Physical exercise in patients treated with hematopoietic stem cell transplantation

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Effects of exercise in patients treated with stem cell transplantation for a hematologic malignancy: A systematic review and meta-analysis

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Abstract

We performed a systematic review and meta-analysis evaluating the effectiveness of exercise interventions compared with usual care on physical fitness, fatigue and health-related quality of life in patients with hematologic malignancies treated with stem cell transplantation. Electronic databases were searched up to June 2012. We included randomized controlled trials comparing exercise with usual care, in which at least 75% of the patients had a hematologic malignancy. Standard mean differences were calculated and pooled to generate summary effect sizes (ES) and 95% confidence intervals (CI). The Cochrane Collaboration Risk of Bias Tool was used to assess the methodological quality of the studies.

Eight studies met our inclusion criteria. Exercise had a statistically significant moderately favourable effect on cardiorespiratory fitness (ES=0.53, 95% CI=0.13;0.94), lower extremity muscle strength (ES=0.56, 95% CI=0.18;0.94) and fatigue (ES=0.53, 95% CI=0.27;0.79). Significant small positive effects were found for upper extremity muscle strength, global quality of life, and physical, emotional and cognitive functioning. In conclusion, exercise seems to have beneficial effects in patients treated with stem cell transplantation. However, all studies had at least some risk of bias, and for cardiorespiratory fitness and lower extremity muscle strength substantial heterogeneity in effect sizes were observed. Further high quality research is needed to determine the optimal exercise intervention and clinical implications.
Introduction

Autologous stem cell transplantation (Auto-SCT) is standard of care for patients with multiple myeloma in first line, and for patients with Hodgkin lymphoma and aggressive non-Hodgkin’s lymphoma at first relapse. The transplant-related mortality is below 5%. Allogeneic stem cell transplantation (Allo-SCT) can improve outcome in patients with standard or high risk acute myeloid leukaemia or acute lymphoblastic leukaemia. However, in 15–20% of cases complications such as graft-versus-host disease and infections lead to transplant-related mortality. Currently, the five year event-free survival for the hematologic malignancies most often treated with stem cell transplantation (SCT) ranges from 5–80%. With 50,000 SCTs performed annually worldwide, the number of SCT survivors increases rapidly.

Despite advances in supportive care, SCT is still associated with serious morbidity. In addition to graft-versus-host disease and infections, short term complications include nausea, diarrhea, mucositis, pain, anxiety and depression. Although most survivors recover adequately from treatment, a substantial proportion continues to experience psychosocial and/or physical long-term and late effects that reduce health-related quality of life (HRQoL). One of the most prevalent and disturbing long-term problems is fatigue.

It is hypothesized that persistent fatigue reflects a self-perpetuating condition: cancer, its treatment and the associated bed rest lead to poor physical fitness. As a result, greater effort is required to fulfil the activities of daily living, and performance of these activities can induce abnormally high levels of fatigue. In order to minimize fatigue, patients will limit their physical activities, which will eventually lead to an even greater decline in physical fitness. An exercise intervention might reverse this downward sequence. Currently, the American College of Sports Medicine states that for certain cancer survivor groups, exercise training is safe and results in improved physical functioning and HRQoL, and reduced fatigue. However, the effectiveness of exercise interventions in patients during or after SCT has not yet been fully established. Liu et al. and Wiskemann et al. concluded in their systematic reviews that exercise has positive effects on physical fitness, HRQoL and psychological well-being, but that this evidence is based on studies of low methodological quality. In a more recent review, Wolin et al. concluded that physical activity for adult SCT patients has numerous potential benefits, but they only found weak evidence (defined as ≥3 high quality studies, but <75% reporting a significant benefit) for a beneficial effect of exercise on physical fitness, fatigue, and HRQoL.

The field of cancer rehabilitation expands rapidly. More studies with larger sample sizes on the effectiveness of exercise during or after SCT have been published since Wolin et al., which warrants a new systematic review of the present evidence. Furthermore, the increasing
number of published studies allows us to apply stricter in- and exclusion criteria concerning study design and study populations in order to reduce heterogeneity. Hence, the objective of the current review is to systematically review the evidence on effectiveness of exercise interventions in comparison to usual care with respect to physical fitness, fatigue and HRQoL in patients treated with SCT for a hematologic malignancy.

