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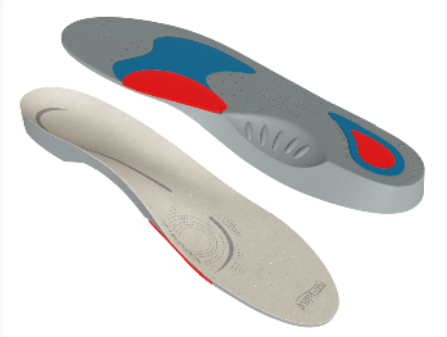

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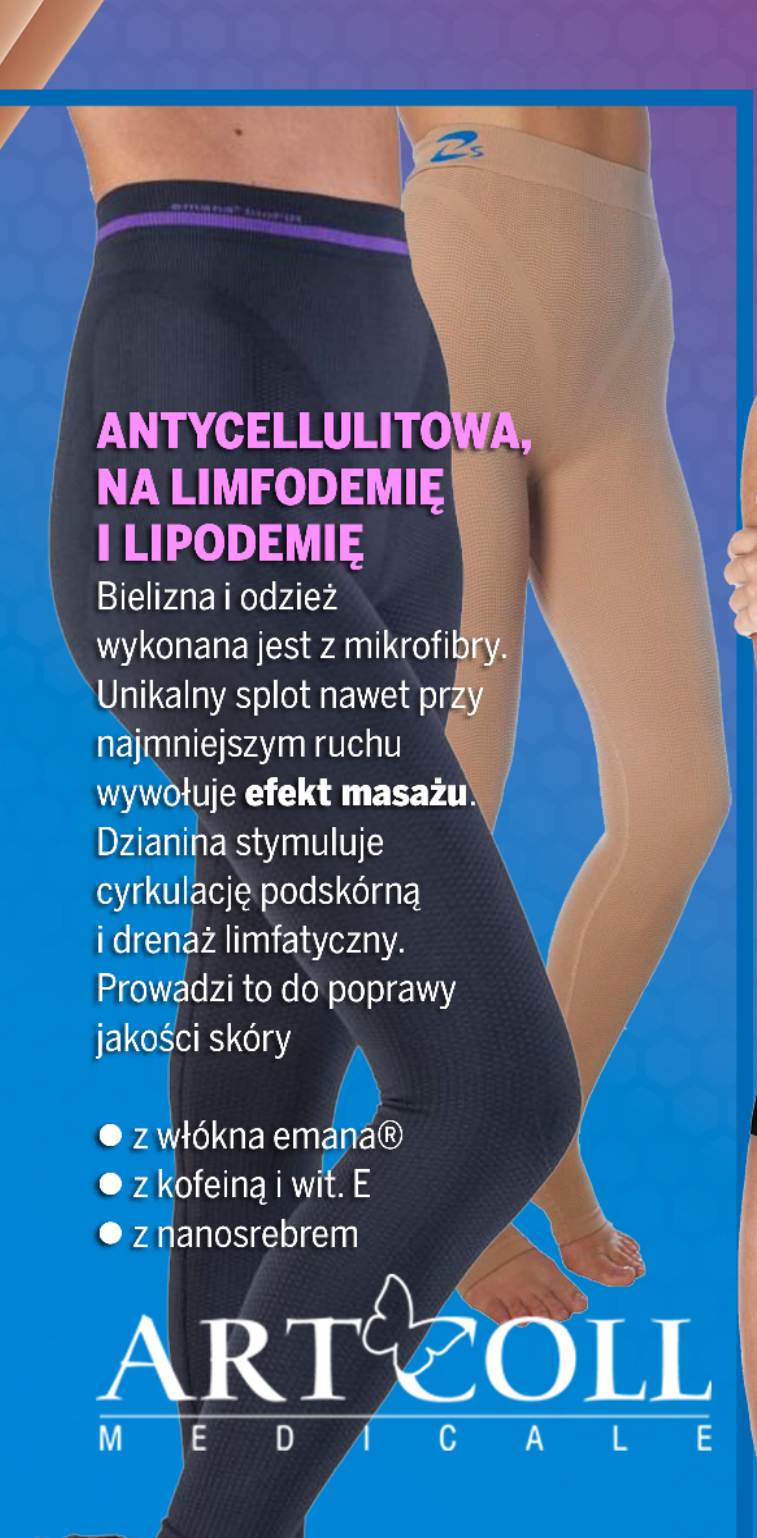

