A meta-analysis on a therapeutic dilemma: to exercise or not to exercise in cachexia

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Abstract

Physical exercise has important effects on secondary prevention or intervention against several diseases. Although there are good reasons to recommend regular physical activity in patient populations, recommending exercise is not a straightforward endeavor in patients with chronic diseases. Cachexia, a severe skeletal muscle wasting syndrome, is often associated with numerous chronic diseases, such as cancer, acquired immune deficiency syndrome, rheumatoid arthritis, chronic obstructive pulmonary disease, renal failure and chronic heart failure. Thus the question arises whether to exercise or not to exercise in cachexia. We performed a meta-analysis on scientific papers from the last decade dealing with exercise conducted by cachectic patients. We observed differential effects exerted by exercise, depending on the pathology considered and the kind of exercise performed: a global positive effect of exercise was observed when all the pathologies considered were pooled together; also, a significantly positive effect of exercise was observed in patients affected by rheumatoid arthritis. On the contrary, when rheumatoid arthritis was excluded from the analysis the effects of exercise on cachexia were not significant. Considering separately the kind of exercises performed, it is interesting to observe how resistance exercise had positive, statistically significant effects on cachexia as opposed to endurance exercise. This is the first study that addresses the effects of exercise training in cachexia independently of a specific chronic disease.

Key Words: Muscle atrophy; cytokines; meta-analysis; effect size; resistance training; endurance training

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Cachexia is a debilitating and life-threatening syndrome in which patients lose weight, muscle and fat and have an impaired response to nutritional support. Cachexia significantly impairs quality of life and response to treatment; in addition, cachexia increases the morbidity and mortality of chronic diseases such as Cancer, Chronic heart failure (CHF), Chronic Kidney Failure (CKF), Chronic Obstructive Pulmonary Disease (COPD), Acquired Immune Deficiency Syndrome (AIDS), Nephritic Syndrome (NS), Rheumatoid arthritis (RA) [4].

The common pathophysiological factors for cachexia in chronic illness include: neurohormonal activation; inflammation and immune activation; hormone resistance syndrome (e.g. GH and insulin resistance); lack or insufficiency of anabolic (counter) responses; activation of specific muscle wasting processes and activation of lipolysis pathways. All together, these pathophysiologic changes determine catabolic-anabolic imbalance. Additional symptoms of cachexia may include: shortness of breath; fatigue and muscle weakness; anorexia and depression [9].

Various interventions have been used to counteract body weight loss in cachexia, including aggressive nutritional support and administration of appetite stimulants. Often these approaches resulted in weight gain due to water retention or fat gain, uncoupled by functional body lean mass gain. Thus, exercise training may potentially decrease muscle wasting experienced by cachectic patients. It is worth noting that exercise used as a support to medical treatments may vary significantly in intensity and metabolic impact. Resistance exercise training is defined as multiple repetitions of static or dynamic muscular contractions performed against a high load or resistance. Resistance training increases muscle mass in healthy subjects and attenuates muscle wasting associated with ageing [8]. Endurance exercise training consists of performing low- to medium-intensity exercise for long periods of time. Endurance training (such as running, cycling, or swimming) involves the use of several large groups of muscles and tends to be aerobic. Adaptations to endurance exercise include improved oxygen delivery to muscles and their increased oxidative capacity [10].

There are many clinically relevant reasons to recommend exercise for patient populations. Exercise training 1) will attenuate the physical deconditioning that patients typically experience upon diagnosis; 2) may optimize functioning when used as adjunctive therapy to standard pharmacological or surgical treatments; 3) may reduce secondary cardiovascular risk factors and attenuate other clinical consequences of the disease and/or treatment; 4) will optimize quality of life and possibly improve overall outcomes by improving physical functioning [8, 21].

Although there are good reasons to recommend regular exercise in patient populations, recommending exercise is not a straightforward endeavor in patients with chronic disease è16+ In fact, physical exercise is known to induce an acute inflammatory response and oxidative stress in healthy subjects as well as in patients [3]. A major concern regarding the use of exercise is exercise-induced damage. In RA the concern that inflamed joints might be exposed to mechanical damage during exercise is widely diffuse. In cancer cachexia a deregulation of the dystrophin-distroglycan complex has been reported suggesting that the skeletal muscle is particularly exposed to mechanical damage in these patients [1].

