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Does Aerobic and Resistance Exercise Reduce Fatigue in Men with Prostate Cancer?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not aerobic and resistance exercise reduces fatigue in men with prostate cancer.

STUDY DESIGN: Systematic review of three randomized controlled trials (RCT's) published in peer reviewed journals between 2013-2017.

DATA SOURCES: Data sources obtained for this review were found in using PubMed and Cochrane Library and chosen based on their relevance to the clinical question and if they included patient oriented evidence that matters (POEMS)

OUTCOMES MEASURED: All three studies measured the effect aerobic and resistance exercise has on fatigue in men with prostate cancer undergoing androgen deprivation therapy and/or radiation therapy using self-reporting questionnaires.

RESULTS: All three studies contained continuous data that could not be converted to dichotomous date. P values were reported for each of the studies. The p values for every trial reported a p value of <.05 thus concluding the data to be statistically significant. Each of the studies selected found with statistical significance that aerobic and resistance exercise reduced the level of fatigue reported by the participants of the trial.

CONCLUSIONS: After analysis of the three trials, exercise can lead to a reduction in fatigue in men diagnosed with prostate cancer undergoing androgen deprivation therapy (ADT) and/or radiation therapy (RT). Exercise is a cost-effective option for patients and can have beneficial effects over other medical conditions. The populations studied in this review focused on men receiving ADT and/or RT. Future studies can focus on other treatment modalities such as chemotherapy. Further research can also include larger sample sizes and longer trials to effectively evaluate the long-term effects of exercise and fatigue.

KEYWORDS: Prostate cancer, exercise programs, and fatigue

INTRODUCTION

Prostate cancer is one of the most common types of cancer in American men and is the second leading cause of death for men in the US.[1] Prostate cancer is a slow growing cancer that originates in the prostate and is often asymptomatic especially in the early stages. If symptoms do arise they can mimic other conditions of the prostate such as benign prostatic hypertrophy. Common symptoms include problems urinating, slow or weak urinary stream, inability to urinate, discomfort in the pelvic area, and blood in semen. The exact cause of prostate cancer is unknown but increasing age and being of African American decent are two identified risk factors.[1] Prostate cancer is rare in men younger then 40 and the prevalence of prostate cancer is highest in men 65 years or older.[1]

One in nine men are diagnosed with prostate cancer in their lifetime and this causes a large financial burden on the healthcare system.[1] In 2018 the United States had an estimated 164,690 new cases of prostate cancer reported.[1] "In the USA, the total estimated expenditure on prostate cancer was 9.862 billion US dollars ($) in 2006. The mean annual costs per patient in the USA were $10,612 in the initial phase after diagnosis, $2134 for continuing care and $33,691 in the last year of life."[2] Once diagnosed, follow up care is essential in maintaining good health and managing side effects of treatment. Prostate cancer treatments come with a wide array of side effects. One adverse effect which significantly effects quality of life is fatigue. "40% or more of those on long term ADT reporting chronic fatigue or clinically-relevant fatigue which interferes with daily functioning."[3] Physician assistants have the opportunity to manage prostate cancer patients and the side effects from the treatments they receive.

Once diagnosed, the treatment modality depends on the stage and progression of the disease. Early stage prostate cancer typically grows very slowly and often remains

asymptomatic. Often treating the cancer would cause more problems than no treatment. Therefore, watchful waiting and active surveillance is often chosen as the treatment modality in these patients. Active surveillance includes monitoring PSA levels, performing digital rectal exams and prostate biopsies to monitor the stage of the cancer.[4] The cancer is monitored closely for signs of progression that would require further treatment. More advanced stages of prostate cancer can undergo radiation, chemotherapy, androgen deprivation therapy, and surgery. Radical prostatectomy can be used in more localized disease and involves surgically removing the prostate, seminal vesicles and ampulla of the vas deferens.[4] Radiation can also be used in localized disease in attempt to kill the cancerous cells.[4] More systemic treatment modalities can be used when the cancer is not localized to a specific area of the body. "The mainstay of treatment of more advanced prostate cancer is androgen-deprivation therapy (ADT)."[5] Male sex hormones such as testosterone help prostate cancer cells grow and causes further progression of the cancer.[6] Androgen deprivation therapy causes lowering of these male sex hormones and can be an effective treatment modality.[6] Androgen deprivation therapy can be achieved by surgical orchiectomy or drugs like luteinizing hormone-releasing hormone (LHRH) agonists.[6] Surgical orchiectomy, also called surgical castration, is a procedure that removes one or both testicles that ultimately reduce the levels of testosterone in the body.[6] Drugs such as LHRH agonists, also called medical castration, can be used to lower male sex hormone levels in the body.[6] Chemotherapy is another treatment modality that is utilized in more systemic disease.[4]