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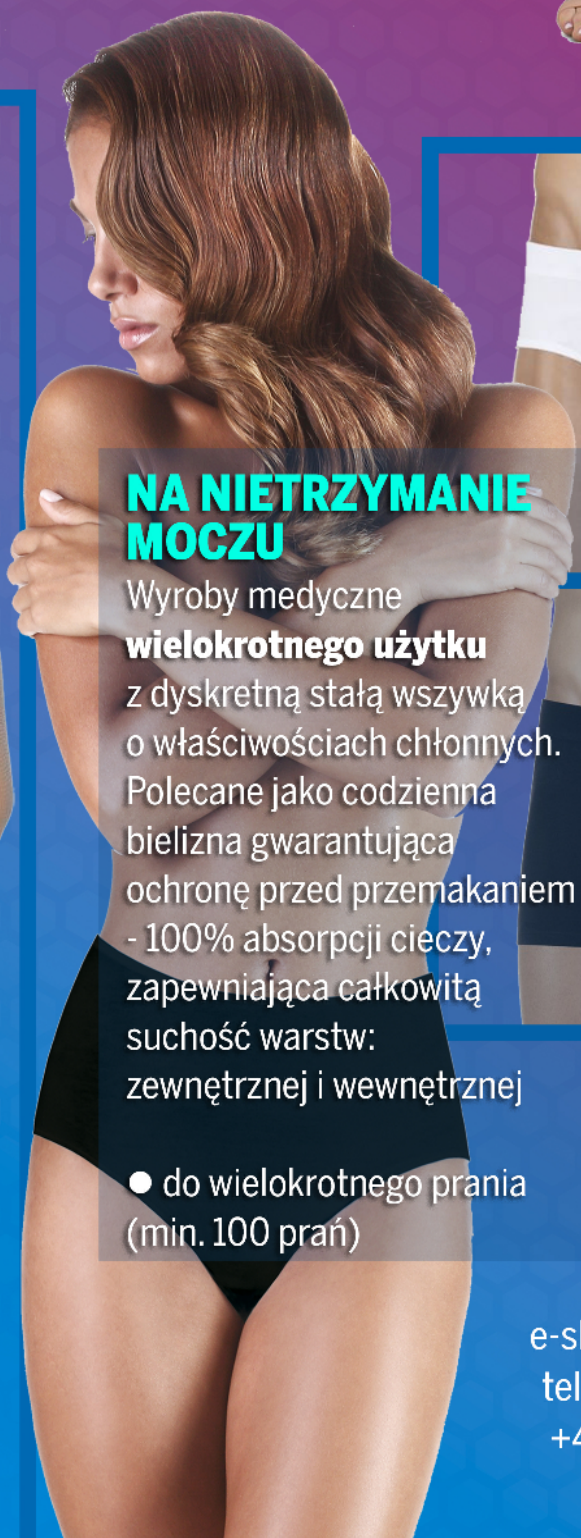

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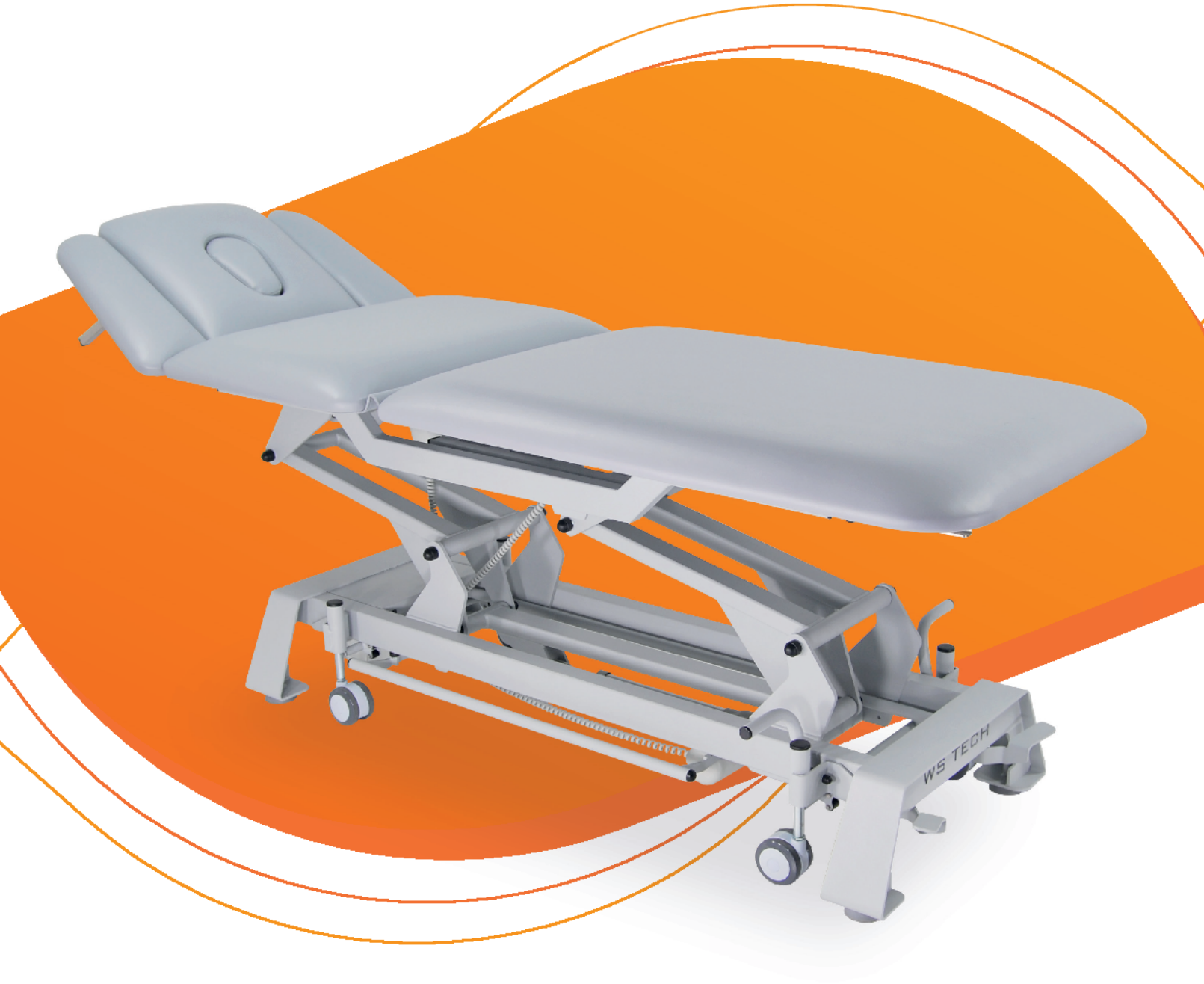

