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Resistive exercises versus aerobic exercises on quality of life in prostate cancer patients undergoing androgen suppression therapy

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Abstract
Androgen suppression therapy (AST) serves an important role in the treatment of patients with prostate cancer. However, AST leads a number of well-established toxicity-related musculoskeletal deficits (e.g., skeletal muscle loss, and strength), osteoporosis and skeletal fractures that can substantially reduce quality of life, physical function, and independence. Physical exercise has been suggested as a key lifestyle intervention due to its potential to limit and even reverse such toxicities.
Purpose: The purpose of the study was to determine which is more effective in improving quality of life in prostate cancer patients undergoing androgen suppression therapy: Resistive or Aerobic exercises?
Subjects and Methods: Thirty patients who had prostate cancer undergoing AST were randomly divided into 2 equal groups each one has 15 patients. Group A included 15 patients who received resistive exercise for two months/ 3times per week, Group B included 15 patients who received low volume aerobic exercise for two months/ 3times per week. Short Form 36-Item Health Survey (SF-36) was used to measure quality of life in both groups.
Results: The results of this study showed significant increase in several aspects of quality of life in group A that used resistive exercises over group B that used aerobic exercise including (PF, P= 0.001; RP, P= 0.01; GH, P= 0.02; VT, P= 0.004; SF, P=0.002; MH, P= 0.01).
Conclusion: It was concluded that resistive exercises had a greater value and more significant effect compared with aerobic exercises in improving QOL in patients with prostate cancer undergoing androgen suppression therapy evaluated by Short Form 36-Item Health Survey (SF-36) and therefore reverses its related side effects.

Keywords: prostate cancer, androgen suppression therapy, resistive exercise, aerobic exercise, quality of life and short form 36-item health survey (SF-36)

Introduction
Prostate cancer PCa is the most commonly diagnosed solid organ malignancy in the United States and remains the second leading cause of cancer deaths among American men. Approximately 220,000 new diagnoses of prostate cancer and over 27,000 deaths were estimated in the U.S. in 2015 [4]. The risk of PC increases with age, and the median age of onset is approximately 70 years. Treatment depends on stage, histology and the serum PSA level, beside the patients' general health and age [5].
Androgen suppression therapy AST is being used in combination with local therapy to treat patients with localized prostate cancer with adverse features [1], thus exposing patients to AST for longer periods, and as a result there are some concerns about the side-effects of prolonged therapy [6]. Changes in body composition related to ADT, including bone loss, muscle loss, and fat gain. These changes lead to significant deconditioning, muscle weakness, fatigue, and depression [7]. These treatment side effects of AST often have massive negative implications on the wellbeing and quality of life of PCa patients. Overcoming these side effects is of major interest for both the attending health care team and their patients [8].
During the last two decades, the perception of physical exercise interventions in cancer patients has gone through a significant change process. Therefore, the recommendation of regular physical activity is a rather new option for cancer patients especially in prostate cancer patients (PCaPs) receiving AST [8].

Patients and Methods
Study Design and population
The study was approved by the local ethics committee of surgery department. Informed consent was obtained from all patients. This study was a comparative study performed from January 2016 to December 2016 and patients were recruited from out-patient clinics of Urology and Nephrology center, Mansoura University. It was carried out on thirty patients with histologically confirmed prostate cancer who had been receiving AST for at least two months or more. Patients participated in the current study were divided randomly into two equal groups in number. Group (A) included 15 patients

who received resistive exercise for two months/ 3times per week. Group (B) included 15 patients who received low volume aerobic exercise for two months /3 times per week.

Inclusion criteria

The patients who participated in this study had the following criteria:

- Age ranged between 55:65 years.
- Histologically documented prostate cancer.
- Minimally prior to exposure to AST longer than 2 months.
- Anticipated to remain hypogonodal for the subsequent 6 months.

Exclusion criteria

The patients who excluded from this study had the following criteria:

- Patients with bone metastatic disease.
- Patients with prostate specific antigen PSA evidence of disease activity.
- Patients with musculoskeletal, cardiovascular, or neurological disorders that can inhibit them from exercising.
- Inability to undertake upper and lower limb exercise.
- Patients who used to do resistance training in the previous 3 months.

