REVIEW

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Physical exercise at the crossroad between muscle wasting and the immune system: implications for lung cancer cachexia

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Abstract

Cachexia is a syndrome characterized by involuntary weight loss and wasting of skeletal muscle mass. It is associated with worse overall survival and quality of life. The cancer-induced systemic inflammation and the consequent host derived catabolic stimuli, trigger cachexia by inhibiting muscle protein synthesis and enhancing muscle catabolism. The muscle itself may further promote chronic inflammation, introducing a vicious catabolic circle. Nutritional support alone plays a limited role in the treatment of cancer cachexia and should be combined with other interventions. Physical exercise lowers systemic inflammation and promotes muscle anabolism. It also attenuates the age-related physical decline in elderly and it might counteract the muscle wasting induced by the cancer cachexia syndrome. This review describes how cancer-induced systemic inflammation promotes muscle wasting and whether physical exercise may represent a suitable treatment for cancer-induced cachexia, particularly in patients with non-small cell lung cancer. We summarized pre-clinical and clinical studies investigating whether physical exercise would improve muscle performance and whether this improvement would translate in a clinically meaningful benefit for patients with cancer, in terms of survival and quality of life. Moreover, this review describes the results of studies investigating the interplay between physical exercise and the immune system, including the role of the intestinal microbiota.

Keywords Cachexia; Systemic inflammation; Physical exercise; Immune system; Gut microbiota

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Introduction

Cachexia is a metabolic disorder characterized by anorexia, involuntary weight loss, wasting of skeletal muscle mass and decreased muscle strength.[1] Cachexia is associated with worse overall survival (OS) and treatment tolerability; it increases fatigue, depression and decreases quality of life (QoL).[2] Cachexia typically associates with chronic systemic inflammation in chronic diseases, such as chronic obstructive pulmonary disease (COPD),[3] rheumatoid arthritis,[4] chronic kidney disease,[5] and especially cancer.[6] Patients with cachexia often present with elevated serum inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6).[1] The muscle wasting occurring in patients affected by cachexia is called sarcopenia.[1] Sarcopenia is a consequence of the systemic inflammation that characterizes the cachexia syndrome. Sys-

temic inflammation has shown to lead to muscle wasting and fat depletion. The cancer-induced systemic inflammation and the consequent host-derived catabolic stimuli trigger cachexia by inhibiting muscle protein synthesis and enhancing muscle catabolism (*Figure 1*).[10] The muscle itself exerts paracrine and endocrine effects by secreting myokines[11] that may further promote chronic inflammation and muscle wasting,[9] thus introducing a vicious catabolic circle. In patients with sepsis, systemic inflammation increases the catabolic processes already in the early phases of the infection.[12] Patients with metastatic cancer—and consequent more pronounced cancer related inflammation—have a higher risk of developing cancer cachexia. However, cachexia occurs already in patients with stage I non-small lung cancer (NSCLC), even without any impairment in caloric intake.[13] About 20% of patients with early stage NSCLC present with signs of cachexia.[14] In patients with stage III NSCLC undergoing curative treatment, weight loss was observed already during the first 3 weeks of concurrent chemo-radiotherapy (CCRT), before any caloric intake decrease was reported.[15] Adequate nutrition and caloric intake are helpful in avoiding body-weight loss, but nutritional support alone has failed to counteract cachexia in several trials, consistently with the inability of nutrition to revert the catabolic process initiated by cancer-induced inflammation.[16] Cachexia differs from fasting in which the organism proportionally preserves muscle integrity, favouring the use of adipose tissue for providing energy.[17] All together, these findings highlight that the key factor determining cachexia—and consequent weight loss—is systemic inflammation and not caloric intake. Therefore, nutrition serves as necessary materials for muscle build-up, but it cannot reverse muscle wasting alone. Physical exercise lowers systemic inflammation (*Figure 1*) and promotes muscle anabolism.[18] It also attenuates the age-related physical decline in elderly and therefore it might counteract the muscle wasting induced by the cancer cachexia syndrome.[19] Herein we describe how cancer-induced