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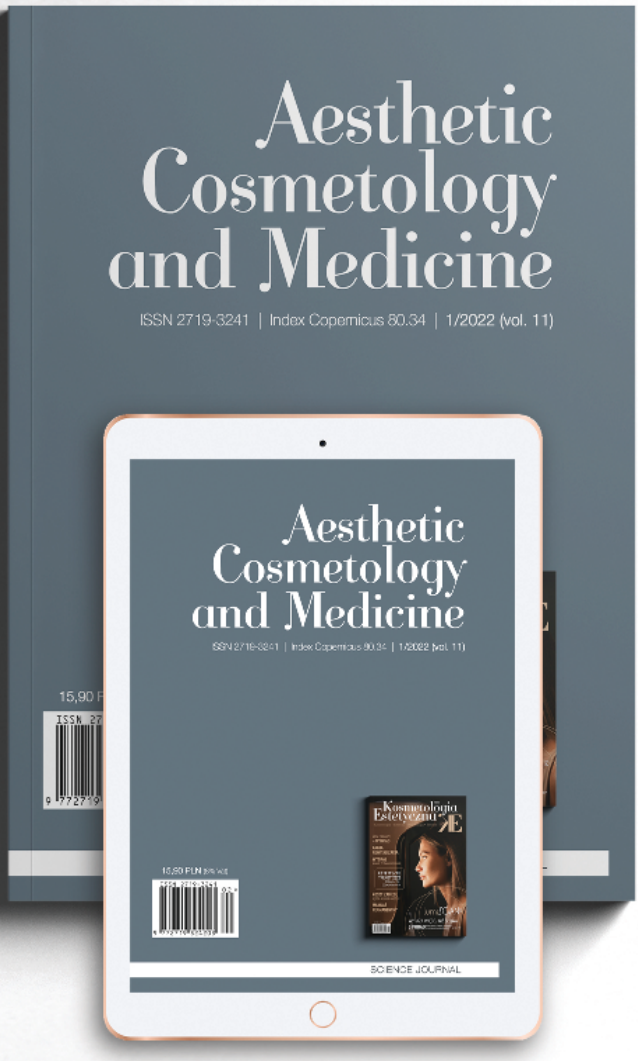

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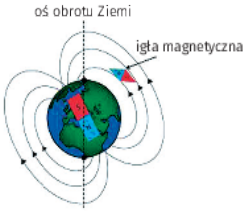

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Effect of aerobic exercise on functional capacity and interleukin-6 level post allogeneic hematopoietic stem cell transplantation: A randomized controlled trial

Wpływ ćwiczeń aerobowych na wydolność funkcjonalną i poziom interleukiny-6 po allogenicznym przeszczepie krwiotwórczych komórek macierzystych: randomizowane badanie kontrolowane

Mohamed Rafat Borham[1(A,B,C,D,E,F)], Azza Abdelaziz Abdelhady[2(B,C,D,E,F)], Gamaleldin Mohamed Fathy[3(A,B,D,E,F)], Emad Mohamed Ibrahim[2(A,C,D,E,F)]

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[2]Department of Cardio-vascular/Respiratory Disorder and Geriatrics, Faculty of Physical Therapy, Cairo University, Cairo, Egypt
[3]BMT & Hematology Department, Nasser Institute for Research and Treatment, Cairo, Egypt

Abstract

Background. Transplantation of hemopoietic stem cells has been extensively used as a curative modality to treat blood malignancies and cases of bone marrow failure. Objective. To examine the effect of aerobic exercises on functional capacity and interleukin-6 levels on patients post allogeneic hematopoietic stem cell transplantation (HSCT). Design. A quasi-experimental, randomized, single-blind design. Setting. Nasser Institute's out-patient clinic for bone marrow transplant and Belqas central hospital. Methods. Forty women having chronic Graft versus Host Disease post hemopoietic stem cell allotransplant, with an age range of 20 to 30 years and body mass index between 18.5 and 24.9 kg/m^2, were randomly designated into two equal groups (n = 20) (A and B). The study group (A) participated in a supervised aerobic exercise program of moderate intensity, with a score of 12-14 on the Borg scale for perceived exertion, together with a specific medication routine, whereas the control group (B) was only given their medication routine. The exercise program consisted of 40 minutes on the stationary bicycle, with a warm-up and a cool-down period of 5 minutes each and 30 minutes as an active phase, 3 times per week for 3 months Both functional capacity, measured by a 6-minute walk test (6 MWT), and interleukin-6 blood level were assessed before starting the aerobic training and medical routine and after 3 months of the intervention. Results. The analysis showed a significant increase (P < .001) in the distance walked and assessed by 6 MWT in the group (A) compared to the control group (B), while there is a decrease in interleukin- 6 levels in the group (A) than in the group (B) without a statistical significance (P = 0.52). Conclusion: Aerobic training can be beneficial in increasing functional capacity.

Key words:
stem cell transplantation, graft vs host disease, aerobic exercise, interleukin-6, six-minute walk test

