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Review of Interventions to Manage Sarcopenia

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List of abbreviations

ADL : Activities of Daily Living

ALM : Appendicular Lean Mass

ATP : Adenosine Triphosphate

BIA : Bioelectrical Impedance Analysis

CSA : Cross-Sectional Area

CT : Computed Tomography

DXA : Dual-Energy X-ray Absorptiometry

EWGSOP : European Working Group on Sarcopenia in Older People

GH : Growth Hormone

GDF5 : Growth Differentiation Factor 5

HRmax : Maximum Heart Rate

IGF-1 : Insulin-like Growth Factor 1

IL-6 : Interleukin 6

MPS : Muscle Protein Synthesis

MRI : Magnetic Resonance Imaging

mTOR : Mechanistic Target of Rapamycin

MuRF1 : Muscle RING-Finger Protein-1

NF- κ B : Nuclear Factor Kappa B

NSAIDs : Non-Steroidal Anti-Inflammatory Drugs

ROS : Reactive Oxygen Species

SARMs : Selective Androgen Receptor Modulators

SPPB : Short Physical Performance Battery

TNF- α : Tumor Necrosis Factor Alpha

TUG : Timed Up and Go Test

UPS : Ubiquitin-Proteasome System

1RM : One Repetition Maximum

Abstract

Objective and aim: sarcopenia is a geriatric syndrome affecting older adults worldwide. There are many interventions that are used to prevent or treat sarcopenia. That is why the aim of this work was to review existing treatment interventions (non-pharmacological and pharmacological) for sarcopenia.

Design: literature review

Methods: Searches were conducted in PubMed, Scopus, and Elsevier using database-specific search terms such as “elderly,” “older adult,” “sarcopenia,” “intervention,” “treatment,” “experimental,” and related keywords; manual searches of guideline websites were also performed. Using the PICOS framework, studies published in English over the past 10 years (2014–2024).

Results: The literature review identified multiple effective interventions for sarcopenia, including resistance training, nutritional supplementation, and pharmacological treatments. Resistance training was shown to be the most effective non-pharmacological intervention, significantly improving muscle mass and strength. Nutritional supplementation, particularly with protein and vitamin D, also demonstrated positive effects on muscle maintenance and function.

Pharmacological treatments, such as selective androgen receptor modulators (SARMs) and myostatin inhibitors, showed promise in increasing muscle mass and strength, but further research is needed to confirm long-term efficacy and safety.

Conclusion: Sarcopenia represents a significant health concern for the elderly, with various interventions available to mitigate its effects. Resistance training and nutritional supplementation are highly effective non-pharmacological treatments, while pharmacological options hold potential but require more research. Early diagnosis and a comprehensive, personalized approach are crucial for improving outcomes in older adults with sarcopenia.

Keywords: sarcopenia, treatment, intervention, aging, older adults, muscle mass

Chapter 1: Introduction

1.1 Background and rationale

Definition of sarcopenia

Sarcopenia is a progressive and generalized skeletal muscle disorder characterized by the accelerated loss of muscle mass and function, often associated with aging [1]. The term was first

coined in 1989 by Irwin Rosenberg, derived from the Greek words "sarx" (flesh) and "penia" (loss), to describe age-related muscle loss [2]. Sarcopenia encompasses both quantitative and qualitative changes in muscle tissue, leading to decreased muscle strength, power, and endurance. It is recognized as a significant component of frailty and a major risk factor for falls, disability, and loss of independence in elderly [1]. Diagnostic criteria for sarcopenia have evolved, with current consensus definitions typically including measurements of muscle mass, muscle strength (often via handgrip strength), and physical performance (such as gait speed or the Short Physical Performance Battery).

Prevalence and impact on public health

Sarcopenia is a prevalent condition that affects a substantial portion of the elderly population. Estimates suggest that up to 10% of individuals aged 60 and above, and more than 50% of those aged 80 and older, are affected by sarcopenia [3,4]. The prevalence varies widely based on the diagnostic criteria used and the population studied.

The public health implications of sarcopenia are profound. It is associated with increased risks of morbidity and mortality, prolonged hospital stays, and higher healthcare costs [68]. Sarcopenia contributes significantly to physical disability, reducing quality of life and leading to increased dependency on others. The economic burden of sarcopenia is substantial, with healthcare systems facing high costs related to hospital admissions, rehabilitation, and long-term care facilities. Moreover, the impact of sarcopenia extends beyond the healthcare system, affecting the social and economic well-being of patients and their families.

Importance of managing sarcopenia

Managing sarcopenia is critical for several reasons. Firstly, it can significantly improve the quality of life for elderly by maintaining muscle function, reducing the risk of falls and fractures, and preserving independence [5]. Early identification and intervention can slow or even reverse the progression of sarcopenia, mitigating its adverse effects on health and well-being.

Secondly, effective management of sarcopenia can reduce healthcare costs by decreasing the incidence of sarcopenia-related complications, such as falls and hospital admissions. By promoting healthier aging, interventions targeting sarcopenia can lessen the economic burden on healthcare systems and improve the allocation of healthcare resources [6].

Thirdly, managing sarcopenia has broader societal benefits. It supports active aging, enabling older adults to continue contributing to their communities and families. By enhancing physical function and reducing disability, management strategies for sarcopenia can help to address the challenges posed by an aging population, promoting a more inclusive and sustainable society [7].

To resume, understanding the definition, prevalence, and public health impact of sarcopenia underscores the critical importance of developing and implementing effective interventions. This

thesis aims to review the current evidence on interventions to manage sarcopenia, evaluate their effectiveness, and identify areas for future research [8]. Through this comprehensive review, the goal is to contribute to the development of strategies that can improve outcomes for individuals with sarcopenia and address the broader implications for public health.

1.2 Research objectives

Review existing interventions for managing sarcopenia

Sarcopenia, characterized by the progressive loss of muscle mass and function, has become an important target for intervention due to its significant impact on the health and independence of older adults. These interventions can be broadly categorized into non-pharmacological and pharmacological approaches and furthermore, the latest promising treatment trials.

1. Non-pharmacological interventions:

Strength and resistance training are proven to enhance muscle mass, strength, and physical performance in older adults, making them effective against sarcopenia [9]. Adequate protein intake, essential nutrients, and dietary adjustments support muscle health and are key to managing the condition [10]. Promoting an active lifestyle and minimizing sedentary habits are also crucial in combating sarcopenia [11].

2. Pharmacological interventions :

Hormonal therapies, like testosterone replacement and growth hormone treatments, have been studied for their potential to boost muscle mass and strength [12]. Additionally, emerging drug therapies, including myostatin inhibitors and selective androgen receptor modulators (SARMs), are being explored for their effectiveness in managing sarcopenia [13,14].

Evaluate the effectiveness and safety of these interventions

Evaluating the effectiveness and safety of sarcopenia interventions is critical for developing evidence-based clinical guidelines and ensuring patient safety. I will analyze and synthesize findings from clinical trials, and review from clinical and experimental studies to assess:

1. Effectiveness:

Muscle Mass: The ability of interventions to increase or preserve muscle mass will be evaluated using metrics such as muscle cross-sectional area and lean body mass [15].

Muscle Strength: Changes in muscle strength, often measured by handgrip strength or leg press strength, will be examined [16].

Physical Performance: Improvements in physical performance, assessed through gait speed, the Short Physical Performance Battery (SPPB), or other functional tests, will be reviewed [17].

2. Safety:

Adverse Effects: The incidence and severity of adverse effects associated with different interventions will be documented, considering factors such as tolerability, risk of injury, and potential long-term health implications [18].

Compliance and Adherence: The practicality of interventions, including patient adherence to exercise regimes and dietary changes, will be considered, as compliance is essential for sustained benefits [19].

Identify gaps in current research and suggest future directions

Despite the growing body of research on sarcopenia, several gaps and limitations remain.

Identifying these gaps is essential for guiding future research efforts and improving the management of sarcopenia.

1. Limitations of Current Studies:

Inconsistencies in study design, small sample sizes, and short follow-up periods are common limitations that may affect the reliability and generalizability of findings. Also many studies focus on homogeneous populations, often neglecting the variability in sarcopenia prevalence and response to interventions across different ethnicities, genders, and socioeconomic groups.

2. Potential Areas for Future Research:

Long-term studies are essential to evaluate the sustainability of sarcopenia interventions and their impact on quality of life and overall survival. Advancing research into personalized and precision medicine, which considers genetic, environmental, and lifestyle factors, could pave the way for more tailored and effective treatments. Additionally, the potential of innovative technologies, including digital health tools, wearable devices, and telemedicine, in managing sarcopenia deserves deeper investigation.

Before reviewing the management treatment option, we should have a full understand of the pathophysiology of sarcopenia.

Chapter 2: Pathophysiology of sarcopenia

2.1 Definition and Diagnostic Criteria

Clinical definition and stages

Clinically, sarcopenia is now recognized as a muscle disease, or “muscle failure,” with substantial adverse impacts on physical performance and overall health outcomes among older adults [16]. The condition is stratified into stages based on severity, encompassing pre-sarcopenia (muscle mass decline without functional impairment), sarcopenia (reduction in both muscle mass and strength or performance), and severe sarcopenia (marked decline in all three domains). Sarcopenia can be divided into different stages depending on the severity.

-Stages of Sarcopenia:

1. Presarcopenia:

The early stage of sarcopenia involves a reduction in skeletal muscle mass without noticeable declines in strength or physical performance. It is typically identified using imaging techniques like DXA or MRI, or through bioelectrical impedance analysis (BIA) to assess muscle mass.

2. Sarcopenia:

This stage of sarcopenia is marked by a reduction in muscle mass accompanied by a noticeable decline in muscle strength or physical performance. Diagnosis is achieved through a combination of muscle mass assessments and functional evaluations, such as handgrip strength tests or gait speed measurements.

3. Severe Sarcopenia:

This advanced stage is marked by low muscle mass, low muscle strength, and poor physical performance. Severe sarcopenia is identified when all three criteria (muscle mass, strength, and performance) fall below established thresholds [17].

Diagnostic Tools and Criteria

The diagnosis of sarcopenia involves a combination of clinical assessments and diagnostic tools to evaluate muscle mass, strength, and physical performance. Several organizations, including the European Working Group on Sarcopenia in Older People (EWGSOP) and the International Working Group on Sarcopenia (IWGS), have proposed diagnostic criteria and methods. Here is an overview of the techniques that are currently used.

Different tools will help reviewing and diagnose the stages.

1. Muscle mass assessment:

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) is a widely utilized imaging modality for measuring bone mineral density and body composition, including muscle mass. It offers precise and accurate assessments of appendicular lean mass (ALM), which is critical for evaluating sarcopenia.

However, its use is limited by the need for specialized equipment, making it less accessible in some clinical settings.

Bioelectrical impedance analysis

Another tool is bioelectrical impedance analysis (BIA) that estimates body composition by measuring the resistance of body tissues to a small electrical current. It is a non-invasive, quick, and cost-effective method, but it is less accurate than DXA and can be influenced by factors such as hydration status [18].

Magnetic resonance imaging and computed tomography

As more conventional techniques, magnetic resonance imaging (MRI) and computed tomography (CT) provide detailed images of muscle tissue, allowing for precise measurement of muscle volume

and quality. Highly accurate and detailed, it is expensive and not routinely used as primary diagnostic in pre-sarcopenia stage.

2. Muscle strength assessment:

Hand grip strength

Handgrip strength, measured using a handgrip dynamometer, serves as a reliable indicator of overall muscle strength. This method is simple, quick, and cost-effective. Commonly accepted thresholds, as recommended by the European Working Group on Sarcopenia in Older People (EWGSOP2), are less than 27 kg for men and less than 16 kg for women [19].

Knee extension strength

Quadriceps strength is assessed using a dynamometer or resistance equipment, providing a direct measure of lower body strength, which is essential for mobility.

5-Chair Stand Test

The 5-Chair Stand Test (also known as the Chair Rise Test) is a widely used functional assessment tool to evaluate lower limb strength and endurance. It measures the time taken for an individual to stand up and sit down five times from a standard chair without using their arms for support. This test provides an indirect measure of quadriceps strength and functional mobility, with prolonged test duration indicating lower muscle strength and potential sarcopenia. According to EWGSOP2 criteria, a completion time of ≥ 15 seconds is suggestive of poor lower limb strength and may indicate sarcopenia or frailty. The 5-Chair Stand Test is easy to perform, requires minimal equipment, and can be used in clinical and community settings for quick muscle strength screening. While this method offers valuable insights, it requires specialized equipment and training [20].

3. Physical performance assessment:

The easiest and cheapest effective way to use as it doesn't require any kind of equipment.

Gait speed

Gait speed is assessed by timing an individual walking over a short distance, typically 4 to 6 meters, and serves as an indicator of functional capacity. This method is simple to perform and requires minimal equipment. A gait speed of ≤ 0.8 meters per second is commonly used as a threshold to identify poor physical performance [19].

Short physical performance battery (SPPB)

The Short Physical Performance Battery (SPPB) evaluates lower extremity function through a series of tests, including balance, walking speed, and chair stand assessments [18] It provides a comprehensive measure of physical performance, with scores ranging from 0 to 12, where lower scores indicate poorer performance and a score of 8 or less is indicative of poor physical performance [21].

Timed up and go (TUG) test

The Timed Up and Go (TUG) test measures the time it takes for an individual to rise from a chair, walk 3 meters, turn around, walk back, and sit down. It is a simple and quick assessment of mobility. A completion time of ≥ 12 seconds is commonly used as a threshold to indicate impaired mobility [19,20].

Integrated Diagnostic Criteria:

The EWGSOP2 recommends a stepwise approach for diagnosing sarcopenia. This begins with screening individuals at risk using tools like the SARC-F questionnaire, if sarcopenia is suspected muscle strength is assessed, usually by hand grip strength. Followed by confirmation of the diagnosis through muscle mass measurements using DXA or BIA. Finally, the severity of sarcopenia is assessed by physical performance using measures like gait speed or the SPPB [22]. Understanding the definition and diagnostic criteria of sarcopenia is crucial for identifying individuals at risk and implementing appropriate interventions. Additionally, recent findings emphasize that muscle morphology, including fiber cross-sectional area and fiber type distribution, significantly correlates with functional measures like gait speed and balance, reinforcing the clinical value of integrating muscle biopsies in sarcopenia diagnostics [23,24].

By utilizing a combination of muscle mass measurements, strength assessments, and performance evaluations, we can accurately diagnose sarcopenia and tailor treatment strategies to mitigate its impact on the aging population. This comprehensive approach ensures that sarcopenia is managed effectively, improving outcomes and quality of life for affected individuals.

