Master Thesis
Research Article

Rikke Dan Olesen
Study Number: 20146969

Translational Medicine
The Faculty of Health and Medicine

September 2018 – May 2019

AALBORG UNIVERSITY
STUDENT REPORT

AALBORG UNIVERSITY

Title:

Effects of 12 weeks of supervised endurance and strength training on muscle strength, physical fitness, body composition and quality of life in patients with prostate cancer undergoing androgen deprivation therapy

Effekter af 12 ugers superviseret konditions,- og styrketræning på muskelstyrke, fysisk sundhedsniveau, kropssammensætning og livskvalitet i patienter med prostatakræft som gennemgår medicinsk kastrationsbehandling.

Semester:	9th and 10th
Semester theme:	Master thesis
Project period:	September 2018 - May 2019
ECTS:	60
Supervisors:	Jesper Franch & Lotte Sander
Project group:	9034 (TM)
Pages:	25 Research Article
	35 Appendix
	29 Working Paper

By signing this document, each member of the group confirms participation on equal terms in the process of writing the project. Thus, each member of the group is responsible for the all contents in the project.

Rikke Olesen

Rikke Dan Olesen
20146969

FORMÅL: At undersøge potentielle fordele af et 12 ugers træningsprogram implementeret i daglig klinisk praksis på muskelstyrke, fysisk sundhed, kropssammensætning og livskvalitet af mænd diagnosticeret med prostatakræft, som gennemgår medicinsk kastrationsbehandling. Yderligere er det undersøgt, hvordan koncentrationen af væksthormon, insulinlignende vækstfaktor-1 (IGF-1) og kortisol responderer på en akut træningsgang tidligt (uge 1) og sent (uge 12) i træningsperioden. **BAGGRUND:** Medicinsk kastrationsbehandling er brugt i behandling af prostatakræft ved at sænke niveauet af testosteron. Kendte bivirkninger af medicinsk kastrationsbehandling er tab af muskelstyrke og fysisk funktionalitet, ændringer i kropssammensætningen (øget fedtmasse og reduceret muskelmasse), samt nedsat livskvalitet. Fysisk aktivitet har vist sig at reducere disse bivirkninger. **METODE:** 23 mænd fra 57-78 år behandlet med medicinsk kastrationsbehandling deltog i et 12 ugers træningsprogram. Superviseret træningssessioner var udført 2 gange om ugen i fitnesscentret på Aalborg Universitetshospital (varighed 1,5 time). Alle sessioner inkluderede både kondition,- og styrketræning. Muskelstyrke var målt som 1 RM estimeret ud fra 12 RM (Brzycki; 1993). Funktionel muskelstyrke var undersøgt ved 30 sek. Rejse-sætte-sig-test og fysisk sundhedsniveau var undersøgt ved en cykeltest kombineret med en snakke test. Kropssammensætning blev målt med InBody370 (impedans) og livskvalitet blev undersøgt ved følgende spørgeskemaer: EORTC QLQ-C30 og EORTC QLQ-PR25. En blodprøve blev taget før og efter en træningssession i uge 1 og 12, og serumkoncentrationen af total testosteron, væksthormon, IGF-1, sex-hormonbindende globulin (SHBG) og dehydroepiandrosteron-sulfat (DHEAS) var undersøgt. Fysiske tests og antropometriske målinger var udført i uge 1 og uge 12. P-værdier < 0,05 var betragtet som signifikante. **RESULTATER:** Muskelstyrke steg signifikant i alle styrkeøvelser (Benpres 62,51 %, Brystpres 33,93 %, Biceps curl 34,89 %, Knæflex 31,55 %, Squat 126,38 % og planke 53,67 %). Funktionel muskelstyrke steg med 15,22 %, og fysisk sundhedsniveau blev forbedret med 12,68 %. Diastolisk blodtryk havde tendens til fald, men ingen signifikante ændringer blev fundet i systolisk blodtryk eller puls. Livvidde blev reduceret med 2,57 %, og en tendens til fald blev fundet i fedtmasse. Ingen signifikante ændringer blev fundet i total kropsvægt, muskelmasse, fedtfri masse eller body mass index. Analyse af hormoner viste ingen ændringer efter intervention. Total score og scoren af subskalaer forblev uændret i EORTC QLQ-C30 og QLQ-PR25. **KONKLUSION:** Kombination af kondition,- og styrketræning forbedrer muskelstyrke, fysisk sundhedsniveau, reducerer livvidde uden træningsrespons i serum af væksthormon, IGF-1 og kortisol eller forbedringer af livskvalitet. Medicinsk kastrationsbehandling holdt testosteron koncentrationen lav under træningsprogrammet, som indikerer at denne intervention er veltolereret og et godt supplement til reducering af bivirkninger fra medicinsk kastrationsbehandling.

Effects of 12 weeks of supervised endurance and strength training on muscle strength, physical fitness, body composition and quality of life in patients with prostate cancer undergoing androgen deprivation therapy

Rikke Dan Olesen

Abstract

PURPOSE: To investigate the potential benefits of a 12 week exercise program implemented in daily clinical practice on muscle strength, physical fitness, body composition and Quality of Life (QoL) in men diagnosed with prostate cancer undergoing androgen deprivation therapy (ADT). Further, it is examined, how the levels of Growth Hormone (GH), Insulin-Like Growth Factor-1 (IGF-1) and cortisol respond to an acute exercise bout early (week 1) and late (week 12) in the training period. **BACKGROUND**: ADT is used in the treatment of prostate cancer by lowering the testosterone level. Known side effects of ADT are loss of muscle strength and physical functionality, changes in body composition (increased body fat mass and reduced skeletal muscle mass) and reduced QoL. Physical activity has shown to reduce these side effects. **METHODS:** 23 men aged 57-78 years treated with ADT participated in a 12 week training program. Supervised exercise sessions were performed twice a week at the fitness center of Aalborg University Hospital (session duration 1.5 hrs.). All sessions included both endurance and strength training bouts. Muscle strength was measured as 1 RM estimated from 12 RM (Brzycki; 1993). Functional Muscle Strength was assessed through the 30 seconds Chair Test (30s-CST) and Physical Fitness level was assessed through the Graded Cycling Test combined with the Talk Test (GCT-TT). Body composition was measured by InBody370 (impedance) and QoL was investigated by following questionnaires: EORTC QLQ-C30 and EORTC QLQ-PR25. A blood sample was taken before and after an exercise session in week 1 and 12 and serum concentrations of total testosterone, GH, IGF-1, cortisol, Sex Hormone-binding Globulin (SHBG) and Dehydroepiandrosterone-Sulfate (DHEAS) were investigated. Physical tests and anthropometric measurements were done in week 1 and week 12. P-values < 0.05 were considered as significant. **RESULTS:** Muscle strength increased significantly in all strength exercises (Leg press 62.51 %, Chest press 33.93 %, Biceps curl 34.89 %, Knee flexion 31.55 %, Squat 126.38 % and the plank 53.67 %). Functional Muscle Strength (30s-CST) increased with 15.22 %, and Physical Fitness Level (GCT-TT) was improved with 12.68 %. Diastolic blood pressure had a tendency to decrease, but no significant changes were found in systolic blood pressure or heart rate. Waist circumference decreased with 2.57 %, and a tendency of decrease was found in body fat mass. No significant changes were found in total body weight, skeletal muscle mass, fat free mass or body mass index. Analyzed hormones did not show any changes after intervention. Total scores and scores of subscales remain unchanged in EORTC QLQ-C30 and QLQ-PR25. **CONCLUSION:** Concurrent endurance and strength training improves muscle strength, physical fitness level, reduces waist circumference without exercise responses in serum GH, IGF-1 and cortisol or improvements in quality of life. ADT kept serum testosterone concentrations low during the exercise program indicating that this intervention is well-tolerated and a good supplement to reduce side effects from ADT.