Methods

Database search

A clinical librarian performed a database search in Pubmed, EMBASE, PsycINFO, CINAHL, PeDro and the Cochrane Library up to November 2011. The search was updated in June 2012. The following search terms were used: stem cell transplantation OR stem cell transplant* OR hematopoietic SCT OR hsct OR bone marrow transplant* OR leukemia OR lymphoma OR myeloma OR hematologic neoplasm OR hematologic malignanc* and exercise therapies OR physiotherap* OR exercise tests OR physical therapy OR physical therapies OR physical activit* OR exercises OR aerobic OR aerobics OR training[tw] OR endurance OR strength. Two authors (SP and KW) also searched the reference list of relevant studies and reviews for additional articles.

Inclusion criteria

A study was included if: (1) it was a randomized controlled trial (RCT) published in a peer reviewed journal; (2) the study sample contained at least 75% adult (≥18 years) patients treated with SCT for a hematologic malignancy; (3) the outcome measures included cardiorespiratory fitness, upper and/or lower extremity muscle strength, fatigue and/or HRQoL measured with a validated multi-item instrument; (4) the intervention consisted of a physical exercise program or a multi-modal intervention aiming to maintain or improve aerobic capacity and/or muscle strength, while the control condition consisted of usual care; (5) it was a full-text article; (6) it was published in English.

Study selection and data extraction

SP and KW independently reviewed the titles and abstracts of the references retrieved from the literature search. Next, the full-text versions of potentially relevant articles were retrieved and checked by the two authors on eligibility. Disagreements were solved by consensus or when necessary, by a third author (MC). Hereafter, SP and KW separately extracted the general study information, the details of the exercise intervention, the number of patients, the results and information about adverse events from every study using a standardized data extraction
form. We contacted the authors of the studies in case of missing results. Based on the article of Campbell et al. SP evaluated whether or not the included studies had applied the well-established principles of exercise training. These principles include specificity (intervention given is based on the primary outcome), progression (the program was progressive and training progression was outlined), overload (the program was of sufficient intensity/exercise prescribed relative to baseline fitness), initial values (selected population has low levels of primary outcome measure and/or baseline physical activity levels), reversibility (inactivity after completion of the intervention leads to diminished results at follow-up measures) and diminishing returns (when patients keep exercising after completing of the intervention, increasing effort is required for further improvement).

Methodological quality

SP and MC assessed the risk of bias in the included studies using the Cochrane Collaboration Risk of Bias Tool. This tool is a domain-based evaluation in which the domains are considered separately. In this study we focussed on the following domains: randomization sequence generation, allocation concealment, blinding (for participants, intervention administrators and outcome assessors), completeness of outcome data (missing outcome data and intention-to-treat analysis), selective outcome reporting and other sources of bias. Each domain was rated as ‘+’ (low risk of bias), ‘−’ (high risk of bias), or ‘?’ (uncertain risk of bias). Differences in the authors’ ratings were resolved by consensus.

Data synthesis and analysis

We performed a meta-analysis if at least two studies had measured the same outcome. In such cases, for each study we calculated the standard mean difference (SMD) to quantify the size of the intervention effect, taking into account the variety of instruments and scales available for similar outcomes. The SMD signifies a difference in mean outcome between the post-intervention scores of the intervention and usual care group divided by the pooled standard deviation of the outcome. An SMD of 0.5 thus indicates that the mean of the experimental group is half a standard deviation larger than the mean of the usual care group. Heterogeneity between studies was quantified using the $I^2$ test, with $I^2 > 50\%$ representing considerable heterogeneity. In addition, we calculated the $Q$ statistic. If the $Q$-value is significant, the null hypothesis of homogeneity is rejected. Since we expected considerable heterogeneity, we chose to perform random effects analysis using the DerSimonian and Laird method. This model assumes that the included studies are drawn from ‘populations’ of studies that systematically differ from each other. Small, moderate and large effects are defined as effect estimates of 0.2, 0.5 and 0.8, respectively. Data from the time point that directly followed
the completion of the intervention were selected for analysis. Individual effect sizes were pooled using Review Manager 5.1.23

