

Influence of Personalized Exercise Recommendations During Rehabilitation on the Sustainability of Objectively Measured Physical Activity Levels, Fatigue, and Fatigue-Related Biomarkers in Patients With Breast Cancer

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Abstract

Purpose. Only one-third of patients with breast cancer reach the recommended activity level of 15 to 25 MET h/wk. The aim of this study was to determine the influence of personalized exercise recommendations during rehabilitation on patients' physical activity level, fatigue, and self-perceived cognitive function as well as on side effect-associated biomarkers. **Methods.** Total metabolic rate, physical activity level, mean MET and steps, fatigue, self-perceived cognitive functioning, and biomarkers (C-reactive protein [CRP], interleukin 6, macrophage migration inhibiting factor [MIF], tumor necrosis factor [TNF]- α , brain-derived neurotrophic factor [BDNF], insulin-like growth factor I [IGF1]) were assessed in 60 patients with breast cancer in the aftercare phase before (t_0) and 8 months after (t_1) the intervention. The rehabilitation program consisted of an initial 3-week period and a 1-week stay after 4 months. **Results.** Paired *t*-test indicated a statistically significant increase in all activity outcomes from t_0 to t_1 . Patients' mean activity level significantly increased from 14.89 to 17.88 MET h/wk. Fatigue and self-perceived cognitive functioning significantly improved from t_0 to t_1 . CRP levels significantly decreased, and BDNF as well as IGF1 levels significantly increased over time. Correlation analysis revealed statistically significant negative associations between fatigue, physical activity, and markers of inflammation (TNF- α and MIF). Furthermore, significant positive correlations between subjective cognitive functioning and all dimensions of fatigue were observed. **Conclusions.** The results support the importance of personalized exercise recommendations to increase physical activity levels in patients with breast cancer. Furthermore, the results highlight an association between physical activity, fatigue, and inflammation.

Keywords

cancer, rehabilitation, exercise, physical activity, fatigue, cognition, inflammation, cytokines, personalized exercise recommendations

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Introduction

Increased physical activity levels are associated with reduced breast cancer risk and mortality.¹⁻³ Furthermore, specific endurance and resistance exercise programs have the potential to reduce disease- and treatment-specific side effects such as fatigue⁴ and lymphedema,⁵ which can severely affect patients' quality of life.⁶ Nevertheless, only 32% of breast cancer patients reach the recommended physical activity level of 15 to 25 MET h/wk.⁷ Therefore, it has become a major issue to maintain, recover, or even increase the physical constitution of breast cancer patients during aftercare.

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Through the anti-inflammatory properties of regular physical exercise, it has been suggested to positively influence survival rates and fatigue.⁸ A reduction in fat mass, an increase in anti-inflammatory regulatory T-cells, and the release of anti-inflammatory cytokines are suspected to be involved in the downregulation of systemic inflammation through exercise.⁹ Increased low-grade inflammation is a major risk factor for metabolic and cardiovascular diseases (eg, diabetes, arteriosclerosis), neurodegenerative disorders (eg, Alzheimer, Parkinson) as well as neoplastic diseases including breast cancer.¹⁰ Additionally, elevated serum levels of inflammation markers (eg, macrophage migration inhibiting factor [MIF], interleukin [IL]-6, tumor-necrosis-factor- α , and C-reactive protein [CRP]) have prognostic properties and have further been observed in patients with cancer suffering from fatigue and cancer-related cognitive impairments (CRCIs).¹¹ Besides its anti-inflammatory role, regular physical exercise has been described to have beneficial structural and functional effects on the central nervous system (CNS).¹²⁻¹⁶ Neurotrophic and neuroprotective factors, such as the brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF1) have been suspected to be potential mediators of at least some of the named positive effects of exercise on the CNS in both healthy subjects and various clinical populations.^{17,18} In detail, BDNF and IGF-1 stimulate neurogenesis in specific brain regions, for example, the hippocampus,¹⁹ which plays an important role in view of specific cognitive functions, such as memory and task flexibility.¹⁴ Moreover, these cognitive domains have been described to be impaired in cancer patients in the context of CRCI.¹⁴

Although several studies have shown that exercise interventions are a promising supportive therapy to counteract fatigue, little is known about the sustainability.⁴ Usually, rehabilitation programs for patients with cancer in Germany last 3 to 6 consecutive weeks and comprise nonstandardized and nonpersonalized exercise programs and recommendations (eg, aerobic, resistance, and balance training) according to local rehabilitation center standards.

