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Review Article

Cancer cachexia and the effects of physical activity

Krooks Daniela*, Johansson Malin*,TheosApostolos*

Sports Medicine Unit, Department of Community Medicine & Rehabilitation, Umeå University, Sweden

***Corresponding author:** ApostolosTheos. Department of Community Medicine & Rehabilitation, Umeå University, Sweden Tel: +46907866619, E-mail: apostolos.theos@umu.se 2#equally contributing authors

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Abstract

Physical activity is, among other things, characterized by an increased quality of life and several physiological positive results such as hypertrophy and counteracting atrophy. Cachexia has been proven to degradate muscle proteins and seems to be a death contributing factor during cancer.Cachectic muscles are resistant to anabolic effects, and this knowledge combined with the many proven positive outcomes on muscle hypertrophy by exercise led this study to investigate the previous studies conducted on this subject further. The Ubiquitin-Proteasome System (UPS) plays a significant role in protein degradation, more specifically the E3 ubiquitin ligases MuRF-1 (Muscle RING Finger protein-1) and MaFbx (Muscle atrophy F-box), which are FoxO (forkhead box-O) transcription factors. The UPS can be inhibited by substrates upregulated by physical activity, such as IGF-1 (Insulin-like Growth Factor-1) and PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha). In conclusion, there are a lot of pathways in both cancer cachexia and physical activity that border on each other, but the molecular mechanisms are complex and not always clear.

Keywords: Muscle hypertrophy; Muscle atrophy; Protein degradation.

Introduction

Cancer is defined as "an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize" (spread) [1]. A cancer tumor caused by the uncontrolled cell proliferation is a malignant tumor on the ground of invasion into other organs, and it spreads into other tissues like a clonal expansion [2].

Most patients with advanced cancer will be affected by cachexia. Cancer cachexia is defined as a multifactorial syndrome, a permanent loss of skeletal muscle mass often accompanied by a loss of fat mass [3]. A condition that eventually leads to disability (functional impairment) and is the cause of nearly one third of all cancer deaths [4].It is suggested that the loss of weight could be because of the fight for fuel in between muscle and tumor, although this is not explaining the development of cachexia since small tumors can induce atrophy while bigger ones not always do [5].

According to Fearon et al.[6], these four aspects are what cachexia consists of 1) skeletal muscle breakdown as a result of inflammation, tumor and neuro-hormonal changes, including hypoanabolism, 2) anorexia and/or reduced nutritional intake, 3) loss of lean mass, sometimes also including loss of fat mass, and 4) physical disabilities and dysfunctions, such as fatigue and psychosocial distress.

Through physical activity we are able to maintain fitness and muscle strength, and that has some significant beneficial effects on metabolic dysfunctions and chronic diseases [7].Physical activity can be described as activities of different intensities, where you perform on either light, moderate or vigorous intensity levels [8]. According to Kushi et al[9] moderate to vigorous levels of physical activity contribute to a reduced risk of developing different types of cancer. Well controlled 4 exercising is a safe and positive improvement strategy in a lot of cancer forms that improves exercise capacity and physical quality of life, and inhibits fatigue [10]. Physical activity provide benefits both during and after cancer treatment. The benefits include among other; psychosocial and physical improvements, greater willingness to complete treatment and less symptoms and side-effects [11].

A mixed model of different treatments, a combination of medication, nutrition and physical activity, seems to be the best treatment method in regards to cancer cachexia [12-14].While cancer leads to, among other things, an increase in pro-inflammatory cytokines, increased angiotensin II, increased proteolysis-inducing

factor, increased calpains, and a decrease in physical activity and a decrease in the mTOR (mammalian Target Of Rapamycin) and p70S6K (serine/threonine kinase), some of the above mentioned effects may be attenuated by resistance training [15]. Therefore the purpose of this review study was to investigate the effects of physical activity as a method of therapy/prevention in cancer cachexia.

