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Cancer-Induced Fatigue and Skeletal Muscle Wasting: The Role of Exercise

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# Abstract

Fatigue is the most frequently reported symptom by cancer patients. Many of these patients perceive fatigue as the most distressing symptom associated with their illness because it imposes limitations on their physical activity level. Skeletal muscle wasting, which occurs as part of cancer cachexia, is one of the mechanisms that contribute to fatigue. Cancer-induced skeletal muscle wasting may occur despite normal food intake and is not prevented by nutritional supplementation. Evidence suggests that endurance exercise ameliorates cancer-related fatigue. There is no compelling evidence to support that exercise-induced reduction in fatigue is related to preservation of muscle mass. Resistance exercise attenuates muscle wasting associated with a variety of catabolic conditions. However, its effects on cancer-induced muscle wasting have not been adequately studied. This article describes the physiological mechanisms implicated in the induction of cancer-related muscle wasting, summarizes findings from endurance and resistance exercise studies in relation to fatigue and muscle wasting during cancer and selected clinical conditions, and proposes directions for future research.

# Key words:

Fatigue, skeletal muscle wasting, cytokines, tumor necrosis factor-α, ubiquitin, physical activity, endurance exercise, resistance exercise

Fatigue is the most frequently reported symptom by persons with cancer (Chang and others 2000). The problem afflicts up to 96% of patients receiving chemotherapy (Nail and others 1991), 78% of patients receiving radiotherapy (Hickok and others 1996), and up to 80% of patients with advanced malignancies (Donnelly and Walsh 1995; Vainio and Auvinen 1996; Stone and others 1999). Cancer-related fatigue has been attributed to a variety of disease-related and/or treatment-related psychosocial as well as physiological mechanisms. These mechanisms are discussed in detail in several review articles (Winningham and others 1994; Nail and Winningham 1995; Dalakas and others 1998; Stone and others 1998).

One mechanism that contributes to cancer-related fatigue is the progressive wasting of skeletal muscle, which occurs as part of cancer cachexia. Significant wasting affects approximately 50% of persons with cancer (Tisdale 1999) and contributes to poor tolerance and responsiveness to cancer treatment (Van Eys 1982), poor prognosis, and shorter survival time (DeWys and others 1980). Wasting is also associated with asthenia, a condition of generalized weakness (Argiles and others 1999) and fatigue. Therefore, interventions that would attenuate not only fatigue but also the deleterious effects of muscle wasting would be of important clinical significance.

Several lines of evidence suggest that endurance exercise can ameliorate cancer-related fatigue. Endurance exercise is defined as a type of muscular activity consisting of a high number of repetitions performed over extended periods of time against relatively low resistance. Whereas endurance exercise training increases muscle resistance to fatigue, resistance exercise increases the mass of healthy muscles and attenuates muscle wasting associated with a variety of catabolic conditions. Resistance exercise involves a relatively lower number of repetitions performed against relatively higher resistance. The purposes of this review article are to (1) describe the physiological mechanisms of cancer-related muscle wasting, (2) summarize the effects of endurance exercise on cancer-related fatigue and muscle metabolism, (3) summarize the effects of resistance exercise on muscle mass and protein synthesis during health and selected catabolic conditions, and (4) propose directions for future research.

# Muscle Wasting during Cancer Cachexia

Cancer cachexia is associated with perturbations in protein metabolism leading to significant wasting of tissue proteins. Skeletal muscle, the major protein compartment in the body, contributes substantially to this state of wasting. Body composition analysis shows that skeletal muscle is the major site of protein loss in patients with solid (nonhematological) tumors (Cohn and others 1981; MacFie and Burkinshaw 1987; McMillan and others 1994). Using compartmental analysis to estimate the mass and protein content of muscle and nonmuscle tissue based on total body nitrogen (determined by prompt gamma neutron activation technique) and total body potassium (determined using a whole-body counter), Cohn and others reported that muscle protein mass in weight-losing cancer patients was approximately 50% lower than that in age-matched controls. Similarly, body composition analysis revealed that weight-losing cancer patients lost significantly more muscle than weight-losing patients without cancer (Moley and others 1987). More recently, Dworzak and others (1998) reported that muscle protein synthesis rate in patients with advanced gastric carcinoma was significantly lower than that of healthy volunteers whereas whole-body protein synthesis did not differ between the 2 groups. What are the mechanisms that underlie cancer-induced muscle wasting?