Streszczenie

Wprowadzenie. Transplantacja hematopoetycznych komórek macierzystych jest powszechnie stosowaną metodą lecznicza nowotworów krwi i przypadków niewydolności szpiku kostnego. Cel. Badanie wpływu ćwiczeń aerobowych na wydolność funkcjonalną i poziom interleukiny-6 u pacjentów po allogenicznym przeszczepie krwiotwórczych komórek macierzystych (HSCT). Projekt. Model quasi-eksperymentalny, randomizowany, z pojedynczą ślepą próbą. Miejsce. Przychodnia Nasser Institute zajmująca się przeszczepem szpiku kostnego i centralny szpital Belqas. Metody. Czterdzieści kobiet z przewlekłą chorobą przeszczep-przeciwko-gospodarzowi po allotransplantacji hematopoetycznych komórek macierzystych, w wieku od 20 do 30 lat i wskaźniku masy ciała od 18,5 do 24,9 kg/m^2, zostało losowo przydzielonych do dwóch równych grup (n = 20) (A i B). Grupa badana (A) uczestniczyła w nadzorowanym programie ćwiczeń aerobowych o umiarkowanej intensywności, z wynikiem 12-14 w skali Borga dla odczuwanego wysiłku, wraz z określonym schematem leczenia, podczas gdy grupa kontrolna (B) była poddawana tylko rutynowemu leczeniu. Program ćwiczeń obejmował 40 minut na rowerze stacjonarnym, z rozgrzewką i chłodzeniem trwającymi po 5 minut, oraz 30 minut fazy aktywnej, 3 razy w tygodniu przez 3 miesiące. Zarówno wydolność funkcjonalna, mierzona testem 6-minutowego marszu (6MWT), jak i poziom interleukiny-6 we krwi były oceniane przed rozpoczęciem treningu aerobowego i rutynowego leczenia oraz po 3 miesiącach interwencji. Wyniki. Analiza wykazała znaczny wzrost (P < 0,001) przebytej odległości i wyniku testu 6MWT w grupie (A) w porównaniu z grupą kontrolną (B). W grupie A nastąpił spadek poziomu interleukiny-6 większy niż w grupie (B), jednak nie był on statystycznie istotny (P = 0,52). Wniosek. Trening aerobowy może być korzystny w zwiększaniu wydolności funkcjonalnej.

Słowa kluczowe
przeszczep komórek macierzystych, choroba przeszczep-przeciwko-gospodarzowi, ćwiczenia aerobowe, interleukina-6, test 6-minutowego marszu

Introduction

Hematopoietic stem cell transplantation (HSCT) represents a recognized process that is greatly evolving for curing many congenital and acquired hematogenic malignancies, together with a variety of bone marrow diseases [1], with more than 60 thousand patients around the world are expected to, yearly, undergo a transplant, especially after establishing the banks of umbilical blood and bone marrow that managed the problem of limited donor's stem cells [2]. According to the source from where the stem cells are collected, the transplantation can be autologous, when using the patient's stem cells, allogeneic, when the collected stem cells are from a donor, or syngeneic when using stem cells from an identical twin [3].

The process of allogenic transplantation involves injecting hematopoietic stem cells from the donor into the patient's body to help rebuild its hemopoietic structure. That step is preceded by exposure to radiation and chemotherapy in large doses to destroy uncontrollably proliferating cells [2].

Receiving HSCT along with supportive treatment has caused a noticeable reduction in the patients' mortality rate as well as an increase in the survival rate by 50% [4,5]. Yet, that kind of treatment is highly demanding and has multiple undesirable effects, with the physical functioning impairment being the earliest effect [6,7]. That impairment could be primarily due to the malignancy itself, the extensive radiotherapy and chemotherapy, anemia, and medical therapy [6]. A commonly associated complaint is the severe levels of fatigue that can result from decreased oxygen consumption and hemoglobin saturation [2], while other side effects include cutaneous changes, breathing problems, gastrointestinal symptoms, anxiety, and dry mouth [8,9]

More importantly, post-HSCT allotransplant patients frequently develop graft-versus-host disease (GVHD), where the donor's cells attack the patient's systems, and thus adversely affecting multiple organs (e.g., gastrointestinal tract, skin, liver, etc.), finally impairing the patient's quality of life [10]. The chronic form of GVHD typically appears after more than 3 months post-transplantation [11], and generally manifests in the eyes, mouth, lungs, body joints, and impaired muscular function [12]. Generally, GVHD comprises a severe level of immune system dysregulation with persistent inflammation, with the interleukin-6 mediator is the most identifiable causative of its pathophysiology [13].

Physical exercises have been implemented in the rehabilitation programs of HSCT patients, in the pre-transplant phase, hospitalization phase, and after discharge, as they positively affect both physical and psychological recovery after transplant therapy and accelerate the patient's return to the baseline functional level [14]. One observed favorable effect of exercise is a higher quality of life achieved by the improvement in cardiorespiratory fitness, upper and lower limbs' strength, increased endurance, lowered levels of fatigue and distress, and better cognitive and emotional functioning [15-17]. So, HSCT allotransplant patients are encouraged to perform an individualized program of physical exercises that may include aerobic training, resistance exercises, relaxation techniques, and stretching [2].

Even with the recognized role of physical exercises in various phases of the HSCT allotransplant rehabilitation program, including several studies investigating the effect of different exercise forms, research is lacking regarding the exact effect of certain types of exercises on HSCT patients during rehabilitation phases, especially on the inflammatory mediators. Also, previous research has examined the impact of physical exercise on multiple proinflammatory cytokines, and it has been shown that regularly practiced moderate exercise could decrease the levels of interleukin 6, which is the mediator connected to weakness, functional deterioration, and predicted disability in HSCT population [18].

Nevertheless, the form to be used and the exact parameters needed to reduce interleukin –6 levels have not been yet established for those patients. Thus, this paper aims to investigate the effect of aerobic exercises, using treadmill and bicycle on the functional capacity and the levels of interleukin-6 levels on patients post HSCT allotransplant.

Materials and methods

Study design and ethical considerations

The study was conducted as an experimental single-blind randomized controlled trial. The study followed Helsinki guidelines for conducting medical research and it was approved by the Research Ethics Committee of Faculty of Physical Therapy, Cairo University, Egypt. Also, approval from both Nasser Institute and Belqas Central Hospital was obtained. The study lasted around a year, starting in January 2020 and ending in February 2021. Before starting, clarification of the procedures was made, then a signed consent was collected from each patient, assuring her about the confidentiality of her data and the right to withdraw at any time.

Participants

Forty-five female patients, who have undergone HSCT with chronic GVHD, aged 20-30 years were selected from Belqas central hospital and Nasser institute's outpatient clinic, as a convenience sample and were explored for eligibility criteria. Patients were recruited in the study when they were medically and clinically stable, could walk independently or with an assistive device, and when they had sufficient cognition to understand the instruction. Exclusion criteria were patients who had cardiopulmonary dysfunction, sensory, visual, or auditory defects, and patients with significant deformity or advanced radiological changes. Accordingly, five patients were excluded, and the rest of the patients were prepared for randomization, as seen in the participants' flow chart, Figure 1.

