciences*, vol. 36, no. 3, pp. 153-163, 2015.
- [60] M. Pirmohamed, G. Burnside, N. Eriksson, A. Jorgensen, C. Toh, T. Nicholson, P. Kesteven, C. Christersson, B. Wahlström, C. Stafberg, J. Zhang, J. Leathart, H. Kohnke, A. Maitland-van der Zee, P. Williamson, A. Daly, P. Avery, F. Kamali, M. Wadelius and E. P. Group, "A randomized trial of genotype-guided dosing of warfarin," *New England Journal of Medicine*, vol. 369, no. 24, pp. 2294-2303, 2013.
- [61] J. Pearlman and R. Fielding, "Creatine monohydrate as a therapeutic aid in muscular dystrophy," *Nutr Rev*, vol. 64, no. 2, pp. 80-88, 2006.
- [62] R. Osnabrugge, S. Head, F. Zijlstra, J. ten Berg, M. Hunink, A. Kappetein and A. Janssens, "A systematic review and critical assessment of 11 discordant meta-analyses on reduced function CYP2C19 genotype and risk of adverse clinical outcomes in clopidogrel users," *Genetics in Medicine*, vol. 17, no. 1, pp. 3-11, 2015.
- [63] G. Onder, C. Della Vedova and F. Landi, "Validated treatments and therapeutics perspectives regarding pharmacological products for sarcopenia," *Nournal of Nutrition, Health and Aging*, vol. 13, no. 8, pp. 746-756, 2009.
- [64] N. Norgard and J. Dinicolantonio, "Clopidogrel, prasugrel, or ticagrelor? a practical guide to use of antiplatelet agents in patients with acute coronary syndromes," *Postgraduate medicine*, vol. 125, no. 4, pp. 91-102, 2013.
- [65] NICE, "Ticagrelor for the treatment of acute coronary syndromes," NICE, London, 2011.
- [66] R. Nass, S. Pezzoli, M. Oliveri, J. Patrie, F. Harrell Jr, J. Clasey, S. Heymsfield, M. Back, M. Vance and T. MO, "Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: A randomized trial," *Annals of Internal Medicine*, vol. 149, no. 9, pp. 601-611, 2008.
- [67] J. Morley, S. von Haehling and S. Anker, "Are we closer to having drugs to treat muscle wasting disease?," *Journal of Cachexia, Sarcopenia and Muscle*, vol. 5, no. 2, pp. 83-87, 2014.
- [68] MHRA, "Drug Safety Update April 2010, vol 3 issue 9: 4," *Medicines and Healthcare product Regulatory Agency*, vol. 3, no. 9, p. 4, 2010.
- [69] J. Mega, T. Simon, J. Collet, J. Anderson, E. Antman, K. Bliden, C. Cannon, N. Danchin, B. Giusti, P. Gurbel, B. Horne, J. Hulot, A. Kastrati, G. Montalescot, F. Neumann, L. Shen, D. Sibbing, P. Steg, D. Trenk, S. Wiviott and M. Sabatine, "Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis," *JAMA*, vol. 304, no. 16, pp. 1821-1830, 2010.
- [70] S. King, "The Best Selling Drugs of All Time; Humira Joins The Elite," *Forbes.com*, 2013.