Introduction

Prostate Cancer and ADT

Prostate Cancer (PC) is the most common cancer type in men in Denmark. The incidence has increased the last couple of years in relation to new diagnostic methods and public awareness (Ammundsen & Engholm, 2018). The Danish incidence rate was 4505 in 2016. The prognosis of the disease is quite good with a 1 year relative survival rate of 98 % and a 5 year survival rate of 87 % (Hansen & Kejs, 2018). Androgen deprivation therapy (ADT) is used to treat PC and to reduce cancer-related morbidity (Culos-Reed et al., 2010; Nilsen et al., 2015). Different kinds of ADT exist, but in general ADT reduces the level of the male sex hormone, testosterone (Dawson et al., 2018). Even though, ADT is a good and effective treatment method against PC the lowered testosterone level is associated with important changes in body composition including reduced lean body mass and increased fat mass which affect muscle strength and functionality (Alibhai et al., 2015; Dawson et al., 2018; Galvão et al., 2006). Furthermore, increased sexual dysfunction, fatigue, risk of cardiovascular diseases, loss of bone-mass, increased risk of diabetes and reduced Quality of Life (QoL) are known side effects of low testosterone levels (Alibhai et al., 2015; Culos-Reed et al., 2010; Galvão et al., 2006; Galvão, Taaffe, Spry, Joseph, & Newton, 2010; Nilsen et al., 2015).

Hormones and Adaptations to Training

Testosterone has anabolic effects in relation to muscle protein synthesis and muscle hypertrophy after physical activity, both in young healthy men, in hypogonadal men (Kvorning, Andersen, Brixen, & Madsen, 2006; Mauras et al., 1998), but also in the elderly male population (Urban et al., 1995). These anabolic effects are also affected by Growth Hormone (GH) and Insulin-Like Growth Factor-1 (IGF-1) which together with testosterone are increasing in physical exercise (Kraemer & Mazzetti, 2008, p. 79). In contrast, cortisol has catabolic effects on protein synthesis and is also released by physical activity (Hall & Guyton, 2011, p. 928)

Type of training, intensity and frequency are important factors influencing training results (for review see Coffey & Hawley, 2007, p. 738). Both endurance and strength training influence induce changes in relation to effects of physical activity. Endurance training improves effects of both the cardiac and pulmonary system, such as reduced blood pressure and resting heart rate, cardiac hypertrophy, increased stroke volume and cardiac output, increased tidal volume and decrease in the respiration frequency. Further, this training type improves the mitochondrial function and the capillary systems which all result in a better aerobic condition (McArdle, Katch, & Katch, 2010, pp. 458–469). Strength training affects muscle hypertrophy by enhancing the cross sectional area of skeletal muscle fibers. These processes are controlled by changes in transcriptional and translational mechanisms of the protein synthesis (Coffey & Hawley, 2007, p. 750). Remodeling of the muscle structure and production of new muscle proteins, primarily the contractile elements; actin and myosin, are the primary mechanism behind muscle hypertrophy. New actin and myosin proteins can either be incorporated in existing sarcomeres, or be used in creation of new sarcomeres which enhances the contractile abilities and increases force production (Coffey & Hawley, 2007, p. 750; Kraemer & Mazzetti, 2008, p. 75).

In general, results in muscle strength after a training period of weeks to months are primarily based on neurological changes with increased firing rate of nerve impulses and better muscle coordination. After months to years muscle hypertrophy will occur and be the primary cause of increased muscle strength (McArdle et al., 2010, pp. 519–521).

IGF-1 increases by contractile activity of the muscles and supports the mechanisms behind muscle hypertrophy by activating the 3-Kinase-Akt-Mammalian Target of Rapamycin Pathway (PI3K-Akt-mTOR pathway) (Coffey & Hawley, 2007, p. 750; Gregory, 2002; Tidball, 2005). One of the upregulated pathways as response to the PI3K-Akt-mTOR pathway is the Mammalian Target of Rapamycin (mTOR) Pathway which enhances the protein synthesis.

Since testosterone, GH and IGF-1 are factors related to growth of muscle cells, it is important to understand how they influence each other. GH and IGF-1 are indirectly stimulated by testosterone (Hobbs, Plymate, Rosen, & Adler, 1993; Weissberger & Ho, 1993). Research has shown that the concentration of IGF-1 mRNA decreases in hypogonadal men (Mauras et al., 1998) and the IGF-1 production increases by supplementation of testosterone (Ferrando et al., 2002) which indicate the importance of testosterone in the IGF-1 production (Mauras et al., 1998).

Is Physical Exercise Beneficial?

