Resistance Training Impact on Mobility, Muscle Strength and Lean Mass in Pancreatic Cancer Cachexia: A Randomized Controlled Trial

Fatma Alzahraa H Kamel\textsuperscript{1,2}, Maged A Basha\textsuperscript{2}\textsuperscript{*}, Ashwag S Alsharidah\textsuperscript{3} and Amr B Salama\textsuperscript{1,4}

Abstract

Objective: To determine the efficacy of a three-month resistance training programme on the mobility, muscle strength and lean body mass of patients with pancreatic cancer-induced cachexia.

Design: Randomized controlled trial.

Setting: Elsahel Teaching Hospital, outpatient clinic of the Faculty of Physical Therapy, Cairo, Egypt.

Participants: Patients with pancreatic cancer-induced cachexia.

Interventions: Participants were randomized to the resistance training group (\(n=20\)) and control group (\(n=20\)).

Main measures: Outcomes including mobility, muscle strength and lean body mass were measured at baseline, three months after surgical resection and 12 weeks after intervention.

Results: The mean (SD) age was 51.9 (5.03) years and body mass index was 21.1 (1.13) kg/m\(^2\); 65\% of patients were male. Compared to the control group, the resistance training group showed significant improvement in mobility: 400-m walk performance (270.3–256.9 seconds vs 266.4–264.2 seconds, respectively) and chair rise (13.82–12.53 seconds vs 13.77–13.46 seconds, respectively). Similarly, muscle strength was also significantly improved in the resistance training group than in the control group; we observed increase in peak torque of knee extensors (\(P=0.004\)), elbow flexors (\(P=0.001\)) and elbow extensors, improvement in lean mass of the upper limb (6.28–6.46 kg vs 6.31–6.23 kg, respectively) and lower limb (16.31–16.58 kg vs 16.4–16.31 kg, respectively).

Conclusion: A three-month resistance training improved the mobility of patients with pancreatic cancer-induced cachexia. Muscle strength and lean body mass also improved.

Keywords
Pancreatic cancer, cachexia, mobility, lean mass, muscle strength, resistance training

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\textsuperscript{1}Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Cairo, Egypt
\textsuperscript{2}Department of Physical Therapy, College of Medical Rehabilitation, Qassim University, Buraidah, Qassim, Saudi Arabia
\textsuperscript{3}Department of Physiology, College of Medicine, Qassim University, Buraidah, Qassim, Saudi Arabia
\textsuperscript{4}Department of Medical Rehabilitation, College of Applied Medical Sciences, Najran University, Najran, Saudi Arabia

Corresponding author:
Maged A Basha, Department of Physical Therapy, College of Medical Rehabilitation, Qassim University, Ali Ibn Abitaleb, P.O. Box: 2100, Buraidah, Qassim 1162, Saudi Arabia.
Email: Bashamaged@gmail.com
Introduction

It has been reported that cancer of the pancreas is the seventh leading cause of cancer related deaths in the world.\(^1\) Cachexia is a syndrome that can affect all cancer survivors, and up to one-third die from cachexia-related complications. It is most commonly seen in patients with pancreatic or gastric and lungs cancers,\(^2\) and progresses in about 80% of individuals with pancreatic cancer through the course of their disease.\(^3\)

Cachexia is a syndrome with multiple factors characterized by continued depletion of the skeletal muscle mass, with or without a reduction in fat mass and cannot be reversed with traditional nutritional therapy.\(^4\) Moreover, diminished skeletal muscle induces a reduction in muscle strength, decreased functional capacity and negative effects on the quality of life because of the reduction in mobility, fatigue and diminished physical function.\(^2\) In pancreatic cancer patients, cachexia was reported to lead to reduced rates of response to radiotherapy, chemotherapy and lower rate of survival.\(^3,5\)

Resistance training is a non-pharmacologic therapy that has an anabolic effect, enhancing hypertrophy of the skeletal muscle, leading to improvements in muscle function, reducing inflammation and oxidative stress, improving insulin sensitivity and boosting muscle metabolism.\(^6\) Furthermore, resistance training enhances the synthesis of myofibrillar protein and increases the levels of contractile proteins in the skeletal muscle.\(^7\) Resistance training enhances muscle preservation and improves the quality of life in some catabolic conditions such as aging,\(^8\) rheumatoid cachexia,\(^9\) head and neck cancer induced cachexia\(^10\) and lung cancer induced cachexia.\(^11\) Thus, resistance training exercise can be integrated with other treatments to treat patients with cachexia.\(^12,13\) However, there is a paucity of randomized controlled trials about the efficacy of resistance training in patients of pancreatic cancer with cachexia.

