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REVIEW

High Intensity Interval Training: A Potential Method for Treating Sarcopenia

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Abstract: Sarcopenia, an age-related disease characterized by loss of muscle strength and muscle mass, has attracted the attention of medical experts due to its severe morbidity, low living quality, high expenditure of health care, and mortality. Traditionally, persistent aerobic exercise (PAE) is considered as a valid way to attenuate muscular atrophy. However, nowadays, high intensity interval training (HIIT) has emerged as a more effective and time-efficient method to replace traditional exercise modes. HIIT displays comprehensive effects on exercise capacity and skeletal muscle metabolism, and it provides a time-out for the recovery of cardiopulmonary and muscular functions without causing severe adverse effects. Studies demonstrated that compared with PAE, HIIT showed similar or even higher effects in improving muscle strength, enhancing physical performances and increasing muscle mass of elder people. Therefore, HIIT might become a promising way to cope with the age-related loss of muscle mass and muscle function. However, it is worth mentioning that no study of HIIT was conducted directly on sarcopenia patients, which is attributed to the suspicious of safety and validity. In this review, we will assess the effects of different training parameters on muscle and sarcopenia, summarize previous papers which compared the effects of HIIT and PAE in improving muscle quality and function, and evaluate the potential of HIIT to replace the status of PAE in treating old people with muscle atrophy and low modality; and point out drawbacks of temporary experiments. Our aim is to discuss the feasibility of HIIT to treat sarcopenia and provide a reference for clinical scientists who want to utilize HIIT as a new way to cope with sarcopenia.

Keywords: Sarcopenia, high intensity interval training, persistent aerobic exercise, aging

Introduction of Sarcopenia

Definition, Prevalence, and Consequences

Sarcopenia is a disease closely related to aging.[1] The first meeting of the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death" performance.[2] The diagnostic criteria include three elements: low muscle mass, low muscle strength and low physical performance.[2] In 2018, EWGSOP2 prioritized decreased muscle strength as the most significant diagnostic parameter for sarcopenia,[3] and confirmed that this disease begins at an early age.[3] An updated consensus of Asia, the Asian Working Group for Sarcopenia (AWGS) 2019, defined sarcopenia as "age-related loss of skeletal muscle mass plus loss of muscle strength and/or reduced physical performance", which suggested the decline of muscle strength and physical performance are attributed to the loss of muscle mass.[4] The Foundation for the National Institutes of Health

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(FNIH) also diagnoses this disease by assessing muscle mass and muscle strength, but there are disparities in cut-off values and measurement modes between FNIH and EWGSOP2.[5] Through assessing the data from eight epidemiological cohorts with large scale, the 2020 Sarcopenia Definitions and Outcomes Consortium (SDOC) strongly emphasized the prognostic value of low grip strength and low gait speed on falls, low mobility, disability in daily life, and mortality, and SDOC suggested that weakness and slowness defined by low grip strength and low gait speed, respectively, should be included into the definition of sarcopenia. However, unlike other criteria, SDOC excluded the lean mass from the definition of sarcopenia.[6]

The prevalence of sarcopenia differs in ages, ethnicities, and sexes. In Europe, defined by EWGSOP standard, 5%–13% in people aged 60 to 70 and 11%–50% in people aged over 80 were suffered from sarcopenia, and the prevalence of sarcopenia was 1–29% (up to 30% in women) for older adults living in the community, 14–33% (up to 68% in men) for those living in long-term care institutions and 10% for those in acute hospital care.[7,8] In Asia, according to AWGS, the prevalence of sarcopenia was 5.5–25.7% in elderly people,[4] and in an elderly Chinese suburb dwelling population, 6.4% in men and 11.5% in women were diagnosed with sarcopenia.[9] Another report using AWGS criteria found that the prevalence of sarcopenia differed with ethnic groups in China, as 22.3% in Han ethnic, 18.2% in Tibetan, 11.8% in Qiang, 34.7% in Yi and 26.7% in Hui.[10] In the USA, the prevalence of sarcopenia ranges from 2.5% to 27.2% in women and ranges from 3.1% to 20.4% in men.[11] A meta-analysis synthesized the results of 41 studies which evaluated the prevalence of sarcopenia through different criteria (including the standard of EWGSOP, AWGS and so on).[12] On the whole, 14% (95% CI: 11–17%) men and 12% (95% CI:10–15%) women were suffered from sarcopenia.[12] In community-dwelling individuals, the prevalence were 11% (95% CI: 8–13%) in men and 9% (95% CI: 7–11%) in women. 51% (95% CI: 37–66%) men and 31% (95% CI: 22–42%) women in nursing-home and 23% (95%, CI: 15–30%) men and 24% (95% CI: 14–35%) women in hospitalized patients were attacked by sarcopenia.[12] Women are more likely to get sarcopenia than men.[9,13,14]

Sarcopenia causes serious loss of muscle quality and function, elderly people with sarcopenia have a higher risk of falling and fracture, difficulties in standing and walking, and they are prone to losing the ability to take care of themselves, causing a heavy burden on families and the society.[1,15] According to data from the UK and the USA, sarcopenia is associated with heavy cost of medical service.[16] And sarcopenia exacerbates heart failure and respiratory diseases, leading to low physical performance.[17,18] Because of inadequate movement, sarcopenia patients are easy to become obese, which further damages their health.[19] Sarcopenia is also associated with impaired cognitive function,[20] osteoporosis[21] and poorer prognosis in patients with surgery.[7]

