SPECIAL ARTICLE

SARCOPENIA TRIALS IN SPECIFIC DISEASES: REPORT BY THE INTERNATIONAL CONFERENCE ON FRAILTY AND SARCOPENIA RESEARCH TASK FORCE

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Abstract: Muscle atrophy occurs as a consequence of a number of conditions, including cancer, chronic obstructive pulmonary disease (COPD), diabetes mellitus, heart failure, and other chronic diseases, where it is generally a predictor of poor survival. It also occurs as a consequence of disuse and an age-related loss of muscle mass and strength (sarcopenia). The aims of the 2016, International Conference on Frailty and Sarcopenia Research (ICFSR) Task Force were to examine how these specific chronic conditions have been employed in treatment trials thus far and how future trials using these patient groups might be designed for efficient identification of effective sarcopenia interventions. Functional limitations assessed as gait speed, distance walked over a set time period, or other attributes of physical performance have been suggested as outcome measures in sarcopenia trials. Indeed, such measures have already been used successfully in a number of trials aimed at preventing disability in older adults.

Key words: Sarcopenia, chronic obstructive pulmonary disease, type 2 diabetes, hip fracture, obesity, frailty.

Introduction

In recent years, there has been increased awareness about the role of muscle disorders in age-related disability. Skeletal muscles are essential for maintaining whole-body health and longevity, yet muscle wasting occurs as a normal part of aging, although some people lose muscle at a faster rate and cross a threshold defined as sarcopenia (1). Sarcopenia, the loss of muscle mass and strength, frequently observed during aging, occurs in up to 29% of community-dwelling older adults and 33% of long-term care populations (2), although it may go unrecognized.

Sarcopenia also occurs as a consequence of a number of chronic conditions, and may be a predictor of increased mortality in these conditions, including cancer (3), chronic obstructive pulmonary disease (COPD) (4), diabetes mellitus (5), heart failure (6), and other chronic diseases. It also occurs as a consequence of disuse due to prolonged bed rest or immobility, such as that due to hip fracture. The overlap of these conditions with age-related muscle loss may provide clues about the multifactorial mechanisms underlying sarcopenia, e.g., increased cytokine activity, decreased anabolic hormones (1). It may also point to candidate populations for clinical trials where early intervention would be possible and an

efficacy signal could be readily discerned.

In 2015, the International Conference on Frailty and Sarcopenia Research (ICFSR) Task Force proposed targeting a number of specific conditions for sarcopenia trials, including individuals over age 75 with frailty, recent fallers, and inactive people; as well as patients with hip fracture, COPD, diabetes, heart failure, and stroke (7). Meeting again in 2016 in Philadelphia, Pennsylvania, USA, the Task Force examined how these conditions have been employed in treatment trials thus far and how future trials might be designed for efficient identification of effective sarcopenia interventions.

Specific diseases: COPD, Diabetes, Hip Fracture, and Obesity

The development of bimagrumab illustrates both how treatments for sarcopenia may be applicable to a range of conditions, and how the lessons learned from treating one condition may help elucidate the mechanisms underlying muscle growth and atrophy. Bimagrumab is a monoclonal antibody that stimulates muscle growth by blocking the binding of myostatin. Developed by Novartis, bimagrumab received breakthrough therapy approval from the U.S. Food and Drug Administration (FDA) in 2013 for the treatment of the rare muscle disease inclusion body myositis (IBM) (8), and has also been shown to promote recovery from disuse atrophy and increase muscle mass in healthy young men, sedentary middle-aged adults, and in elderly people. Approximately one-third of patients with COPD have sarcopenia with a marked decline in Type I muscle fibers (4).

In elderly patients, bimagrumab resulted in a functional benefit: increased distance walked in the 6-minute walking distance (6MWD) test. While this benefit was seen in elderly patients with sarcopenia and baseline slow gait speed, no improvement in distance walked was seen in patients with normal baseline gait speed. In contrast, in a study of patients with COPD-induced cachexia, bimagrumab induced a comparable increase in thigh muscle volume, but no effect on 6MWD among both slow and fast walkers. Additional studies are underway to explore the mechanisms underlying these differences. For example, it may have something to do with the preferential loss of type I vs. type II muscle fibers in COPD. A combination of exercise and nutritional therapy has been demonstrated to improve functional outcomes (9).