Hence, we conducted this study to determine the efficacy of a three-month resistance training programme on improvement of mobility, muscle strength and lean body mass in pancreatic cancer induced cachexia.

Methods

This was a randomized controlled clinical trial conducted between June 2017 and January 2020. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee approved by the Faculty of Physical Therapy Research Ethical Committee, Cairo University, Egypt under reference P.T.REC/012/002451. Participants signed informed consent for participation in accordance with the principals of the Declaration of Helsinki of 1964. The study was retrospectively registered in the Pan African Clinical Trials Registry (PACTR202001818109834).

Participants were recruited from the National Cancer Institute, Cairo, Egypt. During the follow-up appointments, medical oncologists and surgeons referred the patients, and they were screened for eligibility by the primary investigator. The inclusion criteria were patients with resectable or non-resectable pancreatic cancer stage I to IV, adults \(\geq 20\) years of age, weight loss >5% over the past six months and weight loss >2% in patients with body mass index of less than 20 kg/m\(^2\) (international guidelines for cancer cachexia diagnosis).\(^2,4\) Patients who had any musculoskeletal or neurological disorders, severely impaired haematological capacity, uncontrolled hypertension, heart failure and unknown arrhythmia, severe renal impairment, diminished ability to stand or walk, or any other comorbidities that might hinder exercise, were excluded.

Participants were randomly allocated to the resistance training group or control group after baseline assessment. Simple randomization was done by allocating patients with even numbers into the resistance training group and those with odd numbers into the control group. The numbers were placed in opaque and sealed envelopes, and the participants opened the envelopes for group allocation. Due to the nature of the treatment programme, blinding of patients and physical therapists was not possible. However, blinded isokinetic assessments of muscle strength and Dual-energy X-ray absorptiometry assessments of lean mass were completed. The CONSORT diagram in Figure 1 shows the number of participants at each stage of the study.
No exercise regimen was provided to the control group. The physical therapist contacted the patients once a month by phone to inquire about the possible negative outcomes of cancer therapy. Patients received nutritional and psychosocial support. Participants of the control group were allowed to undergo the training programme after completion of the evaluation period.

Patients in the resistance training group received the intervention at Elsahel Teaching Hospital and the outpatient clinic of the Faculty of physical therapy, Cairo, Egypt, twice a week during the 12 weeks of intervention. To ensure safety, proper strength and correct exercise technique, small groups of one to four patients underwent the sessions at a time, supervised by specialized physical therapists. At each session, general flexibility exercises and one set for the first exercise of upper and lower extremities was performed before the training programme at a lower training intensity, to ensure adequate warm-up. The following machine-based resistance exercises were performed: leg press, leg extension, leg curl, seated row, latissimus pull-down, back extension, butterfly reverse and crunch. Following two familiarization
sessions, including 1-repetition maximum testing according to the Brzycki\textsuperscript{14} study, one to two sets of the first five exercises with 20 repetitions were performed by participants for a four-week adjustment phase of low to moderate intensity (50\%–60\% 1-repetition maximum). Beginning week 5, the number of exercises were increased to eight per session; the patients were asked to perform three sets with 8 to 12 repetitions, with a moderate to a high frequency (60\%–80\% 1-repetition maximum). The resistance exercise session was completed in about 60 minutes. Training was progressive in terms of weight increase to the next machine weight level at a minimum of 5\%, after completing three sets of an exercise in three consecutive sessions with 12 repetitions. Resistance training was set up according to the recommendations for cancer survivors exercise by the American College of Sports Medicine.\textsuperscript{15}