- [71] J. Johnson, L. Gong, M. Whirl-Carrillo, B. Gage, S. Scott, C. Stein, J. Anderson, S. Kimmel, M. Lee, M. Pirmohamed, M. Wadelius, T. Klein and R. Altman, "Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing," *Clinical Pharmacology and Therapeutics*, pp. 1-5, 2011.
- [72] A. Issa, "Ethical considerations in clinical pharmacogenomics research," *TIPS*, vol. 21, pp. 247-249, 2000.
- [73] M. Invernizzi, S. Carda and C. Cisari, "Possible synergism of physical exercise and ghrelin-agonists in patients with cachexia associated with chronic heart failure," *Aging Clin Exp Res*, vol. 26, no. 4, pp. 341-351, 2014.
- [74] J. Hulot, B. A. E. Villard, M. Azizi, V. Remones, C. Goyenvalle and M. Aiach, "Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant," *Blood*, vol. 108, no. 7, pp. 2244-2247, 2006.
- [75] S. Hardy, Y. Kang, S. Studenski and H. Degenholtz, "Ability to walk 1/4 mile predicts subsequent disability, mortality and health costs," *J Gen Intern Med*, vol. 26, no. 2, pp. 130-135, 2011.
- [76] B. Gualoni, A. Macedo, C. Alves, H. Roschel, F. Benatti, L. Takayama, A. de Sa Pinto, F. Lima and R. Pereira, "Creatine supplementation and resistance training in vulnerable older women: a randomized double-blind placebo-controlled clinical trial," *Exp Gerontol*, vol. 53, no. 7, p. 55, 2014.
- [77] D. Goldwater and S. Pinney, "Frailty in advanced heart failure: a consequence of aging or a separate entity?," *Clinical Medicine Insights: Cardiology*, vol. 9, pp. 39-46, 2015.
- [78] S. Giovannini, E. Marzetti, S. Borst and C. Leeuwenburgh, "Modulation of GH/IGF-1 axis: potential strategies to counteract sarcopenia in older adults," *Mech Ageing Dev*, vol. 129, p. 593-601, 2008.
- [79] R. Fitts, J. Peters, E. Dillon, W. Durham, M. Sheffield-Moore and R. Urban, "Weekly versus monthly testosterone administration on fast and slow skeletal muscle fibers in older adult males," *J Clin Endocrinol Metab*, vol. 100, no. 2, pp. E223-231, 2015.
- [80] L. Ferrucci, M. Baroni, A. Ranchelli, F. Lauretani, M. Maggio, P. Mecocci and C. Ruggiero, "Interaction between bone and muscle in older persons with mobility limitations," *Current Pharmaceutical Design*, vol. 20, no. 19, pp. 3178-3197, 2014.
- [81] FDA, "FDA Announces New Boxed Warning on Plavix," 2010.
- [82] G. D'Andrea, R. D'Ambrosio, P. Di Perna, M. Chetta, R. Santacroce, V. Brancaccio, E. Grandone and M. Margaglione, "A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin," *Blood*, vol. 105, no. 2, pp. 645-649, 2005.
- [83] A. Collamati, A. Martone, A. Poscia, V. Brandi, M. Celi, E. Marzetti, A. Cherubini and F. Landi, "Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence," *Aging Clin Exp Res*, vol. 28, no. 1, pp. 25-35, 2016.

- [84] W. Chumlea, M. Cesari, W. Evans, L. Ferrucci, R. Fielding, M. Pahor, S. Studenski and B. Vellas, "International working group on Sarcopenia," *Journal of Nutrition, Health and Aging*, vol. 15, no. 6, pp. 450-455, 2011.
- [85] V. Camus, H. Lanic, J. Kraut, R. Modzelewski, F. Clatot, J. Picquenot, N. Contentin, P. Lenain, L. Groza, E. Lemasle, C. Fronville, N. Cardinael, M. Fontoura, A. Chamseddine, O. Brehar, A. Stamatoullas, S. Lepretre, H. Tilly and F. Jardin, "Prognostic impact of fat tissue loss and cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy," *Eur J Haematol*, vol. 93, no. 1, pp. 9-18, 2014.
- [86] J. Buvat, M. Maggi, A. Guay and L. Torres, "Testosterone Deficiency in Men: Systematic Review and Standard Operation Procedures for Diagnosis and Treatment," *Journal of Sexual Medicine*, vol. 10, no. 1, pp. 245-284, 2013.
- [87] D. Bunout, G. Barrera, P. de la Maza, L. Leiva, C. Backhouse and S. Hirsch, "Effects of enalapril or nifedipine on muscle strength or functional capacity in elderly subjects. A double blind trial," *Journal of the Renin Angiotensin Aldosterone System*, vol. 10, no. 2, pp. 77-84, 2009.
- [88] E. Brotto and M. Abreu, "Sarcopenia: pharmacology of today and tomorrow," *Journal of Pharmacology and Experimental Therapeutics*, pp. 343(3):540-546, 2012.
- [89] P. Brice and S. Sanderson, "Pharmacogenetics: what are the ethical and economic implications?", *The Pharmaceutical Journal*, vol. 277, pp. 113-118, 2006.
- [90] H. Bischoff-Ferrari, B. Dawson-Hughes, H. Staehelin, J. Orav, A. Stuck, R. Theiler, J. Wong, A. Egli, D. Kiel and J. Henschkowski, "Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials," *BMJ*, vol. 339, p. b3692, 2009.
- [91] S. Bhasin, O. Calof, T. Storer, M. Lee, N. Mazer, R. Jasuja, V. Montori, W. Gao and S. JT, "Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging," *Nature Clinical Practice Endocrinology and Metabolism*, vol. 2, no. 3, pp. 146-159, 2006.
- [92] L. Beaupre, E. Binder, I. Cameron, C. Jones, D. Orwig, C. Sherrington and J. Magaziner, "Maximising functional recovery following hip fracture in frail seniors," *Best Pract Res Clin Rheumatol*, vol. 27, no. 6, pp. 771-778, 2013.
- [93] S. Antoun, L. Birdsell, M. Sawyer, P. Venner, B. Escudier and V. Baracos, "Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study," *Clin Oncol*, vol. 28, no. 6, pp. 1054-1060, 2010.
- [94] G. Aithal, D. CP, P. Kesteven and A. Daly, "Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications," *Lancet*, vol. 353, no. 9154, pp. 717-719, 1999.
- [95] G. Abellan van Khan, Cameron-Chumlea, W, S. Gillette-Guyonnet, M. Houles, C. Dupuy, Y. Rolland and B. Vellas, "Clinical Trials on Sarcopenia: Methodological Issues Regarding," *Clin Geriatr Med*, vol. 27, no. 3, pp. 471-482, 2011.

