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REVIEW

Therapeutics for Sarcopenia and Functional Disabilities in Older Adults: A Review of Phase 4 Clinical Trials

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Background: Sarcopenia significantly contributes to physical disability and reduced quality of life in older adults, leading to disability. Therapeutics used to manage sarcopenia can improve not only muscle health but also the overall functional capacity of individuals at risk of developing disabilities. This review focuses on the therapeutic interventions evaluated in phase 4 clinical trials to address sarcopenia and its associated disabilities in older adults.

Objective: To review and summarize the therapeutic agents tested in phase 4 clinical trials for the management of sarcopenia and their potential impact on reducing functional disabilities in older adults.

Methods: A review of phase 4 clinical trials was conducted on 6th November 2024, focusing on interventions for sarcopenia in older adults. Data on therapeutic agents, trial outcomes, and their effects on muscle mass, strength, and disability prevention were collected from clinicaltrials.gov database.

Results: Several therapeutic agents, including whey protein powder, eldecalcitol, testosterone enanthate, and Denosumab, have been tested in Phase 4 trials for their ability to enhance muscle mass and function in older adults with sarcopenia. Allopurinol and Pioglitazone were also studied for their potential to improve muscle metabolism, while Medrol (Methylprednisolone) and Levothyroxine offered supportive effects in inflammatory and metabolic disorders that exacerbate muscle loss. Moreover, combination therapies, such as nutritional supplementation with HMB and vitamin D, showed promise in improving muscle function. These interventions demonstrated varying degrees of efficacy in improving muscle strength, reducing physical disability, and enhancing overall functional capacity in older adults.

Conclusion: Therapeutic strategies targeting sarcopenia in older adults have the potential to reduce functional disabilities and improve quality of life. Phase 4 clinical trials provide valuable insights into the long-term safety and effectiveness of these treatments. Continued research and refinement of these therapies are essential to fully address the disabling effects of sarcopenia and promote healthy aging.

Keywords: aging, disability, geriatric, muscles loss, sarcopenia, therapeutics

Introduction

Sarcopenia, a progressive and generalized skeletal muscle disorder characterized by age-dependent loss of muscle mass, function, and quality, is common among older adults, often associated with aging and chronic illnesses, and is associated with adverse outcomes, including falls, functional decline, frailty, and increased mortality.[1–3] It is associated with physical and functional disability in older adults, contributing to higher disability scores and reduced functional capacity, particularly in older adults.[4–6] It can also occur in early adulthood with a range of conditions.[2,7] It is recognized as a key contributor to physical frailty, with age-related declines in skeletal muscle mass and performance underlying mobility loss and mobility disability.[1,8,9]

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The main mechanisms underlying sarcopenia include age-related factors such as mobility restrictions, muscular anabolic resistance, lipotoxicity, alpha-motor neuron death, altered hormone concentrations, increased inflammation, and changes in nutritional status, along with specific muscle alterations like selective fast fiber atrophy, motor unit loss, and an increase in hybrid fibers.[3,10–12] According to different studies, the prevalence of sarcopenia varies widely depending on classification criteria and cutoff points, affecting an estimated 10%–16% of older adults globally, with rates increasing sharply with age to impact approximately 10% of individuals over 60 and up to 50% of those over 80.[13–16] Risk factors for sarcopenia include physical inactivity, poor protein intake, smoking, extreme sleep duration, diabetes, and aging, with additional independent factors, such as prefrailty, low activity, functional capacity, triglyceride levels, and systolic blood pressure.[14,17,18] Moreover, malnutrition, risk of malnutrition especially protein-energy malnutrition.[19,20]

This loss of muscle mass and strength directly correlates with increased disability, as sarcopenia impairs the ability to perform essential daily tasks such as walking, climbing stairs, and lifting objects.[21–23] The decreased muscle strength and functional capacity not only elevate the risk of falls and fractures but also promote sedentary behavior, further perpetuating the cycle of muscle degradation and disability. Individuals with existing conditions like arthritis, multiple sclerosis, and spinal cord injuries are especially vulnerable to the compounding effects of sarcopenia, making early intervention crucial in these populations.[24–26]

With the aging population on the rise, finding effective interventional therapies to prevent or treat sarcopenia has become a priority in research, especially in terms of minimizing disability and improving quality of life. This review aims to review and summarize the therapeutic agents tested in phase 4 clinical trials for the management of sarcopenia and their potential impact on reducing functional disabilities in older adults.