Randomization and blinding

Using SPSS computer software (SPSS Inc., Chicago, Illinois, USA, version 16), a table with randomized numbers was generated. Each patient owned a specific number that was assigned to one of two equal-numbered groups (n = 20). Serially numbered cards were put inside secured opaque envelopes and were opened by a blinded researcher who allocated each patient to her group. There were no dropouts after randomization.

Interventions

Forty women were randomly assigned into two equal groups. Group (A) (study group) consisted of 20 patients who received

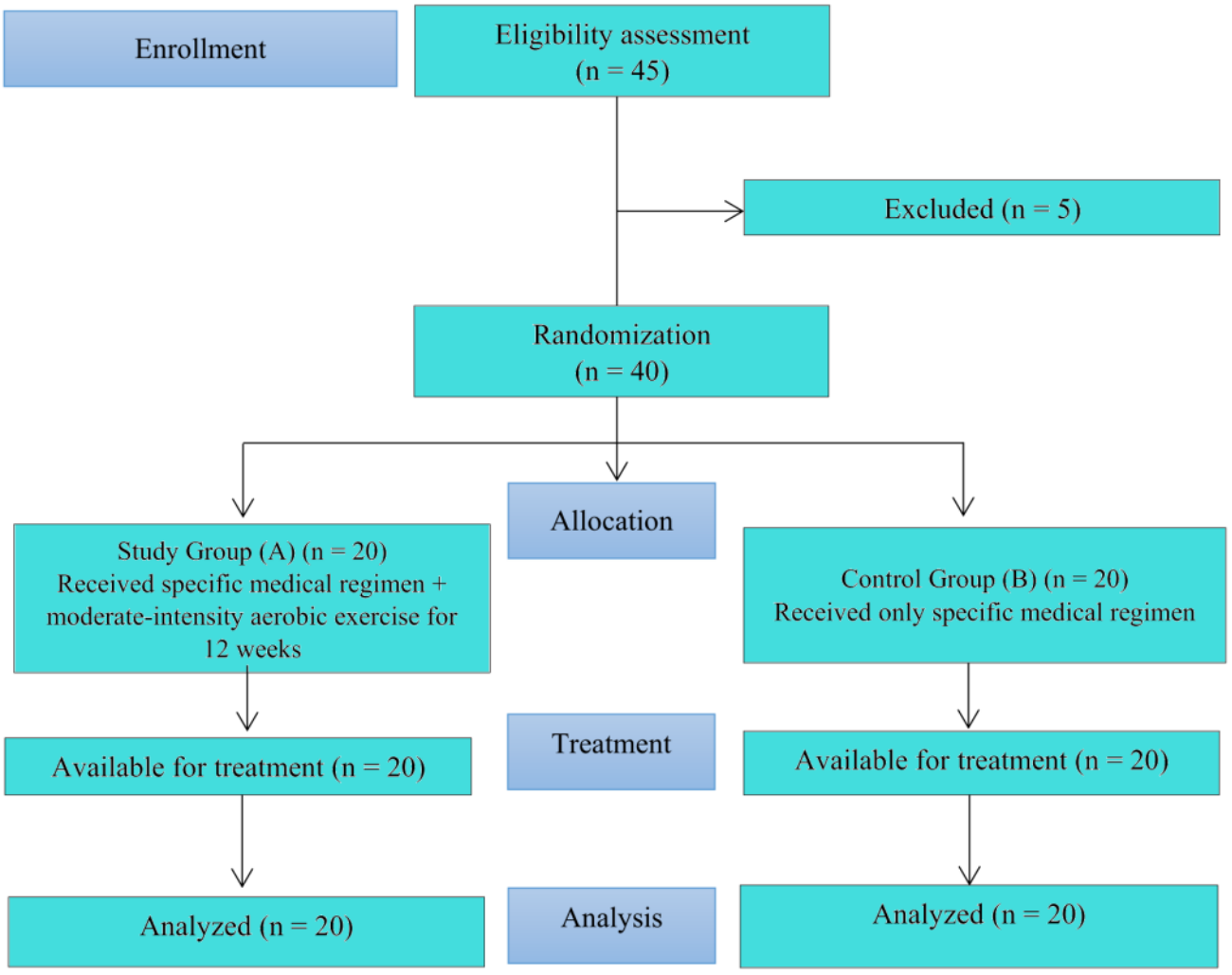

Figure 1. Flow chart of the study

their post-transplant medical routine consisting of immunosuppressants specially prescribed according to each patient's case and diagnosis [19] (Hayes) (corticosteroids, azathioprine, methotrexate, and mycophenolate) together with an aerobic exercise program of moderate intensity, three sessions a week for 12 weeks, whereas Group (B) (control group) consisted of 20 patients, who received only their post-transplant medical routine.

Regarding the aerobic exercise program for women in the group (A), each patient performed 40 minutes of moderate-intensity aerobic exercise 3 sessions/week for 12 weeks at the outpatient clinics of both Nasser Institute and Belqas central hospital. The exercise session was divided into an active phase of 30 minutes using a stationary bicycle preceded by 5 minutes warm-up period and followed by another 5 minutes as a cool-down phase [20]. The exercise intensity was described using the Borg scale, which is commonly utilized to measure the perceived level of exertion throughout physical activity especially exercise testing [21]. Moderate intensity was determined by a score between 12–14 on the Borg scale [22].