It is known that physical exercise increases skeletal muscle mass and strength and modulates body composition in healthy adults (Dawson et al., 2018). Further, the importance of testosterone in the processes of muscle hypertrophy and reduction in fat mass in relation to physical activity is previously investigated in young and healthy men participating in a training program of 8 weeks with a setup containing two groups; one group receiving placebo and one group receiving ADT (Kvorning et al., 2006). Kvorning et al. found, as expected, reduced testosterone levels in the ADT-group, but remained testosterone levels in the placebo-group. The concentration of GH was unchanged in both groups throughout the intervention. The ADT-group did not increase isometric muscle strength after 8 weeks which in contrast was observed significantly in the placebo-group. According to the DXA scan, both groups showed increased lean body mass, but fat mass only increased in the ADT group and decreased in the placebo group (Kvorning et al., 2006). The use of physical activity as supplement to ADT in the aim of reducing the related side effects are not fully investigated in elderly men. A review by Gardner et al. found contrasting results in physical performance, body composition and QoL, but in general the study concluded that exercise is safe and beneficial for men undergoing ADT (for review see Gardner, Livingston, & Fraser, 2014). At least, it is unclear how serum concentrations of GH, IGF-1 and cortisol respond to an acute exercise bout in the early and the late stage of a 12 week training program including endurance and strength training.

The present study is designed to investigate the potential benefits of a 12 week exercise program implemented in daily clinical practice on muscle strength, physical fitness, body composition and QoL in patients diagnosed with prostate cancer undergoing ADT (primary aim). Further, it is investigated how GH, IGF-1 and cortisol respond to physical activity by investigating the serum concentrations before and after an exercise session in week 1 and again in week 12 (secondary aim).

Patients and Methods

Study Design

This prospective observational study evaluated the effects of a 12 week exercise program offered to men with PC undergoing ADT. These men were invited to participate in a "Patient School" through the standard of care at the Department of Urology of Aalborg University Hospital, Denmark. Results will be provided from a "Patient School" in the Autumn of 2018 and from Spring 2019.

Patients

This study included 23 elderly men diagnosed with prostate cancer undergoing ADT. Patient characteristics before start-up of the 12 week exercise program are presented in *table 1.*

Table 1: *Patient Characteristics*

n	23
Age range (years)	57-78
Mean age (years)	70.91 ± 5.93
Height (cm)	174.32 ± 5.80
Total Body Weight (kg)	86.75 ± 11.60
BMI (kg/m^2)	28.37 ± 3.46

Table 1: Patient characteristics before start-up of the 12 week exercise program. Values are means ± SD.

Patients were included in accordance to the inclusion and exclusion criteria from the Patient School. Patients were excluded if the castration treatment was planned to continue less than one year, if they did not understand or comply with the instructions or if they were unable to complete the planned physical activities by having an Eastern Cooperative Oncology Group (ECOG) Score of more than 2. Treatment, comorbidities and health related risk factors are presented in *table 2.* Three patients were treated with a combination therapy of both agonists and super hormones which also is noted in the table.

Table 2: *Treatment, Comorbidities and Health Related Risk Factors*	
ADT treatment, *n* (%)	
Agonists	9 (39.1)
Antagonists	1 (4.4)
Chemotherapy	1 (4.4)
Surgery	1 (4.4)
Super Hormones	8 (34.7)
Agonist + Super Hormones	3 (13.0)
ADT time (days, years)	1045 (2.86)
Comorbidities, *n* (%)	
Diabetes	
Yes	0 (0)
No	23 (100)
COPD	
Yes	3 (13.0)
No	20 (87.0)
Heart disease	
Yes	12 (52.2)
No	11 (47.8)
Health Related Risk Factors, n (%)	
Alcohol intake (units/week)	
0-7	15 (65.2)
8-14	6 (26.1)
> 14	2 (8.7)
Smoking	
Yes	2 (8.7)
No	21 (91.3)

Table 2: Treatment, comorbidities and health related risk factors before start-up of the 12 week exercise program. COPD = Chronic Obstructive Pulmonary Disease.

Patients had to participate in 16 out of 22 (75 %) exercise sessions and beside this, each exercise had to be completed and weight had to be noted in 13 out of 18 (75 %) exercise sessions before data were included in the statistical analysis. Two patients missed six exercise sessions, but in general patients participated in 19 out of 22 exercise sessions (86 %).

This study was conducted in accordance to the Declaration of Helsinki (Association, 2018) and was approved by the local Ethics Committee (N-20180069). All patients were informed of the purpose and eventual risks of the study before they signed a consent form before starting the measurements and exercise program.

Intervention

The Patient School started with an educational lesson lasting 1.5 hour followed by the 12 week group-based exercise program supervised by specially associated physiotherapists. The educational lesson was arranged to give the patients an introduction to prostate cancer, its progression, attendant side effects and an introduction to the newest dietary guidelines from the Danish Health Authority. Exercise sessions were planned twice a week and took place at the fitness center at Aalborg University Hospital. Each session started with a 15 minutes warm-up instructed by the physiotherapists, either on bicycles (Monark Ergomedic 828E) or later in the course stair walking. This was followed by strength and endurance exercises. One exercise session lasted in total 1.5 hour.

Strength training consisted of eight exercises targeting the major muscle groups of the body:

Leg press, Chest press, Biceps curl, Knee flexion, Squat, Crunches, Back extensions and the plank. All exercises, except the plank, were performed in three sets at each exercise session. The number of repetitions (reps) were changing during the 12 weeks; starting with 15 reps in the first weeks changing to 10 reps in the last weeks and variated between 2 or 3 sets in each exercise. The plank was performed as a group-exercise. Lifted weights in kg were supervised and noted by the patients or the physiotherapists.

Endurance training consisted of 500 meters of ergometer rowing (Concept2, model PM4), five minutes on a cross-trainer (Technogym, Synchro Excite 500) and six minutes of exercise on a bicycle (Monark Ergomedic 828E). Endurance exercises were conducted at an individual power focusing on improvements of each session. Physiotherapists recorded any kind of pain during the exercise sessions and adjusted the exercises/weight if necessary.

An overview of the training program for all 12 weeks is shown *appendix 1*. Exercise program and project setup were adapted from a project protocol at Herlev Hospital, Denmark (Østergren et al., 2016).

Measurements

Patients were evaluated and tested by following outcomes in week 1 and week 12.

Anthropometrics

Patients were invited to an individual nurse consultation before and after 12 weeks. Systolic blood pressure (S-BP), diastolic blood pressure (D-BP) and heart rate (HR) were measured by a blood pressure meter (OMRON) after 5-10 minutes seated rest. Height was measured by a stadiometer rounded to nearest centimeter and measurement of waist circumference (WC) was conducted by a tape measure rounded to nearest centimeter.