To ensure adequate improvement, the training weights, number of repetitions and sets were reported by all the participants and documented in the individual exercise logs. In case of the following conditions, resistance training was stopped immediately: infections requiring antibiotic treatment, fever more than 38.0°C, respiratory rate more than 20/minute, resting heart rate more than 100/minute, diastolic blood pressure more than 100 mm Hg or less than 45 mm Hg, nausea, emesis, diarrhoea more than twice daily and impaired haematopoietic capacity or severe pain.\textsuperscript{16} If necessary, the training programmes could be disrupted or discontinued at any time based on the oncologist’s evaluation. The patients themselves were allowed to quit from participation in the study at any time without explaining the reasons. Assessments for outcome parameters, which included mobility, muscle strength and lean mass, were done prior to the start of intervention (baseline) and postintervention (12 weeks). The earliest baseline assessments were performed three months after surgical resection to allow for adequate wound healing. The isokinetic dynamometer was used to measure isometric and isokinetic muscle strength (Biodex Medical System, Shirley, NY, USA). Use of the isokinetic dynamometers is considered as the conventional gold method for assessing strength in patients with cancer.\textsuperscript{17} Maximum isokinetic peak torque for elbow, knee and hip flexors and extensors with angular velocity of 60°/second was measured bilaterally. The range of motion for isokinetic measurements was 10° to 90° flexion in the knee (straight leg 0°), 20° to 110° in the elbow and 10° to 100° in the hip (straight leg 0° in dorsal position). The patients were instructed to move the machine arm as strong and as fast as possible for 10 repetitions. We further checked the maximum voluntary isometric contraction bilaterally for the elbow, knee and hip flexors and extensors. The participants were asked to use maximum force and hold it for six seconds. The values used in the analysis were those of the dominant side. To assess mobility, a battery of functional performance tests were used. Triplicate tests (except the 400 m walk) were conducted with adequate recovery time between the tests.\textsuperscript{18} For the analyses, the fastest recorded time was used. For the 400-m walk test, individuals were asked to walk 400 m to test the walking endurance, by performing 10 rounds on a 20 m track back and forth, as fast as they could for the distance. For the 6-m walk test, gait speed was measured at the usual pace, normal rhythm in which the participants were advised to walk at a speed close to what they would do in common day-to-day events, and at fast pace. Using electronic timing gates, the time taken for the test was measured. Chair rising test: participants sat on a hard-backed seat. They were asked to rise as fast as possible to a standing position and return to a full sitting position, five times. Dual-energy X-ray absorptiometry (DEXA) was used to evaluate the fat mass percent and lean body mass (Hologic Discovery A, Waltham, MA).

**Statistical analysis**

Sample size calculation was performed prior to the study using G*POWER statistical software (version 3.1.9.2; Franz Faul, Universitat Kiel, Germany) \[ F \text{ tests – ANCOVA, } \alpha = 0.05, \beta = 0.2, \text{ large effect size}\], which revealed that the appropriate sample size for this study was \( n = 40 \).

The demographics of the subjects and the baseline evaluation were compared between the groups, using unpaired \( t\)-test for continuous variables and Fisher test for categorical variables. Analyses of
covariance [ANCOVA] was conducted for comparison between the groups post-treatment, with baseline assessment as a covariate. The analysis was conducted on an intent-to-treat basis.

For patients who died, withdrew or had an advanced stage of disease-preventing further participation in the study, the statistics was supplemented by their last observed data. For all variables, distribution of standard values was tested using the Shapiro–Wilk method. Levene’s test for variance homogeneity was performed to ensure group homogeneity. The degree of significance was set at $P < 0.05$ for all statistical tests. The Statistical Package for Social Studies [SPSS] version 25 for Windows [IBM, SPSS, Chicago, IL, USA] performed all statistical analyses.

