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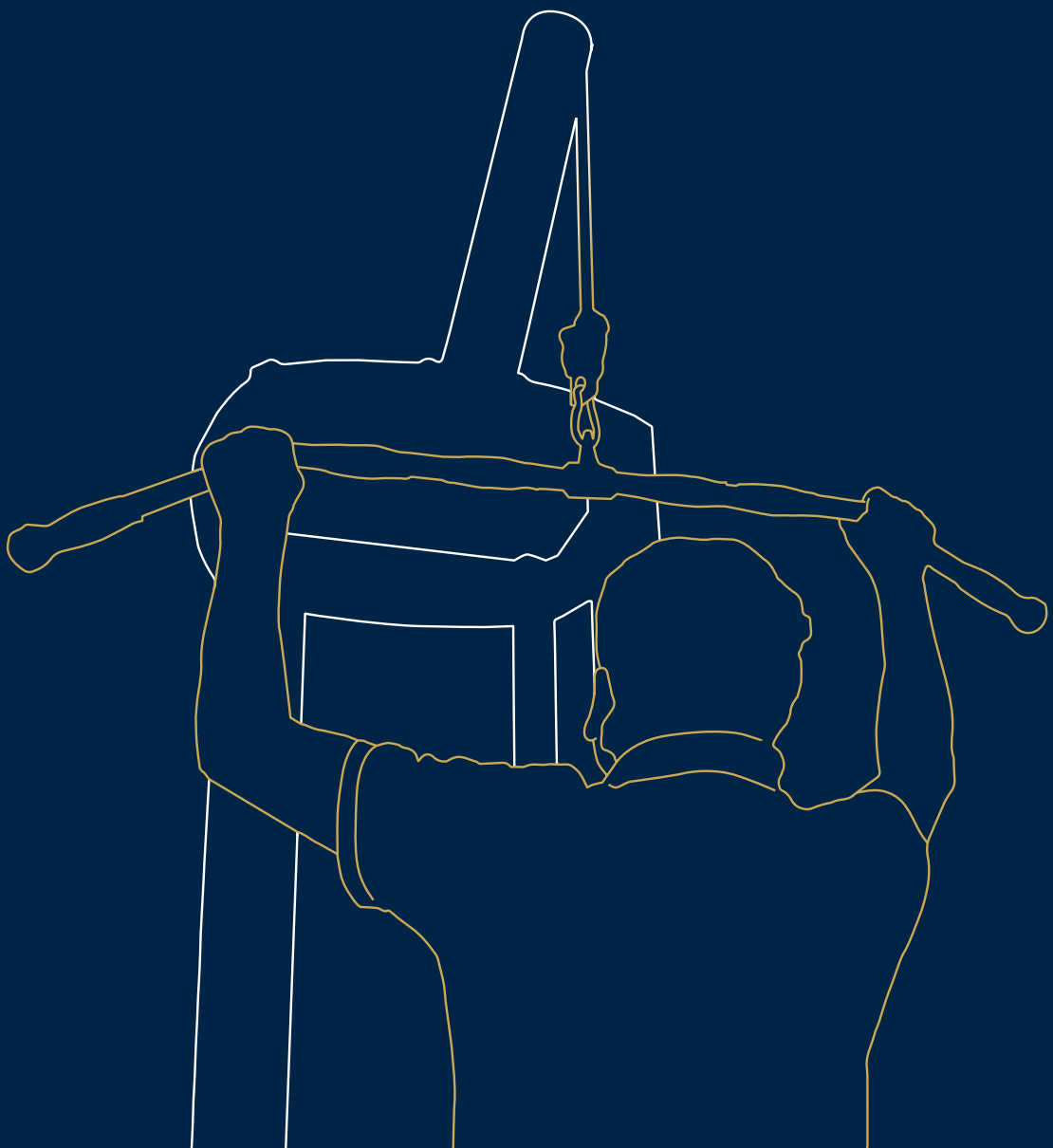
Lisanne H.P. Houben



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The studies presented in this thesis were performed within the NUTRIM, School of Nutrition and Translational Research in Metabolism at Maastricht University, in collaboration with the Netherlands Comprehensive Cancer Organisation (IKNL). The studies were (partly) performed within the framework of TiFN, which in 2023 has merged into Next Food Collective, and were partly funded by KWF Dutch Cancer Society and Arla Food Ingredients. Financial support for the publication of this thesis by Maastricht University, IKNL, Next Food Collective, and the Sint Maartenskliniek, is gratefully acknowledged.

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Dissertation

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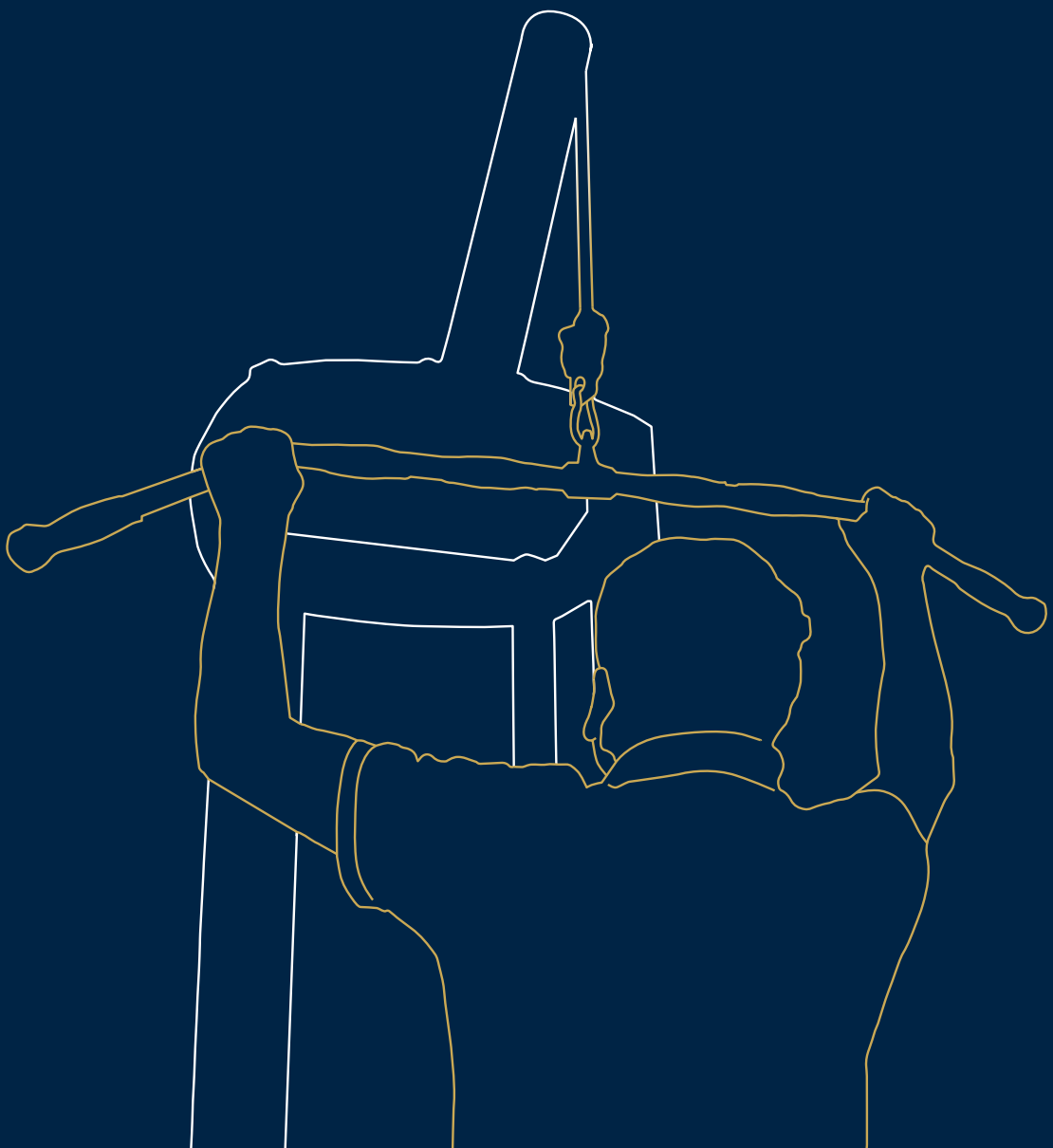

CHAPTER 1

General introduction

There is an increasing interest for the clinical application of physical activity and exercise. Growing evidence shows that regular physical activity reduces the risk of developing several diseases, including cancer, cardiovascular, and chronic metabolic diseases (1). In addition, the importance of exercise as a therapeutic intervention in the management of diseases, e.g. exercise training during and after treatment, is more and more acknowledged (1).

In this thesis, we focus on the application of exercise training during treatment for prostate cancer. Prostate cancer is the most frequently diagnosed form of cancer in European men. In 2020, nearly half a million men were diagnosed with prostate cancer (2). Many of these men will be treated with androgen deprivation therapy (ADT) during their disease process. ADT is the mainstay in the treatment of (locally) advanced prostate cancer and can substantially improve survival (3-5). By suppressing testosterone to castration levels, ADT inhibits prostate tumor progression. However, this also has severe side effect, such as a decrease in skeletal muscle mass with a concomitant increase in body fat mass (6-8). In **chapter 2,** we provide an in-depth introduction on the working mechanism of ADT on prostate tumor tissue and its adverse effects on skeletal muscle mass and function. A promising intervention to counteract the adverse effects of treatment with ADT, is resistance exercise training. Resistance exercise training is known to elicit a strong anabolic stimulus for muscle adaptation in healthy, older adults (9-12). However, during ADT treatment, the suppressed testosterone levels may compromise the capacity of resistance exercise training to increase muscle mass and improve muscle function. In the second part of our introduction (**chapter 2**) we introduce the potential impact of resistance exercise training as a means to counteract the adverse effects of ADT treatment on muscle mass and function based on the existing literature.

In chapters 3 to chapter 6, we describe the outcome of various studies that were performed within a project in which we explored the potential benefits of resistance exercise training to counteract the adverse effect of ADT in patients with prostate cancer. In **chapter 3,** we first assessed the side effects of ADT in prostate cancer patients. We observed a decline in muscle mass and strength, an accompanying increase in fat mass, a decline in aerobic capacity, metabolic disruptions, and a decrease of quality of life. Subsequently, in **chapter 4**, we examined the effectiveness of supervised resistance exercise training during ADT, by conducting a multicenter intervention study in which we subjected a large group of prostate cancer patients to a prolonged, structured and supervised resistance exercise training program. In addition, we examined whether protein supplementation can provide a surplus benefit when combined with resistance exercise training. Protein supplementation has been shown to result in greater muscle mass and strength gains during resistance exercise training in both young and older adults (13, 14). However, data on the benefits of nutritional support for prostate cancer patients on ADT are lacking. We observed that resistance exercise represents an effective means to counteract many of the ADT-induced adverse effects, and can even result in increases in muscle mass and strength, with no additional benefit of protein supplementation. In **chapter 5**, we investigated to what extend the benefits of resistance exercise training are detectable within skeletal muscle tissue that was collected from our patients. The observed effectiveness

of RET during ADT makes it a promising intervention for implementation in clinical practice. However, ADT is generally prescribed for two or more years. Therefore, we examined to what extend the positive benefits of a structured exercise training program are preserved after cessation of the supervised program (**chapter 6**).

In **chapter 7** we shift our focus from exercise training as an intervention to counteract treatment-related side effects, to exercise training as a potential strategy to attenuate tumor progression. By motivating patients to adopt a more sedentary or active lifestyle during the week prior to prostatectomy, we assessed the potential impact of physical activity on prostate (tumor) protein synthesis rates. We conclude this thesis with the general discussion in **chapter 8,** in which we discuss the implications of our findings for clinical practice and formulate recommendations for future research.

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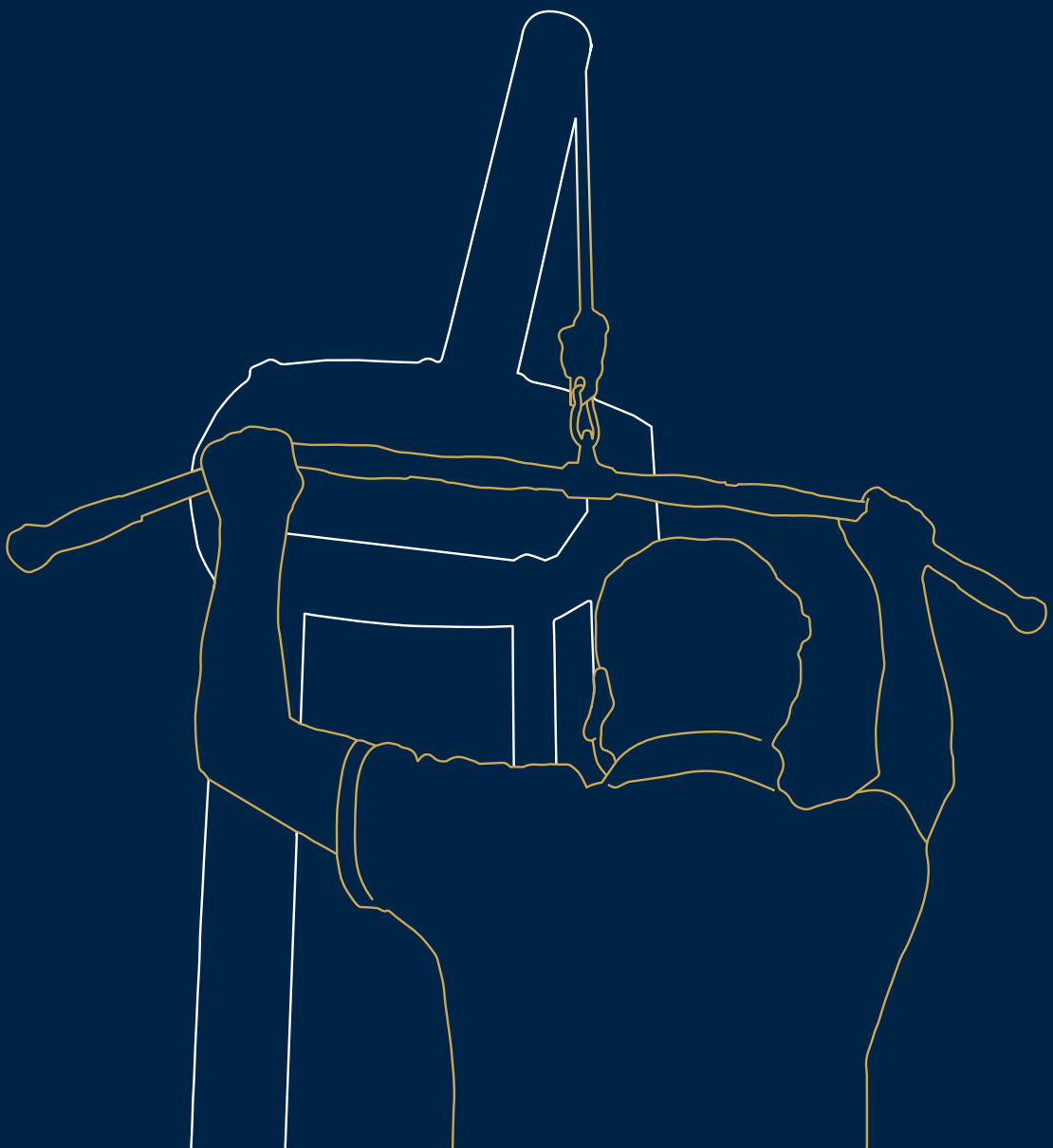

CHAPTER 2

Resistance exercise training, a simple intervention to preserve muscle mass and strength in prostate cancer patients on androgen deprivation therapy

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Abstract

Androgen deprivation therapy (ADT) forms the cornerstone in the treatment of advanced prostate cancer. However, by suppressing testosterone ADT results in a decrease of skeletal muscle mass. In this narrative review, we explore the magnitude and mechanisms of ADT-induced muscle mass loss and the consequences for muscle strength and physical performance. Subsequently, we elucidate the effectiveness of supervised resistance exercise training as a means to mitigate these adverse effects. Literature shows that resistance exercise training can effectively counteract ADT-induced loss of appendicular lean body mass and decline in muscle strength, while the effect on physical performances is inconclusive. As resistance exercise training is feasible and can be safely implemented during ADT (with special attention for patients with bone metastases), it should be incorporated in standard clinical care for prostate cancer patients (starting) with ADT.

Introduction

Prostate cancer is the most frequently diagnosed type of cancer in European men. In 2020, 473.000 men developed prostate cancer, accounting for 20% of all cancer diagnoses in Europa (1). The high incidence of prostate cancer has been attributed to a combination of improved diagnostics and the ageing of the population, with advanced age being a well-established risk factor for the development of prostate cancer (2). Below the age of 50 years, 1.2 per 100.000 men are yearly diagnosed with prostate cancer, while the incidence rate increases to 568 per 100.000 in European men aged 65 years and older (1). Due to improvements in therapeutic modalities, the prevalence of prostate cancer has increased as well, resulting in a European 5-year prevalence of 1.87 million in 2020 (1). So, a substantial number of (older) men are living with prostate cancer (2). Many of these men will be treated with androgen deprivation therapy (ADT) during the course of their disease, as ADT is a mainstay in the treatment of (locally) advanced prostate cancer. In patients with intermediate to high risk localized disease and locally-advanced disease, ADT in combination with radiotherapy is applied with curative intent (3). In metastatic disease, ADT is the first-line treatment, often combined with chemotherapy (4). ADT induces 'chemical castration' by either suppressing serum androgen levels or by blocking the action of androgens on a cellular level, resulting in tumor regression (5). However, androgens also play key roles in maintaining skeletal muscle mass. As a result, ADT results in an accelerated loss of muscle mass (6). This is accompanied by an increase in fat mass (6), a reduction in insulin sensitivity (7), and an increased risk of developing diabetes (8) and cardiovascular disorders (9).

Since two decades there has been an increasing interest in resistance exercise training (RET) as an interventional strategy to counteract the adverse side effects of ADT on skeletal muscle mass and strength. RET, defined as exercise that cause muscles to work or hold against an applied force of weight (10), forms an established intervention to increase muscle mass and strength, and improve physical performance in older adults suffering from sarcopenia (11).

In this narrative review an overview of the effectiveness of RET to preserve skeletal muscle mass and strength during ADT, including relevant background information, is provided. By its nature, this review might not be as comprehensive as a systematic review and no meta-analyses were performed, though we strive to include all relevant RCTs assessing the effects of supervised RET on muscle mass and / or strength during ADT. In the upcoming chapters, we successively describe the working mechanisms of ADT and its effect on skeletal muscle tissue. Thereafter, the effectiveness of RET during ADT in patients with prostate cancer is discussed, followed by implications for its application in clinical practice. Although optimal nutrition is a major component of improving or preserving muscle mass, an extensive elaboration of literature is outside the scope of this review.

Androgens and androgen deprivation therapy

Mechanism of action of androgens and androgen deprivation therapy in prostate cancer
Prostate cancer is an androgen-dependent disease. Androgens, with testosterone as major androgen, exert vital roles in normal prostate development and homeostasis via androgen receptor (AR) signaling (12). However, when prostate cells mutate to cancerous cells, the role of AR signaling shifts from promoting cell differentiation to uncontrolled cell proliferation (12). Interruption of the AR signaling pathway by either surgical (orchiectomy) or pharmaceutical interventions (ADT) impairs further tumor proliferation (13). ADT may comprise of anti-androgens and / or luteinizing hormone-releasing hormone (LHRH) analogues. Anti-androgens block the effect of androgens on a cellular level by competitively binding to the AR (14), and are used usually concomitantly with LHRH agonists (often temporary, to suppress the initial surge of testosterone). LHRH analogues affect the levels of circulating androgens by suppressing the hypothalamic-pituitary-gonadal axis, resulting in an inhibition of testicular testosterone production (14). LHRH agonists, the most frequent used type of ADT, stimulate the LHRH receptor, resulting in an initial surge of serum testosterone, followed by downregulation of the receptor and its downstream signaling (14). As a result, serum testosterone reaches castration levels within 2 to 4 weeks after initiation of ADT (15). The more recent developed LHRH antagonists competitively bind to the LHRH receptor, which results in castration levels of serum testosterone within ~3 days of treatment without the initial testosterone surge (15). For more extensive information about the working mechanism of the different kinds of ADT we refer to the review of Crawford *et al.* (2019) (14).

Mechanism of action of androgens and androgen deprivation on skeletal muscle mass
Besides its role in prostate homeostasis, testosterone is vital for the maintenance of skeletal muscle mass and function (16). The underlying mechanisms by which testosterone acts on muscle tissue are complex. To a large extent, the action of testosterone is mediated by genomic signaling via binding to the AR, resulting in alterations in the expression of many genes involved in the regulation of muscle mass. Eventually, this leads to anabolic and anti-catabolic signals to skeletal muscle tissue (17, 18). In addition, testosterone induces non-genomic signaling pathways. Non-genomic signaling occurs independently of nuclear receptors and subsequent transcriptional responses, requires constant presence of androgens to maintain intracellular signalling, and occurs much faster than genomic signaling (within seconds to minutes instead of hours) (19). Several non-genomic pathways have been described, among pathways increasing intracellular calcium concentrations (important for contractile properties) and activation of mammalian target of rapamycin (mTOR) pathway signaling (central link for the development of muscle hypertrophy) (19-21). It has been suggested that the crosstalk between genomic and non-genomic signaling is important for an orchestrated cellular response induced by testosterone (19, 21). Furthermore, testosterone might promote the differentiation of pluripotent stem cells toward the myogenic lineage instead of the adipogenic lineage (22, 23) and, as such, induce hypertrophy by increasing satellite cell number and myonuclear number (23, 24). Testosterone deficiency, on the other hand, results in the loss of muscle mass (23). Testosterone

deficiency is supposed to induce an imbalance between muscle protein breakdown and muscle protein synthesis pathways (25). Furthermore, testosterone deficiency potentially promotes differentiation of mesenchymal stem cells to adipocytes instead of myocytes (22).

Impact of androgen deprivation therapy on muscle mass and function

Impact on muscle mass

The progressive decline of skeletal muscle mass during ADT treatment is consistently described in literature. Longitudinal studies over a period of 36 to 52 weeks have shown decreases in lean body mass (LBM), a surrogate for muscle mass, ranging between 1.9-3.8% in prostate cancer patients on ADT (26-30). The loss of LBM seems to start rapidly after initiation of ADT. Already after 3 months of ADT treatment, a significant decline in LBM has been observed (31). Furthermore, the degree of LBM loss seems to be most pronounced during the earlier stages of the treatment. Van Londen *et al.* and Smith *et al.* both showed the largest declines in LBM during the first 1 to 1.5 years of ADT treatment. In the following 1-2 years the decline continued, but the rate at which this occurred was substantially lower (32, 33). In addition, Londen *et al*. showed that the loss of muscle loss during acute ADT-treatment (-1.8±0.5 kg of LBM) was higher than in the healthy control group (no significant change). Although the mean age was significantly higher in the ADT-group compared to the control group (71±1 and 63±2 years, respectively), this is an interesting research topic, as since long time it has been recognized that ageing can be accompanied by skeletal muscle mass loss. When severe, this can eventually results in sarcopenia, defined as a progressive and generalized skeletal muscle disorder that involves the accelerated loss of muscle mass and function. However, besides ageing, it is nowadays recognized that many other causes can contribute to sarcopenia, like malnutrition, inactivity, diseases, and iatrogenic factors like drugs (e.g. ADT) (34). Therefore, differentiating the relation between ADT-related muscle loss and sarcopenia - e.g. to explore the impact of ADT on the occurrence and exacerbating of sarcopenia - receives more and more attention (35-37).

Impact of ADT on muscle strength and physical performance

As ADT induces an accelerated loss of muscle mass, one would assume that this would affect muscle strength and physical performance as well. Muscle strength is defined as the amount of force a muscle can produce with a single maximal effort (38). Physical performance is an objectively measured whole body function related with mobility, and goes beyond muscle function measures, as many other organs and systems are involved as well (38).

Upper body muscle strength indeed seems to decrease during ADT. Two cross-sectional studies assessed strength by 1-repetition maximum (1RM) measurements in prostate cancer patients on ADT, and compared this to age-matched control subjects (39, 40). Significant lower values for bench press, chest press, and seated row 1-RM were found during ADT. For lower body strength, results varied. For leg extension 1-RM lower values during ADT were found (40), for

leg press 1-RM no differences between groups were observed (39, 40). Results for hand grip strength have been inconsistent as well. Some studies found a decline in handgrip strength in patients on ADT (41-44), while others failed to observe changes (45, 46).

Patients on ADT subjectively experience a deterioration of their physical performance (47), but objective tests like the Chair Stand Test[1], Timed Up and Go[2], and Short Physical Performance Battery[3] fail to consistently confirm this. The various longitudinal and cross-sectional studies that looked into physical performance, report heterogeneous results. Some showed significant declines in performance during ADT, where others did not find differences (40, 42, 46-50). Factors that could have contributed to the heterogeneous findings may be differences in study design, differences in inclusion criteria leading to study populations differing in age or physical condition, or differences in ADT-treatment duration at baseline. For example, high functioning subjects might all score the maximum amount of points on the Short Physical Performance Battery resulting in a ceiling effect, and / or may have enough reserve to compensate for some degree of muscle mass loss on the physical performance tests.