The treatment options listed above are associated with side effects. The three RCTs that are evaluated in this systematic review focus on men receiving androgen deprivation therapy and radiation treatment. Many side effects are reported by patients receiving these two treatment modalities but one in particular is fatigue. The fatigue experienced by these patients has a great

impact on the individual's quality of life. Patients often feel drained and are unable to carry out their activities of daily living. Physical activity has been shown to improve cardiovascular health and reduce fatigue.[3] Therefore, it is proposed that exercise programs may help improve fatigue experienced by men undergoing prostate cancer treatment. This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of resistance and aerobic exercise programs on fatigue in men with prostate cancer receiving androgen deprivation therapy and/or radiation therapy.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not aerobic and resistance exercise reduces fatigue in men with prostate cancer.

METHODS

Three RCTs that included men diagnosed with prostate cancer undergoing androgen deprivation therapy and/or radiation therapy were selected for analysis. All studies used aerobic and resistance exercises as the experimental intervention and compared the results to participants undergoing usual daily activity or delayed exercise. The Taaffe et al. study compared 2 experimental groups and 1 control group.[3] The 2 experimental groups participated in either impact loading and resistance training (ILRT) or aerobic and resistance training (ART).[3] The ILRT group participated in a twice weekly exercise program at a clinic and twice weekly home exercise program for 12 months.[3] The ART group participated in supervised exercise in the clinic 2 times a week and home aerobic activity for 6 months followed by a home exercise program for the next 6 months.[3] The delayed or usual care group (DEL) served as the studies control.[3] The DEL group was instructed to perform delayed exercise for 6 months with an instruction booklet followed by a 6-month twice weekly stationary cycling exercise.[3]

The Hojan et al. study focused on a 12-month physical exercise program in men with prostate cancer undergoing ADT and RT.[7] The physical exercise program consisted of 5 exercise sessions a week for 8 weeks during RT and then followed by 3 days a week for the next 10 months.[7] The physical activity consisted of aerobic and resistance exercises.[7] Participants in the control group were instructed not to start any formal physical activity, but continue to perform usual daily activity at home.[7]

The Bourke et al. study focused on a 12-week aerobic and resistance exercise program on men receiving ADT.[5] The exercise program started with supervised aerobic and resistance exercises that occurred twice a week for the first 6 weeks and once a week for the remaining 6 weeks.[5] The men were also instructed to perform a self-directed exercise session once a week for the first 6 weeks and then twice a week for the remaining 6 weeks.[5] A dietary plan was also given to the participants in the experimental group.[5] Men in the control group were instructed to perform usual care and no restrictions were placed on their activity.[5] The outcome ultimately measured in the 3 studies was to evaluate the effect aerobic and resistance exercise has on fatigue in men undergoing ADT and/or RT.

All of the articles chosen for this systematic review were published in English in peer review journals and found in the following databases: PubMed, Cochrane Library. The keywords “prostate cancer”, “exercise programs”, and “fatigue” were used to find the articles and then selected based on their relevance to each other, my clinical question and the presence of patient oriented evidence that matters (POEMs). Articles were excluded if a systematic review was present on the clinical topic with the caveat that three RCT’s were published after the systematic review. Inclusion criteria for the selected articles required the use of RCT’s and studies

published in the past 10 years. The statistics reported in the articles include p-value and f-score. The demographics and characteristics of the included studies are presented in table 1.