The aim of this longitudinal subgroup analysis (n = 60) of the Kissinger Individualized Rehabilitation and Activity (KIRA) trial²⁰ was to investigate the influence of personalized exercise recommendations, which were given during stationary rehabilitation, on long-term effects on patients' objectively measured physical activity, fatigue, and CRCI as well as on fatigue-related and CRCI-related biomarkers (inflammation markers: CRP, tumor necrosis factor [TNF]- α , IL-6, MIF; neurotrophic factors: IGF-1, BDNF). Moreover, we were interested in potential relationships between biomarkers and fatigue.

Table 1. Participants' Characteristics of Baseline (t_0) Data.^a

Overall Sample (n = 60)		
Age (years)	54.30 \pm 8.51	
Height (cm)	162.47 \pm 7.13	
Body mass (kg)	70.85 \pm 12.89	
BMI (kg/m ²)	26.79 \pm 4.26	
Time since diagnosis (months)	9.87 \pm 6.41	
Received chemotherapy: yes (%) / no (%)	yes: 26 (43)	no: 34 (57)
Chemotherapy duration (months)	3.68 \pm 1.41	
Received antihormone therapy: yes (%) / no (%)	yes: 44 (73)	no: 16 (27)
Radiotherapy (%)	87 \pm 0.34	
Radiotherapy duration (months)	1.55 \pm 0.6	
Menopause: yes (%) / no (%)	yes: 39 (64)	no: 14 (23)

Abbreviation: BMI, body mass index.

^aValues are expressed as mean \pm SD.

Methods

Compliance With Ethical Standards

The study protocol was approved by the ethics committee of the German Sports University, Cologne, and is in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation. Patients were recruited in the rehabilitation clinic, Klinik am Kurpark, Reha Zentren DRV-BW, in Bad Kissingen.

Inclusion and Exclusion Criteria

For inclusion in the study, participants had to meet the following criteria: primary diagnosis of breast cancer within the last 2 years; age, 18 to 70 years; no acute internal or psychological diseases that prohibit participation in an exercise program (heart attack, stroke, pulmonary embolism, depression, psychosis, etc); and no chronic diseases of the musculoskeletal system, secondary neoplastic disease, metastasis, or drug addiction.

Out of the 194 patients with breast cancer who participated in the KIRA trial, funding was sufficient to include 60 patients for this subgroup analysis. Participants' characteristics (anthropometric data, therapy, etc) are listed in Table 1.

Procedure

After recruitment in the beginning of their initial 3-week stationary rehabilitation period, study participants were interviewed by an exercise therapist to review potential contraindications, physical activity behavior, exercise preferences, and exercise opportunities near their living place.

Based on the participants' individual preferences (exercise modality), aims, and opportunities (exercise opportunities at home: sport-clubs, fitness-center, rehabilitation-groups), personalized exercise recommendations were designed. Thus, personalized exercise recommendations differed between patients in terms of exercise type, intensity, frequency, and duration. However, the common aim of all exercise recommendations was to increase physical activity and not specific aspects of physical capacity/fitness (eg, strength or aerobic capacity). During the initial 3-week rehabilitation stay, participants were supervised in these personalized exercise recommendations. The extent of participants' physical activity during the 3 weeks was supposed to be at least 9 MET h/wk, with a planned further increase up to 15 MET h/wk in the following weeks. In contrast to other rehabilitation programs, consisting of a single rehabilitation stay of 3 to 6 weeks, study participants returned to the clinic for 1-week stays 4 and 8 months after the initial 3-week period to modify their exercise recommendations and receive further psychoeducational support. Additionally, participants received social support by 1 telephone call, which was conducted 1 month after discharge of the initial 3-week rehabilitation stay. For this analysis, data were collected in the beginning of the initial 3-week rehabilitation period (t_0) as well as 8 months after completing it (t_1).