Resistance exercise training and the role of testosterone

In older adults suffering from sarcopenia, RET can prevent the age-related loss of skeletal muscle mass (34), and can even increase muscle mass (51), muscle strength (52), and physical performance (11). Therefore, it is not surprising that RET has been proposed as a strategy to counteract the ADT-induced loss of muscle mass and strength. However, the absence of normal testosterone levels, raises the question on whether RET can be (as) effective during ADT.

As discussed before, testosterone is vital for the maintenance of skeletal muscle mass, and it is considered as one of the more potent anabolic androgenic hormones. Testosterone promotes muscle hypertrophy by stimulating muscle protein synthesis and inhibiting muscle protein degradation (53). Testosterone administration in men with normal testosterone levels (eugonadal), has indeed been shown to increase muscle protein synthesis rates (54, 55). In line, testosterone replacement therapy in hypogonadal (older) men has been reported to increase muscle protein synthesis rates and augment muscle mass (56-58). Following resistance exercise, testosterone is often considered the primary anabolic hormone for muscle adaptation (53, 59). A transient elevation of systemic testosterone and some other anabolic hormones (like growth hormone and insulin-like growth factor-1) occurring directly after a bout of resistance

1 Chair Stand Test, measures how many times in 30 seconds (30s-Chair Stand Test) a patient can stand upright and sit down from a chair, assessing lower body power, balance and endurance; another version known as the 5-times sit-to-stand test records the time to complete five sit-to-stand maneuvers (38).
2 Timed Up and Go, measures the time it take to stand up from a chair, walk three meters, turn around, return and sit down, by that assessing gait and dynamic balance (38).
3 Short Physical Performance Battery, test battery consisting of a balance test, walking speed test, and 5-time sit-to-stand test (38).

exercise, has been suggested to initiate a sequence of molecular events, resulting in adaptations associated with muscle growth. However, this concept is challenged nowadays. Philips and colleagues examined the influence of a 'high' vs 'low' post-exercise elevation in anabolic hormone concentration on the muscle adaptive response. They found no relation between the post-exercise increases of any systemic anabolic hormone including testosterone, and changes in muscle protein synthesis rates or gains in muscle mass or strength (60-62). In contrast, a study using a similar protocol as in the two aforementioned studies of West *et al*., did find a correlation - the group with a high hormonal response showed a greater increase in muscle strength when compared with the group with a low hormonal response - although findings may have been influenced by differences at baseline (63).

Taken together, the role of testosterone in the exercise-induced muscle adaptations is complex and remains to be clarified. As a consequence, the effects of testosterone suppression by ADT on muscle metabolism and its impact on exercise-induced adaptations is a topic of ongoing research. In healthy male subjects, suppressing testosterone levels by ADT resulted in a decrease in whole body protein turnover, lean body mass and muscle strength after 10 weeks (64). Furthermore, during resistance exercise training, testosterone deprivation blocked the acute, post-exercise rise in serum testosterone, prevented gains in muscle strength, and attenuated increases in lean mass, compared to the control group without testosterone deprivation (65, 66). In agreement, in prostate cancer patients on ADT a reduction of basal muscle protein synthesis rates by 39% compared to healthy age-matched control subjects has been found (67). After a single session of resistance exercise followed by protein intake, however, increases in muscle protein synthesis rates of similar magnitudes were observed in the ADT and the control group (67). This suggests that it is still possible to initiate a robust response in muscle protein synthesis rate and, eventually, induce muscle hypertrophy during ADT.

Current knowledge about the effect of resistance exercise training during androgen deprivation therapy

For this review, randomized controlled trials (RCTs) examining the effects of a supervised exercise training intervention with a RET-component and with no other non-exercise interventions, on at least muscle mass or muscle strength, in prostate cancer patients treated with ADT during the study period, were included. In addition, only unique results were included (e.g. in case two articles reported results based on the same primary study, this result was only once incorporated). Up to November 2022, nine RCTs matched these criteria (68-77). Four RCTs performed RET only (68-72). This includes one study with a three-armed study design (resistance exercise training, aerobic exercise training, and control group) in prostate cancer patients initiating radiation therapy with or without ADT. For this review, we included the data of the subgroup analysis of patients with ADT in the resistance exercise and control groups (69). Furthermore, four studies offered a combined resistance and aerobic exercise training program (74-77). Finally, one study had a three-armed design with both a resistance exercise arm, a

combined resistance plus aerobic exercise arm, and a control group (73). More information about the study characteristics, including the exercise training programs, are summarized in **Table 1**.

Muscle mass

Six of the included studies examined LBM by dual-energy X-ray absorptiometry scans (DXA) (69, 70, 72-75) (**Table 2**). For appendicular lean body mass, positive exercise effects were found with adjusted differences of 0.3 - 0.8 kg between the exercise and control group (72-75). Within-group changes as analyzed by Cormie *et al*., showed no significant changes over time in the exercise group, while a loss of 0.7 kg occurred in the control group ($P<0.001$) (75). The study of Newton *et al*. was the only exception, showing no effects on appendicular LBM in the combined resistance and aerobic exercise training arm (73). This is quite remarkable, as the resistance exercise arm without aerobic exercise training did show a significant increase in appendicular LBM. The authors speculated that an interference effect of the aerobic exercise may have compromised the resistance exercise training induced hypertrophic response (73).

RET might also be effective to counteract the decline of total LBM, although results are still inconclusive (**Table 2**). In the studies performing combined exercise training, one out of three studies assessing total LBM, found a significant exercise benefit (74), and one study showed a positive trend ($P=0.078$) (75), with adjusted group differences of 0.7 - 0.8 kg. The combined exercise training arm of Newton *et al*., found no effect of exercise training on the decline in total LBM (73). In the studies performing RET only, three of four studies assessing total LBM found no exercise effect (70, 72, 73). Alberga *et al*. however, did find significant exercise effects on total LBM. Furthermore, with an adjusted group difference of +2.8 kg, the effect was considerably higher than found in the combined exercise training studies. Within-group analyses showed that the effect was due to a significant decrease of 3.1 kg ($P<0.001$) in the control group, with no significant changes over time in the exercise group (-0.3 kg, $P=0.685$) (69).

Ndjavera *et al*. used bioelectrical impedance analyses to estimate fat free mass as an indirect marker for skeletal muscle mass, finding no changes over time (77), and two of the included studies did not assess muscle mass (68, 76). Furthermore, none of the included studies assessed muscle mass with more direct measures than DXA, such as magnetic resonance imaging or computed tomography scans.

Muscle strength and physical performance

The effectiveness of RET to preserve and even increase muscle strength during ADT has consequently been described. As shown in **Table 2**, both studies performing RET only as well as studies performing RET in combination with aerobic exercise training, showed improvements in upper and lower body strength in the exercise group compared to a control group (68, 69, 71-76). Within-groups analysis by Alberga *et al*. and Cormie *et al*., showed (nearly) significant ($P\leq0.055$) increases in muscle strength in the exercise groups, while in the control groups muscle strength of the lower body did not change (leg press and leg extension), and of the

upper body decreased (bench press, chest press and seated row) (69, 75). Ndajvera *et al*. found no differences in muscle strength between groups (77). However, this was most likely because muscle strength was measured by hand grip strength. Although hand grip strength correlates well with measures of leg muscle strength, it is not a valid measure to evaluate changes in muscle strength over time during resistance exercise training in older people (78, 79).

The effect of RET on physical performance during ADT is yet unclear. Despite patients subjectively reporting improvements in physical function (71), results on physical performance tests are inconclusive. The chair stand test is the only performance test consistently showing significant improvements after RET, as the number of repetitions in 30 seconds increased (72) or the time to perform 5 repetitions significantly decreased (72, 74-76) or tended to decrease (71) (**Table 2**). For the stair climb test[4] and the different walk tests[5] results were heterogeneous and no conclusion can be drawn (71, 72, 74-76) (**Table 2**).

4 Stair climb test, measuring the time it takes to ascent, or ascent and descent, a set number of steps.

5 Walk tests, measuring the time to cover a specific distance (for example, 6-meter walk tests, 400-m walk test); or measuring the distance that can be covered while walking pace gradually increases (shuttle walk test); or measuring the walk speed on a specific trajectory (4-m walk speed tests).

Table 1 Characteristics of the included studies

	Patient details	ADT treatment	Study intervention
		Resistance exercise training only	
Segal et al., 2003	PCa. Metastatic disease included, unstable bone lesions excluded. Sample size: EX 82; CON 73 Age: EX 68.2±7.9; CON 67.7±7.5 years	LHRH agonist and / or AA. Scheduled to receive ADT ≥ 3 months. Time on ADT at baseline: EX 375±568; CON 402±665 days Other treatments: N.R.	EX: RE, all sessions supervised, machine-based, whole body. CON: Waiting list. Duration and frequency: 12 weeks; 3x·week^{-1} Training adherence: 79% (average attendance at exercise sessions)
Alberga et al., 2012[a]	PCa scheduled to receive RTx. Metastatic disease excluded. Sample size: EX 23; CON 26 Age[b]: EX 67.1±6.9; CON 65.4±7.6 years	Type of ADT not specified. Time on ADT at baseline: EX 91±89 days; CON 111±136 days Other treatments: All RTx	EX: RE, all sessions supervised, machine-based, whole body, progressive. CON: Asked to maintain pre-study physical activity level and to not initiate exercise Duration and frequency: 24 weeks; 3x·week^{-1} Training adherence[b]: 88% (median of completed sessions)
Winters-Stone, Dieckman et al.,2015 Winters-Stone, Dobek et al., 2015	PCa. Metastatic disease included, but metastases in hip or spine excluded, as well as BMD T-score < -2.5. Sample size: EX 29; CON 22 Age: EX 69.9±9.3; CON 70.5±7.8 years	Type of ADT not specified. Time on ADT at baseline EX 39.0±36.1; CON 28.5±29.2 months Other treatments: Receiving adjuvant treatment at baseline was exclusion criteria.	EX: RE+IL, 2 of 3 sessions supervised. RE: free weights (supervised) or resistance bands (home exercises); multi-joint exercises which emphasized movements common to activities of daily living. IL: 50x two-footed jumps. CON: Stretching and relaxation exercises. Duration and frequency: 12 months; 3x·week^{-1} Training adherence: 84% for supervised sessions, 43% for home-based sessions (median attendance)
Nilsen et al., 2015	PCa, intermediate or high-risk profile. Bone metastases: N.R. Sample size: EX 28; CON 30 Age: EX 66±6.6; CON 66±5 years	LHRH agonist (Zoladex® 10.8 mg). Time on ADT: At baseline: EX 9.0±1.6; CON 9.0±1.8 months Total time: EX 17.0±8.7; CON 18.0±8.2 months Other treatments: All patients had received high-dose RTx (±3 months before start study), which was started 2-6 months after initiation of neo-adjuvant ADT, and this RTx was followed by adjuvant ADT.	EX: RE, 2 of 3 sessions supervised, machine-based, whole body, progressive. CON: Encouraged to maintain habitual activity level and to not initiating RE. Duration and frequency: 16 weeks; 3x·week^{-1} Training adherence: 88% for lower body exercises, 84% for upper body exercises (excluding one outlier of 31%) (average proportion of completed exercises)

Table 1 Characteristics of the included studies (continued)

	Patient details	ADT treatment	Study intervention
Resistance exercise training only + Combined resistance and aerobic exercise training			
Newton et al., 2019	PCa. Bone metastases excluded, nodal metastases N.R. Sample size: RE+IL 57; RE+AE 50; CON 47 Age: RE+IL 68.7±9.3; RE+AE 69.1±9.4; CON: 69.1±8.4 years	ADT (most likely LHRH analogue) with or without AA. Currently treated for ≥ 2 months and anticipated to receive ADT for subsequent 12 months. Time on ADT at baseline: RT+IL 3.0; RT+AE 3.0; CON 2.0 months Other treatments: RTx at baseline: 88% of all patients.	Two exercise groups: 1. RE+IL, 2x·week^{-1} supervised RE+IL AND 2x·week^{-1} home-based IL. 2. RE+AE, 2x·week^{-1} supervised RE+AE AND encouraged to undertake homebased AE to accumulate 150 min·week^{-1}. RT: supervised, machine-based, whole body, progressive, identical for RE+IL and RE+AE. Supervised IL: series of activities that produced ground reaction forces. Supervised AE: 20-30 min, 60-85% of estimated HR_{max} using various modes. CON: Printed exercise information Duration and frequency: 6 months; frequency mentioned above (followed by 6 months with in RE+IL continuation of the identical training program, in RE+AE home-based training, in CON supervised cycling; data not included in this review) Training adherence: RE+IL 65%, RE+AE 70% (attendance at supervised sessions)
Combined resistance and aerobic exercise training			
Galvao et al., 2010	PCa. Bone metastases excluded, nodal metastases included. Sample size: EX 29; CON 28 Age: EX 69.5±7.3; CON 70.1±7.3 years	ADT (most likely LHRH analogue) with or without AA. Currently treated with ADT for > 2 months and anticipated to remain hypogonadal for subsequent 6 months. Time on ADT at baseline: EX 18.2±38.5; CON 10.1±26.8 months RTx at baseline: EX 27.6%; CON 21.4%.	EX: RE+AE, supervised. RE: Machine-based, whole body, progressive. AE: 15-20 min at 65-80% HR_{max}. CON: Usual care. Duration and frequency: 12 weeks; 2x·week^{-1} Training adherence: 94% (average completed exercise sessions)

Table 1 Characteristics of the included studies (continued)

	Patient details	ADT treatment	Study intervention
		Combined resistance and aerobic exercise training	
Cormie et al., 2015	PCa. Bone metastases excluded, nodal metastases N.R. Sample size: EX 32; CON 31 Age: EX 69.6±6.5; CON 67.1±7.5 years	LHRH agonist (leuprorelin) with or without AA. Starting with ADT and anticipated to remain on ADT for ≥ 3 months; no previous ADT. Time on ADT at baseline: EX 6.2±1.6; CON 5.6±2.0 days Other treatments: RTx during intervention: EX 22%, CON 26%.	EX: RE+AE, supervised. RE: Machine-based, whole-body, progressive. AE: 20-30 min at 70-85% HR_{max}. CON: Usual care. Duration and frequency: 3 months; 2x·week^{-1} Training adherence: 96% (average completed exercise sessions)
Newton et al, 2020	PCa. Metastatic disease excluded. Sample size: EX 54; CON: 50 Age: EX 69.0±6.3; CON 67.5±7.7 years	ADT (type unknown). Starting for at least 6 months. Time on ADT at baseline: EX: 6.4±2.1; CON: 5.7±1.9 days Ceasing with ADT during study: EX *n*=10; CON *n*=5 Other treatments: Commencing RTx during first 6 months: EX *n*=40; CON *n*=30	EX: RE+AE+IL, 1 week 2x AE+I and 1x RE+I, next week 2x RE+IL and 1x AE+IL, supervised. RE: machine-based, whole body,6-12 RM, 2-4 sets. AE: 60-85% estimated HR_{max} for 25-40 min. IL: series of activities that produced ground reaction forces of 3.4-5.2x body weight. Additional encouraged to 2x·week^{-1} home-based training of AE (walking, cycling) and modified version of IL. CON: Usual care Duration and frequency: 6 months, 3x·week^{-1} (followed by 6 months with in EX no formal intervention, and in CON the training program; data not included in this review) Training adherence: 79% (attendance at exercise sessions)
Ndjavera et al., 2020	Newly diagnosed PCa. Bone metastases excluded, nodal metastases included Sample size: EX 24; CON 26 Age: EX 71.4±5.4; CON 72.5±4.2 years. All between 50-80 years.	LHRH agonist; use of AA N.R. Starting for at least 6 months; no previous ADT. Time on ADT at baseline: N.R. Other treatments during study: All with or without RTx.	RE+AE, supervised. RE: free weights and body weight, whole body, progressive. AE: 6 repetitions of 5 min bouts at an intensity of 11-15 on the 6-20 Borg Rating of Perceived Exertion Scale. Additional encouraged to 30 min of self-directed structured exercise or physical activity 3x·week^{-1}. CON: Usual care. Duration and frequency: 12 weeks; 2x·week^{-1} (followed by 12 weeks home-based training; data not included in this review) Training adherence: ≥70% (completed exercise sessions)

Values are presented as mean ± SD, *n* of patients, or percentage of patients. [a]This was a three-armed study with a resistance exercise training, aerobic exercise training and control group of PCa patients initiating RTx with or without ADT. For our review, only data of patients with ADT in EX and CON are included. [b]Data as reported for whole group consisting of patients with and without ADT, as data were not provided for subgroup using ADT. AA, anti-androgen; ADT, androgen deprivation therapy, AE, aerobic exercise; CON, control group; CTx, chemo therapy; EX, exercise group; HR, heart rate; HR_{max}, maximal heart rate; IL, impact loading; LHRH, luteinizing hormone-releasing hormone; N.R., not reported; PCa, prostate cancer; RE, resistance exercise; RTx, radiation therapy; VO_2max, maximal oxygen uptake.

Table 2 Results of the included studies for muscle mass, muscle strength and physical performance

	Muscle mass	Muscle strength	Physical performance
Resistance exercise training only			
Segal et al., 2003	N.A.	↑ 1RM LP (EX +11.8, CON -1.6 kg; $P<0.001$)[a] ↑ 1RM CP (EX +13.1 kg, CON -2.6 kg; $P=0.009$)[a]	N.A.
Alberga et al., 2012[b]	↑ Total LBM (2.76 kg; $P=0.005$)	↑ 8RM LE (+23.3; $P=0.001$) ↑ 8RM BP (+14.1; $P<0.001$)	N.A.
Winters-Stone, Dieckman et al.,2015 Winters-Stone, Dobek et al., 2015	↔ Total LBM	↑ 1RM LP ($P=0.01$[c], $P=0.03$[d]) ↑ 1RM BP ($P=0.03$[c], $P=0.01$[d])	(↑) 5-times sit-to-stand test ($P=0.09$[c], $P=0.07$[d]) 4-m usual walk speed ($P=0.37$[c], $P=0.97$[d]) 4-m fast walk speed ($P=0.31$[c], $P=0.13$[d]) ↑ Self-reported physical function (EORTC QLQC30) ($P<0.01$)[c,d]
Nilsen et al., 2015	↔ Total LBM ↑ LBM lower extremities (+0.49 kg; $P=0.002$)[e] ↑ LBM upper extremities (+0.15kg; $P<0.05$)[e] ↑ Appendicular LBM (+0.64 kg; $P=0.001$)[e]	↑ 1RM LP (+42 kg; $P<0.001$)[e] ↑ 1RM CP (+6 kg; $P<0.001$)[e] ↑ 1RM SP (+5 kg; $P<0.001$)[e]	↑ 30 sec chair stand test (+2 reps; $P<0.001$)[e] ↑ Stair climbing test, loaded (-0.27 sec; $P=0.024$)[e] ↑ Stair climbing tests, unloaded (-0.23 kg; $P=0.047$)[e] (↑) Shuttle walk test (+39 m; $P=0.064$)[e]
Resistance exercise training only + Combined resistance and aerobic exercise training			
Newton et al., 2019	RE+IL vs. CON: ↔ LBM ↑ Appendicular LBM (+ 0.3 kg; $P=0.045$) RE+AE vs CON: ↔ LBM ↔ Appendicular LBM	RE+IL vs. CON: ↑ 1RM LP (+12.7 kg; $P=0.012$) ↑ 1RM LE (+7.9 kg; $P<0.001$) ↑ 1RM CP (+3.4 kg; $P=0.003$) ↑ 1RM SR (+6.1; $P<0.001$) RE+AE vs. CON: ↑ 1RM LP (+18.6 kg; $P=0.001$) ↑ 1RM LE (+7.9 kg; $P<0.001$) ↑ 1RM CP (+3.2 kg; $P=0.002$) ↑ 1RM SR (+5.5; $P<0.001$)	N.A.

Table 2 Results of the included studies for muscle mass, muscle strength and physical performance (continued)

	Muscle mass	Muscle strength	Physical performance
Combined resistance and aerobic exercise training			
Cormie et al., 2015	(↑) Total LBM (+0.7 kg; *P*=0.078) ↑ Appendicular LBM (+0.4 kg; *P*=0.019)	↑ 1RM LP (+25.9 kg; *P*<0.001) ↑ 1RM CP (+4.8 kg; *P*=0.004) ↑ 1RM SR (+4.0 kg; *P*=0.026)	↑ 5-times sit-to- stand test (-1.1 sec; *P*<0.001) ↔ Stair climb test ↔ 6-meter walk (usual and fast pace)
Newton et al, 2020	N.A.	↑ 1RM LP (+19.9 kg, *P*<0.001) ↑ 1RM CP (+4.3 kg; *P*<0.001) ↑ 1RM SR (+5.6 kg, *P*<0.001)	↑ 5-times sit-to- stand test (-1.0 sec; *P*<0.001) ↑ Stair climb test (-0.4 sec: *P*<0.001) ↑ 6-m fast walk test (-0.2 sec; *P*<0.001) ↑ 400-m walk test (-9.7 sec; *P*<0.001) ↔ 6-m usual walk test ↔ 6-m backwards tandem walk test
Ndjavera et al., 2020	↔ Fat free mass[e]	↔ Hand grip strength	N.A.

Values are presented as adjusted mean group differences. [a]Data reported as within-group changes, with P-value for difference of change scores between groups. [b]This was a three-armed study with a resistance exercise training, aerobic exercise training and control group of PCa patients initiating radiation therapy with or without ADT. For our review, only data of patients with ADT in EX and CON are included. [c]P-value from intention-to-treat-analyses. [d]P-value from per protocol analyses. [e]Data reported as group difference in mean change from baseline. [f]Measured with bioelectrical impedance. ADT, androgen deprivation therapy; CON, control group; BP, bench press; CP, chest press; EORTC QLQC30, European Organization for Research and Treatment on Cancer Quality of Life Questionnaire; EX, exercise group; fat %, fat percentage; IL, impact loading; ITT, intention-to-treat; LBM, lean body mass; LE, leg extension; LP, leg press; N.A., not applicable; PPB, Physical Performance Battery; RE, resistance exercise; SP, shoulder press; SR, seated row; 1RM, one repetition maximum; 8RM, eight repetition maximum; ↑, significant increase (for body composition or muscle strength outcomes), or significant improvement (for physical performance outcomes), in EX vs CON (*P*<0.05); (↑), tendency to increase in EX vs CON; ↔, no significant difference between EX vs CON.

Implications for clinical practice

Strategies to preserve muscle mass and strength during ADT are warranted, as muscle mass and strength are important to maintain physical abilities, perform activities of daily living, and maintain self-reliance. Resistance exercise training forms a promising intervention to achieve this. For successful implementation in clinical practice, an intervention should be feasible, safe, and effective. Therefore, these aspects will be successively discussed, whereupon a framework for effective exercise intervention will be provided.

Feasibility

The feasibility of a training intervention during ADT can be defined by several factors, like recruitment, retention, and adherence. In the included studies, recruitment percentages varied between 31 and 66% of the eligible patients, and retention varied between 74 and 97% (68-77). Adherence to the training interventions, defined as attendance at or completion of the exercise sessions, seemed to be good (**Table 1**). All studies reported adherence rates equal or higher than 65% (68-73, 76, 77), and two studies even reported excellent attendance rates of more than 90% (74, 75) (**Table 1**). Of course, one could question if these recruitment percentages and adherence rates are representative for clinical practice. It was not a primary goal of these studies to examine recruitment, and recruitment strategies varied between studies and were not always extensively described. For adherence in addition, selection bias could have resulted in the inclusion of mainly motivated patients. It is very likely, however, that in clinical practice also mainly motivated patients will engage in a structured exercise training program, resulting in the same 'selection bias'. An interesting study to mention with regard to feasibility, is the STAMINA-trial, a large study assessing the feasibility and acceptability of embedding a supervised exercise intervention in standard prostate cancer in the United Kingdom, demonstrating encouraging results in a first report (80).

Another aspect requiring attention, is the sustainability of the exercise benefits after cessation of a supervised program. ADT is often prescribed for several years, while supervised exercise programs only cover a set time period. Up till now it is unknown whether prostate cancer patients receiving ADT can autonomously maintain the exercise-obtained effects after cessation of the supervised training intervention when no formal follow-up intervention is offered. Only in a study in healthy older adults, it was shown that the training-induced gains in muscle mass and strength were largely lost within 1 year after cessation of a supervised program (81).

