


Feasibility and Potential Benefits of an Exercise Intervention in a Male With Down Syndrome Undergoing High-Dose Chemotherapy for Acute Lymphoblastic Leukemia: A Case Report

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Abstract

In patients with hematological malignancies, exercise is studied as a supportive measure with potential benefits on therapy and disease-related side effects. However, clinical trials have not yet integrated people with Down syndrome (DS), although this disability is associated with an increased risk for hematological malignancies. Therefore, we examined safety and feasibility of a mixed-modality exercise intervention in a male with DS undergoing high-dose chemotherapy for acute lymphoblastic leukemia. Furthermore, physical capacity and fatigue were assessed. Exercise sessions took place 3 times/wk over a 5-week period. Adherence to the exercise program was 100%, and no serious adverse events occurred. In contrast to the training sessions, applied endurance testing was not feasible. Furthermore, maintenance of fatigue level was observed. In conclusion, cancer patients with DS suffering from leukemia should not be excluded from physical activity or exercise programs.

Keywords

cancer, Down syndrome, leukemia, physical activity, exercise, fatigue

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Background

Exercise interventions are known to positively influence physical and psychological health of cancer patients,¹⁻³ even in patients undergoing chemotherapy.⁴ In patients with hematological malignancies⁵⁻⁹ as well as in patients with Down syndrome (DS),¹⁰ feasibility and safety of physical activity programs have also been validated. This is highly relevant because the incidence of leukemia in people with DS is significantly elevated compared with people without DS and has been estimated to occur 20 to 30 times more frequently.¹¹⁻¹⁴ To the best of our knowledge, exercise programs with cancer patients have not included people with DS. Consequently, this population has been excluded from exercise programs, probably because of safety considerations. Against this backdrop, we evaluated the feasibility and safety of an exercise intervention in a 22-year-old man with DS who was undergoing high-dose chemotherapy for acute lymphoblastic leukemia.

Case Presentation

Participant

The participant investigated here had to be excluded from an ongoing clinical trial¹⁵ because DS was an exclusion criterion. To follow the United Nations Convention on the Rights of Persons with Disabilities and to facilitate access to the exercise intervention, we included the patient in this case report.

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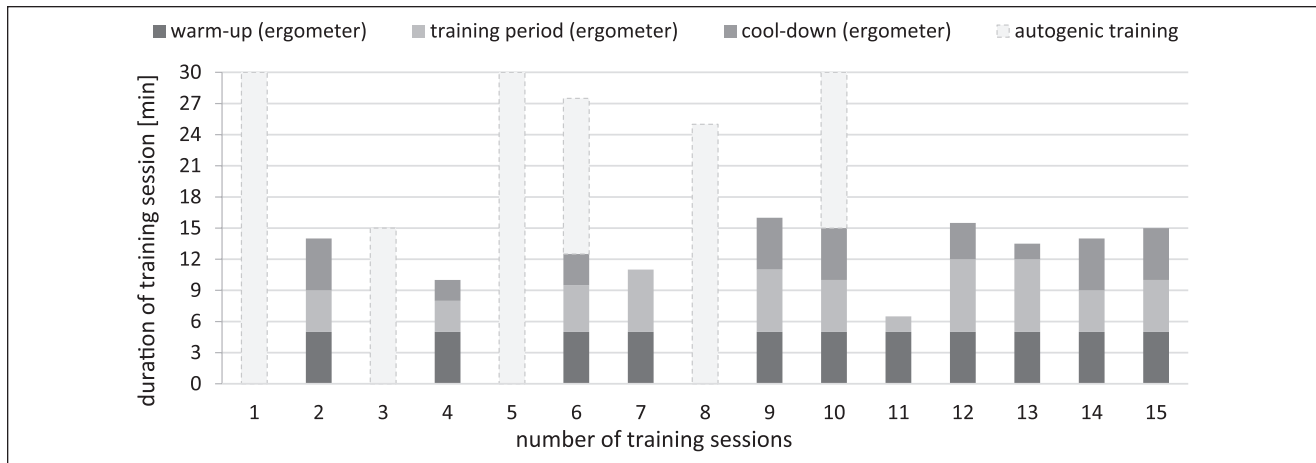


Figure 1. Number and duration of training sessions.