## Results

### Study, participant and intervention characteristics

The searches in Pubmed, EMBASE, PsycINFO, CinAhl, PeDro and the Cochrane Library resulted in 6877 papers. One additional article was found in the database of one of the authors. Hand searching of the reference lists of relevant studies and reviews did not result in any additional articles. After removing duplicates 5685 papers were screened for title and abstract, of which 37 full-text articles were selected for eligibility testing. 28 articles were excluded because of the following reasons: <75% of the patients included received a SCT for a hematologic malignancy (n=13), no RCT comparing exercise with usual care (n=9), the outcome measures did not include cardiorespiratory fitness, muscle strength, fatigue or HRQoL (n=4) or the articles were not retrievable (n=2) by our library. Nine articles based on eight studies met the inclusion criteria. The reviewed studies comprised 472 patients (range: 18–131 patients) with a mean age of 47.1 years and a standard deviation of 5.7 years, 62% of the patients were male and 57% of the patients were treated with Allo-SCT (Table 3.1).

Table 3.2 presents the characteristics of the exercise interventions and usual care. The majority of the interventions (7 out of 8 studies) started before or during hospital admission for SCT; one study started after treatment.24 The exercise sessions were predominantly supervised or partly supervised. Six out of eight studies evaluated the effectiveness of a mixed aerobic and strength24-28 or mixed aerobic and activities of daily living (ADL)-training program.29,30 One study evaluated a strength training program31 and another study an aerobic training program.32 In most programs the exercises were performed at low to moderate intensity. The duration of the intervention and the frequency and duration of the exercise sessions varied widely across studies. Session duration ranged from 20 to 70 min, the number of exercise sessions varied from 2 to 10 sessions per week and duration of the intervention ranged from 4 weeks to 6 months. In the majority of studies the mode of the exercise seemed appropriate to induce changes in the target outcomes (i.e. the exercise prescription was specific to the outcomes). In two studies, however, muscle strength was amongst the primary outcome measures while the intervention consisted predominantly of aerobic exercise.29,30,32 It was often (partly) unclear if or/and how the training progressed over time24-30 and whether the intensity/exercise prescribed was sufficient to induce an adequate stimulus (overload) to improve or maintain fitness.24-28,31,32 All studies included a population at risk for a decline in physical fitness and activity level or with low physical activity baseline levels (initial values). Follow-up measures
Table 3.1. Overview of the study population

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No of patients baseline/follow-up</th>
<th>Mean age (range)</th>
<th>No (%) of women</th>
<th>Treatment autologous SCT/allogeneic SCT</th>
<th>Type of hematologic malignancy (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumann 2010/2011</td>
<td>Germany</td>
<td>64/49</td>
<td>44.5 (?)</td>
<td>29 (45.3)</td>
<td>18/46</td>
<td>CML (3); CLL/NHL (8); ALL (9); AML (25); MDS/MPS (6); MM (9); solid tumour (3); variable immunodeficiency (1)</td>
</tr>
<tr>
<td>Coleman 2003</td>
<td>United States of America</td>
<td>24/13</td>
<td>55 (42–74)</td>
<td>10 (41.7)</td>
<td>24/0</td>
<td>MM (24)</td>
</tr>
<tr>
<td>Coleman 2008</td>
<td>United States of America</td>
<td>69/53</td>
<td>55 (25–76)</td>
<td>22 (31.9)</td>
<td>69/0</td>
<td>MM (69)</td>
</tr>
<tr>
<td>Hacker 2011</td>
<td>United States of America</td>
<td>19/17</td>
<td>46.3 (20–67)</td>
<td>5 (26.3)</td>
<td>13/6</td>
<td>? (19)</td>
</tr>
<tr>
<td>Jarden 2009</td>
<td>Denmark</td>
<td>42/34</td>
<td>39.1 (18–60)</td>
<td>16 (38.1)</td>
<td>0/42</td>
<td>CML (9); ALL (8); AML (16); MDS (2); WM (1); PNH (1); myelofibrosis (1); AA (4)</td>
</tr>
<tr>
<td>Knols 2011</td>
<td>Switzerland</td>
<td>131/114</td>
<td>46.7 (18–75)</td>
<td>54 (41.2)</td>
<td>80/51</td>
<td>CLL (14); ALL (2); AML (31); NHL (25); HL (14); MM (37); osteomyelofibrosis (4); testicular cancer (3); amyloidosis (1)</td>
</tr>
<tr>
<td>Mello 2003</td>
<td>Brazil</td>
<td>18/18</td>
<td>29.1 (18–44)</td>
<td>10 (55.6)</td>
<td>0/18</td>
<td>CML (10); AML (4); NHL/MDS (2); severe AA (1)</td>
</tr>
<tr>
<td>Wiskemann 2010</td>
<td>Germany</td>
<td>105/80</td>
<td>48.8 (18–71)</td>
<td>34 (32.3)</td>
<td>0/105</td>
<td>CML (4); CLL (4); ALL (14); AML (33); lymphoma (20); AA (2); MM (3); MPS (13); MDS (12),</td>
</tr>
</tbody>
</table>

