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Physical Exercise as Therapy for Frailty

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Abstract

Longitudinal studies demonstrate that regular physical exercise extends longevity and reduces the risk of physical disability. Decline in physical activity with aging is associated with a decrease in exercise capacity that predisposes to frailty. The frailty syndrome includes a lowered activity level, poor exercise tolerance, and loss of lean body and muscle mass. Poor exercise tolerance is related to aerobic endurance. Aerobic endurance training can significantly improve peak oxygen consumption by ~10–15%. Resistance training is the best way to increase muscle strength and mass. Although the increase in muscle mass in response to resistance training may be attenuated in frail older adults, resistance training can significantly improve muscle strength, particularly in institutionalized patients, by ~110%. Because both aerobic and resistance training target specific components of frailty, studies combining aerobic and resistance training provide the most promising evidence with respect to successfully treating frailty. At the molecular level, exercise reduces frailty by decreasing muscle inflammation, increasing anabolism, and increasing muscle protein synthesis. More studies are needed to determine which exercises are best suited, most effective, and safe for this population. Based on the available studies, an individualized multicomponent exercise program that includes aerobic activity, strength exercises, and flexibility is recommended to treat frailty.

Introduction

The population aged 65 years and older is expected to more than double between 2012 and 2060 (from 43.1 to 92 million) [1]. The continuing increase in the older population has generated interest toward investigations of older adults who are 'frail'. Frailty is a state of vulnerability that carries an increased risk for adverse outcomes [2]; it can be viewed as a transition phase in older people between good health and poor health. Frail older adults are less capable of tolerating the stress of medical illness, hospitalization, and immobility. Common signs and symptoms are fatigue, weight loss, muscle weakness, and progressive decline in function. Frailty is more prevalent in older people and in those with multiple medical conditions.

Concomitant with age, there is a decline in voluntary physical activity which is associated with decreases in numerous measures of exercise capacity, including peak oxygen consumption (VO_{2peak}), muscle strength, and fatigability, ultimately leading to frailty [3]. Recently, it has been recognized that most older adults who are obese also meet criteria for frailty because of decreased muscle mass and strength that occurs with aging (sarcopenia) and a need to carry greater body mass due to obesity [4]. Because frailty increases the risk for loss of functional independence and decreases the quality of life, the identification of cost-effective interventions to prevent or ameliorate frailty is one of the most important public health challenges. Accordingly, exercise may be an effective strategy to prevent and treat frailty as it can target four of the five commonly used criteria: weakness, low physical activity, slowed motor performance, and poor exercise tolerance [5]. Frailty is not a contraindication to physical activity, rather it maybe one of the most important indications to prescribe physical exercise. Longitudinal studies have demonstrated that regular physical activity extends longevity and reduces the risk of physical disability. In fact, cardiorespiratory fitness has been found to be a significant mortality predictor in older adults, independent of overall or abdominal obesity [6]. In more than 10,000 older adults participating in the EPESE (Established Populations for Epidemiologic Studies of the Elderly) studies, an almost twofold increased likelihood of dying without disability was found among those most physically active compared to those who were sedentary [7].

Aerobic Endurance Training

After age 30 years, aerobic capacity, often measured as VO_{2peak}, declines with age and contributes to a decrease in the older adult's ability to perform activities of daily living. This is largely due to three major causes: (1) a decline in the ability of the cardiopulmonary system to deliver O_2; (2) a decline in the ability of the working muscles to extract O_2, and (3) a decline in metabolic muscle mass and a parallel increase in metabolically inactive fat mass [3]. Indeed, probably one of the most notable effects of endurance training is on VO_{2peak}, which is an important determinant of frailty in older adults [4]. The improvement in VO_{2peak} with endurance exercise training would be thought to reduce frailty in older adults and thus counter the decline in VO_{2peak} with aging and physical inactivity. Whereas VO_{2peak} declines ~1%/year in nontraining individuals [8], this decline is ~0.5%/years in master athletes who participate in aerobic activities [3]. Another important adaptation to endurance exercise training is an increase in muscle oxidative capacity, which results in fatigue resistance or increased muscle endurance. In an interventional trial of 64 frail older men and women, a 9-month program of strength training and walking exercise at 78% of peak heart rate increased endurance by improving VO_{2peak} by ~14% [9]. A similar exercise program for 12 months in 107 frail obese older men and women also increased VO_{2peak} by ~10% [10]. On the other hand, in healthy elderly (77–87 years old), 9 months of endurance training at 83% of peak heart rate increased VO_{2peak} by 15%, as compared to increased VO_{2peak} by 24–30% in healthy elderly 60–71 years old, indicating that the adaptations in aerobic power may be attenuated in advancing age [11]. Data from meta-analyses [12] also showed that endurance training may help to conserve fat-free mass (FFM) during weight loss, although it is probably less effective than resistance exercise. We recently reported that compared to weight loss induced by diet, weight loss induced by aerobic exercise preserved lower-extremity muscle mass (measured by magnetic resonance imaging) and physical work capacity, although the amount of exercise was large [13].