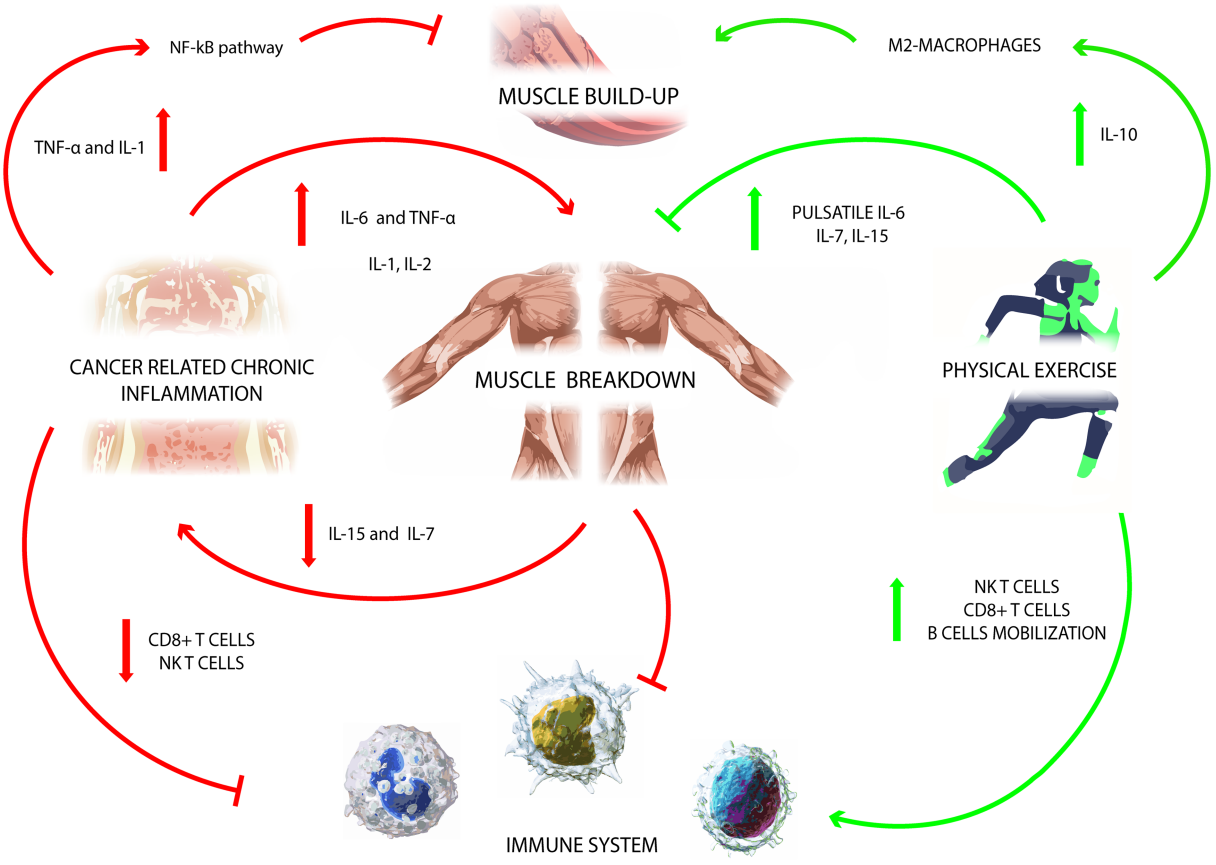

Figure 1 The interplay between muscle wasting, immune system and physical exercise cancer-related chronic inflammation enhances the production of TNF-α, IL-6, IL-1 and IL-2. TNF-α and IL-1 activate NF-κB, which impairs muscle build-up.[7] IL-6 directly promotes muscle wasting when TNF-α co-stimulation is present.[8] In response to exercise, muscle cells secrete IL-6—in a pulsatile manner—IL-7, IL-10, and IL-15.[9] Consequently, physical exercise increases CD8 + T cells, natural killer (NK) T cells and promotes the mobilization of B cells. Secretion of IL-10 promotes macrophage M2-polarization, which can be helpful for the muscle build-up process.[10] The muscle breakdown process itself lowers the levels of circulating IL-7 and IL-15, promoting chronic inflammation. Chronic inflammation results in lower levels of circulating CD8 + T cells and NK T cells.[9] The runner symbolizes physical activity in general, not only endurance training.

systemic inflammation leads to muscle wasting and whether physical exercise in lung cancer may represent a suitable treatment for cancer-induced cachexia. In the present work, we explore the link between cachexia and the immune system, pointing out why physical exercise could represent a crosslink between cachexia and the immune system, counteracting chronic inflammation. To the best of our knowledge, no extensive work has analysed the mutual relationship between the immune system, cancer related cachexia and physical exercise. We focus specifically on lung cancer, as in lung cancer, cachexia represent an issue across all the disease stages and deeply affects the prognosis.[20] Moreover, the majority of the data regarding the interplay between the immune system and cachexia have been studied in patients with lung cancer. We also present data investigating cachexia in other cancer types or other diseases, to illustrate mechanistically the cachexia pathways, and explain how physical exercise could be of benefit.

Aetiology of cancer cachexia

Inflammatory cytokines (TNF-α, interleukin [IL]-6, and IL-1), produced by the tumour and by the host in response to the tumour, lead to muscle wasting. The activation of *Nuclear Factor kappa-light-chain-enhancer of B cells* (NF-κB) might also antagonize the muscle synthesis process.[7] IL-6 can enhance the acute immune response against the tumour, recruiting CD8 + T cells and clearing T regulatory (Treg) cells, when secreted in a pulsatile manner. However, it promotes muscle wasting when TNF-α co-stimulation is present, like in cancer-induced inflammation. In addition to cancer itself, several and potentially coexisting pathophysiological mechanisms contribute in promoting inflammation and cachexia (*Figure 2*).[10] Anorexia—loss of appetite—occurs in about 30% of patients with lung cancer who receive a platinum doublet chemotherapy.[21] It impairs food intake—therefore limiting the resources for muscle build-up—and might increase circulating IL-6 and TNF-α, therefore enhancing systemic inflammation, as shown in patients with anorexia nervosa.[22] In patients with cancer, it is particularly challenging to determine the aetiology of cancer cachexia since anti-cancer treatment itself can enhance systemic inflammation and promote muscle wasting.[23] Chemotherapy directly causes skeletal muscle depletion by activating the NF-κB pathway[23] and by enhancing the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α).[15] Radiation therapy contributes to muscle wasting through off-target radiation to muscle fibres.[24] Although radiation impairs muscle regenerative capacity and promotes fibrosis locally, it is unlikely that systemic muscle wasting evolves as a direct effect of local irradiation. The systemic effects are likely mediated by an inflammatory reaction triggered by radiation. In mouse models, radiation therapy increases the intramuscular production of IL-6, enhancing chronic inflammation, which may be modifiable through physical exercise.[25] This represents an additional incentive

