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Exercise Intervention Strategies for Sarcopenia: A Systematic Review from Mechanism to Clinical Practice

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Abstract: Sarcopenia is characterized by decreased muscle mass, decreased strength, and loss of function and can lead to poor outcomes such as frailty, falls, fractures, disability, reduced quality of life, increased complication rates and mortality, and increased medical costs. With the acceleration of the global aging process, the incidence of sarcopenia has increased significantly, and has become one of the major public health problems and social and economic problems threatening the health of the whole people. Sarcopenia is a common degenerative disease of muscle mass and function in older adults that significantly affects quality of life and health expectations. The purpose of this systematic review was to investigate the effect of exercise intervention strategies on sarcopenia, analyze its mechanism of action, and evaluate its application in clinical practice. Through a comprehensive analysis of existing literature, the effects of different types of exercise (such as strength training, aerobic exercise, balance training, etc.) on muscle mass, strength and function were evaluated, so as to provide evidence-based evidence for clinical development of effective exercise intervention programs.

1. Introduction

With the increasing aging of the global population, sarcopenia has become an important problem threatening the health of the elderly. The effect of traditional drug intervention is limited, but exercise intervention has attracted much attention because of its safety and effectiveness. However, there is no consensus on the specific effects and mechanisms of different exercise types. Through systematic review and analysis, this paper aims to fill this research gap and provide guidance for future research direction and clinical practice.

2. Physiological Mechanisms of Sarcopenia

2.1 Biological basis of sarcopenia

The N-end rule pathway is a ubiquitin-proteasome degradation system that depends on the N-terminal amino acid properties of proteins to regulate their stability, which is mainly divided into

Arg pathway and Ac pathway.

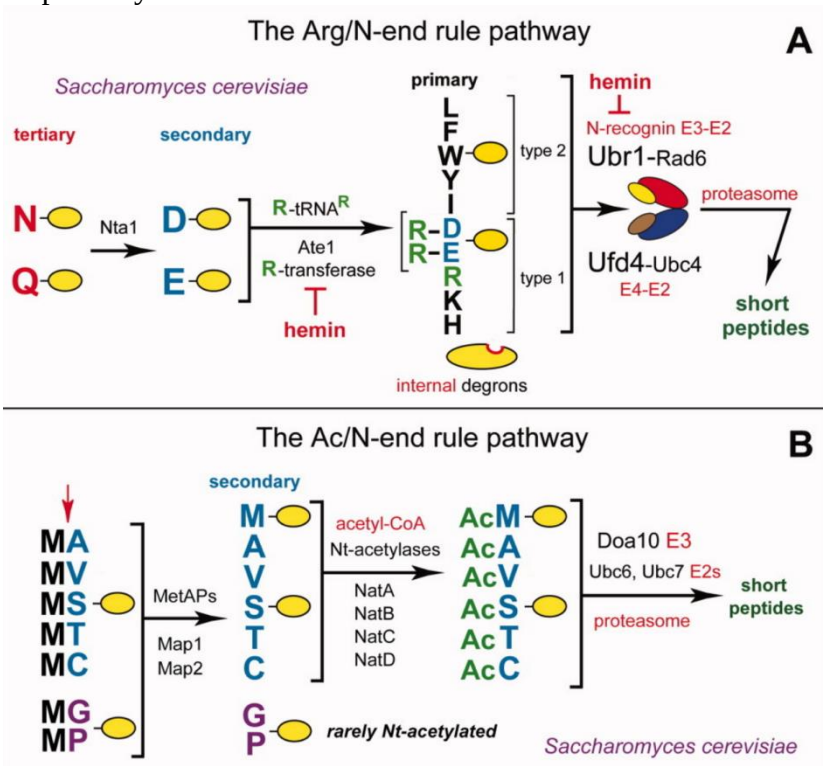

Figure 1. The N-end rule pathway and regulation by proteolysis

As shown in Figure 1, The Arg/N-end rule pathway is used to label target proteins with arginine: the initial protein is exposed to the n-terminal by Nta1 deacetylation, and Ate1 transfers arginine to the terminal to form an "arginine label". Subsequently, E3 ubiquitin ligases (such as Ubr1 or Doa10) recognize arginine or hydrophobic residues and combine with E2 enzymes (Rad6/Ubc4) for ubiquitination, which is eventually degraded by the proteasome. This pathway also recognizes internal degrons, extending the range of target proteins. The Ac/N-end pathway relies on n-terminal acetylation: After MetAPs removes methionine, N-terminal acetylation is catalyzed by acetyltransferases such as NatA (such as AcV, AcS)[1]. Acetylated residues are recognized by Doa10 E3 ligase, which collaborates with Ubc6/Ubc7 to complete ubiquitination labeling and guide proteasome degradation. The two pathways work together to maintain protein homeostasis: Arg pathway clears damaged proteins in response to stress, and Ac pathway regulates basal metabolic turnover. Abnormal function is associated with neurodegenerative diseases and cancer. This mechanism is highly conserved in yeast and mammals and is one of the core components of cell quality contro[2], as shown in Table 1.