Risk Factors and Molecular Mechanisms of Sarcopenia

Aging is the primary risk factor for sarcopenia. Generally, muscle mass is maintained during early life, but then declines at a rate of 1% or 0.5% per year in men or women, respectively.[22] From 20- to 80- year-olds, about 30% of our muscle mass and 20% of our cross-sectional area (CSA) will be lost.[22] Muscle waste in the elderly is mainly due to an imbalance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB),[23] which are balanced in younger individuals.[24] Reduction of type II muscle fiber size accounts for the majority of the muscle waste during aging.[25] During skeletal muscle aging, the mammalian target of rapamycin complex 1 (mTORC1) pathway plays an important role. MTORC1 pathway is activated by phosphoinositide 3-kinase (PI3K)-Akt pathway, which is upregulated by food (especially by protein rich in leucine) or exercise.[26,27] Two downstream targets of mTORC1 pathway, the 70-kDa ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E (eIF4E)-binding protein-1 (4E-BP1), promote the initiation and elongation of translation. After activation, mTOR can phosphorylate 4E-BP1 and S6K1. Phosphorylation of 4E-BP1 will remove the inhibition of eIF4E by 4E-BP1. As a result, eIF4E can directly bind to the 5’ end of mRNA and recruit eIF4G and eIF4A to form the translation preinitiation (eIF4F) complex.[28] Once phosphorylated, S6K1 will phosphorylate lots of translation-related factors, including the 40S ribosomal protein S6 (rpS6), eIF4B and eukaryotic elongation factor 2 (eEF2) kinase (phosphorylation of eEF2 kinase relieves the suppression of eEF2).[28] These events lead to hypertrophy of muscle cells.[29] In young adult muscles, anabolic stimuli such as exercise and feeding stimulate MPS and suppress MPB through mTORC1 signaling. Conversely, with aging, muscle becomes resistant or insensitive to anabolic stimuli, leading to impaired MPS and suppressed inhibition of MPB.[24,30] Twice as much leucine is required in aged rats than in young rats to stimulate the MPS to a predefined level.[31] Genes related to mitochondria, insulin signaling, and muscle growth were downregulated by aging, which may trigger anabolic stimuli-resistance.[32] Scientists hypothesized this phenomenon as the primary cause of muscle mass wasting in the elderly.[23] Atrophy of aged muscle may also be associated with the denervation: a reduction of motor neuron population has been observed in old animals due to impairment of normal cycling of denervation-reinnervation, but the mechanism of age-related denervation remains unclear.[33,34]

Due to dysfunction of antioxidant enzymatic (such as peroxiredoxin 6) and increased oxidative stress in aging, telomere attrition and DNA damage appear.[35,36] Thus, abilities of muscle satellite cells to proliferate and regenerate are impaired.[37] In addition, reports showed that oxidative stress suppressed the phosphorylation of eIF4E and 4E-BP1, and thus inhibited the mTORC1 pathway.[38,39] Simultaneously, oxidative stress damages protein homeostasis and induces proteolysis,[40] and it is reported that protein abundance decreased in the elderly, especially mitochondrial proteins.[32] Moreover, aging downregulates hormones which are crucial for the maintenance of muscle mass, strength and proliferation of satellite cells, including growth hormone (GH), testosterone, thyroid hormone (TH) and insulin-like growth factor-1 (IGF-1).[41–46]

Other risk factors associated with sarcopenia include malnutrition, inactivity, obesity, diseases, and early environment for growth. Dietary protein intake is pivotal in maintaining muscle mass of old people, as amino acids like leucine activate the mTORC1 pathway via the Rag guanosine triphosphatase (Rag GTPase) mechanism.[26,47] Malnutrition aggravates imbalance between MPS and MPB and significantly elevates the morbidity of sarcopenia in people aged over 65,[48,49] which could be prevented through high intake of protein and vitamin D;[50–52] exercise is a key stimulus for mTORC1 pathway,[53–56] but inactivity increases the risk of getting sarcopenia, an inactive period even as short as 2 days can significantly reduce muscle volume,[57] and one-hour increase in sedentary behavior per day led to 1.06 (95% CI = 1.04–1.10) times higher possibility for getting sarcopenia;[58] obesity promotes the infiltration of lipid into muscle, and thereby causing oxidative stress and impairment of mitochondria and leading to lipotoxicity;[59] diseases such as cancer often coincide with sarcopenia:[60] they raise abnormalities in glucose metabolisms,[61] upregulate pro-inflammatory cytokines, myostatin, and proteolysis-inducing factor (PIF), which activates forkhead box O (FOXO) (activation of FOXO causes autophagy and expression of the atrophy-related ubiquitin ligases Atrogin 1 and muscle RING finger-containing protein 1 (MURF1)).[62,63]

Feasibility of High Intensity Interval Training (HIIT) to Deal with Sarcopenia

While exercise has been observed to play a pivotal role in health, various physical activity guidelines have persuaded people to take part in exercise. The American College of Sports Medicine (ACSM) proposed every adult to strengthen and maintain the functions of cardiopulmonary through moderate exercise 30–60 min per day (≥5d per week), or vigorous exercise 20–60 min per day (≥3d per week), or a combination of moderate and vigorous exercise per day (≥3-5d per week).[64] At present, no specific drug has been approved for the treatment of sarcopenia, and hence exercise remains the most effective strategy to deal with sarcopenia.[1] Traditionally, moderate intensity continuous exercise (MICT) with high exercise volume was recommended by most guidelines.[65] MICT is a modality of exercise at approximately 64%–76% of their HR_{max}, or exercised with prescribed intensity as a percentage of VO_{2max}, VO_2R, HRR, or RPE equivalent to 64–76% of HR_{max} with long duration (more than 30 min).[66,67] However, high intensity interval training (HIIT), which is characterized by repeated short to long bouts of relatively high-intensity exercise (≥90%VO2max or >90–95% HRmax for 6 s to 4 min) alternate with recovery periods of either low-intensity exercise or rest (ranging from 20% to 40% VO2max for 10 s to 5 min), emerged as an alternative for traditional continuous training.[68,69]

