Physical exercise in patients with hematological malignancies

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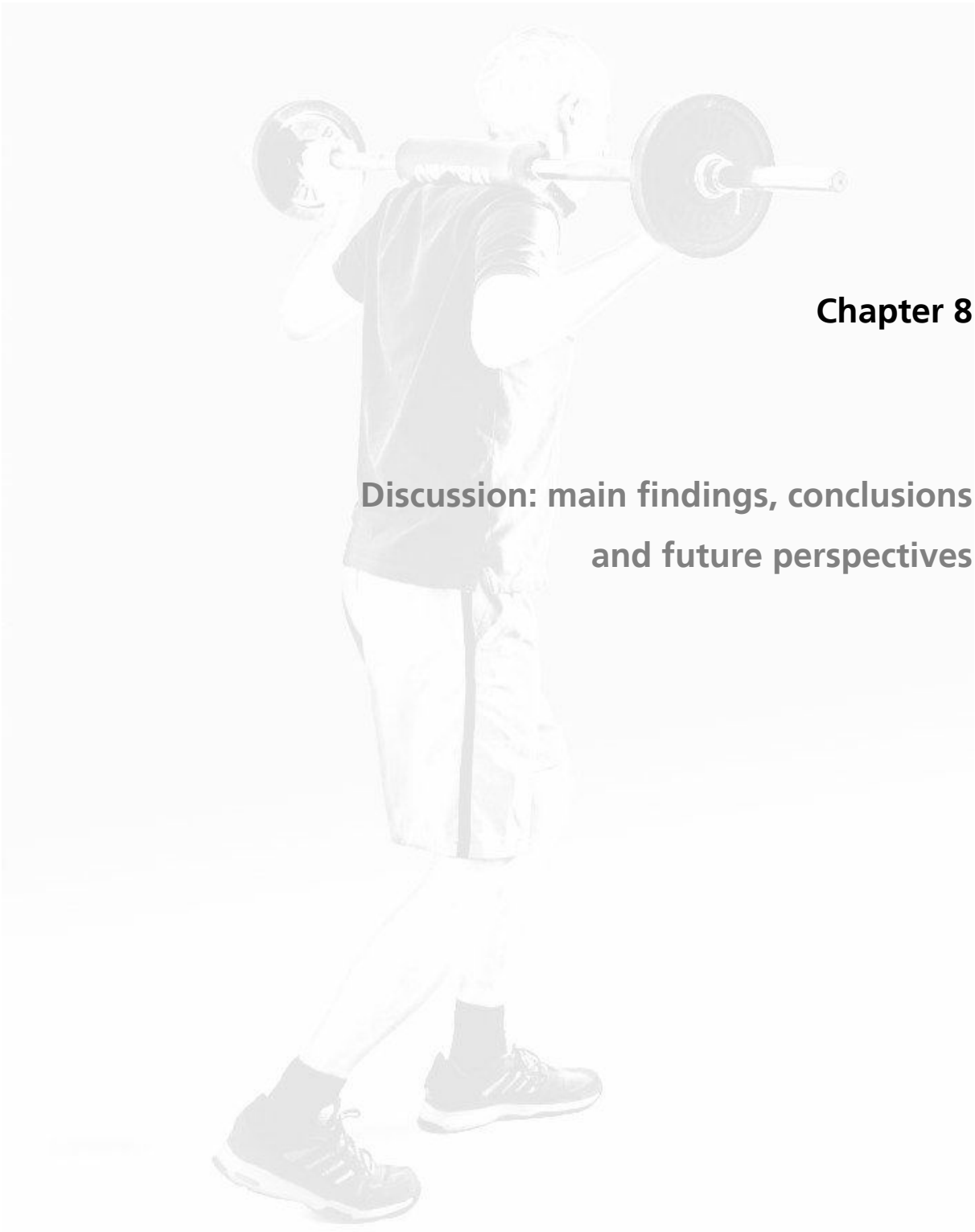