Table 1. Demographics of included studies

Study	Type	#Pts	Age(yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Taaffe et al.[3] (2017)	RCT	163	43-90yrs	-Men with documented prostate cancer and a minimum 2 month exposure to androgen deprivation therapy -Did not contain prostate specific antigen evidence of disease activity -Anticipated to receive androgen deprivation therapy for the next 12 months	-Bone metastatic disease, musculoskeletal, cardiovascular, or neurological conditions that could inhibit them from exercising -Lack the ability to walk 400 meters or perform exercise -Did not receive structured resistance and aerobic training in the previous 3 months	7	-Exercise program: Supervised aerobic and resistance training for 6 months and followed by a 6 month home program
Hojan et al.[7] (2017)	RCT	72	>18yrs	-Men with high or intermediate risk prostate cancer that have scheduled androgen derived therapy for 36 months -Prior to radiation therapy -Good general condition -A minimum age 18 years old	-Distant metastasis or disease progression that resulted in the patient receiving radiation therapy or the introduction of chemotherapy -Uncontrolled HTN or cardiac diseases resulting in circulation failure -Uncontrolled asthma -Insufficiently controlled metabolic disease, endocrine, rheumatic and absorption disorders as well as other tumors -Preexisting bone metastasis at high for fracture -Psychiatric illness or dementia or organic brain disease	6	-12 month aerobic and resistance exercise program
Bourke et al.[5] (2013)	RCT	100	53-87yrs	-Sedentary men with locally advanced or metastatic prostate cancer on long term ADT that had been receiving the therapy 6 months prior to the recruitment for the study	-Unstable angina, uncontrolled hypertension, recurrent myocardial infarction, pacemakers or painful and unstable bone metastasis	32	-12 week lifestyle intervention consisting of aerobic and resistance exercise

OUTCOME MEASURED

The outcome measured in all three RCT's was the effect aerobic and resistance exercise had on fatigue in men with prostate cancer undergoing ADT and/or RT. The Hojan et al. and Bourke et al. studies both used The Functional Assessment of Cancer Therapy-Fatigue Scale and the Taaffe et al. study used The European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 36 to assess fatigue in the participants.[3,5,7] The Taaffe et al. study assessed participants at baseline, 6 months, and 12 months.[3] The Hojan et al. study collected data at baseline, 8 weeks into the program, and at 12 months.[7] The Bourke et al. study conducted their assessments at baseline, 12 weeks and 6 months.[5]

RESULTS

All three studies analyzed in this systematic review are RCTs studying the effect of exercise on fatigue in men with prostate cancer undergoing ADT and or radiation therapy. Inclusion and exclusion criteria differed among the studies as well as the specific exercise intervention the participants received. All three studies contained continuous data that could not be converted into dichotomous data. Among the studies, changes in p value, ANOVA and f-score were analyzed.

The Taaffe et al. study is a three-armed RCT with 163 participants.[3] Participants were randomly assigned by computer to the follow three groups: ILRT (n=57), ART (n=54), and to DEL (n=48).[3] A total of 7 participants had missing data for fatigue leaving a total of 156 men representing in the final analysis for the study.[3] The author of the study states that compliance during the supervised exercise sessions were, "65% and 69% for ILRT at 6 mo and 12 mo, respectively, 69% for ART for the 1st 6-mo period, and 63% for DEL for the 6–12 mo period."[3] During the study, no adverse events from the exercise interventions led to the withdraw of any

participants.[3] All participants included in the study were men diagnosed with prostate cancer and scheduled to receive ADT for the next 12 months.[3] During the trial 31 men in ART, 29 in DEL and 34 men in ILRT also received radiation therapy in combination with ADT.[3] Men with an inability to exercise were excluded from the study and participants had to obtain medical clearance from their physician.[3] Fatigue was assessed using the EORTC QLQ-C36 with higher scores indicating greater levels of fatigue reported by the participant.[3] Each participants EORTC QLQ-C36 score report was not provided in this study however the overall mean score, standard deviation and p values were provided (table 2). At baseline, significant differences in level of fatigue was not seen among groups.[3] The ILRT group saw a fatigue score reduction of 5.7 points from baseline by the 6 month assessment.[3] Further reduction was not recorded by the 12 month mark.[3] The ART group saw a 5.7 point reduction in fatigue by the 12 month mark.[3] The DEL group had a very slight decrease in the fatigue score by the 6 month mark but reported a 5.5 point reduction in fatigue by the 12 month mark.[3] A statically significant reduction in fatigue was seen for all three groups with reported p values <0.05.[3]

