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Cancer-related fatigue: can exercise physiology assist oncologists?

Alejandro Lucía, Conrad Earnest, and Margarita Pérez

Most patients with cancer experience fatigue, a severe activity-limiting symptom with a multifactorial origin. To avoid cancer-related fatigue, patients are frequently advised to seek periods of rest and to reduce their amount of physical activity. This advice is reminiscent of that formerly given to patients with heart disease. However, such recommendations can paradoxically compound symptoms of fatigue, since sedentary habits induce muscle catabolism and thus cause a further decrease in functional capacity. By contrast, there is scientific evidence that an exercise programme of low to moderate intensity can substantially reduce cancer-related fatigue and improve the quality of life of these patients. Current knowledge, combined with findings soon to be published, could launch new opportunities for patients with cancer. In this new century, exercise physiology could soon prove to be very useful for oncologists.

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Figure 1. Fatigue is one of the main problems that influences the quality of life of cancer patients and survivors. This symptom can severely limit their capacity to enjoy many aspects of life, such as outdoor leisure activities.

Clinically, fatigue is a symptom commonly defined as a patient's feeling of lack of energy, weariness, or tiredness.[1] About 70% of people with cancer report feelings of fatigue during radiotherapy or chemotherapy, or after surgery.[1] This form of fatigue is generally much more disruptive than that associated with other diseases such as depression, multiple sclerosis, or arthritis.[2] Irrespective of the type of cancer, the related fatigue influences all parts of a patient's quality of life and aggravates other distressing symptoms such as pain, nausea, and dyspnoea (figure 1).[3] Fatigue is also a serious problem for people who survive cancer; up to 30% experience the symptom for years after the end of treatment.[1]

Several studies have investigated the fatigue associated with radiotherapy.[4–10] Although a gradual increase in fatigue is common during a course of treatment, the symptom generally subsides after completion of the course, and recovery to the state before radiotherapy typically occurs within a few weeks.[5,6] Evidence of long-term persistence of fatigue after therapy comes mainly from a study by Berglund and colleagues.[4] In that study, fatigue persisted (and was the most commonly reported symptom) in 76% of women with breast cancer who had undergone adjuvant radiotherapy 2–10 years previously and were free of recurrence at the time of follow-up. However, results from other studies suggest that fatigue does not persist after completion of adjuvant radiotherapy.[5–8] For instance, Irvine and co-workers[6] assessed fatigue in women with breast cancer during adjuvant radiotherapy and then again at 3 months and 6 months afterwards. Although the degree of fatigue was significantly higher during radiotherapy than before treatment; at both 3 months and 6 months of follow-up, the severity was the same as that before treatment. Another study showed an increase in fatigue during radiotherapy and return to pretreatment severity 2 months after completion of therapy.[8]

Fatigue is also extremely common and distressing during and after adjuvant chemotherapy. One study found that 82% of women with breast cancer experienced fatigue after the first cycle of chemotherapy and 77% after the second.[11] Berglund and colleagues[4] assessed fatigue in a sample of patients who had received adjuvant chemotherapy 2–10 years previously. All had received cyclophosphamide, methotrexate, and fluorouracil for 6–18 months and were free of recurrence at the time of assessment. The investigators reported that 68% of patients were experiencing fatigue at the time of the study. In another study, after a median of 7·5 months since chemotherapy completion, the prevalence of fatigue in women with node-negative breast cancer was 83%, and 60% reported that fatigue interfered with their functioning.[12] Broeckel and co-workers[13] reported that 40% of cancer survivors experienced

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fatigue months or years (average 471 days) after chemotherapy had ended.

Fatigue can also occur after autologous bone-marrow transplantation[14] or after high-dose chemotherapy with bone-marrow transplantation.[15–18] Women with breast cancer assessed an average of more than a year after transplantation were more fatigued than women with no history of cancer[15] or women with breast cancer who underwent surgery and radiotherapy only.[16]

Fatigue is also a side-effect of surgery, although the possible effects of surgery itself are difficult to separate from those of radiotherapy and chemotherapy.[19] In terms of the differences in the degree of long-lasting fatigue experienced by patients according to the different types of treatment, the overall evidence, at least in women with breast cancer, is that patients who have undergone bone-marrow transplantation and chemotherapy tend to have more fatigue than those given adjuvant chemotherapy without bone-marrow transplantation; these patients, in turn, tend to have more fatigue than patients who received radiotherapy.[20]

The aetiology of fatigue in cancer remains to be fully elucidated and seems to be multifactorial; it includes the side-effects of treatment, anaemia, nutritional and fluid imbalance, sleep disturbances, and systemic reaction to tissue injury induced by the disease or treatment (eg, release of cytokines from necrotised tissue after radiotherapy).[1] Psychosocial factors can also have an important role in the genesis of fatigue and its exacerbation when already present. These factors include emotional distress, difficulty of coping with treatment demands, anxiety, or depression.[1] Fatigue is a subjective condition. Some patients perceive it in a way that primarily suggests a psychological alteration—eg, lack of concentration and memory loss, or lack of desire to accomplish anything.[21] Many patients, however, report fatigue as a state of physical disturbance and loss of functional status in which exhaustion is easily brought about during daily tasks involving little physical activity, such as walking a short distance, climbing a few stairs, or completing routine household tasks.[1] This severe activity-limiting fatigue is caused by extreme muscular deconditioning related to both illness and treatment but also to sedentary habits.