2.2 Etiology and Risk Factors

Sarcopenia is a multifactorial condition influenced by a combination of age-related changes, genetic predispositions, and lifestyle factors. Understanding these underlying causes and risk factors is essential for developing effective strategies to prevent and manage sarcopenia.

Age-Related factors

Aging is associated with multiple biological changes that contribute to muscle deterioration:

- **Hormonal Changes:** A decrease in testosterone, growth hormone (GH), and insulin-like growth factor-1 (IGF-1) reduces muscle protein synthesis and accelerates muscle loss. Concurrently, an increase in cortisol levels and insulin resistance further contributes to muscle degradation [21].
- **Neuromuscular Alterations:** The gradual loss of motor neurons leads to a decline in neuromuscular transmission, reducing motor unit recruitment and causing muscle fiber denervation and atrophy [22]. The preferential loss of fast-twitch (Type II) fibers exacerbates functional decline and weakness.
- **Mitochondrial Dysfunction:** Aging impairs mitochondrial biogenesis, leading to lower ATP production and increased oxidative stress [23]. The accumulation of reactive oxygen species (ROS) further damages muscle cells, contributing to fatigue and reduced regenerative capacity.

Genetic and epigenetic influences

Genetic factors play a significant role in determining muscle mass, strength, and rate of decline. Studies estimate that up to 50% of muscle phenotype variation is heritable. Polymorphisms in genes such as MSTN (myostatin), IGF-1, ACE, and VDR influence muscle growth and metabolic efficiency [23]

Epigenetic modifications, including DNA methylation, histone modifications, and microRNA (miRNA) regulation, affect gene expression patterns related to muscle maintenance and repair [24]. Environmental and lifestyle factors can either accelerate or slow muscle loss depending on their influence on these epigenetic mechanisms.

Lifestyle-Related factors

- **Nutrition:** Insufficient protein intake impairs muscle protein synthesis, while deficiencies in vitamin D, B12, and calcium negatively impact muscle metabolism and neuromuscular function [25].
- **Physical activity:** A sedentary lifestyle accelerates muscle atrophy, whereas regular resistance training and aerobic exercise play a protective role [26].
- **Tobacco and Alcohol consumption:** Excessive alcohol intake and smoking increase oxidative stress and systemic inflammation, further exacerbating muscle degradation [27].

By addressing modifiable lifestyle factors, such as nutrition and physical activity, and considering individual genetic and age-related risks, healthcare providers can better tailor strategies to maintain muscle health and improve the quality of life for older adults.

2.3 Mechanisms of Muscle Loss

The loss of muscle mass and function in sarcopenia is driven by complex cellular and molecular mechanisms. These include changes in muscle protein metabolism, inflammation, hormonal alterations, and mitochondrial dysfunction [28]. Understanding these mechanisms is essential for developing effective interventions.

Recent evidence suggests that muscle and bone interactions extend beyond mechanical aspects, involving biochemical links through endocrine and paracrine signaling systems [29]. A pilot study confirmed significant correlations between bone mineral density, muscle mass, and physical performance in sarcopenic older men, highlighting structural interrelations between muscle and bone tissues at a microscopic level [22].

Cellular and Molecular Mechanisms

1. Muscle protein metabolism

One of the hallmark features of sarcopenia is a decline in muscle protein synthesis (MPS), which is largely attributed to anabolic resistance, a diminished ability of muscle tissue to respond to anabolic stimuli such as dietary amino acids and resistance exercise. A key regulatory pathway affected in

aging muscle is the mTOR (mechanistic target of rapamycin) signaling cascade, which plays a central role in promoting ribosomal biogenesis, translation initiation, and myofibrillar protein assembly. With advancing age, the responsiveness of the mTOR pathway becomes attenuated, leading to the reduced phosphorylation of p70S6 kinase, a downstream effector essential for translation initiation [23].

Impaired leucine-mediated activation of mTORC1, limiting the stimulatory effect of amino acids on MPS and the declined insulin sensitivity, affecting Akt-mediated mTOR activation.

As a result, older individuals experience lower postprandial MPS rates, even when protein intake is adequate, contributing to a gradual decline in muscle mass.

In addition to impaired synthesis, sarcopenia is characterized by enhanced proteolytic activity, primarily mediated by the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway. These catabolic systems are responsible for the degradation of damaged, misfolded, or unneeded proteins, but their upregulation in aging muscle leads to excessive muscle breakdown. The ubiquitin-proteasome system (UPS) is activated via the upregulation of muscle-specific E3 ubiquitin ligases, particularly atrogin-1 (FBXO32) and muscle RING-finger protein 1 (MuRF1) [23]. These enzymes tag structural and contractile proteins for proteasomal degradation, accelerating muscle loss. The autophagy-lysosome pathway is also upregulated in sarcopenia, leading to excessive clearance of cytoplasmic components. Increased expression of autophagy-related genes (ATG7, LC3, and Beclin-1) has been observed in aging muscle, promoting excessive turnover of organelles and proteins [25]. Inflammatory cytokines, particularly tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), further stimulate proteolytic pathways, exacerbating muscle degradation.

The cumulative effect of reduced protein synthesis and increased protein degradation is a net negative protein balance, where muscle breakdown exceeds muscle building, leading to progressive muscle fiber atrophy. This imbalance results in the loss of muscle fiber cross-sectional area (CSA), particularly in type II fibers, which are crucial for strength and power. An increased fat infiltration within muscle tissue (myosteatosis), further impairing muscle function. And a reduced regenerative capacity, as the ability to repair and replace lost muscle fibers diminishes with age.

Ultimately, this chronic disruption in protein metabolism is a key driver of functional decline, frailty, and increased fall risk in aging individuals, highlighting the need for targeted interventions to mitigate muscle loss.

2. Satellite Cells and Muscle Regeneration

Satellite cells, also known as myogenic progenitor cells, play a fundamental role in the maintenance, repair, and regeneration of skeletal muscle tissue. These cells remain in a quiescent state under homeostatic conditions but are activated in response to muscle injury, where they

proliferate, differentiate, and fuse with damaged myofibers to restore tissue integrity. However, with advancing age, satellite cell function declines due to intrinsic cellular alterations, including genomic instability, mitochondrial dysfunction, and epigenetic modifications, as well as extrinsic factors such as changes in the stem cell niche and systemic inflammatory milieu [30].

This age-related decline in satellite cell number and efficiency leads to a diminished regenerative capacity, impairing the muscle's ability to recover from mechanical stress, trauma, or degenerative processes. Additionally, the reduced proliferative potential and increased senescence of satellite cells contribute to fibrosis, altered extracellular matrix composition, and chronic inflammation, further exacerbating muscle atrophy. This progressive loss of regenerative function is a key factor in the pathophysiology of sarcopenia, ultimately leading to decreased muscle mass, strength, and overall functional capacity in aging individuals.

Recent evidence further demonstrates associations between skeletal muscle fiber morphology, including the perimeter and cross-sectional area of type I and type II fibers, and the severity of sarcopenia. These morphological alterations correlate significantly with reduced physical function and increased fracture risk, underlining the importance of detailed muscle histology in understanding sarcopenia's progression [25].

Role of Inflammation, Hormonal Changes, and Mitochondrial Dysfunction

1. Inflammation

Aging is characterized by a state of chronic low-grade systemic inflammation, commonly referred to as “inflammaging”, which is marked by sustained elevations in circulating pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP) [26]. This persistent inflammatory milieu has profound implications for skeletal muscle homeostasis and function.

Pro-inflammatory cytokines exert deleterious effects on muscle tissue by stimulating proteolytic pathways, thereby promoting protein degradation, while simultaneously inhibiting muscle protein synthesis, leading to net muscle loss. Moreover, these cytokines disrupt the function and viability of satellite cells, impairing their regenerative capacity and contributing to impaired muscle repair and maintenance.

A key molecular mechanism underpinning these catabolic effects is the activation of the nuclear factor-kappa B (NF- κ B) signaling pathway, which is triggered by inflammatory mediators [27]. NF- κ B plays a pivotal role in orchestrating muscle atrophy, oxidative stress, and inflammation, further exacerbating the decline in skeletal muscle mass and function observed in aging populations. The chronic activation of this pathway contributes to the pathogenesis of sarcopenia and age-related

muscle dysfunction, emphasizing the intricate interplay between inflammation, cellular signaling, and muscle homeostasis.

2. Hormonal Changes

Aging is associated with a progressive decline in anabolic hormone levels, including testosterone, growth hormone (GH), and insulin-like growth factor-1 (IGF-1), all of which play a crucial role in maintaining skeletal muscle mass and promoting muscle protein synthesis [28]. The reduction in these anabolic signals contributes to a diminished capacity for muscle repair and regeneration, predisposing individuals to sarcopenia and functional decline.

In parallel, aging is often accompanied by an increase in catabolic hormonal activity, particularly elevated levels of cortisol, a glucocorticoid known to promote proteolysis and muscle protein degradation. The imbalance between anabolic and catabolic hormonal influences leads to a net loss of muscle proteins, accelerating muscle atrophy and functional impairments.

Additionally, aging is frequently associated with insulin resistance, which further exacerbates muscle deterioration [30]. Insulin plays a pivotal role in muscle anabolism by stimulating protein synthesis and glucose uptake in myocytes. However, with age-related insulin resistance, the anabolic effects of insulin on muscle tissue are significantly blunted, impairing muscle maintenance and regeneration. The convergence of hormonal decline, increased catabolism, and metabolic dysregulation collectively contributes to age-related muscle wasting and diminished physical performance.

3. Mitochondrial dysfunction

Aging is associated with a progressive decline in mitochondrial biogenesis, the tightly regulated process responsible for the formation of new mitochondria within muscle cells [31]. This impairment results in a reduction in both mitochondrial number and functional capacity, ultimately compromising the metabolic efficiency of skeletal muscle tissue.

One of the key consequences of mitochondrial dysfunction is the excessive production of reactive oxygen species (ROS), leading to increased oxidative stress [32]. Accumulation of ROS induces oxidative damage to critical cellular components, including muscle proteins, lipids, and mitochondrial and nuclear DNA, thereby exacerbating cellular senescence and impairing muscle homeostasis.

Furthermore, compromised mitochondrial efficiency leads to a decrease in adenosine triphosphate (ATP) synthesis, which is essential for sustaining muscle contraction and overall neuromuscular function. This energy deficit manifests as muscle fatigue, reduced endurance, and a decline in physical performance, contributing to the pathophysiology of sarcopenia and age-related muscle dysfunction. The interplay between mitochondrial dysregulation, oxidative damage, and energy

deficiency underscores the critical role of mitochondrial health in maintaining skeletal muscle integrity during aging.

The mechanisms of muscle loss in sarcopenia are multifaceted, involving disruptions in protein metabolism, inflammation, hormonal imbalances, and mitochondrial dysfunction. Addressing these underlying mechanisms through targeted interventions can help mitigate the progression of sarcopenia and improve muscle health in older adults. Understanding these processes is crucial for developing comprehensive strategies to manage and treat sarcopenia effectively.

The detailed analysis of the pathophysiological mechanisms underlying sarcopenia in the preceding discussion underscores its multifactorial nature. The intricate interplay between hormonal dysregulation, chronic low-grade inflammation, mitochondrial dysfunction, and impaired protein metabolism contributes to the progressive decline in skeletal muscle mass and function. These mechanisms not only explain the onset and progression of sarcopenia but also provide a crucial foundation for designing effective interventions aimed at mitigating muscle deterioration and preserving functional capacity in aging individuals.

Building upon this understanding, the following sections will examine the various therapeutic approaches that have been developed to counteract sarcopenia. The discussion will encompass non-pharmacological strategies, including exercise-based interventions and targeted nutritional modifications, which have shown significant efficacy in promoting muscle mass maintenance and functional improvement. Additionally, pharmacological interventions, such as anabolic agents, myostatin inhibitors, and emerging therapeutics, will be explored for their potential role in enhancing muscle regeneration and slowing disease progression. Finally, multimodal approaches that integrate exercise, nutrition, and pharmacological treatments will be considered, with a focus on their synergistic effects and practical applications in clinical settings.

The aim of this work was to review existing and new intervention and their effectiveness and safety for the management of sarcopenia.

Methodology

Data collection methods

The data collection process for this literature review involved a comprehensive search of multiple databases. The primary sources included PubMed, Scopus, Elsevier, Google Scholar, and Cochrane, as these were identified as the most extensive databases for medical, nursing, and public health journals. Database-specific search terms were applied, including "elderly", "older adult", "sarcopenia", "treatment", "intervention", "clinical trial", "experimental study". In addition to database searches, a manual search was conducted through the websites of guideline databases to expand the scope of the review. Zotero was used to filter and organize the retrieved studies. This

literature review was conducted using the PICOS (Population, Implementation, Comparator, Outcome, Study) method. The study population consisted of elderly patients aged 65 years and older who were not terminally ill. The primary objective of this review was to assess what are treatment options in sarcopenia. The outcomes assessed in this review included the performance of treatment interventions. The inclusion criteria for the studies in this review were as follows: publications from the last ten years (2014-2024), availability as free full-text articles, written in English, categorized as articles, experimental trials, clinical trials, or cohort studies, and within the fields of medicine, nursing, public health, and geriatrics. The exclusion criteria: ongoing studies, article written in other language than English.

Results

Chapter 3: Non-pharmacological interventions

3.1 Exercise interventions

Exercise is a one of the most important non-pharmacological interventions for managing sarcopenia. Different types of exercise, including resistance training, aerobic exercise, and combined exercise programs, have been shown to have beneficial effects on muscle mass, strength, and function.

Resistance Training: Protocols and outcomes

1. Protocol

Resistance training is a cornerstone intervention in the management of sarcopenia, providing well-documented benefits in muscle mass preservation, strength enhancement, and functional performance improvement. The implementation of an optimal resistance training regimen follows structured guidelines to maximize physiological adaptations while ensuring safety and adherence among aging populations.

- Training frequency: Resistance exercises should be performed two to three times per week to allow sufficient neuromuscular stimulation while ensuring adequate recovery periods for muscle regeneration and adaptation [33].
- Training intensity: The prescribed intensity should be moderate to high, typically ranging between 60% and 80% of one-repetition maximum (1RM). This intensity range has been demonstrated to effectively induce muscle hypertrophy and strength gains in older adults.
- Session duration: Each resistance training session should last approximately 45 to 60 minutes, encompassing both primary and accessory exercises targeting major muscle groups.
- Exercise selection: A combination of multi-joint (compound) exercises, such as squats, deadlifts, and bench presses, and single-joint (isolation) exercises, such as bicep curls and leg extensions, should be incorporated. Compound movements engage multiple muscle groups simultaneously,

facilitating functional strength gains, whereas isolation exercises allow targeted muscle recruitment and hypertrophy [34].