Aims and Methods

The primary aim of this study was to determine the influence of personalized exercise recommendations (respecting patients' preferences and socioeconomic resources) during rehabilitation on patients' physical activity, objectively measured via the SenseWear Armband Pro₃ (BodyMedia Inc, Pittsburgh, PA). The SenseWear Armband Pro₃ is an objective multisensory (accelerometer, heat flux-sensor, galvanic skin response sensor, skin temperature sensor, and a near-body ambient temperature sensor) monitor for activities of daily living. It has been shown to be valid when compared with indirect calorimetry in patients with cancer (underestimation of daily energy expenditure by 9%, $r = 0.68$; $P < .01$) and doubly labeled water in healthy adults (underestimation of daily energy expenditure by 5%, $r = 0.81$; $P < .01$).^{21,22}

Secondary aims were to analyze fatigue using the well-established Multidimensional Fatigue Inventory-20 (MFI-20).²³ This instrument indicates a good to excellent internal consistency (Cronbach α ranging from .79 to .93), and its validity has been shown in comparison to visual analogue scales measuring fatigue.²⁴ In addition, we included the "cognitive function" subscale of the EORTC QLQ-C30 questionnaire (Cronbach $\alpha = .56$) to control for a potential association between neurotrophic factors (BDNF, IGF1) and self-perceived cognitive functioning as well as fatigue.^{25,26}

Furthermore, fatigue-related biomarkers were measured. Inflammation markers, TNF- α , IL-6, and MIF, as well as the neuroprotective/neurotrophic factors, IGF1 and BDNF, were assessed by enzyme linked immunosorbent assay (ELISA). Blood samples were drawn at t_0 and t_1 , and serum was frozen at -70°C . All samples were analyzed by repeated determination after cessation of the study according to manufacturers' instructions (IGF-1, TNF- α , MIF, and BDNF: Ray Bio Human ELISA Kit, RayBiotech Inc, Atlanta, USA; IL-6: Human Quantikine ELISA Kit, R&D Systems, Wiesbaden-Nordenstadt, Germany; ELISA-Reader: Multiscan FC, Thermo Scientific, Massachusetts, USA). Additionally CRP levels were measured (Roche Diagnostics Deutschland GmbH, Mannheim, Germany).

Statistics

Descriptive analysis was performed for participant characteristics (age, BMI, therapy, etc) at baseline ($n = 60$). To determine potential statistical significance of alterations from t_0 to t_1 at all end points in the overall sample, separate paired t -tests were performed (normality of data was assumed from the central limit theorem).²⁷ Cohen's d effect sizes were additionally calculated for each outcome (small to moderate: 0.2-0.5; moderate to large: 0.51-0.8; and large: >0.81).^{28,29} Finally, exploratory Pearson correlation analysis was conducted to look for potential associations of participants' activity levels, fatigue, and biomarkers. For all inferential statistical analyses, significance was defined as a P value less than .05. Two-tailed probability tests were used throughout all inferential statistical testing. All descriptive and inferential statistical analyses were conducted using SPSS 22 (IBM, Armonk, NY).

Results

Participants' baseline characteristics are shown in Table 1. Descriptive data and paired t -test results (P values, effect sizes) for all outcomes are listed in Table 2. A significant increase from t_0 to t_1 was detected for overall energy expenditure, active energy expenditure, steps, and average MET values. In terms of fatigue, patients scored significantly lower at t_1 compared with t_0 on MFI subscales "general fatigue", "physical fatigue," and "reduced activity" whereas no significant changes were detected for "reduced motivation" and "mental fatigue." The inflammation marker CRP decreased significantly while IL-6, TNF- α , and MIF alterations from t_0 to t_1 did not reach statistical significance. In terms of neurotrophic agents, IGF-1 as well as BDNF increased significantly from t_0 to t_1 .

A cross-table illustrating the results of the correlation analysis is attached as supplement (available at <http://ict.sagepub.com/supplemental>). At baseline (t_0), correlation analyses revealed a significant negative association between

Table 2. Results of Paired *t*-Test of Participants' Physical Activity Behavior, Biomarker Levels, and Patient-Reported Outcomes at t_0 and t_1 .^a