Using the stationary bicycle ergometer (Schwinn 270 Recumbent Bike), each patient in the study group sat with each foot resting on the pedals, then she was asked to begin pedaling continuously for 5 minutes in a forward direction with a mild velocity at a baseline speed as a warm-up, then speed was gradually increased through the active phase of exercise for 30 minutes. After that, a cool-down phase was achieved by pedaling again at the baseline speed for the last 5 minutes of the session [20].

Before starting the exercise session, the patient was given important instructions about wearing comfortable clothing and not exercising within 2 hours of the training session. Exercise sessions were performed at nearly the same time to control the effect of time variability and the patient was checked for any exercise contraindications and had her vital signs evaluated just before starting each session.

Outcome measures

The primary outcome for this study was the improvement in functional capacity, measured by the distance walked in the 6-minute walk test (6MWT), while the secondary outcome was the serum level of interleukin-6. The 6MWT was carried out under the supervision of a skilled blinded researcher before starting the study interventions and after 3 months from the study. The blood samples drawn from each patient were obtained by a trained specialist before and after 3 months from the intervention.

Six-minute walk test (6 MWT)

This test was used to evaluate functional capacity for HSCT patients before and after the end of the intervention. The 6MWT represents an alternative to cardiopulmonary exercise testing as it is a simple way to assess the performance and functional state, especially in patients having advanced diseases [23] Moreover, that test is recommended to be performed in many cases pre and post medical interventions to assess patient's response, also to direct cardiac rehabilitation [24]. It is valid and highly reliable (ICC = 0.90, P < 0.0001). It also has moderate-to-good relationships with the peak exercise capacity, making it a strong clinical tool in measuring functional capacity [25].

On a hard, even-surfaced corridor, 30 meters in length, and before starting the 6MWT, the patient was instructed about the test procedures, wearing comfortable clothing, and taking her medications. The patient was asked to walk at a pace that is suitable to her current condition using an assistive device, if she uses any, for 6 minutes and she was permitted to stop or slow down whenever she felt like and continue to walk as soon as possible, knowing that it would be calculated from the time of the test. Once the patient has understood the instructions, she had her vital signs checked (oxygen saturation at baseline, heart rate, and blood pressure), together with recording the Borg scale score for fatigue and dyspnea, to rule out the test contraindications. A mark was put every 3 meters on the walking passage, with cones placed in the U-turns. The patient began the test by walking along the passage for 6 minutes, determined using a stopwatch, during which the supervisor was giving the patient some encouraging phrases. After the time had elapsed, the laps' number was recorded, and the added distance walked was calculated and recorded. Finally, the supervisor recorded the post-test scoring for dyspnea and fatigue on the Borg scale [26, 27]

Serum interleukin-6 level

A blood sample was drawn from each patient to detect interleukin-6 level in the blood, thus evaluating the effect of the intervention on inflammatory mediators that causes, in part, GVHD. The serum samples obtained were stored at -80°C and were analyzed using a high-sensitivity ELSA (Quantikine IL-6, R&D Systems, Oxford, UK), with the same procedure previously described by Blüher et al. [28].

Statistical analysis

Statistical analysis was carried out using SPSS statistical computer software for (Windows version 25, Chicago, IL). Data were tested for normality assumption and homogeneity of variance across groups, using Shapiro-Wilk and Levene's test, respectively. The test findings allowed for parametric analysis as data was normally distributed, with continuous data reported as mean and standard deviation. Chi-squared or Fisher exact test was used to compare baseline diagnoses, conditioning regimens, organ involvement, and treatment of chronic GVHD, while Student's t-test was performed to compare interleukin-6 levels and 6 MWT results within groups (paired t-test) and between the two groups (unpaired t-test), and analysis of covariance (ANCOVA) was performed to test the effect of aerobic exercise on interleukin-6 levels and distance walked in meters in the 6 MWT. Results with a probability value of less than 0.05 ($P \leq 0.05$) was considered statistically significant.

Results

Regarding baseline characteristics, the mean age of participants was 25.3 years, their mean BMI was 23.0 kg/m2. Forty percent of patients were diagnosed with acute myelogenous leukemia and 45% of patients received a busulfan-based conditioning regimen, as shown in Table 1.

Table 1. Baseline characteristics of patients

	Control (N = 20)	Exercise (N = 20)	Total (N = 40)	P
Age [years], mean (SD)	25.4 (2.7)	25.1 (3.0)	25.3 (2.9)	0.745
BMI [kg/m²], mean (SD)	23.2 (1.2)	22.9 (1.5)	23.0 (1.4)	0.441
Diagnosis [n (%)]:				0.862
ALL	2 (10.0%)	3 (15.0%)	5 (12.5%)	
AML	9 (45.0%)	7 (35.0%)	16 (40.0%)	
CML	5 (25.0%)	5 (25.0%)	10 (25.0%)	
MDS	3 (15.0%)	2 (10.0%)	5 (12.5%)	
SAA	1 (5.0%)	3 (15.0%)	4 (10.0%)	
Conditioning [n (%)]:				0.782
BU/CY	8 (40.0%)	10 (50.0%)	18 (45.0%)	
FLU/CY	5 (25.0%)	3 (15.0%)	8 (20.0%)	
TBI/CY	7 (35.0%)	7 (35.0%)	14 (35.0%)	

ALL: Acute lymphoblastic leukemia, AML: ALL: Acute myeloid leukemia, BMI: Body-Mass index, Bu: Busulfan, CML: Chronic myeloid Leukemia, CY: Cyclophosphamide, FLU: Fludarabine, MDS: Myelodysplastic syndrome, SAA: Severe aplastic anemia, TBI: Total body irradiation.

As indicated in Table 2, chronic GVHD was manifested in the liver in 42.5% of patients, in the lungs in 25%, and involved eyes in 10% of patients, while all patients had skin manifestations. All patients received corticosteroids either alone or in combination with methotrexate (32.5% of patients), mycophenolate (30% of patients), and/or azathioprine (25% of patients) (Table 2).