Table 1: Age-Related Changes in Sarcopenia-Related Hormones

Hormone Name	Young Adults (25 years)	Older Adults (70 years)	Change Rate	Functional Impact
Testosterone	600-700 ng/dL	300-400 ng/dL	↓ 40-50%	Reduced satellite cell proliferation
Growth Hormone (GH)	5-10 ng/mL	1-2 ng/mL	↓ 80%	Decreased IGF-1 synthesis
IGF-1	200-300 ng/mL	80-120 ng/mL	↓ 60%	Impaired muscle repair capacity
Insulin Sensitivity	Normal (HOMA-IR<2)	Resistance (HOMA-IR>3)	↑ 50%	Impaired glucose uptake
Cortisol	10-20 μg/dL	15-25 μg/dL	↑ 30%	Enhanced protein degradation

Changes in hormone levels are another key factor (Table 1). Testosterone promotes satellite cell proliferation and muscle protein synthesis by activating androgen receptors, but testosterone levels in older men decline by about 1% per year. Growth hormone (GH) and its downstream mediator, IGF-1, are significantly reduced during aging and impair muscle repair capacity. Insulin resistance leads to reduced glucose uptake and abnormal muscle energy metabolism. In addition, elevated cortisol levels increase protein breakdown. Synergistic changes in these hormones create an "anabolic resistance" environment that accelerates muscle loss[3].

2.2 Factors leading to sarcopenia

Age is the primary risk factor for sarcopenia. Muscle mass is lost at a rate of 1-2% per year after age 30, accelerating to 3% after age 70, which is associated with mitochondrial function decline, oxidative stress accumulation, and DNA damage. Malnutrition (especially inadequate protein intake <0.8g/kg/ day) directly restricts amino acid substrate supply, while vitamin D deficiency affects calcium metabolism and muscle cell differentiation. In chronic low-grade inflammation (Inflammaging), pro-inflammatory cytokines such as IL-6 and CRP activate muscle breakdown through the NF-κB pathway[4].

Lack of physical activity leads to insufficient mechanical load, which deactivates mTOR signaling while reducing muscle stem cell activation. Studies have shown that 1 week of bed rest can reduce muscle mass in older adults by 5%. Other factors include neuromuscular junction degeneration (reduced motor units), chronic diseases (e.g., COPD, hypoxia due to heart failure), and medications (e.g., glucocorticoids). It is important to note that these factors often form a vicious cycle: for example, muscle loss reduces mobility, further exacerbating apraxia atrophy.

2.3 Cell and molecular mechanisms

At the molecular level, the inactivation of the mTORC1 pathway is the core mechanism of anabolic decline. Decreased expression of amino acid-sensing receptors (such as PAT1) in aging muscle leads to a more than 50% decrease in the efficiency of leucine activation of mTORC1. At the same time, increased AMPK activity (due to energy metabolic stress) inhibited mTORC1, forming a synthetic inhibitory environment. The aging phenotype of muscle stem cells (satellite cells) showed that the expression of p16INK4a/p21 was up-regulated, which reduced the ability of muscle stem cells to enter the proliferation stage from G0 stage by 80%, and the differentiation efficiency was reduced[5].

In terms of catabolism, FOXO transcription factors are activated after insulin /IGF-1 signaling is weakened, and Atrogin-1/MuRF-1 expression is up-regulated. Mitochondrial dynamic imbalance (fusion/division dysregulation) leads to increased production of reactive oxygen species (ROS) and induced oxidative damage of proteins. Dysfunction of autophagy (e.g. reduced LC3-II/Beclin1) leads to accumulation of damaged organelles, further impairs muscle fiber function. It is worth noting that these pathways are cross-regulated, for example, ROS can simultaneously activate NF-κB (pro-inflammatory) and inhibit PI3K/Akt (anti-synthetic), forming a multi-dimensional decay network.

