Current Opinion Article

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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

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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 increased risk of fragility fracture [4]. It is also costly; the estimated direct healthcare cost attributable to sarcopenia in 2000 in the USA was $US18.5 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 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/height^2) 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

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.

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 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. They also include a ‘bottom up’ approach using insights from basic biology or ‘omics’ techniques to select pharmacological targets. 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 higher level of anti-oxidants 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 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 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 of statin induced myopathy. Observational studies have also revealed adverse associations with function, for example, 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.

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 (TGFβ) 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.

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, 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. [23].

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].

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.

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 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 provides further advantage to their reappropriation and may pave the way for further 'new tricks for old drugs' [2].

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].

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].

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 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 ($p=0.008$) [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.

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 absorptiometry (DXA), computed tomography (CT) or magnetic resonance imaging (MRI) [35]. CT and MRI scanning in particular have

been used widely in oncology studies 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].

4.3.2 Functional measures including muscle strength

The 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.

4.3.4 Activities of Daily Living and Quality of Life measures

Questionnaires 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].

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].

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.

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.

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

Abbreviations List
4EBP1 4E binding protein 1, AMPK 5'AMP activated protein kinase, BAD Bcl-2 associated death promoter, eIF2B eukaryotic initiation factor 2B, FoxO forkhead box subgroup O, GSK3β glycogen synthase kinase 3 beta, IGF1 insulin-like growth factor-1, LC-3 microtubule-associated proteins 1A/1B light chain 3A, MAFbx muscle atrophy F-box, MAPK mitogen activated protein kinase, MAP2K mitogen activated protein kinase kinase, mTOR mammalian target of rapamycin, MuRF-1 muscle RING-finger protein-1, NFκβ nuclear factor kappa-light-chain-enhancer of activated B cells, PI3K phosphoinositide 3 kinase, PKB protein kinase b, ROS reactive oxygen species, S6K1 ribosomal protein S6 kinase beta-1, TNFα tumour necrosis factor alpha.

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 (DXA, CT, BIA) Muscle strength Quality of life measures Activities of daily living	Bone mineral density
Late	Falls Institutionalisation Hospitalisation Quality of Life measures	Fractures

DXA – Dual energy X-ray absorptiometry

CT – computerised tomography

BIA – Bioelectrical impedance analysis