Test of Muscle Strength

The first two weeks of the training program (four exercise sessions) were used as familiarization with the training program and the training machines and was due to this not included in the statistics. The baseline measurement of strength exercises was the fifth exercise session (week 3) in which the weight of 12 Repetition Maximum (RM) was registered and recalculated to 1 RM by the formula of Brzycki (Brzycki, 1993):

$$1\,RM = \frac{W}{1.0278 - (R * 0.0278)}$$

W is weight in kg for a given exercise and *R* is the number of repetitions (Brzycki, 1993).

Recalculations from 12 RM to 1 RM were done for all mentioned strength exercises in section *"Intervention"*, except crunches, back extensions and the plank. Raw data from the plank was used in the statistics.

Test of Physical Fitness Level

A modified version of the Graded Cycling Test combined with the Talk Test (GCT-TT) was used to evaluate the physical fitness level. GCT-TT is a simple method used to evaluate the working capacity and has been used in different studies before (Nielsen & Vinther, 2016).

The GCT-TT was conducted on an ergometer bicycle (Monark Ergomedic 828E) with individually adjusted saddle height before starting. The physiotherapist asked the patient to pedal, as constant as possible, with 60 revolutions per minute (RPM) during the test. An intensity of 30 watt was set as starting value and increased by 15 watt every minute. In the end of each minute, the patient was asked to read loudly the Danish standardized Talk Test (appendix 2). This procedure continued until the patient reached the “talking limit”, where the Talk Test was audible confused estimated by the physiotherapists. Then, the test was terminated and the result (in watt) was noted by the physiotherapist. Estimation of the “talking limit” was based on the BORG scale reaching a value of 15 (Fysioterapeuter, n.d.-a). The BORG Scale is shown in *appendix 3*. To ensure inter-tester reliability the same bicycle and saddle height were used in both week 1 and 12, and the same physiotherapist tested the same patients in both weeks.

Test of Functional Muscle Strength

The 30 seconds Chair Test (30s-CST) was used to evaluate functional muscle strength in the legs. This method is previously used to evaluate leg muscle strength in the elderly population (60+) with loss of muscle mass and decreased functionality (Fysioterapeuter, n.d.-c). The test was done after the GCT-TT.

The patient was instructed by the physiotherapist to sit at the center of a 43 cm high chair, to hold arms crossed on the chest, to maintain a straighten back and to have the feet placed flat on the floor during the test. During 30 seconds it was counted how many times the patient was able to sit and rise from the chair without leaning forward (Fysioterapeuter, n.d.-b). In both weeks, the same chair was used and the same physiotherapist performed the test to ensure inter-tester reliability.

Body Composition

Body composition was measured by the InBody370 (Biospace Co., Ltd) Impedance Device. Outcomes of the analysis were Total Body Weight (TBW), Body Fat Mass (BFM), Fat Free Mass (FFM), Skeletal Muscle Mass (SMM), Body Fat Mass of Trunk (BFMT) and Body Mass Index (BMI). The patient was instructed to stand on the InBody370 in training clothes and to hold the two handrail handles for 1 minute while the body composition was calculated. The measurement was executed right after the GCT-TT and the 30s-CST.

Blood Sampling

Blood samples were taken 5-20 minutes before and after an exercise session in week 1 and 12. Samples were taken by a medical laboratory technician from an antecubital vein.
Each blood sample quantified approx. 20 ml blood and was used to investigate serum concentrations of total testosterone, cortisol, GH, IGF-1, Dehydroepiandrosterone-sulfate (DHEAS) and Sex-Hormone Binding Globulin (SHBG).

Analysis of Blood Samples

Blood sample analysis of total testosterone, cortisol, SHBG and DHEAS was conducted at the Department of Clinical Biochemistry, Aalborg University Hospital. Analysis of GH and IGF-1 was conducted at Unilabs, Copenhagen. All samples and sample residues were destroyed after analysis.

One patient missed the last blood sample both before and after the exercise session in week 12, and another patient had unmeasurable values in some hormones whereby statistics were done for 22 or 21 patients.

Quality of Life

EORTC *QLQ-C30* (version 3.0) was used to evaluate quality of life by answering 30 questions about physical function, social life, symptoms and overall health and QoL (Aaronson et al., 1993; Fayers P. M. et al, 2001). *EORTC QLQ-PR25* was used to evaluate symptoms and functional problems by answering 25 questions including urinary symptoms, bowel symptoms and hormonal treatment-related symptoms. The last four questions in the last subscale (item 52-55) were not answered in this study (Aaronson et al., 1993; van Andel et al., 2008)(Aaronson et al., 1993). The translated Danish versions were used in both questionnaires (*appendix 4 and 5).* Four answers were possible (1) *Not at all, (2) A little, (3) A lot or (4) Much.* The highest score reflected the highest rate of symptoms in QLQ-PR25 and the lowest score reflected the best QoL in QLQ-C30 (Fayers P. M. et al, 2001; van Andel et al., 2008).

Statistical Analysis

Statistical analysis was made in IBM SPSS 24.0 Software (Armonk, New York, USA). Tests of Normality were used to determine the distribution of data and where considered normally distributed when $p > 0.05$. Depending on the normality test, either parametric or non-parametric tests were used to compare means from week 1 (or 3) and week 12. According to blood samples, tests of normality showed both normally and non-normally distributed data, whereby non-parametric Wilcoxon Tests were made for all blood samples. Statistics from QLQ-C30 and QLQ-PR25 were based on non-parametric Wilcoxon tests investigating changes in the total score and in separated sub-scales between week 1 and 12. Statistical significance was set at $p < 0.05$ (marked with *), and a tendency of significance was defined as a p-value between 0.05 and 0.1 (marked with #). All results are presented as means ± SD and the belonging p-value.