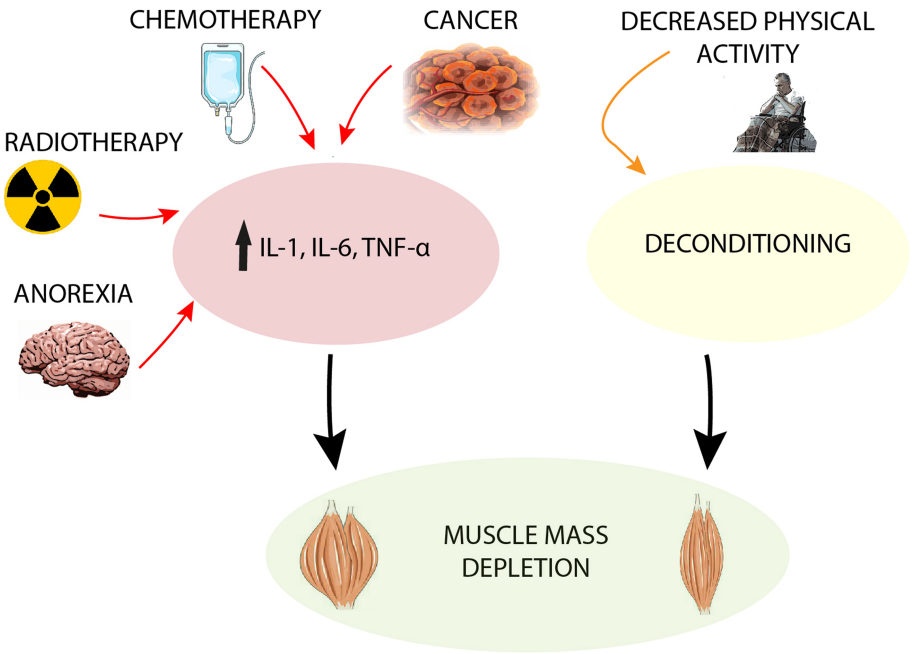

Figure 2 The aetiology of cancer cachexia. Chemotherapy (similarly to cancer) enhances the production of TNF-α, and IL-6, IL-1; anorexia increases IL-6 and TNF-α; radiotherapy can enhance the circulating IL-6 levels. The increase of these cytokines, along with decreased physical activity and deconditioning, results in muscle mass depletion.

to consider physical exercise to modulate muscle wasting in patients with lung cancer. Decreased physical activity, which is typical of patients with cancer, could also translate into deconditioning and muscle mass depletion.[26]

Cachexia diagnosis

The cachexia syndrome is a continuum: It is preceded by a pre-cachectic stage, in which metabolic changes anticipate weight loss, and evolves to refractory cachexia, which is an irreversible catabolic condition.[27] Cancer-induced cachexia is diagnosed in patients who have experienced in the previous 6 months: an involuntary weight loss >5%, or a weight loss >2% if body mass index (BMI) is <20 kg/m^2, or a weight loss >2% and signs of muscle depletion (sarcopenia).[27] Therefore, despite its complex aetiology and heterogeneous clinical features, the diagnosis of cachexia mainly relies on body weight. Weight loss is a well-established negative prognostic factor for patients with cancer, but it cannot picture all the domains involved in the cachexia syndrome and it cannot distinguish between fat and muscle mass loss. Most importantly, weight loss cannot discriminate pre-cachectic from non-cachectic patients, not allowing an early identification of cachectic patients and prompt intervention.[28] Weight loss cut-offs used by this definition have been validated in a cohort of patients with various cancer types. These have a prognostic value for cachectic vs. non-cachectic patients (median OS 139 days vs. 269 days respectively; $P < 0.001$, n = 861), but not for pre-cachectic vs. cachectic patients. Moreover, 56% of the patients enrolled were inpatients and the median Karnofsky Performance Status (KPS) was 70%, thus jeopardizing the utility of these cut-offs for outpatients recently diagnosed with cancer or for those with a good KPS.[28]

Sarcopenia—the low skeletal muscle mass and muscle strength—caused by the cachexia syndrome can anticipate the weight loss and can occur even in patients with overweight.[29] Therefore, diagnostic tools for sarcopenia should not rely on body weight. The gold standard diagnosis of sarcopenia is a two-step approach[29]: first measuring handgrip strength and, if low, assessing the appendicular muscle mass (ASM), which constitutes the four limbs muscle mass to confirm the sarcopenia diagnosis.[30] In *Table 1*, the cut-offs for the diagnosis of sarcopenia are presented, along with alternative and easier to perform measurements.

Why is cachexia a problem in patients with lung cancer?

Cachexia occurs in about 40% of patients with metastatic NSCLC[6] and in approximately 20% of patients with early stage lung cancer.[14] In patients with advanced lung cancer, cachexia at diagnosis is associated with shorter survival (n = 226, median OS 11 vs. 6 months, P = 0.03).[14] Muscle depletion represents a negative prognostic factor for patients with unresectable NSCLC (n = 936) undergoing chemo-radiotherapy with curative intent.[36] Cachexia develops and negatively affects the prognosis also in early-stage cancer, even though the caloric intake is still preserved. This has been shown in non-metastatic breast cancer [n = 3,241, hazard ratio (HR) for mortality 1.41; 95% confidence interval (CI): 1.18–1.69][37]; in Stages I–II colorectal cancer (n = 974, HR 2.22; 95% CI: 1.06–4.68)[38] and in early-stage NSCLC (n = 90, 5 year-survival: 72.8% vs. 85.8%, P = 0.028[39]; n = 215 median OS 32 vs. 112 months).[40] The negative prognostic value of cachexia has also been shown in patients with NSCLC treated with immunotherapy (*Table 2*). Cachexia may undermine the immune system and increase the circulating levels of glucocorticoids, hindering the efficacy of immune checkpoint inhibitors (ICI), but this hypothesis has not yet been confirmed.[41]