Safety

A resistance exercise program can be performed safely during ADT. Firstly, there are no indications that it influences ADT treatment efficacy. There were some concerns around this point, as previous research showed that RET results in acute rises in circulating testosterone levels (53). Following an exercise program during ADT, no exercise-induced changes in serum testosterone, nor in the tumor progression marker 'prostate specific antigen' (PSA), have been observed (82, 83). Secondly, hardly any exercise related adverse events (AE) have been reported

in the studies included in our review. In the study of Nilsen *et al*. three subjects dropped-out due to knee or back-pain, which are common injuries related to RET (72). In addition, in the study reported by Alberga *et al.*, one patient experienced chest pain during exercise, however, subsequent cardiologic investigation was negative (69). The exclusion of patients with bone metastases in several studies, because of the potentially higher risk of bone fractures, is a point of attention. Five of the included RCTs excluded patients with bone metastases (69, 73-75, 77), one excluded patients with metastases in the hip or spine (70, 71), one excluded patients with unstable bone lesions (68) and one did not report whether these patients were included or not (72). In clinical practice, ~ 70% of men with prostate cancer will develop bone metastases throughout the course of their disease (84). Cormie *et al*. were the first to publish a small pilot RCT investigating the safety and effectivity of RET in prostate cancer patients with bone metastases (85). Their results suggest that appropriately designed and personalized supervised RET can be safe and effective for improving muscle mass and strength. A more recent study performing a multimodal supervised exercise program in 57 prostate cancer patients with bone metastasis (86) and a pilot study performing remote resistance or aerobic exercise training in metastatic castrate-resistance prostate cancer patients (87), found no safety concerns as well.

Framework for an effective exercise training program

Given the efficacy of supervised RET to preserve muscle mass and strength during ADT, combined with the finding that it is feasible and safe to perform, we strongly advise a widespread implementation of RET in standard clinical care for prostate cancer patients. Although the optimal exercise training protocol still needs to be defined, we can already provide a framework for an effective exercise intervention. A program of at least three months with twice weekly training sessions has been proven beneficial (74, 75). Of course, a longer period will likely allow more pronounced changes in muscle mass and strength. With regard to the timing of initiation of the program, it is important to realize that both patients starting with ADT as patients already receiving ADT, will benefit from RET. This is confirmed by the trial of Taaffe *et al.* and Newton *et al*., in which the most optimal initiation timing for a training program was examined. After a period of 12 months, no differences in LBM or muscle strength were found between patients that commenced a 6-months combined training program directly at onset of ADT, and patients that started the identical program 6 months later (76, 88).

The exact exercise modalities of the optimal exercise training program remain to be elucidated. To induce muscle adaptations, it is important to apply adequate training stimuli. Hanson *et al.* suggested that training to fatigue might be a critical factor for achieving adequate stimuli during ADT. Although basal muscle protein synthesis rates appear to be reduced during ADT, they showed that a resistance exercise training session until fatigue, followed by protein consumption, was effective to strongly increase muscle protein synthesis rates. (67). Studies in healthy adults have shown that training to fatigue can be reached by a combination of high load with relative less repetitions or by a combination of lower loads with more repetitions. Both protocols are effective to induce muscle hypertrophy (89, 90), with the latter (lower loads, more repetitions) likely safer for more clinically compromised patients. The studies incorporated in

our review did not report working to fatigue. However, seven studies did describe performing progressive exercise training, what is in agreement with the American College of Sports Medicine (ACSM) recommendation for achieving ongoing adaptations in healthy adults (91). Most trials included in this review used machine-based resistance exercise, while Winters-Stone *et al*. performed more functional based resistance exercises using free-weights or resistance bands. Generally speaking, both machine-based exercise training and free weights are effective for increasing muscle strength. Machine-based exercise training is regarded as safer, easier to learn, and can help to stabilize the body and limit joint movements, whereas the use of free-weights may result in a coordination pattern better mimicking movement requirements of a specific task and support more functional strength improvements (91). Furthermore, though beyond the scope of this review, the addition of an aerobic or impact exercise training component (for cardiorespiratory and bone-related health, respectively) may provide added value. Finally, an adequate nutritional status is required for proper exercise training adaptations, with specific attention for protein intake. Awareness for the nutritional status of patients, and if required nutritional support, is therefore important.

To come back to our starting point, a relative 'simple' strategy of exercise training seems incredibly effective to fully offset the adverse effects of ADT. Though the most optimal exercise training program still needs to be defined, a supervised, personalized, resistance exercise training program with a minimum of twice weekly training sessions for at least three months would already be effective. Implementation of resistance exercise training in the standard care during ADT is therefore desired.

Conclusions and future directions

ADT forms the cornerstone in the treatment of (locally) advanced prostate cancer, diminishing cell proliferation by lowering testosterone to castration levels. However, the suppression of circulating testosterone levels has detrimental side effects on muscle mass and strength. Resistance exercise represents an effective interventional strategy to counteract these adverse effects, in both patients starting with ADT as patients already receiving ADT for a prolonged period. Furthermore, resistance exercise training is feasible and can be safely performed by prostate cancer patients during ADT. Consequently, we strongly advise a widespread implementation of resistance exercise training in the standard clinical care for prostate cancer patients starting and receiving ADT.

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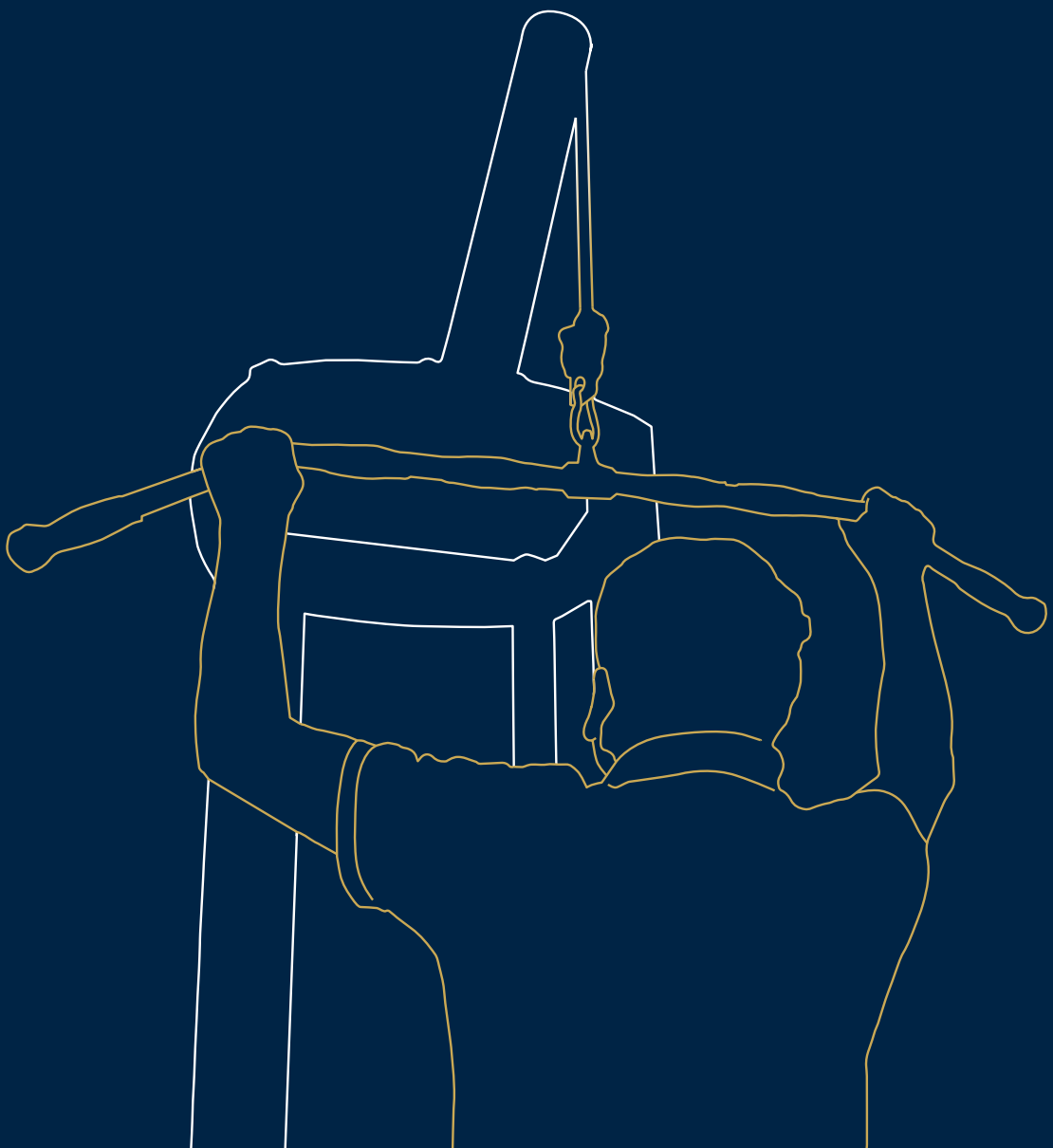

CHAPTER 3

Onset of androgen deprivation therapy leads to rapid deterioration of body composition, physical performance, cardiometabolic health, and quality of life in prostate cancer patients

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Abstract

Objectives: To assess the adverse impact of the first 5 months of androgen deprivation therapy on body composition, physical performance, cardiometabolic health, and health-related quality of life in prostate cancer patients.

Materials and Methods: Thirty-four prostate cancer patients (70±7 years) were assessed shortly after initiation of androgen deprivation therapy and again 5 months thereafter. Measurements consisted of whole-body dual-energy x-ray absorptiometry (body composition), computed tomography scanning of the upper leg (muscle mass), one-repetition maximum leg press (muscle strength), cardiopulmonary exercise testing (aerobic capacity), blood draws (metabolic parameters), accelerometry (habitual physical activity), and questionnaires (health-related quality of life). Data were analyzed with Student's paired *t*-tests.

Results: Over time, whole-body fat mass (from 26.2±7.7 to 28.4±8.3 kg, $P<0.001$) and fasting insulin (from 9.5±5.8 to 11.3±6.9 mU·L^{-1}, $P<0.001$) increased. Declines were observed for quadriceps cross-sectional area (from 66.3±9.1 to 65.0±8.5 cm^2, $P<0.01$), one-repetition maximum leg press (from 107±27 to 100±27 kg, $P<0.01$), peak oxygen uptake (from 23.2±3.7 to 20.3±3.4 mL·min^{-1}·kg^{-1} body weight, $P<0.001$), step count (from 7048±2277 to 5842±1749 steps·day^{-1}, $P<0.01$), and health-related quality of life (from 84.6±13.5 to 77.0±14.6, $P<0.001$).

Conclusions: Androgen deprivation therapy induces adverse changes in body composition, muscle strength, cardiometabolic health, and health-related quality of life already within 5 months after the start of treatment, possibly largely contributed by diminished habitual physical activity. Prostate cancer patients should therefore be stimulated to increase their habitual physical activity immediately after initiation of androgen deprivation therapy, to limit adverse side effects and to improve health-related quality of life.

Introduction

Androgen deprivation therapy (ADT) forms the cornerstone of treatment for (locally) advanced and metastatic prostate cancer (PCa) (1). While being effective in (temporarily) stopping disease progression, ADT can lead to adverse health effects. PCa patients lose muscle mass (~2%) (2), and gain fat mass (~11%) (3) in the first year of ADT. In addition, cross-sectional studies indicate that PCa patients undergoing ADT have decreased aerobic capacity (4), unfavorable blood lipid profiles, and impaired blood glucose homeostasis (5) resulting in a higher risk of developing cardiovascular comorbidities (6).

In contrast to the evident changes in body composition and cardiovascular risk profile, the adverse effects of ADT on muscle strength and physical performance are less conclusive. Studies show that PCa patients either preserve (7), or slightly lose (8) muscle strength, with physical performance remaining unchanged (8) or decreasing (9). Equally uncertain is the impact of ADT on health-related quality of life (HRQoL), which has been shown to decrease among PCa patients in some (10) but not all studies (11).

Discrepancies in literature are likely attributed to the inclusion of PCa patients who were assessed at a variety of stages during their treatment with ADT. To obtain more insight in the early development of these adverse side effects, longitudinal research directly upon ADT initiation is required. Furthermore, previous studies often chose to exclude PCa patients with comorbidities and bone metastases. However, it is important to include these vulnerable patients in order to obtain results that are generalizable to the entire PCa patient population. In addition, longitudinal data on changes in lifestyle factors (e.g. habitual nutritional intake and physical activity) which are likely to contribute to the adverse effects of ADT are generally lacking. Therefore, assessing the wide variety of adverse effects, and modifiable lifestyle factors, following the onset of ADT initiation, will paint a better picture on the magnitude and coherence of the ADT-induced adverse effects. Moreover, this information is crucial to obtain more insight in the type and preferred timing of interventions aiming to counteract the adverse effects of ADT.

Forty patients with diagnosed PCa were recruited to participate in this study that assessed the full spectrum of ADT-induced adverse side effects, including modifiable lifestyle factors, during the first 5 months of treatment. This study provides an extensive overview of the impact of commencing ADT on body composition, physical performance, cardiometabolic health, and HRQoL in PCa patients.

Methods

Patients

From June 2018 to February 2021, 40 PCa patients were included in the study. The inclusion criterium was that patients had to be started with a gonadotropin-releasing hormone (GnRH) agonists or antagonists for at least six months. Exclusion criteria were: any contraindications for maximal exercise testing, an estimated life expectancy <1 year, cognitive disorders, severe emotional instability, or inability to speak, understand or read the Dutch language. The study was approved by the Medical Ethical Committee of the Maastricht University Medical Center+ (MUMC+) The Netherlands (METC 16-3-040), and all patients signed written informed consent. This study was part of a greater project investigating the impact of resistance exercise and protein supplementation on counteracting the adverse effects of ADT in PCa patients and registered at the Dutch Trial Register (International Clinical Trial Registry Platform: NTR6432).

Study design

Potential participants were referred to the investigators by their treating urologist or urology nurse. The investigators provided full oral and written study information. After ≥1 week, interested patients were invited for a screening visit to confirm eligibility, obtain informed consent, evaluate medical history and in- and exclusion criteria, measure blood pressure, and perform a cardiopulmonary exercise test (CPET).

At ADT initiation, baseline anthropometric measurements (height, body weight, waist circumference), computed tomography (CT) of the dominant leg, whole-body dual-energy X-ray absorptiometry (DXA) were performed, and fasting blood samples were collected. After lunch, physical performance tests and maximal strength assessments were done. The screening visit and baseline measurements were preferably separated by at least seven days. During this time period, patients were instructed to wear an accelerometer and to fill out a 3-day food diary and several questionnaires. All baseline measurements were repeated 5 months later at the second assessment day. The CPET was performed at least 48 h before or after the 5 month measurements, to prevent any influence on the other outcome measurements. Throughout the manuscript, causal terminology is used with the awareness that other factors than ADT (e.g. additional treatment) also contributed to the observed changes.

Dietary intake and physical activity

Patients were instructed to refrain from any exhaustive physical activity 48h before the experimental test days and to arrive in a rested and fasted state. In the week prior to the experimental test days, patients reported their dietary intake on two weekdays and one weekend day. Average daily dietary intake was calculated using web-based software Eetmeter (Voedingscentrum, Den Haag, The Netherlands). Patients were instructed to wear a triaxial accelerometer (wGT3X-BT; ActiGraph, Pensacola, FL, USA) on their waist during wakefulness for 7 days prior to the experimental test days. Data were extracted with ActiLife (version 6.13.4;

ActiGraph, Pensacola, FL, USA) and included in the analyses if patients wore the accelerometer for a minimum of 5 days and at least 10 hours per day.

Body composition

Body weight, height and waist circumference were measured after voiding. Quadriceps muscle cross-sectional area (CSA) of the dominant leg was assessed by CT scanning (SOMATOM Definition Flash; Siemens, München, Germany) as described previously (12) and calculated by manual tracing using ImageJ software (version 1.52p, National Institute of Health, Bethesda, MD, USA). Lean mass and fat mass were assessed by whole-body DXA (Discovery A; Hologic, Marlborough, MA, USA [MUMC+ and JBZ] and LUNAR iDXA; GE Healthcare, Chicago, IL, USA [JBZ]).

Physical performance and muscle strength

Physical performance was assessed by the Timed Up and Go Test (13), the 30-Second Chair Stand Test (14), and the Stair Climb Test (15); always performed in the same order. Following, maximal strength was assessed by one-repetition maximum (1RM) tests on the leg press (Technogym, Milan, Italy) and leg extension machines (Technogym, Milan, Italy [MUMC+] and Keiser Corporation, Fresno, CA, USA [JBZ]). Patients started with a warm-up on a cycle ergometer followed by a warm-up of 10 and 5 repetitions at a selected load on the specific exercise machines. Subsequently, the 1RM was determined by increasing the load after each successful single lift until failure (16).

Cardiopulmonary exercise testing

Patients' maximal workload and aerobic capacity was tested with a CPET to exhaustion with continuous electrocardiogram monitoring and respiratory gas analysis. Patients performed an individualized ramp protocol (17) on a cycle ergometer (Lode Corival, Groningen, The Netherlands [MUMC+] or Ergoline; Bitz, Germany [JBZ]). Ventilatory parameters were measured breath-by-breath (Carefusion; San Diego, USA [MUMC+] or Geratherm Respiratory; Bad Kissingen, Germany [JBZ]). Maximal workload (W_{max}) was defined as the final registered workload. Peak oxygen uptake (VO_{2peak}), peak respiratory exchange ratio (RER_{peak}), and peak heart rate were recorded as the final 30-second averaged value of the test.

Blood parameters

Plasma insulin concentrations were determined by commercially available radioimmunoassay kits (Human Insulin specific RIA, Millipore Corporation, MA, USA). Plasma glucose, free fatty acids (FFAs), total cholesterol, and high-density lipoproteins were measured with enzymatic assays on an automated spectrophotometer (ABX Pentra 400 autoanalyzer, Horiba ABX, Montpellier, France). Low-density lipoprotein cholesterol was calculated using the Friedewald formula (18). All blood analyses were performed at MUMC+.

Quality of life and fatigue

HRQoL was questioned with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (19) and the PCa specific EORTC QLQ-PR25 (20). Self-reported levels of fatigue were questioned with the Multidimensional Fatigue Inventory (MFI) (21).

Statistical analysis

Data are expressed as mean ± standard deviations (SD) (normally distributed continuous variables), as median and interquartile range (non-normally distributed continuous variables) and frequency and percentages (categorical variables). Student's paired *t*-tests were performed to assess changes over time for all continuous variables. If the differences between pairs were not normally distributed, the Wilcoxon signed-rank test was performed. Significance was set at $P<0.05$. All analyses were performed with SPSS (version 27.0; IBM Corp., Armonk, NY).

Results

Patients

Of the 40 patients initially included, data of 34 patients were analyzed. Six patients dropped out due to: medical reasons ($n=2$), or the COVID-19 lockdown ($n=4$). Mean age of the study population was 70±7 years at baseline. Patients were slightly overweight (BMI: 26.4±3.6 $kg \cdot m^{-2}$) and most patients suffered from two or more comorbidities (**Table 1**). Patients were on average 26±18 days on ADT (all GnRH agonists) and 56% of patients received either radiotherapy or chemotherapy (6 cycles of docetaxel) during the study period.

Table 1 Patients' baseline characteristics (*n*=34)

Age (years)	70 ± 7
Body weight (kg)	82.2 ± 12.8
BMI (kg·m^{-2})	26.4 ± 3.6
Total body fat (%)	31.2 ± 5.2
Waist circumference (cm)	101 ± 10
Time since PCa diagnosis (months)	23 ± 40
Gleason score	8.4 ± 1.0
PSA (ng/ml)	37.0 ± 49.6
ADT duration (days)	26 ± 18
Bone metastases, *n* (%)	18 (52.9)
Previous prostatectomy, *n* (%)	10 (29.4)
Previous radiation therapy, *n* (%)	6 (17.6)
Previous chemotherapy, *n* (%)	0 (0)
Number of comorbidities*, *n* (%)	
0	10 (29.4)
1	10 (29.4)
≥2	14 (41.2)

Values are mean ± SD, or number and (%) of participants. BMI, body mass index; PCa, prostate cancer; ADT, androgen deprivation therapy. *Comorbidities were assessed by the adapted Self-administered Comorbidity Questionnaire (SCQ) (22).

Body composition

BMI (+0.6±1.1 kg·m^{-2}), waist circumference (+2±3 cm), whole-body fat mass (+2.1±1.8 kg, **Figure 1B**), and fat percentage (+1.9±1.8%) had significantly increased following 5 months ADT (**Table 2**). A significant decrease over time was found for appendicular lean mass (-0.5±1.3 kg) and quadriceps CSA (-1.3±2.5 cm^2, **Figure 1A**).

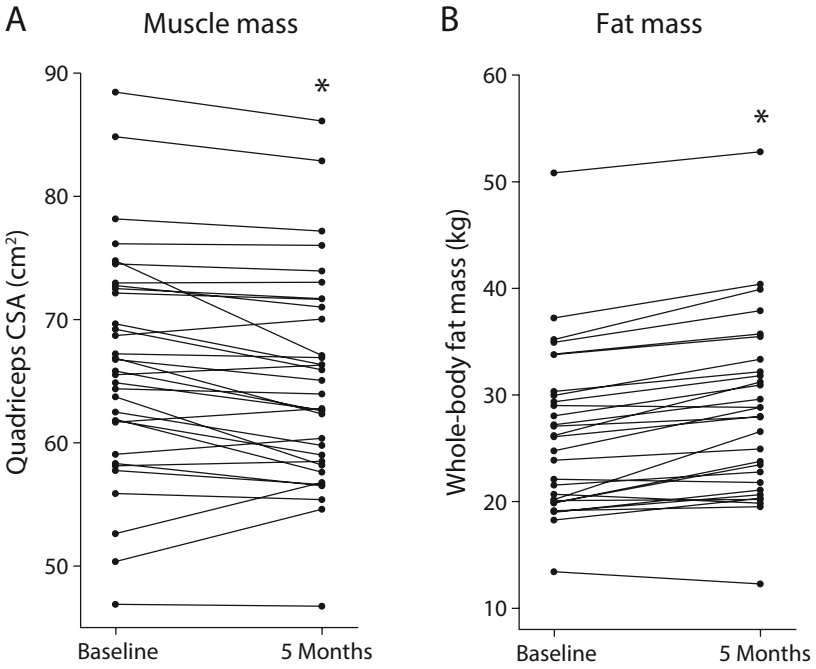

Figure 1 Individual values of quadriceps cross-sectional area (CSA, A) and whole-body fat mass (B) before and after 5 months androgen deprivation therapy in prostate cancer patients. *Significantly different from baseline (A, $P<0.001$; B, $P=0.006$).

Table 2 Changes in body composition in prostate cancer patients following 5 months androgen deprivation therapy

	n	Baseline	5 months	Difference	*P*-value
Body weight (kg)	33	82.8 ± 12.5	84.8 ± 13.0	2.0 ± 3.4	0.002
BMI (kg·m^{-2})	33	26.4 ± 3.7	27.0 ± 3.8	0.6 ± 1.1	0.003
Waist circumference (cm)	34	101 ± 10	103 ± 10	2 ± 3	0.011
Total lean body mass (kg)	29	55.3 ± 6.8	54.5 ± 6.7	-0.8 ± 2.4	0.064
Appendicular lean mass (kg)	29	24.4 ± 3.1	23.9 ± 3.0	-0.5 ± 1.3	0.041
Leg lean mass (kg)	29	17.7 ± 2.4	17.4 ± 2.4	-0.3 ± 1.0	0.133
Total body fat (kg)	29	26.2 ± 7.7	28.4 ± 8.3	2.1 ± 1.8	0.000
Total body fat (%)	29	31.2 ± 5.2	33.1 ± 5.6	1.9 ± 1.8	0.000
Quadriceps CSA (cm^2)	33	66.3 ± 9.1	65.0 ± 8.5	-1.3 ± 2.5	0.006

Values are mean ± SD. BMI, body mass index; CSA, cross-sectional area.

Muscle strength, physical performance, and cardiopulmonary outcomes

Both leg press (-6±11 kg, **Figure 2A**) and leg extension (-3±8 kg) 1RM had significantly decreased following 5 months ADT. Patients needed significantly more time to complete the Stair Climb Test (+0.61±1.60 s). W_{max} (-0.23±0.18 W·kg^{-1} body weight) and VO_{2peak} (-2.9±2.6 mL·min^{-1}·kg^{-1} body weight, **Figure 2B**) significantly decreased during the 5 month period (**Table 3**).