Table 3.2. Characteristics of the interventions and usual care

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Characteristics of the interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumann 2010/201129,30</td>
<td>IG</td>
<td><strong>Duration:</strong> From 6 days before SCT until 1 day before hospital discharge&lt;br&gt;<strong>Setting:</strong> Hospital, supervised&lt;br&gt;<strong>Aerobic exercise:</strong> During aplasia twice a day and during chemotherapy and after engraftment once a day 10–20 min cycling at 80% of the achieved watt load during the modified WHO-test on a bicycle ergometer&lt;br&gt;<strong>ADL training:</strong> During chemotherapy and after engraftment once a day 10–20 min cycling at 80% of the achieved watt load during the modified WHO-test on a bicycle ergometer.***</td>
</tr>
<tr>
<td></td>
<td>UG</td>
<td><strong>Duration:</strong> From 1 day after SCT until 1 day before hospital discharge&lt;br&gt;<strong>Setting:</strong> Hospital&lt;br&gt;<strong>Content:</strong> Mobilization, 10 min/day gymnastics, coordination training, 5 min stretching, massages. Intensity matched Borg score ‘not strenuous’</td>
</tr>
<tr>
<td>Coleman 200325</td>
<td>IG</td>
<td><strong>Duration:</strong> 6 months, from 3 months before the first transplantation until approximately 3 months after the first transplantation&lt;br&gt;<strong>Setting:</strong> Individualized, home based, unsupervised&lt;br&gt;<strong>Aerobic exercise:</strong> Walking, but patients were also allowed to perform running or cycling&lt;br&gt;<strong>Resistance exercise:</strong> Using exercise stretch bands, patients performed exercise for the lower extremities (chair stand, knee flexion and extension) and for the upper extremities (biceps and triceps exclusion and upright row)</td>
</tr>
<tr>
<td></td>
<td>UG</td>
<td><strong>Content:</strong> Encouragement to remain active and walk 20 min at least 3 times a week</td>
</tr>
<tr>
<td>Coleman 200826</td>
<td>IG</td>
<td><strong>Duration:</strong> Probably 30 weeks, from the enrolment in the multiple myeloma treatment protocol until after the first transplantation&lt;br&gt;<strong>Setting:</strong> Individualized, home based, unsupervised&lt;br&gt;<strong>Aerobic exercise:</strong> Walking to tolerance (until tired)&lt;br&gt;<strong>Resistance exercise:</strong> On alternate days: biceps curls with exercise stretch bands, triceps extension with chair push-ups, quadriceps strengthening with chair stand and hamstring strengthening while sitting or standing</td>
</tr>
<tr>
<td></td>
<td>UG</td>
<td>Patients were generally advised to remain as active as possible and try to walk 20 min/day</td>
</tr>
<tr>
<td>Hacker 201131</td>
<td>IG</td>
<td><strong>Duration:</strong> 6 weeks, starting immediately after discharge&lt;br&gt;<strong>Setting:</strong> Hospital and home based, partly supervised&lt;br&gt;<strong>Resistance exercise:</strong> Three times a week, 1–2 sets of 8–10 repetitions of chest fly, biceps curl, triceps extension, shoulder shrug, shoulder upright row, shoulder lateral raise, knee flexion and extension using elastic resistance bands and push-ups, squats and bed sit-ups at a RPE of 13</td>
</tr>
<tr>
<td></td>
<td>UG</td>
<td>Patients received recommendations regarding rest, physical activity and exercise from their HSCT physician</td>
</tr>
<tr>
<td>Study</td>
<td>Group</td>
<td>Duration</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>Jarden 2009&lt;sup&gt;27&lt;/sup&gt;</td>
<td>IG</td>
<td>From the first day of hospital admission until the day of discharge</td>
</tr>
<tr>
<td>Knols 2011&lt;sup&gt;24&lt;/sup&gt;</td>
<td>IG</td>
<td>12 weeks, starting 79 (35) days after SCT</td>
</tr>
<tr>
<td>Mello 2003&lt;sup&gt;32&lt;/sup&gt;</td>
<td>IG</td>
<td>6 weeks, starting directly after bone marrow engraftment</td>
</tr>
<tr>
<td>UG</td>
<td></td>
<td>Usual care</td>
</tr>
</tbody>
</table>

