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Effects of Exercise on Physical Function and Quality of Life in Prostate Cancer Patients Receiving Androgen Deprivation Therapy: High Intensity Interval Training *vs.* Moderate-Intensity Continuous Training

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Abstract

Purpose: We assessed the effects of exercise on the physical function and health Quality of Life (hQoL) in prostate cancer patients underwent Androgen Deprivation Therapy (ADT). Additionally, the effects of High-Intensity Interval Training (HIIT) were compared with Moderate-Intensity Continuous Training (MICT).

Methods: Seventeen prostate cancer patients underwent ADT were prospectively allocated to either HIIT or MICT. Physical function and hQoL were measured before and after 12-week and 3 to 6 months after the exercise, respectively.

Results: Although the whole-body total mass significantly increased after the exercise, it was equivalent regardless of the methods. After the exercise, muscle strength and endurance improved and tended to be maintained until 3 to 6 months later. Improvement in muscle endurance was more prominent after HIIT, and that in muscle strength was more prominent after MICT. Performance in the senior fitness test improved after the exercise, and HIIT was more effective for lower and upper muscle endurance and flexibility although MICT was more effective for the others. hQoL significantly improved at 3 to 6 months after the exercise.

Conclusion: 12-week exercise has a positive effect on the physical function and hQoL in prostate cancer patients underwent ADT. In these patients, HIIT may be a better option for improving muscle endurance, to prevent falls and fracture.

Keywords: High-intensity interval training; Prostate cancer; Androgen deprivation therapy; Body composition; Muscle function

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Introduction

Prostate Cancer (PCa) is the second most frequently diagnosed cancer and fourth most common cause of death in men worldwide [1]. Approximately 85% of patients with PCa were diagnosed with localized disease [2], and commonly treated with active surveillance or definite treatment [3]. However, 15% of patients with PCa were reported to have regional or metastatic disease at the time of diagnosis [2], and 15% to 25% of patients who underwent localized treatment eventually experienced biochemical recurrence and became candidates for systemic therapy, mainly Androgen Deprivation Therapy (ADT) [4]. In the United States, approximately 3% of the whole populations were reported to be treated with ADT [5].

Although ADT is a common treatment for metastatic PCa [6], it is accompanied by a range of adverse effects, including changes in body composition, such as decreased Bone Mineral Density (BMD) and increased body fat [7]. Moreover, ADT is reported to be associated with decreased physical function and muscle strength compared with PCa controls [8]. In addition to age-related physical fragility, ADT-induced fragility is thought to be associated with decreased physical activity and increased risk of injury, which finally resulted in additional medical and socioeconomic costs. Moreover, ADT-induced physical fragility is reported to be associated with decreased health Quality

of Life (hQoL) [9].

During the past few years, physical activities or exercises had been shown to be safe, feasible, and effective methods to improve the physical function and hQoL in patients with cancer, regardless of the cancer type [10,11]. However, because PCa has an additional risk of physical fragility due to ADT, specific methods for preventing physical fragility and improving hQoL are strongly required for these patients. Although exercise could be one of the optimal ways for improving their physical function and hQoL, more reliable studies for assessing the impacts of exercise on the physical function and hQoL in these patients need to be conducted.

Recently, High-Intensity Interval Training (HIIT), a method of workout that alternates between short repeated burst of high-intensity exercise and recovery, is becoming popular because it was studied as a means to improve the performance of elite athletes. In addition, recently, the effects of HIIT were actively studied in a range of populations including patients with cancer. In the current study, we aimed to investigate the effects of exercise on the physical function and hQoL in patients with PCa who underwent ADT and compared HIIT with Moderate-Intensity Continuous Training (MICT).