Progressive Resistance Training

It is well known that muscle strength and mass decreases with advancing age. A 30% reduction in strength between 50 and 70 years of age is generally found, with muscle strength losses being most dramatic after age 70 [14]. Most of the decline in strength can be explained by selective atrophy of type II muscle fibers and the loss of neuronal activation. Based on body composition techniques such as dual-energy X-ray absorptiometry and computed tomography, the relative annual decline in muscle mass was estimated to be between –0.64 and –1.29% per year for older men and –0.53 and –0.84% per year for older women [15]. Although a decline in muscle quality is also involved, several studies have found that the decline in strength in the older adult is primarily due to loss of muscle quantity with age. Several studies have shown that resistance exercise training increases muscle mass and thus muscle strength in both younger and older adults. However, the response to resistance training appears to be attenuated in older adults with mobility limitations or other comorbidities. In healthy older adults, 4 months of progressive resistance training increased muscle mass by 16–23%, whereas it increased muscle mass by 2.0–9% in frail older adults [10, 16–18]. Other studies showed that the gain in FFM in older women and men was only ~58% of that for younger men and women in response to resistance training [19]. Nonetheless, resistance training has still been found to significantly increase strength in older men and women. Several studies have demonstrated that these changes can occur even in the late stages in life [20, 21]. Indeed, based on two recent systematic reviews of randomized controlled trials (RCT) involving resistance training in older adults, it was concluded that resistance training results in significant improvement in muscle strength in older adults [22, 23]. These reviews included studies in both healthy and older adults. Of particular interest is that in frail institutionalized patients, Fiatarone et al. [16] demonstrated that 10 weeks of resistance exercise training increased muscle strength by ~113% as compared to ~3% in nonexercising subjects. Moreover, our group has shown that in frail older men and women, resistance training added to diet reduced FFM loss (from 3.5 to 1.8 kg) during voluntary weight loss and increased both upper- and lower-extremity muscle strength (by 17–43%) despite FFM loss [24]. With respect to aspects of functional limitations, resistance training has been shown to improve gait speed in healthy and frail elders (weighted mean differences = 0.07 m/s based on 14 trials; n = 798) [22]. Specifically, in frail older adults living in a nursing home and community, 10 weeks of resistance training have been shown to significantly improve gait speed [16].

Combined Aerobic and Resistance Training

The physiological adaptations to aerobic exercise and to resistance exercise are distinctly different and both types of exercise also target specific components of frailty. Therefore, the few exercise interventions conducted in frail older populations have mostly used combined aerobic and resistance exercise. A 9-month RCT intervention of aerobic and resistance exercise concomitantly improved scores in VO_{2peak} (95% confidence interval 0.9–3.6 ml/kg/min) and a modified physical performance test (95% confidence interval 1.0–5.2 points) [25]. In addition, a recent 12-month RCT of aerobic and resistance exercise also improved scores in VO_{2peak} and in a modified physical performance test in frail obese older adults, which were additive to the effects of diet-induced weight loss [10]. Finally, the LIFE-P (Lifestyle Intervention and Independence for Elders Pilot) study also reported that a 12-month program of walking, resistance exercise, and flexibility training resulted in a clinically meaningful improvement in physical performance assessed by using the Short Physical Performance Battery [26]. This study also presented promising evidence on the effectiveness of exercise in the prevention of the disability in walking as assessed by the capacity to complete a 400-meter walk.