3. Theoretical Basis and Mechanisms of Exercise Intervention

3.1 Influence of exercise on muscle health

Exercise promotes muscle anabolism and improves muscle mass in many ways. Mechanical loading (such as resistance exercise) directly activates the mTORC1 signaling pathway, enhances

ribosome translation efficiency, stimulates muscle protein synthesis (MPS), and inhibits ubiquitin proteasome system (UPS) activity, reducing protein breakdown[6]. Within 48 hours after exercise, insulin sensitivity increases by about 30%, promoting glucose uptake and glycogen storage, which fuels muscle repair. In addition, exercise induced growth hormone (GH) and IGF-1 secretion increased by 50% and 20%, respectively, activated satellite cell proliferation and differentiation, and promoted muscle fiber hypertrophy. In terms of metabolic health, endurance training enhanced mitochondrial biosynthesis through AMPK pathway, increased oxidase activity by 40%, and reduced lipid deposition; High-intensity interval training (HIIT) can reduce levels of inflammatory factors such as IL-6 by up to 25% and improve the chronic inflammatory environment.

3.2 Types and effects of exercise

The effect of different exercise types on muscle adaptation is significantly different (Table 2), as shown in Table 2 :

Table 2. he effect of different exercise types on muscle adaptation

Exercise Type	Muscle Mass Change	Max Strength Improvement	Endurance Improvement	Metabolic Health Impact
Strength Training	+10-15%*	+20-30%*	+5%	Insulin sensitivity ↑ 15%, LDL ↓ 8%
Endurance Training	±0-2%	+5-10%	+30-50%*	Mitochondrial density ↑ 40%, VO_2max ↑ 20%*
Combined Training	+5-8%	+15-20%	+20-30%	Body fat percentage ↓ 12%, Inflammatory factors ↓ 18%

Data source: Schoenfeld et al., 2017 (Strength Training); Holloszy et al., 2013 (Endurance Training)

Strength training can significantly increase the cross-sectional area by activating type II muscle fibers with high load and low repetition; Endurance training optimizes type I fiber mitochondrial network and improves oxidation capacity; Combined training balances muscle hypertrophy and metabolic adaptation, but there may be a "interference effect" that inhibits unilateral maximum gain[7].

3.3 Relationship between neuromuscular adaptation and exercise intervention

The adaptation of nervous system is the core mechanism of exercise intervention. Strength training through motor unit recruitment enhancement and discharge frequency synchronization, the activation rate of high threshold motor units (such as Ⅱx type fibers) from 50% to 90%, can increase power output by 20% in the short term. Remodeling of the neuromuscular junction (NMJ) (e.g., acetylcholine receptor density ↑ 25%) further optimizes signal transmission efficiency. During long-term training, the plasticity of corticospinal pathway is enhanced, the precision of muscle control by motor cortex is improved, and the coordination is improved, which can reduce compensatory movements and reduce the risk of injury. In addition, the neural drive indirectly promotes muscle hypertrophy by inhibiting myostatin expression[8], as shown in Table 3.

Table 3. Sample comparison of the effects of three types of exercise on muscle mass (kg) and strength (1RM)

Exercise Type	Muscle Mass Change (kg)	Strength Change (1RM or VO_2 max)
Strength Training	+2.5	Bench Press 1RM +30kg
Endurance Training	+0.3	Max VO_2 +8 mL/kg/min
Combined Training	+1.2	Squat 1RM +15kg

Strength training (such as resistance training) has the most significant improvement in muscle mass, with data showing an average increase in muscle mass of 2.5kg and a 1RM (maximum weight per repetition) increase in bench press up to 30kg. This effect is due to the strong stimulation of type II fast muscle fibers by high load (>75% 1RM), which activates the mTORC1 pathway to promote protein synthesis, while enhancing neural drive (e.g. motor unit recruitment rate increased to 90%), and significantly improving power output in the short term[9].

Endurance training (such as long-distance running, cycling) mainly improves metabolic endurance, muscle mass is only slightly increased by 0.3kg, but the maximum oxygen uptake (VO_2max) increases by 8mL/kg/min. Its mechanism lies in the activation of AMPK pathway, the mitochondrial density increases by more than 40%, the oxidation capacity of type I slow muscle fibers is enhanced, and the low mechanical load has limited stimulation of muscle hypertrophy, so the strength increase is weak (squat 1RM only +5kg is not listed in the table 3).