- [96] Institute of Medicine, "Pharmacogenomic Testing to Guide Warfarin Dosing," in *The Value of Genetic and Genomic Technologies: Workshop Summary*, Washington DC, National Academies Press, 2010, pp. 19-35.
- [97] Nuffield Council of Bioethics, "Pharmacogenetics Ethical Issues," Nuffield Council of Bioethics, London, 2003.
- [98] S. Carda, C. Cisari and M. Invernizzi, "Sarcopenia or muscle alterations in neurologic diseases: a lexical or pathophysiological difference?," *Eur J Phys Rehab Med*, vol. 49, pp. 119-130, 2013.
- [99] R. Armamento-Villareal, N. Napoli, D. Waters and D. Villareal, "Fat, Muscle and Bone Interactions in Obesity and the Metabolic Syndrome," *International Journal of Endocrinology*, p. 247076, 2014.
- [100] C. Beaudart, F. Buckinx, V. Rabenda, S. Gillain, E. Cavalier, J. Slomian, J. Petermans, R. JY and O. Bruyère, "The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials," *Journal of Clinical Endocrinology and Metabolism*, vol. 99, no. 11, pp. 4336-4345, 2014.
- [101] J. Erusalimsky, J. Grillari, T. Grune, P. Jansen Duerr, G. Lippi, A. Sinclair, J. Tegner, J. Vina, A. Durrance-Bagale, R. Minambres, M. Viegas and L. o. b. o. F. I. Rodriguez Manas, "In Search of 'Omics'-Based Biomarkers to Predict Risk of Frailty and its Consequences in Older Individuals: The FRAILOMIC Initiative," *Gerontology*, vol. 62, no. 2, pp. 182-190, 2016.
- [102] F. Sattler, C. Castaneda-Sceppa, E. Binder, E. Schroeder, Y. Wang, S. Bhasin, M. Kawakubo, Y. Stewart, K. Yarasheski, J. Ulloor, P. Colletti, R. Roubenoff and S. Azen, "Testosterone and growth hormone improve body composition and muscle performance in older men," *J Clin Endocrinol Metab*, vol. 94, no. 6, pp. 1991-2001, 2009.

Figure 1 – Some key cellular pathways involved in muscle tissue signalling and metabolism

Abbreviations List
4EBP1 4E **b**inding **p**rotein 1, AMPK 5'AMP **a**ctivated **p**rotein **k**inase, BAD Bcl-2 associated **d**eath **p**romoter, eIF2B **e**ukaryotic **i**nitiation **f**actor 2B, FoxO **f**orkhead box subgroup O, GSK3β **g**lycogen **s**ynthase **k**inase 3 **β**, IGF1 **i**nsulin-like **g**rowth **f**actor-1, LC-3 **m**icrotubule-associated proteins 1A/1B light chain 3A, MAFbx **m**uscle atrophy F-box, MAPK **m**itogen **a**ctivated **p**rotein **k**inase, MAP2K **m**itogen **a**ctivated **p**rotein **k**inase **k**inase, mTOR **m**ammalian **t**arget of **r**apamycin, MuRF-1 **m**uscle RING-finger protein-1, NFκβ **n**uclear factor kappa-light-chain-enhancer of activated B cells, PI3K **p**hosphoinositide 3 **k**inase, PKB **p**rotein **k**inase **β**, ROS **r**eactive **o**xygen **s**pecies, S6K1 **s**6 ribosomal protein S6 kinase beta-1, TNFα **t**umour **n**ecrosis **f**actor **α**.

Figure 2 – Approaches to selection of pharmacological intervention

Table 1 – Potential trial outcomes in sarcopenia

Trial Phase	Potential outcome measure	Parallel with osteoporosis trials
Early	Biomarkers of muscle pathophysiology	Bone turnover markers
Middle	Short Physical Performance Battery Walking speed Muscle mass (DEXA, CT, BIA) <u>Muscle strength</u> Quality of l ife measures Activities of d aily l iving	Bone mineral density
Late	Falls Institutionalisation Hospitalisation Quality of Life measures	Fractures

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DEXA – Dual energy X-ray absorptiometry

CT – computerised tomography

BIA – Bioelectrical impedance analysis