Pathophysiology of physical fatigue from the perspective of exercise physiology

Study of fatigue in the clinical setting is complicated by its multifactorial aetiology, psychological factors, and patients' perceptions. The pathophysiology of the physical fatigue experienced by most cancer patients and survivors can be viewed from the perspective of exercise physiology. This science studies the bodily responses and adaptations to physical activity, exercise, or sports. Understanding of the reasons for the phenomenon of fatigue in both healthy and diseased people has been one of its main goals for decades.

Definition

Physical fatigue is defined as the decline in muscle tension (force) capacity with repeated stimulation.[22] This measure can be objectively quantified with specific tests during submaximum or maximum tasks. For instance, fatigue can be identified as the rate of decrease in the force/time curve of the quadriceps muscle during submaximum or maximum voluntary contractions. If this decrease is attenuated in the same individual after a training period, his or her quadriceps muscle is less fatigable—ie, it shows an improvement in functional capacity. Physiological fatigue is also a complex process that can be originated in one or more steps in a chain of interactive events between the central nervous system (CNS) and the skeletal muscle fibre.

CNS

Fatigue sometimes originates at the CNS level. Some neuromodulators such as ammonia or the cytokines secreted by immune cells can act on the CNS to alter the psychic or perceptual state and decrease ability to exercise.[23] Besides the side-effects of anticancer drugs on the CNS, the concentration of cytokines increases in individuals with cancer as a result of the interaction between the tumour and the host defence system.[1]

Insufficient oxygen transport to muscles

Patients with cancer may have several specific problems that make oxygen supply insufficient to meet the oxygen demands of their muscles. This lack can help explain, at least partly, the severe fatigue that patients experience even during normal activities requiring little oxygen consumption by working muscles.

Anaemia, commonly defined as a haemoglobin concentration of less than 12 g/dL, occurs in over 30% of cancer patients at any time, and the frequency increases with progressive disease and treatment.[24] Chemotherapy and radiotherapy can damage bone marrow and produce renal toxicity.[1,24] Erythropoietin, the hormone that stimulates production and maturation of red blood cells, is mainly secreted by the kidneys. As a result, anaemia is further aggravated, with subsequent negative effects on oxygen-carrying capacity of the blood.

In addition, loss of lung volume caused by disease (metastases and pleural effusion) or treatment (eg, lobectomy) can alter the ventilation/perfusion ratio and further reduce arterial blood oxygenation and oxygen supply to the working muscles.[1] Of special clinical relevance is the lung toxicity that occurs after chest irradiation. Acute radiation pneumonitis (also termed sporadic pneumonitis), consisting of cough and dyspnoea out of proportion to the volume of irradiation, in most cases resolves completely with no long-term effects.[25] However, late radiation toxicity results in pulmonary fibrosis, which is a consequence of tissue repair after ionising radiation. Oxygen saturation of arterial blood is then severely compromised by damage to the capillary alveolar membrane, decreased lung perfusion, and lower lung compliance.[25]

Insufficient blood pumping to muscles

Anticancer therapy can affect central cardiac dynamics and thus blood supply to body tissues, particularly exercising muscles. Radiation of the mediastinum and several

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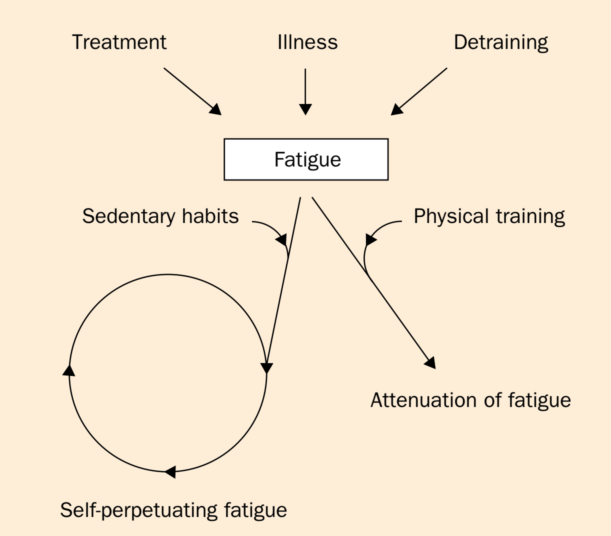

Figure 2. Sedentary habits can make cancer fatigue become a self-perpetuating condition. Only physical training can break the cycle of fatigue.

antineoplastic agents with cardiotoxic effects (especially anthracyclines and cyclophosphamide, but also trastuzumab) can induce myocardial damage (eg, doxorubicin-induced cardiomyopathy), which leads to decreases in cardiac output.[1,26] Cardiac atrophy due to long-term bed rest further reduces cardiac output.[27] Several processes at the peripheral (muscle) level also influence the fatigue of cancer patients.