Chapter 8

Discussion: main findings, conclusions and future perspectives

The core of this thesis is the evaluation of the effects of a physical exercise intervention versus usual care in patients after hematopoietic stem cell transplantation (HSCT). Surrounding this core are a number of additional studies, including: (1) a systematic review of the empirical evidence on the effectiveness of physical exercise in cancer patients during and after medical treatment in general and, more specifically, the effectiveness of physical activity interventions on objectively assessed daily walking activity in cancer survivors; (2) an investigation of the absolute and relative reliability of outcome measures used frequently in evaluating the effectiveness of physical exercise evaluations in hematological cancer patient populations; and (3) an assessment of the relationship between patient-rated outcomes, laboratory measures and real-world functioning measures for walking in patients with hematological malignancies. In this chapter we summarize the results of these studies, discuss their implications for the clinic, and provide recommendations for future research.

Main findings

The systematic review reported in this thesis was undertaken to evaluate the methodological quality of and to summarize the evidence from studies that have investigated the effectiveness of physical exercise in cancer patients during and after medical treatment **(chapter 2)**. Thirty-four studies were included in the systematic review. The trials reviewed were of moderate methodological quality. Together they suggested that cancer patients may benefit from physical exercise both during and after treatment. Various exercise modalities have been applied, differing in content, frequency, intensity, and duration. Positive results were observed for a diverse set of outcomes, including physiologic measures, objective performance indicators, self-reported functioning and symptoms (particularly fatigue), psychological well-being, and overall health-related quality-of-life (HRQOL). The beneficial effects of physical exercise may vary as a function of the stage of disease, the nature of the medical treatment, and the current lifestyle of the patient. Therefore, these latter variables should be included in the design and analysis of future physical exercise studies.

We also investigated the absolute and relative reliability of a strength measurement protocol with a hand-held dynamometer **(chapter 3)** and of daily walking activity with a body-fixed sensor **(chapter 4)** in patients with hematological malignancies. Of particular interest was the question whether the strength measurement protocol and the assessment of daily walking activity were able to detect differences between time points (e.g., before and after a physical exercise intervention). We concluded that a hand-held dynamometer strength measurement protocol **(chapter 3)** and an assessment of two consecutive 7-day recordings of ambulatory walking activity **(chapter 4)** in patients with hematological malignancies may be useful in detecting changes in knee extension strength and walking activity at the individual patient level. The relative reliability parameters for both the strength and walking activity assessments were

good. The study also documented compromised levels of ambulatory walking activity among hematologic cancer patients recovering from high-dose chemotherapy, as compared to healthy controls.

In a cross-sectional study, we investigated the relationship between a patient-rated outcome, a laboratory-based measure, and a real-world measure of walking activity in patients with hematological malignancies **(chapter 5)**. We observed weak relationships between the ambulatory step activity, self-reported physical functioning and the six-minute standardized walking test. Hence, a patient-rated outcome and a laboratory test do not reflect daily walking activity performance. This finding suggests that studies intending to assess this latter parameter should be extended with supplementary outcome measures. In clinical use, ambulatory step activity monitors are recommended as an additional means of assessing day-to-day walking activity in hematological cancer patients.

Based on the results of our own and other systematic reviews, and on our clinical experience, we developed and tested a physical exercise intervention for HSCT recipients. The results of this study are reported in detail in **chapter 6** of this thesis. Briefly, we conducted a randomized clinical trial in which we compared a 12-week ambulatory physical exercise intervention with a usual care control intervention in patients who had recently undergone a HSCT. The results indicated a significant and positive effect of the training program on the physical performance measures of knee strength, walking speed and walking distance in the 6-minute walking test immediately after the program. Knee strength remained significant at the three months follow-up. All outcomes exceeded the smallest detectable difference (SDD) for the strength measurement protocol for the hand-held dynamometer. No significant group differences were observed for daily ambulatory walking activity. Improvement in muscular strength, walking speed and walking distance resulting from the PE program did not translate into improvements in laboratory-based measures (body composition), real-world functioning measures (quantified 7-day walking activity) or patient-reported outcomes (physical activity, health-related quality-of-life, and fatigue).