Table 3 Changes in muscle strength, physical performance, aerobic capacity and habitual physical activity in prostate cancer patients following 5 months androgen deprivation therapy

	n	Baseline	5 Months	Difference	*P*-value
Muscle strength					
1RM Leg press (kg)	31	107 ± 27	100 ± 27	-6 ± 11	0.003
1RM Leg extension (kg)	29	52 ± 15	48 ± 16	-3 ± 8	0.030
Physical performance					
Timed Up and Go Test (s)	34	9.22 ± 0.98	9.11 ± 1.30	-0.11 ± 1.14	0.566
30-Second Chair Stand Test (times)	34	13.6 ± 3.4	13.5 ± 4.0	-0.1 ± 2.8	0.857
Stair Climb Test (s)	34	9.56 ± 2.16	10.17 ± 2.55	0.61 ± 1.60	0.034
CPET					
W_{max} (W)	30	163 ± 39	148 ± 35	-15 ± 15	0.000
W_{max}·kg^{-1} BW (W·kg^{-1} BW)	29	2.02 ± 0.53	1.79 ± 0.48	-0.23 ± 0.18	0.000
VO_{2peak} (mL·min^{-1})	26	1883 ± 360	1685 ± 323	-198 ± 212	0.000
VO_{2peak}·kg^{-1} BW (mL·min^{-1}·kg^{-1} BW)	25	23.2 ± 3.7	20.3 ± 3.4	-2.9 ± 2.6	0.000
Maximum heart rate (beats·min^{-1})	26	145 ± 22	136 ± 18	-9 ± 15	0.007
RER_{peak}	26	1.19 ± 0.11	1.20 ± 0.10	0.01 ± 0.08	0.705
Physical activity levels					
Step count (steps·day^{-1})	33	7048 ± 2277	5842 ± 1749	-1207 ± 1942	0.001
Sedentary (%)	33	72.4 ± 7.0	73.9 ± 6.7	1.5 ± 6.5	0.200
Light (%)	33	21.4 ± 6.1	21.3 ± 5.8	-0.1 ± 5.4	0.928
Moderate to vigorous (%)	33	6.2 ± 3.4	4.8 ± 2.3	-1.4 ± 2.5	0.003

Values are mean ± SD. 1RM, one-repetition maximum; CPET, cardiopulmonary exercise test; W_{max}, maximal wattage; BW, body weight; VO_{2peak}, peak oxygen uptake; RER_{peak}, peak respiratory exchange ratio.

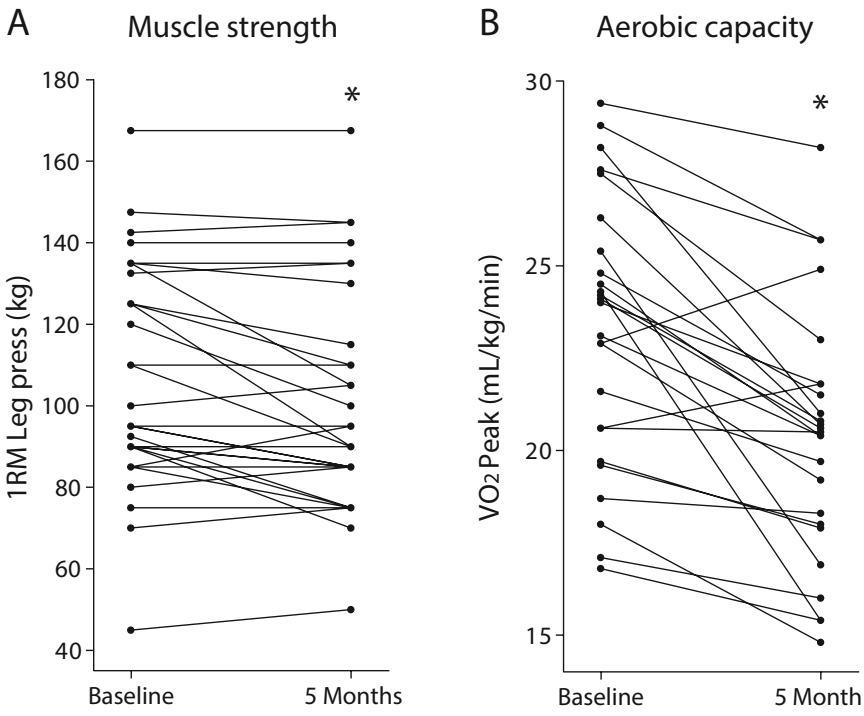

Figure 2 Individual values of one-repetition maximum (1RM) leg press (A) and peak oxygen uptake (VO_{2peak}, B) before and after 5 months androgen deprivation therapy in prostate cancer patients. *Significantly different from baseline (A, P=0.003; B, P<0.001).

Physical activity and nutritional intake

After 5 months ADT, step count had significantly decreased (-1207±1942 steps·day^{-1}, **Figure 3A**) and patients were spending significantly less time performing moderate to vigorous activities (-1.4±2.5%, **Figure 3C**). Nutritional intake had not changed over time and patients were consuming ample amounts of protein (>1.0 g·kg^{-1} body weight·day^{-1}) both at baseline and after 5 months ADT (**Supplementary Table 1**).

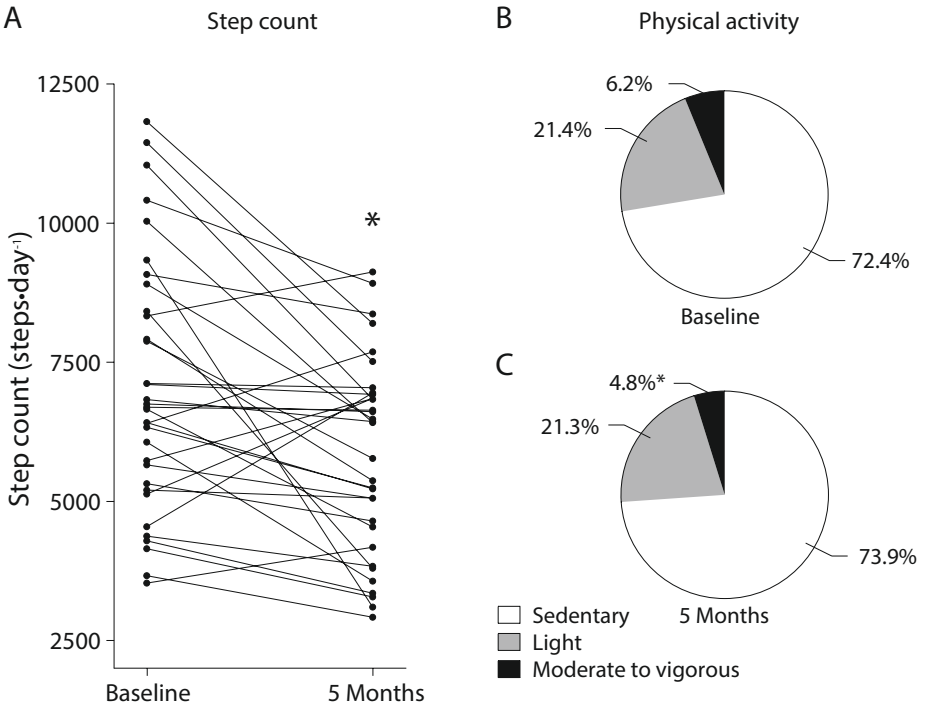

Figure 3 Individual values of step count before and after 5 months androgen deprivation therapy in prostate cancer patients (A). Percentage of the day spent sedentary, performing light activities, or performing moderate to vigorous activities before (B) and after (C) 5 months androgen deprivation therapy in prostate cancer patients. *Significantly different from baseline (A, P=0.001; C, P=0.003).

Blood parameters

Fasting plasma insulin (+1.8±2.5 mU·L^{-1}) and triacylglycerol (+286±489 µmol·L^{-1}) levels had significantly increased after 5 months ADT. No significant changes over time were found for plasma glucose, cholesterol, or FFAs. Homeostatic model assessment as a proxy for whole-body insulin resistance (HOMA-IR) index had significantly increased following the 5 month period (+0.6±0.8, **Supplementary Table 2**).

Quality of life and fatigue

Global health status (-7.6±10.3) decreased and fatigue (+12.5±18.6) had increased significantly following 5 months of ADT. Looking more specifically at fatigue (MFI), both general (+7.3±4.1) and physical (+7.5±3.9) fatigue had significantly increased. In addition, patients had significantly increased negative feelings about their weight gain, more hot flushes, and decreased sexual activity and functioning following 5 months ADT (**Supplementary Table 3**).

Discussion

In the present study, we showed that 5 months of ADT strongly decreased muscle mass and increased fat mass in prostate cancer patients. This was accompanied by a decrease in muscle strength, cardiometabolic health, physical activity levels, and quality of life. These unfavorable changes occurred rapidly and were observed within 5 months after initiating ADT.

Patients had lost as much as 2±5% appendicular lean mass following merely 5 months of ADT (**Table 2**). This decline is in line with the literature but our data extend on previous work by showing that the decline is already achieved well within the previous observed assessment period of 12 months of ADT (2). Therefore, our data imply that changes in body composition occur rapidly following onset of ADT. We complemented DXA measurements with measurements of quadriceps CSA by using CT and confirmed a 2±4% decline in quadriceps CSA within the 5 month assessment period (**Figure 1A**). The combination of DXA and CT measurements in the present study clearly shows that ADT leads to considerable lean mass loss, which is accompanied by a substantial reduction in leg muscle mass. The latter is of importance as a decline in leg muscle mass is generally associated with compromised (metabolic) health and impaired ambulation. In fact, loss of leg muscle mass generally represents a good indicator of diminished physical performance and the loss of independence in older patient populations (23).

Previous work in PCa patients on ADT remains inconclusive with regards to changes in strength and physical performance. Hand-grip strength testing is often applied and studies find either no or only a slight adverse impact of ADT on hand-grip strength (7, 8). Because leg strength is a more important indicator for daily functioning and independent living in older adults, we assessed leg strength. We observed a significant decrease in both leg press (-5±10%, **Figure 2A**) and leg extension (-7±14%) strength following 5 months of ADT. Furthermore, previous cross-sectional studies indicate that there likely is an unwanted effect of ADT on aerobic capacity (4, 24). We however are the first to assess longitudinal changes. Peak oxygen uptake had declined by 12±10% following the 5 months treatment (**Figure 2B**). It is evident that it is of clinical relevance to attenuate or even prevent such declines in muscle strength and aerobic capacity, as both are directly responsible for compromised daily functioning, independent living and self-reliance (23, 25) and strongly modulate perceived HRQoL, health care consumption and societal participation.

The declines in lean mass and physical performance in our patient group were accompanied by a significant increase in fat mass (**Figure 1B**). This is in line with previous research showing that ADT increases fat mass with ~11% during the first year of treatment (3). Again, we observed an 8±8% increase in fat mass following merely 5 months of treatment, indicating that these changes in body composition occur rapidly following onset of ADT. In line, patients experienced a significant increase in waist circumference, which supports the contention that fat mass gain during ADT predominantly occurs in the abdominal region. Increased abdominal fat mass

forms a risk factor for the development of insulin resistance and can eventually lead to type II diabetes. In accordance, patients in the present study had a significantly increased HOMA-IR index after 5 months of treatment. These metabolic derangements need to be diminished to prevent the development of type II diabetes or other cardiometabolic diseases, and its impact on survival in PCa patients on ADT (26).

Lifestyle changes in diet and physical activity can strongly affect body composition, muscle strength, aerobic capacity, and cardiometabolic risk profile. Therefore, it is of importance to assess possible changes in lifestyle factors following onset of ADT as these may contribute substantially to our observed changes in metabolic health and performance. Even though total daily energy intake did not seem to change over time (**Supplementary Table 1**), we observed a significant decline in habitual physical activity. Following ADT initiation, our patients spent over 70% of their day being sedentary (**Figures 3C**). More specifically, daily step count significantly decreased over time with a substantial 13±25% decline in total steps taken per day (**Figure 3A**). Therefore, we cannot exclude that the adverse health effects experienced during treatment are at least partly attributed to the concomitant changes in lifestyle. Also, the impact of the burden of diagnosis and/or disease on habitual physical activity remains unknown in our population, but could be substantial. In an exploratory analysis, we divided patients in 2 groups; patients below and patients above the mean change in step count of the total study population. Indeed, patients in the group with the large decrease in step count (-3286±1344 steps·day^{-1}) seem to be more prone to losing muscle strength compared to the group with no decrease in step count (-18±983 steps·day^{-1}). Physical activity and exercise are modifiable factors that can strongly improve metabolic health and physical performance in these patients (27). Physical activity has also been shown to improve HRQoL in PCa patients (28). In addition, a modest amount of vigorous activity may even substantially improve PCa-specific survival (29). Therefore, it is obvious that PCa patients should be stimulated to adopt a more active lifestyle immediately following the onset of ADT. Awareness amongst urologists about the importance of increasing habitual activity and the application of exercise training is prerequisite. Involved healthcare professionals will be fundamental to prescribe and support lifestyle interventions upon the onset of ADT. Sports physicians, rehabilitation physicians, and/or physical therapists may offer support on how to successfully embed physical activity and exercise in daily life and as such improve HRQoL and survival of patients with (metastasized) PCa. The present study is the first to show this broad spectrum of ADT-induced side effects all within one single population of PCa patients. Preferably, patients only on ADT monotherapy were included, but in order to increase inclusion rates we broadened our inclusion criteria. In a subgroup analysis however, patients who were also treated with additional therapies seem to have a similar decrease in muscle mass and strength compared to patients only treated with ADT (data not shown). Also, comorbidities and metastatic disease might have influenced the outcomes, and should be taken into account when considering the results. However, combining ADT with other therapies is more often used in PCa patients, and comorbidities and metastatic disease are common in this population. Consequently, the generalizability of our results to the entire PCa population receiving ADT is higher.

In conclusion, onset of androgen deprivation therapy leads to a rapid decline in muscle mass, muscle strength, cardiometabolic health, and quality of life in prostate cancer patients. These adverse effects are accompanied by diminished habitual physical activity which should be corrected during the early stages of treatment.

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Supplementary material

Supplementary Table 1 Changes in nutritional intake in prostate cancer patients following 5 months androgen deprivation therapy (*n*=32)

	Baseline	5 Months	Difference	*P*-value
Energy intake (MJ·day^{-1})	9.5 ± 1.8	9.1 ± 1.7	-0.3 ± 1.6	0.278
Total protein intake (g·day^{-1})	90 ± 18	89 ± 20	0 ± 17	0.931
Protein intake (g·kg^{-1} body weight·day^{-1})	1.12 ± 0.30	1.09 ± 0.27	-0.03 ± 0.19	0.313
Total carbohydrate intake (g·day^{-1})	226 ± 69	213 ± 48	-13 ± 48	0.138
Total fat intake (g·day^{-1})	89 ± 24	89 ± 26	0 ± 28	0.951

Data are mean ± SD.

Supplementary Table 2 Changes in fasting blood parameters in prostate cancer patients following 5 months androgen deprivation therapy (*n*=32)

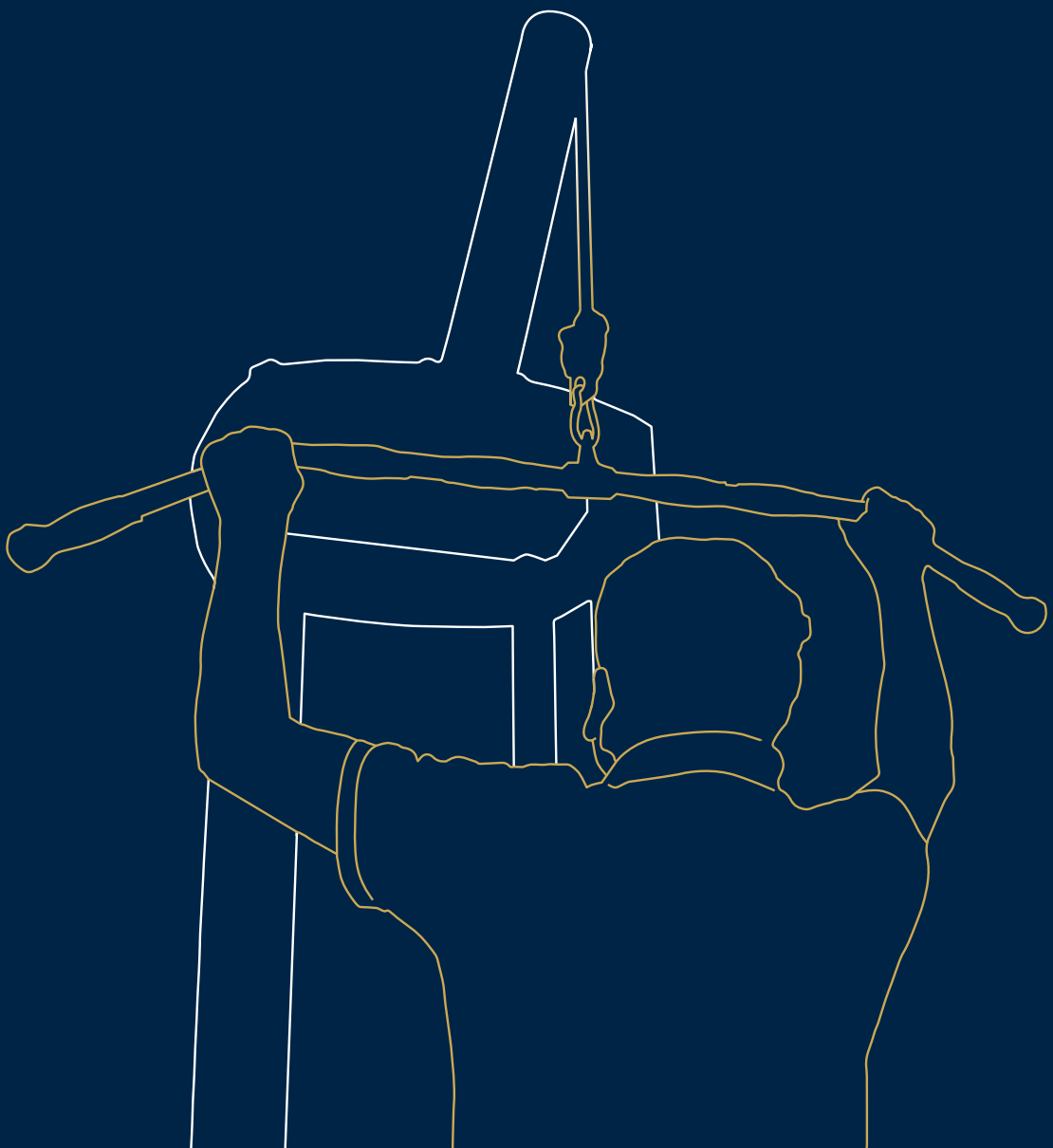
	Baseline	5 Months	Difference	*P*-value
Total cholesterol (mmol·L^{-1})	4.99 ± 1.00	5.01 ± 1.00	0.02 ± 0.72	0.903
HDL (mmol·L^{-1})	1.52 ± 0.32	1.49 ± 0.33	-0.03 ± 0.21	0.456
LDL (mmol·L^{-1})	2.99 ± 0.92	2.91 ±0.83	-0.09 ± 0.60	0.414
FFAs (µmol·L^{-1})	551 ± 236	495 ± 195	-56 ± 205	0.133
Triacylglycerol (µmol·L^{-1})	1062 ± 653	1348 ± 624	286 ± 489	0.002
Insulin (mU·L^{-1})	9.5 ± 5.8	11.3 ± 6.9	1.8 ± 2.5	0.000
Glucose (mmol·L^{-1})	5.8 ± 0.8	6.0 ± 1.3	0.2 ± 0.8	0.098
HOMA-IR	2.5 ± 1.7	3.1 ± 2.1	0.6 ± 0.8	0.001

Data are mean ± SD. HDL, High-density lipoprotein; LDL, Low-density lipoprotein; FFAs, Free fatty acids; HOMA-IR, Homeostatic model assessment for insulin resistance

Supplementary Table 3 Changes in health related quality of life and fatigue in prostate cancer patients following 5 months androgen deprivation therapy

	n	Baseline	5 Months	Difference	*P*-value
EORTC QLQ-C30					
Global health status	33	84.6 ± 13.5	77.0 ± 14.6	-7.6 ± 10.3	0.000
Physical functioning	33	94.7 ± 8.3	92.3 ± 9.6	-2.4 ± 6.8	0.050
Role functioning	33	89.4 ± 17.1	87.9 ± 18.8	-1.5 ± 21.0	0.681
Emotional functioning	33	88.9 ± 13.6	88.6 ± 17.0	-0.3 ± 16.8	0.931
Cognitive functioning	33	94.9 ± 14.1	90.9 ± 11.1	-4.0 ± 13.2	0.088
Social functioning	33	91.4 ± 13.9	94.4 ± 12.3	3.0 ± 12.1	0.160
Fatigue	33	12.5 ± 18.6	21.2 ± 25.4	8.8 ± 24.0	0.044
EORTC QLQ-PR25					
Urinary symptoms	32	21.2 ± 17.8	22.6 ± 15.3	1.4 ± 14.9	0.595
Hot flushes	33	16.2 ± 26.5	41.4 ± 31.2	25.5 ± 28.9	0.000
Painful breasts	33	3.0 ± 9.7	4.0 ± 11.0	1.0 ± 10.2	0.572
Feeling about weight gain	33	9.1 ± 17.2	22.2 ± 28.5	13.1 ± 24.9	0.005
Feeling less manly	33	15.2 ± 22.2	21.2 ± 28.6	6.1 ± 24.2	0.160
Sexual activity and functioning	32	79.7 ± 19.3	89.6 ± 15.1	9.9 ± 15.8	0.001
MFI					
General fatigue	33	7.3 ± 4.1	9.5 ± 4.4	2.2 ± 3.6	0.001
Physical fatigue	33	7.5 ± 3.9	9.5 ± 3.8	2.0 ± 4.1	0.007
Reduced activity	33	8.2 ± 4.2	9.1 ± 4.1	1.0 ± 4.4	0.245
Reduced motivation	33	7.1 ± 3.4	8.2 ± 3.6	1.2 ± 3.6	0.077
Mental fatigue	32	6.3 ± 3.1	7.3 ± 3.3	1.0 ± 3.3	0.108

Values are mean ± SD. EORTC QLQ-C30, European organization for research and treatment of cancer quality of life questionnaire; EORTC QLQ-PR25, European organization for research and treatment of cancer quality of life questionnaire - Prostate cancer module; MFI, Multidimensional fatigue inventory.



CHAPTER 4

Resistance exercise training increases muscle mass and strength in prostate cancer patients on androgen deprivation therapy

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Abstract

Purpose: To assess the effects of 20 weeks resistance exercise training with or without protein supplementation on body composition, muscle mass, muscle strength, physical performance and aerobic capacity in prostate cancer patients receiving androgen deprivation therapy (ADT).

Methods: Sixty prostate cancer patients receiving ADT were randomly assigned to perform 20 weeks of resistance exercise training with supplementation of 31 g whey protein (EX+PRO, *n*=30) or placebo (EX+PLA, *n*=30), consumed immediately after exercise and every night before sleep. A separate control group (CON, *n*=36) only received usual care. At baseline and after 20 weeks, body composition (dual-energy X-ray absorptiometry), muscle mass (computed tomography scan), muscle strength (1-repetition maximum strength tests), physical performance (Timed Up and Go Test, 30-second Chair Stand Test, Stair Climb Test), aerobic capacity (cardiopulmonary exercise test) and habitual dietary intake (food diary), were assessed. Data were analyzed using a two-factor repeated-measures ANOVA.

Results: Over time, muscle mass and strength increased in EX+PRO and EX+PLA and decreased in CON. Total fat mass and fat percentage increased in EX+PRO and CON, but not in EX+PLA. Physical performance did not significantly change over time in either group. Aerobic capacity was maintained in EX+PLA, while it decreased in EX+PRO and CON. Habitual protein intake (without supplements) averaged >1.0 g·kg body weight^{-1}·day^{-1}, with no differences over time or between groups.

Conclusions: In prostate cancer patients, resistance exercise training counteracts the adverse effects of ADT on body composition, muscle mass, muscle strength and aerobic capacity, with no additional benefits of protein supplementation.

Introduction

Androgen deprivation therapy (ADT) forms the cornerstone in the treatment of localized high-risk, locally advanced and metastatic prostate cancer (PCa) (1, 2). It is estimated that approximately 50% of all PCa patients will be treated with ADT in the course of their disease trajectory (3). The working mechanism of ADT is based on reducing androgen levels to castration level, since androgens are known to drive prostate tumor growth. Although ADT substantially improves survival, the decline in androgen levels has numerous adverse effects, including the loss of lean body mass and an increase in body fat mass (4-6).

It has been well-established that resistance exercise training can be applied effectively to counteract the age-related loss of muscle mass and strength in healthy older adults (7-11). For PCa patients on ADT, randomized controlled trials (RCT) consistently show that resistance exercise training increases appendicular lean mass and muscle strength (12-17). The efficacy of resistance exercise training to reduce fat mass, increase physical performance and improve aerobic capacity in PCa patients undergoing ADT is less evident (12-17). However, recent meta-analyses on the impact of prolonged resistance exercise training have reported positive results for these outcomes in the population of PCa patients, not restricted to ADT treatment only (18, 19). We hypothesized that prolonged resistance exercise training represents an effective adjuvant treatment to attenuate the decline in muscle mass, reduce fat mass accrual, increase strength and physical performance in PCa patients on ADT.

Protein supplementation during prolonged resistance exercise training has been shown to result in greater gains in muscle mass and strength in both young and older adults (10, 20) compared to no protein supplementation. It could be speculated that dietary protein supplementation may also augment the anabolic effects of resistance exercise training in PCa patients on ADT. In support, protein ingestion during recovery from exercise has been shown to increase muscle protein synthesis rates in PCa patients on ADT (21). However, pilot work by Dawson *et al*. (17) failed to confirm the benefits of protein supplementation to further increase gains in muscle mass, strength or physical performance following 12 weeks of resistance exercise training in these patients. Clearly, more work is needed to determine the proposed benefits of protein supplementation on the prevention of muscle mass and strength loss in PCa patients on ADT. We hypothesized that protein supplementation augments the benefits of prolonged resistance exercise training to attenuate the decline in muscle mass, reduce fat mass accrual, increase strength and physical performance in PCa patients on ADT.