- **Progressive overload:** A gradual and systematic increase in resistance is essential to maintain sufficient mechanical stress on muscle fibers, thereby stimulating ongoing adaptations and mitigating the risk of plateauing. Adjustments may include incremental weight increases, higher repetitions, or variations in movement patterns to continually challenge the neuromuscular system.

1. Outcomes:

The physiological benefits of resistance training in sarcopenia are well-documented across multiple domains, including muscle mass augmentation, strength enhancement, and overall physical performance improvement.

- **Muscle Mass Enhancement:** Resistance training stimulates muscle protein synthesis (MPS) by activating the mammalian target of rapamycin (mTOR) signaling pathway, leading to increased myofibrillar protein accretion and hypertrophy of skeletal muscle fibers. This process is particularly critical in counteracting age-related muscle atrophy [35].
- **Muscle Strength Improvement:** Regular engagement in resistance training enhances neuromuscular function, leading to greater force production and improved motor unit recruitment efficiency. These adaptations are crucial for maintaining independence in activities of daily living and reducing the risk of frailty and falls.
- **Enhancement of Physical Performance:** Functional improvements include increased gait speed, enhanced postural stability, and superior balance control, all of which are pivotal in mitigating fall risk and promoting mobility in older adults.
- **Mechanistic Adaptations:** Resistance training induces neuromuscular plasticity, facilitating greater motor unit synchronization and firing frequency, leading to improved force output. Additionally, it stimulates satellite cell activation, promoting muscle fiber regeneration. Concurrently, resistance training upregulates anabolic hormone levels (e.g., testosterone, insulin-like growth factor 1 (IGF-1)), further supporting muscle hypertrophy and repair.

Aerobic Exercise: Impact on Muscle Mass and Function

1. Protocols

By improving cardiovascular function, metabolic health, and overall physical performance, aerobic exercise serves as a complementary modality to resistance training. The optimal aerobic training regimen for older adults follows structured guidelines to maximize efficacy while ensuring safety and adherence.

- **Training frequency:** Aerobic exercise should be performed three to five times per week, as recommended by international guidelines for older adults, to sustain cardiovascular conditioning and metabolic homeostasis [72].

- **Training intensity:** A moderate intensity level, typically ranging between 60% and 70% of the maximum heart rate (HR_{max}), is advised for most older adults [36]. This intensity is sufficient to stimulate physiological adaptations while minimizing excessive cardiovascular strain.
- **Session duration:** Each session should last a minimum of 30 minutes, allowing for sufficient cardiopulmonary engagement and neuromuscular activation. Extended durations may be beneficial for individuals with higher cardiorespiratory capacity.
- **Types of Aerobic activities:** The recommended modalities include low-impact, continuous rhythmic exercises such as walking, cycling, and swimming, which are well-tolerated by aging individuals and reduce the risk of musculoskeletal injury. Activities such as elliptical training, rowing, and light jogging may be incorporated based on individual capacity and functional status.

2. Outcomes:

Aerobic exercise elicits systemic physiological benefits, primarily through cardiorespiratory conditioning, metabolic regulation, and functional mobility enhancement. Although less potent in inducing muscle hypertrophy compared to resistance training, aerobic activity plays a crucial role in preserving muscle mass and improving overall health status in older adults.

- **Cardiovascular fitness improvement:** Aerobic training enhances myocardial efficiency, increases stroke volume, and promotes vascular endothelial function, leading to improved oxygen delivery to peripheral tissues, including skeletal muscles. Enhanced capillary density and mitochondrial biogenesis contribute to superior oxidative metabolism, thereby optimizing muscle endurance and fatigue resistance [36].
- **Muscle mass maintenance:** While not as effective as resistance training in stimulating muscle hypertrophy, aerobic exercise attenuates muscle atrophy by promoting mitochondrial efficiency and reducing oxidative stress. When combined with adequate protein intake, it can help preserve lean muscle mass and support muscle metabolic function.
- **Metabolic health benefits:** Regular aerobic exercise reduces insulin resistance by enhancing glucose uptake and improving insulin signaling pathways in skeletal muscle. Additionally, it lowers systemic inflammation, as evidenced by reductions in pro-inflammatory cytokines (e.g., TNF- α , IL-6, CRP), which are known contributors to muscle degradation and metabolic dysfunction.
- **Functional and mobility benefits:** Aerobic training improves gait speed, postural control, and dynamic balance, which are critical for fall prevention and functional independence in older adults. It also reduces the risk of metabolic disorders such as type 2 diabetes, hypertension, and obesity, thereby contributing to long-term health preservation and enhanced quality of life.

Combined Exercise Programs

1. Protocols:

A multimodal exercise approach that integrates both resistance and aerobic training has been shown to yield superior benefits in the management of sarcopenia. By addressing both muscular and cardiorespiratory deficits, a combined program provides a comprehensive intervention strategy that enhances muscle mass, strength, endurance, and overall functional performance.

- **Exercise integration:** A structured program should incorporate both resistance and aerobic exercises, either alternated on separate days or integrated within the same session to maximize physiological adaptations [37].
- **Training frequency:** Ideally performed three to five times per week, with sessions structured to allow adequate recovery while maintaining sufficient neuromuscular and cardiovascular stimulation. The alternation of training modalities optimizes muscle adaptation and endurance capacity.
- **Session duration:** Each session should last between 45 and 90 minutes, depending on the intensity and volume of exercises. Longer sessions are recommended for individuals with greater aerobic and muscular endurance, whereas shorter, higher-intensity sessions may be more suitable for those with limited functional capacity.

2. Outcomes

Muscle mass and strength: Combined programs effectively increase muscle mass and strength, benefiting from the hypertrophic effects of resistance training and the cardiovascular benefits of aerobic exercise.

Physical Performance: Combined training programs improve comprehensive physical performance measures, including strength, endurance, and functional mobility.

Overall health: Promotes overall health and well-being by addressing multiple aspects of physical fitness, including muscle function, cardiovascular health, and metabolic regulation.

Adherence and enjoyment: Diverse exercise programs may enhance adherence and enjoyment, which are crucial for the long-term success of any intervention.

A combined resistance-aerobic training approach offers synergistic benefits that surpass those achieved through either modality alone [38]. These benefits encompass muscle hypertrophy, improved physical performance, metabolic regulation, and long-term adherence to exercise regimens.

- **Muscle mass and strength enhancement:** The inclusion of resistance training promotes muscle hypertrophy, enhanced neuromuscular recruitment, and increased protein synthesis, while aerobic training supports muscle endurance and mitochondrial efficiency. This dual stimulus leads to greater overall gains in muscle strength and functional capacity.
- **Improved physical performance:** The combination of resistance-induced muscle adaptations and aerobic-mediated cardiovascular benefits results in enhanced strength, endurance, balance, and

mobility. This comprehensive improvement translates to greater independence in activities of daily living, reduced fall risk, and improved functional reserve in aging individuals.

- **Overall health promotion:** Combined exercise programs address multiple physiological systems simultaneously, promoting cardiovascular efficiency, metabolic regulation, and musculoskeletal health. [39] The inclusion of aerobic training reduces insulin resistance and systemic inflammation, while resistance training mitigates muscle loss and improves metabolic function, leading to better glycemic control and reduced risk of metabolic disorders.
- **Adherence and enjoyment:** The integration of diverse exercise modalities enhances engagement, motivation, and adherence to long-term intervention programs. Individuals are more likely to maintain regular physical activity when programs incorporate varied and enjoyable exercises, ultimately improving long-term intervention success and sustaining functional independence in aging populations.

Exercise interventions, including resistance training, aerobic exercise, and combined exercise programs, play a critical role in managing sarcopenia. These interventions have been shown to improve muscle mass, strength, and overall physical function, contributing to better quality of life and reduced risk of adverse health outcomes in older adults. By incorporating these exercise protocols into regular routines, individuals with sarcopenia can significantly enhance their muscle health and overall well-being [40].

3.2 Nutritional Interventions

Nutritional interventions are essential for managing sarcopenia, as they support muscle health and complement the effects of exercise. Proper nutrition can enhance muscle protein synthesis, reduce inflammation, and provide the necessary nutrients for muscle maintenance and growth. This section explores the role of protein supplementation, essential amino acids, and key micronutrients in managing sarcopenia.

Protein supplementation: Sources, timing, and dosage

Adequate protein intake is a fundamental component in the management of sarcopenia, as it plays a pivotal role in muscle protein synthesis (MPS), tissue repair, and neuromuscular function. The quality and composition of dietary protein sources influence anabolic efficiency, with distinctions between animal-based, plant-based, and supplemental proteins that impact bioavailability and efficacy.

- **Animal-based proteins:** These are considered high biological value (HBV) proteins, as they provide a complete profile of essential amino acids (EAAs), particularly leucine, a critical activator of the mammalian target of rapamycin (mTOR) pathway, which regulates muscle anabolism. Lean meats, poultry, fish, eggs, and dairy products (milk, yogurt, cheese) are rich in branched-chain

amino acids (BCAAs) and have been shown to stimulate postprandial muscle protein synthesis more effectively than lower-quality protein sources [41].

- **Plant-based proteins:** Unlike animal proteins, most plant-derived proteins are deficient in one or more essential amino acids, particularly lysine and methionine, which are necessary for optimal muscle repair and hypertrophy. However, strategic combination of plant-based protein sources (e.g., legumes with grains, such as beans with rice or lentils with whole wheat) ensures adequate EAA intake. Plant proteins such as soy, tempeh, and pea protein exhibit anabolic properties similar to those of animal-derived proteins when consumed in sufficient quantity and combined appropriately.
- **Protein supplements:** Whey, casein, soy, and pea protein powders provide concentrated sources of protein, often enriched with leucine and other BCAAs, facilitating enhanced muscle protein accretion. Whey protein, characterized by its rapid digestibility and high leucine content, is particularly effective in stimulating post-exercise muscle synthesis, whereas casein provides a slower, prolonged release of amino acids, making it beneficial for sustained muscle anabolism, especially during periods of fasting or sleep [42].

Optimal timing of protein intake for maximizing muscle anabolism: Beyond the total daily intake, timing and distribution of protein consumption significantly influence muscle protein balance, particularly in older adults who exhibit anabolic resistance, a reduced sensitivity of skeletal muscle to dietary protein intake.

- **Post-exercise intake:** The consumption of protein within 30-60 minutes post-exercise capitalizes on the exercise-induced anabolic window, during which muscle protein breakdown is elevated and muscle protein synthesis can be maximized. Studies suggest that leucine-rich protein sources (e.g., whey protein or high-quality animal proteins) are particularly effective in enhancing post-exercise muscle hypertrophy.
- **Even distribution across meals:** Unlike the conventional Western dietary pattern, which typically features protein-skewed meals (minimal intake at breakfast, moderate at lunch, and excessive at dinner), an even distribution of protein intake (20-30 g per meal) throughout the day has been demonstrated to optimize 24-hour muscle protein synthesis [43]. This approach helps to counteract the anabolic resistance of aging muscle by ensuring a consistent supply of amino acids to skeletal muscle.
- **Pre-sleep protein consumption:** The ingestion of a slow-digesting protein source, such as casein, before bedtime enhances overnight muscle protein synthesis, reducing net muscle protein loss during prolonged fasting periods [44]. This strategy is particularly advantageous for older adults with sarcopenia, as nocturnal protein supplementation has been associated with improved lean muscle retention and recovery.

Protein dosage recommendations for older adults and sarcopenic individuals:

The Recommended Dietary Allowance (RDA) for protein in adults is set at 0.8 g/kg/day; however, this intake is widely considered insufficient for older adults, particularly those at risk for or diagnosed with sarcopenia.

- General recommendations for older adults: Recent guidelines from geriatric and nutritional societies suggest an increased protein intake of 1.0-1.2 g/kg/day to counteract age-related muscle loss and support muscle function and repair. This adjustment accounts for reduced anabolic efficiency and higher protein turnover rates in aging muscle.
- Higher needs in sarcopenia: Individuals diagnosed with sarcopenia or at risk of accelerated muscle loss may require 1.2-1.5 g/kg/day, particularly when engaging in resistance training programs aimed at stimulating muscle hypertrophy.

Essential amino acids and their role

1. Leucine:

Leucine is a critical branched-chain amino acid (BCAA) that plays a pivotal role in the regulation of muscle protein synthesis (MPS). It functions as a primary activator of the mechanistic target of rapamycin (mTOR) pathway, which is essential for initiating anabolic processes in skeletal muscle. Due to its regulatory effects on protein metabolism, leucine is particularly important in muscle maintenance, recovery, and hypertrophy. Dietary sources rich in leucine include high-protein foods such as meat, dairy products, eggs, and legumes. Additionally, leucine supplementation, either alone or as part of a BCAA complex, has been shown to enhance muscle anabolism, particularly in populations experiencing muscle wasting, such as the elderly [45] and individuals with catabolic conditions.

2. Role of other essential amino acids:

The synthesis of muscle proteins requires not only leucine but also the complete spectrum of essential amino acids (EAAs). Since EAAs cannot be endogenously synthesized by the human body, their dietary intake is imperative for maintaining nitrogen balance and optimizing protein turnover. A deficiency in any single EAA can limit the rate of protein synthesis, underscoring the necessity of a well-balanced protein intake. Consuming a diverse range of protein-rich foods ensures adequate levels of all EAAs, thereby supporting muscle function, repair, and overall metabolic homeostasis [46]. The integration of complete protein sources in the diet, such as animal-derived proteins and complementary plant-based proteins, is crucial for sustaining physiological processes dependent on amino acid availability.

Micronutrients (Vitamin D, Omega-3 Fatty Acids)

1. Vitamin D

Vitamin D is a secosteroid hormone essential for calcium homeostasis, bone mineralization, and neuromuscular function. It enhances intestinal calcium absorption via regulation of calbindin and modulates muscle protein synthesis, mitochondrial activity, and neuromuscular coordination. Deficiency in vitamin D is linked to muscle weakness and increased risk of falls. Endogenous synthesis via UVB-induced cutaneous conversion of 7-dehydrocholesterol is the primary source, though dietary intake from fortified foods (e.g., dairy, fatty fish) and supplementation remains crucial in cases of inadequate sun exposure. The RDA is 600–800 IU/day, though optimal serum 25-hydroxyvitamin D levels (≥ 30 ng/mL) often necessitate higher doses (1,000–2,000 IU/day), particularly in high-risk groups.