Table 2. EORTC QLQ-C36 mean score at baseline, 6 months and 12 months; p value; mean(SD)

Fatigue	Baseline	6 months	12 months	p value
ILRT	27.9 (20.7)	22.2 (15.4)	22.5 (16.6)	0.0005
ART	23.4 (18.1)	21.9 (18.4)	17.7 (15.0)	0.0005
DEL	25.8 (20.2)	24.6 (17.7)	20.3 (15.3)	0.022

The Hojan et al. study is a 2-arm RCT with 72 participants randomly allocated to an exercise group (n=36) and a usual care group (n=36).[7] During the study, 5 withdrew from the control group and 1 in the exercise group leaving 66 participants represented in the final data in the study.[7] Participant compliance with the weekly supervised exercise sessions was 86% in the exercise group.[7] The author of the study states that no side effects were noted from participants

during the study, however 3 overuse injuries occurred in the exercise group that did not lead to any withdraws.[7] All participants in the study were men greater then 18 years old diagnosed with prostate cancer undergoing ADT and RT.[7] Specific inclusion and exclusion criteria are listed in table 1.[7] The FACT-F scale was used to measure the level of fatigue in participants and higher scores are indicative of less fatigue.[7] The analysis of variance (ANOVA) was used to determine the difference in means among the two groups with regards to fatigue.[7] Participants FACT-F score reports was not provided in this study but the mean score, standard deviation, f value and p value were provided (table 3). The author of the study states that, "ANOVA with repeated measures revealed significant differences between the 3 measurements with regard to all variables in the FACT-F questionnaire."[7] A large drop in the FACT-F score was seen in the control group between assessments 1 and 2 while a slight increase was seen between the same assessments in the exercise group.[7] During assessments 2 and 3 the FACT-F score in the exercise group was significantly higher than the control group indicating less fatigue.[7] The calculated p value <0.0001 indicates the reduction in fatigue is statistically significant (table 3).[7]

Table 3. FACT-F mean score (SD) reported at assessment 1-3 with reported f and p-value

Parameters	Assessment 1 (baseline)		Assessment 2 (8 weeks)		Assessment 3 (10 months)		F	p-value
	Exercise group	Control group	Exercise group	Control group	Exercise Group	Control group		
FACT-F Score	113.4 (3.5)	112.9 (3.9)	117.9 (9.7)	81.5 (9.7)	105.8 (7.7)	75.54 (8.1)	(2.111) =159.75	<0.001

The Bourke et al. study is a two-armed single blinded RCT with 100 participants randomly allocated to a lifestyle program group (n=50) or a usual care group (n=50).[5] During the trial 15 participants withdrew from the intervention group and 17 from the usual care group leaving a total of 68 participants represented in the data in the study.[5] Participant compliance was 94% for the supervised exercise and 82% for the non-supervised exercise during the 12 week

study.[5] The author of the study states there were no skeletal related adverse events that occurred during the study, but one man in the intervention group developed atrial fibrillation leading to withdraw and one death in the usual care group.[5] All participants in the study were sedentary men diagnosed with prostate cancer receiving ADT for a minimum of 6 months prior to the study and plans of long term ADT.[5] Specific inclusion and exclusion criteria for the study are listed in table 1.[5] The FACT-F questionnaire was used to measure the level of fatigue in participants with higher score indicating less fatigue.[5] Participants individual FACT-F score reports were not provided in this study but the mean FACT-F score, mean difference, confidence interval and p-value were provided (table 4). The adjusted mean difference for the FACT-F score between the two groups at the 12 week assessment was 5.3 and 3.9 at the 6 month follow up.[5] The author states that significant clinically relevant improvements in fatigue were seen at the 12 week mark among the two groups.[5] Following the withdraw of supervision at the 6 month assessment these clinically relevant improvements were still present.[5] The data in the study was determined to be statistically significant with reported p values of < 0.05 and a 95% confidence interval for both the 12 week and 6 month assessments (table 4).[5]