## Mediators of Cancer-Related Muscle Wasting

Muscle wasting results from an imbalance between the rates of muscle protein synthesis and degradation. Although the relative contribution of these 2 factors differs among individual studies, evidence suggests that muscle wasting results primarily from accelerated muscle protein degradation. Despite the considerable scientific effort that is being directed toward identifying the precise cellular and molecular mechanisms that underlie cancer-induced muscle wasting, these mechanisms are still not fully elucidated. However, there appears to be a consensus that cancer-induced muscle wasting is a multifactorial process that is mediated by, for example, reduced food intake, proinflammatory cytokines, and proteolysis-inducing factor. The reduced physical activity level that accompanies cancer fatigue can further accelerate muscle wasting.

## Depression in Food Intake

Traditionally, the profound wasting that accompanies malignant tumor growth had been attributed to anorexia and the consequent depression in food intake. Although anorexia is a characteristic feature of cancer cachexia, several lines of evidence suggest that anorexia is only a contributor rather than the sole cause of the problem. First, the metabolic perturbations that accompany cancer cachexia do not resemble those induced by starvation. During acute starvation, liver and muscle glycogen are used to supply the body with the necessary glucose for energy. Following the depletion of glycogen, skeletal muscle proteins are broken and the liberated amino acids are mobilized to the liver for gluconeogenesis (Mitch and Goldberg 1996). In noncancer persons, the body quickly adapts to the lack of nutrients by decreasing its energy expenditure and by oxidizing stored lipids for energy. This metabolic adaptation to decreased food intake is critical for maintaining a functional muscle mass. Cancer-bearing hosts, however, fail to develop such metabolic adaptation and thus continue to deplete their skeletal muscle proteins (Tisdale 1997). For example, persons with cancer have been reported to lose a greater proportion of lean body mass compared to persons with anorexia nervosa, although the total body weight loss in persons with cancer was only one-half of that in patients with anorexia (Moley and others 1987). Thus, for a given degree of weight loss, there is more wasting of muscle in a person with cancer than in a person without cancer.

Second, the degree of wasting in the tumor-bearing host is more pronounced than that in pair-fed weight-matched controls. Tumor-bearing rats whose food intake dropped by 15% lost 20% of their premorbid body weight compared to only 7% in healthy controls who were fed the same amount of food as the tumor-bearing rats (Emery and others 1984). Furthermore, significant muscle wasting occurred in mice bearing the MAC-16 (Smith and Tisdale 1993; Lorite and others 1997) and colon-26 (Tanaka and others 1990) adenocarcinomas when food intake was not significantly different from that of the healthy controls.

Finally, if reduced food intake were the only cause of muscle wasting during cancer cachexia, then supplemental nutrition should reverse the syndrome. Although aggressive nutritional supplementation and/or the administration of appetite stimulants increased body water and fat content (Evans and others 1985; Loprinzi, Michalak, and others 1993), it did not have significant effects on lean body mass (Loprinzi, Schaid, and others 1993; Strang 1997; Simons and others 1998). Therefore, cancer-related muscle wasting cannot be explained solely by the reduction in energy intake, and hence mechanisms other than substrate availability must be involved.

## Cytokines

Cytokines are polypeptides synthesized and released primarily by activated monocytes and macrophages. Cytokines are also produced by some types of tumor cells (Ohnuma 1997). Tumor necrosis factor (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon gamma (IFN-γ) have been implicated in the induction of cancer-related muscle wasting (Argiles and others 1999). Chronic treatment of healthy rats with recombinant TNF- α or IL-1 resulted in a significant decrease in muscle protein content associated with a decrease in muscle mRNA levels for myofibrillar proteins (Fong and others 1989). Similarly, an acute intravenous injection of TNF- α in healthy rats depressed protein content and synthetic rate in the tibialis anterior muscle by 18% and 20%, respectively (Charters and Grimble 1989). In non-weight-losing cancer patients, the administration of recombinant TNF- α increased nitrogen efflux from skeletal muscle (Warren and others 1987). The administration of IL-1 (Goodman 1991) or IL-6 (Goodman 1994) in healthy rats enhanced muscle proteolysis. Conversely, TNF- α, IL-1, and IL-6 failed to consistently induce muscle proteolysis in vitro, suggesting that the effects of these cytokines on muscle proteins may be mediated through other factors.