Firstly, HIIT displays comprehensive effects on exercise capacity and skeletal muscle metabolism. HIIT induces great growth of muscle, prevents skeletal muscle atrophy, and improves the motor function via promoting great phosphorylation of mTOR and rps6 and inducing the expression of transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), which is crucial for mitochondrial biogenesis.[70,71] It is also of importance to the vascularization of muscle.[72] Animal studies have already proved that HIIT significantly enhances physical performance and muscle mass in frail aged mice.[73,74] Some studies showed that elder people received HIIT protocol were observed to have significantly increased muscle mass, muscle quality, physical performance and muscle strength, compared with MICT or control groups.[75–79] In a scoping review, Hayes and colleagues summarized 32 articles related to HIIT. In this review, there were 20 papers tested the effect of HIIT on muscle function, and most of them reported that HIIT could enhance muscle strength and power; 12 studies focused on the effect of HIIT on physical function, all of which showed the improvement of physical performance after HIIT; nevertheless, 22 studies which analyzed the effect of HIIT on muscle quantity had contradictory conclusions, and generally speaking, the effect of HIIT on muscle quality and quantity is unclear.[80]

Secondly, HIIT provides a time-out for the recovery of cardiopulmonary and muscular functions without causing severe adverse effects.[81–83] A pilot study confirmed that HIIT was feasible and safe for hospitalized patients over 65 who were recovering from acute medical condition.[84] Rognmo Ø et al assessed the risk of HIIT and MICT among 4846 coronary heart disease patients (mean age = 57.8), and the results reflected that only one fatal case occurred during MICT (129 456 exercise hours) and two non-fatal cases occurred during HIIT (23,182 hours).[85] Many other studies also showed that HIIT would not cause severe adverse effects on patients with coronary artery disease.[86–88] Interval exercise may be safer than continuous exercise for patients with cardiovascular disease (CVD).[89]

Furthermore, numerous studies have demonstrated that HIIT could improve the cardiopulmonary functions of patients with CVD and the outcomes of diabetes mellitus. CVD patients have been found to acquire higher quality of life and greater heart rate (HR) response to exercise after receiving HIIT.[90] HIIT also reduces insulin resistance and enhances skeletal muscle sugar intake.[91]

Effects of Different Exercise Parameters on Sarcopenia

When evaluating the physiological responses raised by a specific type of exercise, multiple variables should be taken into consideration. The intensity, volume, rest interval between sets, order of exercises, movement velocity, load lifted and training frequency are the main methodological variables of prescription.[92] Exercise-induced physiological strain, also called training load, results from the combination of exercise intensity, volume, and frequency.[93] To demonstrate the rationality of HIIT in the treatment of sarcopenia, we will discuss the effects of different intensities and rest intervals between sets and volumes of exercise on sarcopenia and the elderly, and try to find an optimal combination of these parameters for sarcopenia treatment.

Intensity

Exercise intensity is an important determinant of the physiological responses to exercise training. Methods measuring exercise intensity include percentage heart rate maximum (%HR_{max}), percentage heart rate reserve (%HRR), percentage peak oxygen uptake (%VO_{2max}), percentage VO_2 reserve (%VO_2R), rating of perceived exertion (RPE), metabolic equivalent (MET), or competition pace.[94] VO_{2max} (equation 1) is a physiological characteristic which presents the maximal rates of oxygen utilization in skeletal muscle. And it is determined by the ability of the heart and muscle to deliver and accommodate oxygen, respectively.[95]

Eq.1 VO_{2max}= (left ventricular (LV) end-diastolic volume —LV end-systolic volume) × HR ×arterio-venous oxygen difference

VO_{2max} reflects the exercise ability of a person, which is closely associated with endurance performance.[95] HR exhibits a linear relationship with VO2, particularly between HR of 110–150 beats per minute.[96,97] Because different people respond diversely to the same modality of exercise, scientists prefer to use %HR_{max} and %VO_{2max} for determining the optimal exercise intensity during HIIT.[98] As resting HR and HR_{max} changes with age and fitness level, and therefore %HRR (equation 2) was recommended as a more accurate way to quantify and prescribe exercise intensity.[99]

$$Eq.2\ \%\ \text{heart rate reserve} = \frac{(\text{HRex—HRrest}) \times 100}{\text{HRmax—HRrest}}$$

HR_{ex}: average heart rate of the exercise session; HR_{rest}: resting heart rate.

Metabolic Equivalent (MET), Borg's Rating of Perceived Exertion (RPE) Scale and Repetition maximum (RM) are also being widely used to assess subjective perception of effort during exercise.[100] One MET is defined as the resting metabolic rate, which is the amount of oxygen consumed at rest, approximately 3.5 mL O2/kg/min (1.2 kcal/min for a 70-kg person);[101] the RPE (6–20) scale begins with "no exertion at all" (RPE = 6), and ends with "very, very hard," (RPE = 20);[102] the 1-RM is defined as the greatest load that one can mobilize during the concentric phase of a movement in a single contraction, 40%–50% 1RM (very light to light intensity) was recommended by ACSM for older persons beginning exercise to improve strength.[64] The range of exercise intensity calculated by% HRmax, % VO2max, % 1-RM, RPE scale and MET level is shown in Table 1.