Effect on Frailty as an Outcome Measure

Most exercise intervention trials studied the effects on features of frailty and the adverse outcomes of frailty. There have been relatively few studies designed to determine whether physical exercise can reverse frailty (frail reverse to nonfrail) or if older adults can convert from a greater state of frailty to a lesser state of frailty with exercise. The FIT (Frailty Intervention Trial) study examined whether a multifactorial intervention that included balance, strength, and endurance exercise could reduce frailty and improve mobility [27]. After 12 months of the intervention, there was a lower prevalence of frailty in the intervention group compared with the control group (between-group difference 14.7%), which was associated with a significant improvement in the Short Physical Performance Battery (between-group difference 1.44 points), suggesting that it is possible to successfully 'treat' frailty.

Molecular and Cellular Mechanisms Underlying Exercise Training

Aging and physical inactivity are associated with increased levels of chronic inflammation. Inflammatory cytokines have direct catabolic effects on skeletal muscle: Tumor necrosis factor (TNF)-α suppresses muscle protein synthesis (MPS) [28], while interleukin (IL)-6 inhibits the anabolic effects of insulin-like growth factor (IGF)-1 [29]. These cytokines also induce insulin resistance, which contributes to sarcopenia and frailty by reducing MPS. High concentrations of TNF-α or IL-6 are associated with lower muscle mass or strength and mobility disability [30] and high IL-6 and low IGF-1 levels contribute synergistically to impaired mobility [31]. Accordingly, an important mechanism by which exercise training reduces frailty is by suppressing muscle inflammation and promoting anabolism which leads to an increase in MPS (fig. 1). We previously reported that in frail obese older adults 12 weeks of exercise (aerobic and resistance) but not 12 weeks of weight loss (~7% reduction) decreased IL-6 and TNF-α and increased mechanogrowth factor mRNA of skeletal muscles, which was associated with positive effects on functional status [32]. Moreover, in these frail obese older adults, a multicomponent exercise program increased the mixed muscle protein fractional synthesis rate in the basal, postabsorptive state without affecting the magnitude of the muscle protein anabolic response to feeding [33]. These changes in muscle protein anabolism were accompanied by increases in FFM, appendicular lean body mass, strength, and VO_{2peak}, all of which are important determinants of frailty. There appears to be sexual dimorphism in muscle protein anabolism in that (1) older women have a greater MPS rate in the basal state