Combined with training (alternating strength and endurance) to show balance benefits: muscle mass increase by 1.2kg, 1RM squat increase by 15kg. However, due to the "interference effect" (molecular signal conflict), the muscle-building effect is weaker than pure strength training (about 50% less), and the strength gain is also lower than that of strength training alone. However, combined training can synergistically improve body composition (decrease in body fat percentage) and movement coordination, which is suitable for comprehensive target population who need to take into account strength and endurance.

The choice of exercise type needs to be based on individual needs - strength training prioritizes muscle gain versus absolute strength, endurance training optimizes metabolic health, and combination training balances adaptation but accepts the tradeoff of single-dimensional gains. The data provided empirical basis for the formulation of precise exercise prescription.

4. Clinical Effects of Exercise Intervention for Sarcopenia

4.1 Overall effect of exercise intervention

Exercise intervention is the first-line strategy for the clinical management of sarcopenia, and its core mechanism is to reverse muscle loss through mechanical load and metabolic regulation. Strength training, as the most effective intervention, has been shown in randomized controlled trials (RCTS) to increase muscle mass by 5-8% and leg strength by 20-30% in elderly patients after 12 weeks of resistance training. Its mechanisms of action include activation of the mTORC1 pathway (increased muscle protein synthesis by 40%), inhibition of ubiquitin-proteasome activity (reduced muscle breakdown by 15%), and promotion of satellite cell differentiation (increased cross-section area of type II muscle fibers). Although endurance training has a limited effect on muscle hypertrophy (only a 1-2% increase in muscle mass), it significantly improves metabolic health: six months of aerobic exercise increases mitochondrial biosynthesis by 35%, increases insulin sensitivity by 25%, and reduces levels of the inflammatory factor IL-6 by 30% .

Combined training (strength + endurance) was outstanding in terms of functional improvement: a meta-analysis showed that patients in the combined intervention group improved their walking speed by 0.15m/s (50% higher than the control group) and reduced their risk of falls by 22% (Taaffe, 2006). Clinical evidence further suggests that the effect of exercise interventions is dose-dependent: resistance training $\geqslant$3 times per week at an intensity of $\geqslant$70% 1RM had the most significant muscle mass gain (SMD=0.82, P<0.001), while low-intensity exercise (e.g., Tai Chi) focused on improving balance function (balance test score ↑18%). In addition, exercise combined with protein supplementation (e.g., whey protein) can have a synergistic effect that increases muscle synthesis by an additional 30% (Trouwborst et al., 2018).

4.2 Comparison of effects of different exercise interventions

The efficacy of different exercise regimens for sarcopenia varies according to population characteristics and pathological status. Strength training alone was most effective in healthy older adults: an RCT of 320 patients showed a 7.5% increase in muscle mass in the high-intensity resistance group (80% 1RM) and only a 3.2% increase in the low-intensity group (50% 1RM) ($P<0.01$) . However, for patients with chronic conditions such as heart failure or COPD, low-intensity combined training is more feasible: a 12-week strength-aerobic combined regimen increases muscle strength by 15%, increases 6-minute walking distance by 20%, and is tolerated by 90%.

Gender differences also affect intervention effectiveness: Men have a stronger response to muscle hypertrophy in strength training (40% greater muscle mass gain than women), while women have a more significant improvement in function during flexibility training (joint motion ↑25%). In addition, the timing of intervention is critical: in patients with early SARcopenia (SARC-F score ≤4), 6 months of intervention reversed muscle loss (FFMI↑1.2kg/m²), while in advanced patients (SARC-F≥8), it only slowed progression (FFMI↑0.3kg/m²). It is worth noting that High intensity interval training (HIIT) performs well in young and elderly (65-75 years) (VO_2max↑18%), but can induce excessive fatigue (dropout rate up to 30%) in elderly (>80 years) or frail patients[10].

4.3 Safety and tolerability of exercise intervention

For the elderly population, the safety of exercise intervention should be given priority. A systematic review showed that supervised moderate intensity training (e.g., 50-70% 1RM) had a less than 3% incidence of adverse events, mainly consisting of mild muscle soreness (60% of participants) and joint discomfort (15%). The incidence of severe injuries (such as fractures) was <0.5%). Strength training should avoid high-load rapid centrifugal movements (such as squat jumping) to prevent tendon injury; Endurance training should monitor heart rate (controlled at 60-75% HRmax) to avoid cardiovascular events.