By synthesizing results from clinical trials registered on ClinicalTrials.gov, we provide an overview of nutritional, exercise-based, and pharmacological interventions that have shown promise in maintaining muscle mass and function. These interventions have the potential to alleviate the effects of sarcopenia, particularly in vulnerable populations who are at higher risk of becoming disabled due to muscle loss.

Methods

The primary source of data for this review was ClinicalTrials.gov, a comprehensive repository of clinical studies conducted globally. Relevant trials were identified by searching for studies focused on sarcopenia, muscle wasting, and disability-related outcomes. Inclusion criteria were based on the study's focus on interventions such as dietary supplementation, physical training, and pharmacological treatments. Both observational and interventional studies were included, with particular emphasis on completed studies that provided clear outcomes related to muscle mass, strength, and disability prevention. The results include clinical trials up to date of the search 6th November 2024.

The selected trials were analyzed for their interventions, methodologies, and outcomes. Particular attention was paid to the primary outcome measures, which included changes in muscle strength (eg, hand-grip strength), muscle mass, and physical function (eg, mobility and daily task performance). Secondary outcomes such as quality of life and reduction in disability risks were also considered to assess the broader impact of these interventions.

Results

The analysis of clinical trials related to sarcopenia, as obtained from ClinicalTrials.gov, provides valuable insights into the range of interventions aimed at preventing muscle degradation and disability. The reviewed trials varied in recruitment status, with most being completed or actively recruiting. The distribution of these studies is summarized in Table 1.

A variety of conditions were targeted in these trials, with interventions ranging from behavioral modifications, such as resistance training, to pharmacological treatments, including testosterone and vitamin D analogs. Table 2 presents the frequency of conditions studied and their associated interventions.

The medications evaluated in these trials include a range of pharmacological classes, including xanthine oxidase inhibitors, protein supplements, and androgen therapies. Table 3 lists the medications tested and their respective pharmacological classifications. Summary of interventions and outcome measures in clinical studies on sarcopenia and frailty tabulated at Table 4.

Table 1 Distribution of Studies by Status and Phase, Summarizing the Number of Studies Completed, Recruiting, or Withdrawn in Each Clinical Trial Phase

Study Status	Phases	Count
Active not recruiting	Phase 4	2
Completed	Phase 4	8
Not yet recruiting	Phase 4	1
Recruiting	Phase 4	2
Terminated	Phase 4	2
Unknown	Phase 4	4
Withdrawn	Phase 4	1

Table 2 Frequency of Conditions and Associated Interventions, Detailing the Number of Times Each Intervention Was Tested for Specific Conditions

Conditions	Interventions
Diabetes Mellitus, Type 2 Sarcopenia Weight Loss Frailty	Behavioral: Circuit resistance training (CRT) Behavioral: Vegetarian diet (V-Med diet) Drug: Empagliflozin 10 MG
End Stage Renal Disease Malnutrition Sarcopenia Hemodialysis Complication	Drug: Olimel N12 Drug: Glucose IV
Frailty Sarcopenia	Drug: Transdermal testosterone gel (Testogel 1%) Drug: Matched transdermal placebo gel
Obesity Overweight With Indications for Weight Loss	Drug: Pioglitazone Behavioral: Resistance exercise training to maximize muscle power Behavioral: Hypocaloric diet Drug: Placebo
Osteoarthritis of the Knee Sarcopenia	Other: Knee strengthening exercises with isokinetic dynamometer Other: Strengthening around the knees with home exercise program
Postmenopausal Osteopenia Bone Loss, Age Related Age-Related Sarcopenia Glucose Metabolism Disorders	Dietary supplement: Pendulum WBF-038 Dietary supplement: Pendulum Placebo
Age-related Cognitive Decline	
Sarcopenia	Combination_product: 3-month intensive intervention
Sarcopenia	Behavioral: exercises. Dietary supplement: whey protein powder Drug: Eldecalcitol

(*Continued*)

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Table 2 (Continued).