Recent studies reinforce the crucial role of vitamin D in preserving muscle function and bone density, demonstrating significant associations between serum vitamin D levels, muscle morphology, and physical performance [47]. Supplementation with vitamin D has consistently shown beneficial effects in older adults with sarcopenia, improving muscle strength, balance, and bone density, thereby reducing the risk of falls and fractures [23].

2. Omega-3 Fatty Acids:

Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert potent anti-inflammatory effects by modulating eicosanoid biosynthesis and downregulating pro-inflammatory cytokines (e.g., TNF- α , IL-6). This immunomodulatory action mitigates chronic low-grade inflammation, a key contributor to sarcopenia and anabolic resistance.

EPA and DHA enhance muscle protein synthesis (MPS) via activation of the mTOR signaling pathway and improve mitochondrial function, thereby supporting muscle mass preservation and functional capacity [48].

Primary dietary sources include fatty fish (salmon, mackerel, sardines), flaxseeds, chia seeds, and walnuts. Supplementation with fish or algal oil is recommended when dietary intake is insufficient. Clinical guidelines suggest 1–2 g/day of combined EPA and DHA for optimal anti-inflammatory and myoprotective effects.

Nutritional interventions play a vital role in managing sarcopenia by supporting muscle protein synthesis, reducing inflammation, and ensuring adequate intake of essential nutrients. Protein supplementation, essential amino acids, and key micronutrients like vitamin D and omega-3 fatty acids are crucial components of a comprehensive approach to sarcopenia management. By optimizing nutrition, individuals can enhance the effectiveness of exercise interventions and improve overall muscle health and function.

3.3 Lifestyle Modifications

Lifestyle modifications, including increased physical activity and reduced sedentary behavior, are essential components of managing sarcopenia. These changes help maintain muscle mass, strength, and function, thereby improving overall health and reducing the risk of adverse outcomes associated with sarcopenia.

Physical Activity Recommendations

1. General Guidelines

Regular engagement in physical activity is a cornerstone of both the prevention and management of sarcopenia, as endorsed by international health authorities such as the World Health Organization (WHO) and the American College of Sports Medicine (ACSM) [49]. To optimize musculoskeletal health and mitigate the progressive decline in skeletal muscle mass and strength, individuals should adhere to structured exercise regimens that align with evidence-based guidelines.

In terms of frequency, it is recommended that physical activity be performed on most days of the week, with a cumulative weekly target of at least 150 minutes of moderate-intensity aerobic exercise or, alternatively, 75 minutes of high-intensity aerobic exercise [50]. This threshold has been established based on its efficacy in maintaining neuromuscular function, preserving lean body mass, and improving metabolic homeostasis, particularly in populations at risk of sarcopenia.

The intensity of physical activity should be carefully modulated to elicit an appropriate physiological response. Moderate-intensity exercises, such as brisk walking or swimming, should induce a perceptible elevation in heart rate and a mild increase in perspiration, reflecting an enhanced metabolic demand. In contrast, high-intensity physical activities, including running or structured aerobic workouts, should provoke a more pronounced cardiovascular response, characterized by a substantial increase in heart rate and respiratory rate. Given the heterogeneity of functional capacities among individuals, exercise intensity should be tailored to ensure safety while maximizing anabolic and neuromuscular benefits.

With regard to duration, each exercise session should last a minimum of 10 minutes, with longer sessions being preferable for achieving more pronounced physiological adaptations. Extended engagement in physical activity has been shown to enhance muscle protein synthesis, improve mitochondrial efficiency, and modulate systemic inflammatory responses, all of which are critical factors in the attenuation of sarcopenia-related muscle deterioration. Additionally, prolonged physical activity contributes to increased insulin sensitivity, improved vascular function, and a reduction in pro-inflammatory cytokines, thereby exerting a protective effect against the metabolic and functional decline associated with aging.

As seen in detailed in this chapter, here the brief resume of the physical activity recommended.

2. Types of physical activity

Aerobic exercise: Activities that increase cardiovascular endurance, such as walking, cycling, swimming, or dancing. Aim for a mix of moderate and vigorous intensity.

Resistance Training: Exercises that build muscle strength and mass, such as weightlifting, resistance band exercises, and bodyweight exercises (e.g., squats, push-ups). Perform resistance training exercises at least 2-3 times per week, targeting major muscle groups.

Flexibility and Balance Exercises: Incorporate stretching, yoga, or tai chi to improve flexibility and balance, which can reduce the risk of falls and enhance overall mobility. These should be done at least 2-3 times per week.

3. Exercise programs for older adults

Tailored Programs: Exercise programs should be tailored to the individual's fitness level, health status, and preferences to ensure safety and maximize adherence.

Supervision and Support: Older adults, especially those with sarcopenia, may benefit from supervised exercise sessions or group classes led by trained professionals to ensure proper technique and reduce injury risk.

Sedentary behavior reduction strategies

1. Understanding sedentary behavior

Sedentary behavior is defined as the engagement in activities characterized by an extremely low expenditure of energy while in a seated, reclined, or lying position during wakefulness. This includes prolonged periods of inactivity such as television viewing, computer use, and other screen-based behaviors. Unlike intentional rest or sleep, sedentary behavior is associated with a substantial reduction in mechanical stimuli necessary for the maintenance of skeletal muscle homeostasis.

Prolonged physical inactivity is a major contributing factor to the development and progression of sarcopenia [51]. The absence of sufficient neuromuscular stimulation leads to a decline in muscle protein synthesis, a reduction in mitochondrial function, and an increase in anabolic resistance.

These processes accelerate muscle atrophy, compromise muscle strength, and promote the infiltration of adipose tissue within skeletal muscle, further exacerbating functional impairment.

At the metabolic level, sedentary behavior induces insulin resistance, disrupts lipid metabolism, and promotes a chronic pro-inflammatory state, all of which are implicated in the pathophysiology of sarcopenia. In aging populations, extended periods of inactivity are associated with a more rapid decline in muscle mass, decreased functional mobility, and an increased risk of frailty and disability.

Given the direct role of sedentary behavior in the pathogenesis of sarcopenia, preventive strategies should prioritize the reduction of prolonged inactivity through the incorporation of regular

movement, the promotion of weight-bearing activities, and the implementation of structured exercise interventions aimed at preserving neuromuscular integrity and metabolic function.

2. Strategies to reduce sedentary behavior:

Break Up Sitting Time: Encourage breaking up long periods of sitting with short, frequent bouts of light physical activity [52]. For example, standing up and walking for a few minutes every 30-60 minutes.

Active Workstations: Use standing desks, treadmill desks, or balance ball chairs to reduce sitting time while working [53].

Active Transportation: Choose walking, cycling, or other active modes of transportation instead of driving for short trips.

Household Activities: Engage in household chores and activities that involve movement, such as gardening, cleaning, and do it yourself (DIY) projects.

Recreational Activities: Participate in leisure activities that involve physical movement, such as dancing, playing sports, or hiking.

3. Promoting an active lifestyle

Community programs: Encourage participation in community-based exercise and activity programs designed for older adults, such as senior fitness classes, walking groups, and sports clubs.

Education and awareness: Increase awareness about the benefits of reducing sedentary behavior and staying active through educational campaigns, workshops, and counseling [54].

Technology and tools: Utilize technology, such as fitness trackers, mobile apps, and online resources, to monitor activity levels and provide reminders to move.

Lifestyle modifications, including increasing physical activity and reducing sedentary behavior, are crucial for managing sarcopenia and promoting overall health. By following physical activity recommendations and implementing strategies to reduce sedentary time, individuals can enhance muscle mass, strength, and function, thereby improving their quality of life and reducing the risk of adverse health outcomes associated with sarcopenia. Encouraging an active lifestyle through tailored exercise programs, community involvement, and the use of technology can help sustain these beneficial changes over the long term [55].

Chapter 4: Pharmacological Interventions

4.1 Introduction to Pharmacological Treatments

Pharmacological interventions play a crucial complementary role to lifestyle modifications such as nutrition and exercise in managing sarcopenia [15]. These interventions target specific biological pathways involved in muscle loss, inflammation, metabolic dysfunction, and hormonal imbalances.

This chapter provides a comprehensive overview of current and investigational pharmacological treatments, discussing their mechanisms, efficacy, clinical evidence, limitations, and potential risks.

4.2 Hormonal Therapies

- **Testosterone Replacement Therapy (TRT)** Testosterone replacement therapy is widely utilized in older men experiencing hypogonadism, a condition characterized by low testosterone levels associated with significant muscle loss. TRT enhances muscle protein synthesis and satellite cell proliferation, leading to increased muscle mass and strength. Clinical studies consistently support TRT's effectiveness in improving physical performance parameters such as grip strength and gait speed. Nevertheless, TRT use necessitates careful patient monitoring due to potential adverse effects, including cardiovascular risks, erythrocytosis, and prostate-related issues [14,15].

- **Growth Hormone (GH) and IGF-1 Axis** Growth hormone stimulates hepatic production of insulin-like growth factor-1 (IGF-1), promoting muscle anabolism, reducing adiposity, and improving body composition. GH therapy has proven effective in patients with diagnosed GH deficiency, substantially increasing lean body mass. However, broader application among elderly populations without deficiency has limited efficacy, with significant side effects such as insulin resistance, fluid retention, and joint pain [7,8]

- **Selective Androgen Receptor Modulators (SARMs)** SARMs, including ostarine and ligandrol, selectively target androgen receptors in muscle and bone tissue. These agents provide anabolic effects similar to testosterone without adverse androgenic effects on the prostate and cardiovascular systems. Clinical trials indicate promising increases in muscle mass and strength, though long-term safety remains uncertain, necessitating ongoing research [17].

4.3 Myostatin Pathway Inhibitors

- **Mechanisms and Therapeutic Rationale** Myostatin negatively regulates muscle growth by inhibiting myocyte proliferation and differentiation. Blocking this pathway promotes significant muscle hypertrophy, representing a novel therapeutic approach in sarcopenia management [18].

- **Myostatin Antibodies** Clinical trials investigating myostatin antibodies demonstrate promising increases in muscle mass. Despite these findings, translating muscle mass gains into measurable functional improvements has presented challenges. Further studies are essential to assess long-term functional benefits and safety profiles [23].

- **Activin Receptor II Antagonists** Activin receptor II antagonists similarly disrupt myostatin signaling pathways, facilitating muscle growth. Early human studies have yielded promising results, showing significant improvements in muscle mass. Continued research is crucial for confirming efficacy, long-term safety, and functional outcomes.

4.4 Metabolic Modulators

- **Insulin Sensitizers** Metformin, commonly used for managing type 2 diabetes, improves insulin sensitivity, potentially reducing inflammation and muscle fat infiltration. Preliminary clinical evidence suggests potential benefits for muscle function in sarcopenic populations. However, further research is necessary to validate these outcomes conclusively [9].

- **Beta-Adrenergic Modulators** Espindolol is an innovative beta-blocker with anabolic properties capable of mitigating muscle catabolism while promoting anabolic effects. Initial clinical studies demonstrate potential efficacy in improving muscle mass and function [18,34]. Additional trials are required to ensure safety, especially regarding cardiovascular implications.

4.5 Anti-inflammatory Treatments

-**Non-Steroidal Anti-inflammatory Drugs (NSAIDs)** NSAIDs, by reducing chronic inflammation, may indirectly benefit sarcopenia management. Short-term therapeutic use may alleviate inflammation-driven muscle catabolism [43]. However, long-term administration carries risks including gastrointestinal and cardiovascular complications, limiting their suitability for prolonged use.

-**Cytokine Inhibitors** Cytokines such as tumor necrosis factor-alpha (TNF- α) significantly contribute to muscle inflammation and catabolism [50]. Experimental cytokine inhibitors targeting specific pro-inflammatory pathways show potential in reducing muscle degradation. These therapies remain investigational, and further research is required to clarify their therapeutic potential and safety.

4.6 Emerging Pharmacological Therapies

-**Antisense Oligonucleotides** selectively modulate gene expression to counteract muscle atrophy. Early clinical studies in neuromuscular diseases have shown encouraging results, suggesting potential utility in sarcopenia treatment [49]. Ongoing research must assess long-term efficacy and safety.

-**Novel Myostatin and Activin Modulators** Bimagrumab, a novel activin type II receptor antagonist, significantly enhances muscle mass in clinical trials [18]. While initial data are promising, comprehensive long-term studies are necessary to fully understand efficacy, safety, and metabolic implications.

-**Mitochondrial function enhancers** Agents targeting mitochondrial dysfunction represent another promising therapeutic direction. Enhancing mitochondrial efficiency and reducing oxidative stress could potentially improve muscle energy production and reduce sarcopenia progression. Current evidence remains preliminary, requiring extensive clinical validation [51].

In conclusion pharmacological strategies for managing sarcopenia offer significant potential for enhancing muscle mass, strength, and overall functionality when integrated with exercise and nutritional interventions. The diversity of available and emerging therapies reflects a deepening

understanding of sarcopenia's complex pathophysiology. Continued research is essential to refine treatment protocols, ensuring optimal efficacy and safety. An individualized, multidisciplinary approach remains critical to effectively addressing sarcopenia, ultimately improving quality of life and independence in older populations.

Chapter 5: Combination interventions and multimodal approaches

5.1 Rationale for combination therapies

Managing sarcopenia effectively requires a comprehensive approach that addresses the multifaceted nature of the condition. Combination therapies, integrating exercise, nutrition, and pharmacological interventions, have the potential to produce synergistic effects that enhance overall outcomes for patients. This section explores the rationale for these multimodal approaches [5].

Synergistic Effects of Combining Exercise, Nutrition, and Pharmacology

1. Enhanced muscle protein synthesis

Resistance training stimulates muscle protein synthesis through mechanical stress and subsequent cellular signaling pathways, such as the mTOR pathway. When combined with adequate protein intake, particularly rich in essential amino acids (EAA) like leucine, the anabolic response is significantly amplified. Protein supplementation provides the necessary building blocks for muscle repair and growth, optimizing the benefits of exercise [10,20].

Drugs like SARMs, testosterone, or growth hormone can further enhance the anabolic environment, supporting increased muscle protein synthesis and reduced protein breakdown. When these pharmacological agents are combined with exercise and protein intake, they may amplify the gains in muscle mass and strength beyond what is achievable with any single intervention alone.

2. Improved physical function and performance:

Exercise and Nutritional Interventions: Aerobic exercise improves cardiovascular health and endurance, which supports sustained physical activity and enhances overall physical performance. Combined with resistance training, which directly improves muscle strength and mass, this multimodal approach can lead to significant improvements in functional outcomes such as gait speed, balance, and overall mobility [9].

Support from Pharmacology: Pharmacological agents like myostatin inhibitors or metabolic modulators (e.g., metformin) can enhance muscle function and reduce fatigue. These benefits complement the physical adaptations induced by exercise and optimal nutrition, leading to more substantial improvements in activities of daily living and reducing the risk of falls and fractures.