To test our hypotheses, we enrolled PCa patients (starting) with ADT. Throughout their treatment we assessed the impact of 20 weeks of resistance exercise training with and without additional protein supplementation on body composition, muscle strength, physical performance and aerobic capacity. To adequately assess the various changes in body composition and muscle mass we applied both whole-body dual-energy X-ray absorptiometry (DXA) and leg computed

tomography (CT), and quantified performance by both cardiopulmonary exercise testing and various strength and functional performance tests.

Methods

Patients

Between September 2017 and February 2021 PCa patients starting or continuing treatment with gonadotrophin-releasing hormone (GnRH) agonist or antagonist, with or without anti-androgens, for a least 6 months were recruited. Patients were excluded if they were unable to participate in the exercise training regimen, had comorbidities severely compromising physical activity, exposed a high risk for pathological fractures due to bone metastases (as estimated by their treating urologist), had an estimated life expectancy <1 year, were lactose intolerant or had a whey protein allergy, showed cognitive disorders or severe emotional instability or were unable to speak, understand or read the Dutch language. Potential participants were identified by their urologist or urology nurse, and referred to the investigators who provided them with the full oral and written study information. Interested patients were invited for a screening visit to obtain informed consent and confirm eligibility. Their medical history and in- and exclusion criteria were evaluated and a cardiopulmonary exercise test was performed. All patients were cleared by a sports physician to perform the exercise training program. The study was approved by the local Medical Ethical Committee of Maastricht University Medical Centre + (MUMC+), and confirmed to the principles outlined in the latest version of the Declaration of Helsinki for use of human subjects and tissue. This trial was registered at www.trialregister.nl as NL6258. The study was independently monitored by the Clinical Trial Center Maastricht.

Study design

This study was a multicenter partly RCT, comparing two intervention groups with a separately recruited control group. Patients were recruited in hospitals in the southern part of the Netherlands. For both intervention groups, patients were recruited in the MUMC+, the Zuyderland Medical Centre (Zuyderland MC) and the Máxima Medical Centre (MMC) between September 2017 and March 2020. Patients for the control group (CON) were recruited in the Jeroen Bosch Hospital (JBZ) and Canisius-Wilhelmina Hospital (CWZ) between June 2018 and February 2021, as well as in the MUMC+ and Zuyderland MC between October 2020 and February 2021. Patients for CON were asked to participate in a study about the side effects of ADT and were not informed about the exercise intervention.

At baseline and after 20 weeks, an experimental test day was planned (in MUMC+ for patients of the MUMC+ and Zuyderland MC, MMC for patients of the MMC, and JBZ for patients of the JBZ and CWZ). Anthropometric measurements, whole-body DXA and leg CT were performed. After providing a lunch, physical performance tests and maximal strength assessments were performed. The screening and baseline measurements were preferably separated by at least 7 days, in which patients wore an accelerometer and kept a food diary. At the end of the baseline

test day, patients recruited for the intervention groups were randomly allocated in a double blinded fashion to resistance exercise training with protein supplementation (EX+PRO) or with placebo supplementation (EX+PLA). An independent researcher performed the randomization by means of computer generated random numbers in stratified permuted blocks of 4.

After 20 weeks of intervention or usual care, all procedures from the baseline test day and the cardiopulmonary exercise test were repeated. The cardiopulmonary exercise test was performed at least 48 h before or after the test day, to prevent any influence on the other outcome measurements. Furthermore, during the last week of the intervention or control period, patients again wore the accelerometer and filled in the food diary. Protein or placebo allocation was concealed from the research team and patients until all patients had performed their post-measurements.

Exercise intervention program

Patients in the exercise groups performed a supervised progressive whole-body resistance exercise training program (60 min, twice a week) for 20 weeks. Training started and ended with 5-min warm-up and cooling down on a cycle ergometer, interspersed by training on the leg press and leg extension separated by two upper body exercises. On the leg press and leg extension, 2 warm-up sets and 4 working sets were performed. Upper body exercises were paired (chest press with lateral pulldown and shoulder press with horizontal row) and were performed in an alternating manner between training sessions, with 1 warm-up set, followed by 3 working sets. All sets consisted of 10 repetitions with 1.5 and 3 min rest between sets and exercises, respectively. For lower body exercises one-repetition maximum (1RM) was determined at the baseline test day, for upper body exercises 1RM was determined during the first training week (as this was not an outcome measure). The training program was divided into cycles of 4 weeks. During week 1-3 of the first cycle, the workload on each machine was gradually increased from 60% to 70% 1RM. In week 1-3 of the following cycles, the workload was increased from 65% to 70% 1RM. Every 4th week, workload was reduced to 60% 1RM to allow for proper recovery and minimize the risk of injury. After 4, 8, 12 and 16 weeks of training, 1RM was estimated using the multiple-repetition testing procedure (indirect 1RM) to progressively adjust the workload of the training sessions. For patients experiencing medical complications (e.g. treatment-related issues or injuries), training load was adjusted. Patients received a personalized training log for every training session, in which the actual training program/load was registered. Training adherence was calculated as the amount of performed exercise sets divided by the amount of prescribed sets.

Protein and placebo supplementation

Patients in the exercise groups ingested either a protein or placebo supplement directly after every exercise session and each night before sleep. The protein supplement contained 31 g whey protein (Lacprodan® HYDRO.Rebuild, degree of hydrolysis 10%), 13 g carbohydrate and 1.0 g fat, providing 774 kJ of energy (Arla Foods Ingredients Group P/S, Viby J, Denmark). The placebo supplement contained 1 g protein, 12 g carbohydrate and 0.4 g fat, providing 234

kJ of energy (Arla Foods Ingredients Group P/S, Viby J, Denmark). Supplement provision was performed in a double-blinded fashion by an independent researcher. Patients received sachets containing dried contents, which needed to be dissolved in 250 mL water. All beverages were chocolate flavored to mask their contents. Adherence to the supplement ingestion was assessed by counting returned (full and empty) supplement sachets.

Habitual dietary intake and physical activity

Patients were instructed to refrain from exhaustive physical activity 48 h before the test days and to arrive at the study location by car or public transportation after an overnight fast. The week before both test days, patients recorded their dietary intake and their physical activity to gain insight in their habitual activity pattern and to identify potential changes during the intervention period. To assess dietary intake, patients kept a 3-day food dairy (on two weekdays and one weekend day). Average daily energy intake (MJ), energy percentages (En%) of protein, carbohydrate and fat, and protein intake relative to bodyweight (g·kg body weight^{-1}·day^{-1}) were calculated with web-based software (Eetmeter; Voedingscentrum, Den Haag, The Netherlands). To assess physical activity, patients wore a small-sized triaxial accelerometer (ActiGraph wGT3X-BT; ActiGraph, Pensacola, FL, USA) on the waist during wakefulness for seven days. Accelerometer data were analyzed with ActiLife (version 6.13.4; ActiGraph, Pensacola, FL, USA) and average daily step count, as well as percentage of time spent sedentary or in light, moderate, and (very) vigorous activity intensity were calculated. Data were included if the accelerometer was worn for ≥5 days and ≥10 h per day.

Body composition

Body weight was measured wearing underwear and directly after voiding using a digital scale to the nearest 0.1 kg. Height was measured by a fixed stadiometer to the nearest 0.5 cm. Body mass index (BMI) was calculated as kilograms per square meter. Waist circumference was measured twice at the midpoint between the top of the iliac crest and the lower margin of the lowest palpable rib at the end of a normal expiration using a stretch-resistant tape. A difference between both measurements of ≤1 cm was accepted and averaged to the nearest 0.5 cm. Whole-body and regional lean mass and fat mass were measured with whole-body DXA (Discovery A; Hologic, Marlborough, MA, USA [MUMC+ and MMC] or LUNAR iDXA; GE Healthcare, Chicago, IL, USA [JBZ]).

Skeletal muscle mass

Skeletal muscle mass was assessed with a single-slice CT scan (SOMATOM Definition Flash; Siemens, München, Germany [MUMC + and JBZ] or Ingenuity CT; Philips Medical Systems, Eindhoven, The Netherlands [MMC]) to determine the anatomic cross-sectional area (CSA) of the quadriceps muscle, as described previously (22). A single-slice image was made 15 cm proximal to the top of the patella of both legs. Quadriceps muscle CSA of the dominant leg was calculated by manual tracing using ImageJ software (version 1.52p, National Institute of Health, Bethesda, MD, USA).

Muscle strength

Maximal strength was assessed by 1RM strength tests on the leg press and leg extension machines (Technogym; Milan, Italy). Patients started with a short warm-up on a cycle ergometer. Thereafter proper lifting technique was demonstrated and practiced, and a specific warm-up of 10 and 5 repetitions on ~50 and 70% of the predicted 1RM was performed. This also served as practise session to familiarize the patients with the exercise. Subsequently, 1RM was determined by increasing the load after each successful single lift until failure. Three min rest between attempts was allowed. A repetition was valid if the entire lift was completed in a controlled manner without assistance.

Physical performance

Physical performance was assessed by 3 consecutive performance tests, always performed in the same order. The Timed Up and Go Test measures the time it takes to get up from a standard arm chair, walk 3 meters on a comfortable pace, turn around, walk back and sit down again (23). The 30-second Chair Stand Test assesses how many times the patient can stand upright and sit down from a standard chair with his arms folded across the chest, over a 30 seconds period (24). The Stair Climb Test measures the time it takes to ascend and descend a flight of stairs as quickly as possible but in a safe manner (using the handrail was mandatory).

Aerobic capacity

Aerobic capacity was tested with a cardiopulmonary exercise test to exhaustion with continuous electrocardiography and respiratory gas analysis. Tests were performed on a cycle ergometer (Lode Corival; Groningen, the Netherlands [MUMC+] or Ergoline; Bitz, Germany [MMC, JBZ]). Ventilatory parameters were measured breath-by-breath (Carefusion; San Diego, USA [MUMC+, MMC] or Geratherm Respiratory; Bad Kissingen, Germany [JBZ]). After 3 minutes of unloaded cycling, the workload was increased according to an individualized ramp protocol aiming at a total test duration of 8–12 minutes (25). Patients were instructed to cycle with a pedaling rate of >60 revolutions·min^{-1}. The test was ended when the patient stopped cycling or was not able to maintain the required pedaling frequency. Maximal workload (W_{max}), peak oxygen uptake (VO_{2peak}) and peak respiratory exchange ratio (RER_{peak}) were recorded as the final 30-second averaged value of the test.

Sample size calculation and statistical analysis

Our initial sample size estimate of 72 patients in each exercise group and 64 in the control group was not feasible anymore due to the COVID-19-induced lockdown and its subsequent limitations. Therefore, we performed a new sample size calculation based on our already collected data. To detect a difference in quadriceps CSA (primary outcome) between groups over time, 15 patients per group were required (G-Power; power 90%, alpha 0.05, calculated Cohen's *f* effect size 0.24). As already 30 patients in each exercise group had finished their 20 weeks measurements, this number was enough to show the effect of the exercise intervention. Furthermore, including more patients would not result in identifying an effect of the protein supplementation, as the interim data showed absolutely no indication of any difference

between both exercise groups (Cohen's *d*, -0.035). Therefore, to end up with 3 groups of equal sizes, patient inclusion was continued in the control group only to reach a minimal inclusion of 36 patients (taking into account potential dropouts).

Data were expressed as mean ± standard deviation (SD), or as frequency and percentages. Baseline characteristics between groups were compared using one-way ANOVA with post-hoc Bonferroni corrections (for continuous variables) or a chi-square test (for categorical variables). Data was analyzed on an intention-to-treat basis. A 2-factor repeated-measures ANOVA (time × treatment) with time (baseline vs 20 weeks) as a within-subjects factor and treatment group (EX+PLA vs EX+PRO vs CON) as a between-subjects factor was used. In case of a significant time x treatment interaction, paired-samples t-tests were performed to detect within-group changes over time. Additionally, univariate general linear models with post-hoc Bonferroni corrections were used to detect between-group differences over time. For muscle strength, absolute 1RM values could not be compared due to slight differences in leg press and leg extension equipment at the different study locations. Therefore, percentage changes over time were calculated and compared between groups with univariate general linear models with post-hoc Bonferroni corrections. Effect sizes were calculated using partial eta squared ($\eta^2_{partial}$). Significance was set at $P<0.05$. All analyses were performed with the use of IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY).

Results

Patients

In total, 134 patients were screened to participate in the study, 126 patients were included and 96 patients finished the study. Of the 30 patients that did not finish the study, 26 dropped out due to training and testing restrictions during the COVID-19-induced lockdown, 1 due to screening failure and 3 for medical reasons (**Figure 1**).

Patients' baseline characteristics are presented in **Table 1**. Patients were 71±7 y old and were slightly overweight (BMI 26.9±3.5 kg·m^{-2}). Average time since PCa diagnosis was 24 months, 48% of all patients had bone metastases at study enrollment and mean ADT treatment duration was 107±206 days. Baseline characteristics did not differ between groups, except for ADT duration which was significantly higher in EX+PLA compared to CON, and the number of patients receiving previous chemotherapy (*n*=3 in EX+PLA, none in EX+PRO and CON). During the study period of 20 weeks, 42 patients received additional chemotherapy (CTx) or radiation therapy (RTx) (EX+PLA: CTx *n*=6, RTx *n*=8; EX+PRO: CTx *n*=2, RTx *n=7*; CON: CTx *n=7*, RTx *n*=12), with no significant differences between groups (CTx, *P*=0.264; RTx, *P*=0.652). All statistical analyses were performed with and without 'ADT duration at baseline' as covariate and the unadjusted results are shown. In case of differences, both results are described.

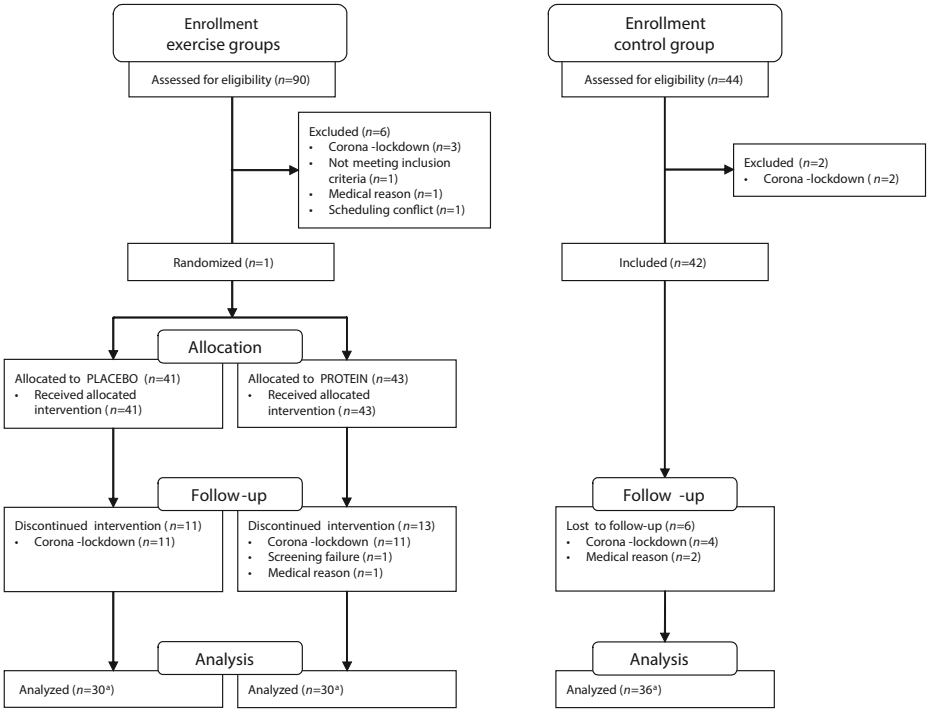

Figure 1 CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.
[a]Not all outcome measurements are available for all patients.

Table 1 Baseline patients' characteristics

	EX+PLA (*n* = 30)	EX+PRO (*n* = 30)	CON (*n* = 36)
Age (y)	71 ± 7	73 ± 7	71 ± 7
Body weight (kg)	84.5 ± 11.1	82.2 ± 13.5	83.0 ± 12.8
BMI (kg·m^{-2})	27.5 ± 3.3	26.7 ± 3.4	26.7 ± 3.7
Total body fat % (%)	30 ± 4	30 ± 5	31 ± 6
ADT duration (days)[a]	190 ± 282[b]	107 ± 208	37 ± 49
Time since PCa diagnosis (months)	12 ± 18	36 ± 52	23 ± 39
Gleason score	8.4 ± 1.0	7.9 ± 1.1	8.3 ± 1.0
Bone metastases, *n* (%)	14 (50.0)	11 (39.3)	19 (52.8)
Previous prostatectomy, *n* (%)	7 (23.3)	5 (16.7)	10 (27.8)
Previous radiation, *n* (%)	4 (13.3)	9 (30.0)	6 (16.7)
Previous chemotherapy, *n* (%)[a]	3 (10)	0 (0)	0 (0)
Number of comorbidities, *n* (%)[c]			
0	5 (17.2)	3 (10.0)	10 (28.6)
1	12 (41.4)	11 (36.7	10 (28.6)
≥2	12 (41.4)	16 (53.3)	15 (42.9)

Values are mean ± SD, or number and (%) of participants. Not all data are available for all patients. Data available for time since PCa diagnosis: *n*=35 (CON); for Gleason score: *n*=35 (CON); for bone metastases: *n*=28 (EX+PLA), *n*=28 (EX+PRO); for number of comorbidities: *n*=29 (EX+PLA), *n*=35 (CON). EX+PLA, exercise training group with placebo supplementation; EX+PRO, exercise training group with protein supplementation; CON, control group; BMI, body mass index; PCa, prostate cancer; ADT, androgen deprivation therapy. [a]Significantly different between groups ($P<0.05$). [b]Significantly different from CON ($P<0.05$). [c]Comorbidity assessed by the adapted Self-administered Comorbidity Questionnaire.

Adherence and safety

Overall adherence to the training sessions was 84±18 and 79±23% in EX+PLA and EX+PRO respectively, and did not differ between groups. Adherence to the intake of the supplements was 94±8 and 86±23% in EX+PLA and EX+PRO respectively, with no differences between groups. During the exercise training, one patient experienced a collapse requiring admission to the emergency department for further cardiac examination. No abnormalities were found. No other serious adverse events during the exercise training or supplemental intake occurred.

Habitual dietary intake and physical activity

Habitual daily dietary intake and physical activity data are presented in **Table 2.** For total energy, protein, carbohydrate, and fat intake no baseline differences between groups or changes over time were found. Overall habitual protein intake averaged 1.1±0.3 g·kg body weight^{-1}·day^{-1}, with no differences between groups nor changes over time. Protein supplementation increased daily protein intake in EX-PRO by an average 34.5±9.3 g·day^{-1}, resulting in a daily protein intake of 1.4±0.4 g·kg body weight^{-1}·day^{-1}. The total protein intake including placebo supplementation in EX-PLA averaged 1.1±0.2 g·kg body weight^{-1}·day^{-1}.

Table 2 Changes in habitual dietary intake and habitual physical activity over time

	EX+PLA (*n*=28[a])		EX+PRO (*n*=30[a])		CON (*n*=34[a])	
	Baseline	**20 weeks**	**Baseline**	**20 weeks**	**Baseline**	**20 weeks**
Habitual dietary intake						
Energy intake (MJ·day^{-1})	9.2 ± 2.0	9.3 ± 2.2	9.0 ± 1.9	8.6 ± 1.8	9.4 ± 1.8	9.1 ± 1.7
Protein intake (g·kg body weight^{-1}·day^{-1})	1.1 ± 0.3	1.1 ± 0.2	1.0 ± 0.3	1.0 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
Protein intake (% of energy)	16 ± 2	16 ± 3	16 ± 3	16 ± 3	16 ± 3	17 ± 3
Carbohydrate intake (% of energy)	38 ± 9	39 ± 8	42 ± 6	40 ± 7	40 ± 8	39 ± 6
Fat intake (% of energy)	38 ± 7	38 ± 7	36 ± 5	38 ± 6	36 ± 7	36 ± 6
Habitual physical activity						
Average steps per day (steps·day^{-1})[b]	6212 ± 2901	5708 ± 2451	5586 ± 2774	5246 ± 2914	7008 ± 2216	5807 ± 1709
% Time sedentary per day (%)[c]	77 ± 7	77 ± 6	79 ± 7[d]	78 ± 9	73 ± 7	74 ± 7
% Time in light activity per day (%)[c]	19 ± 6	19 ± 5	18 ± 6	18 ± 6	21 ± 6	21 ± 6
% Time in moderate activity per day (%)[b,c]	5 ± 3	4 ± 2	4 ± 3[d]	4 ± 3	6 ± 3	5 ± 2
% Time in vigorous and very vigorous activity per day (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0

Values are mean ± SD. No time x treatment interaction was observed for any of the variables. EX+PLA, exercise training group with placebo supplementation; EX+PRO, exercise training group with protein supplementation; CON, control group. [a]For habitual physical activity data, *n*=29 (EX+PLA), *n*=26 (EX+PRO), *n*=35 (CON). [b]Significant time effect ($P<0.05$). [c]Significantly different between groups at baseline ($P<0.05$). [d]Significantly different at baseline from CON ($P<0.05$). The physical activity levels are assessed with the 'Freedson Adult (1998)' filter, using the following cutoff points: sedentary 0-99 counts per minute; light 100-1951 counts per minute; moderate 1952-5724 counts per minute; vigorous 5725-9498 counts per minute; very vigorous 9499 counts per minute and above.

Body composition

Body composition parameters are presented in **Table 3**. No baseline differences between groups were observed. Over time patients gained on average 1.5±3.1 kg body weight (time effect, *P*<0.001) resulting in 1.9±3.9% increase in BMI (time effect, *P*<0.001) and 1.0±3.4 cm increase in waist circumference (time effect, *P*<0.005), with no differences between groups. For DXA measurements, significant differences over time between groups were found for total lean mass, appendicular lean mass, total fat mass (FM) and fat percentage (fat%). For total lean mass and appendicular lean mass, within-group analyses showed no significant changes over time in any of the three groups. However, between-group comparisons showed a significant difference (*P*=0.039) in the change in appendicular lean mass over time between EX+PLA (+0.3±1.0 kg) and CON (-0.4±1.3 kg) which was no longer significant after adjusting for 'ADT duration at baseline' (EX+PLA vs CON 0.7±0.3 kg, *P*=0.039 (unadjusted) and 0.7±0.3 kg, *P*=0.084 (adjusted)). For lean mass, between-group comparisons showed a strong trend (*P*=0.053) toward a difference in the changes between EX+PLA (+0.6±2.0 kg) and CON (-0.7±2.4 kg). For FM and fat%, within-group analyses showed no significant changes over time in EX+PLA, whereas FM and fat% significantly increased over time in EX+PRO (FM +1.1±1.6 kg, fat% +0.8±1.6%; both *P*<0.05) with even larger increases in CON (FM +2.1±1.7, fat% +1.8±1.8%, both *P*<0.001). In accordance, between-group comparisons showed significant differences in the changes in FM and fat% between EX+PLA and CON which became smaller after adjusting for 'ADT duration at baseline' (FM: EX+PRO vs CON, -1.0±0.5 kg, *P*=0.138 (unadjusted) and -0.8±0.5 kg, *P*=0.328 (adjusted); EX+PLA vs CON, -1.7±0.5 kg, *P*=0.002 (unadjusted) and -1.2±0.5 kg, *P*=0.034 (adjusted); fat%: EX+PRO vs CON, -1.0±0.4%, *P*=0.064 (unadjusted) and -0.9±0.4%, *P*=0.155 (adjusted); EX+PLA, - 1.6±0.4%, *P*<0.001 (unadjusted) and -1.3±0.4%, *P*=0.014 (adjusted)).

