Effects of Exercise on Respiratory Muscle Function and Functional Capacity in Patients with Cancer. Systematic Review

Abstract

The objective of this review was to assess the effectiveness of therapeutic exercise interventions in respiratory muscle function and functional capacity in patients suffering from cancer. A systematic review was conducted from November to December 2022 in the following databases: MEDLINE (through its search engine PubMed), PEDro, EMBASE, LILACS, CINAHL, and Google Scholar. Results were reported according to the PRISMA guidelines, and the protocol was previously registered (PROSPERO: CRD42022379018). Two independent reviewers extracted data from the included studies. 12 randomized controlled trials, including 679 patients, were included in this systematic review. 11 assessed the effects of therapeutic exercise on respiratory muscle function, and 6 assessed the effects on functional capacity. The current evidence is limited, and studies offer heterogeneous results. Further studies should be developed implementing structured exercise protocols, and the effects of exercise on different cancer types should also be assessed. However, this review offers a first insight into the potential effectiveness of therapeutic exercise in respiratory muscle function impairment and functional capacity loss.

Keywords: Cancer, Exercise, Muscle strength, Respiratory function test, Systematic review

Introduction

Currently, cancer constitutes one of the main causes of morbidity and mortality worldwide, as estimated by the International Agency for Research in Cancer 18,1 million cases to be diagnosed since the year 2020, and this number to be increased to 28 million cases in the following two decades.[1]

The management of this condition is handled through different therapeutic approaches, including surgery, immunotherapy, chemotherapy, radiotherapy, guided therapy, photodynamic therapy, hyperthermia, hormone therapy, and stem cell therapy.[2-4] Also, the therapeutic choice will depend on the individual clinical presentation and the stage at which the cancer is, even combining different treatments to ensure maximal efficacy. The main purpose of an oncologic treatment plan is to cure cancer, and when this is not possible, the goal is to reduce cancer down to a subclinical stage and ensure the patient’s quality of life as much as possible.[3, 5]

Up to 50% of patients diagnosed with cancer are expected to have a survival rate of ten or more years, and this rate is expected to increase as new effective treatments are developed. However, the longer these patients survive, the higher probability they have to develop associated comorbidities, such as cardiovascular or psychological problems. One of the underdiagnosed issues involves complications with the respiratory system, where a high risk to develop respiratory infections and exacerbations of preexisting conditions is predicted. Undertaking the high prevalence of respiratory complications in the general population, the heightened risk to develop respiratory comorbidities in patients suffering from cancer might have a significant impact on their morbidity and mortality.[6]

To manage these complications, one of the therapeutic available resources used both in the pre and post-surgical stages is a therapeutic exercise. However, there is an existing heterogeneity in the components included in these programs, and unfortunately, the evidence is insufficient and should be furtherly developed. Understanding the potential cost-effectiveness that these programs might have.

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have, interventional programs based on robust scientific evidence must be developed.[7]

Studies have shown the efficacy of resistance and aerobic exercise interventions in these patients regarding both psychological and physical factors. Physical functioning, health-related quality of life, and fatigue improve in these patients when implementing therapeutic exercise,[8] however, effects on the impairment of respiratory function are yet to be assessed. Analyzing these effects through the assessment of respiratory muscle function could enable a better understanding of how therapeutic exercise programs could be applied to effectively manage respiratory complications.

Therefore, the objective of this systematic review is to assess the effects of therapeutic exercise interventions on respiratory muscle function through its maximal respiratory pressures in patients suffering from cancer. Additionally, a secondary objective was the assessment of other factors that are related to respiratory functioning, such as functional capacity.

Materials and Methods

This systematic review adhered to the guidelines established by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement,[9] and the search protocol was previously registered in an international registry of systematic reviews (PROSPERO: CRD42022379018). To conduct this systematic review, the following databases were accessed: MEDLINE (through its search engine PubMed), PEDro, EMBASE, LILACS, CINAHL, and Google Scholar. Additionally, external sources were also consulted.