High intensity exercise has already been studied to cope with sarcopenia. One research compared the effects of high intensity resistance training (HI-RT) and inactive state on sarcopenia patients. Participants in HI-RT group were observed to get an increase in skeletal muscle mass index (SMI) and gait velocity, and hand grip strength was maintained, while both SMI and hand grip strength were reduced in the inactive control group (CG).[103] Other studies also showed HI-RT was of benefit in keeping bone mineral density.[81,104]

Multiple groups investigated the effects of different intensities of resistance training (RT) on muscle quality and physical performance. Lasevicius et al designed a within-subject experiment, in which one leg and arm trained at 20% 1RM (G20) and the contralateral limb was randomly distributed to three groups: 40% (G40); 60% (G60), and 80% 1RM (G80). After 12 weeks, elbow flexion 1RM and muscle CSA increase in G80 condition was significantly higher than those in G20, G40, and G60 conditions.[105] There was no significant difference in the increase in unilateral leg press strength between G60 and G80, but they both displayed more obvious effect than G20 and G40.[105] Seynnes et al found that while both high intensity (HI) (80% 1RM) and low intensity (LI) training (40% 1RM) significantly improved muscle strength and endurance of frail elders compared with the control, high intensity training group elicited significantly better outcomes than low intensity training group.[106] A similar phenomenon was observed by other scientists.[107,108] Results from Sahin and colleagues showed that, though improvement of muscle strength in the HI group was not superior to the LI group, frail elders in the HI group displayed a better physical performance, which was analyzed by walking speed, balance while standing and standing up from a chair.[109] However, when it comes to the gains in muscle mass, low to moderate intensities (30–50% 1RM) have a similar or even greater effect compared with high intensities.[105]

Above all, all the low to high intensities training enhances muscle strength and muscle mass of the elderly, but high intensities displayed greater effect than low-intensity to moderate intensity on increasing strength without causing higher risks.

Rest Interval Between Sets

The staple characters that differentiate HIIT from continuous training are the duration and ratio of high-intensity and low-intensity intervals, which play a pivotal role in the physiological response caused by HIIT.[110] Compared with continuous training, interval training induces greater health benefits when training volumes are equal or similar.[111]

The acute physiological requirements of different interval-training protocols are determined by VO_{2max}, as the improvement of VO_{2max} is linked with the duration of a high level of VO_2. From the perspective of athletic training, three categories of interval training are usually described: long intervals (3–15 minutes, intensity 85–90% VO_{2max}), moderate intervals (1–3 minutes, intensity 95–100% VO_{2max}), short intervals (10 seconds to 1 minute, 100–120% VO_{2max}).[112] From the perspective of the training for old people with CVD, there are also three categories of interval

Table 1 Ranges of Exercise Intensity Calculated Through $\%hr_{max}$, $\%VO_{2max}$, %1-RM, RPE Scale and MET level[64,101,102]

Intensity	$\%HR_{max}$	$\%VO_{2max}$	% HRR	% 1-RM	RPE Scale	MET Level
Light	57 to <64	37 to <45	30 to <40	40–50	9–11	<3
Moderate	64 to <76	46 to <64	40 to <60	60–70	12–13	3 to <6
High	76 to <96	64 to <91	60 to <90	>80	14–17	6 to <8.8
Near maximal	≥96	≥91	≥90		≥18	≥8.8

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training, which may be more appropriate for patients with sarcopenia: long intervals (high/low intensity interval: 3–4/3-4 minutes, intensity 85–95% VO_{2max}), moderate intervals (high/low intensity interval: 1–2/1-4 minutes, intensity 85–95% VO_{2max}), short intervals (high/low intensity interval: 15–60/15-120 seconds, 85–95% VO_{2max}).[90]

Multiple groups have studied the exercise performance for different rest interval lengths. Schoenfeld BJ and colleagues separated twenty-one young resistance-trained men to either a group that performed an RT program with 1-minute rest intervals (SHORT) or with 3-minute rest intervals (LONG), and they found that maximal strength and muscle thickness were significantly greater for LONG compared with SHORT;[113] results from another group suggested that 1-minute rest might be detrimental, which significantly elevates the blood lactate from baseline, compared with resting 3 or 5 minutes.[114] Traditionally, when training with the intention to enhance muscle strength, 3–5 minutes' rest between sets can produce greater effect, because longer rest intervals ensure higher intensities and volumes;[92] moderate-intensity sets combined with short rest intervals of 30–60 seconds might be the best choice for muscle hypertrophy, which induces a greater level of GH.[92]

Many studies compared the effects of HIIT protocols with different rest intervals. Edge and colleagues allocated 12 young women to two groups: subjects performed HIIT regimes with the same training intensity and volume, but either a short (1 min; HIT-1) or a long (3 min; HIT-3) rest intervals. There were no significant differences in the enhancement of physical performance and muscle adaptation (like Na(+), K(+)-ATPase content) between HIT-1 and HIT-3.[115] In the trial of Tucker et al, 14 recreationally active males participated in either a 4 × 4 (four 4-minute intervals at 90–95% HRpeak, separated by a 3-minute recovery at 50 W) or 16 × 1 (sixteen 1-minute intervals at 90–95% HRpeak, separated by a 1-minute recovery at 50 W) protocol on a cycle ergometer, and physiological responses elicited by these two protocols were similar.[116] Schoenmakers and colleagues showed that the total physiological strain endured during training was not greatly affected by the length of recovery durations.[117] However, these trials, as well as other similar studies,[118–120] were all focused on the athletic abilities of young people, which may not be practical for sarcopenia patients.

