ORIGINAL ARTICLE

Inflammation, cardiometabolic markers, and functional changes in men with prostate cancer

A randomized controlled trial of a 12-month exercise program

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KEY WORDS

cytokines, exercise rehabilitation, oncology, physiotherapy, radiation therapy

ABSTRACT

INTRODUCTION Previous studies have shown that physical exercise in cancer patients during radiation therapy (RT) and androgen deprivation therapy (ADT) improves cardiac fitness and quality of life (QoL), as well as reduces fatigue, but it is still not entirely known how it affects inflammation or metabolic factors and what its consequences are in patients with prostate cancer (PCa).

OBJECTIVES The aim of the study was to assess the effect of a 12-month physical exercise program on inflammatory and cardiometabolic parameters, as well as on functional status in patients with PCa undergoing RT and ADT.

PATIENTS AND METHODS This was a randomized controlled clinical trial including 72 men with high-risk and intermediate-risk PCa, allocated to 2 groups before RT. The physical exercise group trained 5 d/wk during RT and then 3 d/wk. The control group received usual care according to recommendations. Measurements were performed at baseline, after RT (8 weeks), and after 10 months. The parameters assessed were proinflammatory cytokine levels, lipid profile, aerobic capacity, body mass index (BMI), waist-to-hip ratio (WHR), and functional status (FACT-F and EORTC questionnaires).

RESULTS We observed an significant improvement in functional capacity, BMI, and WHR, and a decrease in the levels of proinflammatory cytokines and fatigue in the exercise group compared with controls after 12 months. The level of fatigue was significantly higher in controls than in the exercise group, especially after RT.

CONCLUSIONS Long-term supervised exercise training is more effective than educational materials on physical activity in terms of a decrease in cardiovascular risk and improvement in functional status in patients with PCa during RT and ADT.

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INTRODUCTION High-risk and intermediate-risk prostate cancer (PCa) is an aggressive form of the disease with an increased risk of distant metastases and subsequent mortality.[1,2] Multiple randomized trials established that the combination of radiation therapy (RT) and androgen deprivation therapy (ADT) improves overall survival in this group of patients.[2,3] Numerous studies indicated that decreased levels of testosterone during ADT may also negatively influence body structure, mental health, fatigue, and quality of life (QoL) in men with PCa.[4,5] ADT also leads to a number of adverse effects, including increased risk for cardiovascular and metabolic complications (eg, negative lipoprotein profile, abdominal obesity, and reduced insulin sensitivity).[6-9] Additionally, the risk of comorbidities among cancer survivors is higher compared with cancer-free adults. Therefore, improving cardiometabolic health is as important as monitoring cancer

recurrence.[10,11] It has been well documented that the incidence of cardiovascular events is significantly higher for individuals who smoke, have diabetes, hypertension, chronic pulmonary obstruction, high body mass index (BMI), high levels of triglycerides (TGs) and creatinine, and low levels of high-density lipoprotein (HDL) cholesterol. However, even among study participants without these traditional risk factors, elevated levels of inflammatory markers (interleukin [IL]-1β, IL-6, tumor necrosis factor α [TNF-α]) prove to be the best predictors for coronary heart disease and congestive heart failure.[12-14]

Physical exercise has been shown to be an effective, safe, and quite inexpensive method to reduce cardiovascular and metabolic risk factors, and it is currently being assessed with regard to its relevance for cancer-specific morbidity and mortality.[9,15] For example, exercise training has been shown to improve cardiorespiratory fitness, muscle strength, and some aspects of QoL in cancer patients.[16-18] Improving the QoL and psychological well-being of men with PCa through supportive care interventions such as exercise programs is a priority.[17-19] However, the long-term effect of exercise during ADT with RT in patients with high-grade PCa has been less extensively studied so far.[19,20] Given the lack of research into the implications of long-term regular physical exercise interventions for men with PCa during oncologic treatment, we adopted an exploratory approach to physical exercise as a potential predictor of changes in a range of cardiovascular risk factors and inflammatory marker levels as well as fatigue and QoL. Our hypothesis was that compared with physical activity recommendations (eg, perform 30 minutes of moderate/vigorous physical activity 5 d/wk),[21] a supervised exercise intervention would improve inflammatory and lipid status as well as cardiorespiratory capacity, reduce abdominal fat mass, and improve the levels of self-reported QoL and fatigue during 1 year of ADT with and after RT. Thus, we aimed to compare short- and long-term effects of a supervised exercise program in patients with PCa on inflammatory marker levels, cardiovascular risk factors, and functional status.

Outcome measure The primary outcomes were changes in inflammatory factors, abdominal obesity with lipid profiles, and aerobic capacity during 12 months. Secondary outcomes were changes in fatigue and QoL scores, caused by regular physical activity during oncologic treatment.

PATIENTS AND METHODS

Setting and participants This was an outpatient, regional clinical study conducted in the Greater Poland Cancer Centre, Poznań, Poland. Patients treated in the center came from the western region of Poland. Potential eligible participants were identified through a central screening of PCa patients for RT in this hospital. Patients were recruited from December 2012 to December 2014, according to the study criteria. Recruitment was conducted at urology and radiation oncology clinics. The enrollment criteria were as follows: histologically confirmed diagnosis of high-risk or intermediate-risk PCa,[22] ADT (LH-analogue, 10.8 mg every 3 months) scheduled for a total period of 36 months (3 to 5 months prior to RT, during and after completion), patients before RT (a total dose of 76 Gy in 38 fractions),[2,3] good general condition (in Eastern Cooperative Oncology Group, performance status 0–1), and minimum 18 years of age. We excluded patients with distant metastases and/or disease progression resulting in RT or the introduction of chemotherapy; with insufficiently controlled arterial hypertension or cardiac diseases resulting in circulation failure (heart failure above class II according to the New York Heart Association classification) or uncontrolled asthma; with insufficiently controlled metabolic diseases or endocrine, rheumatic, and absorption disorders, as well as other tumors; with preexisting bone metastases at high risk for fracture; or with a psychiatric illness or dementia or organic brain disease.