Diabetes
Older people not only have a high prevalence of sarcopenia but of diabetes as well, yet the intersection or synergy between these two conditions has not been fully elucidated. Disuse atrophy may play a role, since individuals with type 2 diabetes (T2D) are more likely to be hospitalized and have longer durations of hospitalization than those without diabetes. Adults with T2D also have a higher prevalence of mobility-related disability (10) and a lifestyle-intervention study aimed at

improving weight loss and fitness showed an improvement in mobility among overweight adults with T2D (11). Other factors that may explain a connection between diabetes and sarcopenia include impaired glucose tolerance and insulin resistance (12). Obesity is also strongly related to T2D, particularly in middle aged and younger adults, as well as adolescents (13), obesity is less prevalent in the elderly (14). A study by Goodpaster and colleagues suggested that regional fat distribution, rather than obesity per se, contributes to the increased risk of T2D (15)

The Health, Aging, and Body Composition (Health ABC) study demonstrated that older people with T2D have an accelerated loss of leg muscle mass and strength (16). Leenders et al (17) showed that persons with type 2 diabetes had a greater decline in muscle mass, muscle strength and functional capacity with aging. People with diabetes are also have increased intracellular lipids (18) and decreased mitochondrial function in muscles (19), suggesting a possible link between energetics and atrophy. Both increase lipid accumulation and impaired mitochondrial function have also been linked to insulin resistance in skeletal muscle. Further, persons with Type II diabetes mellitus have lower testosterone, greater oxidative damage to muscle and decreased blood flow (5). These studies thus suggest a number of potential treatment targets for sarcopenia. They also indicate that individuals with T2D may represent a useful target population for clinical trials of sarcopenia treatments. However, investigators should keep in mind that the pathophysiologic mechanisms in diabetes may differ between younger versus older individuals; thus treatment targets may also differ.

Hip fracture
In the United States, over 290,000 older adults are hospitalized each year for hip fracture, with three-quarters of these fractures among women (20). Worldwide, the incidence of hip fracture varies substantially (21), totaling about 3.9 million. This number is expected to increase markedly over the next 30 years as the population ages (22). Moreover, despite advances in surgical procedures and post-operative care, hip fractures are substantial causes of death, disability, functional decline, and pain and suffering. The morbidity associated with hip fracture results in large part from changes in body composition: fat mass, lean mass, and bone mineral density (BMD), with marked changes in lean mass and BMD being observed during the first two months after hip fracture (23).

The prevalence of sarcopenia in patients with hip fracture varies depending on sex and the definition of sarcopenia used. Men appear to be at higher risk of sarcopenia after hip fracture, and the prevalence of sarcopenia stabilizes over time; while in women the prevalence of sarcopenia decreases over 12 months. The effects on mobility and other measures of physical function also varies depending on the definition of sarcopenia used. Other functional consequences of hip fracture include effects on cognition, mood, and socialization. Moreover, functional recovery varies across different activities (24). In addition

to functional losses, hip fracture also leads to changes in the inflammatory response (25). Frailty and osteoporosis further complicate recovery from hip fracture (26).

Over the past 30 years, the Baltimore Hip Studies have enrolled and followed more than 4,000 hip fracture patients admitted to Baltimore-area hospitals through observational and interventional studies. These studies have captured data on many outcomes, including mortality and functional recovery; changes in BMD, muscle mass and composition, and bone and muscle strength; and caregiver burden, health care use, and cost.

Obesity. Sarcopenia in combination with obesity increases the risk of disability in the elderly (27), yet as with other prevalence statistics, depends in large part on the definition used. Using the Foundation for the National Institutes of Health (FNIH) definitions for both sarcopenia and obesity, an analysis of data from the 1999-2004 National Health and Nutrition Examination Surveys (NHANES) of non-institutionalized older adults found a prevalence of sarcopenic obesity of 22.7% when sarcopenia was defined as appendicular lean mass (ALM) adjusted for body mass index (BMI) and 24.4% when sarcopenia was defined by ALM alone (28). To be included in the analysis, subjects had to function at a high level at baseline. In both cases, obesity was defined as body fat greater than 25% percent in men and 35% in women. In another study of healthy elderly women, high body fat and high BMI were associated with poorer physical function assessed using a modified version of the Activities of Daily Living Scale, and leg strength measurement (29). Body composition measures, particularly thigh intermuscular fat and total thigh muscle volume, are also associated with gait-speed decline in both men and women (30).