Efforts have been spent to find out whether interval exercise was suitable for old people. Previous study indicated that interval exercise could accelerate cerebral blood flow as effectively as continuous exercise, without leading to a large increase in blood pressure, and therefore interval exercise may be safer than continuous exercise for the elderly, especially for those suffering from CVD.[89] One paper pointed out that a 30-second rest interval was enough for older women to recover between sets of a knee flexor exercise, but younger women needed more time, which indicated that when prescribing rest interval between sets, practitioners should consider age differences.[121] Villanueva MG and colleagues conducted a study on elderly men to assess the different effects of short rest intervals (RI) in between sets (SS, 60 s) and extended RI (SL, 4 min) on body composition and performance. Outcomes showed that after 8 weeks of low-volume and high-intensity strength training, SS group presented a greater increase in lean body mass (LBM).[122] This result was consistent with previous findings which showed that short rest intervals were more beneficial in inducing hypertrophy.[92] However, SS group also showed greater improvement in strength and muscular performance,[122] while previous research suggested that long rest intervals (3–5 minutes) are required for optimizing strength improvement,[92]

So far, previous studies of interval training were mostly focused on young people, and experiments implemented on the elderly or sarcopenia patients are scarce. Additionally, no studies had compared the effects of HIIT with different rest intervals on sarcopenia patients or elderly people. Data from Villanueva et al indicated that a rest interval as short as 60 seconds was more beneficial than a long rest interval for elderly people in high intensity training, but this result was limited by a small sample size (only 22 participants) and short-term intervention (only 8 weeks).[122] Therefore, future research should test the effects of different lengths of rest intervals between sets on sarcopenia patients, and try to find a precise rest interval length in HIIT which can play the optimal role in treating sarcopenia. Furthermore, future research should be carried out with a larger sample size and longer training intervention to determine if the effects of different rest interval lengths led to chronic changes in body composition, muscular performance adaptations, and functional capacity of elderly people.

Volume

Training volume is a measure of the total amount of work (joules) performed in a given time period. The number of sets, the total number of repetitions, the total duration of work and the total work are used to estimate the amount of training in previous studies.[123] The amount of training is commonly described as the product of the number of repetitions × number of sets × intensity load.[124]

Schoenfeld et al studied the increase in strength and muscle mass after different volumes of training.[125] They classified training volume by total number of sets: low-volume group (1SET), moderate-volume group (3SET), high-volume group (5SET) performing one, three or five sets per exercise per training session, respectively. Each group trained three sessions per week. The training times of each session of different groups are 13 min for 1SET, 40 min and 68 min for 3SET and 5SET. Afterwards, 1SET had equal elevation of strength and muscular endurance compared with 3SET and 5SET. Therefore, low volume training can be used as a time-efficient way for strength training.[125] A study conducted on athletes showed that moderate volume exercise contributes more to strength gains in high intensity exercise than low volume and high volume, but this result needed to be verified if it can be applied to old people with sarcopenia.[126] Nevertheless, higher volume was more effective than lower volume training on inducing muscle hypertrophy.[125,127] Meta-analysis depicted the dose–response relationship between training volume and muscle hypertrophy, as a higher increase in muscle mass was induced by higher weekly training volumes.[128]

Physiological responses resulting from low volume HIIT have been studied. Low-volume HIIT (total volume: approximately 225 kJ week (−1)) was as effective as endurance training (total volume: approximately 2250 kJ week (−1)) in increasing skeletal muscle oxidative capacity and inducing specific metabolic adaptations.[129] Low volume HIIT and MICT exhibited similar effects on improvements of functional capacity in elderly women, while mean energy consumption of HIIT was only 45% of energy consumed by MICT.[130] Besides, low volume high intensity training may be even more enjoyable; as a result, prescriptions for low volume training may attract more sarcopenia patients to follow.[131]

To sum up, low volume HIIT might become a time-sufficient and pleasant way to treat old patients with sarcopenia. High volume training is more effective in improving muscle size, which seems to be more suitable for bodybuilders than sarcopenia patients. The time spent on training is negatively associated with the risk of CVD and type 2 diabetes, and therefore high-volume training is also beneficial to sarcopenia patients.[124] Furthermore, high training volume may complement the disadvantages of low intensity training compared with high intensity training, so when patients are reluctant to increase the intensity of load in their training, high volume and low intensity training is also effective.[124] However, no study has compared the effects of high-volume HIIT and low-volume HIIT on muscle, so above experiments can only be considered as indirect evidence, and efforts are needed to make up this problem.

Comparison Between HIIT and Persistent Aerobic Exercise (PAE)

PAE is a traditional exercise method which has already been applied in various fields including management of obesity, maintenance of physical performance, treatment of hypertension and improvement of cardiopulmonary functions.[132–135]Aerobic exercises are cardiorespiratory endurance exercises, such as jogging, running, treadmill walking, stationary cycling, stair climbing and cycling.[67,136] MICT is the foundation of aerobic-based exercise prescription.[90] Most of the PAE training methods were carried out in the modality of MICT.[137–139]

However, the status of PAE is being challenged by HIIT. For instance, studies reported that, both in young and old people, HIIT was more effective than MssssICT in enhancing vascular function[133] and improving cardiorespiratory capacity;[140–143] oxidative stress of the myocardium after myocardial infarction can be better attenuated by HIIT than MICT;[144] and compared with MICT, HIIT displayed similar or greater impacts on reduction of adiposity,[65,145] increase in insulin sensitivity in obese people,[146] reduction of blood triglycerides (TGs) and glucose levels in older individuals,[138,147] and enhancement of immune system with significant reduction of the time commitment.[148] At the same time, both HIIT and MICT displayed similarly high rate of completion and attendance, and low rate of adverse events in patients with CVD.[66,85]