The knowledge gap: what we do not know

Cachexia's negative prognostic impact is well established, but there are no reliable data about its predictive value for anticancer treatment, because all the published studies

Table 1 Most common diagnostic test for sarcopenia

Measure	Test	Sarcopenia diagnostic cut-offs
Handgrip strength	Hand-held hydraulic dynamometer[31]	<27 kg in men, <16 kg in women[32]
ASM	DEXA,BIA[29]	<20 kg in men, <15 kg in women[30]
ASM/height^2	DEXA,BIA	<7.0 kg/m^2 in men, <5.5 kg/m^2 in women[33]
L3SMI	CT scan	**<52.4 cm^2/m^2 in men, <38.5 cm^2/m^2 in women**[34]
L3SMI	**CT scan**	**<53 cm^2/m^2 or <43 cm^2/m^2 if BMI <25 kg/m^2 in men, <41 cm^2/m^2 in women**
L1SMI[35]	CT scan	To be validated
Gait speed	—	≤0.8 m/s[29]
Timed up and go test	—	≥20 s[29]

Abbreviations: ASM, appendicular muscle mass; BIA, bioelectrical impedance analysis; DEXA, dual-energy X-ray absorptiometry; L1SMI, L1 skeletal muscle index, defined as the muscle cross-sectional area (CSA) at L3 (cm^2) divided by the height squared (m^2); L3SMI, L3 skeletal muscle index, defined as the muscle cross-sectional area (CSA) at L3 (cm^2) divided by the height squared (m^2).

Table 2 The prognostic value of cachexia and sarcopenia during immune therapy

ICI (setting)	*N*	Study design	Cachexia/sarcopenia measure	Endpoint	Results (non-cachectic vs. cachectic pts)
Anti PD(L)-1 (advanced NSCLC)[41]	142	Retrospective	>5% weight loss in the previous 6mo.	• DCR • PFS • OS	• 59.9% vs. 41%, OR 2.60 (95% CI: 1–6.58) • Non statistically different • HR 6.26 (95% CI: 2.23–17.57)
Anti CTLA-4 (advanced melanoma)[42]	97	Retrospective	CT SMD < 42HU if BMI < 25 kg/m^2 and <20 HU if BMI ≥ 25 kg/m^2	• PFS • OS	• 2.7 vs. 2.4 months • 17.5 vs. 5.4 months
Anti PD(L)-1 (various cancers)[43]	100	Retrospective	L3SMI by CT (ROC cut-offs)	• PFS • OS	• 7.5 months (95% CI: 2.9–10.9) vs. 3.3 months (95% CI: 2.8–5) • 15.6 months (95% CI: 12–21.9) vs. 4.7 months (95% CI: 4.1–6.6)
Atezolizumab (Advanced NSCLC)[44]	1,434	Post-hoc pooled analysis (4 phase III RCTs)	BMI (18–24.9 vs. 25–29.9 vs. >30)	• PFS • OS (BMI 25.0–29.9 vs. BMI < 25) • OS (BMI > 30 vs. BMI < 25)	• NS • HR: 0.81 (95% CI: 0.68–0.95) • HR 0.64 (95% CI: 0.51–0.81)
Anti PD(L)-1 (advanced NSCLC)[45]	576	Systematic meta-analysis (9 RCTs)	L3SMI, L3PMI.	• PFS • % irAEs • OS	• HR = 1.98 (95% CI: 1.32–2.97) • RR = 0.99 (95% CI: 0.21–4.67) • HR = 1.61 (95% CI: 1.24–2.10)

Abbreviations: BMI, body mass index; CTLA-4, cytotoxic T-lymphocyte antigen 4; DCR, disease control rate; HR, hazard ratio; HU, Hounsfield unit; irAEs, immune-related adverse events; L3PMI, psoas muscle area at L3; L3SMI, skeletal muscle index at L3vertebra; NS, not significant; NSCLC, non-small cell lung cancer; OS, overall survival; PD(L)-1, programmed death ligand-1; PFS, progression free survival; ROC, receiving operator curve; RR, risk ratio; SMD, skeletal muscle radiographic density.

evaluating the association between cachexia and anticancer treatment were retrospective. Multiple factors, such as tumour histology and molecular profile, are predictive for anticancer treatment, and it is difficult to evaluate whether (pre)cachexia also has a negative predictive value, besides its known negative prognostic impact. The presence of cachexia (and sarcopenia) is not systematically addressed in clinical trials, and tumours that induce cachexia cannot be distinguished from a seemingly clinically similar one (e.g. stage, histology, and molecular analysis), that has no systemic impact. Consequently, the response to anti-cancer treatments may be related to the tumour characteristics and not to the presence of cachexia.[46]

Furthermore, the currently used definitions of cancer cachexia and sarcopenia have some limits. Rigid thresholds are used for a cachexia diagnosis, despite being described as a continuum.[27] Thresholds may differ according to the type of cancer and type of treatment and continuous variables instead of ordinal measures may help in identifying pre-cachectic patients. Alternative scores include other domains associated with cachexia (immunosuppression, inflammation, QoL, loss of appetite, and daily activities). However, because of their complexity and variable relation with survival, they are not recommended in clinical practice.[47] Regarding sarcopenia, clinical trials assessed muscle performance through different functional tests (e.g. handgrip test, chair test, 6 min walking test), leading to heterogeneous results. Depending on the test used, patients may be diagnosed with or without cachexia or sarcopenia.[48] More importantly, we do not know whether an improvement in physical functioning would translate to better QoL and survival.