Muscle plasticity

Protein intake generates an increase in plasma amino acids, which thereafter may restrain protein catabolism in body tissues including skeletal muscles [3]. The amino acids are replenished after a meal (containing protein), through the process of protein synthesis. In this cycle of breakdowns and build-ups of muscle proteins the latter has got to exceed the sooner in order to achieve hypertrophy, building muscle or anabolism, through resistance training or growth. Atrophy, on the other hand, refers to muscle protein breakdown or catabolism, and occurs in response to disease or inactivity [16]. This protein degradation and subsequent muscle loss (also called cachexia), is harmful to the body and leads, with high probability, to death [17-19].

The catabolic state causing muscle atrophy is linked to the ubiquitin-proteasome-system (UPS) [20]. The UPS stands for the main protein breakdown in skeletal muscles [21-22]. Denervation, injury, bed rest, fasting, cancer cachexia, inactivity, diabetes, treatment by glucocorticoids, immobilization, sepsis, aging and metabolic acidosis are all factors and conditions that contribute to muscle atrophy and involve the ubiquitin-proteasome-system [22]. Apart from the UPS there are several molecular mechanisms and pathways that contribute to an anabolic state, e.g. the PI3K/Akt-pathway (Phosphoinositide 3-kinase/protein-kinase-B-pathway) that has been proven to be of importance regarding hypertrophy and inhibiting atrophy of the skeletal muscle [20]. The PI3K/Akt-pathway is downregulated during atrophy [23] which leads to an increased activity of FoxO (forkhead-box O) transcription factors [24]. While activation of PI3K/Akt-pathway can inhibit atrophy caused by disuse [25]. FoxO is a transcription factor family involved in diverse regulatory pathways and mechanisms, including the regulation of muscle atrophy [26].

The counterpart of atrophy is hypertrophy; increased muscle mass. Signaling by IGF-1 (Insulin-like Growth Factor-1) is an important mechanism in regards to muscle anabolism [27]. When it comes to fasting and diabetes, which contribute to the protein breakdown [22] insulin is highly involved and a low level of insulin is associated with muscle catabolism [28]. With higher levels of insulin and IGF-1 the PI3K/Akt/mTOR-pathway is up regulated[24]. IGF-1 and insulin also activates the Ras-Raf-MEK-ERK-pathway/MAPK-ERK-pathway which affects fiber type composition and not muscle fiber size [24]. IGF-1 can suppress both FoxO 6 transcription factors [24] and the activity of MuRF-1 (Muscle RING-Finger protein-1) [29].

In order to successfully achieve muscular growth, one should combine resistance training with dietary protein intake on a regular basis, approximately 25-30 grams of protein which according to Paddon-Jones & Rasmussen [30] stimulates muscle protein synthesis maximally. The anabolic effect of protein consuming is lasting a few hours post consumption and then returns to the basal level [19]. In catabolic muscles there is an ongoing combination of energy imbalance with a negative outcome and protein metabolism, which together play a role in the decreased nutritional intake with systemic inflammation and metabolic dysfunctions. [31]. Anabolic resistance is therefore an inescapable feature of cancer cachectic muscle [32].

Cancer cachexia

The two counterparts intake and expenditure are the major causes of energy imbalance in cancer cachexia; energy intake decreases and energy expenditure increases and are regulated by tumor type and growth phase [27]. According to Solheim et al.[33], factors that can cause a loss of weight in cancer patients with cachexia are appetite, reduced lean and fat mass, reduced physical activity or reduced use of muscles and emotional changes that reduce food intake. The metabolism of carbohydrates and lipids is more deregulated when it comes to cancer associated metabolic dysfunction [34]. A study made by DeBoeret al.[35] concluded that the hormone ghrelin and a synthetic ghrelin receptor agonist improves weight gain and increases lean body mass in tumor-bearing rats, because of anti-inflammatory effects and also because it inhibits the central melanocortin system.

