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REVIEW ARTICLE

Sarcopenia: An emphasis on occlusion training and dietary protein

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Abstract

Demographics reveal that the world's population aged 60 years and older will triple from 600 million in 2000 to more 2 billion by the year 2050. To remain independent and healthy, an important factor to consider is the maintenance of skeletal muscle, as the elderly seem to become prone to a progressive loss of skeletal muscle with aging, termed sarcopenia. Interventions should focus on resistance training and optimal nutrition. Low intensity occlusion training may provide a mode of resistance training more applicable to the elderly, due to the lower loads used. Furthermore, an emphasis must be placed on high quality protein adequately distributed throughout the day to maximize protein synthesis. The use of drug therapy may be of some benefit, but it appears exercise and diet likely plays a more prominent role in the preservation of muscle mass and strength than administration of synthetic hormones. Hippokratia 2011; 15 (2): 132-137

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Demographics reveal that the world's population aged 60 years and older will triple from 600 million in 2000 to more than 2 billion by the year 2050. Due to an increased life expectancy, good health is essential for those aging, so they can remain independent and prevent or delay the onset of noncommunicable and chronic metabolic diseases such as heart disease, cancer, stroke and diabetes[1]. To remain independent and healthy, an important factor to consider is the maintenance of skeletal muscle, as the elderly become prone to a progressive loss of skeletal muscle with aging, termed sarcopenia (defined as appendicular skeletal muscle mass / height^2 <7.26 kg/m for males and <5.45 kg/m for females)[2]. This is of importance because skeletal muscle functions as the largest disposal site of ingested glucose[3], plays an important role in lipid oxidation[4, 5], and is one of the single greatest contributors to the resting metabolic rate (RMR)[6].

Age related sarcopenia begins in the 4th decade of life and has numerous adverse consequences[7-11]. The loss of muscle mass is associated with an increased risk of falls[12, 13] and the risk for all-cause mortality is inversely associated with strength levels[14]. The exact cause is multifactorial, however alpha-motorneurons appear largely responsible for the loss of muscle mass with aging[15-17]. In addition some evidence supports an age related desensitization to anabolic stimuli from exercise[18, 19] and nutrition interventions[20-22], compounded by a decline in overall dietary intake[23].

Muscle hypertrophy is thought to occur from an increased rate of protein synthesis that chronically exceeds the rate of protein breakdown. Due to the overall desensitization to anabolic stimuli, some research has focused on the ubiquitin proteasome systems role with increasing protein breakdown. However, a thorough review details that much of this research has been completed in rodents and the conditions in which the studies were completed might not necessarily reflect the physiology of older humans[24]. To illustrate, the ubiquitin ligases MAFbx/atrogin-1 and MuRF1 are activated in conditions of muscle wasting caused by inflammation (e.g. cancer, COPD, severe trauma) but the data is inconsistent in medically stable individuals[24]. Furthermore, a previous study found that insulin-mediated alterations in the protein expression of atrogin-1 and MuRF1 resulted in no changes in muscle protein breakdown[25]. This suggests that if the ubiquitin proteasome system is playing a role in sarcopenia, it is minimal.

As previously stated alpha-motor neuron loss appears largely responsible for the in the loss of muscle mass. The mechanisms behind this loss are not fully understood but could potentially be an age-related decline in the synthesis of a protein (ciliary neurotrophic factor) that promotes the differentiation and survival of alpha-motorneurons in a rodent model[26]. In addition, alterations to the neuromuscular junction have also been proposed. Delbono[27] and Narici and Mafulli[28] have described in detail the degenerative changes, which include fragmentation in the distribution of acetylcholine receptors, and an increase in the incidence of branches or boutons that are spatially separate or only connected by fine nerve filaments, suggesting fragmentation of the terminal. Interestingly, there is evidence to suggest that alterations in the muscle cell can occur independently of those in the neuron. To illustrate, apoptosis of skeletal muscle may be linked to mito-

chondrial dysfunction which is thought to increase with advancing age[29]. Mitochondrial dysfunction coupled with altered respiratory chain function and decreased cell defense against free radicals can cause mitochondrial DNA damage which has been associated with the development of sarcopenia[30].