Results

Absolute mean values, standard deviations (SD) and p-values for all tests are shown in *appendix 6, table 1 to 5.*

Anthropometrics

A tendency of a significant difference was found in D-BP with a decrease from 86.50 mmHg to 83.27 mmHg after 12 weeks of exercise. No significant differences were found in either S-BP or HR after the intervention period. Mean values ± SD are shown in *appendix 6, table 1.*

Strength Exercises

Muscle strength increased during the intervention period with significantly differences from week 3 in all muscle strength exercises. Leg press was improved with 62.51 %, Chest press with 33.93 %, Biceps curl with 34.89 %, Knee flexion with 31.55 % and Squat with 126.38 %. Mean values ± SD are presented in *figure 1* and data presented in *appen-*

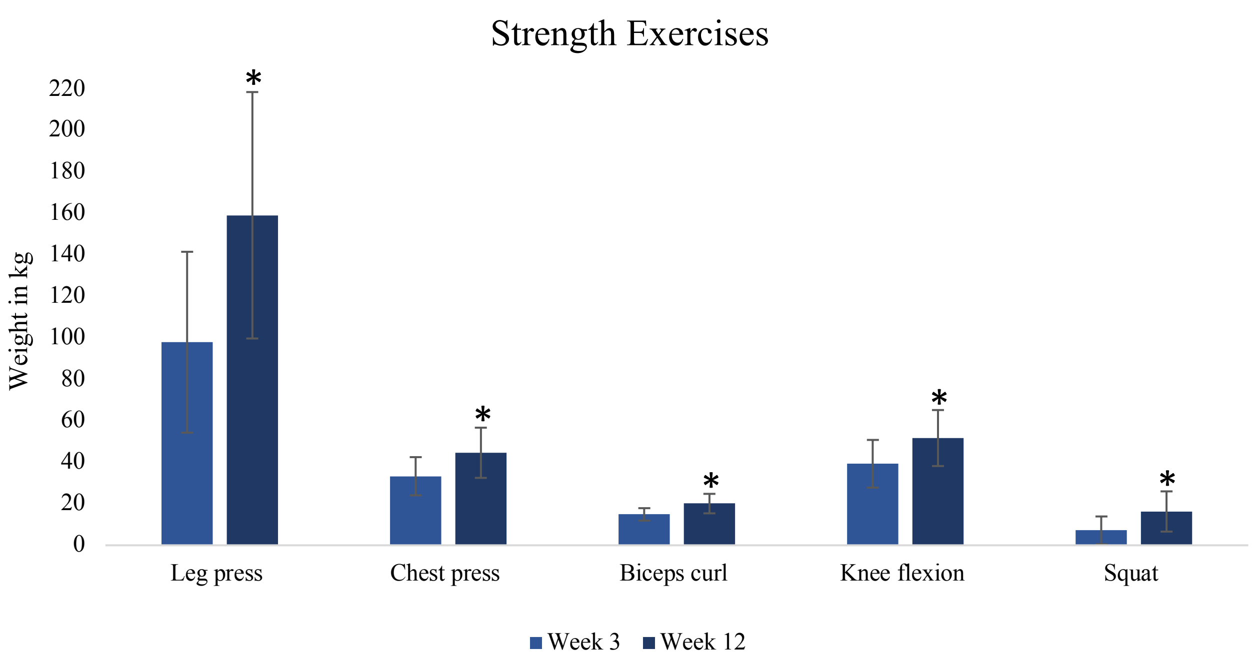

*Figure 1: Strength exercises from the 12 weeks exercise program. Estimated 1 RM values from 12 RM and SD values are presented for week 3 and 12. All exercise values are indicated in kg. Significance is marked with * (p < 0.05).*

dix 6, table 2. The total time of holding the plank in week 12 was significantly different from week 3 with an increase of 53.67 %. Mean values ± are illustrated in *figure 2* and data is presented in *appendix 6, table 2.*

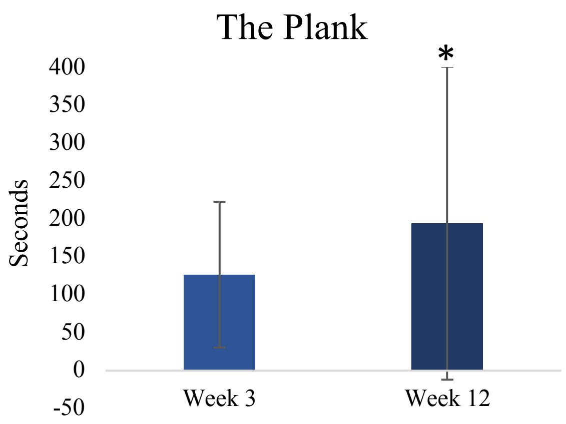

*Figure 2: Means (seconds) ± SD from the plank in week 3 and 12. Significance is marked with * ($p < 0.05$).*

Test of Functional Muscle Strength

30s-CST differed significantly between week 1 and 12 with an increase of 15.22 %. Mean values ± SD are illustrated in *figure 3,* and data is presented in *appendix 6, table 3.*

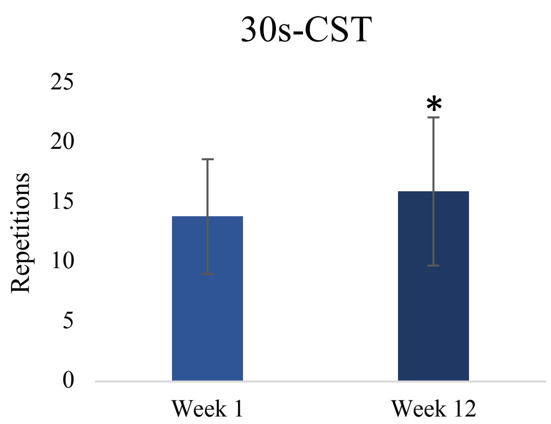

*Figure 3: Means (reps) ± SD from the 30s-CST in week 1 and 12. Significance is marked with * ($p < 0.05$).*

Physical Fitness Level

Significant improvement was found in GCT-TT. The mean value in week 12 differed significantly from week 1 with an increase of 12.68 %. Mean values ± SD are illustrated in *figure 4* and data is presented in *appendix 6, table 4.*

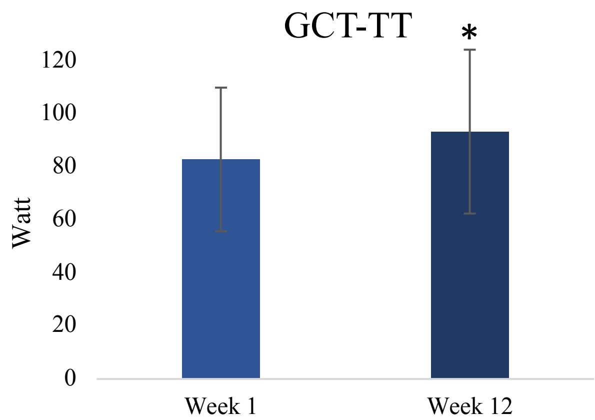

*Figure 4: Means (watt) ± SD from the GCT-TT in week 1 and 12. Significance is marked with * ($p < 0.05$).*

Body Composition Analysis

A significant decrease was found in WC from 109.04 cm in week 1 to 106.24 cm in week 12 (2.57 %). Furthermore, a tendency of a significant decrease was found in BFM from 28.3 kg to 27.6 kg (2.47 %) and in BFMT with a reduction from 14.97 kg to 14.63 kg (2.32 %) after the 12 weeks exercise program. No significant differences were found in SMM, FFM, TBW or BMI after 12 weeks of intervention. Nonetheless, the mean value of BMI decreased insignificantly from 28.39 to 28.20 kg/m^2 and the mean value of TBW decreased from 86.75kg to 85.91kg from week 1 to week 12.