At present, there is no established treatment for cachexia in patients with cancer and the benefits of solely nutritional supplementation on cancer cachexia are evident only for patients with hypo-nutrition as a consequence of mechanical obstacles, such as esophagitis-induced dysphagia.[18] Furthermore, different combinations of muscle-wasting triggers (anorexia, chemotherapy, deconditioning, and cancer itself) might imply different optimal cachexia treatments.[46] Physical exercise has a strong biological rationale for counteracting cancer-cachexia and boosting the immune system (*Figure 1*), but the evidence is currently not sufficient to recommend it as cachexia treatment.[18] Furthermore, rationale and pre-clinical evidences should be coupled with feasibility to translate the evidence into an appropriate intervention for patients with lung cancer.

Could physical exercise improve muscle mass and muscle performance in patients with cancer?

Physical exercise attenuates the age-related physical decline in elderly and improves muscle mass, therefore it might counteract the muscle wasting induced by the cancer cachexia syndrome.[19]

In a pre-clinical study performed in colon carcinoma-bearing mice, physical exercise attenuated body weight loss, muscle mass loss and increased appetite, compared to sedentary tumour bearing controls (P = 0.05). No differences were observed between sedentary and exercised healthy mice in terms of body weight.[49] Alves *et al*. showed that aerobic training improved running capacity and prolonged lifespan in Walker 256 rats bearing bone cancer. Aerobic interval activity also limited muscle mass loss and doubled the proteasome activity (responsible for protein quality control) within the plantaris muscle of exercised rats.[50] A 2020 systematic review of the literature (20 pre-clinical trials) did not find any differences between exercised mice and controls regarding body mass nor muscle mass. Great heterogeneity among trials was reported (Q = 165.8, $P < 0.01$, $\tau 2 = 6.1$, $I^2 = 95.5\%$). Training modalities (duration and intensity) and outcomes measures significantly differed among the trials.[51] In several studies involving tumour-bearing mice, the training period started before the tumour inoculation; therefore, the fitness reached before the tumour inoculation, other than the exercise after the cancer-inoculation, may have determined the results.[51]

In patients with operable lung cancer (RCT, n = 151), preoperative supervised cycle-ergometer training (2–3 times per week) improved the median peak oxygen consumption (+15%, IQR + 9–22%) and the median 6 min walking distance (6MWD) (+15%, IQR + 8–28%, $P < 0.001$).[52] A supervised exercise programme significantly mitigated the decline in VO_2 peak, QoL and fatigue in patients with testicular-, breast- and colon cancer during curative-intent chemotherapy.[53] An RCT (n = 46) investigated the utility of endurance training (6 min walking in the hallway five times a week for 6 weeks plus strength exercise plus staircase exercises) in patients with advanced NSCLC during chemotherapy. Patients undergoing the programme showed an improvement in physical independence but general QoL did not differ.[54] Similarly, Cheville *et al*. showed that 8 weeks of home-based endurance training improved mobility SF (P = 0.01) and FACT-F (P = 0.02) QoL scores in patients with stage IV NSCLC or colorectal cancer. However, global QoL and survival did not differ.[55] A 2019 Cochrane review (6 RCTs, n = 221) highlighted the low quality of scientific evidence about exercise in patients with advanced lung cancer. The 6MWD (3 RCTs, n = 59) was significantly higher in the exercised group, but CIs were extremely wide (+63.33 m; 95% CI: 3.70–122.96), questioning the clinical meaning of this finding. No differences were found in muscle strength, dyspnoea, and fatigue.[56] In 41 patients with advanced cancer, a 12 weeks training programme (electrical muscle stimulation and strength exercise, performed twice a week for 20 min) significantly improved 6MWD (P = 0.006), skeletal muscle mass (P = 0.03) and body weight (P = 0.003).[57] 131 patients—15.6% with NSCLC—with advanced cancer (non-randomized CT) received nutritional support only or combined with a supervised exercise programme two times per week for 12 weeks. The experimental group had a higher mean skeletal muscle mass assessed with bioelectrical impedance analysis (+0.53 kg, 95% CI: 0.08–0.98) and mean body weight (+1.02 kg, 95% CI: 0.05–1.98). Fat mass did not differ between the two groups. The training improved 6MWD (P = 0.037) and KPS (P = 0.025).[58] Combined, these studies suggest that physical exercise in patients with (lung) cancer is feasible and play a role in promoting muscle anabolism and performance.

Does physical exercise improve quality of life and survival?

Physical exercise has been associated with health benefits in several conditions characterized by chronic inflammation. In patients with COPD, walking or cycling highly reduces symptoms and acute dyspnoea episodes.[59] In patients with human immunodeficiency virus (HIV), aerobic exercise (2–3 sessions per week, 30–90 min each) increases both cardiovascular fitness and QoL (systematic meta-analysis, 7 RCTs).[60] Three training sessions/week of 30 min each (80–90% VO_{2max}) in patients with rheumatoid arthritis led to a 38% decrease in disease activity according to the DAS28 score (n = 12). No changes in the circulating cytokines pre-intervention and post-intervention were reported.[61] In ankylosing spondylitis patients (n = 24), a reduction in disease activity was observed following 12 weeks of endurance training.[62]

In a breast tumour-bearing mouse model, 8 weeks of aerobic training increased the CD8+/FoxP3 + Treg circulating cells ratio, slowed tumour growth, and improved survival. Intriguingly, no differences in survival and tumour growth were seen in nude mice (exercised vs. sedentary) implying that the physical exercise effect on survival was mediated by the immune system.[63]