The purpose of this review is to provide a unique look at a novel exercise modality, specifically for those patients who are contraindicated to high intensity exercise, and a dietary protein nutritional intervention which could help prevent or attenuate this age-related disease. Drug and hormonal therapy will also be briefly discussed as possible supplements to exercise and nutrition.

Low-Load Resistance Exercise Intervention

Resistance exercise provides a means of preserving skeletal muscle tissue with age. The positive effects of high intensity resistance training in the elderly population have been well documented[31-34]. Despite the positive effects seen with high intensity exercise, many elderly are contraindicated to high load resistance training and are limited to low-load, low-intensity exercise[35]; resulting in a failure to recruit fast twitch fibers leading to the 20-50% reduction in fast twitch cross sectional area (CSA) reported in the literature[17, 36].

A novel mode of exercise has recently received a lot of attention in the scientific literature as it appears to contradict the resistance training position stand of the American College of Sports Medicine (ACSM). The American College of Sports Medicine (ACSM) recommends lifting a weight of at least 70% of one's one repetition maximum (1RM) to achieve muscular hypertrophy as it is believed that anything below this intensity rarely produces substantial muscle hypertrophy or strength gains[37]. Furthermore, the American Heart Association (AHA)[38] recommends that the initial weight used for resistance training in the eldely be approximately 30-40%1RM for one set of 10-15 repetitions two days per week which may be inadequate to promote gains in muscle mass, due to the importance of exercise volume, particularly with the muscle protein synthesis (MPS) response[39].

Blood flow restricted exercise, also known as occlusion training, offers a novel mode of exercise for the elderly, as it allows the achievement of skeletal muscle hypertrophy at low intensities. Occlusion training involves applying a wrapping device, typically a modified blood pressure cuff; proximal to the muscle being trained[40]. Research indicates that occlusion training can provide a unique, beneficial mode of exercise in clinical settings, as it produces positive training adaptations at intensities equivalent to physical activities of daily life (10-30% of maximal work capacity)[41]. Numerous studies have shown that intensities as low as 20% 1RM with moderate blood flow restriction (100mmHG) can lead to significant increases in skeletal muscle hypertrophy[41-45], strength[34, 41-47], and endurance[43, 46].

Occlusion training works through a variety of mechanisms including the recruitment of fast twitch fibers at low intensities and the stimulation of the protein synthesis pathway mammalian target of rapamycin (mTOR)[48]. Additionally, this type of training has demonstrated growth hormone (GH) responses 290 times above baseline, which is higher than that seen with traditional high intensity exercise[49].

Although a majority of the research has been completed in young healthy subjects, a few studies have demonstrated favorable outcomes with those of advancing age. Takarada et al[34] investigated elbow flexion exercise twice a week for 16 weeks (~50% 1RM) with low intensity exercise (~50% 1RM) with and without occlusion and heavy resistance training (~80% 1RM) in older women (~58 years). Interestingly, low intensity exercise with occlusion increased CSA of the elbow flexors and extensors, as well as isokinetic strength significantly more than low intensity exercise. Isokinetic strength gains were similar to those seen in the high intensity exercise group.

Karabulut et al[47] investigated the effects of occlusion training in older males (50-64 years). A high intensity group (80%1RM) and a low intensity group with and without occlusion (20%1RM) performed three upper body and two lower body exercises three times a week for 6 weeks. They found that the high intensity group and the low intensity group with occlusion had significantly greater strength increases in every exercise when compared with low intensity exercise. However, they did note that the percentage increase in the high intensity groups leg extension strength was significantly greater than low intensity exercise with and without occlusion. The researchers concluded that low intensity occlusion training was almost as effective as high intensity training in older males.