There is increasing proof that the accelerated muscle proteolysis during malignant tumor growth is mediated via the activation of the non-lysosomal adenosine triphosphate–dependent (ATP-dependent) ubiquitin proteasome pathway (Llovera and others 1994; Llovera and others 1995; Lorite and others 1998; Williams and others 1999). For example, the mRNA levels for ubiquitin in the rectus abdominis muscle in cancer patients were 2 to 4 times as high as in controls (Williams and others 1999). Similarly, ubiquitin concentration and gene expression in wasted muscles in rats bearing the AH-130 hepatoma were reported to be significantly higher than those in healthy controls (Llovera and others 1994). Ubiquitin is a peptide that is present in most mammalian cells and is involved in the targeting of proteins undergoing cytosolic ATP-dependent proteolysis. The 1st step in the ubiquitin proteasome pathway is the covalent attachment, in the presence of ATP, of ubiquitin to the proteins targeted for degradation. Proteins with multiple ubiquitin chains are then directed, through multiple enzymatic reactions, to the 26S-proteasome complex where they get degraded into multiple small fragments of peptides and amino acids that can be recycled (Attaix and others 1999; Tisdale 2000). Because ubiquitin proteasome pathway is functional only in the presence of ATP, the inhibition of protein degradation in muscles incubated in an ATP-depleted medium (Temparis and others 1994; Baracos and others 1995) verifies the direct role of this pathway in muscle wasting.

Activation of the ubiquitin proteasome pathway occurs in the presence of TNF- α as evidenced by increased levels of conjugated and free ubiquitin (GarciaMartinez and others 1993) as well as ubiquitin gene expression (Garcia-Martinez and others 1994; Llovera and others 1998) in the skeletal muscle of healthy rats treated with TNF- α. Similar changes in ubiquitin gene expression were also observed when rats were injected with IL-1 or IFN-γ (Llovera and others 1998). Finally, this group of researchers demonstrated that treatment with anti-TNF- α antibodies reduced ubiquitin gene expression in skeletal muscle of tumor-bearing rats. The final link in the purported role of TNF- α in increasing activity of the ubiquitin pathway for degradation of skeletal muscle is the recent report that exposure of muscle cells (myocytes) to TNF- α increases the expression of cytokine receptors on these cells. Thus, TNF- α can upregulate cytokine receptors, providing evidence for amplification of cytokine responses at the level of the muscle cells (Zhang and others 2000).

Alternatively, recent evidence suggests that TNF- α induces muscle wasting via inhibition of pathways involved in muscle cell differentiation and regeneration (Guttridge and others 2000). Exposure of myoctes to TNF- α activates the transcription factor nuclear factor kappa B (NF-kB), which in turn inhibits muscle cell differentiation by suppressing the synthesis of MyoD. MyoD is a transcription factor that is essential for muscle cell differentiation and for repair of damaged muscle tissue (Guttridge and others 2000). It should be noted that activation of NF-kB is also involved in upregulation of cytokine synthesis, which can contribute to paracrine effects of cytokines on skeletal muscle tissue as described above. Thus, cytokine-induced skeletal muscle wasting is probably a multifactorial process, involving increased protein degradation and reduced myocyte regeneration and repair (Tisdale 2000).