Physician's approval and parental consent were received prior to intervention. Further inclusion criteria were age above 18 years and no current symptoms of coronary illness or orthopedic disease, which would contraindicate cycling. The patient was 22 years of age and 161 cm tall and had an initial weight of 60 kg; thus, body mass index at baseline was 24.7 kg.m². Type of trisomy 21 was a nondisjunction trisomy, and intellectual disability was mild to moderate according to patient's family and opinion of involved study personal. Leukemia was classified as Ph/BCR-ABL-negative common-B-ALL. Hypothyroidism, which was treated by daily medication of L-thyroxin, preexisted, as did a moderate mitral and tricuspid valve insufficiency. In addition, prior to being hospitalized because of the leukemia diagnosis, a gastric infection was detected and still persisted during the intervention. The leukemia disease was treated according to the GMALL 08/13-protocol (EudraCT Number: 2013-003466-13). Before being diagnosed with leukemia, the participant worked in a disabled workshop as a gardener and waiter. Concerning physical activity, he reported attending a dance theater with 1 to 2 hours training a week for about 1 year.

Exercise Intervention

In addition to usual clinical care, the study participant received an exercise program 3 times per week over a 5-week period, targeting 30 minutes per session. The intervention began about 10 days after starting the first phase of induction therapy in the hospital and about 4 weeks after the first diagnosis of leukemia. Each session was supervised by a sports science student (LB). The individual program included aerobic endurance training on a cycle ergometer as well as autogenic training modified for people with cognitive impairments.¹⁶ Blood pressure- and heart rate (HR)-monitored ergometer training consisted of a 5-minute warm-up, an exercise period targeting 20 minutes at an

intensity of 70% to 80% of HR_{max}, and a 5-minute cooldown. After finishing an exercise session, the rate of perceived exertion (RPE) was documented to gain feedback on exercise intensity. The cycling sessions were stopped early if the patient wished to do so. If there were any complications present, such as anemia (hemoglobin < 7 g/dL), thrombocytopenia (platelets < 10 000/μL), no medical approval, or ongoing infusions, or if the patient was feeling generally unwell, autogenic training was carried out instead of cycling. All exercise sessions and blood status were tracked in a training log.

Assessments

The participant was examined at 3 time points (t_0 : preintervention, at the start of high-dose chemotherapy; t_1 : postintervention; t_2 : 2 weeks postintervention). At each time point, endurance performance was tested on the cycle ergometer using a modified World Health Organization schema for oncological patients.^{7,17} The protocol started at 20 W, and performance increased by 10 W every minute until voluntary exhaustion. The test was terminated early in case of dizziness, nausea, shortness of breath, chest pain, or blood pressure values >250/110 mm Hg. The patient was advised to cycle at about 70 rpm. Additionally, at each stage of the cycling protocol, RPE and HR were assessed. Fatigue was evaluated with the Multidimensional Fatigue Inventory-20 (MFI-20) questionnaire¹⁸ via face-to-face interview with one of the investigators (LB).

Results

The study participant was able to complete all training sessions (11× ergometer and 6× autogenic training, adherence 100%; Figure 1). Autogenic training was carried out after ergometer training for motivational purposes twice (Figure 1).