Design and procedures This was a 2-arm parallel randomized controlled trial. The study obtained ethics approval from the Poznan University of Medical Sciences (UMP No10/2012) and was registered at the ISRCTN Registry (Identifier ISRCTN80 765 858). After obtaining primary oncologist's approval, potential patients were approached by a research physiotherapist or nurse and provided written informed consent to participate in the study.

Randomization and blinding For allocating the participants, a computer-generated list of random numbers was used. Patients were randomly assigned to one of the study groups (exercise group vs usual-care [control] group) following simple randomization procedures. Concealed randomization was conducted using sequentially numbered opaque envelopes containing group assignments provided to participants following the baseline assessment.

All patients underwent a series of baseline assessments over 2 days, including completion of an on-study form and a clinical record form, and were subsequently randomized to the intervention condition consisting of RT and ADT plus an individually tailored exercise program. The analysis excluded data of patients who withdrew from the study before completing the 12-month period of the study or patients in the control group who performed regular physical activity.

This study was not fully blinded; however, group allocation was concealed from the patients and the physiatrist until after the completion of the baseline assessments. A clinical research coordinator obtained patient consent, collected all the self-reported assessments, and explained the exercise program to participants. Laboratory assistants, study statistician, and data managers remained blinded at all times.

Exercise intervention All exercise training sessions in the exercise group consisted of 5 exercise sessions/wk for 8 weeks (during RT—between assessments I and II), and 3 d/wk for the next 10 months. The physical activities were performed either individually (strength training performed with the assistance of a physiotherapist) or in groups (exercises on treadmills or cycle ergometers, supervised by a therapist) and took place at a rehabilitation department.

During RT, optional progressive exercise training included brisk walking, running indoors or on a treadmill, various cycling activities (30 min), and 25-minute resistance exercises (2 sets of 8 repetitions of 5 different exercises: bicep curl, triceps extension, leg extension, leg curl, and abdominal crunch) at 70% to 75% of their estimated one-repetition maximum.[23] All activities lasted approximately 65 to 70 minutes. The workout consisted of a 5-minute warm-up and 55 minutes of physical activity, followed by a 5-minute relaxation period. The physical activity was moderate, with a maximal heart rate of 65% to 70% (220-age).

After RT, the exercise group performed a very similar exercise program 3 times/wk (ie, 1 day of exercise and 1 day of rest), but 1.5 h/d in our department. Exercise sessions consisted of 5 minutes of light warm-up and stretching, 40 minutes of middle-impact aerobics, 35 minutes of resistance training, and a 10-minute cool-down including relaxation. The prescribed aerobic intensity was 70% to 80% of heart rate reserve.

Usual care Patients randomized to the control group received usual care and physical activity according to recommendations.[21] Clinicians provided medical clearance prior to the patients' involvement in the study. Patients in this group were given standard physical activity recommendations and were instructed via printed materials to perform 30 minutes of moderate physical activity 5 d/wk (150 min/wk). Patients randomized to this group were instructed not to begin any formal physical activities and perform usual daily activity at home.

We measured the intensity of physical activity at baseline in both groups, and during assessment II and at the end of the study in the control group, using the Godin Leisure-Time Exercise Questionnaire (GLTE).[24] Participants were asked to report their average weekly duration of light-, moderate-, and vigorous-intensity activity in a typical week in the past month.[24] They were asked if they regularly engaged in any physical activity during their leisure time. If the answer was positive, they were also asked to choose activities from a list of 20 activities and describe the frequency (times/wk) and the duration (minutes) for each of the activities chosen.[24] If the patient performed 3 of the 20 regular exercise or sports activities more than 3 times/wk and longer than 15 minutes, the data were not used for further analysis.

Our participants (in both groups) followed a normal, balanced diet (not restricted), which we monitored using the Mini Nutritional Assessment (MNA).[25]

Assessment scheme Participants underwent 3 outcome measure assessments: assessment I, at baseline (1 week before the onset of RT); assessment II, 1 week after the end of RT (after 8 weeks of the program in the exercise group); assessment III, final assessment after 10 months (12 months of the study time).

Measurements Demographic characteristics were age, education, and marital status. Clinical characteristics were cancer stage and comorbidities (eg, high blood pressure, heart disease, arthritis, diabetes, asthma/emphysema, pain). This information was collected through self-report.

Laboratory assays The levels of inflammatory markers were measured in the Immunology Department. Sera were stored at –80°C until the assay was performed. Serum levels of IL-1β, IL-6, and TNF-α were measured using the BD™ Cytometric Bead Array Enhanced Sensitivity Set system (BD Biosciences, San Diego, California, United States), according to the manufacturer's protocols. A standard curve was generated using known concentrations of the recombinant form of the human cytokine of interest. Samples were analyzed using a BD FACSCanto flow cytometer (BD Biosciences), and the results were calculated using FCAP Array™ Software Version 3 (BD Biosciences). The results were expressed in fg/ml. The detection limit of the assay for IL-1β was 48.4 fg/ml; for IL-6, 68.4 fg/ml; and for TNF-α, 67.3 fg/ml.