Studies comparing the effects of HIIT and MICT on aged skeletal muscles and sarcopenia are emerging. An animal experiment showed that both HIIT and MICT increased running time to exhaustion and maximum running speed of aged rats similarly, but HIIT improved grip power performance greater than MICT.[74] This phenomenon was also observed by Li and colleagues, and meanwhile they found that rats in HIIT group showed a larger increase in muscle weight compared with MICT group, and HIIT was more powerful than MICT in ameliorating oxidative stress and inflammation aggravated by aging.[149,150] Multiple studies compared the effects of HIIT and MICT on muscle strength of the elderly. A study on older women (age = 67.8 ± 6.2 years) showed that HIIT improved upper limb strength better than MICT, but there were no statistical differences between their effects on cardiorespiratory function, strength of lower limb and gait/dynamic balance.[76] Nemoto K and colleagues designed an experiment to test the effects of high-intensity interval walking training (3-minute low-intensity walking at 40% of peak aerobic capacity and 3-minute high-intensity walking above 70% of peak aerobic capacity) and moderate-intensity continuous walking training, and results showed that the high-intensity interval walking training was significantly better than MICT in increasing thigh muscle strength (examined by isometric knee extension and flexion), along with the peak aerobic capacity for cycling and walking.[151]

Some studies were concentrated on physical performance and muscle mass. A group of elderly people were randomly divided into three conditions: no walking training, moderate-intensity continuous walking training, or high-intensity interval walking training. Outcomes showed that in HIIT group, all of the isometric knee extension, isometric knee flexion, peak aerobic capacity for cycling, and peak aerobic capacity for walking got better augmentation than those in MICT group.[151] Keogh and colleagues tested the change in physical function (measured by Timed Up and Go (TUG), Sit to Stand (STS) and preferred gait speed) of osteoarthritis patients after receiving home-based HIIT or MICT. HIIT displayed superiority in improving TUG, but there were no statistical differences between the changes in STS, gait speed and muscle mass in HIIT and MICT groups.[152] However, for overweight/obese postmenopausal women, only the combination of HIIT and RT could significantly enhance muscle mass, while HIIT or MICT alone did not have this function.[153] Although in some cases, compared with MICT, HIIT did not present superior capacity in enhancing muscle function and physical performance, HIIT and MICT displayed similar effects, and HIIT seemed to be more acceptable: participants in HIIT group tended to complete more sessions than those in MICT group.[84]

Expressions of certain genes are influenced by HIIT and MICT, which might explain the phenomena happening in skeletal muscles after such training. Animal experiment revealed that while phosphorylated mTOR protein levels of sarcopenic rats were similarly elevated by HIIT and MICT, HIIT group exhibited higher level of PGC1-α.[145] Both MICT and HIIT can strengthen the antioxidative system through inducing the expression of succinate dehydrogenase (SDH) and superoxide dismutase 2 (SOD2), promote the function of mitochondria through upregulation of oxidative phosphorylation (OXPHOS) proteins, and sustain the calcium homeostasis, but only HIIT can significantly upregulate levels of autophagy-related gene (Atg)-3, microtubule-associated protein 1 light-chain 3-II (LC3-II), B-cell lymphoma 2 (Bcl-2), the Bcl-2/Bcl-2-associated X protein (Bax) ratio, AMP-activated protein kinase (AMPK), p-AMPK, and ADP receptor 1.[74] Elevated expression of Bcl-2 and Bcl-2/Bax ratio prevent age-related apoptosis of skeletal muscle cells, and elevated expression of Atg-3, LC3-II, AMPK and ADP receptor 1 indicated that HIIT had a greater potential than MICT to improve autophagy damaged by aging.[74]

Overall, compared with PAE, HIIT is more effective at improving the physical performance and attenuating the process of sarcopenia. Simultaneously, HIIT is superior to PAE in ameliorating patients' physical fitness and motor function in various aspects. Furthermore, the time expenditure of HIIT is much less than MICT and HIIT is more enjoyable for people to perform.[154,155] Therefore, HIIT may be a valid and time-efficient way to slow down the progression of sarcopenia. However, the study performed directly on sarcopenia patients is devoid. Therefore, the above results still need to be further studied.

Metabolic Changes During and After HIIT

HIIT will raise remarkable metabolic changes in sarcopenia patients. Firstly, acute skeletal muscle responses will occur. HIIT upregulates 22 mitochondrial genes in older people, including genes participating in translational regulation and mitochondrial tRNA transferase, thereby resulting in a significant increase in protein abundance.[32] HIIT's impact on mRNA expression and MPS is predominant in both young and older people, and even greater among the elderly, and thus HIIT may overcome the anabolic stimuli-resistance associated with aging.[32] Phosphorylation of AMPK and the p38 mitogen-activated protein kinase (MAPK) will increase after HIIT. During contraction, p38 MAPK, which might be activated by growing level of reactive oxygen species, stimulates upstream transcription factors of PGC-1a gene.[156,157] AMPK directly phosphorylates PGC-1α and activates Sirtuin 1 (Sirt1) by increasing the level of NAD^+, and thereby Sirt1 can promote the deacetylation of PGC-1α.[158] PGC-1α coactivates two key nuclear respiratory factors (NRFs), NRF-1 and NRF-2, which activate mitochondrial transcription factor A (Tfam) and bind to promoter regions of nuclear genes encoding subunits of complexes in mitochondrial electron transport chain (ETC), thereby reinforcing respiratory capacity of mitochondria.[159,160] PGC-1α protects muscle mass and retards the atrophy induced by denervation, and inhibits the ability of FOXO to bind to the promoter of atrogin-1.[161,162] Akt also can suppress FOXO pathway.[161] HIIT can enhance glucose transportation, insulin sensitivity and C reuptake of sarcoplasmic reticulum (SR), so as to improve energy supply and working ability.[163] Akt/PKB, which is required for the translocation of glucose transporter 4 (GLUT4), is upregulated by HIIT, and simultaneously, upregulation of AMPK, Ca^{2+} and p38 MAPK during HIIT induces the expression of GLUT4 gene.[164,165] Then, GLUT4 can increase insulin sensitivity.[156]