## Proteolysis-Inducing Factor

Recently, a proteolysis-inducing factor that induces muscle wasting was purified from the cachexia-inducing MAC-16, a murine adenocarcinoma. A proteolysis-inducing factor of identical characteristics and molecular weight was detected in the urine of persons losing weight due to pancreatic or gastrointestinal cancers but not in the urine of weight-stable patients with cancer or weight-losing noncancer patients (Todorov and others 1996). The exogenous administration of the proteolysis-inducing factor to healthy mice resulted in a 50% decrease in muscle protein synthesis and a 50% increase in muscle protein degradation (Lorite and others 1997). Pretreatment of mice bearing the MAC-16 adenocarcinoma with monoclonal antibody against the proteolysis-inducing factor completely blocked the adverse effects of the tumor on muscle protein synthesis and degradation rates (Lorite and others 1997). Like TNF- α and IL-1, proteolysis-inducing factor appears to induce muscle wasting via the activation of the ubiquitin proteasome pathway (Hussey and others 2000).

In summary, skeletal muscle wasting during cancer cachexia is well documented. Although the exact mechanisms responsible for this state of wasting have not been completely elucidated, evidence suggests that the problem is a multifactorial process that is mediated by host-released and tumor-released factors. Apparently, these factors disturb the balance between the rates of muscle protein synthesis and muscle protein degradation, leading to muscle protein depletion and, hence, muscle wasting.

## Fatigue and Reduced Level of Physical Activity

One factor that can be viewed as a contributor to, as well as a consequence of, skeletal muscle wasting is fatigue. Atrophy of skeletal muscle leads to asthenia and weakness, which causes affected persons to reduce their physical activity level. The resultant reduced physical activity leads to more muscle deconditioning and disuse atrophy, which in turn aggravate the feeling of fatigue. Thus, an intervention that may potentially attenuate muscle wasting and/or reduce fatigue in cancer patients is physical exercise training. Data generated from healthy humans and from experimental animals demonstrate that regular endurance exercise training of submaximal intensity (below maximal heartbeat) increases muscle endurance and resistance to fatigue (Holloszy and Coyle 1984; Spina and others 1996). On the other hand, resistance exercise training increases the mass of healthy muscles and attenuates muscle wasting associated with some catabolic conditions.

# Effects of Endurance Exercise on Patients with Cancer and on Tumor-Bearing Animals

Since the early 1980s, nurse researchers and others have shown that endurance exercise has beneficial effects for persons with cancer. For example, the engagement in endurance exercise increased oxygen consumption, a marker of functional capacity, by 40% in women with stage II breast cancer (MacVicar and others 1989), reduced nausea (Winningham and MacVicar 1988), reduced depression (Segar and others 1998), and improved self-reported quality of life (Young-McCaughan and Sexton 1991).

Endurance exercise has also been shown to attenuate cancer-induced fatigue. For example, unsupervised self-paced walking for 20 to 30 minutes per day improved self-reported fatigue compared to baseline and to control values in women receiving a 6-week radiation therapy for stage I and stage II breast cancer (Mock and others 1997). Similarly, an exercise program consisting of daily biking on a bed ergometer at 50% of cardiac reserve, performed for 30 minutes a day during hospitalization, reduced self-reported fatigue in a mixed group of patients receiving high-dose chemotherapy for various types of cancers (Dimeo and others 1999). Endurance exercise consisting of treadmill walking at 80% of cardiac reserve performed for 30 minutes per day, 5 times per week for 6 weeks has also been shown to reduce self-reported fatigue in patients with solid tumors and non-Hodgkins lymphoma (Dimeo and others 1997). Schwartz (1999) suggested that the effect of endurance exercise on quality of life in women with breast cancer might be mediated by the positive effect of exercise on fatigue.

Endurance exercise has also been demonstrated to improve physical performance. The improvement is assessed by comparing the distance walked before and following the completion of the exercise program using the total distance walked (Dimeo and others 1996), the 6-minute walk test (Nieman and others 1995), or the 12-minute walk test (Mock and others 1997; Courneya and Friedenreich 1999; Schwartz 1999). Taken together, the aforementioned studies on fatigue provide evidence that endurance exercise improves self-reported fatigue in patients with cancer. However, the physiological and cellular mechanisms underlying the exercise-induced reduction in fatigue have not been explored in any of these studies. In healthy subjects, regular endurance exercise training of submaximal intensity increases muscle endurance and resistance to fatigue by increasing mitochondrial enzyme activity, which results in an increase in the oxidative capacity of the muscles (Holloszy and Coyle 1984; Spina and others 1996). It is not known whether the exercise-induced amelioration of cancer-related fatigue was a consequence of similar changes within the exercising muscles of cancer patients. However, the improvement in distance walked may suggest exercise-induced improvement in muscle endurance.