Venous blood samples collected to measure prostate-specific antigen were analyzed in EDTA with XT-2000i™ (Sysmex Corporation, Kobe, Japan). Biochemical markers (lipid profile: total cholesterol, HDL cholesterol, low-density lipoprotein cholesterol, TG, aspartate transaminase [AST], and alanine transaminase [ALT]) were measured using the Cobas 6000™ clinical chemistry analyzer (Roche, Mannheim, Germany).

Anthropometric parameters Anthropometric parameters included body weight, BMI (weight [kg]/height [m^2]), and waist-to-hip ratio (WHR; waist [cm]/hip [cm] circumference).

Aerobic capacity Functional capacity was estimated using the 6-minute walk test (6MWT) protocol, which is used in clinical exercise trials to estimate aerobic capacity in cancer patients.[26] The 6MWT was performed according to the American Thoracic Society guidelines.[27] It was followed by a short cool-down period conducted in a hospital corridor (30 meters). Secondary measures included dyspnea after the test using a modified Borg scale (0–10) and metabolic equivalents (METs). This test can be used as

a predictor of functional (distance) and objective (VO_{2max}) fitness.[28] Different studies have independently shown that both the 6MWT and aerobic fitness are predictive of morbidity and mortality, and equations relating the 6MWT to peak oxygen consumption (peak VO_2) have been recently developed for patients with cardiopulmonary disorders.[28,29] The MET was calculated as a result of evidence suggesting that 3.5 ml/kg/min does not accurately represent the resting metabolic rate of a general population, standardized METs = (VO_2/3.5 ml/kg/min) and measured METs = VO_2/pretest metabolic rate. The pretest metabolic rate was deduced as the mean VO_2 in the minute prior to commencing the test. Gas analysis (Oxycon Mobile, CareFusion, Germany) was then used.

Questionnaires The Functional Assessment of Cancer Therapy–Fatigue (FACT-F) scale was employed for a subjective assessment of fatigue in daily life of the patients. The FACT-F questionnaire (version 4) is used to assess 5 domains of life in chronically ill patients.[30] Cella et al[31] also developed a 13-item subscale for the FACT-F specifically to measure cancer-related fatigue. After accounting for reverse-scored items, the answers are summed across the subscales and added to provide a total score, with higher scores indicative of less fatigue. All responses are scaled with a 5-point Likert-type scale. The total score varies from 0 (worst condition) to 4 (best condition). In the present study, the Polish version of FACT-F (version 4), obtained from the supplier's website (www.facit.org/FACITOrg/Questionnaires) was used.

The QoL was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) questionnaires: QLQ-C30 version 3.0 and a specific module for prostate cancer—QLQ-PR25. QLQ-C30 is a self-administered questionnaire specifically designed for the evaluation of QoL in cancer patients during clinical trials, and QLQ-PR25 is a supplementary measure for PCa patients.[32,33] The EORTC approved the use of these questionnaires in this study.

Data analysis A priori, we calculated the sample size necessary to detect a significant, clinically important difference in outcome measures over time (group × time interaction effect, F statistic) between the exercise and control groups. The parameters of this calculation were as follows: α level of 0.05, power = 0.80, minimum 60 participants required because the sample size randomized to the exercise and control groups was 30 per each group.

Data analyses were conducted using the SPSS software (for Windows). Unless otherwise stated, all statistical tests were performed at the 2-tailed 5% level of significance. Exercise was the intersubject factor, while the intraobject factor comprised individual variables reflecting blood parameters, anthropometric measures, functional capacity, fatigue, and QoL. For missing data, the last observation carried-forward method was used. This analysis imputes the last value observed before dropout, regardless of when it occurred. The quantitative data was described using the mean and standard deviation. Homogeneity between samples was examined using the Komologorov–Smirnov 2-sample test. The analysis showed that most parameters measured had normal distribution compatibility. Baseline characteristics of the 2 groups were compared using 2-sample *t* tests for continuous variables and χ^2 tests for categorical variables. The analysis of variance (ANOVA) was used to examine the difference in means between the groups with regards to blood count levels, fatigue, and QoL. A correlation analysis using the Pearson's r correlation coefficient was performed to establish the relationship between blood parameters and functional capacity, as well as blood parameters and Qol or fatigue. The weighted κ statistic was used as a measure of intraexaminer reliability, and intraclass correlation coefficients were used as a measure of interexaminer reliability for each method. A method-comparison analysis was performed to determine the 95% limits of agreement for all examiners. To avoid intertester variation, the same tester carried out all tests in the same individual.

RESULTS

Study patients From a total of 826 patients with PCa screened for the study, 100 men enrolled in this trial were invited to participate by their oncologist (according to the study criteria). Seventy-four patients completed baseline testing, but 2 men resigned from the study because of psychological contraindications (distress and depression) after general medical assessment. As shown in the CONSORT diagram (FIGURE 1), 72 participants were randomly assigned to the exercise group (n = 36) or the control group (n = 36). During 1 year of the study, there were 5 dropouts (14%) in the control group and 1 (3%) in the exercise group; 66 men completed the intervention and their data were included in the statistical analysis.

Patients who were excluded from the study due to cancer progression (in most cases, metastases to the bone tissue, internal organs) were first of all provided with oncologic treatment and had the possibility of individual rehabilitation under separate conditions; one patient was excluded because of a stroke and was treated in a neurology ward and referred to a neurorehabilitation ward; one patient from the control group withdrew from the study.

Baseline characteristics of the participants are presented in TABLE 1.