Secondly, cardiac adaptation will be observed. Like skeletal muscles, the mTORC1 pathway in myocardium will also be activated, resulting in physiological hypertrophy.[163] Intermittent training can restore the contractile function damaged by sedentary, which reinforces synchronicity of SR Ca^{2+}release, density of T-tubule, and activity of SR Ca^{2+}ATPase.[166] Furthermore, cardiac structure will be protected and improved by HIIT: HIIT could ameliorate end-diastolic pressure and systolic pressure, reduce left ventricular hypertrophy, and left ventricular end-diastolic diameter.[167–169] HRR, MET capacity and VO_{2max} can all be improved by HIIT.[167,170,171]

Furthermore, if patients suffer from obesity, which potentiates the progress of sarcopenia,[59] HIIT is capable of enhancing skeletal muscle and reducing adiposity at the same time. High-intensity exercise significantly increases catecholamine responses, which promotes fat oxidation (Fox) by β-adrenergic receptors. Plasma catecholamine levels and sympathetic neural activity grow exponentially over intensity and time, especially at work intensity above 70% VO2max.[172,173] HIIT can also elevate β-adrenergic receptor sensitivity in adipose tissue.[171] Furthermore, the rise of β-Hydroxyacyl acyl-CoA dehydrogenase, citrate synthase and fatty acid-binding protein during HIIT promote the consumption and transportation of free fatty acid.[174] Collectively, HIIT significantly reduces fat in the blood and liver.[163] Nevertheless, HIIT may not reduce body weight while reducing body fat because of muscle hypertrophy.[171] The molecular mechanisms of HIIT on treating and preventing sarcopenia are shown in Figure 1.

Conclusion

A growing number of scientists have realized the clinical importance of sarcopenia. Studies have revealed multiple risk factors for this disease, including genes, malnutrition, inactive lifestyle, obesity, hormone imbalance, evolutionary basis and so on. Despite spectacular progress in science and technology, effective treatments of sarcopenia are still devoid, and the specific pathophysiology of the age-related loss of muscle remains unclear.

HIIT is a potential method to treat sarcopenia, and its feasibility has been demonstrated in various aspects. High intensity training is more effective than low to moderate intensity in increasing strength without causing higher risks; compared with the continuous training, the interval training raises more acute physiological responses, and provides a rest time to restore muscle strength and cardiorespiratory functions, making it easier for body to adapt; low volume training elicits similar increase in strength compared with moderate-to-high volume training with less expenditure on time. In addition, relative to PAE, HIIT is more effective on improving the physical performance, and it also has greater impacts on reinforcing cardiorespiratory function for long-term training, reducing body fat and improving the effectiveness of energy use through managing diabetes, but the time expenditure of HIIT is much less than MICT, so HIIT is a potent alternative for PAE; moreover, HIIT elicits great level of mRNA expression and protein abundance in both young and old people, and therefore HIIT might overcome the anabolic-stimuli resistance in elderly. Above all, low HIIT is a time-efficient exercise strategy for attenuating the progress of sarcopenia and improving the living quality of patients.

However, multiple questions remain to be figured out. Short rest interval is demonstrated to be the best choice for inducing muscle hypertrophy, but there are controversial results of the effects of short or long rest interval between sets on the improvement of muscle strength, which is required to be elucidated; low volume HIIT is time-efficient and beneficial to muscle strength, but the effects of low to moderate intensity and high-volume training on promoting muscle hypertrophy and reducing the risks of CVD and type 2 diabetes should not be ignored; and experiment comparing the effects of HIIT protocols with different volumes or different rest intervals on the elderly was still scarce. Besides, previous studies were limited by short-term intervention and small sample size, and many results were achieved in animal experiments. Furthermore, it is worth mentioning that no study was conducted directly on sarcopenia patients.