Table 3 Changes in body composition over time

		Baseline	20 weeks	Time effect	Time x treatment interaction	Within-group changes over 20 weeks	
	n	Mean ± SD	Mean ± SD	*P*-value	*P*-value ($\eta^2_{partial}$)	Mean ± SD	*P*-value
Body weight (kg)				<0.001	0.291 (0.026)		
EX+PLA	30	84.5 ± 11.1	85.4 ± 10.4			0.8 ± 3.5	
EX+PRO	30	82.2 ± 13.5	83.8 ± 13.9			1.6 ± 2.5	
CON	36	83.0 ± 12.8	85.0 ± 13.3			2.1 ± 3.3	
BMI ($kg \cdot cm^{-2}$)				<0.001	0.327 (0.024)		
EX+PLA	30	27.5 ± 3.3	27.8 ± 3.1			0.3 ± 1.1	
EX+PRO	30	26.7 ± 3.4	27.2 ± 3.4			0.5 ± 0.8	
CON	36	26.7 ± 3.7	27.3 ± 3.9			0.7 ± 1.1	
Waist circumference (cm)				0.005	0.251 (0.029)		
EX+PLA	30	104.6 ± 10.5	105.0 ± 9.6			0.4 ± 3.5	
EX+PRO	30	103.5 ± 11.9	104.3 ± 11.4			0.8 ± 3.1	
CON	36	102.3 ± 10.6	104.0 ± 10.3			1.7 ± 3.4	
Total lean mass (kg)				0.466	0.032 (0.077)		
EX+PLA	30	57.6 ± 6.9	58.3 ± 6.6			0.6 ± 2.0[a]	0.088
EX+PRO	28	55.4 ± 7.0	55.9 ± 7.4			0.5 ± 1.9	0.161
CON	31	55.5 ± 6.6	54.8 ± 6.6			-0.7 ± 2.4	0.125
Appendicular lean mass (kg)				0.913	0.028 (0.080)		
EX+PLA	30	25.0 ± 3.3	25.3 ± 3.1			0.3 ± 1.0[b]	0.104
EX+PRO	28	23.5 ± 3.2	23.7 ± 3.4			0.2 ± 1.1	0.378
CON	31	24.4 ± 3.0	23.9 ± 3.0			-0.4 ± 1.3	0.072

Table 3 Changes in body composition over time (continued)

		Baseline	20 weeks	Time effect	Time x treatment interaction	Within-group changes over 20 weeks	
	n	Mean ± SD	Mean ± SD	*P*-value	*P*-value ($\eta^2_{partial}$)	Mean ± SD	*P*-value
Total fat mass (kg)				<0.001	0.003 (0.127)		
EX+PLA	30	25.6 ± 6.0	26.0 ± 5.4			0.4 ± 2.2[b]	0.311
EX+PRO	28	25.6 ± 7.8	26.7 ± 7.6			1.1 ± 1.6	0.001
CON	31	26.9 ± 7.9	29.0 ± 8.4			2.1 ± 1.7	<0.001
Fat percentage (%)				<0.001	0.001 (0.145)		
EX+PLA	30	29.5 ± 4.5	29.7 ± 4.0			0.2 ± 1.7[b]	0.544
EX+PRO	28	30.1 ± 5.1	30.9 ± 4.6			0.8 ± 1.6	0.011
CON	31	31.6 ± 5.3	33.4 ± 5.5			1.8 ± 1.8	<0.001

EX+PRO, exercise training group with protein supplementation; CON, control group; BMI, body mass index. [a]Changes over time are borderline significantly different from changes over time in CON (P=0.053). [b]Changes over time are significantly different from changes over time in CON (P<0.05).

Skeletal muscle mass

At baseline, no significant differences in quadriceps CSA were observed between groups. However, changes over time were significantly different between groups (time x treatment $P<0.001$). Within groups, quadriceps CSA increased over time in EX+PLA (+2.0±3.0 cm^2, $P=0.001$) and EX+PRO (+1.9±2.7 cm^2, $P<0.001$), and decreased in CON (-1.2±2.5 cm^2, $P=0.008$). Between-group comparisons revealed significant differences in the changes over time between both EX+PLA ($P<0.001$) and EX+PRO ($P<0.001$), when compared with CON, with no differences between both exercise groups (**Figure 2**).

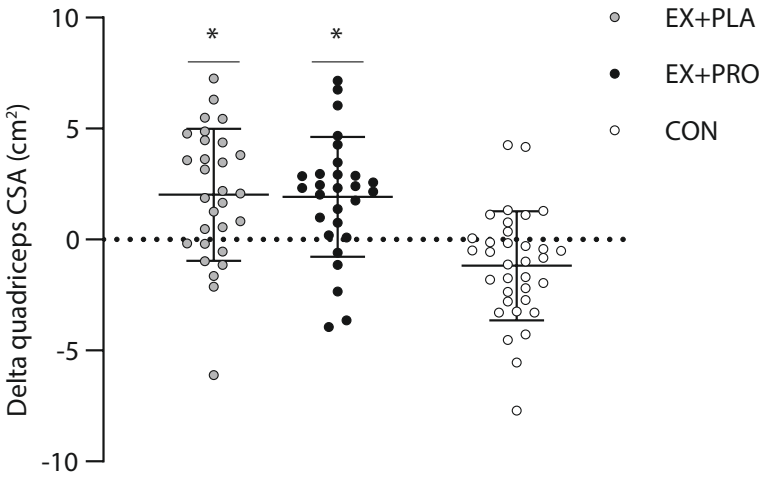

Figure 2 Changes in quadriceps cross-sectional area over the 20-weeks intervention period. *Changes over time are significantly different from changes over time in CON ($P<0.001$).

Leg strength

In both exercise groups, 1RM leg press and 1RM leg extension increased over time (EX+PLA, +12±14% and +19±15% respectively; EX+PRO, +13±11% and +15±19% respectively). In CON, 1RM leg press (-5±11%) and leg extension (-6±15%) decreased over time. For both exercise groups, changes over time in leg muscle strength were significantly different from the changes in CON (both $P<0.001$), with no differences between both exercise groups (**Figure 3)**.

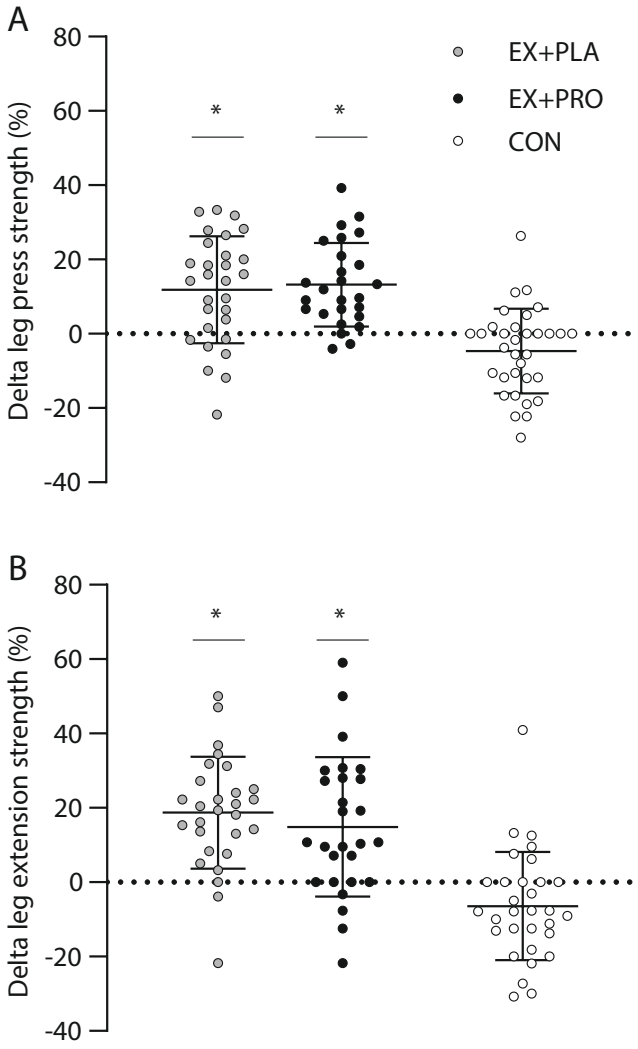

Figure 3 Percentage changes in 1-repetition maximum leg press (A) and leg extension (B) strength over the 20-weeks intervention period. *Changes over time are significantly different from changes over time in CON ($P<0.001$).

Physical performance and aerobic capacity

Results are presented in **Table 4**. On the physical performance tests no differences in baseline values or changes over time between groups were observed. For aerobic capacity, baseline differences between groups were found for W_{max}, W_{max}·kg body weight^{-1} and VO_{2peak} (all $P<0.05$). Changes over time were significantly different between groups for W_{max}·kg body weight^{-1}, VO_{2peak} and VO_{2peak}·kg body weight^{-1} (all $P<0.05$). Subsequent within-group analyses showed no changes over time in EX+PLA for all cardiopulmonary exercise test variables, whereas in EX+PRO VO_{2peak} and VO_{2peak}·kg body weight^{-1} decreased (both $P<0.05$). Furthermore, in CON, VO_{2peak} and VO_{2peak}·kg body weight^{-1} declined even more, and W_{max}·kg body weight^{-1} declined as well (all $P<0.001$). As a result, changes over time were significantly different between EX+PLA and CON (all $P<0.05$). Changes in RER_{peak} values did not differ between and within groups over time.

Table 4 Changes in physical performance tests and cardiopulmonary exercise tests over time

		Baseline	20 weeks	Time effect	Time x treatment interaction	Within-group changes over 20 weeks	
	n	Mean ± SD	Mean ± SD	*P*-value	*P*-value ($\eta^2_{partial}$)	Mean ± SD	*P*-value
Physical performance tests							
Timed Up and Go Test (sec)				0.993	0.653 (0.009)		
EX+PLA	30	9.6 ± 1.5	9.6 ± 1.5				
EX+PRO	28	9.6 ± 1.5	9.7 ± 1.7				
CON	36	9.3 ± 1.0	9.2 ± 1.3				
30-sec Chair Stand Test (times)				0.011	0.092 (0.052)		
EX+PLA	29	12.7 ± 2.9	13.9 ± 3.5			1.2 ± 2.6	
EX+PRO	27	11.6 ± 2.3	12.5 ± 2.8			1.0 ± 2.2	
CON	36	13.4 ± 3.3	13.3 ± 4.0			-0.1 ± 2.8	
Stair Climb Test (sec)				0.024	0.862 (0.003)		
EX+PLA	29	9.4 ± 3.2	9.8 ± 3.9			0.3 ± 2.3	
EX+PRO	28	10.7 ± 3.3	11.1 ± 3.8			0.4 ± 1.4	
CON	36	9.7 ± 2.2	10.3 ± 2.5			0.6 ± 1.6	
Cardiopulmonary exercise test							
W_{max} (W)[a]				<0.001	0.054 (0.070)		
EX+PLA	28	156 ± 48	153 ± 43			-4 ± 21	
EX+PRO	24	130 ± 38[b]	124 ± 41			-6 ± 18	
CON	32	164 ± 38	149 ± 34			-15 ± 15	

Table 4 Changes in physical performance tests and cardiopulmonary exercise tests over time (continued)

		Baseline	20 weeks	Time effect	Time x treatment interaction	Within-group changes over 20 weeks	
	n	Mean ± SD	Mean ± SD	*P*-value	*P*-value ($\eta^2_{partial}$)	Mean ± SD	*P*-value
W_{max} ($W \cdot kg\ BW^{-1}$)[a]				<0.001	0.015 (0.100)		
EX+PLA	28	1.84 ± 0.52	1.77 ± 0.47			-0.07 ± 0.26[c]	0.149
EX+PRO	24	1.58 ± 0.46[b]	1.49 ± 0.52			-0.09 ± 0.22	0.065
CON	31	2.01 ± 0.51	1.78 ± 0.46			-0.23 ± 0.18	<0.001
VO_{2peak} ($mL \cdot min^{-1}$)[a]				<0.001	0.008 (0.122)		
EX+PLA	28	1832 ± 459	1811 ± 408			-21 ± 239[c]	0.653
EX+PRO	23	1615 ± 365	1510 ± 363			-106 ± 199	0.018
CON	27	1886 ± 353	1672 ± 324			-215 ± 225	<0.001
VO_{2peak} ($mL \cdot min^{-1} \cdot kg\ BW^{-1}$)				<0.001	0.004 (0.139)		
EX+PLA	28	21.5 ± 4.7	21.0 ± 4.1			-0.6 ± 2.8[c]	0.284
EX+PRO	23	19.5 ± 4.3	18.0 ± 4.6			-1.5 ± 2.3	0.004
CON	26	23.1 ± 3.6	20.1 ± 3.6			-3.0 ± 2.7	<0.001
RER_{peak}				0.204	0.294 (0.032)		
EX+PLA	28	1.18 ± 0.11	1.17 ± 0.08				
EX+PRO	23	1.18 ± 0.09	1.15 ± 0.08				
CON	27	1.19 ± 0.11	1.20 ± 0.10				

Values are mean ± SD. EX+PLA, exercise training group with placebo supplementation; EX+PRO, exercise training group with protein supplementation; CON, control group; W_{max}, maximal workload; VO_{2peak}, peak oxygen uptake; BW, body weight; RER_{peak}, peak respiratory exchange ratio. [a]Significantly different between groups at baseline ($P<0.05$). [b]Significantly different at baseline from CON ($P<0.01$). [c]Changes over time are significantly different from changes over time in CON ($P<0.05$).

Discussion

The present study showed that 20 weeks of resistance exercise training was feasible, safe and well tolerated and effectively counteracted the negative impact of ADT treatment on body composition, muscle mass, leg strength, and aerobic capacity in men with advanced PCa. Protein supplementation did not further augment the benefits of resistance exercise training.

ADT is an important strategy in the treatment of advanced PCa. However, ADT is accompanied by detrimental side effects. In our control group in which patients only received usual care, total body weight and fat mass increased while leg muscle mass, leg muscle strength, and aerobic capacity decreased. These findings are in line with previous studies on undesirable changes in body composition (4-6) and performance capacity (26, 27) in men with PCa receiving ADT.

In order to combat these adverse effects, we subjected 60 PCa patients on ADT to 20 weeks of supervised progressive resistance exercise training. The exercise training program was effective to counteract the most prominent ADT-induced side effects. In agreement with previous RCT's on the effects of resistance exercise training in PCa patients on ADT (15-17), we showed improvements in appendicular lean mass. Furthermore, resistance exercise training effectively increased total lean mass and diminished fat mass gains during ADT treatment. The latter observations have not generally been reported in earlier RCT's performing resistance training only during ADT (12-15, 17). In addition to body composition measurements using DXA, we directly assessed quadriceps muscle mass by upper leg CT. We observed a significant ~3% increase in quadriceps muscle CSA in response to the resistance exercise training program. This was accompanied by a ~10-20% increase in leg press and leg extension strength. In comparison, in the control group we observed a ~2% decrease in quadriceps muscle CSA and a ~5% decline in leg strength. Our data seem in line with previous findings reporting a 16% increase in quadriceps muscle thickness (28) and 6.4% increase in thigh muscle volume (29) as assessed by ultrasound and CT, respectively, following vigorous progressive resistance training interventions. A small pilot study applying a less conventional resistance exercise training program, however, failed to detect changes in quadriceps muscle volume with magnetic resonance imaging (30).

Despite the observed increases in leg muscle mass and strength, no significant improvements were observed on the physical performance tests. This seems to be in line with other (13, 17) but certainly not all (15) studies on the impact of exercise training on physical performance in PCa patients on ADT. The absence of improvements in physical functioning is likely attributed to the limited sensitivity of the various tests used to assess physical function combined with insensitivity to detect changes in a well-performing population (ceiling effect). However, optimizing muscle mass and strength is unarguably important as strong associations between low muscle mass and strength to poorer clinical outcomes in cancer patients have been reported (31, 32).

It has been well established that protein supplementation can further augment exercise-induced gains in muscle mass and strength (10, 20, 33). Previously, we observed that protein supplementation was required to allow measurable gains in fat free mass during prolonged resistance exercise training in pre-frail older adults (10). In the present study, we observed no surplus benefits of protein supplementation on any of the outcome parameters. A plausible reason could be the already sufficient habitual protein intake in our population (1.1±0.3 g·kg body weight^{-1}·day^{-1}). This is in line with earlier studies in which we also reported no additional benefits of protein supplementation during prolonged exercise training in healthy, older populations habitually consuming ample protein (9, 34, 35). Furthermore, based on Dawson *et al.* (17) it could be speculated that the provided protein dose was insufficient to compensate for the anabolic resistance likely caused by inactivity and testosterone deprivation in this PCa patient population (21, 36). Nonetheless, it seems safe to conclude that protein supplementation is not required to achieve gains in muscle mass and strength during a period of resistance exercise training in PCa patients. However, it should be evident that nutritional interventions to allow sufficient dietary protein intake should be considered in older PCa patients with a poor nutritional status.

Besides improvements in body composition, muscle mass and strength, our intervention diminished the ADT-induced decrease in aerobic capacity. Similar findings have been reported in studies applying a combined endurance and resistance exercise training program (37-39). However, we only offered resistance exercise training, indicating that even resistance exercise training can effectively offset the negative effects of ADT on skeletal muscle oxidative capacity. This provides further support to advocate resistance exercise training as an adjuvant treatment strategy during and/or after ADT. In addition, the positive effects of resistance exercise training on oxidative capacity and body composition provide important health benefits, as both a decreased oxidative capacity as a higher fat percentage are associated with poorer oncologic prognosis (40-42) and a higher risk of comorbidities like cardiovascular disease (43-45).

In our study all exercise sessions were supervised and group-based. This enabled us to provide patients with optimal guidance and to tailor the program to variations in their daily condition (e.g. during chemotherapy), which is important for the prevention of injuries and optimizing the training load. Our exercise intervention was feasible, safe and well-tolerated with an overall adherence score of 82±21%. In agreement with previous studies (46), we experienced that the group-based setting of the exercise training enabled social interactions, provided unconstrained peer support and increased pleasure. This all could have contributed to the excellent adherence and compliance to our exercise training program. However, our study also has limitations. The shorter ADT treatment duration in the control group could have potentially affected the outcome. Furthermore, due to the COVID-19 pandemic, the total group of included patients was 96 instead of the initially aimed 208 patients. As a consequence, we were underpowered to detect small but potentially clinically relevant differences between the protein supplemented and placebo group.

Despite these limitations, our study clearly shows the many benefits of resistance exercise training that completely offset the negative side effects of ADT on muscle mass and function. Combined with a high compliance and adherence to the exercise program, we strongly advise the implementation of personalized and supervised resistance exercise training in PCa patients treated with ADT. Exercise should become part of the standard urological care for these patients. Therefore, specialists should actually prescribe exercise to all patients (starting) with ADT, including patients with bone metastases. Although it was no specific goal, our study adds evidence to earlier studies (47-49) that a well-designed resistance exercise program can be applied safely in patients with bone metastases, providing that there are no medical objections (e.g. high risk for pathological fractures). We advise an exercise program supervised by an exercise physiologist with PCa specific expertise, delivered in small PCa specific groups. Resistance exercise training should be a major component of this program, while the addition of an aerobic component might possibly have added value.

In conclusion, resistance exercise training is safe, feasible and well tolerated in patients with advanced PCa on ADT. Resistance exercise training overcomes the negative side effects of ADT on body composition, muscle mass, muscle strength and aerobic capacity in men with advanced PCa. Protein supplementation is not required to further augment gains in muscle mass and strength following resistance exercise training in PCa patients who habitually consume ample protein (> 1.0 g·kg body weight^{-1}·day^{-1}).

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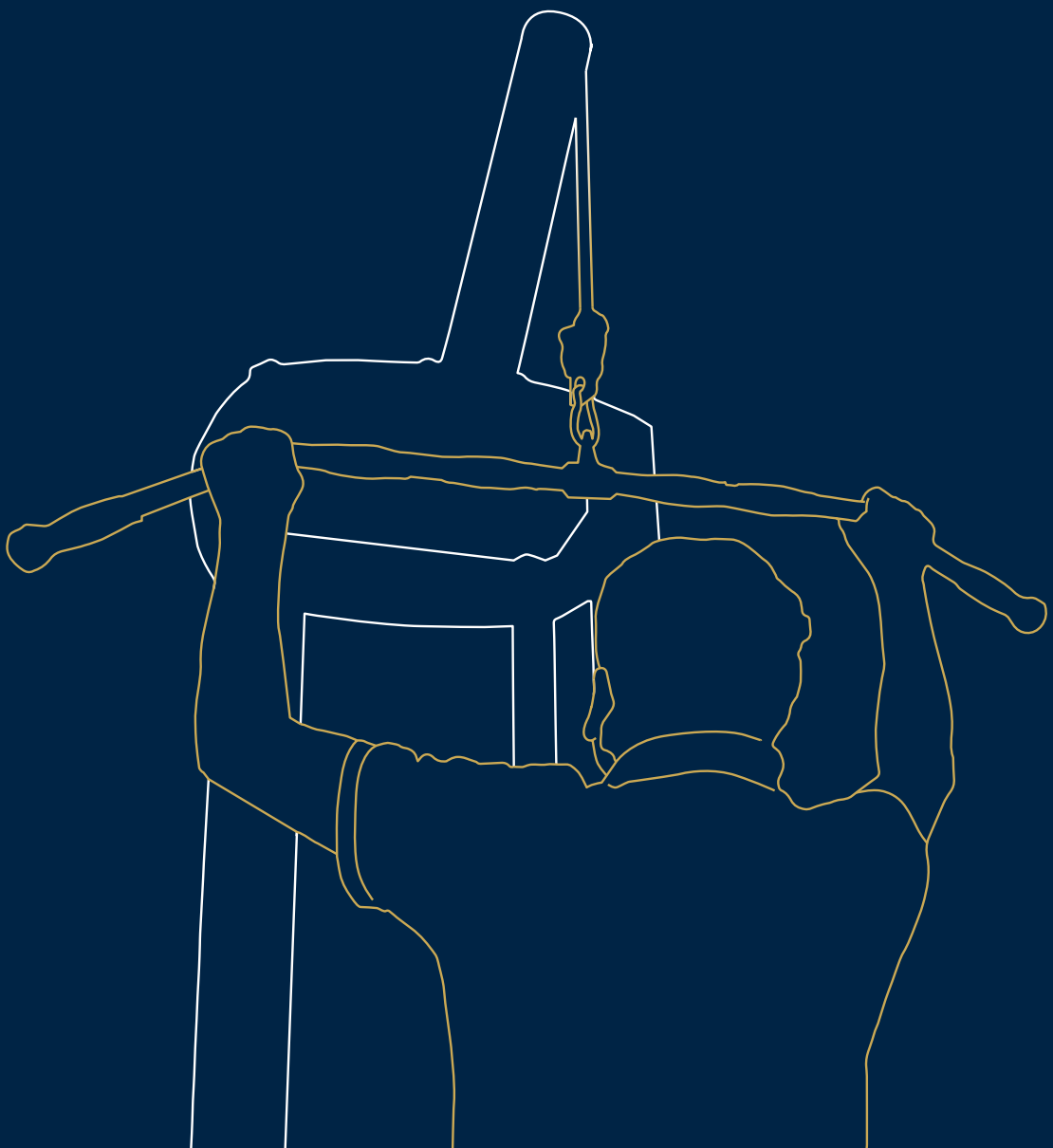

CHAPTER 5

Resistance exercise counteracts the impact of androgen deprivation therapy on muscle characteristics in cancer patients

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Abstract

Context: Androgen deprivation therapy (ADT) forms the cornerstone in prostate cancer (PCa) treatment. ADT however also lowers skeletal muscle mass.

Objective: To identify the impact of ADT with and without resistance exercise training on muscle fiber characteristics in PCa patients.

Methods: Twenty-one PCa patients (72±6 y) starting ADT were included. Tissue samples from the *vastus lateralis* muscle were assessed at baseline and after 20 weeks of usual care (*n*=11) or resistance exercise training (*n*=10). Type I and II muscle fiber distribution, fiber size, and myonuclear and capillary contents were determined by immunohistochemistry.

Results: Significant decreases in type I (from 7401±1183 to 6489±1293 μm^2, *P*<0.05) and type II (from 6225±1503 to 5014±714 μm^2, *P*<0.05) muscle fiber size were observed in the usual care group. In addition, type I and type II individual capillary-to-fiber ratio (C/F*i*) declined (-12±12 and -20±21%, respectively, *P*<0.05). In contrast, significant increases in type I (from 6700±1464 to 7772±1319 μm^2, *P*<0.05) and type II (from 5248±892 to 6302±1385 μm^2, *P*<0.05) muscle fiber size were observed in the training group, accompanied by an increase in type I and type II muscle fiber myonuclear contents (+24±33 and +21±23%, respectively, *P*<0.05) and type I C/F*i* (+18±14%, *P*<0.05).

Conclusions: The onset of ADT is followed by a decline in both type I and type II muscle fiber size and capillarization in PCa patients. Resistance exercise training offsets the negative impact of androgen deprivation therapy and increases type I and II muscle fiber size and type I muscle fiber capillarization in these patients.

Introduction

Prostate cancer (PCa) is the second most common type of cancer in men, with a yearly estimated 1.4 million new cases and 375,000 deaths worldwide (1). Androgen deprivation therapy (ADT) forms the cornerstone in (locally) advanced PCa treatment. ADT suppresses serum testosterone to castration levels, resulting in an increased life expectancy (2). However, low testosterone levels also induce the loss of skeletal muscle mass in PCa patients (3). Whereas the impact of ADT on whole-body muscle mass has been well established, its impact on muscle fiber characteristics remains largely unexplored.

The age-related loss of skeletal muscle mass and strength, termed sarcopenia, has been at least partly, attributed to the decline in circulating testosterone levels in older men (4). As such, it is not surprising that ADT prescription accelerates muscle loss in older adults (3, 5). This results in a further increase in the risk for falls (6), a decline in mobility (7), and a lower quality of life (8) in older PCa patients. On the muscle fiber level, age related muscle loss is characterized by the specific decline in type II muscle fiber size (9-11). Thus far, only one study has assessed the impact of ADT on muscle fiber size in PCa patients. Nilsen *et al.* (2016) showed no significant changes in type I or type II muscle fiber size following 16 weeks of ADT in older PCa patients. In this study, the initial muscle biopsy sample was obtained approximately 9 months after the onset of ADT (12). As the largest decline in lean body mass has been reported to occur during the first months following ADT initiation (3), this may explain the lack of any measurable changes in muscle fiber size and fiber composition in the study by Nilsen and colleagues. Hence, more data are required to elucidate the impact of starting ADT on muscle fiber characteristics in PCa patients.