Data generated from studies of experimental tumor-bearing rodents provide further support for the beneficial role of endurance exercise during cancer. For example, endurance exercise such as running, treadmill walking, and swimming has been associated with smaller tumors and greater food consumption (Deuster and others 1985; Cohen and others 1988; Baracos 1989; Daneryd and others 1995). Whereas there are no published data on the effect of endurance exercise on muscle protein metabolism in patients with cancer, a few animal studies, summarized in Table 1, have examined the effect of this type of exercise on muscle protein synthesis, muscle protein content, and muscle mass in tumor-bearing subjects. Two of these studies reported that endurance exercise was associated with an increase in muscle protein synthesis and in muscle to body weight ratio (Deuster and others; Daneryd and others). It should be emphasized, however, that the exercised animals had smaller tumors and consumed more food compared to the sedentary tumor-bearing animals. Therefore, it is not clear whether the observed positive change in muscle protein metabolism was a consequence of smaller tumors and higher food intake or a consequence of a direct effect of the exercise on the muscles.

In summary, endurance exercise has been demonstrated to have several beneficial effects in patients with cancer as well as in tumor-bearing animals. However, there is no compelling evidence that endurance exercise attenuates cancer-related skeletal muscle wasting. First, the effects of endurance exercise on muscle mass have not been examined in persons with cancer. Second, although data generated from animal models of cancer cachexia suggest that endurance exercise may attenuate cancer-induced muscle wasting, findings from these studies should be interpreted with caution, since the exercised animals had smaller tumors and consumed more food compared to the nonexercised animals.

# Effects of Resistance Exercise on Muscle Protein Metabolism and Muscle Mass

Resistance exercise is a potent physiological intervention that increases muscle mass (Evans and others 1998). An increase in muscle mass occurs when myofibrillar protein synthesis exceeds myofibrillar protein degradation. Resistance exercise training increases muscle mass by accelerating the rate of protein synthesis in the contracting muscles. A single bout of resistance exercise increased the rate of mixed and myofibrillar protein synthesis in the tibialis anterior muscle of rats by up to 51% and 56%, respectively (Wong and Booth 1990). In humans, protein synthesis rate of the biceps brachii muscle of the exercised arm increased by 50% and 109% in the 4 hours and 24 hours, respectively, following a single bout of resistance exercise compared to that of the nonexercised arm (Chesley and others 1992). Studies summarized in Table 2 showed the anabolic effects of resistance exercise training on muscle mass in healthy humans and experimental animals.

## Resistance Exercise as a Countermeasure for Muscle Wasting

Cancer, prolonged bed rest, HIV infection, aging, and hind-limb suspension are conditions in which muscle wasting is a common feature. Resistance exercise training during these conditions has been shown to attenuate muscle protein breakdown and/or muscle wasting. Prolonged bed rest is known to accelerate muscle protein breakdown leading to muscle wasting. Ferrando and others (1997) reported that resistance exercise training of the leg during a 2-week period of bed rest increased protein synthesis rate in the vastus lateralis muscle of young healthy men by 46% compared to nonexercised controls.

Resistance exercise training also attenuates muscle wasting associated with HIV infection. Spence and others (1990) reported that resistance exercise training performed 3 times per week for 6 weeks resulted in a significant increase in the combined midarm and midthigh circumference in HIV-infected men compared to nonexercised HIV-infected controls. Similarly, HIV-infected men who participated in 12-week resistance exercise training (3 times per week) had significantly greater lean body mass, determined by dual energy x-ray absorptiometry, compared to the age and disease-matched nonexercised group (Sattler and others 1999).