Severe impairment of skeletal-muscle function

Severe muscle-mass atrophy is a common problem that results from the catabolic effects that sedentary habits and long-term bed rest induce in skeletal-muscle tissue.[28] In cancer, this problem is further aggravated both by the production by tumours of factors that elicit an inflammatory response (prostaglandin E_2) in muscle tissue and result in muscle wasting[29] and by the adverse effects of immunosuppressive drugs (eg, high-dose glucocorticoids, cyclosporin, or cyclophosphamide) on the ultrastructure and function of skeletal muscles. These effects include a decline of myofibrillar mass, altered aerobic metabolism (due to decreased mitochondrial volume or mitochondrial myopathy), or reduced capillarisation.[30–32] Fatigue also occurs in human beings when energetic substrates are depleted in muscle fibres. Depletion of phosphocreatine, an intracellular high-energy compound, reflects a mismatch between ATP synthesis and degradation inside muscle fibres and can cause fatigue during submaximum exercise.[33] Intramuscular stores of phosphocreatine are partly supplied by dietary creatine (especially in meat). Oral supplementation of creatine can increase athletic performance and has attenuated muscle fatigue in several population groups (elderly people and patients with cardiac failure or neurological disorders) who are commonly severely detrained and have muscle atrophy.[34,35] Further research should confirm the potential benefits of oral creatine supplementation in patients with cancer.

According to the latest knowledge, muscle fatigue in human beings is mainly caused by a failure of the excitation-contraction (E-C) coupling process. E-C coupling is the mechanism by which the electrical discharge on the muscle-fibre membrane brought about by nerve impulses initiates chemical events inside the fibre—release of intracellular calcium from the sarcoplasmic reticulum. Calcium release is the signal for immediate contractile activity. It is followed by calcium reuptake to initiate the relaxation process. Coupling (contraction) and uncoupling (relaxation) continuously operate during any type of exercise or physical activity. Despite common belief, lactate accumulation and lactic acidosis do not alter E-C coupling and thus are not major determinants of muscle fatigue. Other factors independent of lactic-acid build-up are more likely to alter E-C coupling and thus to cause fatigue in healthy people, such as accumulation inside working muscle fibres of inorganic phosphate due to an insufficient rate of ATP resynthesis[36] or accumulation of reactive oxygen species derived from aerobic metabolism.[37]

In cancer patients, E-C coupling can be also impaired by the side-effects of treatment. Ionising radiation can alter membrane cells of muscle fibres with subsequent changes in the calcium release and reuptake mechanisms in the sarcoplasmic reticulum.[38] This process results in impairment of E-C coupling and early fatigue during exercise (eg, during sustained isometric muscle contractions at 80% of maximum voluntary contractions).[38]

Metabolically active molecules such as tumour necrosis factor α (TNFα) released from tumour or mast cells can necrotise muscle membranes and thus impair E-C coupling.[39,40] This effect could explain, at least partly, the increase in muscle fatigue induced by TNFα.[41]

We emphasise that fatigue is a physiological, non-pathological phenomenon that protects body tissues such as myocardium from excessive damage.[42] There is a central 'programmer' (located in the CNS), which is able to anticipate the total activity and metabolic changes that body systems can sustain to complete a given exercise. This programmer decreases the efferent neural command to working muscles with subsequent decline in muscle force generation–ie, fatigue–before bodily damage occurs.[42]

Current situation in more developed countries

In the past, physicians traditionally advised patients with chronic diseases, such as cardiovascular disorders, to avoid physical activity. However, the investigation of cardiac rehabilitation in the 1960s showed, through a series of clinical studies, the benefits of early mobilisation after myocardial infarction. These programmes and the recommendations of the World Health Organization in 1964 and thereafter expanded the development of cardiac rehabilitation.[43] Although several studies published in the 1980s showed the benefits of exercise for functional status in cancer, at present physical activity programmes are not well defined or included in the list of possible interventions for management of cancer fatigue. For example, hospitals from the Spanish social security system frequently advise cancer patients to seek periods of rest and to lower their degree of

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activity. These well-meaning recommendations create a paradox, whereby inactivity induces muscle catabolism and causes further detraining. As a result, a self-perpetuating detraining state with easily induced fatigue can persist for years after treatment (figure 2).[1] When physical activity is recommended for cancer patients, little specification is given about proper, personalised exercise prescription, in terms of mode, frequency, or intensity of exercise.