For optimal muscle tissue function and health, adequate perfusion is of critical importance as it is responsible for the delivery of oxygen, growth factors and nutrients, and removal of waste products (13). Oxygen and metabolic substrates are delivered to the nuclei, located at the periphery of muscle fibers. These myonuclei are key in the transcription and translation machinery prerequisite for muscle fiber maintenance, as well as repair and growth (14). Age-related type II muscle fiber atrophy is accompanied by a fiber type specific decline in muscle fiber myonuclei (14, 15) and capillarization (16-18). Also, low muscle fiber capillarization has been associated with impairments in cardiorespiratory fitness (19), physical function (20), and aggravates various indices of sarcopenia (19, 21). In both animal as well as human studies, testosterone levels have been implicated as a potential regulator of angiogenesis and myonuclear accretion (22, 23). However, no studies to date have assessed the potential impact of starting ADT on these various muscle fiber characteristics in PCa patients. Insight in the negative effect of ADT on specific muscle fiber characteristics could aid in designing specific intervention strategies minimizing the adverse effects of ADT on skeletal muscle mass and function. We hypothesize that the onset of ADT leads to a decline in muscle fiber size, myonuclear content, and capillarization in PCa patients.

Resistance exercise training is an effective intervention strategy to counteract the ADT-induced loss of muscle mass in older PCa patients (24, 25). In accordance, Nilsen *et al.* reported significant type II muscle fiber hypertrophy following 16 weeks of resistance exercise training in PCa patients who had already been exposed to ADT over an extensive period of time. Whether resistance exercise training can offset the changes in muscle fiber characteristics following the onset of ADT remains to be determined. We hypothesize that progressive resistance exercise training counteracts the impact of ADT on muscle fiber characteristics and increases fiber size, myonuclear content, and capillarization in PCa patients starting ADT.

In the present study we assessed the changes in muscle fiber characteristics following 20 weeks of ADT with and without resistance exercise training in PCa patients.

Methods

Patient recruitment

This study was part of a greater project investigating the impact of prolonged resistance exercise training and protein supplementation on counteracting the adverse effects of ADT on body composition, strength, aerobic capacity, and quality of life in PCa patients (26). PCa patients starting with gonadotropin-releasing hormone agonist or antagonist treatment were recruited to participate in either a 20-week resistance exercise training program, or they were recruited for the control group receiving only usual care. Exclusion criteria were any contraindications for participating in an exercise training protocol. Additional exclusion criteria were: an estimated life expectancy <1 year, cognitive disorders or severe emotional instability, or the inability to speak, understand, and/or read the Dutch language. All patients were asked if they were willing to undergo an optional muscle biopsy as an additional measurement, as this was not obligatory to participate in the overall project. A total of 21 PCa patients were selected for the current study, based upon the availability of both a baseline as well as a 20-week muscle biopsy sample. Patients were informed of the nature and possible risks of the experimental procedures before their written informed consent was obtained. The study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre+, the Netherlands (METC 16-3-040) and complied with the guidelines set out in the most recent version of the Declaration of Helsinki. This study was registered at the Dutch Trial Register (International Clinical Trial Registry Platform: NTR6432) and was independently monitored by the Clinical Trial Centre Maastricht.

Study design

Patients were recruited at Jeroen Bosch Hospital (JBZ; 's-Hertogenbosch, the Netherlands), Maastricht University Medical Centre+ (MUMC+; Maastricht, the Netherlands), and Zuyderland Medical Centre (Zuyderland MC; Sittard/Heerlen, the Netherlands). Potential participants were identified and referred to the investigators by their treating urologist or urology nurse. Medical history (e.g. Gleason score: score for the aggressiveness of the tumor) was obtained from the

electronic patients file. Baseline measurements were performed as soon as was practically feasible following the initiation of ADT. These consisted of anthropometric measurements (height and body weight), whole-body dual-energy x-ray absorptiometry (DXA) scanning, computed tomography (CT)-scanning of the dominant leg, and muscle biopsy sampling. Patients recruited for the training intervention (EX) were enrolled in a 20-week resistance exercise training protocol. Patients recruited for the control group (CON) received only usual care. In the week following the exercise intervention or the usual care period, baseline measurements were repeated (>3 d after the final training session). To avoid variation in methods and procedures, all muscle biopsies were obtained in the MUMC+ by the same medical doctor. Furthermore, all measurements were performed in a rested and overnight fasted state.

Exercise intervention program

Patients in the EX group performed a 20-week, twice weekly, progressive whole-body resistance exercise training program. Following a 5 min warm-up on a cycle ergometer patients performed two warm-up sets and four working sets in both the leg press and leg extension machines (Technogym, Rotterdam, The Netherlands). Upper body exercises were paired (chest press with lateral pulldown and shoulder press with horizontal row) and were performed in an alternating manner between exercise sessions. Four sets, including one warm-up set, were performed for each upper-body exercise. Each exercise session was ended with a 5 min cool-down on the cycle ergometer. Resting periods of 1.5 and 3 min were allowed between sets and exercises, respectively. During the first 3 weeks of exercise training, workload was increased from 60% one-repetition maximum (1RM) to 70% 1RM (10 repetitions). Every 4th week, workload was reduced to 60% 1RM (10 repetitions) to allow for proper recovery and minimize the risk of injury. Workload intensity was adjusted based on 1RM measurements performed before, and after 4, 8, 12 and 16 weeks of the exercise training program. 1RM was determined as described previously (15).

Habitual dietary intake and physical activity

Patients were asked to report their habitual dietary intake on two weekdays and one weekend day in the week prior to the experimental test days. Average daily dietary intake was calculated using web-based software Eetmeter (Voedingscentrum, Den Haag, The Netherlands). In this same period, patients were instructed to wear a triaxial accelerometer (wGT3X-BT; ActiGraph, Pensacola, FL, USA) on their waist during wakefulness for 7 days. Data were analyzed with ActiLife (version 6.13.4; ActiGraph, Pensacola, FL, USA) and included in the analyses if patients wore the accelerometer for a minimum of 5 days and at least 10 hours per day. The assessment period for the 20-week measurements was performed during the final week (week 20) of the intervention.

Body composition

Body weight was measured, wearing underwear and directly after voiding, using a scale to the nearest 0.5 kg. Height was measured by a fixed stadiometer to the nearest 0.5 cm. Whole-body lean mass and fat percentage were assessed by DXA (Discovery A; Hologic, Marlborough,

MA and LUNAR iDXA; GE Healthcare, Chicago, IL, USA). Anatomic cross-sectional area (CSA) of the quadriceps muscle was assessed by CT scanning (SOMATOM Definition Flash; Siemens, München, Germany) as described previously (27). A single-slice image was made 15 cm proximal to the top of the patella of both legs. Quadriceps muscle CSA of the dominant leg was calculated by manual tracing using ImageJ software (version 1.52p, National Institute of Health, Bethesda, MD, USA).

Muscle biopsy sampling

Percutaneous needle biopsies were taken from the *vastus lateralis* muscle approximately 15 cm above the patella of the dominant leg (28). Muscle samples were prepared for analyses as previously described (29, 30)

Immunohistochemistry

From all biopsies, 5-µm-thick cryosections were cut at -20°C using a cryostat. Samples were thaw-mounted onto uncoated pre-cleaned glass slides. Care was taken to properly align the samples for cross-sectional orientation of the muscle fibers. Samples were stained for muscle fiber typing, capillaries, and myonuclei as described previously (31). In short, after 5 min fixation in acetone, the cryo-sections were incubated for 1 h with CD31 (RRID:AB_2114471; dilution 1/50; M0823; Dako, Glostrup, Denmark) in a phosphate-buffered saline (PBS) with 0.05% Tween. Slides were then washed three times in the Tween-PBS solution. Next, slides were incubated with horse anti-mouse (HAM) Biotine (RRID:AB_2313581; 1:500, Vector Laboratories, Burlingame, CA, USA) in Tween-PBS. Following three washing steps, the sections were incubated with Avidine Texas Red (RRID:AB_2336751; A2006, dilution 1/400; Vector Laboratories), and antibodies against Myosin Heavy Chain-I (RRID:AB_528384; MHC-I, A4.840, dilution 1/ 25; DSHB), and laminin (RRID:AB_477163; polyclonal rabbit anti-laminin, dilution 1/50; Sigma) in Tween-PBS. Following another triple washing step in PBS, samples were finally incubated with appropriate secondary antibodies: goat anti-mouse (GAM) IgM AlexaFluor488 (RRID:AB_141357), goat anti-rabbit (GAR) IgG AlexaFluor647 (RRID:AB_2535807; Molecular Probes), and 4',6-diamidino-2-fenylindole (RRID:AB_2629482; DAPI, Molecular Probes). After a final triple washing with PBS, slides were mounted with Mowiol (Calbiochem). This staining procedure resulted in images with laminin in white, MHC-I in green, DAPI in blue, and CD31 in red (**Figure 1**).

Slides were viewed and automatically captured using 10x objective on a modified Olympus BX51 fluorescence microscope with a customized disk-spinning unit (DSU, Olympus, San Jose, CA, USA), computer-controlled excitation and emission filter wheels (Olympus), 3-axis high-accuracy computer-controlled stepping motor specimen stage (Grid Encoded Stage, Ludl Electronic Products, Hawthorne, NY, USA), ultra-high sensitivity monochrome electron multiplier CCD camera (C9100-02, Hamamatsu Photonics, Hamamatsu City, Japan) and controlling software (Stereo Investigator; MBF Bioscience, Williston, VT, USA). Before analyses, slides were blinded for both group and time point. All areas selected for analysis were free of 'freeze fracture' artefact, and care was taken such that longitudinal fibers were not used in the analysis. Muscle fibers on the periphery of muscle cross sections were not used in the analysis. Quantitative analyses

were performed using ImageJ software package (version 1.52p, National Institute of Health, MD, USA (32)). On average, 166±106 muscle fibers were analyzed per muscle biopsy sample collected to determine muscle fiber type distribution, CSA, myonuclear content and domain size. The quantification of muscle fiber capillaries was performed on at least 30 type I and 30 type II muscle fibers/patient/time point, based on previous work (33). Quantification consisted of capillary contacts (CC), the capillary-to-fiber ratio (C/F*i*), capillary-to-fiber perimeter exchange (CFPE) index, and capillary density (CD).

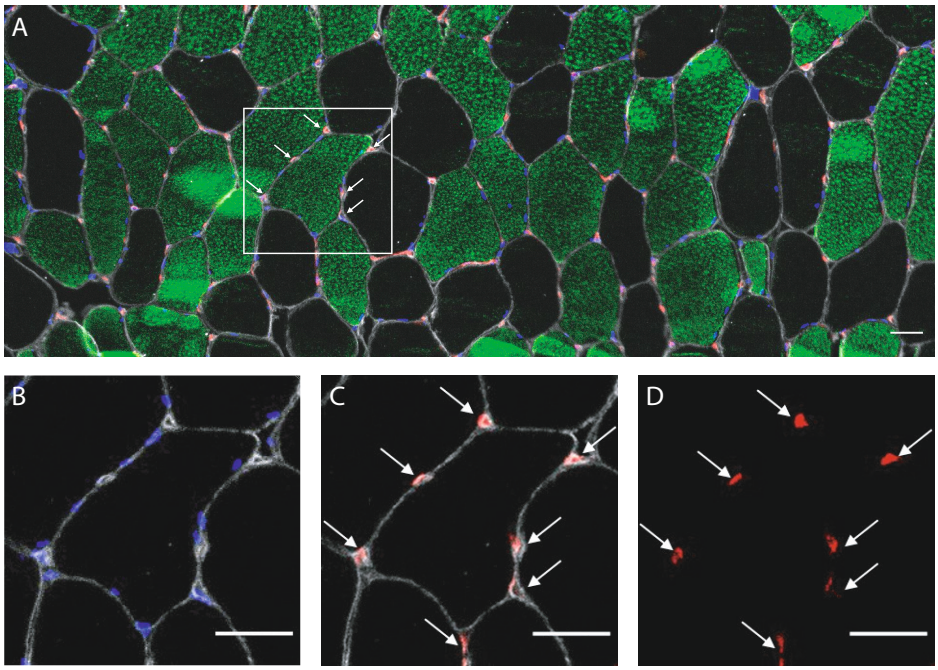

Figure 1 Representative images of the analyses for muscle fiber characteristics. (A) Laminin (white; cell borders), DAPI (blue; myonuclei), MHC1 (green; type I muscle fibers), CD31 (red; capillaries). (B) Laminin (white), DAPI (blue). (C) Laminin (white), CD31 (red). (D) CD31 (red) only. White line represents 50µm. Arrows point at the capillaries.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Baseline characteristics between groups were compared by using a Student's unpaired *t*-test. Exercise training induced changes were analysed using repeated measures ANOVA with time (baseline vs. 20 weeks) and fiber type (type I vs. type II) as within-subject factors and group (CON vs. EX) as the between-subject factor. In the event of significant *time x group* interactions, groups were analysed separately. In the event of significant *time x fiber type* interactions, type I and type II muscle fibers were analysed separately. Bonferroni correction was applied to correct for multiple testing. Significance was set at $P<0.05$. All calculations were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristics

In the overall project, patients in the EX group were randomly provided either a protein or placebo supplement throughout the 20-week exercise training program (26). As no differences were observed in muscle strength and body composition over time between the placebo and protein-supplemented group and both groups were equally represented in the current study (protein, *n*=5; placebo, *n*=5), all subsequent muscle biopsy analyses were performed with all patients in one EX group (*n*=10). Patients included in the CON group (*n*=11) did not receive any nutritional co-intervention. For one patient in the EX group, the muscle biopsy sample quality was insufficient to perform quantification of capillaries. All patients received treatment with a GnRH agonist, and a total of six patients (EX, *n*=2; CON, *n*=4) received chemotherapy (6 cycles of docetaxel) during the study period. At baseline, no differences in age, body weight, height, BMI, fat percentage, whole-body lean mass, ADT duration, and Gleason score were observed between groups (**Table 1**).

Table 1. Patients' characteristics

	CON (*n*=11)	**EX (*n*=10)**
Age (y)	72 ± 3	73 ± 8
Height (m)	1.77 ± 0.08	1.78 ± 0.05
Weight (kg)	80.4 ± 10.4	82.6 ± 15.1
BMI ($kg \cdot m^{-2}$)	25.7 ± 2.5	26.1 ± 3.8
Fat percentage (%)	28.1 ± 7.2	28.3 ± 5.1
Step count ($steps \cdot day^{-1}$)	7027 ± 2373	6213 ± 3317
ADT duration (days)	39 ± 21	33 ± 22
Gleason score	8.6 ± 0.5	8.3 ± 1.2
Bone metastases, *n* (%)	6 (55)	5 (50)
Previous prostatectomy, *n* (%)	4 (36)	1 (10)
Previous radiation, *n* (%)	1 (9)	1 (10)
Previous chemotherapy, *n* (%)	0 (0)	0 (0)

Values are mean ± SD. CON, usual care control group; EX, exercise training group; BMI, Body mass index; ADT, androgen deprivation therapy.

Habitual dietary intake and physical activity level

No significant differences in energy or any macronutrient (protein, carbohydrate, and fat) intake was observed between the CON and EX group at baseline (**supplemental Table S1**) (34). Energy intake tended to decline (main of effect of time, P=0.050) following 20 weeks of ADT, with no difference between the two groups. In contrast, protein, carbohydrate and fat intake remained unchanged over time (**supplemental Table S1**) (34).

At baseline no significant difference in daily step count was observed between the CON and EX group (**supplemental Table S1**) (34). Daily step count was significantly lower following 20 weeks of ADT compared to baseline (Main effect of time, P<0.05), with no difference between the two groups.

Total lean body mass and quadriceps muscle cross-sectional area

No significant difference in total lean mass was observed between the CON and EX group at baseline (**Figure 2**). Total lean mass remained unchanged over time in both groups. A significant *time x group* interaction effect (P<0.001) was observed for quadriceps muscle CSA. Subsequent within group analyses showed a significant decline in quadriceps muscle CSA following 20 weeks of ADT in the CON group (**Figure 3**, P<0.05). In contrast, quadriceps muscle CSA increased significantly in response to 20 weeks of resistance exercise training in the EX group (**Figure 3**, P<0.05).

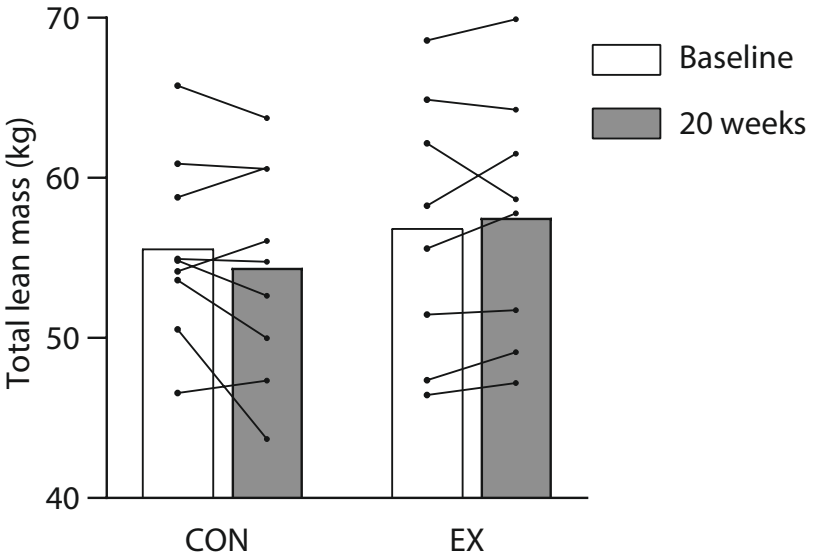

Figure 2 Total lean mass at baseline and following 20 weeks of usual care (CON, *n*=9) or resistance exercise training (EX, *n*=8) in prostate cancer patients on androgen deprivation therapy. Bars represent means. Dots represent individual data points, with change over time indicated with the connecting lines.

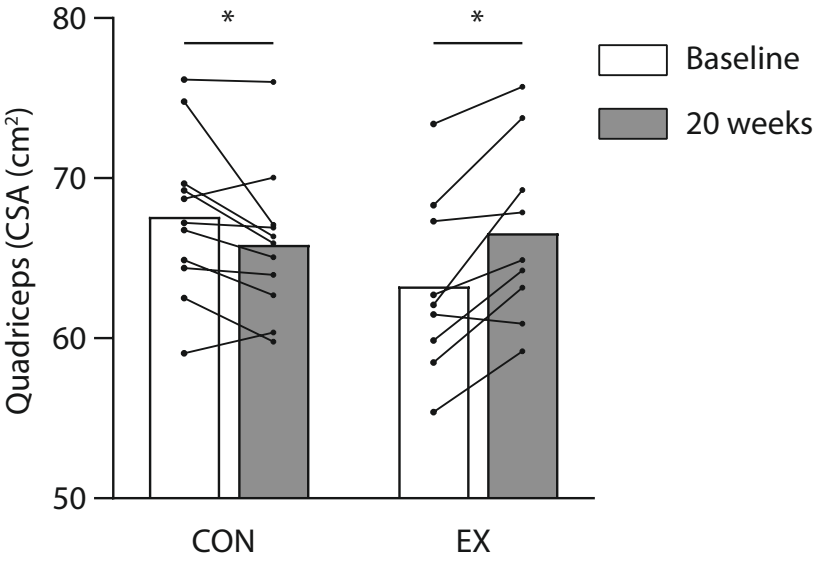

Figure 3 Quadriceps muscle cross-sectional area (CSA) at baseline and following 20 weeks of usual care (CON, *n*=11) or resistance exercise training (EX, *n*=9) in prostate cancer patients on androgen deprivation therapy. Bars represent means. Dots represent individual data points, with change over time indicated with the connecting lines. * Significantly different compared with baseline ($P<0.05$).

Muscle fiber size and distribution

No significant differences in type I and type II muscle fiber size were observed between the CON and EX group at baseline (**Figure 4**). A significant *time x group* interaction ($P<0.01$) was observed for muscle fiber size, as such, the CON and EX groups were subsequently analysed separately. In the CON group, significant decreases in type I (from 7401±1183 to 6489±1293 μm^2) and type II (from 6225±1503 to 5014±714 μm^2) muscle fiber size were observed (main effect of time, $P<0.05$, **Figure 4**). In the EX group, significant increases in type I (from 6700±1464 to 7772±1319 μm^2) and type II (from 5248±892 to 6302±1385 μm^2) muscle fiber size were observed in response to the 20-week exercise training program (main effect of time, $P<0.05$, **Figure 4**). The proportion of type I muscle fibers, expressed as % of total fibers as well as expressed as % CSA occupied, was significantly lower at baseline in the EX compared with the CON group (both main effect of group, $P<0.05$, **Table 2**). No changes in muscle fiber type distribution were observed over time in the CON and EX group (**Table 2**).

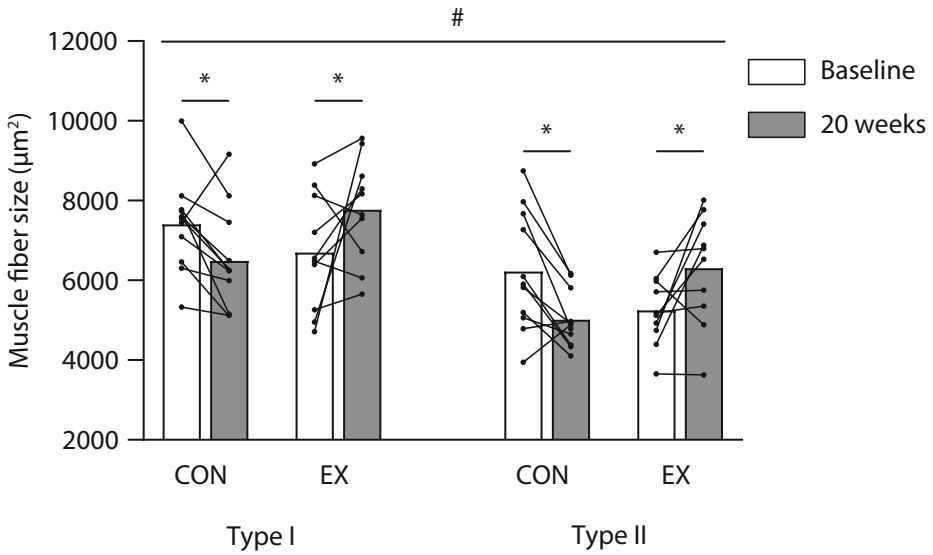

Figure 4 Type I and type II muscle fiber size at baseline and following 20 weeks of usual care (CON, $n=11$) or resistance exercise training (EX, $n=10$) in prostate cancer patients on androgen deprivation therapy. Bars represent means. Dots represent individual data points, with change over time indicated with the connecting lines. * Significantly different compared with baseline ($P<0.05$). # Significant main effect of fiber type ($P<0.001$).

Table 2 Type I and type II muscle fiber characteristics at baseline and following either 20 weeks of usual care (CON) or resistance exercise training (EX) in prostate cancer patients on androgen deprivation therapy.

	CON (*n*=11)		EX (*n*=10)	
	Baseline	**20 weeks**	**Baseline**	**20 weeks**
Fiber type distribution (fiber %)				
Type I	52 ± 11	50 ± 13	39 ± 15**	41 ± 12
Type II	48 ± 11	50 ± 13	61 ± 15	59 ± 12
Fiber type distribution (CSA %)				
Type I	56 ± 12	57 ± 11	44 ± 15**	46 ± 9
Type II	44 ± 12	43 ± 11	56 ± 15	54 ± 9
Myonuclei (n·fiber^{-1})				
Type I	3.50 ± 0.84	3.11 ± 0.63	3.12 ± 1.16	3.66 ± 0.92*
Type II	3.25 ± 1.01	3.02 ± 0.61	2.66 ± 0.71	3.12 ± 0.69*
Myonuclear domain (μm^2)				
Type I	2202 ± 549	2226 ± 749	2319 ± 715	2191 ± 376
Type II	2006 ± 539	1759 ± 549	2117 ± 728	2063 ± 484
Capillary contacts				
Type I	4.15 ± 0.67	3.69 ± 0.43*	3.62 ± 0.80	4.20 ± 0.65
Type II	3.73 ± 0.80	3.09 ± 0.61*	3.52 ± 0.98	3.85 ± 0.78
Mixed	2.48 ± 0.39	2.08 ± 0.32*	2.20 ± 0.45	2.45 ± 0.41
CFPE-index (capillaries·1000μm^{-1})				
Type I	4.99 ± 1.11	4.53 ± 0.85	4.45 ± 0.80	4.97 ± 1.12
Type II	3.88 ± 0.63	3.45 ± 0.86	3.91 ± 0.67	4.15 ± 1.11
Capillary density (capillaries·mm^{-2})				
Type I	271 ± 79	256 ± 61	266 ± 63	274 ± 89
Type II	227 ± 46	233 ± 71	260 ± 60	268 ± 98

Values are mean ± SD. CSA, cross-sectional area; CFPE, capillary-to-fiber perimeter exchange. *Significantly different compared with baseline (P<0.05). **Significant baseline difference between groups.