Search strategy

The search was conducted between November and December of 2022. The PICO elements were used to formulate the search string. The population included adult (>18 years) patients diagnosed with cancer, the intervention included therapeutic exercise in any of its modalities, either aerobic, resistance, or combined, the control group was usual care, and the included outcomes were respiratory muscle strength assessed through the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), and functional capacity assessed through the 6-Minute Walk Test (6MWT).

A search was conducted using the MeSH (Medical Subject Headings) terms “respiratory muscle”, “cancer”, and “exercise”, all combined with the Boolean operator “AND”. (Table 1) presents a summary of the search strategy applied for each of the accessed databases.

<table>
<thead>
<tr>
<th>Database</th>
<th>Search string</th>
<th>Filters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedro</td>
<td>“Respiratory muscle” “cancer” “exercise”</td>
<td>Clinical trial 2012 – 2022 &gt;18 years.</td>
</tr>
<tr>
<td>EMBASE</td>
<td>“Respiratory muscle” AND “cancer” AND “exercise”</td>
<td>Randomized controlled trials. &gt;18 year.</td>
</tr>
<tr>
<td>LILACS</td>
<td>“Respiratory muscle” AND “cancer” AND “exercise”</td>
<td>Randomized clinical trial.</td>
</tr>
<tr>
<td>CINAHL</td>
<td>“Respiratory muscle” AND “cancer” AND “exercise”</td>
<td></td>
</tr>
<tr>
<td>Google Scholar</td>
<td>“Respiratory muscle” AND “cancer” AND “exercise”</td>
<td></td>
</tr>
</tbody>
</table>

Study selection

Two independent reviewers conducted the study selection by screening the titles and abstracts of the studies that the search yielded. If necessary, the full text of the study was accessed, and further discrepancies were solved by consensus. Studies were included if they were (1) randomized controlled trials, (2) published in the last ten years, (3) included adult (>18 years) patients diagnosed with any type of cancer, (4) implemented a therapeutic exercise intervention centered in improving respiratory muscle strength, and (5) assessed at least one of the outcomes included in the review, either respiratory muscle strength through the MIP and MEP, or functional capacity through the 6MWT. Studies not meeting either of the aforementioned criteria were excluded.

Data extraction

Two independent reviewers registered data and tabulated results in a spreadsheet according to the PICO elements to facilitate the analysis. The analysis was structured around the main objective, type of therapeutic exercise, and type of cancer. Data was extracted through a protocol that ensured the extraction of the most relevant data for each study. Study design, duration, sample characteristics, intervention, assessed outcomes, and results were extracted from every study included in the review.
Outcomes
Respiratory muscle strength
Respiratory muscle strength is commonly assessed by using a non-invasive pressure gauge to register maximal respiratory pressures at the oral cavity.[10] Maximal respiratory pressures include the MIP and the MEP.

Functional capacity
Functional capacity is usually assessed through the 6MWT, a simple and practical test where the patient is asked to walk the maximum distance possible in a 30.48 meter (100 feet) corridor for a total of six minutes.[11] This test assesses all of the systems that are involved in exercise and activities of daily living, as it is considered a submaximal effort test.

Risk of bias assessment
The risk of bias was assessed using the PEDro scale, a valid measure of the methodological quality of clinical trials.[12] The PEDro scale assesses 11 items, including selection criteria, random allocation, blinding, follow-up, and intention to treat analysis. Items are given a value of 1 if they are present in the clinical trial or 0 if they are not, and an overall score is obtained. The lower the scores the higher risk of bias a study has, and authors report that total PEDro scores of 0-3 are considered “poor”, 4-5 “fair”, 6-8 “good”, and 9-10 “excellent”.[13]

Results and Discussion
The systematic search yielded a total of 301 studies. 13 of them were duplicates, 256 were excluded after reading the title and abstract, and 20 studies were also excluded for not being related to the research objective. 12 studies were finally included in this review. A flow diagram illustrating the study selection process is shown in (Figure 1).