Overall Sample (n = 60)				
	t_0	t_1	P Values	Effect Size
Physical activity data				
TMR (kcal/d)	2429.57 ± 382.51	2537.52 ± 405.31	.009 ^b	0.273
Active MET h/wk	14.89 ± 7.67	17.88 ± 8.32	.001 ^b	0.372
Steps	16739.47 ± 6630.47	20286.05 ± 6903.43	.000 ^b	0.524
Mean MET/d	1.52 ± 0.30	1.60 ± 0.30	.005 ^b	0.283
Biomarkers				
CRP (mg/dL)	0.24 ± 0.35	0.16 ± 0.23	.032 ^b	0.23
TNF- α (pg/mL)	3.47 ± 1.21	3.48 ± 1.18	.967	0.006
IL-6 (pg/mL)	0.60 ± 1.18	1.13 ± 4.73	.401	0.154
MIF (ng/mL)	32.54 ± 21.86	30.48 ± 14.32	.411	0.107
BDNF (ng/mL)	129.08 ± 38.86	154.29 ± 47.46	.000 ^b	0.579
IGF-1 (ng/mL)	102.74 ± 38.11	113.20 ± 35.47	.011 ^b	0.284
Patient-reported outcomes				
sCF	64.73 ± 31.90	73.06 ± 27.29	.017 ^b	0.278
MFI-GF	12.77 ± 3.37	10.93 ± 3.23	.000 ^b	0.555
MFI-PF	11.40 ± 2.75	9.75 ± 2.83	.000 ^b	0.592
MFI-RA	11.38 ± 3.11	9.78 ± 3.27	.002 ^b	0.501
MFI-RM	8.68 ± 2.92	9.42 ± 2.84	.068	0.254
MFI-MF	10.93 ± 3.50	10.20 ± 3.45	.096	0.211

Abbreviations: MET, metabolic equivalent of task; TMR, total metabolic rate; CRP, C-reactive protein; TNF, tumor necrosis factor; IL, interleukin; MIF, macrophage migration inhibiting factor; BDNF, brain-derived neurotrophic factor; IGF, insulin-like growth factor; sCF, self-perceived cognitive function; MFI, Multidimensional Fatigue Inventory; GF, general fatigue; PF, physical fatigue; RA, reduced activity; RM, reduced motivation; MF, mental fatigue.

^a t_0 : Baseline and beginning of rehabilitation; t_1 : 8 months after rehabilitation; effect size (Cohen's *d*); values are expressed as mean ± SD.

^bIndicates significant difference between groups at $P < .05$.

total metabolic rate as well as active MET h/wk and the inflammation marker TNF- α ($r = -0.271$, $P = .036$; $r = -0.272$, $P = .036$), indicating that increased physical activity levels are associated with decreased levels of inflammation marker TNF- α . Additionally, step counts were negatively correlated with the inflammation marker MIF. At t_1 , step counts were still negatively correlated with MIF levels ($r = -0.271$; $P = .036$).

Physical fatigue was negatively associated with the total metabolic rate ($r = -0.279$; $P = .031$) and the step counts ($r = -0.350$; $P = .006$) at t_0 . Furthermore, TNF- α showed a significant correlation with physical fatigue at baseline ($r = 0.286$; $P = .027$) and with global fatigue ($r = 0.346$; $P = .007$), reduced activity ($r = 0.497$, $P < .001$), reduced motivation ($r = 0.355$; $P = .005$), and mental fatigue ($r = 0.263$; $P = .042$) subscales at t_1 .

Self-perceived cognitive functioning indicated a negative correlation with CRP levels at t_1 ($r = -0.333$; $P = .009$). Finally, self-perceived cognitive function was negatively associated with all fatigue subscales at t_0 (global fatigue: $r = -0.296$, $P = .022$; physical fatigue: $r = -0.375$, $P = .003$; reduced activity: $r = -0.323$, $P = .003$; reduced motivation: $r = -0.359$, $P = .005$; mental fatigue: $r = -0.687$, $P < .001$) as well as with reduced activity ($r = -0.291$, $P = .024$),

reduced motivation ($r = -0.417$; $P = .001$), and mental fatigue ($r = -0.443$; $P < .001$) subscales at t_1 .