In terms of tolerability, compliance among older patients was strongly correlated with intervention design: completion of individualized programs (such as home elastic band training) was significantly higher (85%) than group gym training (65%). People with cognitive impairment or depression need to incorporate behavioral interventions (e.g., goal-setting + reward mechanisms) to increase engagement. Barriers to long-term adherence (>6 months) included lack of transportation (40%), fear of pain (25%), and lack of social support (30%). Potential risks need targeted management: osteoporosis patients should avoid high-impact exercise and use water resistance training; Exercise of diabetic patients should be combined with blood glucose monitoring to prevent hypoglycemic events.

Exercise interventions have a clear effect on sarcopenia, but they need to be tailored to the individual's health status, functional baseline and psychosocial factors, while collaborating with a multidisciplinary team (physician, physiotherapist, dietitian) to optimize safety and long-term compliance.

5. Exercise Intervention Strategies in Clinical Practice

5.1 Design and implementation of exercise intervention

The design of personalized exercise intervention program should be based on the patient's age, health status, functional baseline and psychosocial factors. Older adults (>65 years of age) should prioritize safety and use resistance training of low to moderate intensity (50-70% 1RM) combined

with balance training (e.g., standing on one leg) to reduce the risk of falls. For patients with chronic diseases (such as diabetes, heart failure), exercise intensity should be adjusted according to cardiopulmonary function tests (such as VO_2peak), such as diabetes patients exercise heart rate control at 60-70% of the reserve heart rate, and avoid fasting exercise in the morning to prevent hypoglycemia. Patients in the early stage of weakness (Fried frailty phenotype $\geqslant 1$) are recommended to adopt progressive combined strength-endurance training, which is mainly low load (30% 1RM) and high repetition (15-20 times/group) at the early stage, and gradually increase the intensity. In addition, patients with cognitive impairment need to simplify motor commands, incorporate visual cues (such as video demonstrations) and family involvement to improve compliance. In clinical practice, individual needs are quantified by physical fitness tests (e.g., grip strength, 6-minute walking test) and biomarkers (e.g., serum IL-6, muscle attenuation index) to dynamically adjust intervention regimens.

5.2 Formulation of exercise prescription

Based on the FITT principles (frequency, intensity, time, type), the exercise prescription for sarcopenia needs to be scientifically stratified:

Frequency: Resistance training 2-3 times per week (interval $\geqslant$48 hours), endurance training 3-5 times per week (can be alternated);

Intensity: Strength training should be 60-80% 1RM (starting from 50% for the elderly), endurance training intensity should be 50-70% of the reserve heart rate or Borg scale 12-14 (feeling slightly tired);

Time: Each training 45-60 minutes, including 10 minutes warm up (dynamic stretching) and 10 minutes cold (static stretching), main training (such as squats, bench press) 8-12 times per group, a total of 2-3 groups;

Type: Multi-joint complex movements (such as hard pulling and rowing) are preferred to activate muscle groups throughout the body, supplemented by functional training (such as sit-stand conversion) to enhance daily living ability. In patients with joint degeneration, water exercise or the use of instruments (such as leg lifts) to reduce load shock are recommended. The timing of protein intake (20-30g whey protein supplementation within 30 minutes after exercise) further enhances the anabolic effect.

5.3 Clinical challenges and implementation barriers

In clinical practice, exercise intervention faces multiple challenges:

Patient compliance: About 40% of elderly patients quit due to fear of pain, inconvenient transportation or lack of motivation, and the dropout rate of cognitive impairment groups is as high as 60%;

Resource constraints: primary medical institutions lack professional exercise instructors and equipment, and only 15% of community centers are equipped with resistance training equipment;

Safety concerns: Patients with osteoporosis or cardiovascular disease are prone to exercise-related injuries (such as a two-fold increased risk of fracture) and need to be closely monitored.

Inadequate assessment standardization: Muscle mass tests (e.g. DXA) are costly, and base-level reliance on simple scales (e.g. SARC-F) can lead to missed diagnosis. In addition, cultural differences (such as women's resistance to strength training) and lack of social support (30% of older adults living alone) further limit the intervention's effectiveness.

6. Conclusions

This article reviews the intervention strategies of exercise for sarcopenia, and discusses its mechanism and clinical application in depth. Studies have shown that appropriate exercise interventions can effectively slow or reverse the progression of sarcopenia and improve muscle mass and function in the elderly. Different types of exercise, such as resistance training, aerobic exercise, and combination training, all work at different mechanistic levels and have a positive impact on improving muscle strength, quality of life, and reducing health risks associated with sarcopenia. However, although there are some current studies supporting the effectiveness of exercise interventions, larger and longer clinical trials are needed to further verify the optimal effects of different intervention regimens and their safety.

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