Study characteristics
A total sample of 679 patients was included in this review. The patient’s age range was between 36 and 69 years. 418 patients were male and 261 were female. 5 studies involved patients suffering from lung cancer,[14–18] 3 esophageal cancer,[19,21] 2 breast cancer,[22,23] and 2 studies involved patients with any type of cancer.[24,25] Every study was reported in English, except for a study in Portuguese.[25] Six studies performed their analysis during a presurgical phase, and the remaining six at a postsurgical phase. Characteristics of every included study are summarized in (Table 2).

Table 2. Description of the included study characteristics

<table>
<thead>
<tr>
<th>Author/s &amp; Year</th>
<th>Method</th>
<th>Sample</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brocki et al., 2016</td>
<td>2 groups</td>
<td>-Patients included in a pulmonary resection surgery -High risk to develop complications</td>
<td>Respiratory muscle training n=34 Control group n=34</td>
<td>-Respiratory muscle function (MIP and MEP) -No significant difference between groups in MIP or MEP</td>
<td></td>
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<tr>
<td></td>
<td>2 weeks</td>
<td>Inclusion:</td>
<td></td>
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<tr>
<td></td>
<td>RCT</td>
<td>Exclusion:</td>
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<tr>
<td></td>
<td></td>
<td>-Physical or psychological impairment -Unable to understand Danish -Previous ipsilateral pulmonary resection -Tumor activity in a different system -Major surgery within the last year.</td>
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<tr>
<td></td>
<td></td>
<td>Age range: 36-69 years. All female</td>
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</tr>
<tr>
<td>Dahhak et al., 2022</td>
<td>2 groups</td>
<td>-Breast cancer -Reduced MIP -Dyspnea</td>
<td>Therapeutic exercise + IMT n=10</td>
<td>-Respiratory muscle strength (MIP and MEP) -MIP increased significantly in the intervention group (from -74 ± 11 to -93 ± 19 cmH2O). MEP increased non-significantly in the intervention group (from 139 ± 25 to 144 ± 28 cmH2O)</td>
<td></td>
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<tr>
<td></td>
<td>12 weeks</td>
<td>Inclusion: -Presence of chronic cardiovascular or respiratory diseases</td>
<td>Therapeutic exercise n=10</td>
<td>-Functional capacity (6MWT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pilot RCT</td>
<td>Exclusion:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Duration</td>
<td>Inclusion</td>
<td>Exclusion</td>
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<tr>
<td>de Almeida et al., 2020</td>
<td>RCT</td>
<td>5 weeks</td>
<td>Hospitalized patients, Age: ≥18/≤65</td>
<td>Smokers, alcoholics, Previous cardiovascular disease, Physically active, Patients with metastasis</td>
<td></td>
</tr>
<tr>
<td>Guinan et al., 2019</td>
<td>RCT</td>
<td>3 weeks</td>
<td>Esophageal carcinoma, Cognitive capacity to perform IMT, Programmed esophagectomy, Able to understand English, Adult &gt;18 years</td>
<td>Tracheotomy, Myasthenia gravis, Unstable coronary artery disease, Unable to perform resistance testing</td>
<td></td>
</tr>
<tr>
<td>Laurent et al., 2020</td>
<td>RCT</td>
<td>3 weeks</td>
<td>Adult patient planned for NSCLC resection surgery, Written informed consent</td>
<td>Diseases from the gastrointestinal tract, Hypertension, Diabetes, Heavy smokers, Chronic obstructive pulmonary disease, Addiction to alcohol, Chemotherapy, Radiation therapy, Unstable respiratory function (PaO₂ &lt; 55 mmHg), Tracheostomy, Severe cardiopathy or limb weakness</td>
<td></td>
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<tr>
<td>Liu et al., 2021</td>
<td>RCT</td>
<td>6 weeks</td>
<td>Lung cancer, Willing to participate in the study</td>
<td>Unstable pH, Hemodynamical instability, Severe cardiopathy or limb weakness</td>
<td></td>
</tr>
<tr>
<td>Messaggi-Sartor et al., 2019</td>
<td>Pilot RCT</td>
<td>8 weeks</td>
<td>Age &lt;80 years, Lung cancer resection, Diagnosis NSCLC stage I or II</td>
<td>Adjuvant treatment, Postsurgical complications, unable to perform the test, History of thoracic surgery</td>
<td></td>
</tr>
</tbody>
</table>