From the above the question arises whether to exercise or not to exercise in cachexia. With the aim of addressing this therapeutic dilemma, we performed a meta-analysis on scientific studies from the last decade dealing with exercise performed by cachectic patients.

Materials and Methods

Objectives

The aim of this study was to evaluate the effectiveness of exercise to combat cachexia syndrome in patients with chronic diseases.

Source of data.

Studies were carried out through an extensive search of electronic databases. The sources of data included MEDLINE, and the clinical trials listed in www.clinicatrials.org. For the literature searches through MEDLINE, the key words “exercise” and “cachexia” were used with a time frame ranging from 1998 to 2008. Additional literature was obtained through the analysis of the bibliography in selected papers.

Studies were included in the review if they assessed the effects of exercise on biological parameters relevant to cachexia. In particular, only physical activities actually engaging the musculature were defined as exercise (e.g. physiotherapic manipulations were excluded). Any chronic disease known to be associated with cachexia was included.

Data collection and analysis

We have converted the individual study statistics to a common metric: “the effect size r”. The effect size r is a measure of the strength of the relationship between two variables. Some procedures were applied to correct biases caused by various sources of errors, such as sampling errors, measurement errors and range restriction, according to the Hunter and Schmidt methods [12]. Finally, we have considered moderator variables in order to perform subgroup analyses: type of chronic disease (RA vs others) and type of exercise (Resistance vs Endurance).

Results

We pinpointed about 50 full papers, including experimental studies and reviews. Detailed reading of this literature allowed us to select a total of 14 papers. The content of these papers is summarized in Table 1. Abstracts and unpublished data were excluded from the analysis. There are ongoing clinical trials having “exercise” as an intervention, but their results could not be included in the analysis. The 14 reports included in the analysis (Table 1) were initially classified according to the pathology considered: Cancer, CHF, CKF, COPD, AIDS, NS, RA. The reports were also classified in two categories, according to the type of exercise performed: endurance and resistance training. We highlighted the effects of exercise on muscle status or performance, as well as those on factors known to affect muscle biology. In order to compare data of different studies, we have converted the individual study statistics to a common metric: the effect size r. The latter is a correlation coefficient (ranging from –1 to +1), whereby we expressed a positive effect of exercise on muscle condition with a positive r value. The r for all the diseases, considering both exercises types, was = 0.73; the r for the studies on RA only was = 0.65; the r for the studies on all the other diseases was = 0.65. In addition, the r obtained from the studies regarding resistance training was = 0.51, while the r for the studies regarding endurance training was = 0.12. Thus, we observed that overall exercise had a beneficial effect on cachexia. Also, exercise yielded a positive effect on cachexia in RA patients. Considering the type of exercise, resistance exercise exerted a more beneficial effect than endurance exercise on cachexia.

We also calculated the significance of any reported effect, which is dependent on the r value as well as on the number and dimensions of the studies analyzed.

We expressed the significance as p values, assuming $p < 0.05$ as the threshold for significance.

As shown in Figure 1, a significant effect of exercise on cachexia was observed when all pathologies were considered together (p=0.003). We noted that RA had been the object of more studies related to exercise than other chronic diseases, thus RA could be analyzed as a homogeneous subgroup: in this case, the positive effect was significant (p=0.020).

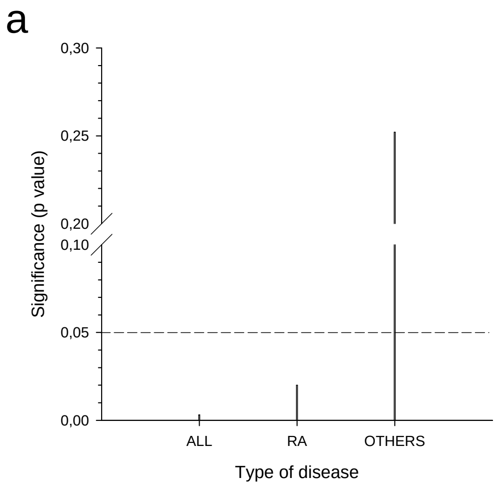
When the other pathologies were pooled together no