Materials and Methods

Study population

Patients with PCa who underwent ADT for more than 3 months in Boramae Medical Center were initially eligible for the current study. The exclusion criteria were as follows: ≥ 80 years old, ≥ 6 metastatic lesions or bone metastasis of the hip or femur lesion, untreated or uncontrolled hypertension, and T-score ≤ -2.5 on BMD. Initially, 28 patients were selected for the current study, and among these, 4 were excluded because they were judged to be inadequate to participate in the exercise program based on the results of physical activity readiness questionnaire from the health and exercise science laboratory in Seoul National University. A total of 24 patients consequently participated in the 12-week exercise program after being fully aware of the objectives and providing consent to research. They were assigned to each of the following groups: HIIT (n=12) and MICT (n=12). Among these, 7 patients were dropped out, and finally, 17 (HIIT, n=9; MICT, n=7) completed the exercise program and follow-up measurements. The current study was approved by the Institutional Review Board of our institute.

Exercise program

The exercise program was conducted for 12 weeks. Patients were allowed a 4-week adaptation to do the exercise training. From weeks 5 to 8 and 9 to 12, the patients used a resistance band to progressively increase the exercise intensity. The center-based HIIT program consisted of a 60 min session twice a week for 12 weeks. It included warm-up and cooldown for 15 min each and HIIT for 30 min (Supplementary Figure 1). Two sets of seven workouts targeting the major muscles of the upper and lower body were performed with a 1-min interval, including squat, jumping jack, sit-up, and push-up (Supplementary Figure 2). Heart rate was monitored individually. Exercise intensity was gradually increased from 75% to 85% of the maximum heart rate, and the Rate of Perceived Exertion (RPE) was increased from 14 to 17 every 4 weeks. When their heart rate exceeded the target heart rate, the patients were instructed to stop their workout and slowly walk in place. The averages of patients' heart rate were 77.4%, 80.9%, and 82.7% at 1 to 4, 5 to 8, and 9 to 12 weeks, respectively.

The home-based MICT program took 60 min to perform, that is, 30 min each for walking and resistance exercise, twice a week for 12 weeks. Exercise intensity was set to an RPE of 12 to 15. Patients were recommended to walk "somewhat hard" and perform resistance exercise according to the exercise program brochure. Patients in the MICT group received exercise education at the center at the beginning and in the middle of the intervention (Supplementary Figure 2). They were provided a resistance band to increase their exercise intensity steadily. The amount of exercise was monitored by a pedometer record and daily log file (Supplementary Figure 3). The compliance rate for exercise was calculated as the number of patients who engaged in the exercise divided by the total number of patients. Consequently, the compliance rates in the HIIT and MICT groups were 87.8% and 89.8%, respectively.

Physical evaluation

BMD and body composition were measured using Dual-Energy X-Ray Absorptiometry (DEXA, Hologic Discovery W, Waltham, MA, USA). To evaluate muscle strength, the peak torque was measured by 5 repetitions of knee extension and flexion with participants' dominant leg at an angular velocity of 60°/s. To evaluate muscle endurance, the peak torque was measured by 15 repetitions of knee extension and flexion at an angular velocity of 180°/s. Before the test, baseline exam was conducted with 4 to 5 repetitions at an effort rate of 50%, considering that most of the patients had no experience with isokinetic measurement. Handgrip strength was measured using a handgrip dynamometer (Takei, Grip D, T.K.K. 5401; Niigata City, Japan) to estimate upper body muscle strength. After finishing the practice trial at a submaximal power, the patients were instructed to squeeze the handgrip maximally for 3 s. The grip strength was measured twice in each hand alternatingly. Moreover, the average of these values was used as data.

In addition, the senior fitness test, which was developed to evaluate the physical function of elderlies, was performed [12]. This test included the chair stand, arm curl, 6-min walk, chair sit and reach, back scratch, and Timed Up and Go (TUG) tests. The 30-s chair stand test was performed to evaluate lower body muscle endurance. The arm curl test was conducted to evaluate the functional fitness of upper body muscle endurance using the patient's dominant arm with a 4 kg dumbbell. The 6-min walk test was performed to evaluate cardiovascular ability. The chair sit and reach test was conducted to evaluate flexibility. The back scratch test was performed to evaluate shoulder mobility. Furthermore, the TUG test was conducted to evaluate motor ability. After placing the patient on a chair, measure the time until the cone in front of 2.44 m turns fast and sit back.