Alves *et al*. showed that in tumour-bearing mice, short-term high-intensity running could slow tumour progression and improve survival.[64] Contradictory results were also reported: Survival and tumour growth were not affected in mice with tumour-induced cachexia practicing resistance training (climbing).[65]

A higher weekly physical activity (90th percentile of physical activity compared with 10th percentile) reduced the incidence of various cancer, including lung cancer (HR = 0.74, 95% CI: 0.71–0.77), irrespective of BMI and smoking status (n = 1.44 mil.).[66] In the non-metastatic setting, a post-diagnosis higher level of physical exercise was associated with lower cancer-specific mortality. However, causality between increased physical activity and reduced tumour growth has not been investigated. Moreover, the most active group was compared with the less active group, but minimal protective physical activity levels were not investigated.[67]

In an RCT (exercise data already described above), including patients with lung cancer, the improvement in the peak

oxygen consumption and 6MWD did not translate into less postoperative adverse events (primary endpoint) but the incidence of pulmonary complications (23% vs. 44%, $P = 0.018$) and atelectasis (12.2% vs. 36.4%, $P < 0.001$) decreased.[52]

A 60 min supervised exercise programme (strength and balance exercises) twice a week for 3 months, combined with nutritional counselling session in patients with advanced cancer (RCT, $n = 58$, 30% NSCLC), did not show any improvement in global QoL (primary endpoint, assessed through EORT-QLQ-C30), and survival.[68] A Phase II RCT ($n = 46$) comparing multimodal intervention (nutritional supplements, FANS administration, and training programme) with standard care in patients with lung and pancreatic cancer did not find any differences in OS (secondary endpoint) ($P = 0.57$).[69] A single-arm trial ($n = 59$) investigated the combination of nutrition counselling, fish oil supplementation, NSAID administrations, and physical exercise (9 weeks of twice per week lower body strength exercise and brisk-pace walking) in patients with metastatic NSCLC. A gain in skeletal muscle was associated with treatment response, but causality was not investigated.[70] A supervised exercise programme, comprising cardiovascular and resistance training for a total of 9 h/week for 6 weeks during chemotherapy, both in the adjuvant and metastatic setting, led to a statistically significant improvement in fatigue ($P = 0.02$) and emotional well-being. However, global QoL did not improve (RCT, $n = 269$).[71] Similarly, Oldervoll *et al*. (RCT, $n = 231$) found that a physical exercise intervention (60 min of circuit training twice a week for 8 weeks) improved handgrip strength but did not affect QoL.[72] Taken these studies together, there currently is a lack of high-quality evidence that physical activity translates into a survival benefit. This is likely due to the small sample sizes and heterogeneity of patients included in the trials.

Do we know the most beneficial exercise intensity and duration?

The World Health Organization (WHO) recommends for all adults, also those affected by chronic conditions, 150–300 min of moderate-intensity (*Table* 3) aerobic physical activity per week and resistance training of major muscle groups twice a week.[73] The principal investigated exercise schedules in patients with cancer comprise 2–3 sessions per week of 30–90 min-aerobic or resistance training. A session >60 min was correlated with an improvement in lower and upper body muscle strength and supervised exercise appears to improve muscle strength and aerobic fitness (in terms of peak oxygen uptake).[74] The clinical meaning of these findings is not known. In patients receiving adjuvant therapy for breast cancer (RCT, $n = 301$) 60 min sessions (three times per week) of aerobic exercise are superior to 30 min sessions in reducing pain ($P = 0.02$), endocrine symptoms ($P = 0.02$), and in improving physical functionality, assessed trough Medical Outcomes Survey-Short Form (SF)-36 ($P = 0.04$).[75] A systematic meta-analysis ($n = 136$ CTs) presents a non-linear dose–response association between post-diagnosis physical activity and all-cause mortality in breast cancer survivors. Five, 10, 20, 30, and 65 MET-hours per week were associated with an all-cause mortality reduction of 22%, 43%, 59%, 69%, and 108%, respectively. The steep improvement in survival was lower for physical activity >15 MET-hours per week.[76] However, this association does not imply causality. A single bout of 45 min of moderate-intensity aerobic training increased muscle blood flow and amino acid delivery to the muscle in the elderly (70 ± 3 years, $n = 6$), regardless of the overall weekly physical activity.[77] Aerobic moderate-intensity training (cycle-ergometer) increased the volume of the quadriceps muscle in young ($n = 7$; mean age 20 ± 1 years) and older adults ($n = 6$; mean age 74 ± 3 years) by a similar amount, despite the elderly group completing half of the mechanical work.[78] Young men (median age 24.8 years) and older men (median age 70 years) received the same volume of resistance training for 12 weeks ($n = 38$). Older men experienced a significantly greater increase in triceps muscle volume, assessed through MRI ($P < 0.05$).[79] These findings suggest that the basal muscle status determines the volume of exercise needed to improve muscle mass.[80] In summary, the optimal exercise volume and type needed for patients with cancer is currently unknown. Moreover, the most crucial parameter for a training programme effective in counteracting cachexia might not be the total amount of

Table 3 Exercise intensity definitions[72]

Metabolic equivalent of task (MET)	The ratio of the energy used up during an activity divided by the energy expended at rest (e.g. a 4 MET activity requires four times more energy than at rest).
Aerobic exercise (also named endurance activity)	Activity in which large muscles are used in a rhythmic manner. During aerobic activity, the body produce energy using oxygen (e.g. bicycling, walking, and running).
Resistance exercise	Muscles contracts and work against a force or a weight (e.g. heavy lifting, push-ups).
Light intensity physical activity	Activity performed between 1.5 and 3 METs, without increasing heart rate (e.g. walking at a slow pace).
Moderate intensity activity	Activity performed between 3 and 6 METs.
Vigorous physical activity	Activity performed at >6.0 METs.