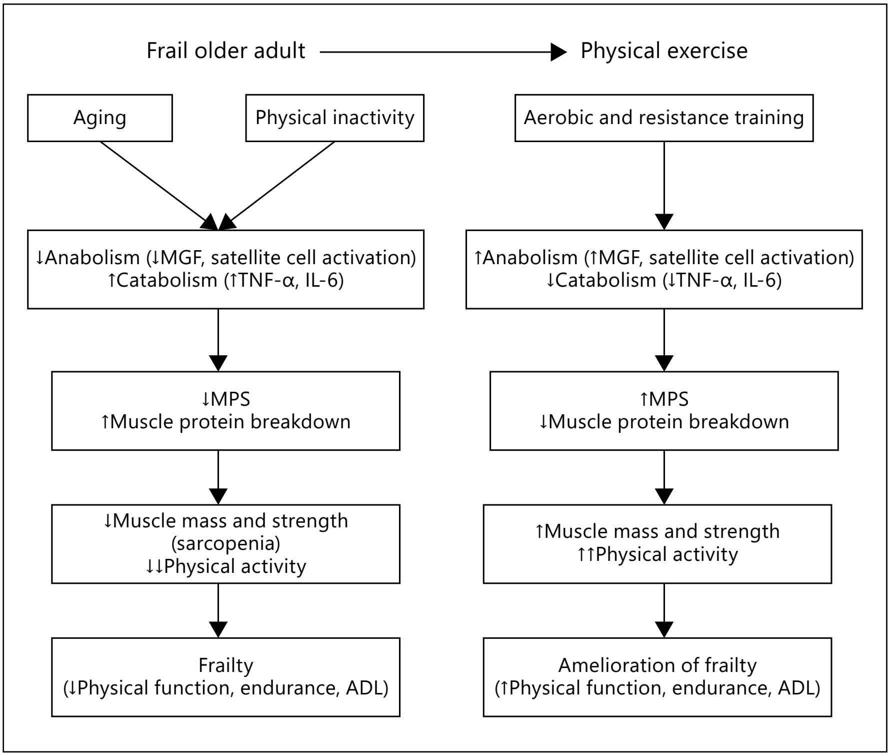

Fig. 1. Theoretical framework for the molecular and cellular mechanisms by which physical exercise ameliorates frailty in older adults. MGF = Mechanogrowth factor; ADL = activities of daily living.

but less anabolic response to mixed meal than older men [34] and (2) older women have less MPS rate increase in response to exercise training in the basal state than older men [35]. These findings may explain not only the lower muscle mass in older women but also perhaps the need for greater exercise stimuli to achieve the same anabolic response seen in older men [36].

Recommendations and Future Directions

In a systemic review of the effectiveness of exercise interventions for the management of frailty, it was found that even though the participants were frail, the exercise adherence was high with no adverse events in most reported studies, supporting that exercise was safe and feasible in this older population [37]. Although exercise uniformly had a positive impact on functional measurements, exercise seemed to be more beneficial in frail people living in long-term care

Table 1. Exercise recommendations for frail older adults

Aerobic exercise
Moderate-to-vigorous activity enough to raise the pulse rate to 70–80% of the maximum heart rate
Activity performed for a minimum of 20–30 min at least 3 days per week
Resistance exercise
The progressive resistance program should involve all major muscle groups of the upper and lower extremities and trunk
One set of 8–10 different exercises, with 10–15 repetitions per set, performed 2–3 nonconsecutive days per week
Moderate-high intensity training is recommended, in which moderate intensity is 5 or 6 on a scale from 0 to 10
Flexiblity and balance exercise
Stretching to the point of tightness and holding the position for a few seconds
Flexibility activities are performed on all days that aerobic or muscle strengthening activity is performed
Balance training exercise 2–3 times per week

The exercise program should be individualized according to an older individual's medical conditions and disability. The program should start at a low-to-moderate intensity, duration, and frequency to promote compliance and minimize musculoskeletal injuries.

facilities compared to the community (probably due to floor and ceiling effects of some outcome measurements) and in the earlier stages of frailty compared to the later stages of frailty (probably due to less ability to exercise with greater degree of frailty). With respect to the specific types of exercises, a multicomponent training was found to have a more positive effect on the functional ability and adverse health consequences of the frail people. Interventions lasting longer than 5 months seemed to result in greater benefits on the adverse health consequences of the frail people. The duration for each session of exercise that was most beneficial was 30–45 min, which is less than what is usually recommended for healthier older adults. Clearly, more RCT are required that include robust sample sizes and participants with different degrees of frailty, and examine age and potential sex dimorphism of the positive effects of exercise in frail older adults. More studies are also needed to determine which exercises are best suited, most effective, and safe (type, setting, duration, frequency, and intensity) for this population. Whether these exercise interventions would require supervision by rehabilitation personnel or could be safely and effectively conducted in the community or even at home needs further investigation. Based on currently available evidence, a multicomponent exercise program that includes aerobic activity, strength exercises, and flexibility is recommended in frail older adults (table 1).

It is worth mentioning that changes in the lifestyle habits of frail, older persons may present special challenges. Multiple medical problems, depression, sensory impairments, and cognitive dysfunction may make it difficult to change lifestyle. The increase in chronic disabilities with aging reduces physical activity and exercise capacity. To facilitate adherence to lifestyle changes that include regular physical exercise, program participation by the spouse or caregivers may need to be encouraged. In addition, special consideration should be given to hurdles faced during learning by frail older adults, such as impaired vision and hearing, orthopedic conditions, multiple comorbidities, and limited financial resources.

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Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the contents of the chapter.

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