Adherence and safety No significant differences were observed in daily physical activity levels (according to the GLTE) at baseline, and in daily meals (according to the MNA) at baseline and during the 12 months of the study between the groups. Generally, the average adherence to the weekly supervised sessions was 86% in

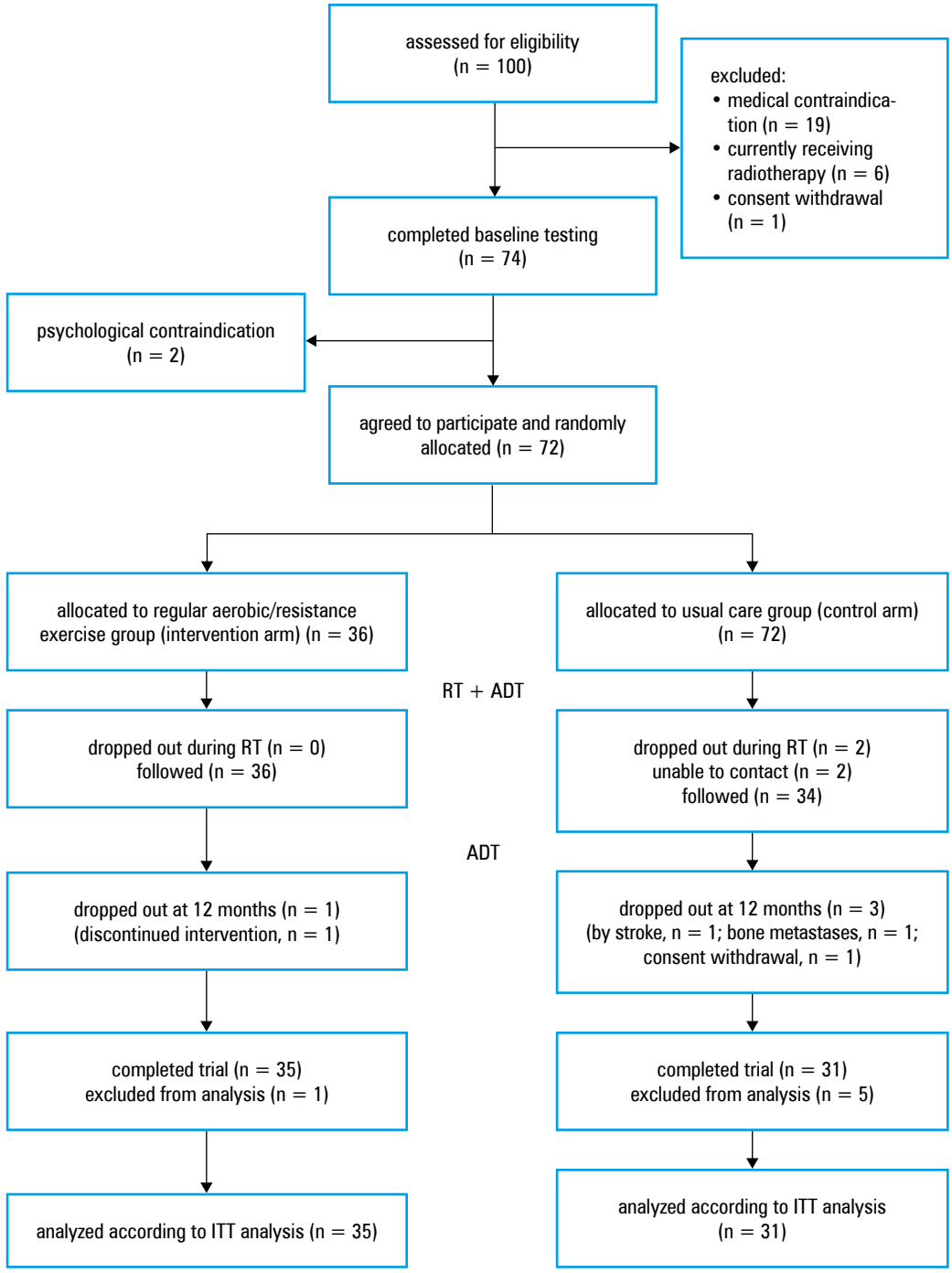

FIGURE 1 CONSORT diagram
Abbreviations: ADT, androgen deprivation therapy; ITT, intention to treat; RT, radiation therapy

the exercise group. As regards the intervention based on exercises at home in the control group, trainees returned their training diaries reporting that they had accomplished vigorous home training 0.8 times/wk and endurance training 1.1 times/wk. The average time of an endurance training session was 48 minutes.

Participants did not take any anelgesics before exercise sessions. No severe side effects were reported in any of the groups. However, 3 overuse injuries to the lower extremities were reported in the exercise group (ie, muscle pain and stiffness). However, all these symptoms occurred after the first weekend break from exercise training, after which all these participants returned to their training. Those patients took no more than 2 tablets (only on the first day of the break): paracetamol (0.5 g) or ibuprofen (0.25 g), which could not have affected the results because the dose was clinically insignificant.

Anthropometric parameters As regards body weight, violation of sphericity occurred and so the Greenhouse–Geisser correction was applied. Tests demonstrated significant differences between the exercise and control groups. After 12 months, body weight differed significantly from the measurements in assessments I and II. There were important differences between the groups: body weight was significantly higher in controls. Similar differences were observed for BMI and WHR.