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physical activity but its increase compared with baseline. Tailoring the physical activity on the patients' attitude and basal fitness would also improve compliance, considering that patients with cancer cannot be expected to train at the same intensity levels of a healthy individual.

Can physical exercise counteract chronic inflammation?

In healthy humans (CT, *n* = 16) injected with *Escherichia coli* endotoxin, mimicking chronic inflammation, TNF-α was increased by two-fold to three-fold in the resting cohort. In contrast, TNF-α did not increase in subjects performing 3 h of cycling at 75% VO_2 peak after the injection.[81] Physical exercise protects from chronic inflammation avoiding an increase in visceral fat. A reduction from 10 000 steps per day to 1500 steps per day for 14 days in healthy individuals increased abdominal visceral fat while reducing BMI and lean mass.[82] A 3 months exercise programme in obese individuals led to weight and visceral fat reduction, which lasted even 12 months after the intervention. Subjects achieving the same weight loss through dietary restriction alone re-gained the visceral fat at 12 months.[83] A meta-analysis (RCT and CT = 83, *n* = 3769) showed that physical exercise reduced C-reactive protein (used as a proxy of systemic inflammation). The decrease in CRP was associated with decreased BMI and percentage of visceral fat.[84] An RCT performed in patients with breast cancer receiving adjuvant radiotherapy (*n* = 103) showed that IL-6 was increased in the sedentary group during treatment, while no change was noted in the patients undergoing physical exercise. Fatigue and pain, measured through EORTC- QLQ-C30, were also significantly reduced in the exercised group.[85] IFN-γ decreased significantly in patients with non-metastatic cancer (*n* = 292) who received chemotherapy and a 6 week training programme (prescribed number of daily steps, which increases 5–20% per week, and completing a prescribed number of sets and repetitions of resistance exercises), compared to chemotherapy alone. However, IL-6 and IL-10 levels did not differ.[86]

Physical exercise might also lower systemic inflammation by enhancing the metabolism of mitochondria, consequently decreasing mitochondrial reactive oxygen species (ROS) production. In age-associated sarcopenia, mitochondria appear to be reduced and dysfunctional, thus leading to an increased accumulation of ROS within the muscles. The ROS increase ultimately promotes local and systemic inflammation, as observed in obese individuals.[87] In mice, treadmill running has shown to decrease muscle ROS accumulation.[88] Twelve weeks of resistance training has shown to lower oxidative stress also within the muscles of elderly subjects.[89] The implications of mitochondria metabolism for immune activity against cancer cells need to be further investigated.

The reduction of systemic chronic inflammation mediated by physical exercise may also translate into a more effective host immune system.

Can physical exercise boost the immune system?

Muscle cells can secrete over 600 *myokines*, exerting paracrine and endocrine effects. Muscle cells also release IL-6, IL-7, and IL-15 influencing the immune environment, both locally and at a systemic level.[9] IL-15 promotes muscle cell regeneration, reduces adiposity and expands and activates natural killer (NK) and CD8 + T cells.[90] In rodents, 45 min exercise bouts promote leukocytes' recirculation between peripheral tissues (lung, spleen, and muscle) and the bloodstream.[91] Batista *et al*. investigated exercise training in rats with heart failure (which is associated with a change in skeletal muscle, possibly due to chronic inflammation after heart failure). After an 8 week programme, the trained rats had lower serum levels of TNF-α protein (−26%, $P < 0.05$) and lower levels of TNF-α mRNA within the soleus muscle, while IL-10 was 2.6-fold higher ($P < 0.001$).[92] In breast cancer-bearing mice, physical exercise increased the NK lymphocytes infiltrating tumour tissue[93] and lowered intra-tumour myeloid-derived suppressor cells.[94] IL-15 serum levels increase in humans in response to physical exercise.[95] In a Phase-I clinical trial performed in patients with melanoma (*n* = 5), recombinant IL-15 injection promoted NK lymphocytes and CD8 + T cells mobilization from the blood into peripheral tissue.[96] Low IL-7 levels are associated with a senescent immune system[97] and physical exercise in the elderly (*n* = 255) maintains adequate IL-7 levels.[98] During training, IL-6 is secreted by muscle pulsatile in the absence of TNF-α and promotes muscle anabolism.[11] Physically active subjects present higher levels of circulating CD8 + lymphocytes and lower levels of IL-6 compared with sedentary subjects.[98] In healthy individuals, IL-6 levels are increased in response to exercise. The most critical factor for IL-6 increase is exercise duration.[99] After 30 min of running at 75% VO_2 peak, IL-6 increased five-fold[100] while it increased to 8000-fold, after an extreme effort, such as running for 246 km.[101] IL-6 increases exponentially during exercise, reaching the peak at the end of the training and rapidly decreasing afterward.[100] The intensity of the exercise also influences IL-6: in marathon runners (*n* = 53), IL-6 increase was directly correlated with running intensity (calculated as running speed divided by VO_2 max).[102] IL-6 mRNA in the human *vastus lateralis* muscle, assessed through biopsies, increased up to 100-fold at the end of the training (*n* = 6).[103] The same study showed how TNF-a mRNA did not increase during exercise.[103] Injection of recombinant human IL-6, mimicking exercise-secreted IL-6, increased IL-10 and IL-1 receptor agonist (IL-1ra) in healthy individuals (placebo-controlled trial, *n* = 12).[104] In patients with HIV (*n* = 30), physical exercise reduced the levels of circulating IL-6, TNF-a and IL-1, while

increasing CD8+ and IL-10 levels.[105] Physical activity prevents immunosenescence during aging and improves immune response to vaccinations.[106] Importantly, the majority of the findings on how the exercise influences the immune system are derived from healthy individuals and are valid for certain physical-activity thresholds: We do not know whether the same mechanisms would still work in patients with cancer and whether they would improve the patients' outcomes.