Table 2. Chronic GVHD treatment and the organs involved

	Control (N = 20)	Exercise (N = 20)	Total (N = 40)	P
Organ involved [n (%)]:				
Liver	7 (35.0%)	10 (50.0%)	17 (42.5%)	0.337
Lung	6 (30.0%)	4 (20.0%)	10 (25.0%)	0.716
Eyes	1 (5.0%)	3 (15.0%)	4 (10.0%)	0.605
Skin	20 (100%)	20 (100%)	40 (100%)	
Treatment [n (%)]:				
Methotrexate	4 (20.0%)	9 (45.0%)	13 (32.5%)	0.176
Mycophenolate	6 (30.0%)	6 (30.0%)	12 (30.0%)	1.000
Azathioprine	5 (25.0%)	5 (25.0%)	10 (25.0%)	1.000

GVHD: graft-versus-host-disease

Similarly, there was no significant difference detected in neither 6 MWT results nor blood levels of interleukin-6 l among groups at baseline (Table 3).

Table 3. Baseline 6 MWT distance, and interleukin-6 levels

	Control (N = 20) Mean (SD)	Exercise (N = 20) Mean (SD)	Total (N = 40) Mean (SD)	P
Baseline Il-6	32.4 (20.0)	32.1 (16.3)	32.3 (18.0)	0.962
Baseline 6-MWT	271.6 (21.4)	266.6 (18.5)	269.1 (19.9)	0.439

6 MWT: 6-minute walk test, Il-6: Interleukin 6

On comparing both groups, the distance covered during 6 MWT was significantly higher in the exercise group than the control group with 317.2 meters and 272.8 meters, respectively ($P < 0.001$). However, mean values of interleukin-6 levels were lower in the exercise group than the control group (34.3 pg/ml vs. 30.5 pg/ml), but the difference did not reach a statistically significant level ($P = 0.521$) (Table 4).

Table 4. Mean values of 6 MWT and interleukin-6 levels among groups at end of the study

	Control (N = 20) Mean (SD)	Exercise (N = 20) Mean (SD)	Total (N = 40) Mean (SD)	P
Post-study IL-6 levels	34.3 (20.2)	30.5 (16.9)	32.4 (18.5)	0.521
Post-study 6 MWT	272.8 (21.8)	317.2 (19.5)	295.0 (30.4)	< 0.001

6 MWT: 6-minute walk test, Il-6: Interleukin 6

Within groups, on comparing pre to post-intervention mean results, exercise had a significant impact on post-study interleukin-6 levels ($F = 10.07$, $P = 0.003$) (Table 5). While adjusting for baseline interleukin-6 levels, exercise marginally decreased interleukin-6 levels on average by 3.53 pg/ml (95% CI: 5.79 – 1.28, $P = 0.003$) (Table 6, Figure 2).

Table 5. ANCOVA table showing the correlation between exercise and interleukin-6 levels while adjusting for baseline interleukin-6 values

	Df	Sum of Squares	Mean Squares	F	P
Baseline Il-6	1	12728	12728	1025.89	< 0.001
Exercise	1	125	125	10.07	0.003
Residuals	37	459	12		

Table 6. Marginal effects of exercise on post study interleukin-6 levels

Predictors	Estimates	95% CI	P
(Intercept)	1.79	−0.81 – 4.40	0.171
Marginal baseline IL-6 effect:	1.00	0.94 – 1.07	< 0.001
Marginal exercise effect:	−3.53	−5.79 – −1.28	0.003
R^2 / R^2 adjusted	*0.966 / 0.964*		

Il-6: Interleukin 6

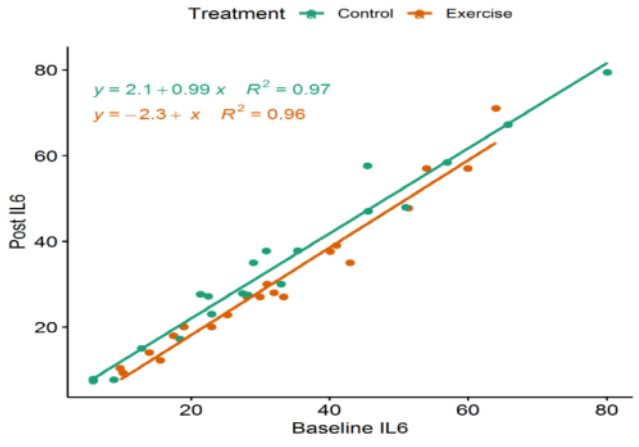

Figure 2. The marginal impact of aerobic exercise on post-study interleukin-6 (Il-6) levels

Regarding 6 MWT post-study results, exercise also had a significant impact (F = 299.6, P < 0.001) (Table 7). While adjusting for baseline 6 MWT results, exercise marginally increased the distance walked in the post-study 6 MWT results by an average of 49.04 meters (95% CI: 43.29 – 54.78, P < 0.001) (Table 8, Figure 3).