Table 1. *Summary of the papers included in the meta-analysis.*

Authors	Year	Disease	Type of Exercise	Results (goods)	Results (odds)
Cupisti et al. [6]	1998	Nephritic Syndrome	cycle ergometer 20 min @ 60 rpm x 1 (*Endurance training*)		↑ plasma CK; ↑ urinary protein excretion
Bhasin et al. [5]	2000	AIDS	not specified 3 times /wk x 16 wks (*Resistance training*)	↑ body weight; ↑ muscle volume; ↑ muscle strength;	
Al-Majid et al. [2]	2001	Cancer	walking 20 min/d Bed ergometer 30 min/d (*Endurance training*) Curls, bench press, retractors, sit-ups, extensions 3 /wk (*Resistance training*)	↑ O2 consuption; ↑ resistance to fatigue ↑ urinary creatinine excretion	
		AIDS	not specified 3 /wk x 6 wks (*Resistance training*)	↓ muscle wasting; ↑ midarm diameter	
Schulze et al. [20]	2002	CHF	not specified (*Endurance training*)	↑ aerobic metabolism	
De Jong. et al. [7]	2003	Rheumatoid Arthritis	bicycling, gymnastic sport 2.5h /wk x up to 108 wks (*Endurance training*)	↑ muscle strength; ↑ aerobic metabolism; ↑ functional ability	
Hakkinen et al. [11]	2004	Rheumatoid Arthritis	body weight, rubber bands,dumb-bells 45 min x 2 times /wk x 108 wks (*Resistance training*)	↑ muscle force	
Stevinson et al. [22]	2004	Cancer	cycle ergometer, walk 3 times/wk x 12-26 (*Endurance training*) gym 3 /w x 10 wks (*Resistance training*)	↑ muscle strenght = resistance to fatigue	
Watson et al. [24]	2004	Cancer	cycle ergometer, walk 3 times/wk x up to 12 wks (*Endurance training*)	↑ resistance to fatigue	
Linke et al. [13]	2005	Cardiac Heart Failure	cycle ergometer 20 min x 3 times/wk x 24 wks (*Endurance training)*	↑ catalase activity oxidative stress; ↓IL-1, TNF expression; ↓ apoptosis;	
Marcora et al. [14]	2005	Rheumatoid Arthritis	press, extensions, push down 2.5 times/wk x 12 wks (*Resistance training*)	↑ lean body mass; ↑ protein;	
Hakkinen et al. [10]	2005	Rheumatoid Arthritis	not specified 45 min x 2 times / kw x 108 wks (*Endurance training*)	↑ O2 consumption; ↑ muscle thickness; ↑ muscle force; ↑ EMG activity;	
Van Helvoort et al [23]	2006	Chronic Obstructive Pulmonary Disease	cycle ergometer 30 min at 50% Wmax x 1 (*Endurance training*)		↑ plasma IL-6; leucocytosis; ↑ oxidative stress;
Piva et al. [18]	2007	Rheumatoid Arthritis	not specified NMES + volitional exercise x 16 wks (*Resistance training*)	↑ lean body mass muscle strength; physical funtion	
Painter et al. [16]	2008	Chronic Kidney Failure	not specified (*Resistance training*)	↑ muscle strenght; ↑muscle CSA	

Abbreviations: CSA: Cross Sectional Area; wk: week; NMES , neuromuscular electrical stimulation; EMG, electromyographic significant effects of exercise on cachexia were observed, due to the fact that studies reported conflicting results.

Considering the kind of exercise performed, resistance exercise demonstrated a positive, significant effect on cachexia (p=0.012), while endurance exercise did not show any significant effect on cachexia (p=0.342).