Intestinal microbiota: the missing piece of the puzzle?

The role of the intestinal bacteria—the so called gut microbiota—in influencing the interplay between the immune system and cancer is an emerging topic, and it might also influence the cancer-cachexia development. The mechanisms by which the intestinal microbiome can influence immune system and muscle metabolism are still under investigation. Lipopolysaccharide (LPS) is a major component of gram-negative bacteria and can elicit inflammation by binding to extracellular toll-like receptor-4 (TLR-4). Continuous translocations of LPS from intestinal wall into bloodstream can induce chronic inflammation. A higher proportion of gram-positive microorganisms, such as *Lactobacillus*, within the microbiome might lower the proliferation rate of gram-negative microorganisms and consequently, lower LPS production. Exercise training has also shown to lower LPS blood levels in healthy individuals.[107] Consistently in mice, a lower proportion of bacterioides (gram negative) in the intestinal microbiome has been correlated with lower systemic inflammation.[108] The microbiome diversity and the *Lactobacillus* spp. were reduced in mice models of cancer-induced cachexia compared to healthy controls. Moreover, restoring the *Lactobacillus* spp. by oral supplementation led to a reduction of atrophy markers (MuRF1, Atrogin-1, LC3, and Cathepsin L) in the gastrocnemius muscle, along with a reduction in circulating IL-6.[109] A subsequent study, performed in leukaemic mice, confirmed that *Lactobacillus* population was restored by administering live *Lactobacillus reuteri*, and this translated into a diminished cancer cell proliferation, an attenuated muscle wasting and an increased survival.[110] Butyrate is a short-chain fatty acid, which can suppress the activation of NF-κB and inhibit IFN-γ signalling, thus reducing chronic inflammation and is mainly produced the *Ruminococcaceae* within the intestinal microbiome.[111] The diversity of the gut microbiome along with high levels of *Ruminococcaceae* and *Agathobacter* have been associated with better survival in patients with cancer.[112] Pötgens *et al*. showed that in cachectic colon cancer bearing mice the levels of *Ruminococcaceae were reduced* compared to healthy controls.[113] Moreover, preliminary studies suggest that microbiome diversity might even enhance immunotherapy response in patients with cancer.[114] In mice with depleted intestinal microbiota after broad-spectrum antibiotics treatment, the running capacity and the muscle contractile capacity were decreased. After the natural restoration of microbiota, the physical performance was also normalized. The antibiotics exposure altered the gene expression of glucose transporters in the ileum and the glycogen levels in the muscle, suggesting that the gut microbiome might influence the muscle performance also through the glucose/glycogen metabolism.[115] The relation between intestinal microbiome and physical activity seems to work also the other way around: in healthy individuals (n = 41) the cardiorespiratory fitness—estimated through VO_2 peak—predicted microbiome diversity.[116] Moreover, intestinal microbiome diversity has been found to be increased in professional rugby players compared with healthy and BMI-matched controls (n = 86).[117] Physical activity in healthy individuals has not only shown to increase gut microbiota diversity but also to enhance benign micro-organisms levels, such as *Ruminococcaceae*.[117] Investigating the link between nutrition, physical exercise, the microbiome and the immune system would be of the utmost importance in the next years in order to reach an actual personalized immunotherapy treatment for patients with cancer.

Future perspectives

We need a deeper understanding of cachexia development and its relation with the immune system to provide adequate interventions to patients with cancer, especially as ICI or other immunotherapeutic agents are, or will become, standard of care in multiple histology. Future trials should dynamically follow the evolution of cancer cachexia and immune system changes during cancer treatment (e.g. with circulating biomarkers or muscle mass CSA measurements). Patients with pre-cachexia, cachexia, and refractory cachexia, should not be mixed in clinical trials, in order to properly evaluate the efficacy of novel interventions and to achieve a better mechanistic understanding of the cachexia process. Nutrition and physical exercise should be investigated agnostically, considering that they might also be detrimental. We do not know if boosting the immune system through exercise could result in hyper-progression, as has been described for ICI treatment. Trials should stratify patients according to different cachexia mechanisms and tumour characteristics, aiming to achieve a personalized cachexia treatment, similar to for example oncogene-addicted NSCLC.

Methods

In the present narrative review, we included animal models of cancer cachexia that investigated whether exercise or nutrition would improve muscle mass or muscle performance; whether exercise would influence the immune system;

whether exercise would provide a survival benefit; whether exercise would influence tumour growth. Animal models were included if their findings were mechanistically relevant to explain the effect of physical exercise on human muscle and immune system. We did not include clinical trials in humans investigating solely the feasibility of an exercise programme. Furthermore, trials were not included if only the abstract was available or the manuscript's full text was not available in English.

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Conflict of interest

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Ethics statement

All authors comply with the Ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[118] The manuscript does not contain patient data.

Artwork

The artwork present in the manuscript has been prepared with Adobe Illustrator 2020®.

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