Equipment and tools

Measurement tools

- **Short Form 36-Item Health Survey (SF-36):** Quality of life was measured with the SF-36 questionnaire.

Therapeutic equipment:

- **Different weights** (0.5, 1, 1.5, 2, …, etc)Kg were used to perform resistive exercise for group (A).
- **Electronic treadmill ((Neutilus):** T916, made in USA) was used to perform low volume aerobic exercise for group (B).

Procedure of the study

Measurement procedures

Each patient in each group was assessed before and after the treatment (8 weeks) using:

- **Short Form 36-Item Health Survey (SF-36):** This survey asks for views of the patient about his health. The questionnaire was described for the patient and it's benefit as this information would help him keeping track of how he feel and how well he is able to do his usual activities, then he was asked to answer every question by selecting the answer as indicated and if he was unsure about how to answer the question, he was asked to give the best answer he can. The eight domains of the SF-36 address the health concepts of physical function, social function, bodily pain, emotional well-being, energy/fatigue (vitality), general health perceptions, role limitations due to physical problems and role limitations due to emotional problems.

It consists of items or questions which present respondents with choices about their perception of their health. The physical functioning dimension, for example, has 10 items to which the patient can make one of three responses: 'limited a lot', 'limited a little' or 'not limited at all'. These responses are coded 1, 2 and 3, respectively, and the 10 coded responses summed to produce a score from 10 to 30. These raw dimension scores are transformed onto a 0–100 scale, which are not comparable across dimensions. All domains are scored

on a scale from 0 to 100, with 100 representing the best possible health state [9].

Therapeutic procedures

Resistive Exercise

- Before the start of training of resistance exercise, one familiarization session was designed to habituate participants with different resistance exercises and to familiarize them with performing the 1-RM test. Intensity progressed from 40 to 60% of his 1-RM (According to Delorm Method the one repetition maximum is the maximum amount of resistance that can be moved through the full range of motion of an exercise for no more than one repetition) at the end of the eight week. During the familiarization session, it was ensured that all participants would use the correct techniques prior to taking part in the main training sessions.
- The session was started with warming up for 5-10 minutes consists of stretching exercises for the involved muscle group and cooling down about 5:10 minutes. All sessions were supervised to ensure correct technique and to monitor the appropriate amount of exercise and rest intervals. Resistive training exercise began with light weights that could be lifted comfortably and slowly through a full range of motion allowing adequate time to lift the weight (concentric contraction) as well as to lower the weight (eccentric contraction) using good posture and mechanics. Individuals had to avoid breath holding and straining (valsalva maneuver) by exhaling during the contraction or exertion phase of the weight lifting and inhaling during the relaxation phase.
- Each session consisted of number of exercises and each exercise performed by number of sets (2 sets) each set consisted of number of repetitions (8:12 repetitions), there was a time of rest between sets (1:2 minutes) and intensity progressed from 40 to 60% of his 1- RM at the end of the eight week. Exercise forms: chest press, seated row, shoulder press and triceps extension, leg press and leg extension, leg curl, with abdominal crunches also performed.

Aerobic Exercise

- Low volume aerobic exercise at 35:60 % of maximum heart rate was about 30 minutes consisted of warm up phase consisted of slow walking on treadmill for 5 minutes, training phase for 20 minutes on intervals increased gradually till reaching continous-20 minutes at the end of eight week and cooling down phase in the form of slow walking on treadmill for 5 minutes.
- The predicted maximal heart rate (220-age) was determined for each patient participated in the aerobic exercise training. Heart rate was measured by heart rate monitor related to the electronic treadmill. The warm-up period was a gradual increase in pace and intensity of the exercise. This allows for the body to increase blood flow to the muscles, and decreases the likelihood of a muscle or joint injury. The warm-up had to last between 5 and 10 minutes. The cool-down session lasted a similar amount of time as the warm-up, with the pace gradually decreased. Stretching exercises would be appropriate after aerobic exercise.