Sarcopenic obesity also may contribute to exercise intolerance in older adults with the most common form of heart failure, i.e., heart failure with preserved ejection fraction (HFPEF) (31). Indeed, these patients show abnormalities in skeletal muscle composition, specifically increased fat infiltration into the skeletal muscle, which appears to result in reduced peak oxygen uptake (Peak VO2) and thus, exercise intolerance (32). Investigators at Wake Forest School of Medicine thus targeted these patients in a clinical trial that explored the effects of caloric restriction and aerobic exercise on exercise capacity and quality of life in obese older patients with HFPEF (NCT00959660). Using a 2X2 factorial design, they randomized 100 patients to one of four 20-week interventions: supervised exercise alone, caloric restricted diet alone, exercise plus diet, or an attention control group that received telephone calls every two weeks. The primary outcome measure was peak VO2. Both exercise alone and diet alone significantly improved peak VO2, and the combination of exercise and diet was additive. In addition, the change in peak VO2 was accompanied by improvements in total body mass, fat mass, percent lean mass, and skeletal muscle to intermuscular fat ratio (33).

Table 1

Evaluating sarcopenia treatments across specialties – Target populations

Condition	Inclusion Criteria	Exclusion criteria
COPD	Ability to complete 400m walk	Wheelchair bound
Diabetes	Focus on individuals with low gait speed, muscle strength and mass, and cardiovascular fitness	Use of exogenous insulin
Hip Fracture	Focus on those in the mid-range with regard to functionality	Impairment too severe to tolerate study requirements
Obesity	Focus on those with functional impairment and relative weakness (not lean mass cutpoint)	Osteoarthritis (severe)

Lifestyle interventions across specialties

While bimagrumab and other pharmacologic therapies being developed represent biological intervention aimed at addressing muscle dysfunction, many treatment trials for sarcopenia across all specialties have assessed the impact of comprehensive lifestyle interventions, including diet and exercise, as well as other components such as counseling, stress management, and smoking cessation. The rationale for this approach is two-fold: Unhealthy lifestyles are thought to contribute to the development of sarcopenia and lifestyle factors may be more controllable than systemic changes such as inflammation or oxidative stress. In 2005, the American Society for Nutrition and the Obesity Society recommended diet, behavioral therapy, and regular exercise for older obese persons (34). Subsequently, a randomized controlled trial showed that a combination of diet and exercise resulted in greater improvement in physical function than either intervention alone (35). Similarly, clinical trials of comprehensive lifestyle interventions have demonstrated benefits for persons with obesity and T2D (36); and physical activity has been shown to benefit people with sarcopenia (37). Singh et al. (38) also found that exercise twice a week markedly reduces the negative effects of hip fracture. In all of these trials, sarcopenia is just one of several potential causes of poor function being addressed.

Roadblocks to clinical trials for sarcopenia

Task Force members agreed that the lack of a common nomenclature across the field has stymied the development of effective therapies for sarcopenia. One advance in this regard came in April 2016, when the Centers for Disease Control and Prevention established an ICD-10-CM code for

sarcopenia. This new code, M62.84, will be available beginning in October, 2016, according to the Aging in Motion Coalition, which led efforts to secure an ICD-10 code for sarcopenia. However, while the code should promote increased recognition of the validity of sarcopenia as a condition requiring diagnosis and treatment, more work is needed to reach consensus on a universal definition and the clinically relevant aspects of the disease.

An international group of sarcopenia experts recently proposed a framework for classifying muscle wasting diseases (39). This framework incorporates the concepts of muscle wasting, sarcopenia, frailty, and cachexia, as well as the various etiologies such as those discussed above. Yet this framework, as well as the criteria proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) (40) and a consensus conference convened by the Society of Sarcopenia, Cachexia, and Wasting Disorders (41), fail to address the role of adiposity in muscle wasting diseases. Original studies of sarcopenic obesity suggested that muscle mass was the determining factor in function (42, 43). However, studies done in establishing cut-points using the FNIH criteria show that adiposity alters the relationships between muscle mass and weakness, especially in women (44, 45). In COPD, sarcopenic obesity is related to worse physical performance and a higher inflammatory burden (46). Adiposity is related to insulin resistance and markers of inflammation (28), aerobic capacity and physical function in patients with HFPEF (47), and prevalence of sarcopenia in patients with COPD (48). Muscle wasting and adiposity also affect outcomes in colon cancer (49).