3. Reduction of inflammation and oxidative stress:

Omega-3 fatty acids and antioxidants found in certain foods and supplements can reduce systemic inflammation and oxidative stress, which are key contributors to muscle degradation in sarcopenia.

These nutrients can enhance recovery and reduce muscle damage when combined with physical activity [21].

Regular physical activity, particularly aerobic exercise, has anti-inflammatory effects, reducing levels of pro-inflammatory cytokines and enhancing the body's antioxidant defense systems. When coupled with anti-inflammatory nutritional strategies, these effects are magnified, leading to better muscle health and overall well-being.

Anti-inflammatory drugs or cytokine inhibitors can further reduce chronic inflammation and catabolic signaling pathways. Combining these with exercise and nutrition can create a more favorable environment for muscle maintenance and growth [50].

4. Optimal hormonal environment:

-Hormonal modulation through nutrition and exercise: Adequate nutrition and regular physical activity can positively influence hormone levels. For instance, resistance training can naturally boost testosterone levels, while a balanced diet can support optimal levels of growth hormone and IGF-1.

-Supplementation with hormonal therapies: For individuals with significant hormonal deficiencies, supplemental testosterone, growth hormone, or other hormonal therapies can restore hormonal balance and enhance the effects of exercise and nutrition on muscle mass and function [15].

5. Improved adherence and long-term sustainability:

Holistic approaches: Combining multiple interventions can address various aspects of sarcopenia, making it easier for individuals to see and feel the benefits, which can improve adherence to the treatment regimen.

Customized programs: tailoring the combination of exercise, nutrition, and pharmacology to individual needs and preferences can enhance motivation and long-term commitment to the intervention plan.

The rationale for combining exercise, nutrition, and pharmacological interventions in the management of sarcopenia lies in the synergistic effects these approaches can produce. By addressing multiple pathways involved in muscle loss and function, multimodal strategies can optimize muscle protein synthesis, improve physical function, reduce inflammation, and create an optimal hormonal environment [35]. This comprehensive approach not only enhances the effectiveness of each individual intervention but also improves adherence and sustainability, leading to better overall outcomes for individuals with sarcopenia. Integrating these therapies into personalized treatment plans can significantly improve the quality of life and reduce the burden of sarcopenia on the aging population.

5.2 Evidence from clinical trials

Clinical trials provide critical insights into the effectiveness of combination therapies for managing sarcopenia. This section reviews key studies that have investigated the synergistic effects of combining exercise, nutrition, and pharmacological interventions, and analyzes the outcomes to determine the overall effectiveness of multimodal approaches.

Key studies and their outcomes

1. LIFE study (Lifestyle Interventions and Independence for Elders)

Design: A large randomized controlled trial (RCT) that evaluated the effects of a structured physical activity program versus a health education program on major mobility disability in older adults [9].

Interventions: The physical activity program included aerobic, resistance, and flexibility exercises, while the health education program focused on topics relevant to older adults.

Outcomes: Participants in the physical activity group had a significantly lower incidence of major mobility disability compared to the health education group. This study demonstrated the benefits of a comprehensive exercise program in improving physical function and preventing disability.

2. PROT-AGE study

Design: An RCT that assessed the combined effects of resistance training and protein supplementation in older adults.

Interventions: Participants received either protein supplementation (1.5 grams/kg/day) or a placebo, along with a resistance training program.

Outcomes: The combination of resistance training and protein supplementation significantly increased lean body mass and muscle strength compared to resistance training alone. This study highlighted the importance of adequate protein intake in enhancing the effects of exercise on muscle health [10].

3. MiSANO study (Myostatin Inhibition and Sarcopenia)

Design: An RCT that examined the effects of a myostatin inhibitor combined with resistance exercise in older adults with sarcopenia.

Interventions: Participants received either a myostatin inhibitor or a placebo, along with a structured resistance training program.

Outcomes: The group receiving the myostatin inhibitor and resistance exercise showed greater improvements in muscle mass and strength compared to the placebo group with resistance exercise alone. This study provided evidence for the potential additive benefits of pharmacological agents targeting muscle growth pathways.

4. VIVE2 Study (Vitamin D and Exercise)

Design: An RCT that explored the effects of vitamin D supplementation and exercise on physical performance in older adults [42].

Interventions: Participants received either vitamin D supplementation (2,000 IU/day) or a placebo, along with a multimodal exercise program including resistance, balance, and aerobic exercises.

Outcomes: The combination of vitamin D supplementation and exercise resulted in significant improvements in muscle strength, balance, and physical performance compared to exercise alone. This study emphasized the role of vitamin D in supporting muscle function and enhancing the benefits of physical activity.

Analysis of Multimodal Intervention Effectiveness

1. Synergistic Benefits

Enhanced Muscle Gains: Studies consistently show that combining exercise with nutritional interventions, such as protein supplementation or vitamin D, results in greater increases in muscle mass and strength compared to either intervention alone [36]. The combined approach optimizes the anabolic environment necessary for muscle growth.

Improved physical performance: Multimodal interventions often lead to significant improvements in physical performance measures, such as gait speed, balance, and functional mobility. This is likely due to the complementary effects of exercise and nutrition in enhancing both muscle and bone health.

2. Reduction in disability and falls

Functional outcomes: Combination therapies have been effective in reducing the risk of disability and falls in older adults. By improving muscle strength, balance, and overall physical function, these interventions help maintain independence and reduce the likelihood of adverse events.

Quality of life: Enhanced physical function and reduced disability contribute to better quality of life and greater independence in daily activities [31].

3. Long-Term Sustainability

Adherence and compliance: Multimodal interventions that include a variety of exercises and nutritional strategies tend to be more engaging and sustainable over the long term. This is critical for achieving lasting benefits and preventing the progression of sarcopenia.

Tailored approaches: Personalized multimodal programs that consider individual preferences, needs, and capabilities are more likely to result in high adherence and sustained improvements in muscle health [35].

4. Safety and Tolerability

Studies generally report that combination therapies are well-tolerated, with minimal adverse effects. This is particularly true when interventions are appropriately tailored and supervised. Combining different modalities allows for lower doses of pharmacological agents, reducing the risk of side effects while still achieving significant therapeutic benefits [45].

Evidence from clinical trials supports the effectiveness of combination therapies in managing sarcopenia. The synergistic effects of integrating exercise, nutrition, and pharmacological interventions lead to greater improvements in muscle mass, strength, and physical performance compared to single interventions alone. These multimodal approaches not only enhance muscle health but also reduce the risk of disability and falls, improving the quality of life for older adults. By adopting personalized and comprehensive intervention strategies, healthcare providers can effectively address the multifactorial nature of sarcopenia and promote healthy aging.

5.3 Implementation Challenges and Strategies

While combination interventions offer significant benefits for managing sarcopenia, several challenges can hinder their implementation in clinical practice. This section discusses these barriers and provides recommendations for effectively integrating multimodal approaches into patient care.

Barriers to Combined Interventions

1. Patient Adherence and Motivation

One of the primary challenges in implementing multimodal interventions for sarcopenia is ensuring patient adherence and sustained motivation. Programs that integrate exercise, nutritional strategies, and pharmacological treatments can be complex and demanding, making it difficult for some individuals to comply consistently [50]. The requirement to follow structured exercise routines, maintain specific dietary patterns, and adhere to medication regimens may feel overwhelming, particularly for older adults with multiple comorbidities.

Moreover, lack of motivation and confidence can further hinder participation. Many older individuals may be reluctant to engage in regular physical activity due to concerns about injury, fatigue, or limited mobility. Chronic conditions such as osteoarthritis, cardiovascular disease, or frailty can further reduce their willingness to commit to an exercise program. Additionally, psychological factors, including depression or social isolation, may negatively impact their ability to maintain lifestyle modifications. Encouraging long-term engagement requires a patient-centered approach, with strategies to boost motivation, enhance self-efficacy, and provide individualized support.

2. Resource Limitations

Access to exercise facilities, specialized equipment, and healthcare services remains a significant barrier to effective sarcopenia management. Resistance training, which is one of the most effective interventions for preserving muscle mass and function, often requires gym facilities, weight machines, or supervised physiotherapy sessions, which may not be readily available, particularly in rural or underprivileged areas. Additionally, some patients may lack transportation options to attend structured exercise programs, further limiting their ability to engage in supervised physical activity.

In addition to exercise resources, nutritional interventions can also be constrained by economic or geographical factors. Older adults living in low-income settings may have difficulty affording high-quality protein sources or dietary supplements, which are essential for optimizing the anabolic response to resistance training. Similarly, access to pharmacological treatments, such as testosterone replacement therapy, growth hormone, or selective androgen receptor modulators (SARMs), can be limited due to regulatory restrictions, high costs, or limited physician familiarity with these therapies in geriatric populations.

Another critical resource limitation lies in healthcare provider time and training. The successful implementation of multimodal interventions requires expertise from various healthcare professionals, including geriatricians, physiotherapists, dietitians, and pharmacists. However, many healthcare professionals lack specialized training in the management of sarcopenia, and time constraints in clinical practice often prevent in-depth counseling on exercise and nutrition. Integrating sarcopenia management into routine healthcare requires structured training programs and policy changes to ensure that healthcare providers can effectively guide patients through these interventions.

3. Financial Constraints

The cost of multimodal interventions represents another significant challenge, particularly for older adults who may be on fixed incomes or lack comprehensive insurance coverage. Engaging in long-term supervised exercise programs often requires gym memberships, physiotherapy sessions, or personal trainers, which can be financially prohibitive. Similarly, the ongoing cost of nutritional supplements and protein-rich diets may be difficult for some individuals to sustain over time. Pharmacological interventions, while potentially beneficial, are also associated with high costs, particularly for agents like SARMs, growth hormone, or testosterone therapy, which may not be covered by public or private health insurance. Out-of-pocket expenses for these treatments further limit their accessibility, restricting their use to individuals with sufficient financial resources. Additionally, reimbursement issues within healthcare systems further exacerbate these financial barriers. Many healthcare policies do not adequately cover preventive or rehabilitative interventions for sarcopenia, despite their proven long-term benefits in reducing disability and healthcare costs. This lack of reimbursement creates a financial disincentive for both patients and providers, making it difficult to implement multimodal interventions on a large scale. Addressing these issues requires policy reforms to incorporate sarcopenia management into public health strategies and insurance coverage plans [24].

4. Coordination of Care

Given the multifactorial nature of sarcopenia, effective management requires a multidisciplinary approach, involving physicians, physiotherapists, dietitians, pharmacists, and other healthcare

professionals. However, ensuring seamless coordination and communication between these providers remains a challenge. Many healthcare systems operate in a fragmented manner, making it difficult to integrate exercise, nutrition, and pharmacological treatments into a unified care plan. Without a structured approach to multidisciplinary collaboration, patients may receive inconsistent guidance, leading to confusion, suboptimal adherence, and reduced intervention efficacy. Beyond professional collaboration, patient education and ongoing support are crucial for ensuring adherence to multimodal interventions [30]. Older adults often require continuous reinforcement to understand the rationale behind each component of their treatment plan. Without proper education, patients may disregard exercise recommendations, fail to adhere to dietary modifications, or be hesitant about pharmacological treatments. Implementing structured education programs, digital health tools, and support networks can improve patient engagement and long-term adherence.

Recommendations for clinical practice

1. Simplifying and personalizing interventions

To enhance adherence, interventions should be tailored to individual needs, taking into account physical capacity, comorbidities, and lifestyle. Programs that are simple, flexible, and easy to integrate into daily routines are more likely to be sustainable. Setting realistic goals and regularly monitoring progress can help maintain motivation while allowing for necessary adjustments based on patient response.

2. Enhancing access and availability

A major challenge in sarcopenia management is limited access to exercise facilities, nutritional resources, and specialized care. Encouraging the use of community resources such as senior centers, local gyms, and group classes can help improve accessibility. Telehealth solutions provide an effective alternative for remote supervision, allowing patients to receive exercise guidance, nutritional counseling, and follow-up consultations without the need for in-person visits. For those with mobility limitations, home-based exercise programs requiring minimal equipment should be prioritized.

3. Training and education for healthcare providers

Healthcare providers play a key role in sarcopenia management but often lack specialized training in multimodal interventions. Interdisciplinary training programs should be developed to emphasize the synergy between exercise, nutrition, and pharmacology in preserving muscle function. Encouraging continuing medical education in geriatric care will ensure that clinicians remain up to date with the latest evidence-based approaches to sarcopenia treatment.

4. Financial support and policy advocacy

The cost of exercise programs, nutritional supplements, and pharmacological treatments can limit patient access. Expanding insurance coverage and reimbursement policies for sarcopenia-related

interventions is essential to promote early and effective management. Additionally, subsidized programs and partnerships with local organizations could help reduce costs for patients by offering discounted gym memberships, affordable nutritional support, and telehealth services.

5. Promoting multidisciplinary collaboration

A coordinated approach involving physicians, dietitians, physical therapists, and pharmacists is essential for optimizing sarcopenia management. Establishing integrated care teams and regular interdisciplinary meetings can facilitate seamless communication, ensuring that each aspect of treatment is effectively implemented. Involving patients in decision-making and educating them on the benefits of their treatment plan further enhances adherence and long-term success.

6. Patient education and support

Educating patients on the importance of sarcopenia management is critical for adherence. Providing accessible educational materials such as brochures, videos, and online resources helps reinforce key concepts. Additionally, support groups and peer networks can offer motivation and encouragement, helping patients stay engaged with their exercise and dietary regimens over time.

Implementing combination interventions for sarcopenia presents several challenges, including patient adherence, resource limitations, financial constraints, and the need for coordinated care. By addressing these barriers through tailored and simplified programs, enhancing access and availability, training healthcare providers, advocating for financial support, promoting multidisciplinary collaboration, and providing patient education and support, healthcare providers can effectively integrate multimodal approaches into clinical practice. These strategies can help optimize muscle health, improve physical function, and enhance the quality of life for individuals with sarcopenia.

5.4 Future research directions in managing sarcopenia

Further research is needed to refine long-term interventions, personalized treatment approaches, digital health integration, and behavioral strategies in sarcopenia management [5]. While current multimodal strategies have shown promising results, their sustained benefits and long-term safety profiles remain insufficiently explored. Future studies should focus on assessing how exercise, nutrition, and pharmacological interventions influence muscle mass, strength, and physical function over extended periods. It is hypothesized that combining these interventions will lead to lasting improvements, with fewer adverse effects compared to single treatments. Understanding these long-term outcomes will help optimize intervention protocols and ensure that benefits extend well beyond initial treatment phases.