TABLE 1 Characteristics of the study groups at baseline

Parameter	Overall sample (n = 72)	Exercise group (n = 36)	Control group (n = 36)	*P* value
age, y	66.23 ±4.94	65.7 ±6.2	67.9 ±4.9	0.161
weight, kg	83.25 ±7.50	83.58 ±8.8	83.33 ±6.7	0.882
BMI, kg/m^2	28.69 ±3.4	26.42 ±2.8	29.25 ±3.7	0.386
WHR	0.99 ±10.2	0.98 ±6.22	0.99 ±7.51	0.448
PSA after 3-month ADT, ng/ml	4.23 ±2.26	4.08 ±1.57	4.73 ±2.28	0.226
Gleason score	8.76 ±1.89	9.02 ±1.20	8.88 ±1.92	0.386
ECOG	0.62 ±0.8	0.74 ±0.6	0.51 ±0.9	0.26
LTPA	1.3 ±0.4	1.1 ±0.7	1.4 ±0.2	0.75
employed full time, n (%)	48 (66.6)	25 (69.4)	23 (63.9)	–
education (>high school), n (%)	39 (54.2)	19 (52.8)	20 (55.5)	–
married or cohabiting, n (%)	62 (86.1)	30 (83.3)	31 (86.1)	–

Data are presented as mean ±SD unless otherwise stated.

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; LTPA, Leisure Time Physical Activity; PSA, prostate-specific antigen; WHR, waist-to-hip ratio; others, see **FIGURE 1**

Blood parameters There were no significant differences in the lipid parameters between the measurements. However, the analysis showed significant differences in the levels of AST and ALT between the measurements, but not between the groups.

Inflammatory markers As for cytokines, there was no significant difference in IL-1β levels between the groups (P = 0.18). In the case of IL-6 levels, there were significant differences between individual measurements. The highest IL-6 level was observed after RT, and this result was significantly higher in both groups compared to the other measurements. There were also differences (at the level of statistical significance, P <0.1) in TNF-α levels between individual measurements. The highest TNF-α level was observed in assessment II, and it was significantly higher than in assessments I and III. The results in the exercise group were lower than in the control group, but the difference between the groups was not significant.

Aerobic capacity The analysis of the 6MWT distance did not show any significant differences between measurements at baseline in both groups (P = 0.88). However, in subsequent assessments, the distance was significantly higher in the exercise group. As for MET, the data tests did not reveal any significant differences between assessments I and II (P = 0.89) but revealed significant differences between the groups in assessments II and III (MET was significantly higher in the exercise group).

The results of anthropometric measures, laboratory assays, and 6MWT are presented in **TABLE 2**.

Fatigue The ANOVA with repeated measures revealed significant differences between the 3 measurements with regard to all variables in the FACT-F questionnaire. In assessments II and III, patients in the exercise group showed significantly higher scores for all functional assessment dimensions (except for scores related to family and social life and factors of fatigue), compared with controls. The results are presented in **TABLE 3**.

Quality of life The analysis of the QLQ-C30 questionnaire scales revealed that there were no differences in general health status. As for physical functioning, we observed significant differences between assessments I and II, as well as I and III. The differences between the groups were not significant. With regard to role functioning, there were no significant differences between the measurements or the groups studied. As for cognitive functioning, we observed significant differences between assessments I and II. Men in the exercise group obtained significantly higher results compared to those in the control group. There were significant differences in emotional functioning between assessments I and II, and the differences between the groups were significant in assessment III. With regard to social functioning, there were nonsignificant differences between the measurements or the groups, and other parameters analyzed. The result of the QLQ-PR25 subscale analysis for sexual activity was P = 0.85. However, there were significant differences in sexual functioning between assessments I and II, and in the case of assessment III, a significant difference between the groups was observed. There were no significant differences in urinary problems between the measurements (P = 0.28). However, we noted a significant difference between the groups after RT: significantly higher result in the control group. As for bowel disorders, the exercise group showed a significant alleviation of symptoms. There were nonsignificant differences in side effects of hormonal therapy between the measurements: P = 0.12, and there was a difference between the groups at 12 months (P <0.05). QoL changes are presented in **TABLE 4**.

DISCUSSION

The role of physical exercise in preventing diseases such as cardiovascular disease, type 2 diabetes, and cancer has been extensively studied.[15-17] To our knowledge, our study was one of the first to assess the physiological and psychological effects of a long-term supervised exercise program in men with high-grade PCa during oncologic therapy. This trial was an extension of our previous study,[34] which focused on the impact of exercise training during RT on radiation toxicity in these patient group. The idea to conduct our study stemmed from the research on the role of regular exercise in preventing diseases associated with chronic low-grade systemic inflammation (eg, metabolic syndrome, cardiovascular disease),[35,36] especially in PCa patients.

TABLE 2 Changes in anthropometric, blood, and functional capacity parameters in both study groups during the study