Questionnaires

Questionnaires were utilized to qualitatively assess patients' hQoL and physical activity. The multidimensional Functional Assessment of Cancer Therapy-Prostate (FACT-P) [13] and Korean version of Physical Activity Scale for the Elderly (K-PASE) were used to assess the hQoL and physical activity of patients [14], respectively. Furthermore, the hQoL in patients with PCa was assessed using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire [15]. Every questionnaire was obtained before, immediately after, and 3 to 6 months after the exercise program.

Statistical analysis

The results are presented as means ± standard deviation calculated using descriptive statistics. P values were two sided, with

Table 1: Baseline characteristics of participants.

	Total	HIIT	MICT	p
Number of patients, n (%)	17 (100)	9 (52.9)	8 (47.1)	
Age, years, mean ± SD	74.2 ± 4.3	72.8 ± 4.1	75.8 ± 4.3	0.163
Height, cm, mean ± SD	164.7 ± 9.8	165.5 ± 11.1	163.9 ± 8.7	0.746
Weight, kg, mean ± SD	65.5 ± 8.1	68.5 ± 8.2	62.2 ± 7.0	0.115
BMI, kg/m^2, mean ± SD	25.3 ± 2.2	26.1 ± 1.5	24.4 ± 2.7	0.116
Diabetes, n (%)	2 (11.8)	1 (11.1)	1 (12.5)	0.929
Hypertension, n (%)	8 (47.1)	5 (55.6)	3 (37.5)	0.457
Gleason grade, n (%)				0.431
1	3 (17.6)	1 (11.1)	2 (25.0)	
2	2 (11.8)	2 (22.2)	0 (0.0)	
3	5 (29.4)	2 (22.2)	3 (37.5)	
4	3 (17.6)	1 (11.1)	2 (25.0)	
5	4 (23.5)	3 (33.3)	1 (12.5)	
Radical prostatectomy, n (%)	4 (23.5)	3 (33.3)	1 (12.5)	0.312
Metastatic prostate cancer, n (%)	5 (31.2)	3 (33.3)	2 (28.6)	0.838
PSA, ng/mL, median (IQR)	0.83 (0.12-4.67)	0.35 (0.12-6.3)	2.63 (0.54-60.3)	0.3

$p<0.05$ considered statistically significant. The normal distribution was confirmed through the normalization test of two independent groups. The t-test was used to examine the differences of the results among groups in age, height, body weight, lean mass, fat mass, Body Mass Index (BMI), and blood pressure. Two-way ANOVA with repeated measures was performed to evaluate the effects of exercise and compare between the groups. Statistical analysis was performed using SPSS version 23.0 (SPSS, Chicago, IL).

Results

The mean age of the total study population was 74.2 years, and the mean BMI was 25.3 kg/m^2 (Table 1). Diabetes and hypertension were present in 2 (11.8%) and 8 (47.1%) patients, respectively. Radical prostatectomy was performed in 4 patients (23.5%), and 5 (31.2%) had metastatic disease on radiographic studies. The median PSA level was 0.83 ng/mL. No significant difference was noted in demographic and clinical characteristics according to the exercise types.

Before the exercise program, the whole-body total mass was 65.5 kg, and the whole-body % fat was 28.8%. The BMD and T-score were 1.10 and -1.07, respectively (Table 2). After the exercise program, the whole-body total mass significantly increased (65.5 kg *vs.* 67.1 kg, p=0.012) although it was not statistically significant at 3 to 6 months after the exercise program. However, the whole-body % fat was equivalent at immediate post-exercise and 3 to 6 months after exercise. There was no significant difference in the whole-body total mass and whole-body % fat according to the exercise types. In addition, no difference in the BMD and T-score was noted at immediate post-exercise and 3 to 6 months after exercise compared with the pre-exercise values, respectively. Moreover, there were no statistically significant differences in body composition and BMD according to the exercise types. Knee flexor strength significantly improved immediately after exercise (65.2 *vs.* 80.4 Nm, p=0.003) and maintained (65.2 *vs.* 78.6 Nm, p=0.004). Knee extensor strength significantly improved in the MICT group compared with that in the HIIT group. Knee extensor (95.2 *vs.* 103.4 Nm, p=0.001) and flexor muscle endurance (45.4 *vs.* 55.4 Nm, p=0.005) significantly improved after exercise at immediate post-exercise. However, knee flexor muscle endurance was not statistically significant improved at 3 to 6 months after exercise although knee extensor muscle endurance significantly improved (95.2 *vs.* 100.6 Nm, p=0.001). The improvements in knee extensor muscle endurance were more prominent in the HIIT group compared with the MICT group not only just after exercise but also 3 to 6 months after exercise.