Scientific evidence for attenuation of fatigue with exercise training

The first report on the benefits of exercise in people with cancer showed that those who exercise during treatment experience mood-enhancing effects.[44] Further studies have shown the positive psychosocial effects of regular exercise for patients receiving chemotherapy.[1] There have also been several investigations on the effects of exercise training on the functional capacity and tolerance to physical fatigue of people with cancer[14,17,18,45–50] and survivors of the disease.[51,52] During these trials, functional capacity and fatigue tolerance were quantified by means of validated measures commonly used in clinical exercise physiology. The studies included population samples, mostly of women with breast cancer,[17,45–48,50] though men and women with other types of solid tumours,[18,49] haematological malignant disorders,[14] or Hodgkin's[49] and non-Hodgkin lymphoma have also been studied.[18] In two recent studies, male and female survivors of colon cancer, breast cancer,[51] or Hodgkin's disease have also been studied.[52] Patients started the training programmes during chemotherapy[48,50] or after bone-marrow transplantation.[14] Training programmes also started during[17] or shortly after high-dose chemotherapy with transplantation of peripheral stem cells[18] or after surgery (in breast-cancer patients receiving radiotherapy[47] or chemotherapy).[45,46] Training duration ranged from about 2 weeks to 4–6 months, although most training periods lasted 6–10 weeks. A typical training programme included three to five training sessions per week, and in most programmes the duration of sessions was gradually increased until continuous exercise for about 30 min was achieved. The most common training mode was treadmill or outdoor walking, although pedalling exercise on a cycle or bed ergometer (for hospital inpatients) has also been used. Training intensity was objectively measured by some researchers and ranged between 60% and 85% of patients' maximum heart rate. In exercise physiology, this is classified as moderate-intensity exercise.

With the exception of two studies,[14,49] a group of untrained patients served as controls. The population size was variable and small by clinical and epidemiological standards, ranging from five[49] to 72.[50] Keeping in mind the statistical limitations brought about by small sample sizes, we emphasise that sample sizes of about ten people are common in classic exercise physiology studies that have shown the adaptive responses (molecular, physiological, or neurohormonal) induced by training in human beings.

The results of these studies unanimously showed both the absence of detrimental effects of exercise training on cancer patients or survivors and a significant improvement in their functional capacity after training and increased tolerance to physical fatigue and exertion. Improvements in functional capacity were quantified with valid indicators commonly used in clinical exercise physiology: increased maximum walking velocity or distance covered during a treadmill test; a decrease in heart rate and blood lactate concentration at submaximum workloads; and higher maximum oxygen uptake. As a result of their improved functional capacity, most patients could carry out normal daily activities with no fatigue.

Of special interest are the findings of Dimeo and colleagues;[14,18,49] they measured the effects of training on classic physiological variables with profound physiological implications (heart rate and blood lactate concentrations at submaximum intensities). The reported training-related decreases in both variables reflect improved functional status and increased metabolic efficiency for a given workload. Improved metabolic efficiency is one of the main adaptations induced by endurance training. It is due largely to changes in characteristics of skeletal-muscle fibres—namely, an increase in the proportion of oxidative fibres and a decrease in the proportion of glycolytic fibres.[22] Oxidative fibres produce less lactate than glycolytic fibres; also, they can remove lactate from blood and oxidise it as a fuel, and they are less fatigable and more efficient—ie, they consume less oxygen for a given task. Increased muscle efficiency explains how most trained patients with cancer can carry out normal daily activities with lower energy input and thus less fatigue. By contrast, muscle atrophy and a decrease in the population of efficient, oxidative fibres are common findings in detrained people with chronic disease.[53] Owing to the very low muscle efficiency induced by illness and deconditioning, routine activities such as walking a short distance or completing routine household tasks could represent a near-maximum effort for many people with cancer. Not surprisingly, fatigue becomes a self-perpetuating condition for them, which limits most of their life activities.

The maximum oxygen uptake of cancer patients and survivors improves with endurance training.[45,48,51,52] This variable can be directly measured with an open-circuit spirometry metabolic cart (figure 3) or indirectly estimated with valid, population-specific regression equations. The maximum oxygen uptake reflects the greatest volume of oxygen that can be consumed by body cells for any given time; it is expressed in mL of oxygen per min or more commonly in mL of oxygen per kg body mass per min, since most physical and sport activities are weight-bearing activities. During exercise, more than 80% of the consumed oxygen is used by working muscles. The maximum oxygen uptake is an integrative indicator of the maximum capacity of the different bodily tissues—lungs, heart, blood, working skeletal muscles—involved in the chain from the delivery of atmospheric oxygen to the mitochondria of the muscle fibres. Thus, in all human beings, any increase in maximum oxygen uptake brought about by exercise training involving large muscle mass (eg, walking, pedalling, running, or swimming) is mostly attributable to an improvement of cardiorespiratory function, but also of blood oxygen transport and muscle aerobic capacities (mitochondrial density or capillarisation of muscle fibres).[22]

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Figure 3. Measurement of maximum oxygen uptake in a trained cyclist during a cycle-ergometer test. The person breathes through a low-resistance mouthpiece, and the collected air passes through cables to a metabolic cart. The maximum oxygen uptake is a an excellent indicator of functional capacity. Cancer patients have very low values,[48] about five times lower than those of trained athletes.