The final piece of research reported in this thesis is a systematic review/meta-analysis, including seven RCTs, of the effectiveness of physical activity interventions on objectively assessed daily walking in cancer survivors **(chapter 7)**. Combined physical activity and counseling improves daily step activity in (breast) cancer survivors. Studies that define a step goal appear to be more effective in improving daily walking activity than studies that do not do so. The seven studies reviewed were of good methodological quality. However, because clinical and statistical heterogeneity was observed in the studies reviewed, the results need to be interpreted with some caution.

Methodological issues

Generalizability

In general, given that the studies reported in this thesis (chapters 3-6) recruited a series of consecutive patients from the target population, we believe that the results can be generalized to the larger population of patients with hematological malignancies. However, there are some methodological limitations that should be mentioned. First, an important factor that had a major, negative influence on patient recruitment was the fact that almost 30% of all patients were ineligible, mostly due to severe illness or other medical reasons (e.g., progressive hematological disease, instable osteolyses, lesions of the central or peripheral nervous system, uncontrolled cardiovascular disease). Additionally, 31% of eligible patients declined to participate, primarily because of lack of interest in physical exercise. Ultimately, approximately one-third of the patients could be included in the trial. This percentage is in line with that reported in a study of breast cancer patients [1]. The percentage of dropouts from the study was approximately 20% after three months follow-up. Sixteen patients left the study due to progressive disease. Only two patients left the study due to lack of interest.

Second, there may have been some (self) selection bias in these studies, because more active or fit patients may have been more interested in participating in the trial. This selection bias may have led to an overestimation of the physical performance levels, real-world functioning assessments and the patient-rated outcomes. On the other hand, it is unlikely that *only* fit and active patients participated in our studies, given the fact that all of the patients had undergone high-dose chemotherapy or stem cell transplantation, both of which are known to have debilitating side effects. Moreover, we documented that the patients had compromised levels of daily walking activity as compared to healthy participants **(chapter 4)**.

Systematic reviews

The Delphi list, a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews **(chapter 2)** [2] and the PEDro scale [3], which is based on the Delphi list, were used to determine the methodological quality of the studies included in the systematic reviews. The challenge in using the Delphi list and the PEDro scale was that two of the three criteria relating to the use of blinding were not rated because of the difficulty, if not the impossibility, of blinding the participants and care providers to treatment assignment.[4] Therefore, both of these items were scored as non-applicable. Another challenge was to determine a cut-off point for the (reduced) Delphi list used in this systematic review. How many of the items needed to have a positive score to qualify as methodologically satisfactory? We considered setting the cut-off point at four items (> 50% of the total score) for the Delphi list. However, this was rejected as being too arbitrary. Rather, we decided to let the scores on both the Delphi list and the PEDro scale speak for themselves. In general, the studies included in the

review were of moderate methodological quality **(chapter 2)**. The three items reported least frequently were blinding of the outcome assessor, concealment of treatment allocation and the use of an intention-to-treat analysis **(chapter 2)**.

The randomized controlled trials reviewed in chapter 7 were of generally good methodological quality. However, (information about the) use of 'blinding of the outcome assessors' was not always observed in the trials. Information about 'intention-to-treat analysis' was reported in all of the RCTs included in this latter review.

Design of the intervention study

Patient recruitment

Recruitment of patients into the RCT proved to be very difficult (see paragraph `generalizability`). It took almost four years to recruit the target number of participants. In both the University Hospital Zurich and the Cantonal Hospital of St. Gallen, the responsible oncologist or hematologist first screened the candidates for inclusion in the study. Then each patient was informed about the aims, content and procedures of the study. This was done before or after the stem cell harvest in the hospital, at the hematological transfusion unit. Candidates for the study received both an information brochure and an informed consent form. The patients were ensured that the costs of the measurements, costs of the intervention and their travel expenses would be covered by the study. All patients were given the opportunity to carefully consider whether they wanted to participate in the study. During admission at the hospital and before the start of the high-dose chemotherapy and HSCT, the patients were asked to make their decision known. In some cases, patients were asked to participate during the last days of their stay at the stem cell unit or shortly after discharge from the hospital. This turned out to be an unfavorable point in time for recruitment, as most patients were extremely tired at that point in time, and probably more disinclined to consider participating in the trial than if they had been approached at another time point (e.g., before admission to hospital for HD and HSCT).