All components of the senior fitness test significantly improved immediately after exercise. After 3 to 6 months, the chair stand (14.5 *vs.* 17.9/30 s, p=0.001), arm curl (15.8 *vs.* 19.4, p<0.001), 6-min walk (506.0 *vs.* 529.2 m, p=0.008), and chair sit and reach (-7.3 *vs.* -1.2 cm, p=0.031) tests significantly improved compared with the pre-exercise values, respectively. In addition, the chair stand, arm curl, and chair sit and reach tests significantly improved after HIIT compared with MICT although the others were more improved in the MICT group.

The K-PASE and FACT-P did not improve after exercise (Table 3). However, the EPIC significantly improved 3 to 6 months after exercise (17.5 *vs.* 11.1, p=0.016) but not at immediate post-exercise (17.5 *vs.* 15.7, p=0.222). Furthermore, no difference was noted in the EPIC according to the type of exercise methods.

Discussion

Physical activities or exercises were regarded as safe, feasible, and effective methods for improving the physical function and hQoL in patients with PCa who underwent ADT. However, more reliable evidence for the effects of exercise on these patients was clinically needed. In addition, effective delivery methods of physical activities to improve the physical function and hQoL have yet to be elucidated in these patients. In this study, we prospectively enrolled patients with PCa who underwent ADT. The results showed that the 12-week exercise program effectively improved the physical function and hQoL in these patients. Moreover, we demonstrated that HIIT is more effective in improving muscle endurance in these patients compared with MICT.

In the current study, regardless of the exercise type, the 12-week

Table 2: Changes of body composition and bone mineral density, muscle strength, endurance and senior fitness test.