Duration of autogenic training ranged from 15 to 30 minutes because formats were different.¹⁶ The targeted duration on the cycle ergometer could not be reached (mean = 13 minutes, range = 6.5-16; Figure 1). On 5 occasions, the exercise session was stopped early by the patient because of difficulties, including dizziness, gastric pain, headache, or muscle ache. However, no serious adverse events occurred, even when exercising immediately after infusion of chemotherapy (see Table 1 for a complete overview of medical treatment in relation to training sessions). Results of physical performance and the MFI-20 are shown in Figures 2A and 2B. Overall, except for the scale of reduced motivation, no further increase in fatigue could be observed from t_0 to t_1 . However, 2 weeks postintervention (t_2), most subscales reincreased toward baseline levels (t_0). Endurance performance testing at t_0 was stopped early by the participant before physical exhaustion because of dizziness. Thus, an invalid performance testing resulted (see Figure 2A). Therefore, intensity for ergometer training was calculated using the following formula: $200 - \text{Age} \times (0.7-0.8)$.¹⁹ Reasons to terminate the endurance testing at t_1 were gastric pain and dizziness combined with decreased blood pressure. Similar to t_0 , complications were related to the leukemia disease and not to the existence of trisomy. At t_2 , the participant was able to reach his subjective performance maximum (RPE 19). Of note, bodyweight decreased from 60 kg at baseline to 54 kg at t_1 and 52 kg at t_2 .

Discussion

This study examined whether an exercise intervention is feasible in a man with DS suffering from acute lymphoblastic leukemia and whether potential benefits in fatigue and physical performance exist.

The exercise intervention was feasible and well accepted by the participant, reflected in an adherence rate of 100%. In addition, family members and clinical staff reported after the intervention that the participant kept asking for the training sessions. We suppose that the individual coaching and the good relation with the supervisor (LB) was helpful for adherence. The assumption is supported by results from Wilde et al,²⁰ who showed higher active behavior for people with DS when they were receiving higher amounts of attention or had intensified interaction with another person. Although both aspects are present in individual coaching, it must be mentioned that the Wilde et al²⁰ study included children with DS and examined a behavior of playing—not the participation in an intervention program. Furthermore, we think that it was not only the type of coaching that was helpful for adherence, but also the multimodal program adapted to the patient's daily condition. Rapid changes in health condition is a problem of exercise therapy in patients with hematological malignancies, especially during induction chemotherapy.²¹ Degree of adherence in this study was

higher compared with a physical activity intervention in patients suffering from acute leukemia.⁸ When considering adherence in this study without the alternative of autogenic training, compliance is comparable to the study by Bryant et al,⁸ who did not integrate relaxation techniques in their program. Thus, autogenic training as a relaxation technique might be an adequate way to enhance compliance of leukemia patients in physical activity programs. In addition, there is evidence of moderate positive effects of relaxation training in cancer patients²² as well as in people with cognitive impairments.²³ High rates of adherence in people with DS have also been reported in the literature. However, these studies have mostly centered on a walking program.^{24,25}

In contrast to feasibility of the training sessions, physical endurance testing was not feasible. Neither a high level in RPE nor a HR near HR_{max} could be reached (Figure 2). This was also the case when accounting for a lower predicted HR_{max} because of chronotropic incompetence in people with DS.²⁶⁻³⁰ Better outcomes of endurance testing at t_2 might be explained by the termination of chemotherapy treatment 1 week prior, resulting in a better condition of the patient. Even though the testing procedure used is recommended for cancer patients,¹⁷ at this point, studies applying this strenuous testing method on patients suffering from acute lymphoblastic leukemia and DS were not found in the literature. In addition, the testing procedure used might be regarded as too intense, if one keeps in mind different cardiorespiratory, cardiovascular, and metabolic characteristics of people with DS (eg, lower fitness, HR_{peak} , chronotropic incompetence, or VO_{2max}).²⁷⁻³¹ Consequently, submaximum performance testing similar to the 6-minute walk test, which is recommended for weak oncological patients¹⁷ and which has previously been shown to be feasible in leukemia patients³¹ and people with DS^{25,32} should be used instead. Another option might be treadmill exercise testing because it seems to be valid and reliable in people with DS.³³ Overall, a valid endurance assessment is needed and indispensable for adequate training.