Results

SF-36 profile values (Physical Functioning PF, Role Physical RP, General Health GH, Social Functioning SF and Mental Health MH) are much increased in group A than group B. This leads to improvements in most of QOL aspects of PCaPs.

Table 1: Results of statistical analysis and comparison of post treatment mean values of SF-36 between both groups

Measure	Group A $\bar{X}$ ±SD	Group B $\bar{X}$ ±SD	MD	t- value	p-value	Sig
Physical functioning	76.56 ± 3.52	72.14 ± 3.23	4.42	3.56	0.001	S
Role physical	64.68 ± 13.47	53.57 ± 9.07	11.11	2.6	0.01	S
Bodily pain	65 ± 7.41	63.92 ± 5.86	1.08	0.43	0.66	NS
General health	61.87 ± 4.78	57.5 ± 5.45	4.37	2.33	0.02	S
Vitality	52.5 ± 4.83	47.5 ± 3.79	5	3.11	0.004	S
Social functioning	78.12 ± 7.21	68.75 ± 8.13	9.37	3.34	0.002	S
Role Emotional	60.35 ± 13.42	52.32 ± 17.1	8.03	1.43	0.16	NS
Mental Health	59.75 ± 3.41	57.14 ± 1.87	2.61	2.53	0.01	S

$\bar{X}$: Mean, MD: Mean difference, p value: Probability value,
SD: Standard deviation, t value: Unpaired t value, NS: Non significant, S: Significant

Discussion

Hormonal therapy for prostate cancer has been shown to negatively affect health-related quality of life. As such, reduced physical function and general health have also been reported in men on ADT- compared to non-ADT-treated men and healthy matched controls [10].

In patients with symptomatic metastatic disease, such adverse effects are often acceptable when balanced against the substantial benefits of this therapy in reducing symptoms; however, the effects of long-term ADT on health and QOL in men with 'early-stage' asymptomatic (M0) disease might be unacceptable and should be balanced against the sometimes questionable improvements in survival [11].

Exercise has been shown to improve cardiovascular fitness, muscle strength, body composition, fatigue, anxiety, depression, self-esteem, happiness, and several components of quality of life (physical, functional, and emotional) in cancer survivors [12].

Cancer clinicians should remember that exercise is safe for most cancer survivors and does not interfere with their ability to complete or benefit from medical treatments [13].

A recent randomized controlled trial [14] with 51 prostate cancer survivors (PCaS) on (ADT) was performed to investigate the effect of resistance exercise on improving

strength, physical function, and disability among these patients who were randomized to moderate to vigorous intensity resistance training or stretching (placebo control) for 1 year 3 times/ week. The study concluded that one year of resistance training improved muscle strength and perceptions of physical function in androgen-deprived PCaS. A similar study [15] of (20-week) progressive resistance exercise intervention twice weekly revealed that progressive resistance exercise has beneficial effects on muscle strength, functional performance and balance. Findings from these studies contribute to the mounting evidence that exercise should become a routine part of clinical care in older men with advanced prostate cancer and hence affecting positively on QOL.

An observational study [16] performed a high-intensity strength exercise program consisted of 12 weeks three times per week. Functional Assessment of Cancer Therapy-Prostate questionnaire (FACT-P) was administered as indicator of QOL. This study revealed that strength training elicits muscle hypertrophy even in the absence of testosterone and is effective in counteracting the adverse functional consequences of ADT in older black men with PCa. These improvements are associated with improved QOL. Another study [17] of 18-week high-intensity strength training program in cancer survivors as the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTC QLQ-C30) was developed to assess the HRQOL showed that a supervised, high-intensity strength training program seems to be an effective means to improve muscle strength, cardiopulmonary function, and HRQOL and should be incorporated in cancer rehabilitation programs.