Fry et al[50] reports perhaps the most interesting acute study to date with low intensity occlusion training in the elderly (~70 years). This groups of researchers found that bilateral knee extensor exercise at low intensities (~20% 1RM) with occlusion was able to significantly stimulate protein synthesis. This is of great importance, because as previously stated, many elderly are unable to train at higher intensities, and this study demonstrated that low intensity exercise without occlusion does not increase protein synthesis. Thus, low intensity exercise without occlusion would likely not produce a stimulus strong enough to promote muscle hypertrophy or maintain muscle mass. Additionally they monitored for the risk of deep vein thrombosis by measuring D-dimer (marker of intravascular clot formation), which was unaffected with either condition.

In conclusion, numerous studies show the benefits of occlusion training with respect to skeletal muscle hypertrophy, strength, and endurance. In addition, the few studies completed on the elderly with occlusion showed favorable outcomes similar to that of higher intensity exercise. It should be noted that adaptation occurs without significant elevations of any known markers for muscle damage (myoglobin, lipid peroxide, creatine kinase)[41, 49].

Nutrition Intervention

In addition to training, proper diet with respect to dietary protein is essential in preserving skeletal muscle

mass. With aging comes a decline in the bodies sensitivity to amino acids and numerous studies suggest that the protein requirement for the elderly is elevated compared to the young[51-53]. The United States recommended daily allowance (RDA) for protein is .8 g/kg/day which is the amount of protein necessary to sustain life, not optimal function. Newer research suggests that we should focus not on the overall daily amount of dietary protein, but instead the optimal dose needed to maximally stimulate MPS and the optimal amount of time between meals until we can maximally stimulate MPS again[54, 55].

It is generally accepted that 25-30g of high quality protein, is the amount needed per meal to maximally stimulate MPS in the elderly[56, 57]. To illustrate, Symons et al[58] found that 60g of protein stimulated MPS to no greater degree than 30g per meal. This phenomenon is referred to as refractory; meaning ~30g of protein appears to be the ceiling for the anabolic response to a meal.

In addition to the protein dose at a meal, Norton et al[54] investigated the duration of MPS from a complete meal in which they showed MPS was elevated for three hours before returning to baseline. Interestingly, although MPS had returned back to baseline, plasma leucine concentrations and the initiation factors for MPS remained elevated. They concluded that eating another meal three hours following the previous meal would likely fail to elevate MPS because the initiation factors for MPS were still elevated[55]. Infusion research supports these findings as Bohe et al[59] found that MPS returned to baseline after two hours despite purified essential amino acids (EAA) being infused for eight hours. Norton and Wilson[55] suggest that amino acid levels should be spiked with a meal, then given time to fall back towards baseline, followed by another amino acid spike 4-5 hours later. This strategy seems especially important in aging, when optimal nutrition for skeletal muscle maintenance is of absolute importance. Unfortunately, most people regardless of age inadequately distribute their protein throughout the day, consuming over 65% of their daily protein after 1830 h[60]. Emphasis should be placed upon equal distribution of protein, resulting in more maximal protein stimulations throughout the day, theoretically improving skeletal muscle health.

In conclusion, adequate distribution of protein throughout the day is important to maximize muscle anabolism. The elderly should focus on consuming at least 25g of protein three times a day, separated by approximately 4-5 hours. Eating at 800h, 1300h, and 1800h would maximally stimulate protein synthesis three times a day promoting skeletal muscle hypertrophy and/or maintenance of muscle mass.

Resistance Training and Nutrition Interventions

Research has shown that when resistance training is combined with a nutritional intervention, benefits in both strength and body composition are observed. Campbell and colleagues provide the most convincing evidence that emphasis be placed not only on resistance training but also dietary protein[61]. They compiled data over 15 years from 106 men and women between the ages of 50 and 80 years who had participated in one of their diet and resistance training studies. The training programs they used for all studies were similar in duration, intensity, exercises, frequency and equipment used. In addition, the dietary protein intakes ranged from .4g/kg to 1.7g/kg. Upon compiling the data they found an apparent loss of fat-free mass by many of their older subjects when they consumed the RDA for protein (0.8g/kg), despite the anabolic stimulus from the resistance training bout. They concluded from their analysis that an older subject who consumed the RDA for protein would theoretically lose about 0.2 kg of fat-free mass after a 12-week resistance training program and protein intakes of 1.0, 1.2, 1.4, and 1.6g/kg would translate into fat free mass increases of 0.0, 0.3, 0.5, and 0.8 kg , respectively[61].