Furthermore, maximum oxygen uptake can be viewed as a health indicator because there seems to be a positive association between high values and longevity.[54] Besides the well-documented improvements that endurance training induces in the function of cardiac and skeletal muscles, improved physiological function can attenuate the adverse effects of anthracyclines and myeloablative therapies in the tissues involved in oxygen supply to working muscles (myocardium or bone marrow). Regular exercise also protects the myocardium against the toxicity of anthracyclines[55] and stimulates erythropoiesis with a subsequent increase in the oxygen transport capacity of the blood. With 6 weeks of training, the mean haemoglobin concentration of men and women with various types of cancer increased from 10·1 g/dL to 13·1 g/dL.[18] Furthermore, repeated exercise can attenuate the effects of muscle atrophy and cachexia due to both cancer and the toxicity of cancer therapy through suppressing inflammatory responses and improving immune function, rates of protein synthesis, and antioxidant enzyme activities.[29]

The minimum oxygen uptake, the basal metabolic rate, needed for an average 70 kg man or 55 kg woman to sustain vital functions under basal conditions is 3·6 mL kg^{-1} min^{-1}.[22] Before a training intervention in cancer patients, maximum oxygen uptakes approximating 14 mL kg^{-1} min^{-1} are not untypical, as is a maximum exercise capacity only four times that of rest.[48] These values are similar to those of people with other chronic diseases.[56] The evidence implies that many cancer patients are forced to reach their maximum oxygen uptake just to carry out leisure activities such as walking outdoors (estimated oxygen cost 16 mL kg^{-1} min^{-1} for a 70 kg man). Because human beings cannot tolerate exercise intensities eliciting maximum oxygen uptake for more than a few minutes, severe fatigue inevitably occurs. Therefore, other recreational activities such as gardening (oxygen cost 19 mL kg^{-1} min^{-1}) are barely accomplishable for these patients. As a result, they can only perform activities requiring few body movements, and a severe detraining condition is perpetuated, if not worsened. Fortunately, little training intervention is needed to induce significant improvements in the functional capacity of severely detrained individuals. For example, the maximum oxygen uptake of women (about 70 kg mean bodyweight) with breast cancer receiving chemotherapy increased from 14 to 21 mL kg^{-1} min^{-1} after a 10-week training programme.[48] With this type of improvement in functional capacity, most daily and leisure activities such as walking, house-keeping, and gardening become submaximum, rather than maximum activities, and thus can be carried out before fatigue occurs.

Lance Armstrong's contribution

A great tribute is due to cycling champion, Lance Armstrong, who was diagnosed with advanced testicular cancer accompanied by lung and brain metastases in October, 1996. His treatment included surgery and aggressive chemotherapy (etoposide, ifosfamide, and cisplatin) that, as recorded on his website, "weakened me well beyond anything I had ever experienced". Despite severe fatigue and muscle weakness that forced him to re-educate his muscles for pedalling, he used a progressive training programme that eventually allowed him to return to competition in the winter of 1998. He won the Tour de France five times between 1999 and 2003. To comprehend the full magnitude of this feat, one must appreciate that this 3-week cycle race is one of the most demanding sports events (and the hardest endurance race) that human beings can undertake. The energy output during each daily stage (duration 4–6 h) ranges from 25 MJ (6000 kcal) with extremes up to 40 MJ (9600 kcal), and the maximum oxygen uptake required to succeed in professional cycling races exceeds 70 mL kg^{-1} min^{-1}, a value more than twice the usual maximum oxygen uptake values of healthy, sedentary young people.[57]

Armstrong's case reflects the great plasticity and adaptability of skeletal muscles and bodily tissues with appropriate training stimuli despite a previous state of severe fatigue and muscle atrophy. Both people with cancer and their physicians should view his achievements as a highly motivating reference and a testimony to the usefulness of exercise in promoting physiological function.

Possible contributions of exercise physiology to oncology

Many studies in exercise physiology/biology have shown the clinical benefits of regular exercise, both as a form of preventive medicine and as a primary intervention for the

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treatment of various chronic diseases.[58] Exercise has gained acceptance as an integral part of rehabilitation programmes for chronic and disabling diseases.[22] As a result, the role of clinical exercise physiologists has gained recognition as a part of a team approach to total patients' care. Clinical exercise physiologists work in laboratories located in clinical settings, and their main role is to improve patients' functional capacity and overall mobility, while working closely with physical and occupational therapists and physicians.[22] Measurement instruments such as specific ergometers (treadmill, cycle ergometers, arm ergometers), metabolic carts, electrocardiographic recorders, and blood lactate analysers allow study of a patient's responses and adaptations to exercise from an integrative perspective. There are a growing number of qualified certifications for professionals involved in prescription of physical activity for preventive and rehabilitative purposes. These professionals can be grouped together as fitness specialists.

We propose that the contribution of exercise physiology can be equally valuable for oncology departments. Clinical exercise physiologists, working together with fitness specialists and providing constant feedback to oncologists, can assist in the task of rehabilitating cancer patients to a degree of function that allows a much better quality of life. Pretraining stress tests on specific ergometers would allow physiologists to assess the functional capacity of each patient and the personalised training programme that is most suitable for him or her. A detailed training programme (exercise mode, timing, intensity, and frequency) could then be prescribed by the physiologist and fitness specialist for each individual case. Fitness specialists should be responsible for supervising each training session and giving advice and feedback information to patients day-to-day. Several instruments (eg, heart-rate monitors) are readily available for continuous monitoring of exercise with no discomfort for the patient (figure 4). We also propose that patients enrolled in exercise programmes should take specific performance tests periodically (eg, every 2 months) to confirm that their functional capacity is consistently improving; such tests include treadmill or cycle-ergometer tests for measurement of maximum oxygen uptake or specific tests to quantify improvements in muscle strength. Both the acknowledgement of these consistent improvements and frequent, positive feedback from fitness monitors should increase the self-confidence of cancer patients.