Parameters	Assessment I (baseline)		Assessment II		Assessment III		F	*P* value[b]
	exercise group	controls	exercise group	controls	exercise group	controls		
anthropometric measures								
weight, kg	85.58 ±8.8	83.33 ±6.7	85.55 ±9.2	85.4 ±10.7	85.82 ±9.9	92.32 ±15.6	(1.64) = 65.17	<0.001
BMI, kg/m^2	28.85 ±3.28	28.36 ±3.53	28.84 ±3.28	28.38 ±3.35	28.95 ±3.11	30.7 ±3.57	(1.63) = 65.079	<0.001
WHR	0.96 ±0.05	0.97 ±0.04	0.96 ±0.05	0.97 ±0.04	0.98 ±0.03	1.02 ±0.03	(1.63) = 40.810	<0.001
blood tests								
TC, mg/dl	208.7 ±44.9	196.7 ±49.1	198.7 ±43.5	199.3 ±39.8	201.1 ±42.6	211.2 ±48.9	(2.124) = 1.086	0.34
HDL-C, mg/dl	54.6 ±10.9	53.6 ±16.5	52.7 ±10.9	51.4 ±14.1	53.8 ±12.9	51.7 ±17.9	(2.107) = 1.67	0.19
LDL-C, mg/dl	138.5 ±40.4	131.5 ±44.1	128.6 ±38.9	129.7 ±37.7	140.7 ±47.9	162.6 ±172.9	(1.66) = 1.578	0.21
TG, mg/dl	174.3 ±100.5	131.6 ±51.4	161.2 ±86.0	155.6 ±70.2	161.6 ±172.9	161.3 ±88.1	(2.122) = 0.383	0.68
AST, U/l	35.19 ±19.77	32.77 ±14.96	38.75 ±22.68	31.32 ±15.31	25.31 ±16.22	25.33 ±10.46	(2.32) = 1.378	0.06
ALT, U/l	28.95 ±12.71	26.63 ±9.95	23.81 ±13.24	23.9 ±8.11	27.81 ±7.67	29.44 ±3.43	(2.32) = 1.219	0.08
total PSA, ng/ml	4.08 ±1.57	4.73 ±2.28	3.08 ±4.57	3.73 ±6.28	2.47 ±5.81	3.64 ±10.07	(1.37) = 7.662	<0.01
IL-1, ft/ml	106.6 ±226.6	117.1 ±212.6	142.9 ±196.9[a]	147.2 ±186.8[a]	150.6 ±1933.8	174.6 ±221.8	(2.97) = 1.789	0.18
IL-6, ft/ml	3158.1 ±1675.2	3249.4 ±2044.8	5306.1 ±5055.1[a]	5883.7 ±3050.7[a]	3095.9 ±2623.1	3618.2 ±2227.1	(1.91) = 19.951	<0.001
TNF-α, ft/ml	32.8 ±161.1	32.93 ±96.2	51.3 ±186.1[a]	67.8 ±196.8[a]	84.6 ±262.7	211.6 ±313.6	(2.21) = 0.039	0.71
6-minute walk test								
METs	2.95 ±0.41	3.04 ±0.41	3.09 ±0.33	2.91 ±0.28	3.17 ±0.03	2.80 ±0.36	(2.126) = 0.116	0.89
distance, m	411.2 ±86.2	430.4 ±86.3	439.4 ±70.7	401.1 ±59.6	456.9 ±77.4	378.4 ±76.3	(2.126) = 27.39	<0.001
dyspnea, points	2.17 ±1.16	2.25 ±1.29	2.01 ±0.83	2.41 ±1.20	1.76 ±0.78	2.61 ±0.88	(2.126) = 4.122	<0.05

Data are presented as mean ± SD.

a significant differences between assessments II and I of the parameter in the same group
b the level of statistical change between assessments I, II, and III of the parameter

Conversion factors to SI units are as follows: PSA, 1.0; TC, LDL-C, and HDL-C, 0.0259; TG, 0.0113; AST and ALT, 0.0167; IL-1β and IL-6, 0.131, and TNF-α, 0.318.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoprotein; IL-1, interleukin 1; IL-6, interleukin 6; LDL, low-density lipoprotein; MET, metabolic equivalent; TG, triglyceride; TNF-α, tumor necrosis factor α; others, see **TABLE 1**

Recent papers have underlined the problem of the effect of oncologic treatment on cardiovascular risk in this group of patients.[9-11] In our study, we observed that supervised regular exercise training decreased inflammation, reduced cardiovascular risk, and improved functional status in men with high-grade PCa during ADT with RT. The exercise program prescribed (duration, frequency, and intensity) was designed in accordance with the American Cancer Society recommendations for cancer patients.[21] It has been recognized that ADT is conducive to obesity and thus can increase the risk of cardiovascular diseases or metabolic syndrome,[6,7,9,11] especially when combined with RT[10] in men with PCa. On the other hand, the cytokines measured are well known as clinically useful mediators of cardiovascular diseases and risk factors.[12-14,37] In our study, we measured weight (BMI) and central obesity (WHR) and lipid profile as important predictors of cardiovascular diseases.[38]

Cross-sectional studies demonstrated an association between physical inactivity and low-grade systemic inflammation and cardiovascular risk in healthy subjects or in elderly people.[15,36,39] The results of the study by Leisegang et al[40] suggested

TABLE 3 Results measures from the Functional Assessment of Cancer Therapy General (FACT-G) and Fatigue (FACT-F) questionnaires in the study groups at particular stages of the study

Parameters	Assessment I (baseline)		Assessment II		Assessment III		F	*P* value[b]
	exercise group	controls	exercise group	controls	exercise group	controls		
FACT-G score	70.7 ±2.1	70.2 ±1.9	73.3 ±6.3	55.3 ±3.9[a]	65.91 ±4.8	50.74 ±3.6	(2.111) = 101.250	<0.001
FACT-F score	113.4 ±3.5	112.9 ±3.9	117.9 ±9.7	81.5 ±9.7[a]	105.8 ±7.7	75.54 ±8.1	(2.111) = 159.755	<0.001
physical well-being	24.9 ±1.4	25.42 ±1.5	23.6 ±1.4	16.83 ±2.6[a]	22.1 ±1.6	15.19 ±2.2	(2.126) = 169.750	<0.001
social/family well-being	13.7 ±3.3	13.4 ±2.8	15.8 ±3.4	14.2 ±3.9	12.47 ±3.5	13.35 ±3.4	(2.105) = 9.561	<0.001
emotional well--being	16.2 ±2.6	15.5 ±2.7	16.9 ±0.9	14.1 ±0.7	15.1 ±2.3	11.1 ±1.5	(2.104) = 36.284	<0.001
functional well--being	15.5 ±3.1	15.7 ±2.8	16.8 ±2.3	10.1 ±1.0[a]	16.47 ±1.8	11.06 ±2.4	(2.104) = 16.247	<0.001
fatigue	42.7 ±2.1	42.7 ±2.5	44.7 ±5.0	26.1 ±4.5[a]	39.8 ±3.7	24.8 ±2.9	(2.10) = 103.356	<0.001