These findings highlight an importance of not only resistance training but also adequate dietary protein distributed throughout the day. It should be noted that while occlusion training has resulted in significant elevations in protein synthesis, no study has investigated this stimulus in combination with a nutritional intervention; however the authors hypothesize the response to be similar to that of higher intensity exercise.

Drug Intervention

As with any disease or condition, numerous drugs are developed in hopes of combating the negative effects of the condition and to improve clinical outcomes. With aging, circulating levels of numerous muscle anabolic hormones decline; such as testosterone, GH and insulin-like growth factor-one (IGF-1)[62]. The research thus far is conflicting; however it does appear that exercise, regardless of the drug employed, is necessary for the greatest gain in strength and muscle mass.

In males, bioavailable testosterone levels decline by as much as 64% between the ages of 25 and 85, while women drop only 28%[63, 64]. The reasoning behind testosterone administration is that satellite cells decrease with sarcopenia and when testosterone is given there appears to be an increase of satellite cells in a dose dependent manner[65, 66]. Several studies have shown a direct relationship between serum testosterone and muscle strength in older men, however this relationship does not hold true for women[9, 67, 68]. Ryall et al[62] believe the disparity lies with the more than twofold increase in sex hormone-binding globulin (SHBG) over a lifespan in males, which remains unchanged in females. SHBG functions include binding anabolic hormones, which could possibly account for decrease in strength observed in males but not females.

Circulating GH is another anabolic hormone that progressively declines after age 30 at an average rate greater than 1% per year[69, 70]. Although GH exerts many actions through its production of IGF-1, GH is capable of promoting skeletal muscle growth independent of

IGF-1[71]. Despite the requirement for endogenous GH to maintain muscle and bone, exogenous GH does not

increase functional (no concomitant strength increase) fat free mass (FFM) [72]. The increased FFM is attributed to fluid retention or an increase in collagen[73]. The lack of benefit seen with exogenous GH administration is attributed to the complexity of the GH/IGF-1 pathway itself and the numerous GH isoforms; all of which contribute to the difficulty of synthetically mimicking the effects of endogenous GH secretion. It is conceivable that the endogenous response from low intensity blood flow restricted exercise could potentially play a more important role than the synthetic form[49].

Recently, work has focused on the effects of IGF-1 administration combined with its predominant circulating binding protein IGFBP-3 on the elderly[74]. Boonen et al[75] reported that the use of this combination allows for a higher dose of IGF-1, without the negative effects of hypoglycemia noted with IGF-1 alone. The combination also preserved femoral bone mass and increased grip strength in elderly women. While the results of this study are promising drawing any definitive conclusions is difficult due to a small sample size.

Drug administration may have some protective role with the aging population to help maintain muscle mass and strength, but exogenous administration of those hormones has produced confounding outcomes. Proper exercise and diet likely play a more prominent role in the preservation of muscle mass and strength than administration of synthetic hormones, without the potential negative side effects of drug use.

Conclusion

The actual cause of sarcopenia is unknown but appears multifactoral. Interventions should focus on resistance training and adequate nutrition. A novel training stimulus such as occlusion training might make resistance training more applicable to the elderly, because this mode of training involves a low-load, low-intensity bout of exercise. Furthermore, an emphasis must be placed on high quality protein adequately distributed throughout the day to maximize protein synthesis. Additionally, drug therapy might offer some help but the research remains equivocal. In summation, proper training and nutrition might not be able to completely stop sarcopenia, but it may attenuate its progression.

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