In addition to long-term efficacy, precision medicine approaches represent a key area for future research. Identifying genetic and biomarker profiles that influence treatment response could allow for the development of personalized intervention plans, ensuring that patients receive the most

effective strategies based on their individual physiological characteristics. Tailoring interventions in this way is expected to improve adherence and treatment efficacy, particularly in populations with variable responses to standard therapies.

Another promising avenue lies in the integration of digital health technologies, including wearable devices and mobile applications, to enhance monitoring, adherence, and real-time feedback. By tracking physical activity, dietary intake, and physiological parameters, these tools can provide objective data that help adjust interventions dynamically. It is expected that their use will increase patient engagement and optimize outcomes by providing continuous support outside clinical settings.

Beyond physiological factors, behavioral and psychological determinants of adherence must also be explored. Many patients struggle with maintaining long-term commitment to exercise and dietary changes, often due to lack of motivation, psychological barriers, or limited awareness of sarcopenia's impact. Developing targeted educational programs that address these challenges could enhance adherence and encourage greater patient autonomy in disease management. Evaluating the effectiveness of such programs will be crucial in improving overall engagement with sarcopenia interventions.

To explore these research priorities, longitudinal cohort studies will be necessary to evaluate the long-term effects of multimodal interventions, while randomized controlled trials (RCTs) should be conducted to compare standard treatments with personalized, biomarker-driven approaches. Additionally, pilot studies testing the feasibility of digital health solutions and wearable technology could determine their practical applications in real-world settings. Meta-analyses and systematic reviews will further help synthesize existing evidence and identify areas where data remains insufficient, guiding future research.

While these research directions aim to enhance the effectiveness of existing sarcopenia management strategies, new frontiers in molecular therapies are emerging, offering entirely novel approaches to combating muscle degeneration. Recent discoveries in the field of neuromuscular rejuvenation and growth differentiation factor 5 (GDF5) are shifting the paradigm, presenting new possibilities for regenerating muscle tissue and restoring neuromuscular function. These innovations represent a significant leap forward and warrant further discussion as we explore the latest breakthroughs in sarcopenia treatment.

Chapter 6. New Insights: GDF5 and Neuromuscular Rejuvenation

Despite advancements in multimodal interventions, the search for targeted regenerative therapies remains a major focus of research. Growth Differentiation Factor 5 (GDF5), a member of the TGF- β superfamily, has recently emerged as a promising candidate for neuromuscular rejuvenation and

muscle regeneration [56]. Recent preclinical studies suggest that GDF5 may address key mechanisms underlying age-related muscle degeneration, making it a potential therapeutic breakthrough in the management of sarcopenia [57].

6.1 Background on GDF5

GDF5 is a secreted signaling protein known for its role in skeletal development, cartilage homeostasis, and synovial joint maintenance [56]. It is widely expressed during embryonic development, where it regulates the differentiation and proliferation of chondrocytes, tenocytes, and osteoblast progenitors. In adult tissues, GDF5 continues to play a role in tissue repair and regeneration, primarily in the musculoskeletal system [56].

Recent research has uncovered a novel role for GDF5 in neuromuscular maintenance and repair. Age-related decline in motor neuron-muscle connectivity and chronic inflammation are major contributors to sarcopenia. Studies now suggest that GDF5 exerts protective effects on muscle tissue, neuromuscular junctions (NMJs), and inflammatory pathways, positioning it as a key player in age-related muscle dysfunction and neuromuscular degeneration [65].

6.2 Mechanism of Action

The therapeutic potential of GDF5 in sarcopenia is attributed to three primary mechanisms:

1. Enhancing Muscle Regeneration

GDF5 exerts its anabolic effects through the activation of the SMAD signaling pathway, which plays a critical role in muscle stem cell (satellite cell) activation, differentiation, and proliferation (Figure 1). Satellite cells are the primary contributors to muscle regeneration and hypertrophy, and their function declines with age [56].

- Upon GDF5 binding to its receptors (BMPRII and ACVR1) on muscle progenitor cells, intracellular SMAD1/5/8 phosphorylation occurs, leading to the upregulation of myogenic regulatory factors (MRFs) such as MyoD and Myogenin [57].

- This enhances muscle fiber regeneration and hypertrophy, counteracting age-related muscle atrophy (Figure 1).

- Unlike myostatin inhibition, which indiscriminately promotes muscle growth, GDF5 maintains a balanced regulation of myogenesis, reducing the risk of dysregulated muscle hypertrophy.

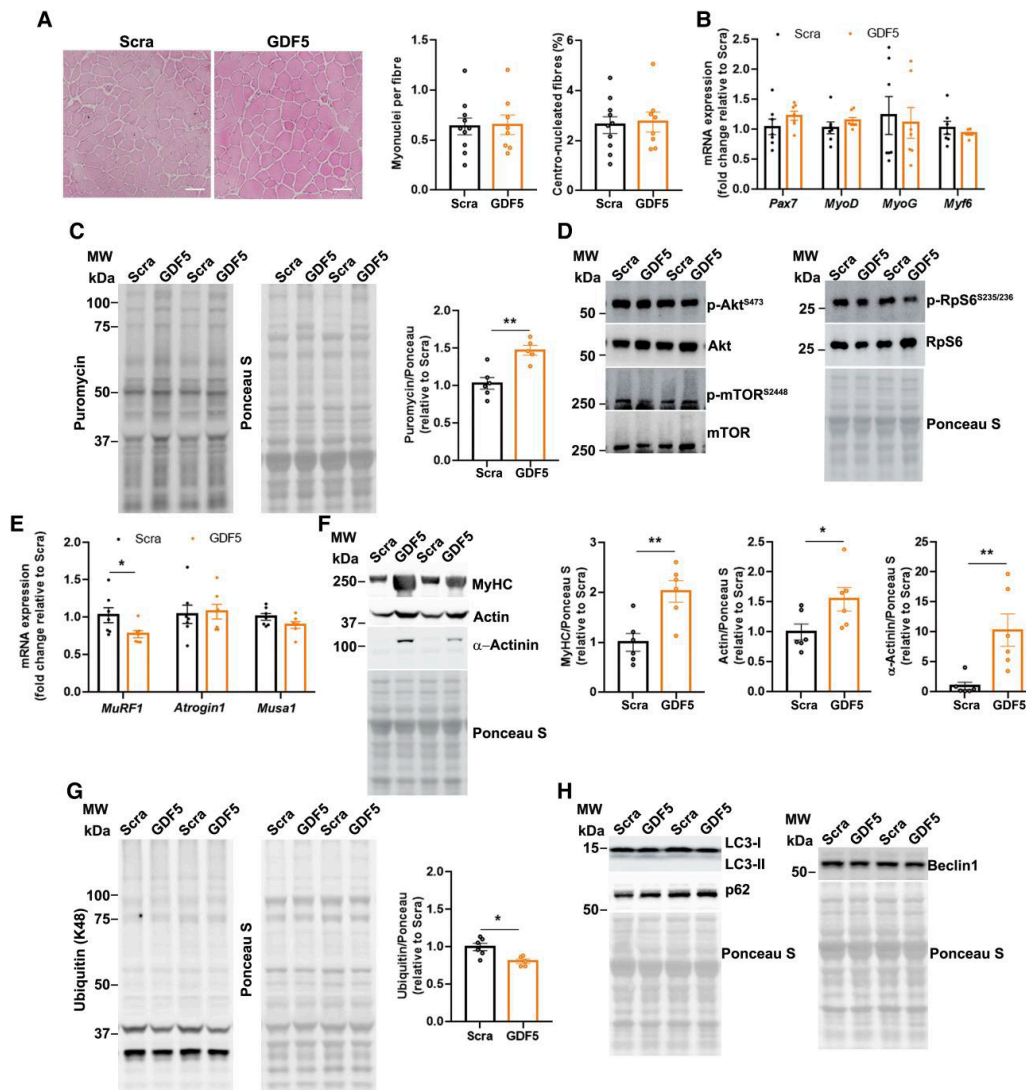


Figure 1. Local GDF5 overexpression in old mice leads to muscle hypertrophy. (A) Representative images of tibialis anterior (TA) cryosections from 21-month-old mice injected with AVV-Scramble (Scra) or -GDF5 (GDF5), stained with haematoxylin and eosin; scale bar = 100 μ m. Number of myonuclei per fibre and proportion of centro-nucleated fibres were determined using an ImageJ-based machine learning algorithm (Scra $n = 10$; GDF5 $n = 8$). (B) Real-time quantitative PCR (RT-qPCR) for *Pax7*, *Myod*, *Myog* and *Myf6* analysed in TAs injected with Scra ($n = 7$) or GDF5 ($n = 7$). (C) Representative western blot showing the level of puromycin-labelled proteins in TAs injected with Scra or GDF5. Relative signal intensity of puromycin-labelled proteins was determined (Scra $n = 6$; GDF5 $n = 5$). Ponceau S staining was used as loading control. (D) Representative western blot showing the level of phosphorylated and total Akt, m-TOR and Rps6 proteins in TAs injected with Scra or GDF5. (E) RT-qPCR for *MuRF1*, *Atrogin1* and *Musa1* analysed in TAs injected with Scra ($n = 7$) or GDF5 ($n = 7$). (F) Representative western blot showing the level of MyHC, Actin and α -Actinin proteins in TAs injected with Scra or GDF5. Relative signal intensity of proteins was determined (Scra $n = 6$; GDF5 $n = 6$). Ponceau S staining was used as loading control. (G) Representative western blot showing the level of ubiquitinated proteins in TAs injected with Scra or GDF5. Relative signal intensity of ubiquitinated proteins was determined (Scra $n = 6$; GDF5 $n = 5$). Ponceau S staining was used as loading control. (H) Representative western blot showing the levels of LC3-I, LC3-II, p62 and Beclin1 proteins in TAs injected with Scra or GDF5. Ponceau S staining was used as a loading control. All data are shown as the mean \pm standard error of the mean.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. (A–H) P -values were calculated by unpaired t -test. MW = molecular weight.

Source: Massire Traoré [58]

2. Preserving Neuromuscular Junction (NMJ) Integrity

The neuromuscular junction (NMJ) is a specialized synapse that facilitates signal transmission between motor neurons and skeletal muscle fibers. NMJ degeneration is a hallmark of sarcopenia, leading to impaired muscle contraction, denervation-induced atrophy, and progressive loss of motor function [37].

- GDF5 has been shown to enhance NMJ stability by upregulating agrin expression, a key protein involved in acetylcholine receptor clustering and NMJ maturation [56].
- It prevents synaptic disassembly by maintaining the expression of MuSK (Muscle-Specific Kinase) and Rapsyn, two critical components for NMJ integrity.
- In aged animal models, GDF5-treated muscles exhibit greater NMJ preservation, preventing motor unit loss and maintaining efficient neuromuscular communication (Figure 2).

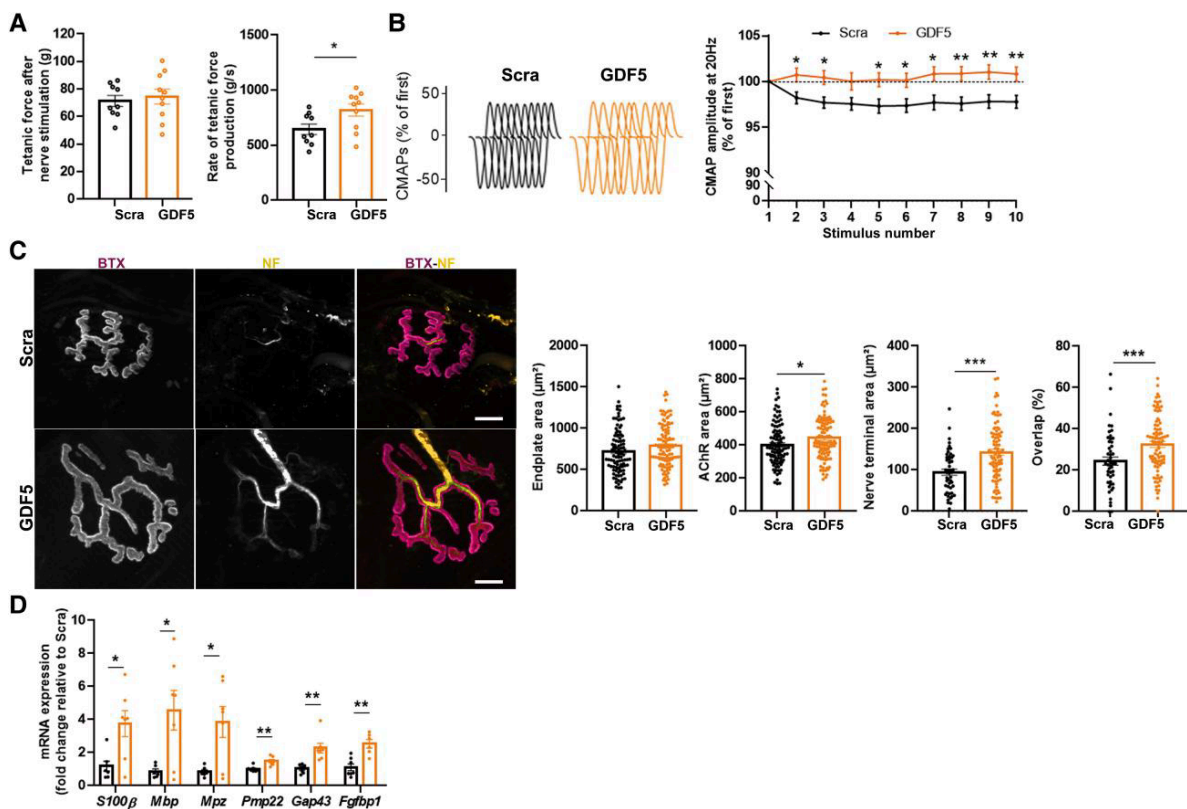


Figure 2. GDF5 overexpression improves neuromuscular connectivity and neuromuscular junction morphology. (A) Absolute tetanic force and rate of force production measured in tibialis anterior (TA) from 21-month-old mice injected with AAV-Scramble (Scra $n = 9$) or -GDF5 (GDF5 $n = 10$). (B) Representative electroneuromyography (ENMG) traces and CMAPs amplitudes recorded in TAs injected with Scra ($n = 9$) or GDF5 ($n = 10$). (C) Representative images of neuromuscular junction from TAs injected with Scra or GDF5, immunostained with neurofilament (NF: staining nerve terminal) and bungarotoxin (BTX: staining acetylcholine receptor); scale bar = 10 μ m. Endplate area, acetylcholine receptor (AChR) area, nerve terminal area and overlap (nerve terminal area/AChR area ratio) parameters were

determined in Scra ($n = 4$) or GDF5 ($n = 3$) using an ImageJ-based workflow. (D) Real-time quantitative PCR Source: Massire Traoré [58]

3. Anti-Inflammatory and Anti-Catabolic Effects

Chronic low-grade inflammation (inflammaging) is a key driver of muscle degradation in aging. Pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β contribute to muscle catabolism, oxidative stress, and impaired satellite cell activation.