Even if the alternative calculation of the HR for training prescription seems to be an adequate method for acute leukemia patients for moderate and high intensities,³³ there are several other formulas for prescription in the literature. For example, the German Cancer Aid Society³⁴ suggests a formula of $180 - \text{Age} \pm 10$ bpm, with the tendency to be lower than 150 bpm for leukemia patients, whereas Baumann³⁵ recommends a HR of $180 - (\text{Age} \times 0.8)$ for people suffering from acute leukemia, especially while undergoing chemotherapy. The targeted HR while exercising was about 11 bpm higher in this case report when compared with that of Baumann.³⁵ In addition, these calculations as well as the formula used in this study do not account for the different cardiovascular characteristics of people with DS.²⁷⁻³¹ According to Fernhall et al,²⁷ the peak HR in people with DS is about 30 bpm lower than the one predicted by the

Table I. Details of Treatment.

Phase	Induction I			Induction II			Induction II			Induction II			Post-induction		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Training Session															
Hemoglobin (g/dL)	8.1	8.6	8.3	8.2	8.3	8.1	Not evaluated	8.7	10	8.4	Not evaluated	9.1	10	9.7	7.7
Thrombocytes (/ μ L)	40 000	47 000	48 000	102 000	147 000	265 000	Not evaluated	230 000	130 000	24 000	Not evaluated	31 000	36 000	27 000	41 000
Day of GMALL protocol	18	20	21	22	23	24	30	33	35	37	38	40	43	44	47
Treatment	None	Vincristine, PEG-asparaginase	None	None	Antibody	Cyclophosphamide	None	Cytarabine, mercaptopurine	Cytarabine, mercaptopurine	Mercaptopurine	Mercaptopurine	Cytarabine, mercaptopurine	Cytarabine, mercaptopurine	Cytarabine, mercaptopurine	Antibody, cytarabine, mercaptopurine
Reasons for AT	Gastric pain, exhausted		Gastric pain, ongoing infusion		Ongoing infusion, pain (bone marrow biopsy)	Motivation		Gastric pain, dizziness		Motivation					
Reasons for shortened session			Dizziness, headache, tachycardia			Gastric pain	Dizziness, loss of motivation				Gastric pain, dizziness	Exhausted	Exhausted	Muscle ache, exhausted	exhausted

Abbreviation: AT, autogenic training.

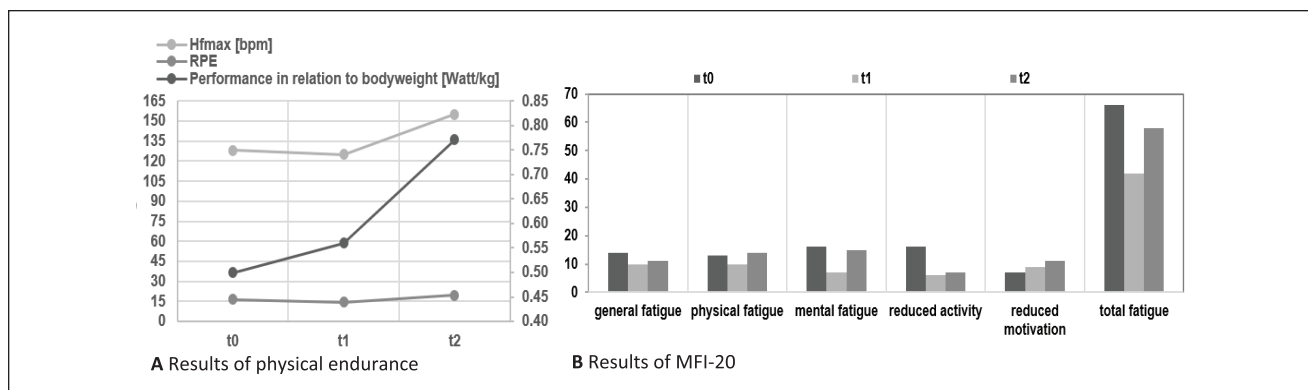


Figure 2. Results of physical endurance testing and MFI-20 across all measurement time-points. Abbreviation: RPE, rate of perceived exertion; Hfmax, maximal heart frequency.

standard formula of $220 - \text{Age}$. When subtracting 20 bpm because of training on the cycling ergometer,¹⁹ a difference of about 10 bpm results. This difference is equal to the difference from the formula of Baumann.³⁵ Consequently, the exercise intensity could have been too high for the participant, resulting in the observed shortened ergometer training periods, whereas the average RPE of 13.9 during the ergometer training contradicts this assumption. Nonetheless, the application of a formula to identify an adequate HR for people with DS or exercising with lower intensity, in intervals or separated into more sessions per day, might be more satisfying and could lead to longer exercise periods in the future.

