Exercise is Medicine
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Resistance Exercise for Cachexia

Cachexia, disease-related wasting of muscle tissue, is a poorly understood condition with few viable clinically effective treatment options. Recently it has been understood that increased muscle loss is the most important mechanism involved, but a decreased ability to make new muscle is also present. Based on the current understanding of the mechanisms involved in cachexia, there is reason to believe that weight training may be the most valuable clinical tool to combat the condition. Resistance training has been shown in the few studies that have been done to have a positive impact. Although more studies need to be done, it is useful for practitioners to know how resistance exercise may work to combat the condition and what may be the best way to prescribe it.

Current Review of Cachexia

Cachexia results from decreased protein synthesis and increased protein breakdown resulting in a loss of muscle mass. Two major factors in decreased protein synthesis come from increased levels of tumor-secreted compounds called proteolysis inducing factor (PIF) and angiotensin II. The latest understanding is that these compounds, which are highly elevated in cancers associated with wasting, interrupt the ability of muscle cells to make new protein. In addition, it is now thought that decreased phosphorylation of the intramuscular signaling molecules mammalian target of rapamycin (mTOR) and p70 S6 Kinase (p70S6k) are also affecting muscle cells. These two signaling molecules play a major role in the initiation of translation during protein synthesis. These molecular effects are compounded by lack of physical exercise as a result of cancer-related fatigue either from the disease itself or its treatment. This has dire consequences, since muscle contraction is a major stimulus for muscle protein synthesis. As troublesome as the issues with protein synthesis are, cachexia is more related to accelerated protein breakdown. Normal muscle tissue has several different mechanisms for breaking down muscle tissue. PIF and angiotensin II play a role in muscle protein degradation as well as muscle protein synthesis. Recent understanding implicates two more mechanisms in cancer-related muscle loss. These include a calcium-dependent protease system called calpains, as well as an ATP-dependent ubiquitin-proteosome system (UPS). Calpains break down the protein structures that allow the muscle cell myofibrillar elements to line up correctly. The calpains do not actually degrade these proteins, but they make it so they are able to be degraded by other mechanisms. That other mechanism is the UPS system. The UPS system acts to "label" damaged or defective proteins so they can be removed. In cancer cachexia, this "labeling" system becomes overactive and results in accelerated muscle protein breakdown. Another known mechanism involved in muscle protein loss is the cytokine system. The proinflammatory cytokines TNF alpha, IL-1, IL-6, and IFN gamma are all are now implicated in cachexia.

What About Nutrition?

The current approach by many practitioners to combat cachexia revolves around nutrition. The rationale behind this approach is logical. Cancer disease progression or treatment often leads to a decreased intake of food. However, McDonald et al. showed in 2003 that this decreased energy consumption is probably not the reason for muscle wasting. Additionally, several human trials show that increased food intake and/or supplementation increases fat mass, but not muscle tissue. This seems to be the case with or without appetite stimulants. One place of nutrition research that does show promise is the use of leucine, a branched chain amino acid. It appears that leucine, as opposed to other nutritional interventions and amino acids, may have a strong potential in attenuating cachexia.
Exercise

With nutritional intervention seeming to be of little help, exercise seems the next logical step. However, the research into exercise and cachexia is dominated by aerobic exercise, which cannot increase muscle mass and may actually decrease it. Despite the potential negative effects of aerobic exercise on muscle maintenance, the research into exercise and cachexia is dramatically biased towards aerobic exercise. A 2008 review by Cheema et al. examined 11 exercise studies on women with breast cancer, only 2 of which looked at resistance training alone. This is despite the fact that resistance training has several unique mechanisms that seem to address several of the underlying mechanisms of cachexia.

For resistance exercise to be effective, it would need to show activity against decreased muscle synthesis and, more importantly, act against increased muscle breakdown. Resistance exercise can increase phosphorylation of mTOR and p70S6k. This would suggest that it has the potential to block a major contributor to decreased muscle synthesis. However, it has not yet been determined if resistance exercise can affect angiotensin II and PIF, although there is one study in a tumor mouse model that has shown that anaerobic exercise significantly decreased PIF and improved outcomes. Resistance training also is a powerful modulator of UPS activity by way of inflammatory cytokine modulation. Two recent review articles in 2007 by Al-Majid et al. and Pajak et al. do a very nice job of breaking down the complicated mechanisms of how resistance exercise works. Resistance exercise seems to be most effective through the release of IL-6, which is anti-inflammatory when released by muscle, and IL-15, which is strongly anabolic. Muscle-derived IL-6 works to strongly suppress TNF alpha and IL-1. This action strongly decreases the overactivity of UPS, which may be the most important component of cancer cachexia. IL-15 then works to increase the type II muscle fibers that seem to be selectively lost in cachexia.

Prescription

Currently, few studies have looked at resistance training and cachexia, despite the obvious mechanistic benefits it seems to provide. Those studies that have been completed hint that resistance training may indeed provide benefit in actual cases. The review by Al-Majid et al. highlights four studies, three of which are randomized controlled trials. Two of these studies are very interesting because they involve androgen deprivation therapy in prostate cancer. This shows that resistance training is working from a mechanism other than anabolic hormone stimulation. From these studies, it appears that a favorable resistance-training program for cachexia would employ 2 to 3 sets of 8 to 12 repetitions for each major muscle group 1 to 3 times per week. The weight used should be heavy enough to induce failure on the last rep. Three minutes of rest between sets is appropriate. One clinical note on using resistance training to bolster muscle mass is to use the anabolic potential of the lower extremities, which constitute the largest area of muscle mass on the body, to generate a large anabolic hormone release as well as a greater cytokine potential. Although this technique has not been studied, we have employed it with many of our patients and seen favorable results.

Notes