Table 4. FACT-F mean score, mean difference, CI and p value for baseline, 12-week and 6 month assessments

	Control	Intervention	Adjusted analysis		
	Mean	Mean	Mean difference	(95% CI)	p
Baseline FACT-F	41.4	40.3			
12 week FACT-F	42.4	45.8	5.3	(2.7-7.9)	<0.001
6 month FACT-F	41.9	43.6	3.9	(1.1-6.8)	0.0007

DISCUSSION

The three RCT'S discussed in this systematic review suggest that exercise can be utilized to mitigate fatigue experienced by men with prostate cancer undergoing treatment. The three

arms in the Taaffe et al. study had a decrease in the level of fatigue experienced by the participants.[3] The DEL group in this study participated in an exercise program only during the last 6 months of the trial.[3] A larger decrease was seen in the DEL group during these last 6 months.[3] The addition of the exercise program in the DEL group provided even further support that exercise can lead to a reduction in fatigue. The ART group interestingly continued to see a decrease in the level of fatigue at the 12-month assessment.[3] Participants were instructed to perform a home-based exercise program for this 6-month duration.[3] Therefore, participants continued to see a reduction in fatigue even when the exercise regimen was not supervised.

The Hojan et al. study data also saw a similar reduction of fatigue in the exercise group.[7] Differing from the Taaffe et al. study, participants in the control group were instructed not to start any formal physical activity.[7] All participants at baseline were undergoing ADT and 1 week away from starting RT treatment.[7] During assessment 2, all participants were 1 week post RT.[7] As seen in table 3 the level of fatigue decreased in the exercise group and increased in the control group.[7] Even with the addition of radiation therapy, a decline in fatigue was still seen in the experimental group and maintained during the final assessment.

The Bourke et al. study focused on sedentary men diagnosed with prostate cancer and treated with ADT.[5] During the 12-week assessment the level of fatigue reported by participants in the intervention group was lower than the levels reported by the control group.[5] After the withdrawal of supervision the fatigue levels increased from the 12-week assessment but still decreased from the baseline assessment.[5] Similar to the Taaffe et al. study, participants were still able to maintain a continual reduction in their fatigue level after withdrawing supervision.

There were some limitations to the studies due to the lack of a sufficient population size. All studies included a sample size less then 160 after withdraws which is not a sufficient

population size to be comparable to the general population. The Taaffe et al. study noted that a possible confounding factor was that the participants in the trial were generally healthy and non-smokers.[3] Other limiting factors in the trial were that the exercise sessions allowed interactions and sharing of information amongst participants and that the men were in the first year of ADT so the results may not be comparable to longer durations of therapy.[3] The Hojan et al. study noted the confounding factors in their trial to be an absence of a comparable control group.[7] The Bourke et al. study noted there was improved exercise behavior in the control group that could have contributed to the reduced difference between the experimental group at the 6-month assessment.[5] Double blind studies were not conducted in any of the three trials that could have led to researcher bias. Limitations present in this systematic review are due to differences in type of treatment, specific regimens, and length of treatment compared in the three studies. All three studies focused on ADT as a treatment modality; however, the Taaffe et al. study and the Hojan et at. study included men undergoing RT. Exercise regimens and length of treatment discussed in detail in the methods section differed among the studies as well.

CONCLUSION

Based on these three studies, aerobic and resistance exercise in men diagnosed with prostate cancer undergoing ADT and/or radiation therapy reduced the level of reported fatigue. Exercise is a cost-effective therapy for patients and can provide many other health benefits such as improving cardiorespiratory fitness. Medical providers can thus utilize exercise as a valuable tool in clinical practice. All three clinical trials were conducted on men undergoing only ADT and or radiation therapy. Future studies can investigate the effects that exercise has on fatigue in men receiving other common treatment modalities such as chemotherapy. Future studies can also include a larger population size and longer treatment trials.

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