Discussion

The results of this study indicate that physical activity, measured by an objective assessment, can be significantly increased within the following 8 months after personalized exercise recommendations are given. Regarding the primary aim of the study, it was shown that patients' physical activity increased and reached the recommended 15 to 25 MET h/wk (increase from 14.89 to 17.88 MET h/wk).⁷ Overall, physical activity data (Table 2) suggest small to moderate effects (Cohen's $d = 0.27$ - 0.37), with the exception of step counts, with moderate to large effects (Cohen's $d = 0.52$). Because of the lack of a control group, it is inappropriate to conclude from this subgroup analysis that the increase in physical activity is driven by the personalized exercise recommendations. However, previously published results of this study (including this subgroup) have shown that common less-personalized exercise recommendations did not significantly increase patients' physical activity in the long term.²¹ Nevertheless, results of many RCTs in the field of exercise and cancer suggest sustainable positive

effects of less “patient preferred” exercise interventions on cancer and treatment-specific side effects (eg, fatigue).⁴

The increase in physical activity is accompanied by a significant reduction in fatigue, self-perceived cognitive function, and the inflammation marker, CRP. Effect sizes indicate moderate to large effects (Cohen’s $d = 0.56-0.98$) on general fatigue and physical fatigue as well as small to moderate effects (Cohen’s $d = 0.50$) on reduced activity subscales of the MFI-20 questionnaire. These results underline those of many other investigations in this field.⁴ The decrease in CRP levels is not sufficient to state a “clinical relevance” (small effect size), in view of a manifest inflammatory environment. However, results may still be of importance because chronic low-grade inflammation has been frequently reported to be involved in fatigue and a decline in cognitive function.¹⁴ Furthermore, the results suggest that the neuroprotective/neurotrophic factors BDNF and IGF1 increased within the same period of time (t_0 to t_1). Although the clinical relevance of these changes is difficult to interpret, it is worth stating that patients with neurological disorders (eg, depression) show decreased BDNF serum levels. In patients suffering from depression, exercise has been proven to normalize BDNF concentrations.³⁰ These results support our findings indicating a medium effect on resting BDNF levels.

As mentioned above for patients’ physical activity levels, the study design does not allow concluding that changes in the investigated biomarkers are driven by an increase in physical activity. Nevertheless, the hypothesis that physical activity has anti-inflammatory properties is supported by the detected negative correlations between objectively measured physical activity parameters and TNF- α as well as MIF serum concentrations. Interestingly, higher fatigue levels are also negatively correlated with TNF- α and MIF levels, indicating an association and a potential mediating role of physical activity. These results support previous findings of Schmidt et al³¹ and others¹⁵ who reported a mediating effect of physical activity on fatigue through a reduction in inflammatory cytokines.

Although all assessed fatigue categories improved during this study, correlation analysis revealed that the “physical fatigue” and “reduced activity” subscales of the MFI20, especially, were positively associated with the activity level. Similar results were reported by numerous other studies.^{4,31,32}

Regarding the increase in BDNF and IGF1, our results are in line with those of many other studies indicating a positive association between physical activity levels and neurotrophic factors.^{18,33} Because animal models revealed that cancer itself is associated with decreased BDNF levels, increased inflammation, and a subsequently reduced hippocampal function, it cannot be ruled out that the concentration of these factors alters after medical treatment of cancer.³⁴ However, these factors were related to neither

self-perceived cognitive functioning nor to fatigue. Further studies should use more comprehensive questionnaires (eg, the FACT-Cog questionnaire³⁵) or even objective neuropsychological tools to measure CRCI in order to verify a potential relation. Fatigue in general and especially the “mental fatigue” subscale correlated with self-perceived cognitive function (correlation at t_0 and t_1). It remains speculative if these phenomena influence each other or if they have a certain overlap. Against this background, fatigue should be assessed when investigating CRCI and vice versa. The detected correlation of CRP and self-perceived cognitive functions supports previous findings reporting an association between CRCI and inflammation.³⁶

The results of this study should be seen within the context of its limitations. Because no control group was assessed in this subgroup analysis, it remains speculative if alterations in all outcomes were influenced by the personalized exercise recommendations. A time effect cannot be ruled out. Values for IL-6 were very low and partially below detection thresholds, revealing the importance of using highly sensitive ELISA kits in the future. Additionally, further studies should use more detailed measures of self-perceived cognitive functioning, such as the FACT-Cog questionnaire. Finally, most reported correlations seem to be weak. However, it should be kept in mind that reported correlations affect multifactorial processes, and therefore, strong association should not be expected

Conclusion

Personalized exercise recommendations during rehabilitation represent a promising tool to improve physical activity behavior and decrease fatigue levels in patients with breast cancer. Future studies might include CRCI as a potential confounder when investigating fatigue and vice versa. The reported associations between fatigue, inflammation markers, and physical activity underline the findings of previous studies and warrant further research.

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