Data are presented as mean ± SD.

a significant differences between assessments II and I of the parameter in the same group
b the level of statistical change between assessments I, II, and III of the parameter

that TNF-α, IL-1β, and IL-6 play a direct role in metabolic syndrome. On the other hand, the same cytokines are clinically useful as radiation-related biomarkers, and oncology studies have focused on their use in predicting tumor response.[41,42] After the study, we observed a lower increase of those parameters in the exercise group compared with controls after RT and at the end of the study. This was possible due to anti-inflammatory effect of the physical training performed by the exercise group.[43] Our patients demonstrated a significant increase of cytokine levels after RT (smaller in the exercise group), which was the result of radiation toxicity.[34]

Our results confirm the conclusions reached by other authors about the positive effect of exercise on anti-inflammatory factors in patients with high risk of metabolic syndrome and cardiovascular diseases.[39,44,45] Following the statistical measurement of the relationship between cytokine levels and lipid or anthropometric parameters, we did not observe any significant correlations in any of the groups during our study, despite clinically positive observations in the exercise group. However, the lipid profile did not change significantly in any of the groups during the study, and the levels of lipid parameters were not clinically important (our patients had similar diet measured by the MNA). Cormie et al[39] did not observe important changes in the same lipid parameters after 3 months of exercise training in patients with PCa starting ADT.

Another aspect of cardiovascular risk monitoring in our trial was the functional/aerobic capacity, measured with the 6MWT according to recommendations for cancer patients.[26,29] We observed a signficant improvement of functional capacity (increase in the 6MWT distance and decrease in dyspnea measured with the Borg scale) in the exercise group after RT and 1 year of study and deterioration of this parameters in the control group. Similar effects were observed by other researchers.[17,19]

The second outcome of our study was the subjective assessment of the functional status of the patients, measured with the EORTC and FACT questionnaires as scores recommended for cancer patients.[30-32] Since the groups did not differ much at baseline, we assumed that improvements in a greater number of EORTC functions and symptoms after RT and 12 months in the exercise group might be due to a better use of the physical training program. Even though we did not observe significant changes in the general health status in any of the study groups, physical or emotional functioning was better in the exercise group in contrast to controls. Fatigue levels were higher in the exercise group at baseline. This changed significantly in the measurement after RT and after 1 year of study—fatigue levels in the exercise group were significantly lower compared with controls. A similar effect of the exercise program in the exercise group was observed with regard to side effects of ADT, which were considerably less pronounced and burdensome; thus physical activity considerably alleviated problems caused by ADT. Similar results were observed by numerous authors.[16-19]

The results of our study also indicated that physical activity is conducive to good sexual functioning. Even though at baseline men in the control group assessed their sexual functioning more positively compared with the exercise group, physical activity undertaken during the treatment improved the quality of sex life in the exercise group. These results are similar to those obtained by other authors (Cormie et al[39] and Dahn et al)[46], suggesting that exercise has a beneficial effect on

TABLE 4 Results from the European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-PR23 questionnaires in the study groups at particular stages of the study