**Results**

Forty patients (mean (SD): age 51.9 (5.03) years) met the inclusion criteria, all participants completed the baseline assessment and post intervention assessments were available for 17 [85%] patients in resistance training group and 16 [80%] patients in the control group. Figure 1 shows the number of participants recruited and available for assessment at each time point including reasons for missing data.

The patients’ baseline demographic characteristics are presented in Table 1, and clinical characteristics are presented in Supplemental Table 1. Analysis of the two groups indicated no significant differences in the demographic characteristics. The comparison revealed no significant differences in clinical characteristics for type of adenocarcinoma, types of surgery and tumour treatment ($P > 0.05$) at baseline.

Comparisons of functional performance tests before and after 12 weeks of intervention between the groups are presented in Table 2. There was no significant difference between the resistance training group and the control group at baseline ($P > 0.05$). There was a significant increase in the walking efficiency in the 400 m walk test ($P = 0.005$), 6-m usual walk test ($P = 0.001$) and chair rise test ($P = 0.001$) in the resistance training group compared to the control group, while there was no significant difference in the 6-m fast walk test between the two groups ($P = 0.12$).

Supplemental Table 2 displays the descriptive data and compares the peak torque and maximum voluntary isometric contraction of the flexors and extensors of the hip, knee and elbow. The peak torque showed statistically significant differences post-treatment between the resistance training group compared to the control group: knee extensors ($P = 0.004$), elbow flexors ($P = 0.001$) and elbow extensors ($P = 0.001$). Similarly, the maximum voluntary isometric contraction of the knee and elbow flexors and extensors significantly increased in the resistance training group compared to the control group ($P < 0.01$).

The lean mass of the upper limb, lower limb and appendicular skeletal muscles significantly increased in the resistance training group compared to that in the post-treatment control group ($P < 0.001$). There was, however, no significant difference in body fat percentage between the groups after treatment (Table 3).

**Discussion**

Our results revealed that three months of resistance training programme in patients with pancreatic cancer induced cachexia led to improvement in mobility and isokinetic and isometric muscle strength, with significant outcomes for some muscle groups. In addition, there was an increase in the lean mass of the upper and lower limb. This improvement in the outcomes is clinically meaningful because these functions are expected to decline after chemotherapy, surgery and due to the progression of cachexia, which is associated with loss of muscle mass and strength.3,19

The 12-week resistance training improved mobility (functional performance measures) compared to the control group. Our findings are important since they clearly indicate a high reserve capacity in such patients. They also suggest that daily activities can be carried out even more conveniently with a lower percentage of maximum strength and endurance, thus promoting enhanced independence. These improvements in functional performance are consistent with the previous studies on resistance
Table 1. Baseline demographic characteristics of resisted training and control groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Resistance training group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 20)</td>
<td>(n = 20)</td>
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<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.6 ± 5.18</td>
<td>52.25 ± 4.91</td>
<td>0.68</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (60%)</td>
<td>14 (70%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>8 (40%)</td>
<td>6 (30%)</td>
<td></td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>21.15 ± 1.45</td>
<td>21.06 ± 0.81</td>
<td>0.82</td>
</tr>
<tr>
<td>Days after surgery</td>
<td>110.75 ± 18.1</td>
<td>104.8 ± 17.88</td>
<td>0.3</td>
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<tr>
<td>Days after first chemotherapy</td>
<td>48.35 ± 8.08</td>
<td>50.8 ± 15.56</td>
<td>0.53</td>
</tr>
<tr>
<td>Exercise in the year before diagnosis, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>0 to &lt; 9 MET × hours/week</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
<td></td>
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<tr>
<td>9 to &lt; 18 MET × hours/week</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
<td>0.9</td>
</tr>
<tr>
<td>≥ 18 MET × hours/week</td>
<td>2 (10%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (60%)</td>
<td>14 (70%)</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; P value: level of significance; MET: metabolic equivalent (in hours per week).

Table 2. Functional performance assessments of the resistance training group and control group.