(a) Change of body composition and bone mineral density							
		Pre-treatment (1)	Immediate (2)	12-24weeks (3)	p	p (1-2)	p (1-3)
Whole body total mass, kg	Total	65.5 ± 8.1	67.1 ± 8.1	66.4 ± 8.8	0.039	0.012	0.233
	HIIT	68.5 ± 8.2	70.4 ± 8.7	70.4 ± 9.3	0.068	0.089	0.068
	MICT	62.2 ± 7.0	63.3 ± 5.8	61.9 ± 6.0			
Whole body % fat, %	Total	28.8 ± 5.6	31.7 ± 5.3	30.7 ± 5.6	0.588	0.371	0.602
	HIIT	29.5 ± 4.5	32.2 ± 4.0	32.2 ± 4.6	0.478	0.654	0.381
	MICT	28.0 ± 5.6	31.2 ± 6.7	29.0 ± 6.4			
Whole body BMD, g/cm^2	Total	1.10 ± 0.13	1.10 ± 0.13	1.10 ± 0.14	0.789	0.908	0.6
	HIIT	1.13 ± 0.10	1.12 ± 0.10	1.12 ± 0.11	0.501	0.485	0.482
	MICT	1.07 ± 0.17	1.08 ± 0.17	1.07 ± 0.17			
T-score (score)	Total	-1.07 ± 1.51	-1.07 ± 1.48	-1.12 ± 1.54	0.745	0.97	0.593
	HIIT	-0.77 ± 1.07	-0.81 ± 1.10	-0.87 ± 1.12	0.447	0.426	0.441
	MICT	-1.41 ± 1.91	-1.36 ± 1.86	-1.40 ± 1.91			
(b) Change of muscle strength							
		Pre-treatment (1)	Immediate (2)	12-24weeks (3)	p	p (1-2)	p (1-3)
Grip strength, kg	Total	31.3 ± 6.2	33.0 ± 6.1	32.2 ± 5.6	0.012	0.014	0.13
	HIIT	34.2 ± 3.5	35.7 ± 4.5	34.8 ± 3.5	0.035	0.037	0.032
	MICT	28.0 ± 7.1	29.9 ± 6.5	29.2 ± 6.3			
Knee extensor, Nm	Total	150.4 ± 35.9	154.3 ± 29.1	156.2 ± 32.2	0.329	0.352	0.228
	HIIT	169.7 ± 30.8	171.7 ± 17.6	172.3 ± 22.4	0.008	0.006	0.012
	MICT	128.8 ± 29.0	134.8 ± 27.5	138.1 ± 33.1			
Knee flexor, Nm	Total	65.2 ± 27.8	80.4 ± 16.8	78.6 ± 20.0	0.001	0.003	0.004
	HIIT	72.8 ± 32.0	85.7 ± 21.4	83.2 ± 23.2	0.218	0.194	0.258
	MICT	56.8 ± 20.9	74.4 ± 6.7	73.5 ± 15.7			
(c) Changes of muscle endurance							
		Pre-treatment (1)	Immediate (2)	12-24weeks (3)	p	p (1-2)	p (1-3)
Knee extensor, Nm	Total	95.2 ± 19.3	103.4 ± 19.5	100.6 ± 19.4	0.005	0.001	0.001
	HIIT	104.0 ± 15.4	114.0 ± 11.2	109.7 ± 13.8	0.02	0.019	0.03
	MICT	85.3 ± 19.1	91.5 ± 20.5	90.4 ± 20.4			
Knee flexor, Nm	Total	45.4 ± 16.6	55.4 ± 10.4	50.1 ± 14.5	0.005	0.005	0.074
	HIIT	50.3 ± 17.0	60.7 ± 11.2	52.7 ± 15.5	0.138	0.069	0.274
	MICT	39.8 ± 15.0	49.5 ± 5.3	47.3 ± 13.6			
(d) Change of senior fitness test							
		Pre-treatment (1)	Immediate (2)	12-24weeks (3)	p	p (1-2)	p (1-3)
Chair stand, counts / 30 sec	Total	14.5 ± 3.1	19.7 ± 6.4	17.9 ± 4.9	<0.001	<0.001	0.001
	HIIT	15.6 ± 2.8	23.4 ± 3.8	21.6 ± 2.5	0.001	0.009	0.001
	MICT	13.3 ± 3.2	15.5 ± 6.2	13.9 ± 3.4			
Arm curl, counts / 30sec	Total	15.8 ± 5.0	18.6 ± 6.4	19.4 ± 4.8	0.001	<0.001	<0.001
	HIIT	18.2 ± 1.9	22.1 ± 2.7	22.4 ± 2.6	0.006	0.017	0.006
	MICT	13.1 ± 6.2	14.8 ± 7.2	15.9 ± 4.3			
6 min walk, m	Total	506.0 ± 98.5	528.2 ± 98.2	529.2 ± 99.9	0.035	0.049	0.008
	HIIT	569.8 ± 32.5	579.1 ± 66.0	583.6 ± 39.8	0.006	0.004	0.004
	MICT	434.3 ± 99.3	471.0 ± 99.9	468.1 ± 113.7			
Sit & reach, cm	Total	-7.3 ± 12.0	0.1 ± 12.9	-1.2 ± 13.8	0.014	0.012	0.031
	HIIT	-4.8 ± 10.6	4.9 ± 8.9	4.2 ± 8.6	0.117	0.157	0.146
	MICT	-10.3 ± 13.6	-5.4 ± 15.0	-7.3 ± 16.4			

Back scratch, cm	Total	-26.4 ± 13.0	-21.8 ± 14.9	-25.2 ± 15.2	0.072	0.043	0.571
	HIIT	-18.2 ± 7.2	-13.6 ± 7.0	-17.9 ± 8.4	0.006	0.003	0.006
	MICT	-35.7 ± 13.0	-31.1 ± 16.3	-33.4 ± 17.3			
TUG, sec	Total	6.0 ± 1.3	5.7 ± 1.2	5.9 ± 1.2	0.066	<0.001	0.472
	HIIT	5.3 ± 0.4	5.1 ± 0.5	5.2 ± 0.5	0.008	0.017	0.004
	MICT	6.8 ± 1.5	6.3 ± 1.4	6.7 ± 1.2			

Table 3: Changes in self-reported questionnaires.