Lacking adequate testing of endurance capacity, no clear statement on changes in physical performance can be made. Still, it is observable that the participant needed less alternative autogenic training in the latter phase of the intervention, resulting in a more stable participation and training period on the cycling ergometer (training sessions 9-15; see Figure 1). Apart from cardiovascular function, improvements may be attributable to a better economy and coordination of cycling. Similarly, Millar et al³² suggested a better walking economy for observed improvements in walking distance and walking endurance in people with DS without a change in cardiovascular function. However, existing studies in both patients with acute leukemia^{6,31,36} and people with DS³⁷ have reported improvements in physical performance after a physical activity program, albeit with substantial differences in the applied exercise protocols. In patients with acute leukemia, exercising on a cycling ergometer is common because it is well controlled and has a reduced risk for injuries.^{17,35,38} On the other hand, walking programs are more established in people with DS.³⁷ Additionally, according to the review by Dodd and Shields,³⁷ an intervention should last for about 12 to 16 weeks with 3 weekly sessions to gain positive effects in fitness of people with DS. Thus, the shorter intervention period in this study

resulting from the protocol of chemotherapy and the hospital setting could have been a limiting factor for improvements in physical performance. Nevertheless, no serious decrease in endurance capacity could be observed, supporting the assumption of a potential benefit of the intervention because the (passive) control groups of other exercise intervention studies in similar settings^{6,8,31,32} did decline.

Unfortunately, the MFI-20 has not been validated in people with DS yet, but the study participant seems to be similarly affected by fatigue compared with other cancer patients¹⁸ (see Figure 2B). In contrast to the increase in reduced motivation of the MFI-20 at t_1 the rate of participation in the intervention does not indicate a decreased motivation (see Figure 1). The stable overall fatigue at t_1 and the resurgence at t_2 (2 weeks postintervention) might support a potential benefit of the program, if one considers that other cancer patients show a pronounced increase in degree of fatigue while undergoing chemotherapy without an exercise intervention.³⁹ Nonetheless, regarding studies including patients with acute leukemia, several cases of decrease in fatigue have been observed while exercising, but no significant results were reported in the meta-analysis by Zhou et al.³¹ However, it has to be acknowledged that this meta-analysis had a small number of included studies with small sample sizes. Besides, the high adherence might have influenced the maintenance in level of overall fatigue. According to Schulz et al,¹ good adherence is related to a positive effect on fatigue.

Conclusion

Exercise, except for testing of maximum endurance capacity, was feasible and well accepted by the leukemia patient with DS. Similar to physical activity interventions in leukemia patients without DS⁷ and other studies with DS,³⁷ no unexpected withdrawal or superior negative effects occurred, supporting the safety of the program. Furthermore,

the results of the assessments allow us to assume that the intervention was helpful to counteract a further increase in fatigue as well as a further decrease in physical endurance. Therefore, we recommend that exercise interventions should also be offered to people with DS while suffering from acute leukemia. This is especially important when considering the higher rate of incidence of leukemia in people with DS and the inferior prognosis for this cancer population.^{13,40,41} Overall, because of the study design and the applied assessments, these findings need to be interpreted cautiously and further examined in randomized controlled trials. In addition, it seems like the program needs to be further adapted to this special patient group (eg, modified HR intensities, exercising in intervals, longer duration of intervention, testing of walking distance). Nevertheless, this case report is a first step toward finding an adequate and effective intervention.

Authors' Note

Thomas Elter and Philipp Zimmer contributed equally.

Declaration of Conflicting Interests

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