<table>
<thead>
<tr>
<th></th>
<th>Resistance training group</th>
<th>Control group</th>
<th>MD</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 20)</td>
<td>(n = 20)</td>
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<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
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<tr>
<td>400 m walk (seconds)</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>270.3 ± 32.17</td>
<td>266.4 ± 21.25</td>
<td>3.9</td>
<td>−13.55:21.35</td>
<td>0.65</td>
</tr>
<tr>
<td>12-weeks*</td>
<td>256.9 ± 34.16</td>
<td>264.2 ± 22.4</td>
<td>−7.3</td>
<td>−12.17:−2.4</td>
<td>0.005</td>
</tr>
<tr>
<td>6-m walk usual (seconds)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.88 ± 0.53</td>
<td>4.82 ± 0.55</td>
<td>0.06</td>
<td>−0.29:0.4</td>
<td>0.74</td>
</tr>
<tr>
<td>12-weeks*</td>
<td>4.55 ± 0.61</td>
<td>4.74 ± 0.57</td>
<td>−0.19</td>
<td>−0.28:−0.08</td>
<td>0.001</td>
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<tr>
<td>6-m walk fast (seconds)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.62 ± 0.42</td>
<td>3.6 ± 0.39</td>
<td>0.02</td>
<td>−0.24:0.28</td>
<td>0.87</td>
</tr>
<tr>
<td>12-weeks*</td>
<td>3.41 ± 0.44</td>
<td>3.51 ± 0.39</td>
<td>−0.1</td>
<td>−0.24:0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>Chair rise to stand (seconds)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.82 ± 2.87</td>
<td>13.77 ± 2.52</td>
<td>0.05</td>
<td>−1.67:1.78</td>
<td>0.94</td>
</tr>
<tr>
<td>12-weeks*</td>
<td>12.53 ± 2.66</td>
<td>13.46 ± 2.73</td>
<td>−0.92</td>
<td>−1.33:−0.51</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SD: standard deviation; MD: mean difference; CI: confidence interval; P value: level of significance; S: seconds.

*Adjusted for base line value.

Several treatment approaches aimed at preventing or reducing the progression of cachexia include the use of pharmacological treatments with antica- chectic agents; however, the outcomes remain inaccurate, as the anti-tumour necrosis factor therapy showed no improvement in muscle mass.22 However, recently Anamorelin showed increase in training in patients with pancreatic cancer,10 head and neck cancer,10 and lung cancer11 induced cachexia and other types of cancer survivors.13 These changes are clinically important as patients with pancreatic cancer induced cachexia have physical activity levels comparable to individuals with spinal cord injury or cerebral palsy.21
lean mass, but no significant improvement in the handgrip strength test.\textsuperscript{23}

Our resistance training programme reversed the loss of regional lean mass compared to that in the control group with an increase in the lean mass of upper limbs, lower limbs and appendicular skeletal muscle by 2.8\%, 1.6\% and 2.0\%, respectively. Furthermore, there was an increase in the isometric and isokinetic muscle strength in the upper and lower extremities.

A number of randomized controlled trials have shown promising gains in muscle strength and lean mass as a result of resistance training. Our results showed lesser improvements in muscle strength compared to other studies about muscle strength during cancer treatments. Niels et al.\textsuperscript{20} for example showed an improvement of 30\% in muscle strength and maintained the body weight in patient with advanced pancreatic cancer during medical treatment. Therefore, the outcomes cannot be compared. Few randomized trials have used stationary isokinetic dynamometry, which is considered to be the standard method to examine muscle strength.\textsuperscript{17} One study investigating the efficacy of a six month resistance training in pancreatic cancer patients showed a slightly higher increase in the isokinetic knee extension after 24-weeks compared with our results [7.0\% vs 9.6\%].\textsuperscript{26} Another study in patients with head and neck cancer after radiotherapy reported a higher increase in isokinetic muscle strength in the knee extensors [20.4\% vs 9.6\%].\textsuperscript{27}

Increased muscle mass and strength can help in performing the tasks more easily with less fatigue. Hence, we think that the reversal of muscle mass and loss of strength following the programme intervention for pancreatic cancer induced cachexia is clinically significant. Moreover, exercise initiated as early as possible after surgery and during chemotherapy might provide important benefits by reducing the loss of muscle and its associated adverse effects.