Conditions	Interventions
Sarcopenia	Drug: Allopurinol Drug: Lactose tablets
Sarcopenia	Drug: Alfacalcidol Drug: Placebo Drug: Denosumab
Sarcopenia	Drug: Testosterone enanthate Drug: Testosterone enanthate Drug: Placebo
Sarcopenia	Drug: Testosterone injection Drug: Testosterone gel Drug: Medrol
Sarcopenia in Elderly	Drug: Denosumab Drug: Zolendronic Acid
Sarcopenia Hypogonadism Muscular Diseases	Drug: Topical testosterone gel 1% (active formulation) Drug: Topical gel (placebo formulation)
Sarcopenia Osteoporosis	Drug: Denosumab Drug: Zoledronic Acid Others: Denosumab Placebo
Subclinical Hypothyroidism Sarcopenia	Drug: Levothyroxine Drug: Placebo

Table 3 List of Medications Used in Phase 4 Clinical Trials and Their Pharmacological Classes

Medication	Pharmacological Class
Allopurinol	Xanthine Oxidase Inhibitor
Lactose tablets	Placebo/Inactive Control
Alfacalcidol	Vitamin D Analog
Denosumab	RANK Ligand Inhibitor
Testosterone enanthate	Androgen
Testosterone gel	Androgen
Medrol	Corticosteroid
Zoledronic Acid	Bisphosphonate
Levothyroxine	Thyroid Hormone
Olimel N12	Parenteral Nutrition
Glucose IV	Nutrient
Pendulum WBF-038	Probiotic Supplement
Pendulum Placebo	Placebo/Inactive Control

(*Continued*)

Table 3 (Continued).

Medication	Pharmacological Class
HMB and vitamin D	Nutritional Supplement
Pioglitazone	Thiazolidinedione (Antidiabetic)
Empagliflozin	SGLT2 Inhibitor (Antidiabetic)
Eldecalcitol	Vitamin D Analog
Whey protein powder	Protein Supplement
Transdermal testosterone gel	Androgen
Topical testosterone gel	Androgen
Placebo	Placebo/Inactive Control

Table 4 Summary of Interventions and Outcome Measures in Clinical Studies on Sarcopenia and Frailty

Interventions	Measures
Combination Products	3-month intensive intervention (eg, protein supplementation + exercise)
Drug-Based Interventions	
- Allopurinol & Lactose Tablets	Investigates muscle function improvement
- Testosterone-Based Therapies	
• Testosterone enanthate injections	Hormone therapy for muscle mass and strength
• Testosterone transdermal gel (Testogel 1%)	Alternative testosterone delivery method
• Testosterone injections	Direct administration for muscle growth
Primary Outcome Measures	
- Muscle Mass & Strength	
• Appendicular Muscle Mass Index (AMMI)	Assesses muscle quantity
• Bioelectrical Impedance Analysis (BIA)	Body composition measurement
• Muscle Strength Measurement	Includes grip strength
- Hormonal & Metabolic Indicators	
• Serum Total Testosterone Levels	Measured before and after treatment
Secondary Outcome Measures	
- Fat Mass Measurement	Bioelectrical impedance analysis (BIA)
- Functional Performance Tests	
• Short Physical Performance Battery (SPPB)	Assesses mobility and balance
• 6-Minute Walk Test	Evaluates endurance
- Risk Assessments	Evaluates factors such as prostate health
- Limb Strength Measurements	Upper and lower limb strength at 6 months

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Discussion

This review draws on data obtained from clinical trials registered on ClinicalTrials.gov, focusing on interventions that target sarcopenia with the goal of preventing disability. The trials included in the analysis identified a range of approaches, from nutritional supplementation and resistance training to different pharmacological treatments.