**Mean age and gender:**

- Cough, et al.: Mean age: 43.6 ± 15.2 years and 46.6 ± 13.2 years. Gender: 84.1% female
- de Almeida et al.: Mean age: 64.13 ± 7.8 years. Gender: female: male 18:8 ratio
- Laurent et al., 2020: Mean age: 64.2 years (SD=5.9)
- Liu et al., 2021: Mean age: 64.6 years (SD=8.5)
- Messaggi-Sartor et al., 2019: Mean age: 64.6 years (SD=8.5)

**Exercise effects:**

- MIP improved significantly in the intervention group (−37.6 (95% CI −27.2–−47.9) cmH₂O) and the control group (−31.5, (95% CI −19.9–−43.1) cmH₂O) after surgery.
- 6MWT reduced significantly in the intervention group (194.6 (95% CI 107.8–281.4) meters) and the control group (134.7 (95% CI 102.1–167.4) meters) after surgery.
- MIP improved significantly in the intervention group (from 86.4 ± 34.9 to 103.1 ± 44.6 cmH₂O). MEP showed no difference.
- MIP improved significantly in the intervention group at week 6 (from 71.6 ± 34.9 to 94.3 ± 32.8 cmH₂O). MEP improved significantly at week 12 (from 76.1 ± 20.2 to 98.6 ± 35.3 cmH₂O).
- MIP showed a non-significant improvement in the intervention group (Mean difference 13.0% of predicted value). MEP showed a non-significant improvement in the intervention group (Mean difference 9.5% of the predicted value).
Morano et al., 2013
2 groups
4 weeks
Pilot RCT
Mean age: 67 years.
Inclusion:
- Lung resection
- Previous lung disease
- Obstructive Airways disease or interstitial disease with functional impairment

Pimpão et al., 2021
3 groups
Pilot RCT
Age range: 40-69 years
Inclusion:
- Patients diagnosed with cancer and referred to surgery
- Age: 20-70 years
- Not participating in another study
Exclusion:
- Patients with unstable hemodynamics
- Previous resection surgery
- Not physically fit

Valkenet et al., 2018
2 groups
3 weeks
RCT
Mean age: 63.1 years (SD=7.5)
Gender: female: male 68:27
Inclusion:
- Patients with esophageal cancer referred to surgery
- Scheduled esophagectomy
- Ability to perform IMT programs
Exclusion:
- Language barriers
- Participation in another study
- Underage <18 years

van Adrichem et al., 2014
2 groups
3 weeks
Pilot RCT
Inclusion:
- Esophageal cancer referred to surgery
- Age range 18-65 years
- Ability to perform a spirometry
Exclusion:
- Neuromuscular impairment
- Unstable asthma
- History of spontaneous pneumothorax
- Cognitive impairment

Respiratory muscle resistance training group
n=12
- MIP improved significantly in the respiratory muscle resistance training group (from 90 ± 45.9 to 117.5 ± 36.5 cmH2O).
- MEP improved significantly in the respiratory muscle resistance training group (from 79.7 ± 17.1 to 92.9 ± 21.4 cmH2O).

Lung expansion group
n=9
- 6MWT improved significantly in the respiratory muscle resistance group (from 425.5 ± 85.3 to 475 ± 86.5 meters).

Kinesio-therapy group
n=10
- MIP improved significantly in the Kinesiotherapy group (from 60.5 ± 16.4 to 80 ± 16.3 cmH2O).
- MEP improved non-significantly (from 64 ± 19.6 to 72.5 ± 23.2 cmH2O).

IMT group
n=10
- MIP improved significantly in the IMT group (from 44 ± 22.7 to 72 ± 19.3 cmH2O).
- MEP improved significantly in the IMT group (from 55 ± 18.4 to 74 ± 16.4 cmH2O).