Mean values ± SD are shown in *appendix 6, table 5.*

Blood Sample Analysis

The ADT treatment kept the total testosterone level at a very low concentration in all patients during the exercise period. Moreover, total testosterone concentrations were not affected importantly by a single exercise bout, neither early or late (*table 4*).

Delta values of all measured variables were unchanged with respect to the exercise period, but showed minor insignificant variations. Δ-total testosterone varied from 0.17 to 0.08 nmol/L, Δ-GH varied from 0.44 to 0.75 µg/L, Δ-IGF-1 varied from 0.23 to 1.45 nmol/L, Δ-cortisol varied from 145.55 to 125 nmol/L, Δ-SHBG varied from 1.18 to 0.09 nmol/L, and Δ-DHEAS varied from 65.05 to 98.45 nmol/L. Delta serum concentrations ± SD are presented in *table 3*.

Moreover, absolute values (before and after an exercise bout) of GH and cortisol concentrations were significantly increased from before to after an exercise session in week 1 and 12. Absolute values of IGF-1 concentrations were unchanged, but showed minor insignificant variations from before to after an exercise session. Absolute mean values ± SD and p-values are presented for all measured blood sample variables in *table 4.*

Quality of Life

QLQ-C30 showed no significant differences in total score across all subscales after the intervention period. Further, no significant differences were found in the total score of health, the total score of quality of life or in separated topics from the questionnaire. *QLQ-PR25* showed no significant change in the total score across all multi-item scales or in the sub-questions, separately.

Table 3: Delta Serum Concentrations

Variables	**Week 1** Δ ± SD	**Week 12** Δ ± SD	**p-value**	**Ref. values**
Testosterone (n = 21)	0.17 ± 0.26	0.08 ± 0.21	0.157	8.6-30.7 nmol/L
GH (n = 22)	0.44 ± 0.94	0.75 ± 1.66	0.258	< 3.0 µg/L
IGF-1 (n = 22)	0.23 ± 3.38	1.45 ± 6.42	0.337	3-26 nmol/L
Cortisol (n = 22)	145.55 ±218.70	125 ±188.65	0.485	133-537 nmol/L
SHBG (n = 22)	1.18 ± 4.92	0.09 ±16.43	0.204	28-101 nmol/L
DHEAS (n = 22)	65.05 ±154.77	98.45 ±141.28	0.931	910-6760 nmol/L

*Table 3: Blood Sample Analysis: Delta Serum Concentrations± SD calculated from the absolute values before in week 1 and 12. Significance is marked with * (p < 0.05). Reference intervals are belonging to the age group in this study.*

Discussion

The primary aim of this study was to investigate potential benefits on muscle strength, physical fitness, body composition and QoL after a 12 weeks exercise program in men diagnosed with PC undergoing ADT. The secondary aim was to investigate how the concentrations of GH, IGF-1 and cortisol respond to physical activity, by investigating the serum concentrations before and after an exercise session in week 1 and again in week 12.

Adaptations to Strength Training, Hormone Responses and Body Composition

ADT suppress the level of testosterone acting as an effective treatment against PC (Dawson et al., 2018). The importance of testosterone in the processes of increased muscle mass and strength are previous investigated, both in young healthy men (Kvorning et al., 2006; Mauras et al., 1998) and in the elderly male population (Gonzalez et al., 2016)

In the present study, all strength exercises increased significantly from week 3 to 12 with improvements of at least 31 % in all exercises. Improvements of muscle strength after an exercise program are previously reported in men undergoing long-term ADT (Dawson et al., 2018; Galvão et al., 2010; Segal et al., 2003). Three studies investigated the difference in muscle strength between an exercise group and a control group during 12 weeks (2-3 training session/week and intensity of 6-12 RM) with significant improvements in Leg press and Chest press (Dawson et al., 2018; Galvão et al., 2010; Segal et al., 2003). These findings support the results in the present study. Another study, investigating effects of strength training in the beginning of ADT, also found significant improvements in Leg press and Chest

Table 4: Absolute Serum Concentrations

Variables	Week 1 BES *Mean* ± SD	Week 1 AES *Mean* ± SD	Week 1 p-value	Week 12 BES *Mean* ± SD	Week 12 AES *Mean* ± SD	Week 12 p-value	Ref. values
Testosterone (n = 21)	0.44 ± 0.09	0.62 ± 0.31	0.006 *	0.41 ± 0.05	0.49 ± 0.21	1.000	8.6-30.7 nmol/L
GH (n = 22)	0.73 ± 1.09	1.17 ± 1.12	0.039 *	1.00 ± 1.34	1.75 ± 1.53	0.45	< 3.0 µg/L
IGF-1 (n = 22)	18.09 ± 7.33	18.32 ± 8.99	0.756	16.64 ± 11.15	18.09 ± 10.22	0.300	3-26 nmol/L
Cortisol (n = 22)	277.27 ± 159.48	422.82 ± 247.59	0.005 *	219.95 ± 97.14	344.95 ± 207.76	0.005 *	133-537 nmol/L
SHBG (n = 22)	96.68 ± 73.25	97.86 ± 75.27	0.273	94.09 ± 68.48	94.18 ± 73.05	0.980	28-101 nmol/L
DHEAS (n = 22)	1799.95 ±1187.54	1865 ± 1271.20	0.062	1574.77 ±1054.53	1673.23 ±1088.81	0.004 *	910-6760 nmol/L

*Table 4: Blood Sample Analysis: Delta Serum Concentrations± SD calculated from the absolute values before in week 1 and 12. Significance is marked with * ($p < 0.05$). Reference intervals are belonging to the age group in this study.*

press after 3 months (Cormie et al., 2015). This is opposite the present study with a mean ADT time of 1045 days (*table 2*).
Further, several studies found significant increase of appendicular lean mass (kg) after an intervention period (Cormie et al., 2015; Dawson et al., 2018; Galvão et al., 2010). The present study did not find any significant increase in fat free mass or skeletal muscle mass which otherwise would have indicated muscle hypertrophy. The study by Segal et al. did not find changes in body weight, BMI, waist circumference or in measured subcutaneous skinfolds after 3 months, but the results still showed enhanced muscle strength in both upper and lower strength exercises in the intervention group (Segal et al., 2003). These findings are similar to the results in the present study and the increased muscle strength may then indirectly be explained by neurological adaptations to strength training as no significant muscle hypertrophy was found.

