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Physical exercise in patients with hematological malignancies

Hematological malignancies are relatively rare diseases, but have been of great interest because of major advances in treatment over the last decades. Due to modern treatment options, the large majority of patients go into remission and an increasing number of patients are cured. However, during and after medical treatment, patients often experience high levels of both physical and psychological distress. Such distress can occur even if medical treatment is successful.

Physical activity has been increasingly researched as a non-pharmacological intervention to combat the physiologic and psychological effects of treatment among patients with several cancer types (i.e., breast, prostate, head-and-neck, ovarian, testicular and colorectal cancer). Improvement in physiological and psychological outcomes has also been reported for patients with hematological malignancies, in general, and for patients who undergo hematopoietic stem cell transplantation (HSCT), more specifically. However, despite these promising findings, methodological limitations of the reported studies suggested the need for further research on the effectiveness of physical exercise interventions in patients with hematological malignancies. A challenge for researchers (and health care professionals) is that many HSCT patients are quite ill and unable to follow the standard guidelines for physical exercise; therefore, we designed and tested a graded outpatient exercise intervention for patients after HSCT.

The introductory **chapter 1** describes the several intermediate research activities/steps that were necessary to conduct this physical exercise intervention. These steps are reported in separate chapters in this thesis.

Given the growing population of survivors and the growing volume of literature on physical exercise interventions for cancer survivors, there was a need to evaluate and determine the extent to which physical exercise during and after treatment is appropriate. Toward this end, we conducted a review of the evidence from trials examining the effectiveness of physical exercise in improving the level of physical functioning and psychological well-being of cancer patients during and after medical treatment, and we evaluated the methodological quality of these studies. In this systematic review, as described in **chapter 2**, we concluded that in cancer patients, the beneficial effects of physical exercise both during and following cancer treatment varies as a function of the stage of disease, the nature of the medical treatment, and the current lifestyle of the patient. The studies reviewed were judged to be of moderate methodological quality.

Knee-extension strength was one of the key outcomes in this thesis. The research question dealt with in **chapter 3** was whether the CompuFet hand-held dynamometer is able to detect a difference over time (e.g., before and after a resistive strength intervention) in knee-extension strength. We also investigated the relative reliability of a strength measurement protocol with this hand-held dynamometer. When taking measurement error into account, we

found that a significant increase in knee extension strength after participation in a resistive strength intervention can be measured with a (CompuFet) hand-held dynamometer. The intra- and inter-rater reliability for the average of 3 maximum voluntary peak-torque knee strength assessments was good.

It is important that cancer survivors be encouraged to follow the general population recommendations for physical activity, because higher levels of physical activity are associated with a reduced risk of mortality. Another methodological issue addressed in this thesis was the assessment of daily walking activity in hematological cancer patients. Step activity levels were assessed with the CYMA step activity monitor 3 (SAM3). The first objective of the study reported in **chapter 4** was to determine the (relative) reliability and absolute reliability (agreement) of the assessment of ambulatory walking activity during 2 consecutive weeks in patients with hematologic malignancies recovering at home from their medical treatment. The results of this study indicate that a significant increase in walking activity after, for example, participation in a walking intervention, can be measured with the activity monitor and that the relative reliability of the assessment of walking activity in hematological cancer patients is good.

The second objective of this study was to compare the daily walking level of hematologic cancer patients after high-dose chemotherapy with that of healthy subjects. We found compromised levels of ambulatory walking activity among the hematologic cancer patient group.

In **chapter 5** we report the results of a study that examined the degree of association between self-reported physical function (assessed with the physical functioning scale of the EORTC QLQ-C30), standardized walking (assessed with a 6-minute walking test) and quantified physical activity (assessed with a step activity monitor SAM3 over a 7-day period) in HSCT patients. We found relatively low correlations between these measures, indicating that it is possible to make a distinction between three conceptually distinct levels of physical activity: (1) hypothetical (i.e., self-perceived functional capacity), (2) experimental (i.e., physical performance on a laboratory test), and (3) enacted functioning (i.e., physical activity in daily life). The use of step activity monitors adds 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 HSCT.

In **chapter 6** we report on a randomized clinical trial of the effectiveness of a physical exercise intervention. We hypothesized that a moderate intensity, supervised outpatient physical exercise program for HSCT recipients would be superior to usual care in enhancing physical performance, body composition, quantified walking activity, self-reported physical activity, fatigue, and self-reported health-related quality of life (HRQOL) as assessed both immediately following the training program and at 3-month follow-up. Patients were randomly allocated to a supervised 12 week physical exercise intervention in their home setting (n=64) or to a usual care

control group (n=67). Statistically significant group differences favoring the intervention group were observed in muscular strength, walking distance and walking speed at the immediate post-program assessment, but not at the 3 month follow-up. The observed positive program effects on short-term physical performance outcomes did not translate into improvements in laboratory-based measures (body composition), real-world functioning measures (quantified walking activity) or patient-reported outcomes (physical activity, fatigue and HRQOL).

The last step paper in this thesis is a systematic review of the effectiveness of physical activity interventions in enhancing daily walking activity in cancer patients (**chapter 7**). Five relevant randomized clinical trials (RCTs) were identified, reviewed for substantive results, and for methodological quality. In general, these studies were of good methodological quality. Together, they suggest that combined physical activity and counseling improves daily step activity in (breast) cancer survivors. Studies that define a step goal seem to be more effective in improving daily walking activity than studies that do not make use of such a step goal.

In **chapter 8**, the main findings, conclusions and future perspectives are discussed. While the results of the RCT reported in chapter 6 are promising, additional efforts are needed to strengthen the effect of physical exercise interventions in HSCT recipients. Future research should 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, the combination of physical exercise training and other treatment approaches (e.g., counseling) should be evaluated. Finally, studies with a longer follow-up are required in order to examine the long-term therapeutic sustainability of physical activity 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.