Usual care +IMT
n=120
- Respiratory muscle strength (MIP)
- MIP improved significantly in the intervention group (from 76.2 ± 26.4 to 89.0 ± 29.4 cmH2O) and in the control group (from 74.0 ± 30.2 to 80.0 ± 30.1 cmH2O).

Usual care
n=121
- 6MWT improved non-significantly in the Kinesiotherapy group (from 408 ± 77.7 to 405 ± 51.4 meters).

- 6MWT improved non-significantly in the IMT group (from 432 ± 47.3 to 452 ± 34.3 meters).
Exercises for another significant improvement only in aerobic exercise, non-statistically significant in the Aerobic exercise group (from 509.16 ± 40.97 to 603.01 ± 48.82 meters) and in the Aerobic exercise group (from 93.85 ± 29.56 meters).

Exercise modalities
Every study implemented respiratory muscle training-centered exercises using external devices, except for a study that implemented aerobic exercise combined with Yoga, an indirect training of the respiratory muscles. Another study focused specifically on resistance training exercises for respiratory muscles. Six studies combined specific respiratory muscle training exercises with other exercise modalities, such as aerobic exercise, or high-intensity training. The duration of the intervention ranged from two weeks to three months, with most of the interventions lasting around a period of four weeks.

Outcome measures
Regarding respiratory muscle function, 8 studies assessed both MIP and MEP; and 3 studies assessed MIP alone. Regarding functional capacity, 6 studies assessed the 6MWT. Studies assessing respiratory muscle function showed results as the mean difference in centimeters of water (cmH\textsubscript{2}O), except Messaggi-Sartor et al. who presented the mean difference of predicted value as a percentage. Every study assessing functional capacity showed changes in meters in the 6MWT. Every study presented its results either with the standard deviation or the 95% confidence intervals.

3 studies found a significant improvement in MIP and MEP; 4 studies found a significant improvement only in MIP; 3 studies found non-significant improvements in MIP; 6 studies found non-significant improvements in MEP; and 1 study reported a worsening of MIP after surgery. 4 studies showed significant improvements in the 6MWT; 1 found non-significant improvements; and 1 found a worsening in 6MWT.

Risk of bias assessment
Results of the risk of bias assessment for the included studies are shown in Table 3. The overall risk of bias was good to excellent. 1 study showed “excellent” scores; 9 studies showed “good” scores; and only 2 studies showed scores considered to be “fair”.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1</td>
</tr>
<tr>
<td>Brocki et al. 2016</td>
<td>8/10</td>
</tr>
<tr>
<td>Daahhak et al. 2022</td>
<td>9/10</td>
</tr>
<tr>
<td>de Almeida et al. 2020</td>
<td>7/10</td>
</tr>
<tr>
<td>Guinan et al. 2019</td>
<td>4/10</td>
</tr>
<tr>
<td>Laurent et al. 2020</td>
<td>7/10</td>
</tr>
<tr>
<td>Liu et al. 2021</td>
<td>7/10</td>
</tr>
<tr>
<td>Messaggi-Sartor et al. 2019</td>
<td>6/10</td>
</tr>
<tr>
<td>Morano et al. 2013</td>
<td>7/10</td>
</tr>
<tr>
<td>Pimpão et al. 2021</td>
<td>8/10</td>
</tr>
<tr>
<td>Valken et al. 2018</td>
<td>8/10</td>
</tr>
<tr>
<td>van Adrichem et al. 2014</td>
<td>6/10</td>
</tr>
<tr>
<td>Vardar-Yağlı et al. 2015</td>
<td>5/10</td>
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</tbody>
</table>

Survival rates of over ten years in patients suffering from cancer are increasing as therapeutic options develop. One of the common impairments found in these patients is related to the respiratory system, and this is closely linked with muscle function loss. Despite therapeutic exercise being proposed as an effective therapy to overcome these impairments, protocol
components of these programs are heterogeneous, and the understanding of the real effects of therapeutic exercise on respiratory muscle function is not fully developed. Therefore, this systematic review aimed at assessing the effectiveness of therapeutic exercise in respiratory muscle function and functional capacity in patients suffering from cancer.