These data suggest that two sets of sarcopenia definitions are needed: a wasting form and an adiposity form. Such a framework would have to acknowledge that some conditions involve both wasting and adiposity, and could also incorporate poor muscle quality to distinguish older people with sarcopenic obesity from those with obesity but no sarcopenia.

Alternatively, sarcopenia could be viewed as a geriatric syndrome rather than a disease. This would enable the recognition of multiple risk factors and perhaps disentangle the links among sarcopenia, frailty, disability, and mortality (40). It would also allow the use of less selective inclusion and exclusion criteria, which could make recruitment easier and result in more representative, "real-life" populations. Currently, the inclusion and exclusion criteria developed for many clinical trials make it nearly impossible to recruit older people (50), in part because these populations have multiple conditions and diseases (51). As a result, there are currently few clinical trials that enroll older people (52).

The multi-modal intervention in diabetes in frailty (MID-Frail) study took a different approach, designing inclusion and exclusion criteria that are as simple and few as possible (53) in order to optimize recruitment, follow-up, and compliance, while ensuring the exclusion of those with unacceptable risks, co-morbidities that would interfere with the intervention or measurement of the outcome, as well as those unlikely to receive benefit from the treatment or unlikely to adhere to the intervention. It is suggested that the SARC-F may be a rapid screening tool for clinical trials (54, 55).

The tradeoffs that accompany a widening of inclusion criteria include the potential for a high number of adverse events and increased variability, which can increase sample size and decrease power. However, it may be that without these changes in how trials are done, it will be impossible to test drugs in older populations for whom these treatments are intended.

Primary endpoints for sarcopenia trials across specialties

In addition to reaching consensus on a definition of sarcopenia, developing efficacious interventions requires broad agreement on the most appropriate endpoints to be used in clinical trials of new treatments (56). Functional limitations assessed as gait speed, distance walked over a set time period, or other attributes of physical performance have been suggested as outcome measures in sarcopenia trials. Indeed, such measures have already been used successfully in a number of trials aimed at preventing disability in older adults, as well as in observational studies. For example, the Health ABC study showed that an increase of one-minute in the time it takes to walk 400 meters is significantly associated with mortality, cardiovascular disease, mobility limitations, and disability (57). Specialty areas have also begun to look at functional limitations as screening tools and outcome measures for clinical trials. For example, in a study of adults receiving chemotherapy, the Short Physical Performance Battery (SPPB) was shown to be the strongest predictor of survival (58).

The FDA approves clinical outcome assessments either as part of a drug application review or under the Drug Development Tool Qualification Process (59). The Aging in Motion Coalition proposed, in a letter of intent to the FDA, qualification of SPPB and gait speed as outcome measures acceptable in clinical trials related to sarcopenia. However, the FDA responded by recommending targeting of particular instruments to particular diseases or conditions, with a clear definition of the disease or condition for which qualification is sought. Thus, it appears that qualification will have to be sought one condition at a time, in contrast to the usual scenario in older adults where several conditions are usually present in combination, participating jointly in producing loss of function. A previous Task Force meeting outlined the critical next steps that will be needed to achieve acceptance of outcome measures in hip fracture trials, and these steps remain true for other areas as well (60): 1) development of an evidence base of key measures and their behavior in diverse target populations over time; 2) correlations of physical performance measures to self-report information; 3) identification of minimum clinically relevant thresholds and biomarkers of skeletal muscle mass modifications; and 4) development of better patient-

reported outcome scales. It will also be necessary to describe clearly what each endpoint is thought to mean from both clinical and pathophysiologic perspectives; for example, the clinical meaningfulness and pathophysiologic meaning of an improvement in gait speed or another marker of performance.