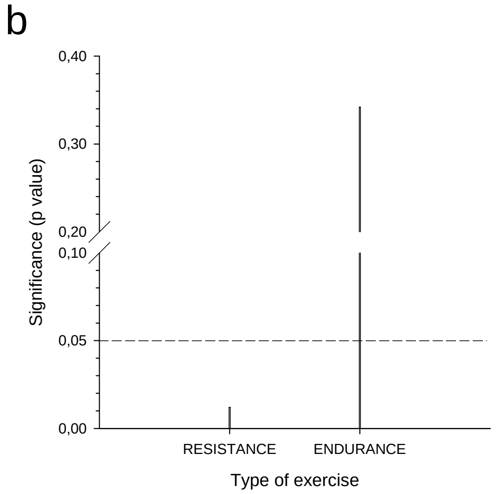


Fig. 1 *Statistical analysis of the effects of different interventions on cachexia. a) p values of the effects on cachexia according to the type of disease. The results are shown for the whole pool of studies included in the meta-analysis (all), for the studies on RA patients only (RA) and for the studies on all the other diseases except RA (others). b) p values of the effects on cachexia according to the type of exercise performed as an intervention, i.e. resistance and endurance training. A positive, statistically significant effect of exercise on cachexia was observed when all pathologies were considered, as well as for RA patients. Resistance exercise alone has a statistically significant effect against cachexia.*

Discussion

Physical exercise has long been taken into account as a possible adjuvant treatment for many neuromuscular diseases. The underlying idea in favor of exercise training in pathological conditions is that using musculature is beneficial for the musculature itself. On the other hand, there is a concern that physical exercise may cause more harm than benefits. For instance, in RA patients the authors in favor of physical exercise claim that this practice is beneficial to muscle performance, while the authors against it argue that it may further exacerbate the joint damage. To this regard, Plasqui et al. conclude that there is a lot more evidence in favour of prescribing physical activity for patients with RA than there is against it [19]. The conclusion is in full agreement with the statement of Nordemar et al. that the risk for a patient of being too inactive is much higher than being too active [15].

With the aim to address whether physical exercise is beneficial or not for muscle homeostasis and function, we performed this meta-analysis by pooling studies conducted on patients with many different chronic diseases. The novelty of our approach consists in evaluating the effects of exercise training on cachexia independently of the specific primary disease. Given that cachexia is characterized by a cytokine-driven accelerated loss of muscle mass and function, we considered a wide array of factors (summarized in table 1) as markers of beneficial or negative effects of exercise on the cachectic state.

We demonstrated that exercise training has a significantly positive effect on cachexia (Fig. 1). This holds true when considering cachexia associated specifically with RA. To the contrary, exercise does not have a significant effect on cachexia when the studies describing all the other pathologies included in this meta-analysis are pooled together. We conclude that while physical exercise appears to be beneficial for RA, further studies are needed on the effects of exercise on muscle wasting associated with other chronic diseases.

Once established that physical exercise has a global positive effect on cachexia, we wondered which type of exercise was effective. We found that it was resistance training, and not endurance training, that had a significant effect on cachexia (Fig. 1). Resistance exercise training reportedly increases the mass of healthy muscle and ameliorates muscle wasting associated with a variety of catabolic conditions [25]. Additional findings indicate that resistance training increases muscle aerobic metabolism and protein content balance, muscle strength and resistance to fatigue (Table 1). However, there is no compelling evidence to support that exercise-induced reduction in fatigue is related to preservation of muscle mass [2]. Given its anabolic effects on healthy and wasted muscles, resistance exercise should be examined as a potential intervention in order to attenuate cachexia.

Based on the results of our meta-analysis, we conclude that prolonged, resistance exercise training significantly counteracts muscle wasting and loss of performance in cachexia associated with a variety of chronic diseases. The beneficial effects of physical exercise include increased muscle performance and self-reported wellness, which both highlight the importance of interventions against cachexia for patients' quality of life. We hope that future studies, including currently open clinical trials with exercise as an intervention against cachexia, will provide further data to conclusively identify more efficient protocols to counteract cachexia.

Abbreviations

AIDS, Acquired Immuno Deficiency Symdrome; BMI, Body Mass Index ; CHF, Chronic Heart failure; CKF, Chronic Kidney Failure; COPD, Chronic Obstructive Pulmonary Disease; NS, Nephritic Syndrome; RA, Rheumatoid Arthritis

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