Participation of physiotherapists

The recruitment of senior physical exercise trainers into the study went well. First, a physiotherapy clinic close to the patient's home was identified. The physiotherapist was informed about the aim of the project and received general information about the physical exercise intervention, the workload, safety procedures for immune suppressed patients, and the financial compensation for carrying out the intervention. If the physiotherapist agreed to carry out the physical exercise intervention, an instructional session was arranged at the local physiotherapy clinic. This session lasted approximately 60 minutes. A protocol for the physical exercise intervention, an exercise manual and forms to document the process were provided, as was contact information if the physiotherapist had any additional questions or concerns.

Patients in the intervention group were asked by the study coordinator to contact the local physiotherapy clinic within a week to arrange an appointment for the physical exercise intervention. The study coordinator contacted the physiotherapist after the first half of the physical exercise program had been completed to discuss the patient's progress, and again shortly before the end of the intervention to arrange follow-up appointments.

In total, 39 physiotherapy practices treated one patient each, and 7 practices treated two or more patients (total of 25). Three clinics declined to participate in the project; two had no interest and one indicated having no time.

Physical exercise intervention

In designing the physical exercise intervention (PE), we drew on components of other intervention protocols that had proven to be feasible and successful when used with patients following HSCT [5-7]. Our intervention included the combination of endurance and strength elements. The specific exercise prescription (mode, frequency, intensity, duration, and progression) used followed the recommendations of the American College of Sports Medicine [8]. During the physical exercise program, the patients were supervised by a physiotherapist with extensive expertise and practical experience in exercise and strength training. To prevent the risk of infection, patients were strongly advised to perform the PE program alone or, if that was not possible, to attend the physiotherapy practice outside the peak visiting times. The physical exercise program was very well accepted by the participants. We received positive feedback from the participating physiotherapist about the program. They indicated that the program was easy to teach and most patients could follow the program with little difficulty.

Clinical implications

Previous clinical trials have provided evidence that physical exercise programs can be effective in improving both physical and psychosocial outcomes during and/or following medical treatment among patients with breast [9], prostate [10], and head-and-neck cancer [11], with lymphomas [12], with a mixed population of (breast, ovarian, testicular, lymphomas and colorectal) cancers [13] and patients who have undergone HSCT [14] Our RCT could only partially confirm these earlier findings. Our results indicate that a combined endurance/strength program yields significant gains in muscle strength, walking distance and walking speed, with moderate effect sizes. However, these performance outcomes did not translate into significant improvement in physical functioning in daily life or in quality of life outcomes.

We believe that our moderate, combined physical exercise intervention can be used to improve the physical fitness levels of HSCT patients following treatment. At the same time, several steps should be undertaken to improve the effects of the PE intervention on patients rated outcomes and daily activities in HSCT patients. First, we suspect that the effects of a PE

intervention program on patient-reported outcomes such as fatigue and HRQOL might be stronger if the frequency of the aerobic exercise intervention was to be increased from two to three times a week, and the duration of the aerobic activity from 20 to 45 minutes per session. [12] This hypothesis is supported by two studies that were performed during HSCT treatment [15,16].

Second, the length of PE program could be extended (e.g., from 3 to 6 months). This is supported by two studies that observed improvements in objectively assessed daily walking activity [17], and pulmonary function [18] in breast cancer survivors after a six month PE intervention.