Table 7. ANCOVA table showing the correlation between exercise and post-study 6 MWT values while adjusting for baseline 6 MWT results interleukin-6 values

	Df	Sum of Squares	Mean Squares	F	P
Baseline 6 MWT	1	9371	9371	118.6	< 0.001
Exercise	1	23663	23663	299.6	< 0.001
Residuals	37	2923	79		

Table 6. Marginal effects of exercise on post study interleukin-6 levels

Predictors	Estimates	95% CI	P
(Intercept)	18.48	−21.41 – 58.37	0.354
Marginal baseline IL-6 effect:	0.94	0.79 – 1.08	< 0.001
Marginal exercise effect:	49.04	43.29 – 54.78	< 0.001
R^2 / R^2 adjusted	*0.919 / 0.914*		

6 MWT: 6-minute walk test

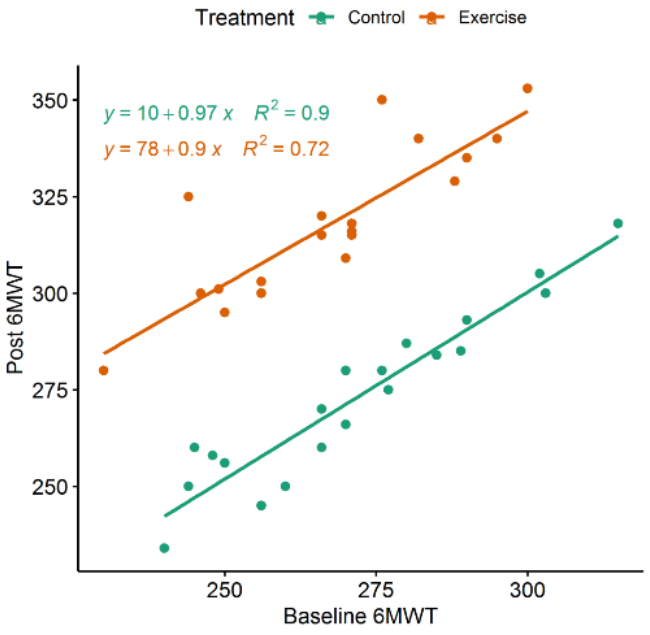

Figure 3. The marginal impact of aerobic exercise on post-study 6 MWT

Discussion

This study aimed to explore the effect of an aerobic exercise program on functional capacity and the level of serum interleukin-6 in patients, who have undergone allogeneic HSCT. The study findings indicated that performing a moderate intensity supervised aerobic exercise for 40 minutes 3 times/week for 3 months, using a stationary bicycle could significantly increase functional capacity, evidenced by the increased distance covered in the 6 MWT, and cause lowering in interleukin 6.

In the present study, 6 MWT was used as the evaluative tool for functional capacity, as it is a well-recognized method that can substitute performing cardiopulmonary exercise testing with accepted validity and reliability [23, 25]. For assessing the impact of the exercise on inflammatory mediators, a certain cytokine was chosen for evaluation (i.e., interleukin 6), as it is an inflammatory mediator greatly contributing to the GVHD pathology, involved in both acute and chronic inflammatory processes, and can largely predict future disability in patients undergoing HSCT [18].

Stationary bicycle as the form of applying aerobic exercise program was chosen, owing to its easiness in use, its availability in most of the physical therapy outpatient clinics as well as being appropriate for study purpose, as previously reported by multiple studies [16, 20].

Results showed that there was a statistically significant improvement in the 6 MWT results of the study group (A) on comparing pre and post-study mean values, also, there is a statistically significant increase in the functional capacity, presented by increased distance walked by patients, in the group (A) than in the control group (B).

These findings could be explained by the well-known effect of regular exercise on cardiovascular aspects. It was proven that engaging in physical exercise is strongly linked to a lowered cardiovascular mortality rate. Also, physically active persons were found to have lower blood pressures, a higher degree of insulin sensitivity, with an enhanced lipid profile than sedentary-life individuals [29].

Similar to these results, Yildiz Kabak et al. [30] investigated the effects of a supervised exercise program, done at discharge and continued till 3 months after, on multiple physical and psychological components of pediatric post-HSCT and found that a home exercise program could lead to an improvement in functional capacity, indicated by an increase in the distance walked during 6 MWT, together with increased muscular strength, decreased fatigue, enhanced emotional state, and a better overall quality of life, after 3 months of following the exercise program.

Moreover, Knols et al. [31] studied the effectiveness of 12 weeks of an outpatient supervised physical exercise program, including aerobic and strengthening exercises for patients post allogeneic HSCT, and found that there was an improvement regarding physical performance after the intervention. However, other variables (e.g., body composition, fatigue, daily living activities) showed no improvement.

The present study results also demonstrated a decline in the levels of interleukin 6 levels after 3 months of exercise. That finding can be explained by immunoregulatory and immuno-protective impacts of physical exercise in general that are exerted through keeping a balanced state between pro-inflammatory and anti-inflammatory cytokines. Additionally, regular exercising can modulate cytokines, especially interleukin 6, by reducing its initial levels, in a process called the anti-inflammatory reaction to physical effort [32, 33].

These findings were congruent with those from a study conducted by Steensberg et al. [34], who stated a negative correlation between the amount of physical activity practiced regularly and the basal resting serum levels of interleukin 6. Conversely, higher interleukin 6 levels were directly linked to physical inactivity. Moreover, training causes a downregulation to interleukin 6 basal levels, but at the same time, it causes an upregulation to interleukin 6 receptor, leading to increased in-

terleukin 6 sensitivity. According to the current data, few studies tried to explore the effect of aerobic exercise on certain cytokines and, this is the first to investigate that effect in patients after allogeneic HSCT. So, this study provides important findings with many points of strength in it. First, the sample chosen was only females, who have undergone a certain type of HSCT transplant (i.e., allogeneic type). That made the study better controlled regarding external factors that might affect the study results. The second thing is that the patients were randomized with blinding of the assessors to ensure less bias in the study. Also, the study employed objective tools in the assessment of the outcomes making the results more reliable.

Though, there are some limitations to the study. The medical routine was inevitably variable according to each patient's case. That variability could affect the patient's response to the exercise intervention and her measured values. Additionally, there is a lack of a follow-up period that might be necessary to monitor the long-term effects of the intervention.

Conclusion

Based on the results from the present study, it could be concluded that moderate-intensity aerobic exercises done for 3 months can positively affect functional capacity and interleukin 6 serum levels in patients post allogeneic HSCT.

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