-GDF5 downregulates NF- κ B signaling, a key pathway involved in pro-inflammatory cytokine production, leading to a reduction in muscle inflammation.

- It also promotes M2 macrophage polarization, which enhances tissue repair and reduces fibrosis in aged muscles [37].

- These effects collectively create a pro-regenerative environment, improving muscle recovery, mitochondrial function, and metabolic efficiency [30,56] (Figure 3).

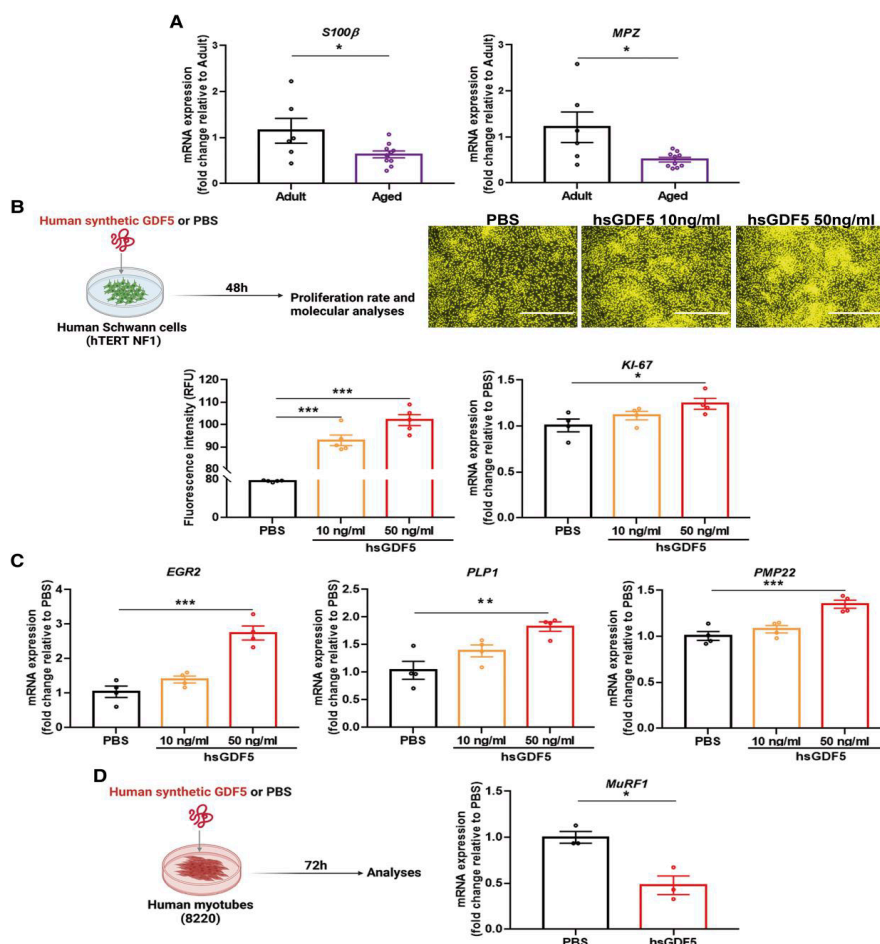


Figure 3. Human synthetic GDF5 enhances human Schwann cell proliferation and decreases MuRF1 expression Source: Massire Traoré [58]

6.3 Preclinical Evidence

Extensive preclinical studies have demonstrated the therapeutic potential of GDF5 in mitigating age-related muscle degeneration and neuromuscular decline. These investigations have provided compelling evidence that GDF5 can enhance muscle mass, improve functional performance, and preserve neuromuscular connectivity, making it a promising candidate for future clinical applications in sarcopenia management.

- Localized overexpression of GDF5

Animal studies have explored the effects of targeted overexpression of GDF5 in specific muscle groups. In aged murine models, localized overexpression of GDF5 has been shown to increase muscle mass by up to 30%, indicating a significant anabolic effect. This hypertrophic response was accompanied by marked improvements in functional performance, particularly in grip strength and endurance, which are key indicators of neuromuscular integrity. Histological analyses of these muscles revealed greater fiber cross-sectional area, enhanced satellite cell activation, and reduced fibrosis, suggesting that GDF5 promotes muscle regeneration and counteracts age-related atrophic processes [56].

Additionally, the localized administration of GDF5 has been observed to enhance vascularization within skeletal muscles, a factor crucial for nutrient and oxygen delivery [51]. This increased capillary density may contribute to improved mitochondrial function and metabolic efficiency, further supporting the role of GDF5 in muscle health and recovery.

- Systemic Administration of GDF5

Beyond localized effects, systemic administration of recombinant GDF5 has demonstrated widespread benefits across multiple muscle groups [24]. Studies in aged rodents receiving intravenous or intramuscular GDF5 injections have shown substantial increases in lean muscle mass, with improvements observed in both fast-twitch and slow-twitch muscle fibers.

Importantly, GDF5-treated muscles exhibited preserved neuromuscular junction (NMJ) morphology, a critical factor in maintaining efficient motor neuron-muscle communication [50]. Age-related NMJ deterioration is a major contributor to muscle weakness and atrophy, leading to progressive functional decline. GDF5 has been shown to stabilize NMJ architecture, enhance synaptic integrity, and improve acetylcholine receptor clustering, thereby ensuring more effective neuromuscular transmission. These findings suggest that GDF5 may play a neuroprotective role in aging skeletal muscle, preventing denervation-induced muscle atrophy and prolonging motor function.

Additionally, systemic GDF5 administration has demonstrated anti-inflammatory effects, with reductions in circulating levels of TNF- α , IL-6, and other pro-inflammatory cytokines that are implicated in muscle catabolism. These findings further highlight GDF5's potential as a therapeutic agent for combating inflammaging, a key driver of sarcopenia.

- Synergistic Effects of GDF5 and Resistance Training

Given the well-established benefits of resistance exercise in muscle preservation, researchers have investigated whether GDF5 could enhance the adaptive response to training. Preclinical studies have shown that when GDF5 therapy is combined with resistance training, the effects on muscle hypertrophy, strength, and endurance are significantly amplified compared to either intervention alone.

Mechanistically, GDF5 appears to facilitate greater muscle protein synthesis post-exercise, possibly through the upregulation of myogenic regulatory factors (MRFs) such as MyoD, Myogenin, and Pax7. This suggests that GDF5 may potentiate exercise-induced muscle regeneration, leading to more pronounced gains in muscle mass and function. Additionally, improvements in muscle fiber recruitment and neuromuscular coordination were noted, further reinforcing the potential for multimodal treatment strategies combining GDF5 with structured resistance training (Figure 1 and Figure 3)

Furthermore, GDF5-treated and exercised animals demonstrated enhanced mitochondrial biogenesis, suggesting improved energy efficiency and metabolic resilience. This synergistic effect between GDF5 and resistance exercise highlights the possibility of integrating GDF5 therapy into comprehensive sarcopenia management programs aimed at optimizing muscle regeneration, functional capacity, and overall mobility in aging individuals [56, 57].

Preclinical studies provide strong evidence supporting the efficacy of GDF5 in reversing age-related muscle decline (Figure 4). Whether through localized muscle overexpression, systemic administration, or combination with resistance training, GDF5 consistently demonstrates anabolic, neuroprotective, and anti-inflammatory effects.

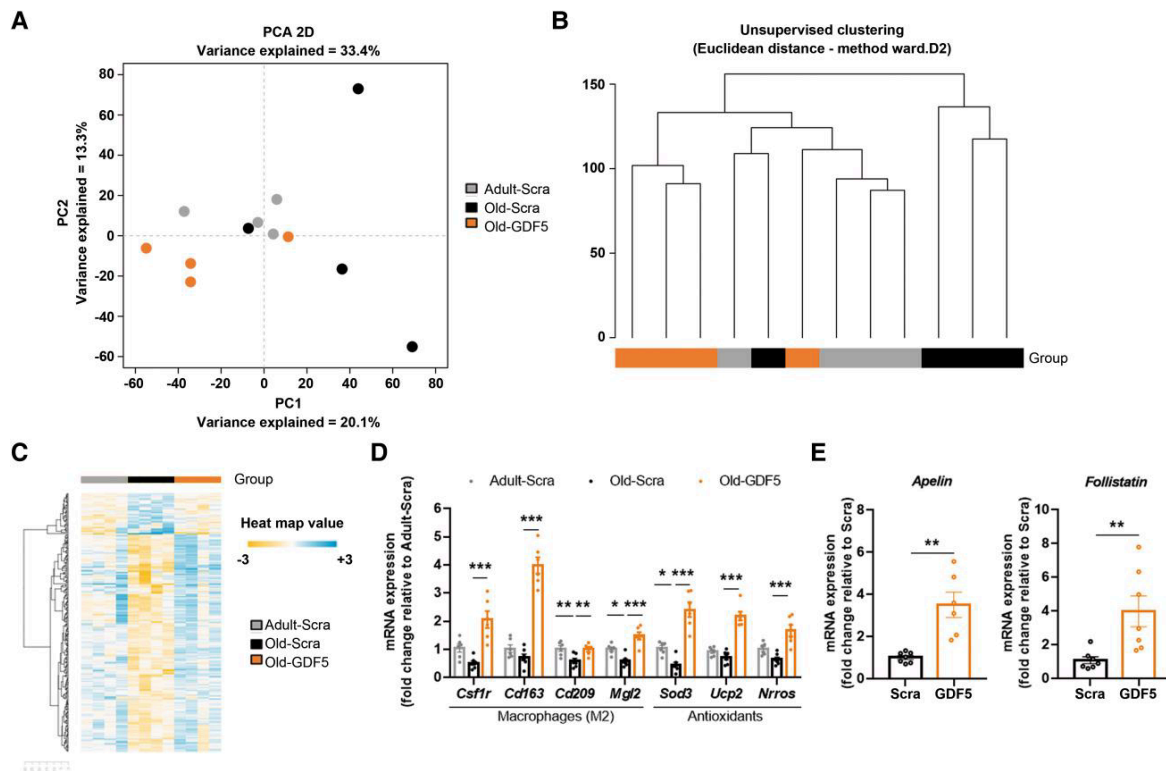


Figure 4. GDF5 overexpression rejuvenates old whole muscle transcriptomic → Demonstrates the transcriptional impact of GDF5 on aging muscle. Source: Massire Traoré [58]

6.4 Clinical Implications

The promising preclinical findings surrounding GDF5 suggest its potential as a therapeutic intervention for sarcopenia and other neuromuscular disorders. By promoting muscle regeneration, preserving neuromuscular junction integrity, and reducing chronic inflammation, GDF5 represents a novel approach to counteracting age-related muscle decline (Figure 5). However, before this therapy can be integrated into clinical practice, several key challenges must be addressed to ensure efficacy, safety, and practical applicability.

One of the primary concerns is the long-term safety profile of GDF5 therapy. While initial studies indicate beneficial effects on muscle hypertrophy and neuromuscular function, it remains essential to evaluate whether prolonged exposure to GDF5 could lead to unintended tissue growth, such as ectopic bone formation or excessive muscle hypertrophy in non-targeted tissues. These risks necessitate long-term toxicological studies to monitor for potential adverse effects and to define the therapeutic window in which GDF5 remains both effective and safe.

Another critical aspect of clinical translation is identifying the optimal delivery method for GDF5 administration. Various approaches are currently being explored, including localized intramuscular injections, systemic intravenous administration, and gene therapy-based delivery. Each of these methods presents distinct advantages and limitations. Localized injections allow for targeted muscle treatment but may require repeated administration. Systemic delivery, on the other hand, provides a broader therapeutic effect but poses potential risks related to off-target activity. Gene therapy

represents a promising long-term solution but introduces additional regulatory and safety considerations, particularly regarding viral vector use and immune response. Further research is needed to determine the most efficient and clinically viable approach [56, 57].

In addition to defining how GDF5 should be administered, it is crucial to establish the appropriate dosage and treatment regimens. The balance between efficacy and safety depends on determining the optimal concentration, frequency, and duration of GDF5 therapy. Overstimulation of muscle growth pathways could lead to unintended consequences, while insufficient dosing may fail to produce significant therapeutic effects. Future dose-escalation studies and pharmacokinetic analyses will be essential in refining treatment protocols to maximize clinical benefits while minimizing potential risks.

Beyond monotherapy, GDF5's therapeutic efficacy may be further enhanced when combined with existing interventions, such as resistance training and protein supplementation (figure 4). Given its ability to stimulate muscle regeneration and enhance neuromuscular communication, integrating GDF5 therapy into multimodal treatment strategies could amplify muscle hypertrophy, improve strength gains, and enhance functional performance. Clinical trials should assess the synergistic effects of GDF5 in combination with structured exercise programs and optimized nutrition plans, ensuring that treatment regimens are holistic, patient-centered, and adaptable to individual needs. While GDF5 holds significant potential, further research is necessary to bridge the gap between preclinical success and clinical application. Moving forward, well-designed human trials will be required to validate its efficacy, determine safety parameters, and define its role within the broader landscape of sarcopenia therapeutics. As advancements continue, GDF5-based therapies may pave the way for a new era of neuromuscular rejuvenation, offering a transformative approach to preserving muscle health, mobility, and independence in aging populations.