Resistance exercise training counteracts age-related reduction in muscle protein synthesis rate. For example, a progressive moderate to high-intensity (60% to 90% of maximum strength) resistance exercise training performed 5 days per week for 2 weeks increased protein synthesis rate in the quadriceps muscle of older men and women (63 to 66 years) to levels comparable to those of young (24 years) individuals (Yarasheski and others 1993). Similarly, resistance exercise training performed 3 days per week for 3 months significantly increased protein synthesis rate in the vastus lateralis muscle of physically frail men and women (76 to 92 years) compared to untrained age-matched controls (Yarasheski and others 1999). Recently, Greiwe and others (2001) found that the levels of TNF- α mRNA and TNF- α protein content in the muscles of frail elderly persons (average age = 81 years) were significantly higher than those of young people (average age = 23 years). Resistance exercise training performed by frail elderly persons 3 days per week for 3 months significantly reduced the levels of TNF- α mRNA and TNF- α protein content in the muscles compared to baseline values. In addition, muscle protein synthesis rate in these subjects was inversely related to the levels of TNF- α, suggesting that the anabolic effects of resistance exercise training on the muscles of frail elderly may be mediated by suppressing the levels of TNF- α.

The anabolic effect of resistance exercise training on aged skeletal muscle is further supported by animal research. Klitgaard and others (1989) reported that resistance exercise training consisting of 10 to 15 repetitions of hind-limb extensions with weights lifted over the shoulders performed 2 times per day, 4 days per week for 36 weeks increased the soleus and plantaris muscle weights by 26% and 19%, respectively, compared to age-matched controls. A resistance exercise protocol consisting of 3 sets of 10 repetitions of manually resisted chin-ups performed 2 times per day, 5 times per week for 3 months increased the weight of the palmaris longus muscle by 20%, 50%, and 36% in 21-, 24-, and 27-month-old rats, respectively (Brown 1989).

Resistance exercise training has also been shown to ameliorate muscle wasting induced by hind-limb suspension, a model of simulated microgravity that induces disuse atrophy of muscles. Table 3 summarizes studies that used resistance exercise training and those that used endurance exercise training as countermeasures for suspension-induced atrophy. Findings from these studies demonstrate that both types of exercise attenuate muscle atrophy. However, comparing the amount of atrophy prevented to the total number of minutes spent in the exercise suggests that resistance exercise is more efficient than endurance exercise in attenuating suspension-induced atrophy. More precisely, the percentage of atrophy prevented per resistance exercise time is greater than the amount of atrophy prevented per endurance exercise time.

Table 1. Effects of Endurance Exercise Training on Muscle Protein Synthesis, Degradation, Mass, and Protein Content in Tumor-Bearing Rats

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Exercise** | **Muscle** | **Protein Synthesis** | **Protein Degradation** | **Protein Content** | **Muscle Weight** | **Muscle Body Weight Ratio (g muscle/kg body weight)** | **Reference** |
| Running wheel (free access for 4 weeks) | Extensor digitorum longus (in vitro) | +15% | +23% (3 hours postexercise) |  |  |  |  |
|  | Quadriceps (in vivo) | +18% | –11% (6 hours postexercise) | NR | NR | +10% | Daneryd and others (1995) |
| Swimming (120 min/day, 5 days/week for 3 weeks) | Epitrochlearis | NA | NA | NS | NS | NS | Baracos (1989) |
| Treadmill (running on 20-degree incline 20 m/min, 100 min/session, 3 times/week for 7 weeks) | Gastrocnemius | +36% | +31% | NR | NR | +22% | Deuster and others (1985) |

NOTE: Values are expressed as percentages relative to age-matched tumor-bearing sedentary rats. Some percentages were derived from data provided by the authors of the studies. NR = not reported, NA = not measured, NS = not significantly different.

The effect of resistance exercise on muscle mass in cancer patients has not been adequately studied. In one study, Cunningham and others (1986) examined the effect of resistance exercise on muscle protein turnover in persons undergoing bone marrow transplant for leukemia. In that study, patients performed 15 repetitions each of bicep-tricep curls, bench press, shoulder retractors, sit-ups, and knee extensions 3 to 5 times per week during the 35 days of hospitalization. Urinary creatinine excretion, a marker of muscle mass, was found to be higher in the patients who participated in the exercise program compared to those who remained sedentary, suggesting that the exercisers had a greater muscle mass. Findings from this study must be interpreted with caution because of the huge variations between subjects in terms of baseline body composition.