Parameters	Assessment I (baseline)		Assessment II		Assessment III		F	*P* value[b]
	exercise group	controls	exercise group	controls	exercise group	controls		
QLQ-C30 (general)								
global health status	53.7 ±18.2	54.1 ±23.0	55.4 ±19.9	55.1 ±17.7	57.4 ±19.7	52.3 ±17.8	(2.126) = 2.169	0.11
physical functioning	79.7 ±18.9	81.9 ±15.4	70.5 ±18.1	63.9 ±18.8[a]	78.4 ±17.8	65.1 ±19.5	(2.126) = 6.23	<0.01
role functioning	88.7 ±19.4	86.2 ±17.1	84.9 ±23.3	78.9 ±22.5	87.8 ±21.5	82.3 ±19.2	(2.126) = 2.481	0.08
emotional functioning	109.4 ±14.7	107.7 ±19.5	67.1 ±15.8[a]	53.9 ±22.3[a]	76.1 ±20.3	53.2 ±19.8	(1.66) = 5.575	<0.01
cognitive functioning	50.5 ±23.1	41.9 ±22.9	54.8 ±23.3	40.4 ±24.8	58.7 ±21.1	35.6 ±25.8	(2.118) = 3.612	<0.05
social functioning	82.1 ±27	78.9 ±18.9	75.6 ±25.9	67.4 ±25.8[a]	76.3 ±20.8	69.4 ±26.6	(2.126) = 1.575	0.21
fatigue	29.7 ±19.7	28.5 ±21.9	30.3 ±21.4	39.4 ±23.6[a]	21.6 ±16.7	35.1 ±22.7	(2.126) = 4.315	<0.05
nausea and vomiting	7.7 ±13.5	7.9 ±11.1	6.2 ±6.7	8.7 ±14.1	4.7 ±10.3	7.8 ±12.5	(2.118) = 0.462	0.63
diarrhea	7.7 ±14.3	10.1 ±15.7	18.5 ±21.4[a]	21.7 ±31.1[a]	6.8 ±13.3	9.9 ±22.5	(2.126) = 2.116	0.12
financial difficulties	33.3 ±47.1	40.5 ±18.9	23.1 ±27.9[a]	31.8 ±34.1[a]	31.5 ±30.5	35.7 ±23.3	(2.126) = 2.116	0.12
pain	22.4 ±19.4	22.7 ±17.7	18.9 ±27.9	29.8 ±34.1[a]	17.1 ±8.6	20.1 ±19.9	(2.116) = 1.057	0.35
dyspnea	16.1 ±25.3	24.2 ±27.1	16.6 ±30.2	33.3 ±26.5[a]	15.8 ±31.2	34.5 ±29.7	(2.113) = 0.455	0.61
insomnia	26.9 ±29.8	28.9 ±28.8	27.5 ±28.1	33.3 ±25.5	27.8 ±29.2	35.8 ±30.2	(2.126) = 0.072	0.93
appetite loss	11.5 ±24.8	12.1 ±18.6	14.9 ±66.1	24.7 ±24.7[a]	15.5 ±34.4	27.8 ±25.7	(2.105) = 1.057	0.05
constipation	7.4 ±18.3	10.2 ±19.1	15.9 ±29.8[a]	17.5 ±27.8[a]	8.7 ±16.8	14.6 ±25.7	(2.126) = 1.953	0.14
QLQ-PR23 (prostate cancer)								
sexual activity	67.3 ±22.3	67.4 ±24.8	71.1 ±22.1	63.0 ±20.7	73.8 ±24.2	60.1 ±24.7	(2.126) = 0.157	0.85
sexual functioning	70.7 ±26.2	82.25 ±26.1	52.9 ±39.8[a]	49.8 ±44.4[a]	64.8 ±28.7	50.1 ±32.3	(1.76) = 5.808	<0.05
urinary symptoms	30.9 ±19.2	32.5 ±17.2	31.8 ±16.2	48.9 ±20.7[a]	30.3 ±16.7	47.5 ±18.5	(1.77) = 1.228	0.28
bowel symptoms	72.3 ±9.5	48.2 ±9.6	15.4 ±14.7[a]	18.8 ±20.5[a]	20.7 ±10.6	20.5 ±12.7	(1.66) = 8.469	<0.01
HT-related symptoms	15.3 ±13.9	18.3 ±13.8	15.8 ±11.8	22.2 ±21.5[a]	16.1 ±8.9	24.2 ±9.9	(1.72) = 2.09	0.12
incontinence aid	2.5 ±20.9	2.9 ±20.1	11.7 ±19.5[a]	13.9 ±29.1[a]	0.1 ±5.7	3.22 ±13.3	(2.126) = 6.838	<0.01

Data are presented as mean ± SD.

a significant change after assessment II to I of the parameter in the same group
b the level of statistical change between assessments I, II, and III of the parameter

Abbreviations: HT, hormonal therapy; others, see **TABLE 3**

preserving sexual function in men who were sexually active before initiating ADT.

The results of our study confirm scientific data indicating that regular physical activity reduces the levels of systemic inflammatory mediators, and thus exercise may constitute an accessible and cost-effective means of reducing the proinflammatory effect of obesity, improving nonspecific cancer-related symptoms, cardiovascular risk factors related to cancer treatment, and improving QoL in patients with PCa.[47] Physical activity positively correlates with improvement in sexual functioning and mental health and decreases side effects of oncologic therapy,

including fatigue, in those patients who underwent RT and ADT during PCa treatment. We believe that the differences in our results between the control and exercise groups were caused by poorer ability of patients on usual care to follow the physical activity program, possibly because of a lower level of motivation due to emotional reasons. This might have reduced the ability of these patients to participate in daily physical activity despite recommendations from the medical staff.

Strengths and limitations Our study has methodological strengths. First, it was a randomized controlled trial adequately powered to detect changes in the levels of inflammatory and metabolic parameters between the control and exercise groups. Second, our laboratory staff were blinded to group assignment. Third, we standardized exercise activity using a training routine that had strict parameters for training volume (repetitions, sets, heart rate, etc.). Fourth, we utilized both objective and subjective validated measures of well-being. Another strength was the use of well-established self-rating instruments with good psychometric properties. A limitation of this study was the lack of a relevant comparison group and more data regarding medical scans (imaging) during our trial.

Conclusions To conclude, the long-term supervised exercise training is more effective than educational materials on physical activity in decreasing cardiovascular risk and improving functional and emotional status or fatigue in patients with high-grade PCa during RT and ADT.

Future large-scale efficacy trials are needed to replicate our findings across a wider range of men with PCa, to examine more biomarker outcomes at longer follow-up periods, and to help determine the mechanisms (ie, psychological and emotional factors and/or improved physical fitness or bone strength) responsible for these outcomes. Our findings can help determine the effectiveness of rehabilitation for the prevention and management of metabolic diseases in men with PCa.

Implications for clinical practice There is strong evidence for the use of exercise/physical rehabilitation in reducing cardiometbolic risk, fatigue, and improving functional status during oncologic therapy of PCa. There is preliminary evidence indicating that a number of areas, such as sexual and emotional functioning, may be improved by exercise interventions in men with PCa during ADT.

Contribution statement KH was the principal investigator responsible for study conception , participant recruitment, and drafting the manuscript; EK was an outcome assessor and was responsible for study conception and final approval of the manuscript; EL was responsible for study conception, critical revision for intellectual content, laboratory usage, and final approval of the manuscript; PM was responsible for study conception, critical revision for intellectual content, and final approval of the manuscript.

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