		Pre-treatment (1)	Immediate (2)	12-24weeks (3)	p	p (1-2)	p (1-3)
K-PASE	Total	125.8 ± 65.4	137.5 ± 41.4	108.3 ± 33.4	0.14	0.315	0.345
	HIIT	144.8 ± 73.7	141.1 ± 50.7	112.4 ± 27.7	0.28	0.315	0.199
	MICT	104.5 ± 50.9	133.5 ± 30.6	103.6 ± 40.3			
FACT-P	Total	102.5 ± 19.0	106.7 ± 20.5	104.3 ± 18.8	0.41	0.164	0.645
	HIIT	109.6 ± 12.8	120.6 ± 8.6	113.9 ± 8.8	0.01	0.009	0.032
	MICT	94.5 ± 22.4	91.1 ± 18.8	93.5 ± 21.6			
EPIC	Total	17.5 ± 8.9	15.7 ± 6.4	11.1 ± 3.1	0.01	0.222	0.016
	HIIT	15.7 ± 5.0	12.0 ± 4.0	9.5 ± 2.2	0.17	0.13	0.328
	MICT	18.7 ± 11.0	18.1 ± 6.8	12.2 ± 3.2			

exercise program improved the muscle strength and endurance, which was consistent with the previous studies [16-18]. Although the statistical significance was not reached in some components, these findings may have resulted from the small number of participants. In addition, the senior fitness test, which was developed to measure the physical function for daily activities in elderlies [19], showed significant improvements after the 12-week exercise program. In the previous study, patients with risk of falling showed inferior results in the senior fitness test compared with those without risk of falling [20]. Although these remained to be validated in the future study, the exercise program could be useful not only for improving the physical function but also for decreasing the risk of falling and fracture, which were reported to commonly occur after ADT [21]. Moreover, the hQoL in these patients seemed to be slightly improved after the exercise program, which was also similar to prior studies [22,23].

In addition, the current study demonstrated that HIIT showed slightly superior efficacy for muscle endurance, including the chair stand and arm curl tests, which could be more effective for daily activities in elderly patients. Previously, muscle fatigue has been reported to affect stability, and thus, muscle endurance is significant to prevent falls in elderlies [24]. Patients with metastatic PCa, who were regarded as the primary candidates for ADT, are at higher risk of fracture, and it is extremely significant to prevent them from falling [25]. Based on the current study, although the overall efficacy of HIIT and MICT seemed to be similar, HIIT is thought to be more effective for muscle endurance, while MICT is thought to be more effective for muscle strength. In other words, for patients with PCa who underwent ADT, HIIT could be a better exercise method to prevent fracture by enhancing muscle endurance compared with MICT although further studies have yet to be performed.

The current study has several limitations, including the small number of patients and non-randomized study design due to the IRB's disapproval of the randomization. However, it is clinically useful for patients with PCa who were treated with ADT because it demonstrated the effects of exercise on the physical function and hQoL in these patients. Moreover, this study may be especially useful to recommend a specific exercise program for patients with risk of falling because HIIT could be a better option for these patients to reduce the risk of falling and fracture by enhancing muscle endurance.

In conclusions, in patients with PCa who underwent ADT, the exercise program is an effective way to improve their physical function and hQoL. Moreover, the effects of the 12-week exercise program tend to remain for at least 3-6 months after the exercise program. Although HIIT showed similar overall efficacy with MICT in these patients, HIIT seemed to be superior in improving muscle endurance. Because muscle endurance is thought to be important for the prevention of falls and fracture, HIIT may be a better option for these patients although these need to be validated in the future studies.

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