Nieman and others (1995) examined leg extension strength, measured on a Kin Com computerized testing station, in a group of women with breast cancer who participated in the exercise training. The training protocol in this study involved both endurance and resistance muscular activities. Subjects performed endurance exercise consisting of walking on an indoor track at 75% of maximal heart rate for 30 minutes per session. During the remaining 30 minutes of the sessions, subjects completed 2 sets of 12 repetitions of 7 exercises that involved progressive weight lifting. The exercise sessions were performed 3 times per week for 8 weeks. Because of the nature of the training in this study, it is unclear whether the reported trend toward an increase in muscle strength was a result of endurance or resistance exercise or a combination of the 2. In summary, an anabolic effect of resistance exercise training on healthy muscles is well documented. More important, this type of exercise attenuates muscle wasting in a variety of conditions that induce muscle atrophy. Nevertheless, it cannot be concluded, based on current literature, that resistance exercise training will have significant anabolic effects on the muscles of patients with cancer or reduce their perceptions of fatigue.

Table 2. Effect of Resistance Exercise Training on Muscle Mass in Adult Human Subjects and Adult Rats

|  |  |  |  |
| --- | --- | --- | --- |
| **Exercise** | **Muscle** | **Girth/Muscle Mass** | **Reference** |
| Humans |  |  |  |
| Triceps push-down, close-grip bench press, triceps kickbacks, biceps curl (4 sets of 8-12 reps/exercise, 3 days/week for 12 weeks) | Triceps brachii | +5% | Jurimae and others (1996) |
| Squat, leg press, and leg extension (2 sets of 12 reps/exercise followed by 3 sets of up to failure reps/exercise, 2 days/week for 6 weeks) | Leg muscles |  | Staron and others (1990) |
|  | Knee | +2% |  |
|  | Midthigh | +5% |  |
|  | Gluteal | +5% |  |
| Animals |  |  |  |
| Electrical stimulation (10 sets of 6 reps/session, 2 times/week for 6 weeks) | Extensor digitorum longus | +14% | Baar and Esser (1999) |
|  | Tibialis anterior | +14% |  |
| Electrical stimulation (4 sets of 10 reps/session, 16 sessions on alternate days) | Medial gastrocnemius | +8% | Caiozzo and others (1996) |
| Squat training with weight lifting (15 sets of 15 reps/session, 4 to 5 days/week for 12 weeks) | Plantaris | +31% | Tamaki and others (1992) |
|  | Gastrocnemius | +18% |  |
| Electrical stimulation with or without weight lifting (192 reps every 4th day for 20 weeks) | Tibialis anterior (no weight lifting) | +16% | Wong and Booth (1990) |
|  | Tibialis anterior (with weight lifting) | +30% |  |
| Mesh cylinder climbing with weight lifting (20 reps/day, 5 days/week for 8 weeks) | Rectus femoris | +8% | Yarasheski and others (1990) |
| Electrical stimulation with weight lifting (4 sets of 6 reps every 4th day for 16 weeks) | Gastrocnemius | +18% | Wong and Booth (1988) |
|  | Plantaris | +18% |  |
|  | Soleus | +13% |  |
|  | Tibialis anterior | +16% |  |

NOTE: In humans, values are expressed as percentages relative to pretraining values. In rats, values are expressed as percentages relative to nonexercised contralateral leg muscles except for the last reference, in which values are expressed relative to age-matched sedentary rats. + = muscle increased in size or weight in response to the exercise.