Table 3.2 continues on next page
<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Characteristics of the interventions</th>
</tr>
</thead>
</table>
| Wiskemann 2010 | IG    | **Duration:** From 1–4 weeks before admission to the hospital until 6–8 weeks after discharge from the hospital  
**Setting:** Hospital and home based, during hospital admission partly supervised  
**Aerobic exercise:** Three times a week during outpatient setting and up to five times a week during hospital admission 20–40 min walking or bicycling at RPE 12–14  
**Resistance exercise:** Twice a week, 2–3 sets of 8–20 reps using colour coded stretch bands aiming to achieve an RPE 14–16. Three different strength training protocols were used (1) focussed on extremities, (2) the entire body, (3) bed exercises (during hospital admission)  |
|               | UG    | Patients were told that moderate physical activity is favourable during the treatment. Patients received step counters with the request to wear and record the steps daily. During hospitalization, physiotherapy was offered up to three sessions per week. Controls were visited by the study personnel with the same frequency as the IG group. Throughout these visits, patients were asked about their current health status and feelings. They had access to ergometers and treadmills during hospitalization  |

IG: Intervention group; UG: usual care group; ADL: activities of daily living; BP: blood pressure; HR: heart rate; HRmax: maximal heart rate; ROM: range of motion; RPE: rating of perceived exertion. SCT: stem cell transplantation.
were only included in two studies, but it was unclear if the interventions complied with the principles of reversibility and diminishing returns. Five out of eight studies reported the number of sessions followed by the patients, details about achieved intensity and duration of the exercises performed were missing in all studies. In general, participating in an exercise intervention program seems to be safe for patients with hematologic malignancies treated with stem cell transplantation. Five out of eight studies reported explicitly that no sustained injuries were observed, the remaining studies did not discuss adverse events.

In four studies patients in the usual care group received some form of encouragement to become or remain physically active, without further supervision. In three studies usual care incorporated some form of physical therapy and in one study the study personnel also visited the patients in the usual care group with the same frequency the intervention group to avoid attention bias. During these visits, patients were asked about their current health status and feelings. Mello et al. did not specify their usual care, and Knols et al. provided only standard care.

**Effect of exercise on physical fitness**

Six studies evaluated the effect of exercise on cardiorespiratory fitness. The tests used to assess cardiorespiratory fitness varied across the studies; three studies used the six minutes walking test, two studies used a submaximal cycle ergometer test and one study used a modified Balke protocol. Overall, exercise interventions provided a moderate positive effect on cardiorespiratory fitness when compared to usual care (ES=0.53, 95% CI=0.13;0.94, Figure 3.1A).

Seven studies assessed upper and/or lower extremity muscle strength. Four studies used dynamometry, one study determined the estimated 1-RM and one study included both dynamometry (upper extremity) and the timed stair climb test (lower extremity) to assess muscle strength. A significant moderate positive effect was found for exercise on lower extremity muscle strength (ES=0.56, 95% CI=0.18;0.94, Figure 3.1B). The summary effect size for exercise on upper extremity strength was significant but small (ES=0.32, 95% CI=0.08;0.57, Figure 3.1C). For one study, no specific effect size for lower and/or upper extremity muscle strength could be calculated because of insufficient data provided.

**Effect of exercise on health-related quality of life**

The effect of exercise on HRQoL was assessed in five studies and all used the EORTC quality of life questionnaire. Exercise had a significant but small positive effect on global quality of life (ES=0.41, 95% CI=0.18;0.64), physical functioning (ES=0.38, 95% CI=0.15;0.61), emotional
functioning (ES=0.31, 95% CI=0.08;0.54) and cognitive functioning (ES=0.36, 95% CI=0.13;0.59) when compared to usual care. No significant effects were found on role functioning (ES=0.21, 95% CI=-0.02;0.43) and social functioning (ES=0.10, 95% CI=-0.13;0.33; Figure 3.2).