During muscle atrophy the skeletal muscle fibers have a smaller cross-sectional area, and they are also not generating as much force as the normal, healthy muscle fibers do. These athrophic muscle fibers do, however, keep most of their structural characteristics [36]. A study made by Acharyya et al.[4] suggested that muscle catabolism is very selective when it comes to the targeting of key muscle gene products, and not regulated by the downregulation of myofibrillar proteins. In most cases of atrophy, the rate of protein synthesis is suppressed while the rate of degradation is increased [37]. As mentioned earlier the ubiqutin- proteasome system (UPS) is the main system responsible for the skeletal muscle protein breakdown [15,21,22]. The UPS is regulating and degradating damaged and redundant proteins in the cell nucleus and cytosol. There are three different types of enzymes playing the main roles in this multistep pathway; E1, E2 and E3. Ubiquitin is a small protein, activated by E1, and attaches to the damaged proteins as a signal for disassebly. E2 (ubiquitin-conjugating enzymes) acts as an escort for ubiquitin to the E3 (ubiquitin-protein ligase). The E3 recruits the E2-complex and allows the ubiquitin to be transferred to the target protein. Eventually the degradation occurs in a proteolytic complex called 26S proteasome [38-39]. Furthermore Khal et al. [38] found that the enzyme E2 increased simultaneously with the increase in weight loss (up to 20%) among cachectic cancer patients. This also indicates that ubiquitination of substrates and proteasomal degradation increases in skeletal

muscles of patients with this disease.

It is well known that the E3 ubiquitin ligases MuRF-1 and MaFbx (muscle atrophy F-box)/atrogin-1 are highly expressed in skeletal muscle during muscle atrophy [23,24,40,41]. NF-κB (nuclear transcription factor kappa B) that regulates MuRF-1 and MaFbx is a central integration site for pro-inflammatory signals [42]. This 8 transcription factor can become activated by for example PIF, proteolysis inducing factor [5], which is upregulated during cancer [15], and by stressors including inflammation and cytokines [43]. The pro-inflammatory cytokine TNF-α (tumor necrosis factor-alpha) can induce activity of NF-κB [24]. Cachexia leads to an increase in pro-inflammatory cytokines such as interleukin (IL)-6 and TNF-α [44]. IL-6 promotes tumor development both directly on cancer cells and indirectly by arranging a tumor-friendly microevironment [45].Anemia, abnormal liver function, fatigue and vomiting are all symptoms of cachexia and can, according to Weidle et al. [46], be caused by the IL-6 administration.

An example of the vicious circle of UPS and tumor cells is that tumor cells activate the transcription factor STAT3 (signal transducer and activation of transcription 3) which upregulates the ubiquitin-proteasome system and caspase-3 and will ultimately provide the UPS with substrates through cleaving of the proteins in the muscle. The activated STAT3 also leads to an increased expression of MaFbx and myostatin through C/EPB-delta [5]. During the early stages of cachexia, rate of protein synthesis is reduced through suppressing mTORsignaling, but the underlying mechanism is, according to Gordon et al. [47] still not understood.

Physical activity

Physical activity seems to prevent the formation of cancer tumors and contributes to various effects in our bodies [48]. Aerobic exercise and strength training gives different responses mediated by a lot of various mechanisms and pathways [7]. If you put mechanical stress on skeletal muscles it will trigger signaling proteins, which activate genes that, in turn, activate translation of mRNA (messenger-RNA) of each 9 gene [49]. In cancer cachexia the muscles can show a two- to fourfold increase in mRNA-levels for a chain of ubiquitin and a few proteasome subunits [37]. Physical activity increases the expression of the transcriptional coactivator and regulator of skeletal muscle mass PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) in both cardiac and soleus muscle, and this finding shows that PGC-1α via exercise could help protect cardiac and skeletal muscle atrophy by inhibiting FoxO pathway activity [40]. With erythropoietin administration and moderate exercise Pin et al. [50] found that promotion of mitochondrial biogenesis through PGC-1α and muscle quality is improved.