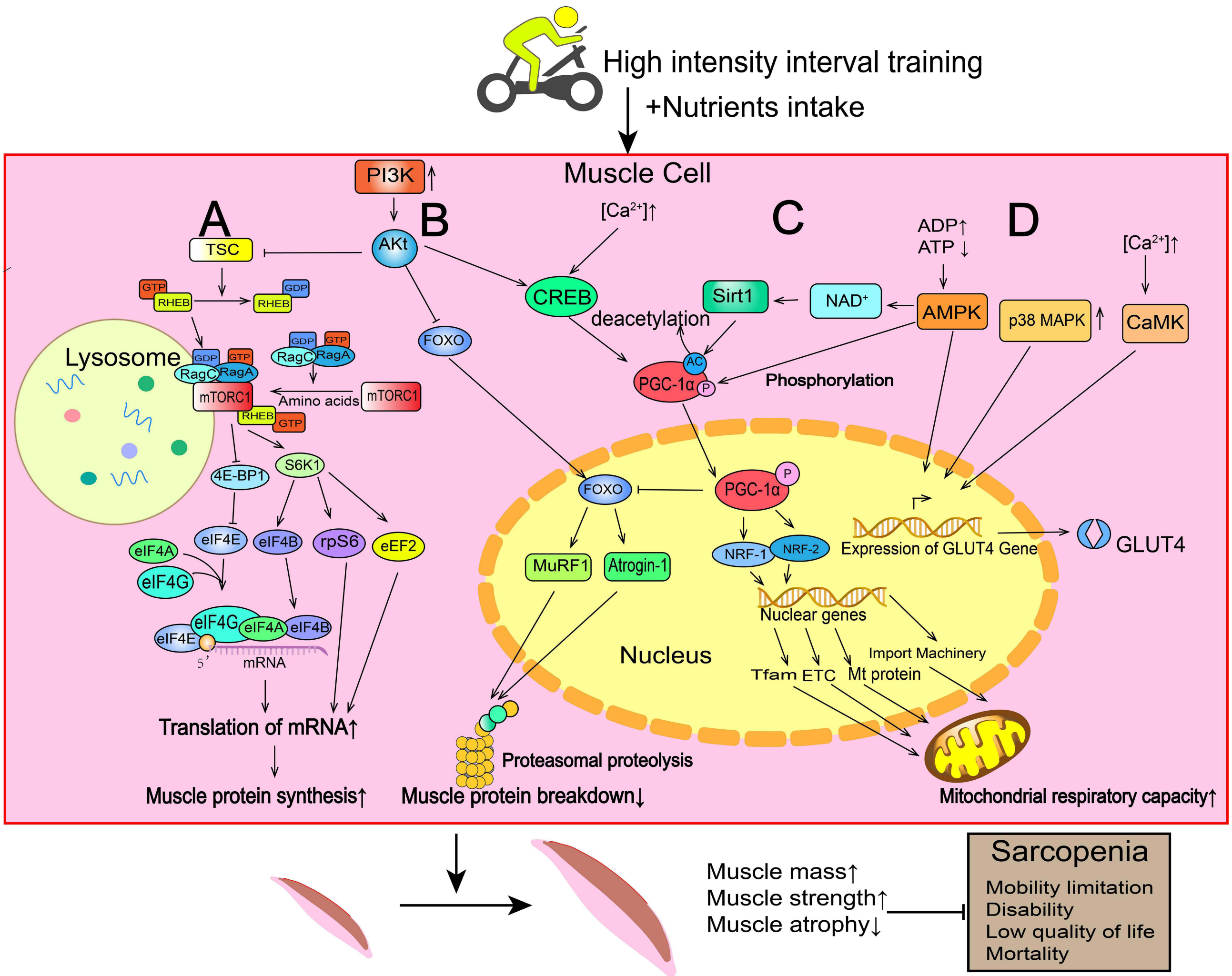

Figure 1 Molecular mechanism of HIIT on treating and preventing sarcopenia. (**A**) Promotion of muscle protein synthesis. HIIT and enough nutrient supplementation upregulate PI3K/Akt pathway. Akt inhibits tuberous sclerosis complex (TSC) through phosphorylation. TSC facilitates the conversion of RHEB-GTP to RHEB-GDP, thereby inhibiting the function of RHEB-GTP to activate mTORC1. Thus, mTORC1 pathway is relieved from the inhibition of TSC. And with the existence of amino acids, Rag guanine triphosphatases (Rag GTPases) promote the translocation of mTORC1 to lysosome where RHEB-GTP activates mTORC1. Thus, muscle protein synthesis is triggered. (**B**) Inhibition of muscle protein breakdown. Akt-mediated phosphorylation inhibits FOXO and the expression of the atrophy-related ubiquitin ligases Atrogin 1 and MURF1, and thus suppresses muscle protein breakdown caused by Proteasomal proteolysis. (**C**) Enhancement of mitochondrial biogenesis. Concentration of Calcium ion and expression of AMPK in muscle cells are unregulated by HIIT. Calcium ion and Akt promote PGC-1α pathway through CREB, and AMPK activates PGC-1α through direct phosphorylation and SIRT1-dependent deacetylation. PGC-1α enhances the expression of NRF1 and NRF2, which stimulate mitochondrial biogenesis and increase of mitochondrial respiratory capacity. (**D**) Promotion of the GLUT4 expression. AMPK, Ca^{2+} and p38 MAPK can induce the expression of GLUT4 gene.

Abbreviations: Akt, protein kinase B; AMPK, AMP activated kinase; eIF, eukaryotic initiation factor; mTORC1, mammalian target of rapamycin complex 1; 4E-BP1, eukaryotic initiation factor 4E (eIF4E)-binding protein-1; Rag, Ras-related GTPase; rpS6, ribosomal protein S6; S6K1, p70 ribosomal S6 kinase 1; CaMK, calcium/calmodulin-dependent protein kinase; CREB, cAMP response element-binding protein; ETC, electron transport chain; NRF, nuclear respiratory factor; PGC-1α, proliferator-activated receptor γ coactivator 1α; SIRT1, sirtuin 1; Tfam, mitochondrial transcription factor A; Mt, mitochondria; GLUT4, glucose transporter 4; MAPK, mitogen-activated protein kinase.

Hence, it is necessary to implement clinical trials on elderly people with long-term intervention and large sample size in the future.

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Disclosure

The authors declare that they have no competing interests.

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