A pilot study [18] with ten men underwent a 12-week resistance exercise training protocol produced clinically significant prostate cancer-specific improvements in the QOL for five men on ADT, compared with those on usual care. Another two-site study [19], 155 men prostate cancer who were scheduled to receive ADT for at least 3 months participated in a resistance exercise program three times per week for 12 weeks or to a waiting list control group demonstrated that men assigned to resistance exercise had higher quality of life than men in the control group. The Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale was used in the two previous studies. Both studies reported that resistance exercise reduces fatigue and improves quality of life in men with prostate cancer receiving androgen deprivation therapy and this form of exercise can be an important component of supportive care for these patients. While in a 20-men study [20] with bone metastases secondary to prostate cancer resistance exercise and control group for 12 weeks exercise prescription based on the location of the bone lesions (affected regions not targeted) found no significant differences between groups in QOL assessed by (SF-36) Health Survey.

A prospective, three-armed, randomized controlled trial [21] of 121 PCa patients initiating radiotherapy with or without ADT were randomly assigned to usual care, resistance, or aerobic exercise 3 times per week for 24 weeks demonstrated that resistance training improved quality of life QOL and therefore generated a longer-term improvements and additional benefits for QOL than aerobic component. While when comparing home-based aerobic training with home-based resistance training 5 times/ per week for 24 weeks in 66 prostate cancer survivors received at least 12 months of ADT it was found that after 6 months QOL was not significantly different between the two groups [22].

The results of our study can be explained by many factors depending on the studies' designs although both exercise groups had long and intense contact with interventionists, a degree of health professional contact that could have improved perceptions of QOL independent of the effect of exercise. Therefore, improvements in these outcomes may have been masked by variability in the types of exercise, intensity and duration of the interventions [23].

In these patients various factors influence a range of different QOL domains like disease-specific QOL and fatigue and seem to be the most meaningful domains to evaluate the effect of exercise intervention programs in those patients who receive AST [24].

Resistance training exercise has beneficial effects on different aspects of quality of life and reduces fatigue. Muscle strength was strongly related to physical functioning before treatment, and changes in muscle strength were correlated with changes in physical functioning as there was a strong association (from 0.56 to 0.75; $p<0.01$) between all strength exercises and the physical functioning scale from HRQOL. Several biopsychosocial mechanisms may explain the quality of life improvements in cancer survivors that result from exercise training, including cardiopulmonary adaptations, endorphins distraction, mastery achievements, positive feedback, and social interaction [17].

Accordingly it was found that an improvement in physical health was mediated by upper body muscle strength and walking speed while an improvement in general health was mediated by walking speed and fatigue [25].

Resistance training was found to produce significant improvements in walking speed in aging men as moderate but significant relationship was observed between muscle strength and walking speed. Therefore resistance training should be beneficial for both physical and general health whereas aerobic training did not show any effect on walking speed [26].

This would explain why patients improved their VO2peak in the resistance exercise group, while those of the aerobic exercise group did not. During an aerobic capacity test on an inclined treadmill, PCaPs on ADT might be primarily limited due to their muscular weakness and not because of their limited endurance capacity [27].

On the other hand, testosterone remains suppressed even immediately following an acute bout of high intensity resistance exercise. This is important given that several studies have demonstrated considerable elevation of testosterone in older men as a result of an acute bout of resistance training. These findings collectively suggest that non-androgen-mediated mechanisms, such as neurological adaptations to training, and possible acute exercise-induced elevations in other muscle growth mediators, such as HGH and IGF-1, are likely responsible for the observed changes in muscle function following resistance training [28].

We found that a broad range of objective improvements to QOL aspects resulted from a relatively brief exposure to exercise. These changes were accompanied with improvement to patient perceived well-being. The training regimen was well

tolerated in these patient groups and there were no adverse events, therefore resistive exercise program could be recommended for patients undergoing AST as an effective countermeasure for treatment-related adverse effects to the musculoskeletal system and to improve well-being.

Conclusion

Within the limitations and from the obtained data of the present study, the most notable conclusions are: Resistive exercises had a greater value and more significant effect compared with aerobic exercises in improving QOL in patients with prostate cancer undergoing androgen suppression therapy evaluated by Short Form 36-Item Health Survey (SF-36) and therefore reverses its related side effects.

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