Third, patient-rated outcomes (e.g., fatigue and HRQOL) might be improved by also employing cognitive behavioural therapy (CBT) techniques [19]. CBT could be targeted at dysfunctional cognitions with respect to the disease itself [20], and at fatigue [14], anxiety and depression [21], (low) social support and negative social interactions [21], and deregulation of physical, role and/or social activities [14, 22].

Fourth, group-based physical training interventions may be more effective in improving fatigue and HRQOL in cancer survivors [13, 23]. Group-based training can have psychosocial benefits that accrue when group cohesion is created, providing social support and positive social comparisons. Additionally, cancer patients and survivors indicate that exercising in groups can increase their motivation to overcome their physical limitations [23].

Fifth, a physical exercise program should be easy to learn and to follow, preferably in an unsupervised form, after initial instruction. Such an intervention should also require only minimal reinforcement from a physiotherapist or other health care professional and should not require any special, expensive equipment [24]. The need for simple and unsupervised physical exercise interventions cannot be overstated. Although transplant centers have moved away from strict patient isolation, concerns persist about minimizing exposures for immune-compromised patients. Transplantation centers may lack exercise rooms; thus, patients would need to be transported to the physiotherapy department. Outpatient transplant facilities may also not always be designed for physical exercise interventions. As discussed earlier, many patients are quite ill and unable to participate in a physical exercise interventions, as currently designed. A graded PE routine based on functional ability (e.g. walking programs) could be designed for "weaker" patients [24]. The components of such a program could be the same as those recommended by the American College of Sport Medicine, in general. However, the frequency, intensity, duration and progression of a PE program would be modulated to a lower level (e.g. 30% of the heart rate reserve) and individualized to the specific needs of the patient [8].

Sixth, we were able to demonstrate that the hand-held dynamometer (of the type CompuFET) is a feasible method to detect changes in muscle strength in hematological patients and potentially other types of cancer. However, in order to obtain valid measurements, it is

important that the assessments are performed by the same observer, that observers are sufficiently experienced, and that the strength of the observers exceeds that of the patient [25]. The reliability of the step activity monitoring (of the type SAM3 is good for the assessment of two consecutive 7-day recordings of ambulatory walking activity. Moreover, we found that the measurement error is small enough to detect clinically relevant changes in the daily walking activity of hematologic cancer patients who are recovering from intensive medical treatment. Muscle strength measurements and walking activity assessed with these measures can thus be implemented in other research projects and in daily practice, if desired.

Seventh, we found that self-reported physical functioning and a standardized walking test do not reflect daily walking activity as assessed objectively. Step activity monitors add additional information to that obtained from self-report measures of physical functioning and clinic-based performance tests for evaluating the physical activity level of patients who have undergone treatment for hematological malignancies. Therefore, the use of step activity monitoring can be recommended for monitoring and evaluating patients' physical activity levels. Ultimately, the choice of which instrument or method to use in assessing patients' level of physical activity is a function of the research question, participant burden and available resources to the researcher or the practitioner [26].

Conclusions and future perspectives

The results of our RCT are promising, but additional efforts are needed to strengthen the effect of physical exercise interventions in HSCT recipients. Future studies should examine how to reduce barriers to program participation and to improve patients' adherence to exercise programs. In this context, clinical and psychological factors associated with hematological cancer patients' preference for several types of ambulatory exercise training should be identified. Future research should also identify what kind of PE intervention (endurance versus strength training versus combined endurance and strength) or graded "home-based" exercise program is the most effective for patients after HSCT. Also, physical exercise training could be combined with other treatment approaches (e.g. counseling) and evaluated for its effectiveness.

At a more basic level, future research might be directed towards unraveling the dynamics of interactions between stress-related effects on the immune system and immune reconstitution after HSCT. Finally, studies with a longer follow-up are required in order to examine the long-term therapeutic sustainability of the applied intervention strategies. Such studies will require large sample sizes to ensure sufficient statistical power. The conduct of such large scale studies calls for multicenter efforts, with collaboration between stem cell transplantation centers within Switzerland and the European Union.

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