Considerable levels of heterogeneity were found both in the therapeutic exercise interventions used and the types of cancer, so it is challenging to obtain accurate conclusions. Despite 5 of the included studies (42%) dealing with patients suffering lung cancer,\textsuperscript{[14-18]} a type of cancer that could be a priori linked with considerable respiratory afflictions, a further analysis assessing the effects of therapeutic exercise in different types of cancer could be an interesting approach, to determine if the effectiveness varies depending on the type of cancer suffered.

Studies implementing interventions of at least 4 weeks showed significant improvements in MIP and MEP.\textsuperscript{[16, 18, 22, 24]} Studies not showing significant improvements implemented relatively short interventions, such as the studies conducted by Brocki et al.\textsuperscript{[14]} (2 weeks) or Laurent et al.\textsuperscript{[15]} (3 weeks). Conversely, the study with the longest intervention, conducted by Dahhak et al.\textsuperscript{[25]} (12 weeks) showed significant improvements in every outcome. This aligns with evidence that establishes that to observe an improvement in muscle function, the intervention must be sustained for a minimum period of 4 weeks.\textsuperscript{[26]} However, the study conducted by Messagi-Sartor et al.\textsuperscript{[17]} implemented a relatively long intervention (8 weeks), yet were unable to evidence significant improvements, and this might be due to the limited sample (16 participants in the intervention group) they used, that might’ve been unable to reach statistical significance. Contrary to that, Valkenet et al.\textsuperscript{[20]} used a larger sample (120 participants in the intervention group) and were able to reach statistical significance after only 3 weeks of intervention. This evidences that results should be interpreted with caution, as both time and sample size seem to be relevant when reaching statistical significance.

Studies assessing functional capacity showed significant improvements in 6MWT,\textsuperscript{[16, 18, 22, 23]} except for the studies conducted by Guinan et al.\textsuperscript{[19]} and Pimpão et al.\textsuperscript{[22]} Firstly, Guinan et al. presented a study that is embedded within another included study in this review,\textsuperscript{[19]} and they assessed their outcomes before and after a surgical esophagectomy. Even though significant improvements were found in the other study, advocating for the benefits of exercise prehabilitation, Guinan et al. evidenced that despite implementing a therapeutic exercise intervention before surgery (which they called “preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophageal resection”, or PREPARE) this intervention is insufficient to prevent muscle function loss, and they allude to an insufficient training period and differences between baseline characteristics of their sample groups to discuss these results. Additionally, reasons for the non-significant improvements in 6MWT results for Pimpão et al. could be aligned with the latter explanation of insufficient sample size (10 participants per group).

Limitations
This study presents several limitations. As the authors wanted to review the latest published evidence, retrieved studies were limited to the last ten years, potentially omitting the inclusion of studies that might’ve influenced the interpretation of results. Also, further analyses involving different types of cancer should be conducted, as different types of cancer require different forms and intensities of exercise. Finally, any type of cancer and at any stage of treatment was considered for this review, and this could influence the generalizability of results.

However, this study also presents several strengths. Six different databases were accessed to retrieve studies, and no language restrictions were applied. Also, the review protocol was previously registered in the international registry PROSPERO. All of these elements ensure that this systematic review is not incurring several biases, assuring methodological quality as best as possible. The methodological quality of the included studies was also assured by the risk of bias assessment, as 83% of the included studies showed “good” to “excellent” scores on the PEDro scale.

Conclusion
Studies assessing the effectiveness of therapeutic exercise on respiratory muscle function and functional capacity in patients suffering from cancer are limited and remain controversial. Further research is needed to gain a more thorough understanding of the effects of different types of exercise on different types of cancer, as therapeutic exercise has the potential to overcome the adjuvant impairments that might be present in these populations.

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Conflict of interest
None.

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None.

Ethics statement
None.

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4. Georgievna PO, Andreeva NM, Tokhiriyon B, Aleksandrovna DL, Mikhaylovich PV. The Effectiveness and Functional Properties of the