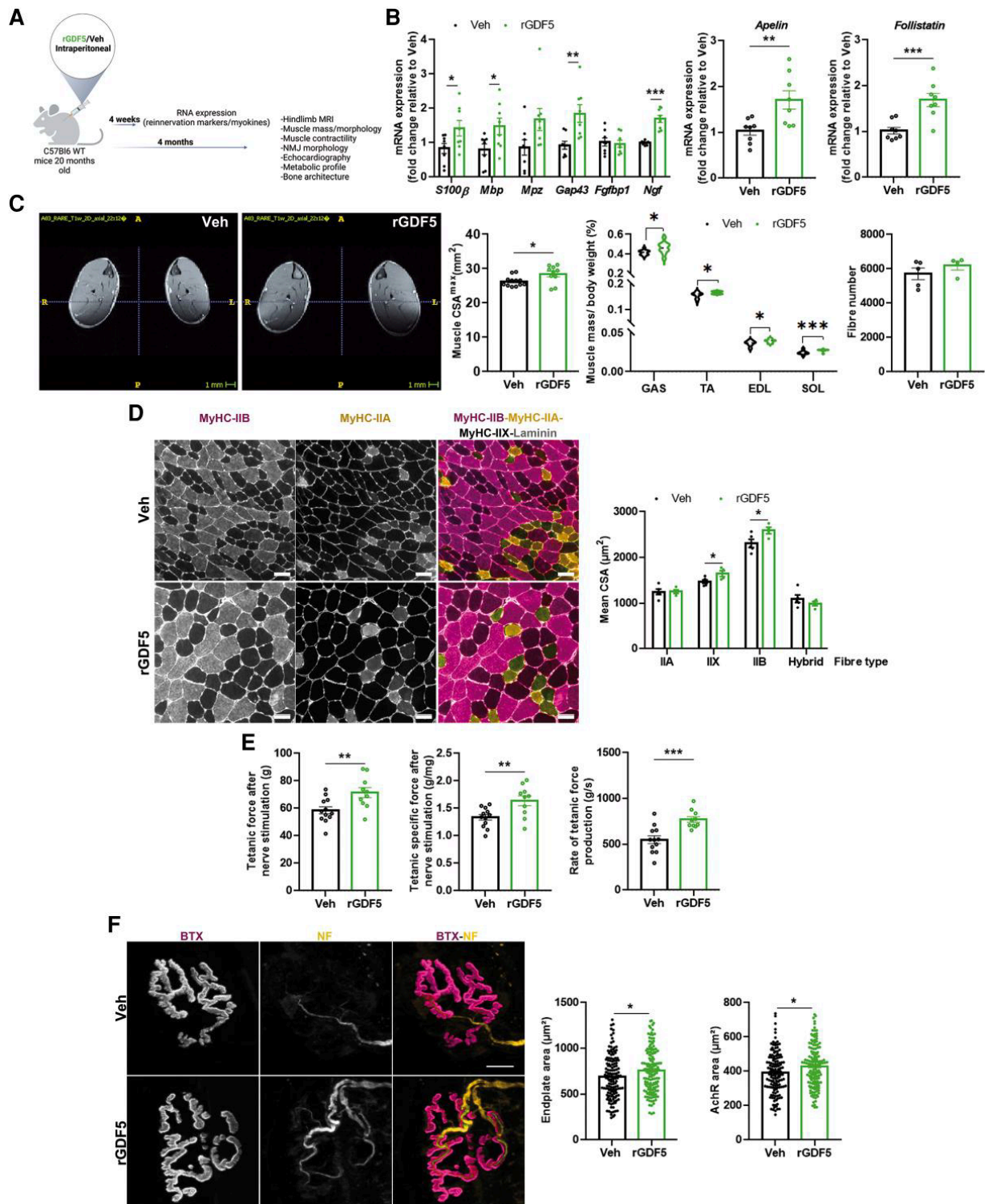


Figure 5. Chronic GDF5 systemic administration in ageing mice preserves against age-related muscle wasting → Highlights the protective effects of GDF5 on muscle mass and neuromuscular connectivity. Source: Massire Traoré [58]

6.5 Future Research Directions

While the preclinical findings on GDF5 have demonstrated its potential in reversing age-related muscle decline, the next crucial step is clinical translation. To fully establish GDF5 as a viable

therapeutic option for sarcopenia and neuromuscular disorders, further research is required to address key challenges, refine treatment protocols, and optimize patient outcomes [56, 57]. A fundamental priority in this process is the initiation of human clinical trials. Transitioning from animal models to human studies is essential to validate the safety, pharmacokinetics, and dose-response relationships of GDF5 therapy. Early-phase clinical trials should focus on establishing the maximum tolerated dose, evaluating potential adverse effects, and determining the most effective administration route. Given the complexity of muscle physiology and its systemic interactions, rigorous phase I and II trials will be necessary to confirm whether the promising effects observed in preclinical models translate effectively to human subjects.

Another critical aspect of advancing GDF5 therapy is the identification of biomarkers that can predict individual responses to treatment. The development of predictive biomarkers would enable a personalized medicine approach, allowing clinicians to identify patients most likely to benefit from GDF5 therapy while minimizing the risk of ineffective treatment. Biomarkers related to muscle regeneration, neuromuscular junction integrity, and inflammatory modulation could serve as valuable indicators for monitoring treatment efficacy and disease progression.

Beyond short-term clinical outcomes, longitudinal studies will be essential to evaluate the long-term effects of GDF5 on muscle function, quality of life, and healthcare utilization. Given that sarcopenia is a chronic, progressive condition, understanding how GDF5 influences functional independence, fall risk, mobility, and overall health outcomes over time is crucial. These studies should also assess potential side effects emerging from prolonged exposure, ensuring that the therapeutic benefits outweigh any associated risks [56, 57].

Finally, technological advancements in drug delivery systems may further enhance the efficacy of GDF5-based therapies. The use of nanoparticle carriers, controlled-release formulations, and gene therapy approaches could improve the precision, stability, and bioavailability of GDF5 administration. By refining targeted delivery mechanisms, researchers could minimize off-target effects and maximize therapeutic impact, paving the way for a more efficient and scalable clinical application. As research continues to expand in this field, it is clear that GDF5 holds significant promise in the development of next-generation treatments for sarcopenia and neuromuscular degeneration (Figure 5). However, its successful integration into clinical practice will depend on addressing these critical research questions, optimizing treatment parameters, and ensuring long-term safety and efficacy. With ongoing scientific advancements and a growing emphasis on precision medicine, GDF5-based interventions could represent a transformative breakthrough in aging and muscle health.

Chapter 7: General Discussion and Clinical Perspectives

7.1 General Discussion

Sarcopenia is increasingly recognized as a critical geriatric syndrome characterized by progressive muscle loss, reduced strength, and impaired physical function. Throughout this thesis, we have explored the multifactorial nature of sarcopenia, addressing its complex interplay of physiological, genetic, hormonal, and lifestyle factors. Comprehensive diagnostic criteria and standardized measurement techniques have been discussed, underscoring the importance of accurate assessment for effective clinical management. Despite advancements, numerous challenges remain in fully understanding and managing this condition [31].

7.2 Limitations of Current Research

Current research in sarcopenia presents several important limitations that hinder its effective clinical management:

- Methodological heterogeneity: a key issue in sarcopenia research is the lack of standardized diagnostic criteria and assessment tools, leading to heterogeneous methodologies across clinical studies. This heterogeneity complicates comparison and integration of results, reducing the reliability and generalizability of findings [35].
- Limited population diversity: most sarcopenia research has involved relatively homogenous groups, often excluding certain subpopulations, such as the very old, individuals with comorbid conditions, or diverse ethnic backgrounds. This limits the generalizability and applicability of research outcomes across broader patient populations [42, 45, 50].
- Duration and scope of clinical trials: clinical trials evaluating pharmacological and non-pharmacological treatments frequently lack adequate duration, making long-term safety and efficacy assessments challenging. Short-term trials fail to capture chronic or delayed effects and do not sufficiently inform long-term treatment strategies.
- Inconsistencies in diagnostic tools and outcome measures: There remains considerable variability in the diagnostic criteria and outcome measurements used across clinical studies. This inconsistency complicates data interpretation, comparisons between studies, and integration of findings into coherent clinical guidelines [31].

7.3 Future Research Directions

Addressing these limitations will require targeted future research in several key areas:

- Standardization of diagnostic and outcome measures: developing universal, standardized diagnostic criteria and outcome measures is essential for harmonizing research methodologies. Consensus among leading scientific and clinical organizations could facilitate clearer comparisons and more robust conclusions [37].
- Longitudinal and diverse population studies: There is a critical need for large-scale, long-term randomized controlled trials (RCTs) including diverse populations. Such studies would offer

insights into sarcopenia progression, effectiveness of interventions over time, and specific needs of underrepresented patient groups.

- Development of innovative pharmacological therapies: ongoing research into novel pharmacological treatments, such as myostatin inhibitors, SARMs, metabolic modulators, and mitochondrial enhancers, shows promising potential. However, extensive clinical trials are still needed to confirm efficacy, determine safety profiles, and understand their practical implications for clinical use. [42].
- Personalized and precision medicine future research should prioritize the development of personalized medicine approaches, including the identification and validation of predictive biomarkers. Understanding individual variability in response to treatments could lead to tailored therapeutic strategies that optimize patient outcomes [51].

7.4 Clinical perspectives and recommendations

Clinically, sarcopenia management should adopt an integrative approach combining established non-pharmacological interventions with emerging pharmacological treatments:

- Comprehensive diagnostic approach: clinicians should use standardized diagnostic tools (DXA, BIA, grip strength, gait speed, SPPB) to accurately identify sarcopenia stages and severity. Early detection and precise staging are essential for timely intervention [37].
- Multimodal treatment strategy: combining nutritional support, resistance and aerobic exercise programs, and pharmacological interventions may offer superior results compared to single-treatment approaches. Therapeutic decisions should consider individual patient characteristics, preferences, comorbidities, and potential risks associated with pharmacological treatments [9,10].
- Monitoring and long-term follow-up: regular follow-up using validated diagnostic and functional performance tools (e.g., DXA, BIA, grip strength, gait speed) should be implemented. Periodic reassessment helps evaluate treatment effectiveness, facilitates adjustments, and identifies potential side effects early [31,45].
- Patient education and engagement: Patients and caregivers should be educated on the nature of sarcopenia, the importance of compliance with multimodal interventions, and lifestyle adjustments to ensure long-term adherence and optimal clinical outcomes.

Sarcopenia represents a significant challenge in geriatric medicine, demanding a comprehensive understanding and multidisciplinary management approach. Current research has made meaningful strides but is constrained by methodological limitations and variability in clinical applicability. Addressing these challenges through structured, diverse, and rigorous future studies will significantly enhance therapeutic outcomes and patient quality of life. The ongoing integration of clinical and research perspectives, coupled with innovative therapeutic strategies, holds promise for substantial advancements in sarcopenia management and patient care.

Conclusions

Physical exercises and a diet rich in proteins and amino acids are two fundamental components in the prevention and management of sarcopenia. These interventions have shown consistent benefits in preserving muscle mass and strength, as well as improving mobility and quality of life in older adults. In parallel, several clinical trials have explored pharmacological options with encouraging preliminary results. Agents such as selective androgen receptor modulators, myostatin inhibitors or GDF5-related molecules appear promising, although further studies are required to confirm their effectiveness and evaluate long-term safety.

Combining physical activity, appropriate nutrition, and, when indicated, pharmacological treatment may represent a comprehensive and effective strategy. In this context, the development of personalized, evidence-based interventions remains a key objective to address the growing impact of sarcopenia in ageing populations.

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Appendices

Appendix A: Diagnostic Criteria for Sarcopenia

EWGSOP2 Criteria for Sarcopenia Diagnosis:

1. Probable Sarcopenia: Low muscle strength (e.g., handgrip strength < 27 kg for men and < 16 kg for women)
2. Confirmed Sarcopenia: Low muscle strength and low muscle mass (e.g., DXA-measured appendicular lean mass/height² < 7.0 kg/m² for men and < 5.5 kg/m² for women)
3. Severe Sarcopenia: Low muscle strength, low muscle mass, and low physical performance (e.g., gait speed ≤ 0.8 m/s or SPPB score ≤ 8)

Appendix B: Study Protocols for Key Interventions

1. Resistance Training Protocol:

- Frequency: 3 times per week
- Intensity: 60-80% of 1RM (one-repetition maximum)
- Duration: 45-60 minutes per session
- Exercises: Multi-joint exercises (e.g., squats, deadlifts) and single-joint exercises (e.g., bicep curls, leg extensions)
- Progression: Increase weight/resistance every 4 weeks based on individual progress

2. Aerobic Exercise Protocol:

- Frequency: 3-5 times per week
- Intensity: Moderate (60-70% of maximum heart rate)
- Duration: 30-45 minutes per session
- Activities: Walking, cycling, swimming, or other continuous rhythmic activities

3. Combined Exercise Program:

- Frequency: 3-5 times per week
- Intensity: Combination of resistance and aerobic exercise intensities
- Duration: 60-90 minutes per session
- Activities: Combination of resistance exercises followed by aerobic activities within the same session or on alternate days

Appendix C: Nutritional Intervention Details

1. Protein Supplementation:

- Dosage: 1.2-1.5 grams of protein per kg of body weight per day
- Sources: Lean meats, poultry, fish, eggs, dairy products, legumes, nuts, and protein powders
- Timing: Distribute intake evenly across meals, with an additional intake post-exercise and before bed

2. Vitamin D Supplementation:

- Dosage: 800-2000 IU per day
- Sources: Sun exposure, fortified foods (milk, orange juice), and supplements
- Monitoring: Regular blood tests to ensure adequate vitamin D levels

3. Omega-3 Fatty Acid Supplementation:

- Dosage: 1-2 grams of EPA and DHA per day
- Sources: Fatty fish (salmon, mackerel, sardines), flaxseeds, chia seeds, walnuts, and supplements

Appendix D: Questionnaires and Assessment Tools

SARC-F Questionnaire:

- Strength: How much difficulty do you have in lifting and carrying 10 pounds?
- Assistance with walking: How much difficulty do you have walking across a room?
- Rise from a chair: How much difficulty do you have transferring from a chair or bed?
- Climb stairs: How much difficulty do you have climbing a flight of 10 stairs?
- Falls: How many times have you fallen in the past year?

Scoring: Each item is scored from 0 (no difficulty) to 2 (unable), with a total score of 0-10. A score of 4 or higher suggests sarcopenia.

Short Physical Performance Battery (SPPB):

- Balance Tests: Side-by-side stand, semi-tandem stand, and tandem stand
- Gait Speed Test: Timed 4-meter walk
- Chair Stand Test: Time to complete five chair stands

Scoring: Each test is scored from 0 (unable) to 4 (best performance), with a total score of 0-12.

Lower scores indicate poorer physical performance.

Sample Consent Form for Clinical Trial Participation:

- Introduction: Brief description of the study, purpose, and sponsor
- Procedures: Detailed explanation of what participation involves, including interventions, assessments, and duration
- Risks and Benefits: Description of potential risks and expected benefits
- Confidentiality: Assurance of data privacy and how personal information will be protected
- Voluntary Participation: Statement that participation is voluntary and can be withdrawn at any time without penalty
- Contact Information: Contact details for the research team and ethics committee

Ethical Considerations:

- Approval: Ensure the study has been approved by an institutional review board (IRB) or ethics committee
- Informed Consent: Obtain written informed consent from all participants
- Risk Minimization: Implement strategies to minimize risks and discomfort to participants
- Data Confidentiality: Maintain strict confidentiality of participant data and use it solely for research purposes