Testosterone levels and muscle mass are also related to functional muscle strength (Dawson et al., 2018). This is supported by findings of decreased physical function after starting treatment of ADT in prostate cancer patients (Gonzalez et al., 2016). Though, physical function is known to be reduced by ADT, findings in this study show a significant improvement of 15.22 % in functional muscle strength assessed through 30s-CST. A number of studies found similar improvements by investigating functional muscle strength which may show the ability of improving functional muscle strength in this patient group (Galvão et al., 2006, 2010; Nilsen et al., 2015).
The present study used an impedance device measuring the body composition. As mentioned before, several studies found an increase in muscle mass (appendicular lean mass), but assessed changes in body composition by a DXA scan (Cormie et al., 2015; Dawson et al., 2018; Galvão et al., 2010). The setup in all these studies is quite similar (12 weeks, resistance and/or strength straining) and quit similar to the present study. The difference in results with regard to changes in body composition may be explained by the different measuring methods and may indicate that the DXA scan gives better and more precise results than the impedance device method.

Lowering testosterone levels by ADT is previously found to affect body composition with a reduction in fat free mass (muscle mass) (Mauras et al., 1998), and an increase in body fat mass (Kvorning et al., 2006; Mauras et al., 1998). In the present study, the circumference of the waist was significantly decreased with 2.57 % after the 12 week exercise program which is supported from other studies (Culos-Reed et al., 2010; Gaskin et al., 2016).

Reductions in waist circumference and the tendencies of reductions in body fat mass indicate that the training program positively affect the body composition. However, no significant reduction in total body weight or body mass index was seen in the present study. Results in the literature are controversial. Some studies found significant reductions in body fat mass (Cormie et al., 2015; Dawson et al., 2018; Wall et al., 2017).
The training period in the study by Wall et al. was 6 months (24 weeks) (Wall et al., 2017). The training period in the study by Dawson et al. was 12 weeks, but the training frequency was 3 times pr. week instead of 2 times pr. week as in the present study (Dawson et al., 2018). Further, changes in body fat mass was measured by a DXA scan in the mentioned studies and not by an impedance device as in the present study (Cormie et al., 2015; Dawson et al., 2018; Wall et al., 2017). Other studies did not find a decrease in body fat mass. The duration of these studies was quite similar as the studies who found a reduction in body fat mass (20, 12, 16 and 12 weeks) (Galvão et al., 2006, 2010; Nilsen et al., 2015; Segal et al., 2003). This could indicate that the length of the training intervention itself is not paramount for the body fat mass results. The training frequency (exercise sessions pr. week) and the measuring method also seem to have an important effect on the results of body fat mass. This statement is supported by a previous study investigating the difference of using a DXA scan and an impedance device for measuring body composition with best results by the DXA scan (Day et al., 2018). To obtain more significant results it may be an idea to lengthen the training period of the present study in combination with increased intensity and time duration of all endurance exercises, but also change the body composition measuring method to DXA scan, supported by the study of Day et al. (Day et al., 2018).

This is the first study to investigate how the levels of GH, IGF-1 and cortisol respond to an acute exercise bout early (week 1) and late (week 12) during a training period in men undergoing ADT. No significant differences were found in delta values of all measured blood sample variables, but the acute response after an exercise session increased significantly in GH and cortisol in week 1 and 12. A previous study has investigated the difference in testosterone, GH and cortisol after 20 weeks of exercise in elderly men during ADT. Blood samples were taken while the patient was in rest in week 1, 10 and 20, but no changes were observed (Galvão et al., 2006). This is supported by the study of Kvorning et al. who did not find changes in GH after 12 weeks of intervention in young healthy men with suppressed testosterone levels (Kvorning et al., 2006).

Due to the literature, testosterone, GH and IGF-1 increase with physical activity in healthy men (Kraemer & Mazzetti, 2008). Abovementioned results show unchanged levels of GH and IGF-1 when the testosterone level was reduced (Galvão et al., 2006; Kvorning et al., 2006). This may indicate that testosterone plays an important role in the response of GH and IGF-1 after physical exercise. The findings of no increase in muscle mass after 12 weeks of strength training in the present study may support this. A study by Borst et al. supports these findings. The study investigated the response of IGF-1 after strength training in healthy middle-aged men and woman and they observed increased concentrations of IGF-1 after 13 weeks (Borst et al., 2001). Though, serum concentrations of GH increased significantly after an exercise session in week 1, it did not seem to be enough to mediate muscle hypertrophy in men with suppressed testosterone levels.

To sum up, this study found increased muscle strength in all strength exercises, but no changes in body composition with regard to muscle mass, nor significant change in concentrations of hormones related to muscle hypertrophy after 12 weeks of intervention. This indirectly show that the increase in strength not is caused by increased muscle mass, but instead explained by other mechanisms as neurological adaptations, but these adaptations cannot be measured beside the observed increased strength. According to the blood samples *(table 3),* delta values of GH (week 1 = 0.44; week 12 = 1.75) and IGF-1 (week 1 = 0.23; week 12 = 1.43) show small increases from week 1 to 12. None of these increases in GH and IGF-1 were significant which indirectly substantiate the results of no changes in skeletal muscle mass and further support that observed muscle strength in the present study may be explained by neurological adaptations.

Changes in Physical Fitness Level and related Anthropometrics

It is well known that regular endurance training reduces diastolic,- and systolic blood pressure. Reductions are seen both in rest and during exercise (Beydoun et al., 2014; Culos-Reed et al., 2010; McArdle et al., 2010, p. 467). In the present study, a tendency of a decrease was found in diastolic blood pressure, but no significant differences were found in systolic blood pressure or heart rate after the 12 week exercise program.