Biomarkers and imaging

Biomarkers have greatly advanced the drug development process in a number of fields, but in regards to drug development for sarcopenia, validation of a biomarker has proven elusive. Theoretically, a biomarker could be a symptom or a clinical, laboratory, or imaging measure of muscle mass, muscle performance, or physical function that has been shown to be predictive of health outcomes. Indeed, muscle mass and strength meet many of the criteria for an ideal biomarker, as defined by Baker and Sprott in 1988 (61), to identify people at risk of disability or a bad health outcome. That is, muscle mass and strength can be measured accurately and precisely in a clinical setting and are related to the biological pathway of the disease. However, much work remains to establish and validate muscle mass and strength cutpoints. Moreover, their relation to change in functional performance and clinical endpoints has not been demonstrated clearly and it is unclear how they may be affected by comorbidities and other physiologic impairments.

The selection of appropriate biomarkers for sarcopenia could be guided by the putative mechanistic pathway by which promyogenic agents might improve outcomes (Figure 1). Imaging modalities such as dual energy X-ray absorptiometry (DXA), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) may be useful to assess muscle mass and composition, body composition, skeletal muscle fiber tracking, sarcomere size, and muscle biochemistry and energetics. Indeed, DXA and CT/MRI have proven useful in phase 1 and 2 studies of promyogenic molecules to demonstrate increases in muscle mass and guide early go-no-go decisions for further development of these as therapeutic agents. However, these methods require additional data to demonstrate their relation to function. Tracer methods for tracking changes in muscle mass and protein turnover are promising techniques, but currently in early stages of development and used primarily for research.

Figure 1
Putative Pathways by Which Promyogenic Drugs Might Improve Health Outcomes
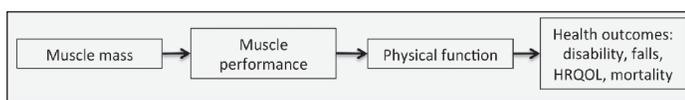
HRQOL: Health-related Quality of Life

For regulators, the context of use and the clinical meaningfulness of biomarkers are of paramount importance.

Regarding context of use, for example, biomarkers might be used for prognosis; demonstration of disease activity, progression, or severity; or as surrogate markers or predictors of a treatment response.

Regulatory considerations for sarcopenia as a potential indication

A major roadblock to gaining regulatory approval of a treatment for sarcopenia has been the fact that sarcopenia is not recognized as a condition (62). The acceptance of an ICD-10 code, discussed earlier, may help address this roadblock. However, there remain many other issues that will need to be clarified: How to define the populations to be treated, what characteristics (such as severity) justify pharmacologic intervention and how those will be measured, how a clinically meaningful effect will be measured, and how confounding factors will be dealt with, including those associated with comorbidities discussed in this paper, such as hip fracture, COPD, diabetes, and obesity. In terms of a clinically meaningful effect, more data are needed to demonstrate whether, for example, improved strength leads to functional improvement and what is the minimal level of improvement that provides benefit.

Other questions that will need to be answered include whether a minimum data set should be required for all sarcopenia trials; whether interventions should be tested on a background exercise and dietary regimen; to what extent comorbidities should be used as inclusion and/or exclusion criteria; and whether co-primary outcomes of a performance-based measure plus a patient-reported outcome should be required.

Conclusions

A large body of data from prospective observational studies and randomized controlled trials is beginning to shed light on the optimal ways to conduct trials of treatments for sarcopenia. While Task Force members agreed that it is important to choose the correct definition of sarcopenia, there may be different forms of sarcopenia, for example an adiposity-predominant form and a wasting-predominant form.

Sarcopenia is also closely related to frailty, and recently there have been efforts to merge the two into a new clinical entity, the physical frailty and sarcopenia syndrome (PF&S) (63). These individuals are at especially high risk for mobility disability. The Innovative Medicines Initiatives has funded a research project to test multi-component treatment strategies (the SPRINT-T project) in this population (64). It should be recognized that not all frail persons are sarcopenic and their causes of frailty, e.g., sleep apnea, depression, will not necessarily respond to treatments for sarcopenia (46, 65).

The preponderance of co-morbidities in sarcopenia both complicates clarification of the condition and provides potential

opportunities for testing interventions. However, designing clinical trials in populations with particular co-morbidities such as COPD, T2D, obesity, and hip fracture also introduces additional complexity in trial design and interpretation of results.

Disclaimer: The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

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