There is not yet a position statement by the American College of Sports Medicine (ACSM) for exercise prescription in cancer patients and survivors (as opposed to other diseases). Furthermore, exercise prescription should be personalised, given the many factors that can influence the exercise tolerance of each patient (eg, severity of the disease, age, chemotherapy dose). Nevertheless, some general recommendations (and precautions and contraindications) can be addressed on the basis of the body of knowledge accumulated by decades of research in exercise physiology, ACSM general recommendations for maintaining and improving functional capacity in the overall population,[59] and a review paper by Courneya and colleagues.[60]

Training mode

Exercise involving large muscle groups (walking, swimming, or cycling), should be the core part of each training programme, given the adaptations that this type of exercise induces in muscle endurance or the ability to perform repeated contractions for extended periods. Resistance (strength) exercise (with free weights or specific machines) must be included whenever possible in the training programme of patients with cancer. This exercise mode should be an important component of any training programme. Besides the potential beneficial effects on many risk factors and diseases (including cancer),[61] resistance training attenuates sarcopenia, such as that induced by high-dose glucocorticoids.[62] Specific stretching exercises to improve the joint flexibility should also be included in the programme. Joint flexibility is required in most daily activities and is therefore a component of physical health.[63] Previous research has shown the functional (increased joint range of motion) and psychological benefits of stretching exercises in women with breast cancer.[64]

Training duration and frequency

According to the ACSM, a minimum frequency of two endurance-training sessions per week consisting of 20–60 min continuous exercise is recommended for maintaining and improving the functional capacity of the overall population.[59] However, most people with cancer cannot achieve this goal in the early phases of training, especially during treatment or in more severe illness.[60] In these cases, the emphasis should be on periods of low to moderate aerobic activity several times daily rather than a single, strenuous bout of continuous exercise; one approach is to combine short exercise sessions (3–5 min) with rest intervals.[60] The duration of each period should be gradually increased from the start of the programme. Studies by Dimeo and colleagues[14,17,18,49] showed that cancer patients who could not sustain continuous walking for more than 3 min were able to complete walking sessions of up to 30 min at the end of a 6-week training programme.[18,49] The good news from exercise physiology studies is that training effects are cumulative; the benefits obtained from three 10 min exercise bouts throughout the day almost equal those of a continuous 30 min session.[22] Furthermore, skeletal muscle is such a plastic tissue that molecular adaptations to training—activation of specific genes related to metabolic efficiency—occur within hours of a single exercise session.[65] All the benefits of resistance training can be obtained with only two 15–20 min sessions per week.[61] Just one set of different exercises with low weight loads (allowing completion of 10–15 repetitions per exercise) is sufficient to obtain significant benefits in untrained individuals.[22]

Training intensity

The intensity of endurance exercise should be between 55% and 85% of maximum heart rate (as recorded during a previous stress test or assumed to be equal to 220 minus the person's age).

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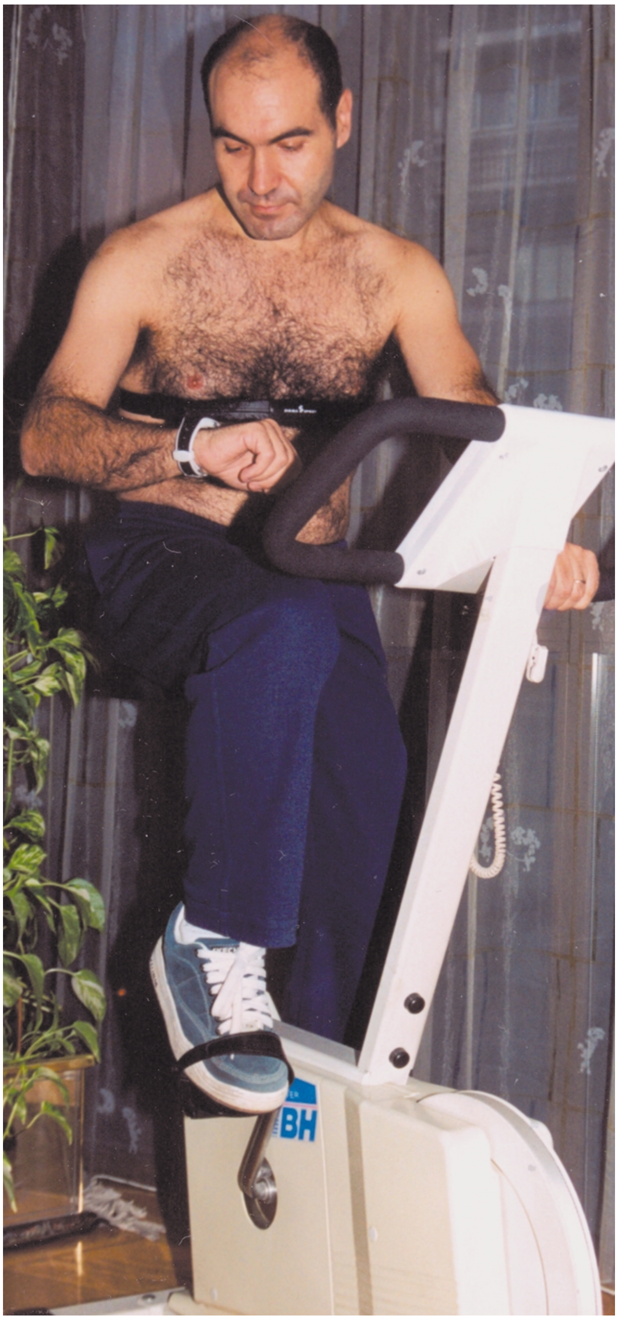