Muscle degradation in sarcopenia is primarily driven by an imbalance between protein synthesis and protein breakdown.[27–29] As individuals age, the anabolic response to dietary protein and resistance exercise declines, leading to insufficient muscle protein synthesis to counteract muscle loss.[30–32] Furthermore, decreased physical activity, often associated with aging and chronic illnesses, exacerbates muscle wasting.[33–35] Hormonal shifts, such as reductions in growth hormone, insulin-like growth factor-1 and testosterone, play critical roles in diminishing muscle anabolism.[36–38] In contrast, catabolic factors, such as increased levels of myostatin and chronic low-grade inflammation, accelerate muscle protein breakdown.[39–42] The findings from the reviewed studies highlight the effectiveness of anabolic interventions, particularly testosterone-based therapies, in counteracting muscle loss and improving functional outcomes in individuals with sarcopenia and frailty. This loss of muscle mass and strength directly correlates with increased disability, as sarcopenia impairs the ability to perform essential daily tasks such as walking, climbing stairs, and lifting objects. The decreased muscle strength and functional capacity not only elevate the risk of falls and fractures but also promote sedentary behavior, further perpetuating the cycle of muscle degradation and disability.

The data analyzed comes from studies such as Nutritional biomarkers of sarcopenia, which examined the impact of leucine-enriched supplements on muscle mass and strength. This finding is supported by previous studies indicating that leucine-enriched supplementation plays a crucial role in stimulating muscle protein synthesis, preserving lean muscle mass, and improving strength in older adults with sarcopenia.[43–45] Leucine, a key branched-chain amino acid, has been shown to activate the mTOR signaling pathway, which is essential for muscle growth and maintenance, particularly in individuals experiencing age-related muscle decline.[43,46,47]

Integrated Physical Training with protein diet, which explored the benefits of combining high-protein diets with physical exercise in enhancing muscle function. Virtual Reality-Based Rehabilitation introduced innovative exercise modalities to improve muscle strength and prevent functional decline. Blood Flow and Muscle Regeneration in Sarcopenia, an observational study looking at the role of satellite cells in muscle regeneration and potential pharmacological targets. These studies provide valuable insights into the efficacy of multi-modal interventions that integrate exercise, diet, and pharmacology to address sarcopenia.

The findings from this dataset highlight the diverse interventions used in clinical trials addressing sarcopenia and frailty. Most studies focus on pharmacological treatments, particularly testosterone-based therapies, aimed at improving muscle mass and strength in older adults. Additionally, some trials investigate nutritional supplementation and exercise regimens as alternative or complementary interventions.

The primary outcome measures emphasize muscle mass, strength, and functional mobility, which are crucial indicators of sarcopenia progression and treatment effectiveness. Secondary outcome measures provide further insights into body composition, endurance, and risk factor assessments, reflecting the multifactorial nature of muscle deterioration in aging populations. Table 1 summarizes the interventions and outcome measures used in clinical studies related to sarcopenia and frailty.

Phase 4 clinical trials play a critical role in evaluating the long-term safety and efficacy of therapeutics after their initial approval. This review presents an analysis of various therapeutic agents tested in these trials for sarcopenia. Agents like whey protein powder and eldecalcitol are used to enhance muscle mass and bone density, particularly in older adult populations. Hormone replacement therapies, including testosterone enanthate, testosterone gel, and testosterone injections, are evaluated for their role in treating hypogonadism, improving muscle strength, and increasing bone density in men.[36,48,49] This finding aligns with previous literature, which suggests that testosterone replacement therapy significantly enhances muscle strength, lean body mass, and bone mineral density in hypogonadal men, as demonstrated in randomized controlled trials and meta-analyses evaluating its anabolic effects on musculoskeletal health.[49–51] Levothyroxine addresses hypothyroidism, improving metabolic regulation, while Medrol (Methylprednisolone) offers anti-inflammatory effects in autoimmune and inflammatory diseases. Renamezin and Olimel N12 serve critical functions in kidney support and parenteral nutrition, respectively, while Pioglitazone is used to improve insulin sensitivity in patients with type 2 diabetes. These pharmacological interventions align with existing research on metabolic and inflammatory contributors to sarcopenia, where thyroid hormone regulation,

inflammation control, renal function support, and insulin sensitivity improvement have been linked to muscle preservation and reduced muscle wasting.[42,52,53]

These findings highlight the ongoing post-marketing research aimed at optimizing therapeutic regimens, managing chronic conditions, and improving patient outcomes through targeted, long-term pharmacological interventions.

Conclusion

The results from these clinical trials highlight the potential of novel therapies to preserve muscle function and reduce disability in older adults and those with chronic impairments. These medication could improve the quality of life for disabled people.

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Disclosure

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