Effect of exercise on fatigue

Four of the included studies evaluated the effect of exercise on fatigue. In two studies24,27 fatigue was assessed using the fatigue subscale of the Functional Assessment of Cancer Therapy/Anemia Scale37 and two studies25,28 used the fatigue subscale of the Profile Of Mood States questionnaire.38 Compared to usual care, exercise had a significant moderate favourable effect on fatigue (ES=0.53, 95% CI=0.27;0.79, Figure 3.3).
Methodological quality

The results of the methodological quality assessment are shown in Figure 3.4. None of the studies was free from risk of bias. All eight studies were described as RCTs, but the method of random sequence generation was described clearly only in five papers. Allocation concealment was adequate in three studies and unclear in the remaining. One study reported the blinding of test administrators. This could however only be achieved for the objectively tested outcomes, as patients are the test administrator for self-reported outcomes. None of the studies reported the blinding of patients or care providers. In five studies, outcome data were complete or missing data were adequately explained and were unlikely to cause bias. The study protocol was available for three studies.

Other forms of risk of bias included baseline differences in demographics and outcome measures, contamination (patients in the usual care group started exercising after talking to patients in the intervention group), small sample size (n<20), inclusion of pilot data in the analysis and uncertainty about the timing of the outcome assessment after the SCT. Only one study was free from all these other sources of bias.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumann 2010</td>
<td>57.5 ± 21.4</td>
<td>54.2 ± 23.3</td>
<td>0.54 (0.03, 1.11)</td>
</tr>
<tr>
<td>Hacker 2011</td>
<td>78.1 ± 12.2</td>
<td>59.3 ± 18.5</td>
<td>1.02 (0.01, 2.05)</td>
</tr>
<tr>
<td>Jarden 2009</td>
<td>61.3 ± 17.2</td>
<td>52.0 ± 16.7</td>
<td>0.48 (0.20, 1.17)</td>
</tr>
<tr>
<td>Knols 2011</td>
<td>73.7 ± 14.9</td>
<td>67.7 ± 15.7</td>
<td>0.39 (0.02, 0.76)</td>
</tr>
<tr>
<td>Wiskemann 2011</td>
<td>61.7 ± 22.2</td>
<td>57.1 ± 17.3</td>
<td>0.23 (0.21, 0.67)</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>148</td>
<td>0.41 (0.16, 0.64)</td>
</tr>
</tbody>
</table>

Figure 3.2. Meta-analysis of post-test means for the HRQoL domains (continues on next page).

Total: sample size.
Figure 3.2. Meta-analysis of post-test means for the HRQoL domains (continued).
Total: sample size.

Figure 3.3. Meta-analysis of fatigue post-test means for exercise versus usual care.
Total: sample size.
Discussion

In this review, we summarized and analyzed the results of eight RCTs evaluating the effectiveness of exercise on physical fitness, HRQoL and fatigue in patients treated with a SCT for a hematologic malignancy. Although the studies varied in intervention characteristics, statistical pooling was considered appropriate for studies that measured the same outcome. The meta-analysis showed that exercise had a favourable effect on physical fitness, fatigue and HRQoL when compared to usual care.

The effect of an exercise intervention program on physical fitness is influenced by the mode of exercise, the length of the program, and the frequency, duration and intensity of exercise sessions, as well as by compliance to the protocol. The intervention programs evaluated varied widely, which may partly be explained by the differences in the timing of the intervention. For instance, during hospital admission, it may be desirable to reduce the intensity of the exercise sessions and to increase training frequency to ensure both sufficient training volume and
safety. In the outpatient rehabilitation phase, however, it might be more practical to decrease the training frequency and to increase the intensity of the training sessions. Unfortunately, in some of the included studies the principles of exercise training\textsuperscript{19} were not always correctly applied, crucial information about important program characteristics was missing or adherence to the program was not always clear. As previously mentioned by Campbell et al.,\textsuperscript{19} studies in which suboptimal or inappropriate interventions are prescribed might fail to find significant results and might underestimate the efficacy of exercise. Other factors that may have influenced the effectiveness of exercise interventions in this population are differences in diagnoses and treatment. We only included studies with study samples containing at least 75% of patients treated with SCT for a hematologic malignancy. It is therefore unlikely that our results are influenced by the small number of patients (n=40, 8%) that did not receive SCT for a hematologic malignancy. However, substantial differences exist between patients with different types of hematologic malignancies and the associated symptoms and treatments.