Figure 4. Heart-rate monitors are very easy to use during training sessions with no discomfort or stress for the patient. A transmitter placed on the chest continuously sends heart-rate data via telemetry to a watch. The watch's screen displays the data and thus provides continuous feedback to the patient and fitness monitor. The data can be also downloaded to a computer for further analysis by fitness specialists and exercise physiologists.

Contraindications and precautions

To date there are no reported detrimental effects of exercise training on people who have cancer or have survived it. Thus, this treatment for cancer-related fatigue is both useful and safe. Nevertheless, caution is necessary in some conditions.[60] Intense exercise is contraindicated in patients with severe anaemia (haemoglobin below 8 g/dL), fever (temperature above 38°C), or severe cachexia (loss of more than of 35% premorbid weight). High-impact exercises and contact sports should be avoided in patients with increased risk of bone fractures (primary or metastatic bone cancer) and in those with a platelet count lower than 50×10^9/L. Swimming can increase the risk of bacterial infection and should not be undertaken if the neutrophil count is $0{\cdot}5\times10^9$/L or less; swimming should be also avoided in patients with nephrostomy tubes, central venous access, or urinary bladder catheters. In patients experiencing ataxia, dizziness, or peripheral neuropathy, walking outdoors and mostly cycle-ergometry training are preferable to other activities that also involve large muscle groups but require additional balance and coordination (eg, treadmill walking, outdoor cycling). Exercise should be concentrated solely on leg muscles (pedalling on a cycle or bed ergometer[17]) in individuals with limitations in the range of motion of the arms (eg, due to breast, axillary, or thoracic surgery). As a general recommendation, walking or pedalling exercise (either on cycle or bed ergometry) is the safest option in those cases in which special caution is needed.

Potential further interventions: nutrition and electrical stimulation

Research efforts must continue in the area of exercise physiology applied to people with cancer. Future studies should explore the potential benefits of nutritional supplements, such as creatine and n-3 fatty acids, which are known to alter physical performance favourably. High-carbohydrate diets (more than 60% total caloric intake as carbohydrate) have also proven useful to improve fatigue tolerance during exercise. During intense exercise, carbohydrate is the main fuel for skeletal muscles; maintenance of high carbohydrate muscle stores is an effective means for preventing muscle catabolism during these efforts.[22] Whether such high carbohydrate intake is necessary in people with cancer is debatable. However, in many cancer patients, routine daily activities such as walking represent intense exercise. Thus, monitoring of the potential benefits of maintaining adequate carbohydrate intake in these patients and ensuring overall energy balance might be worthwhile.

Patients in hospital who are too weak to start any type of activity can start training (and thus undergoing training adaptations) even in bed. Transcutaneous neuromuscular electrical stimulation (NMES) can be easily applied to skeletal muscles in bed. In those conditions that temporarily contraindicate intense physical exercise, NMES can be useful. When applied for several weeks in untrained muscles, this method can mimic the effects of regular training—hypertrophy of muscle fibres, increased capillarisation, and beneficial changes in the proportions of efficient, oxidative fibres and inefficient, glycolytic fibres.[66] The functional capacity of patients with chronic diseases such as chronic obstructive pulmonary disease[67] or those who had undergone heart transplantation significantly improved after a 6–8-week NMES programme in the quadriceps femoris muscle.[56] A short-term NMES programme of practical applicability and little discomfort to the participants (30 min

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daily, on 3 days per week for 6 weeks) in the vastus lateralis of healthy but untrained individuals induced a large decrease in type IIX muscle fibres (the most inefficient subpopulation of glycolytic fibres),[68] which was reflected by a significant increase in work efficiency during cycle exercise.[69]

Special oncology populations

Children

Little research has focused on cancer-related fatigue in children. Fatigue is common in children with cancer, but it is under-recognised and under-treated by health professionals.[70] A few studies have assessed the functional capacity of short-term[71] or long-term survivors of acute leukaemia.[72] Exercise capacity was below predicted in most cases, and some subtle cardiac abnormalities persisted in short-term survivors of acute lymphoblastic leukaemia (1–7 years [mean 5] after treatment).[71] The functional capacity, including maximum oxygen uptake, of long-term survivors (mean age 17 years; 1–22 years [mean 11] after diagnosis) was, however, normal; anthracycline therapy induced no lasting cardiotoxic effect.[72]