Table 3. Effects of Endurance and Resistance Exercise Protocols on the Absolute Weight of the Soleus Muscle in Hind-Limb Suspended Rats

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Exercise | Type of Exercise | Minutes of Exercise/Day | Total Minutes of Exercise | Percentage of Atrophy Prevented | Reference |
| Electrical stimulation, isovelocity contractions on alternate days (4 sets of 10 reps/day for 4 weeks) | Resistance (concentric) | 2.6 | 37 | 25 | Diffee and others (1993) |
| Electrical stimulation, isometric contractions on alternate days (5 sets of 10 reps/day for 4 weeks) | Resistance (concentric) | 5 | 70 | 27 | Diffee and others (1993) |
| Electrical stimulation on alternate days (4 sets of 6 reps/day for 5 days) | Resistance (eccentric) | 1 | 5 | 74 | Kirby and others (1992) |
| Daily ladder climbing (1 m at 85-degree incline, 4 sets of 8 reps/day with load equal to 75% body weight for 7 days) | Resistance | 6 | 42 | 45 | Herbert and others (1988) |
| Treadmill running (17 m/day on 0-degree incline with 3:1 days exercise:rest ratio, 10 minutes initially with 5-minute increment per day up to 60 min/day for 21 days) | Endurance |  | 740 | 31 | Norman and others (2000) |
| Daily treadmill running (20 m/min on 30-degree incline, 90 min/day for 4 weeks) | Endurance | 90 | 2520 | 43 | Graham and others (1989) |
| Daily treadmill running (5 m/min on 19-degree incline, 40 min/day for 1 week) | Endurance | 40 | 280 | 50 | Hauschka and others (1988) |
| Daily treadmill running (20 m/min on 30-degree incline, 90 min/day for 4 weeks) | Endurance | 90 | 2520 | 40 | Thomason and others (1987) |

NOTE: Values are expressed as percentage atrophy prevented in the soleus muscle of hind-limb suspended exercised rats compared to nonexercised hind-limb suspended controls. The total number of minutes is based on data provided by authors.

# Conclusion

A majority of cancer patients experience weakness and fatigue. Wasting of skeletal muscle contributes substantially to this experience of weakness and fatigue. Skeletal muscle wasting also contributes to the morbidity and mortality of cancer. Nursing interventions that would attenuate muscle wasting are of important clinical significance.

Evidence suggests that endurance exercise decreases self-reported fatigue and increases activity tolerance in persons with cancer. However, the physiological and cellular mechanisms underlying these favorable effects of endurance exercise in these patients have not been examined. Exploring the physiological and cellular mechanisms by which endurance exercise alleviates cancer-related fatigue and improves activity tolerance will help in designing more specific countermeasures for the problem of fatigue. Endurance exercise has also been shown to alleviate depression and anxiety and to improve quality of life in women with breast cancer. Whether these benefits resulted from lower fatigue levels or other physiological or psychological effects should also be explored.

Resistance exercise training increases the mass of healthy muscles and ameliorates muscle wasting associated with a variety of catabolic conditions. Given its anabolic effects on healthy and wasted muscles, resistance exercise should be examined as a potential intervention for attenuating cancer-induced muscle wasting. There are several methods for quantifying the exercise-induced changes in muscle mass. In humans, muscle mass can be roughly estimated by comparing the circumference or girth of the exercised limb to the nonexercised limb. More precise measures of muscle mass in humans include magnetic resonance imaging, computerized tomography, and dual-energy x-ray absorptiometry. Although they are relatively expensive, these methods have the advantage of being noninvasive and, therefore, are easier to perform on human subjects. In animals, muscle mass can be determined by comparing the weight and protein content of the exercised muscle to that of the nonexercised muscle.

Exercise-induced changes in muscle mass should be pursued in terms of changes in muscle protein synthesis and muscle protein degradation pathways in the exercised versus the unexercised muscles, both of which have been implicated in cancer-induced muscle wasting. There is increasing evidence that muscle wasting during cancer is mediated in part by TNF- α, which activates the ubiquitin proteasome pathway leading to increased muscle protein degradation. There are multiple biochemical and molecular laboratory techniques to measure changes in gene expression and protein levels of purported proteolytic factors in muscle tissues subjected to experimental conditions and interventions. The opportunities for nurses to learn and use these research methods to explore and explain clinical phenomena and to improve practice is one of the most exciting developments in nursing education and research training.

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