In addition to the diversity in interventions, also the outcome instruments used to assess cardiorespiratory fitness and muscle strength varied across studies. Although we calculated SMDs it is possible that these different instruments measured different domains of these outcomes. To clarify this matter, it is desirable that future studies use equal measurement instruments for which reliability and validity has been established in the relevant patient population.

The results of the current review should be interpreted with caution. Only a small number of studies was available per outcome and the sample size was often rather small. Furthermore, all of the studies included at least some risk of bias. An important issue was the lack of blinding. Double blinding is evidently preferred, but often impossible in exercise intervention studies.\textsuperscript{39} In addition, fatigue and HRQoL are usually measured using questionnaires, with the patient being the outcome assessor.\textsuperscript{39} Consequently, for the self-reported outcomes a lack of blinding of the patients directly implies a lack of blinding of the outcome assessors. It seems therefore that a certain amount of risk of bias has to be accepted in this kind of research. Other important issues concerning risk of bias include the incomplete description of the randomization sequence generation method and the allocation concealment, incomplete data (the presence of selective dropouts and/or no intention-to-treat analysis performed) and baseline differences in demographics and outcomes between groups.

The findings of this review are in line with recent reviews that studied the effects of exercise on cardiorespiratory fitness,\textsuperscript{41} quality of life\textsuperscript{42,43} or fatigue\textsuperscript{44} in cancer patients in general and with the previously published reviews focussing on patients treated with SCT.\textsuperscript{16-18} A major strength of the current review is the fact that we also conducted a meta-analysis. Furthermore, additional studies were available, enabling compliance with stricter inclusion criteria. For instance,
five of the eight studies included in this review were published after the search of Wolin et al.\textsuperscript{18} and only three of the thirteen studies that were included by Wolin et al.\textsuperscript{18} met our strict inclusion criteria. When compared to Wolin et al.,\textsuperscript{18} the most discriminative criterion was the design of the trial, which for inclusion in our analysis had to be an RCT. For the evaluation of therapeutic interventions in general, RCTs are considered to be the gold standard,\textsuperscript{45} as they are least susceptible to bias. We attempted to reduce heterogeneity in the study population by setting the minimum percentage of patients with a hematologic malignancy in the study sample at 75\% compared to 50\% in the review by Wolin et al.\textsuperscript{18} However, this did not influence the results of the current review.

Despite the strengths of this review, it has some limitations that should be addressed. First, heterogeneity was present for cardiorespiratory fitness and lower extremity strength. Due to the low number of studies, exploration of the diversity by subgroup or meta-regression analysis was not possible. Possible explanations for the heterogeneity are the range of exercise interventions evaluated in the included studies and the wide variety in outcome instruments used across studies. A second limitation is that publication bias may be present. It was not possible to test for publication bias due to the small number of studies included in the analysis.\textsuperscript{20} Third, this review did not look at the sustainability of the results. In the analysis we only included data that were obtained directly following the completion of the intervention. The studies of Jarden et al.\textsuperscript{27} and Knols et al.\textsuperscript{24} included long-term follow-up assessments but did not find significant effects of exercise on fatigue or HRQoL in the long term. The fourth limitation concerns the clinical relevance of the findings. Since our conclusion is mainly based on statistical associations and effect sizes, the clinical implications of exercise on physical fitness, fatigue and HRQoL need to be confirmed.

Unfortunately, there is insufficient evidence to conclude what is the best exercise prescription for patients during or after SCT. Further methodologically sound studies that examine exercise interventions that comply with the principles of exercise training are needed to determine the optimal exercise prescription for certain subgroups of patients. To facilitate comparison between studies and to allow replication, it is essential that these studies describe the content of the exercise intervention in detail. Furthermore, adherence rates should be available to give insight into the exercise dose received by the patients.\textsuperscript{19}

In summary, exercise seems to have a beneficial effect on physical fitness, HRQoL and fatigue when compared to usual care in patients treated with a SCT for a hematologic malignancy. Further high quality studies are necessary to determine the optimal exercise program and to assess the clinical relevance of the results.
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