When the muscles contract repeatedly, the muscle increases production of IGF-1 which stimulates protein synthesis and anabolism through Akt/PI3K. Akt phosphorylates FoxO transcription factors which lead to an inhibition of their transcriptional functions [20]. Furthermore, PGC-1α is increased with physical activity and thus mitochondrial biogenesis is enhanced, plus it inhibits activity of FoxO [40,51]. Transcriptions depending on FoxO is a central point in controlling gene networks during cancer cachexia [52]. If inhibition of the FoxO transcriptional activity occurs, satellite cell proliferation and fusion with muscle fibers increases in control muscles according to Reed et al. [53], and the inhibition also has effects on skeletal muscle hypertrophy. According to Stitt et al. [54], the IGF-1/PI3K/Akt-pathway not only promotes hypertrophy, but also suppresses atrophic pathways that otherwise might fight hypertrophy. The activity of this pathway requires an inhibition of FoxO[54].

Both aerobic exercise and high intensity exercise or resistance training increase the production of reactive oxygen species (ROS) [55]. Aerobic exercise may also reduce inflammation which in cachexia truly is an important factor [56]. Production of ROS can cause oxidative stress that is an imbalance between the level of ROS and antioxidant capacity [57], and according to Lenk et al. [58] it is associated with several chronical diseases. The excess production of ROS can lead to activation of the FoxO-signalling pathway, which in turn increases the transcription of FoxO-target-genes such as MuRF-1 and MaFbx [57] and these contribute to skeletal muscle atrophy. Interestingly, both exercise and disuse leads to oxidative stress according to Powers et al. [57]. While exercising improves the expression of proteins that regulate mitochondrial biogenesis, this attenuates protein degradation even when levels of IL-6 are as increased as they are in cancer cachexia [59].

A study made by Khamoui et al. [56]. On mice in CT (control group), AT (aerobic training group) and RT (resistance training group) showed that neither AT nor RT could prevent tumor-induced weight loss, and that exercise parameters such as duration and intensity are of high relevance in order to avoid an increased weight loss. For some of the mice in the RT group, euthanasia was necessary because of their impaired condition. In fact, some of the RT mice required to be put down because of their worsened condition. However, this study showed that aerobic exercise, defined as low muscular tension sustained for a prolonged period, may have attenuated the loss of muscle mass to a mild extent, together with improved maintenance of functions of the body, such as daily activities being less strenuous.

IL-6 and TNF-α can be prevented by proteins upregulated by aerobic exercise, such as GLUT4 (Glucose transporter), GSH (glutathione) and SOD (Superoxid-Dismutase) by inhibiting either the pro-inflammatory cytokines or the increased activity of ROS, or by increasing glucose transport and thus inhibiting the increase in insulin 11 resistance produced by the pro-inflammatory cytokines [60]. The authors further disclose that resistance training ultimately leads to an increased protein synthesis, courtesy of substrates like IGF-1, mTOR or Akt. In order to achieve an increase in levels of Akt, IGF-1 and insulin, a supply of amino acids and glucose is needed [24].

Conclusions

Anabolic resistance is an inescapable feature of cancer cachectic muscle [32]. We conclude that the molecular mechanisms of cancer cachexia remain unclear, but that they are similar to some of the important pathways that either promote or inhibit muscle hypertrophy via exercise. Cancer cachexia inhibits activity of mTOR[47].while increased levels of insulin and IGF-1 upregulates the PI3K/Akt/mTOR-pathway [24]. This pathway is important promoting hypertrophy and inhibiting atrophy of the skeletal muscle [20]. If the pathway is inhibited, an increased activity of FoxO transcription factors occurs [24]. The UPS is the main system responsible for skeletal muscle protein breakdown [15,21,22] and the E3 ubiquitin ligases MuRF-1 and MaFbx are the most crucial when it comes to atrophy. According to Mahdiabadi et al. [61] duration and intensity of exercise are important factors to consider when it comes to cachectic cancer patients' treatment in order to avoid an increased weight loss. In conclusion there is not much evidence suggesting that muscle mass and strength are affected when it comes to physical activity as a treatment for cancer cachexia patients and therefore further research is needed.

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