### Table 3. Lean mass and body fat of the resistance training group and control group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Resistance training group</th>
<th>Control group</th>
<th>MD</th>
<th>95% CI</th>
<th>P value</th>
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<tr>
<td></td>
<td>(n = 20)</td>
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<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
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</table>

**Lean mass (kg)**

**Upper limb**

Baseline: 6.28 ± 0.77 vs 6.31 ± 0.63, MD = −0.03, 95% CI: −0.49:0.42, P = 0.89

12-weeks*: 6.46 ± 0.79 vs 6.23 ± 0.58, MD = 0.23, 95% CI: 0.14:0.33, P = 0.001

**Lower limb**

Baseline: 16.31 ± 2.51 vs 16.4 ± 2.12, MD = −0.09, 95% CI: −1.58:1.4, P = 0.9

12-weeks*: 16.58 ± 2.47 vs 16.31 ± 2.09, MD = 0.27, 95% CI: 0.19:0.35, P = 0.001

**Appendicular skeletal muscle**

Baseline: 22.6 ± 2.42 vs 22.72 ± 2.27, MD = −0.12, 95% CI: −1.62:1.37, P = 0.86

12-weeks*: 23.06 ± 2.34 vs 22.54 ± 2.23, MD = 0.52, 95% CI: 0.38:0.65, P = 0.001

**Body fat (%)**

Baseline: 27.41 ± 2.78 vs 27.33 ± 2.73, MD = 0.08, 95% CI: −1.69:1.84, P = 0.93

12-weeks*: 27.33 ± 3 vs 27.48 ± 2.9, MD = −0.15, 95% CI: −0.65:0.35, P = 0.55

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SD: standard deviation; MD: mean difference; CI: confidence interval; P value: level of significance.

*Adjusted for base line value.
Resistance exercise is known to be a potent stimulus of muscle synthesis even in catabolic situations like cachexia, via several mechanisms like increased action of insulin in the peripheral tissues following exercise, which can inhibit the breakdown of muscle protein. Exercise also stimulates the development of muscle fibre cytokines and interleukin-6, which increases the insulin sensitivity and decreases production of pro-inflammatory cytokine. In a rodent cachexia model, resistance exercise protocol reduced systemic and tissue inflammation, reducing hyperlipidaemia associated with cachexia and shifting the adipose tissue IL-10/TNF ratio. The efficacy of resistance exercise would be beneficial in patients with cancer induced cachexia as systemic inflammation levels are related with decrease in weight, functional capacity and survival.

There are some limitations associated with this study. First, patients were well functioning individuals who were motivated to engage in the exercise programme, and they might not be representative of all participants. Second, the small sample size does affect the accuracy of our findings; these outcomes could be coincidental and not real. Moreover, due to the relatively small sample size, no sub-group analysis could be performed to examine if the response to the exercise intervention differed according to the stages of cancer induced cachexia. Third, the relatively short follow-up period could not evaluate whether the improvements persisted over the long term. Hence, future studies are necessary to assess the long-term effects. Fourth, participants in the control group could not undergo any training programme.

To validate these results in a larger sample size, more studies are required in the future. In addition, more studies are needed to examine the role of nutritional support with exercise to reverse cachexia and optimize the gain in muscle mass, and compare the efficacy of different exercises, intensities, duration and timing to assess the best exercise routine for patients with pancreatic cancer induced cachexia. Exercise should be recommended as a part of complementary therapy for pancreatic cancer induced cachexia patients.

### Clinical messages

- In patients with pancreatic cancer induced cachexia, resistance training exercises lead to an improvement in function, in terms of mobility, as well as muscle strength and lean mass.
- Resistance training could potentially be a promising intervention strategy for the prevention and treatment of cancer-related cachexia.

### Declaration of conflicting interests

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### Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

### ORCID iD

Maged A Basha [https://orcid.org/0000-0002-3422-6193](https://orcid.org/0000-0002-3422-6193)

### Data sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Supplemental material

Supplemental material for this article is available online.

### References