A study by Culos-Reed et al. found a decrease in both diastolic and systolic blood pressure after 16 weeks of intervention. Fifty three patients (intervention group) with prostate cancer receiving ADT for at least 6 months completed the intervention including a combination of home-based exercise sessions and weekly group meetings with aerobic and light strength training (Culos-Reed et al., 2010). These findings partly support the present study showing a tendency of decrease in diastolic blood pressure. In contrast, a study by Gaskin et al. did not find any significant difference in blood pressure after 12 weeks of exercise, but a significant reduction in heart rate (Gaskin et al., 2016). Another study supports these results with no findings in blood pressure after intervention (Cormie et al., 2015).

Factors as initial level of aerobic capacity, training intensity, frequency and duration play an important role of getting good aerobic training responses (McArdle et al., 2010, p. 470). Some of these factors are different in the mentioned studies which may explain the various results (Cormie et al., 2015; Culos-Reed et al., 2010; Gaskin et al., 2016). The set-up in the present study, and the studies by Cormie et al. and Gaskin et al. is broadly the same (12 weeks with 2-3 sessions pr. week and combined endurance and strength training), whereby the study by Culos-Reed et al. has an intervention period of 16 weeks with 3-5 exercise sessions pr. week (Cormie et al., 2015; Culos-Reed et al., 2010; Gaskin et al., 2016). The duration and frequency of the intervention program seem to be important factors to reduce blood pressure levels. Furthermore, it can be difficult to get reliable results by measuring blood pressure and heart rate due to nervousness and the white coat effect at the hospital.

Endurance training improves factors related to the use and transport of oxygen in the active muscles. Effects of prolonged aerobic training are often independent of gender, age, race and sometimes also independent of health status (McArdle et al., 2010, p. 458). The number of mitochondria increases and the muscular capillary system is improved by increased amounts of capillaries pr. muscle fiber after a period of endurance training. These improvements result in increased O_2 diffusion and extraction. This results in a better capacity to work aerobically before lactate production and accumulation (McArdle et al., 2010, pp. 458–459).

In this study, Physical Fitness Level assessed through GCT-TT was significantly improved with 12.68 % from week 1 to 12. Positive results of investigating physical fitness level are also found in other studies (Cormie et al., 2015; Dawson et al., 2018; Galvão et al., 2006; Gaskin et al., 2016). Several studies used the 6-min walk test to asses physical fitness level, and found a significant improved walk distance after the intervention period (Galvão et al., 2006; Gaskin et al., 2016). Other studies used the 400 m walk test to investigate physical fitness level and found also improved results in men undergoing ADT after a training intervention period (Cormie et al., 2015;

Dawson et al., 2018; Galvão et al., 2006, 2010). These studies have an intervention period of 12 to 20 weeks. In contrast, Culos-Reed et al. did not find a significant improvement in the 6-min walk test after an intervention period of 16 weeks (Culos-Reed et al., 2010). Previously, a decrease in physical function was found in men after treatment with ADT (Alibhai et al., 2015; Gonzalez et al., 2016). The studies show that it is possible to enhance the physical function in this patient group after an intervention period of at least 12 weeks.

According to abovementioned studies with regard to improvements in physical function, inequalities may be explained by the initial level of aerobic fitness level, weekly activity, differences in the intervention program or just be related to individual changes and functionalities. To obtain most reliable results and have a partly homogenous intervention group, it may be a good idea take the initial fitness level and weekly activity into account before starting the intervention.

Quality of Life

The impact of ADT on QoL is previously investigated by Alibhai et al. where QoL was assessed through the 36-Item Short Form Health Survey (SF-36) including a physical and a mental scale. Results showed that QoL decreased in the ADT group in the first six months compared to baseline and control groups (Alibhai et al., 2015). In the present study, QoL and symptoms in cancer patients were investigated through QLQ-C30 and QLQ-PR25, respectively. No significant changes were found in the total score or in subscales investigated separately. Two studies did not find any difference after 16 weeks of exercise between an exercise group and a control group using the QLQ-C30 which support the findings in the present study (Culos-Reed et al., 2010; Nilsen et al., 2015). QoL can also by assessed through the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale which includes 27 general questions and 12 questions specific to prostate cancer and its treatment. Increased QoL is previously investigated through the FACT-P after 12 weeks of exercise (Dawson et al., 2018; Segal et al., 2003).

A possible explanation of different results may be explained by the different use of questionnaires. It seems like the QLQ-C30 not is as good and effective to assess differences in QoL in such a short time period (12 weeks) as the FACT-P. Another explanation of unchanged results of QoL could be the time when the questionnaire is answered. Uncontrolled progress of tumors, increased PSA levels or other private things at home may indirectly influence QoL in a negative way, along with the good physiological effects of the training program seen in the tests. Thus the findings of no change in QoL may not be a negative result. Different kinds of treatments exist against PC (radiation therapy, radical proctectomy, ADT and combinations). A study by Adam et al. investigated QoL, functionality and symptoms (QLQ-PR25) in groups receiving different treatment forms. Results showed that the ADT-group report the worst QoL and highest rate of symptoms compared to the other treatment forms (Adam et al., 2019). According to this findings, it is important to increase functionality and decrease the symptom rate in these patients. Results in the present study did not find any significant changes in the EORTC-PR25 which indicates that this training program did not worsen QoL but did not either have a positive effect on QoL and symptoms.

According to safety and effectiveness of a training intervention for men undergoing ADT it is important to investigate the response of the testosterone and the PSA level. Kvorning et al. has previously investigated the response of testosterone levels in young healthy men undergoing ADT with results showing a decrease in the ADT group and constant testosterone levels in the control group (Kvorning et al., 2006). Moreover, the levels of testosterone and PSA were not affected by physical training (Culos-Reed et al., 2010; Galvão et al., 2006). These findings are supported by the results in the present study and may indicate that physical training is good and safe in respect to elderly prostate cancer patients undergoing ADT and may reduce some of the ADT related side effects.

In conclusion, concurrent strength and endurance training improves muscle strength, physical fitness level, reduces waist circumference without exercise responses in serum GH, IGF-1 and cortisol or improvements in quality of life. ADT kept serum testosterone concentrations low during the exercise program indicating that this intervention is well-tolerated and a good supplement to reductions of side effects from ADT.

Acknowledgements

The author would like to address a special thanks to my internal supervisor Jesper Franch who has supported and guided me throughout the conduction of this study. Additionally, the author would like to thank the external supervisor Lotte Sander and research nurse Kirsten Steffensen (Department of Urology, Aalborg University Hospital) for their initiative and collaboration within this project and also for a good introduction of the clinical life at the hospital. The study is supported by the Department of Urology, Aalborg University Hospital.

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