Although more research is necessary, exercise interventions are expected to be especially successful and time-efficient in children with cancer for two reasons. First, one of the problems that aggravates fatigue in adult cancer patients and survivors, including the elderly—chronic deconditioning before the disease—does not occur in children. Second, the plasticity of body tissues and their adaptability to training is greater during childhood than at older ages. To the best of our knowledge, however, no investigation has specifically assessed the possible effects of programmed exercise training on the functional capacity and fatigue of children with, or survivors of, cancer. The issue is further complicated in children younger than 10 years owing the difficulty of prescribing programmed, structured exercise sessions that are appealing to them. We have undertaken pilot training interventions during chemotherapy in children with acute lymphoblastic leukaemia (unpublished) and found good adherence to training if the core part of the training programme (3 weekly sessions of about 60 min) consisted mostly of games played under safe conditions (eg, simulation of soccer games with soft balls and a soft floor) combined with other types of exercises (games aimed at improving coordination skills, and strength and stretching exercises). Parents' assistance and participation in the training sessions were greatly encouraged since it seemed to improve children's motivation and adherence to the programme. Improvement of the functional capacity of children with cancer up to that of healthy children is especially relevant for ameliorating the quality of life of this population group. During childhood, physical and outdoor activities are an essential part of daily routine.

Elderly

To date, no study has focused on the potential benefits of physical conditioning in the oldest cancer populations. In previous interventional studies that have assessed the effects of exercise training on the functional capacity and tolerance to physical fatigue of cancer patients[14,17,18,45–50] or survivors,[51,52] the mean age of the study population was 40 years, with a maximum age of 65, exceeded in only two studies: an upper limit of 69 years in women with breast cancer[50] and 74 years in survivors of Hodgkin's disease.[52] Thus, studies are needed with old cancer patients and survivors. There is some bias and therapeutic nihilism in treatment of elderly cancer patients, and those older than 70 are generally under-represented in research studies.[73]

In the past, exercise was generally considered inappropriate for frail or very aged individuals because of both low expectations of benefit and exaggerated fears of exercise-related injury.[74] Fortunately, extensive research (including participants aged 90 years or more) provides reassurance of the safety of exercise in the oldest adults (including those with various types of chronic diseases)[75] and shows that participation in a regular exercise programme is an effective intervention to prevent (or at least significantly reduce) several functional declines that accompany ageing (particularly, loss of muscle mass and strength and decline in cardiovascular function).[74] Other benefits include bone health and status, improved postural ability (thus reducing the risk of falling and associated bone fractures), increased flexibility and range of motion and psychological benefits (alleviation of depression, improved self-concept and self-efficacy), and increased dietary intake thus reducing the risk of malnutrition.[74]

Thus, although more research is needed, there are no scientific arguments against exercise prescription in cancer patients of any age.

Cost/benefit ratio of exercise as a complementary therapy in cancer

No study has specifically carried out a cost-effectiveness analysis of adding exercise training programmes to treatment protocols for cancer. Nevertheless, the findings of previous training studies with cancer patients and survivors suggest that the cost/benefit ratio is likely to be very low. No new facilities are needed in hospitals; those already in place, such as cardiac or physical rehabilitation rooms, can also be used to train patients with cancer. Moreover, patients can start training in hospital rooms from the start of chemotherapy, by bed ergometry.[17] Although more research is needed, such training intervention decreases the average duration of the hospital stay.[17] However, home-based exercise programmes taught and monitored by nurses[47] or fitness monitors are cheap and well tolerated by cancer patients and survivors.[52]

Clinical exercise physiologists are professionals with a solid scientific and research background whose role in any hospital would be most useful, being in charge of physical

Useful websites

American College of Sports Medicine: www.acsm.org
Specific recommendations and contraindications for exercise in cancer patients/survivors: www.physsportsmed.com/issues/2000/05_00/courneya.htm
Lance Armstrong homepage: www.lancearmstrong.com

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Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE (up to April, 2003) and references from relevant articles. A textbook of exercise physiology was also included. Search terms were "cancer", "fatigue", "exercise", and "training". Only papers published in English were included. Papers published before 1990 were included only if they reported pioneer findings in this area of study.

training programmes to improve the functional capacity of patients with various types of diseases, including cancer. Several departments (cardiology, neurology, oncology) could benefit at the same time from the work of these health professionals, improving the overall cost-effectiveness of their incorporation to the hospital staff.

Conclusion

The fatigue of cancer patients is a severe activity-limiting symptom, which both reflects and perpetuates extreme muscular deconditioning. There is scientific evidence that exercise training can attenuate fatigue and improve the quality of life of cancer patients and survivors. Exercise physiologists can assist oncologists in prescribing exercise programmes for attenuating cancer-related fatigue.

Conflict of interest

None declared.

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