Myonuclear content and domain size

No significant differences in type I and type II myonuclear contents were observed between the CON and EX group at baseline (**Table 2**). A significant *time x group* interaction ($P<0.05$) was observed for myonuclear content, as such, the CON and EX groups were subsequently analysed separately. In the CON group, no significant changes in type I and type II myonuclear content were observed in response to 20 weeks of ADT (**Table 2**). In the EX group, significant increases in type I and type II myonuclear content were observed in response to 20 weeks of resistance exercise training (main effect of time, $P<0.05$; **Table 2**). At baseline, no significant differences in type I and type II myonuclear domain size were observed between the CON and EX groups (**Table 2**). Type I and type II myonuclear domain size remained unchanged over time in both the CON and EX groups (**Table 2**).

Muscle fiber capillarization

At baseline, no significant differences were observed in type I and type II muscle fiber capillarization, expressed as CC, C/F*i*, CFPE-index or CD, between the CON and EX group (**Table 2**). A significant *time x group* interaction ($P<0.05$) was observed for CC, consequently, the CON and EX groups were analysed separately. Significant decreases over time were observed in type I, type II, and mixed CC in the CON group (main effect of time, $P<0.05$, **Table 2**). Type I, type II, and mixed CC tended (main effect of time, $P=0.055$) to increase in response to 20 weeks of resistance exercise training in the EX group (**Table 2**). Based on a *time x fiber type* interaction ($P<0.05$) for C/F*i*, type I and type II muscle fibers were analysed separately. Subsequently, a *time x group* interaction was observed for type I and type II C/F*i* (both $P<0.05$). In the CON group, significant decreases in type I (from 1.81±0.30 to 1.58±0.25) and type II (from 1.37±0.30 to 1.07±0.25) C/F*i* were observed (main effect of time, $P<0.05$). Whereas no changes were observed in type II C/F*i*, type I muscle fiber C/F*i* increased significantly over time (from 1.59±0.31 to 1.85±0.31, $P<0.05$) in response to 20 weeks resistance exercise training in the EX group (**Figure 5**). For CFPE-index a significant *time x group* interaction ($P<0.05$) was observed. However, post-hoc analyses revealed no significant changes over time in both the CON and EX group separately (**Table 2**). Type I and type II CD remained unchanged over time in both the CON and EX group (**Table 2**).

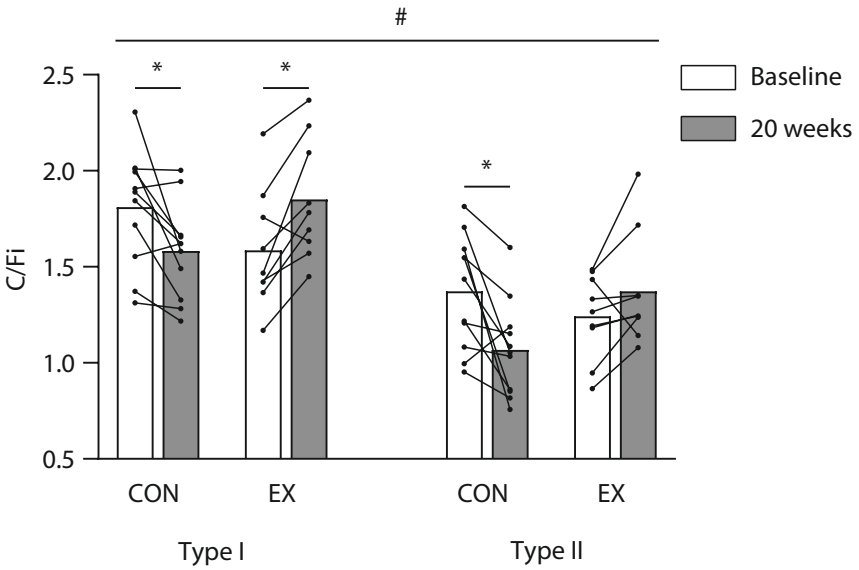

Figure 5 Type I and type II muscle fiber capillary to fiber ratio (C/Fi) at baseline and following 20 weeks of usual care (CON, *n*=11) or resistance exercise training (EX, *n*=9) in prostate cancer patients on androgen deprivation therapy. Bars represent means. Dots represent individual data points, with change over time indicated with the connecting lines. * Significantly different compared with baseline ($P<0.05$). # Significant main effect of fiber type ($P<0.001$).

Discussion

The present study is the first to show a significant decrease in type I and II muscle fiber size and capillarization 20 weeks after the onset of ADT in PCa patients. In response to progressive resistance exercise training, these ADT-induced adverse effects were fully prevented, with muscle fiber size and capillarization being increased throughout the 20 weeks of resistance exercise training.

ADT forms the cornerstone in PCa treatment, but has a negative impact on muscle mass (3). In accordance, we show a decline in quadriceps muscle CSA following 20 weeks of ADT in PCa patients. The ADT-induced loss of leg muscle mass was accompanied by a decline in both type I and type II muscle fiber size. These results differ from previous reports by Nilsen *et al.* who did not find significant changes in muscle fiber size following 16 weeks of ADT in older PCa patients (12). The apparent discrepancy may be explained by differences in patient inclusion characteristics with regards to the onset of ADT. In the present study, the baseline muscle biopsy was taken within the initial weeks (5.0±3.2 weeks) following the onset of ADT. In contrast, Nilsen and colleagues recruited patients approximately 9 months following onset of ADT. As the loss of lean tissue mass occurs mainly in the first months upon treatment initiation (3), it is possible that Nilsen *et al.* may have missed much of the atrophy that had occurred prior to the patients enrollment in the study. In contrast, we clearly show fiber atrophy in PCa patients during the weeks following onset of ADT. Interestingly, this decline in muscle fiber size was not accompanied by a decline in myonuclear number. As myonuclei are key in the transcription and translation of proteins, they are of critical importance in muscle tissue homeostasis, repair, and growth (14). The fact that myonuclear content remained unchanged during the initial months of ADT in these patients, suggests that this will most likely not form a limiting factor in the response readiness of muscle tissue to quickly upregulate synthesis rates following resistance exercise. However, whether the myonuclear efficiency is hampered as a result of ADT, remains to be further investigated.

In order to maintain skeletal muscle function and health, adequate amounts of oxygen, nutrients, and growth factors delivered by the muscle fiber capillary network are of critical importance (13). Low muscle fiber capillarization has been reported to be a limiting factor in muscle tissue repair, maintenance, and growth following exercise training, which may be of even greater importance in older adults (35, 36). The current study is the first to examine capillarization in PCa patients, and shows a substantial decline in type I (-12±12%) and type II (-20±21%) muscle fiber capillarization after 20 weeks of ADT. To our knowledge, merely two previous studies also evaluated changes in muscle fiber capillarization in cancer patients. Christensen and colleagues (2014) found no significant changes in muscle fiber capillary density in germ cell cancer patients undergoing 9 weeks of chemotherapy (37). In contrast, in a recent study by Mijwel *et al.* (2018) a significant decline in muscle fiber capillary density (~17%) was observed in breast cancer patients following 16 weeks of treatment (38). However, treatment in this study population consisted of adjuvant chemotherapy for all patients. Animal

studies clearly show that chemotherapeutic agents have a major negative influence on various muscle fiber characteristics (39), although data on the impact on capillarization is lacking. In our CON group four PCa patients received additional chemotherapy (docetaxel, once every three weeks for six cycles) during the study period. Interestingly, additional post-hoc analyses showed a significantly greater reduction in type I and type II CFPE-index and CD in patients who received both adjuvant chemotherapy combined with ADT, compared with patients who only received ADT (**supplemental Table S2**) (34). This suggests that chemotherapy may exacerbate the negative impact of ADT on muscle fiber capillarization in older PCa patients. However, additional research including larger group sizes is warranted to more firmly establish these results. Apart from the possible direct adverse effects, adjuvant chemotherapy as well as ADT itself, may indirectly effect skeletal muscle tissue by changes in lifestyle factors like habitual dietary intake (for example due to loss in appetite) and physical activity level (for example due to increased fatigue). In the present study, habitual dietary intake was assessed at baseline and in week 20 of the ADT intervention period. Whereas energy intake tended to decline by a small degree, we observed no significant changes in protein, carbohydrate or fat intake during the intervention period in both groups. In contrast, we do report a significant decline in the number of daily steps in response to the 20-week intervention, with no difference between the two groups. As such, we cannot exclude the possibility that the atrophy observed in the CON group may, in part, be explained by a decline in habitual physical activity level. However, larger cohort studies will be required to elucidate the impact of changes in lifestyle factors on skeletal muscle mass and function during ADT in PCa patients.

Prolonged resistance exercise training is an effective intervention strategy to counteract ADT-induced loss of muscle mass in older PCa patients (12, 24, 25). In line, we show a significant increase in quadriceps muscle CSA following 20 weeks of resistance exercise training in PCa patients. On the muscle fiber level, resistance exercise training resulted in significant type I and type II muscle fiber hypertrophy (**Figure 4**), which was accompanied by myonuclear accretion in both muscle fiber types. These results are in line with Nilsen *et al*. who also showed significant muscle fiber hypertrophy following 16 weeks of resistance exercise training in PCa patients who had been on ADT for an extended period. Together, these studies clearly show that even though serum testosterone levels are reduced to castration level, skeletal muscle growth in response to prolonged resistance exercise training is viable in PCa patients. For muscle fiber capillarization, previous studies have reported mixed results on the impact of prolonged resistance exercise training in (healthy) older adults. Whereas some do (40), others do not (35) show an increase in muscle fiber capillarization following whole-body resistance exercise training in older adults. It has been suggested that, apart from duration of the training period, exercise intensity and/or volume of the resistance exercise training program may explain some of these discrepant results. Therefore, it is quite astonishing that in the present study we observed a substantial (~20%) increase in muscle fiber capillarization following a resistance exercise training program performed merely twice weekly in this compromised patient population (**Figure 5**). This shows that next to the considerable hypertrophic response, testosterone does not seem to be essential to obtain a significant angiogenic response.

The loss of skeletal muscle mass is one of the hallmarks of initiating ADT, and clearly accelerates the age-related muscle loss in older PCa patients. Age-related muscle loss is mainly characterized by the loss of type II muscle fiber size, myonuclear content and capillarization (9, 11, 16-18). The current study is the first to show that ADT initiation in PCa patients results in a decline in both type I and type II muscle fiber size, as well as a decline in capillarization. Although the gradual age-related lowering in testosterone levels may contribute to the age related muscle loss (4), the severe decline in testosterone levels following ADT in PCa patients clearly has a larger and more acute impact on muscle tissue health. This is evident from the sheer magnitude in muscle fiber atrophy (type I: -12±14%, type II: -17±17%) and loss in muscle fiber capillarization (type I: -12±12%, type II: -20±21%) in both muscle fiber types observed over such a short period of time in our patients. More importantly, the present study demonstrates that merely bi-weekly resistance exercise training does not only prevent the decline in muscle mass, it actually increases muscle fiber size and capillarization in PCa patients who recently started ADT. In addition, these improvements even negate the potential negative impact of the reduced physical activity level (expressed as steps per day) observed in the CON as well as the EX group during ADT. This underlines the clinical relevance of including resistance exercise training in the weekly routine and overall treatment strategy of PCa patients to effectively preserve and even improve muscle health. With a training session adherence of ~80% in our complete study population and relatively low side effect-induced training disturbances, resistance exercise training seems feasible. However, because of the long duration of ADT treatment (sometimes life-long), maintaining adherence could be a challenge. Therefore, it will be important to develop an exercise routine that can be implemented effectively in the daily routine of PCa patients. Implementation of the exercise regimen within a social context with fellow patients might maximize adherence and compliance (41), and further contribute to the interventional strategy to maintain function and quality of life in this growing patient population.

It is important to note that the present study utilized a non-randomized design, i.e. participants were included at two different hospital sites within the south of the Netherlands. At one hospital site, patients were enrolled in the EX group, whereas at the second site they were allocated to the control condition. There were, however, no baseline differences between groups on any disease or other outcome measure. This non-randomized approach was chosen to avoid selection bias by patients preferring the exercise or control condition. Moreover, patients recruited in a separate control group are less likely to start exercising themselves or dropping out when they are not informed about a second exercise group (42).

In conclusion, androgen deprivation therapy reduces both type I and II muscle fiber size and capillarization in PCa patients. Supervised resistance exercise training prevents this decline and effectively increases muscle fiber size and capillarization in PCa patients following the onset of androgen deprivation therapy.

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Supplementary material

Table S1 Habitual dietary intake and physical activity level at baseline and following either 20 weeks of usual care (CON) or resistance exercise training (EX) in prostate cancer patients on androgen deprivation therapy

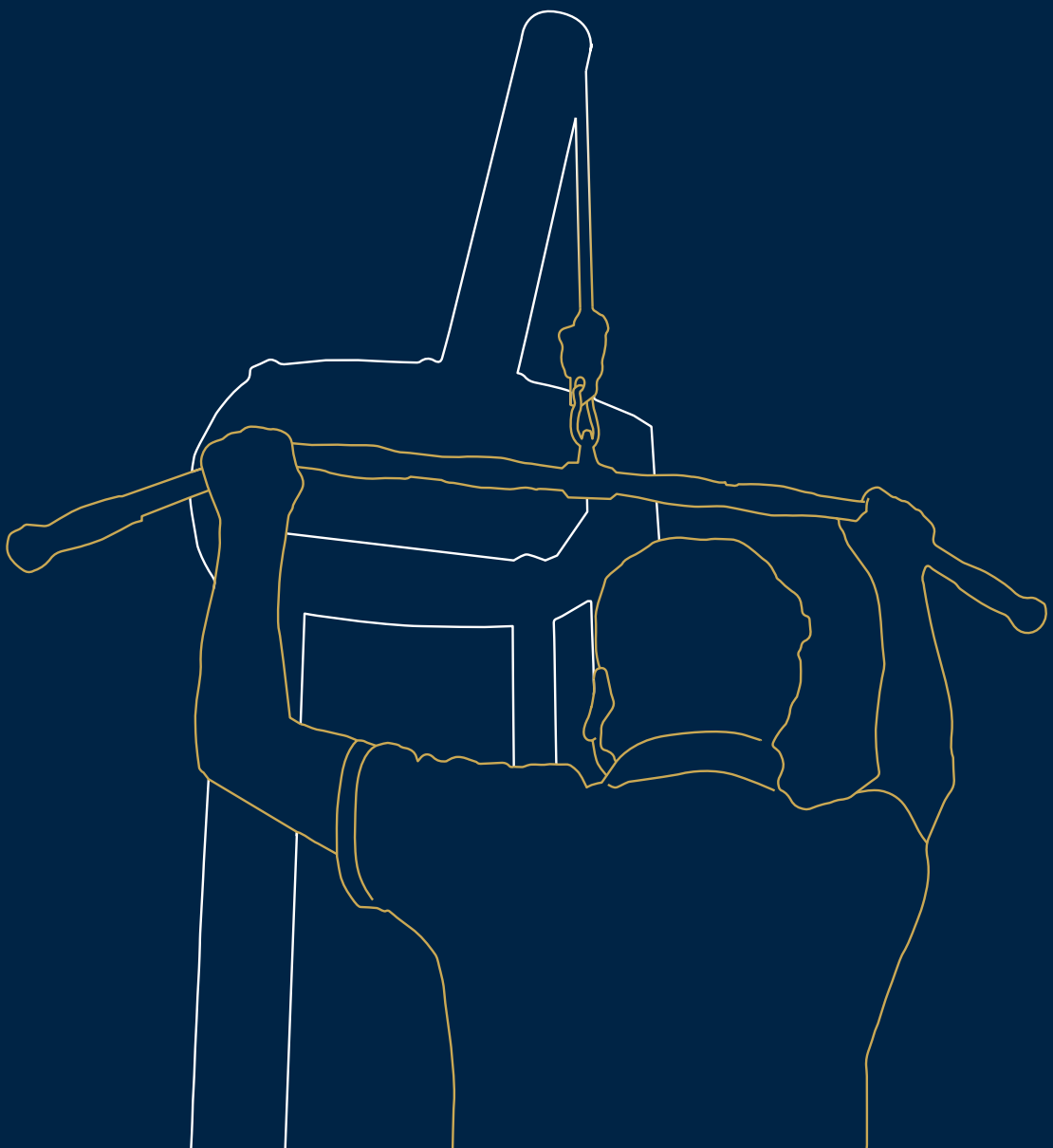
	CON		EX	
	Baseline	**20 weeks**	**Baseline**	**20 weeks**
Habitual dietary intake[a]				
Energy intake (kcal·day^{-1})	2188 ± 416	2112 ± 493	2301 ± 445	2025 ± 438
Protein intake (g·day^{-1})	88 ± 19	83 ± 19	90 ± 17	81 ± 25
Protein intake (g·kg body weight^{-1}·day^{-1})	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.2
Carbohydrate intake (g·day^{-1})	210 ± 89	08 ± 61	224 ± 56	199 ± 41
Fat intake (g·day^{-1})	92 ± 24	87 ± 34	93 ± 21	85 ± 26
Habitual physical activity[b]				
Step count (steps·day^{-1})	7027 ± 2373	5911 ± 1609*	6213 ± 3317	5038 ± 1865*

Values are mean ± SD. [a]Habitual dietary intake, *n*=9 (CON), *n*=9 (EX). Dietary intake values for EX are without the 9 weekly protein (185 kcal) or placebo (56 kcal) supplements. [b]Habitual physical activity level, *n*=10 (CON), *n*=10 (EX). *Significantly different compared with baseline ($P<0.05$).

Table S2 Type I and type II muscle fiber characteristics at baseline and following 20 weeks of androgen deprivation therapy (ADT only) or androgen deprivation therapy combined with chemotherapy (ADT + Chemotherapy) in prostate cancer patients

	ADT only (*n*=7)		ADT + chemotherapy (*n*=4)	
	Baseline	**20 weeks**	**Baseline**	**20 weeks**
Fiber type distribution (fiber %)				
Type I	52 ± 12	52 ± 15	52 ± 11	48 ± 10
Type II	48 ± 12	48 ± 15	49 ± 11	52 ± 10
Fiber type distribution (CSA %)				
Type I	57 ± 9	58 ± 14	56 ± 17	55 ± 7
Type II	43 ± 9	42 ± 14	44 ± 17	45 ± 7
Muscle fiber size (μm^2)				
Type I	7292 ± 693	6068 ± 796	7593 ± 1905	7225 ± 1780
Type II	6170 ± 1482	4843 ± 646	6320 ± 1764	5313 ± 822
Myonuclei ($n \cdot fiber^{-1}$)				
Type I	3.40 ± 0.81	3.16 ± 0.78	3.68 ± 1.00	3.02 ± 0.26
Type II	3.06 ± 0.70	3.11 ± 0.43	3.59 ± 1.48	2.87 ± 0.90
Myonuclear domain (μm^2)				
Type I	2240 ± 557	2028 ± 569	2136 ± 613	2571 ± 986
Type II	2093 ± 622	1586 ± 232	1855 ± 383	2063 ± 840
Capillary contacts				
Type I	4.07 ± 0.68	3.75 ± 0.36	4.29 ± 0.72	3.59 ± 0.59
Type II	3.59 ± 0.72	3.24 ± 0.66	3.96 ± 0.98	2.83 ± 0.47
Mixed	2.45 ± 0.42	2.17 ± 0.34	2.54 ± 0.39	1.94 ± 0.25
C/F*i*				
Type I	1.76 ± 0.25	1.60 ± 0.24	1.90 ± 0.39	1.56 ± 0.30
Type II	1.36 ± 0.32	1.15 ± 0.27	1.40 ± 0.30	0.93 ± 0.14
CFPE-index (capillaries·1000μm^{-1})				
Type I	4.80 ± 0.80	4.67 ± 0.86	5.33 ± 1.60	4.28 ± 0.88*,**
Type II	3.74 ± 0.63	3.76 ± 0.87	4.11 ± 0.64	2.91 ± 0.56*,**
Capillary density (capillaries·mm^{-2})				
Type I	261 ± 60	273 ± 59	289 ± 114	228 ± 63**
Type II	220 ± 40	262 ± 68	239 ± 60	184 ± 47**

Values are mean ± SD. ADT, androgen deprivation therapy; Chemotherapy, docetaxel given every 3 weeks for 6 cycles; CSA, cross-sectional area; C/Fi, individual muscle fiber capillary-to-fiber ratio; CFPE, capillary-to-fiber perimeter exchange. *Significantly lower compared with baseline (P<0.05), **Significant time x group interaction (P<0.05).



CHAPTER 6

Benefits of resistance training are not preserved after cessation of supervised training in prostate cancer patients on androgen deprivation therapy

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Abstract

Resistance exercise training is effective to counteract the adverse effects of androgen deprivation therapy (ADT) on body composition, muscle mass and leg strength in prostate cancer patients (PCa). However, it is unknown whether these effects can be autonomously maintained after cessation of the supervised program.

Sixty-eight PCa patients on ADT were included. The exercise intervention group (EX, *n*=37) performed 20 weeks of supervised resistance exercise training. Thereafter, patients were advised to autonomously continue exercise training. The control group (CON, *n*=31) only received usual care. Outcome measures were compared between baseline and after one year. Changes during the intervention (baseline *vs* 20 weeks) and follow-up period (20 weeks *vs* 1 year) were descriptively explored.

In EX, 83% reported to have continued exercise training themselves. After 1 year, fat mass gains were attenuated in EX compared to CON (1.2±2.6 and 2.8±1.9 kg, respectively; time x treatment effect *P*=0.032). Fat percentage increased, and lean mass and quadriceps muscle cross-sectional area decreased over time, with no differences between groups (overall 1.6±2.1%, -0.7±2.3 kg and -2.2±2.9 cm^2, respectively; time effects, all *P*<0.05). For muscle strength, an increase of ~5% in EX was observed, significantly different from the ~10% decrease in CON (*P*<0.001). Subsequent analyses showed that the initial exercise training-obtained gains in lean mass, muscle mass and strength in EX compared to CON, declined during the follow-up period.

In conclusion, PCa patients on ADT are not capable to autonomously maintain the exercise-obtained gains of a 20-weeks supervised training program over a subsequent 1-year period.

Introduction

Androgen deprivation therapy (ADT) is the cornerstone in the treatment of (locally) advanced prostate cancer (PCa) (1, 2). About half of the men with PCa will be treated with ADT during their disease trajectory (3). By decreasing androgen concentrations to castration level, ADT inhibits disease progression. However, ADT also causes numerous detrimental side effects, such as a decrease in muscle mass with a concomitant increase in body fat mass (4-6). These adverse effects can effectively be counteracted with supervised resistance exercise training. We and others have shown that resistance exercise training increases muscle mass and strength (7-13), and can even reduce fat mass gains in PCa patients treated with ADT (7).

Although the efficacy of resistance exercise training in PCa patients on ADT is well described, little is known about the sustainability of the improvements in body composition and muscle strength after cessation of the supervised exercise training. Detraining studies in healthy older adults showed that gains in muscle mass and strength obtained during training, decline rapidly after complete termination of resistance exercise training (14-21). In free-living situations however, people have the possibility to continue resistance exercise training themselves. Only limited data are available about the sustainability of exercise training-obtained gains in free-living situations. Two studies examining the preservation of exercise training-obtained gains in healthy and chronically diseased older adults, showed that the obtained increases in muscle mass were completely lost and the improvements in strength only partly preserved one year after termination of the supervised program (22, 23). In the subjects reporting to have autonomously continued resistance exercise training, only an attenuating effect on the declines in muscle mass (22) or in strength, and improvements in waist circumference (23), were observed.

Among PCa patients receiving ADT, data concerning preservation of training-induced improvements after cessation of a supervised resistance exercise training program are lacking. However, it is important to have insight in the long-term sustainability of those exercise-obtained gains, especially as ADT is often prescribed for several years. Therefore, the aim of this study was to assess whether exercise training-obtained improvements in body composition, muscle mass and muscle strength are maintained after discontinuation of the supervised resistance exercise training program in PCa patients on ADT.

Materials and methods

Patients

Between September 2017 and February 2021, PCa patients were recruited in five hospitals in the southern part of the Netherlands, as previously reported (7). Patients were eligible if they started or continued treatment with a gonadotrophin-releasing hormone (GnRH) agonist or antagonist for at least 6 months. Exclusion criteria were inability to participate in the exercise training regimen, comorbidities that severely compromised physical activity, a high risk of pathological fractures due to bone metastases (as estimated by their treating urologist), an estimated life expectancy <1 year, lactose intolerance or a whey protein allergy, cognitive disorders or severe emotional instability, or unable to speak, understand or read the Dutch language. Potential participants were identified by their treating urologist or urology nurse, and eligible patients were cleared by a sports physician to perform the exercise training program. All patients were provided with the full oral and written study information and signed informed consent before participation. The study was approved by the local Medical Ethical Committee of Maastricht University Medical Centre + (MUMC+), and complied to the principles outlined in the latest version of the Declaration of Helsinki for use of human subjects and tissue. The study was independently monitored by the Clinical Trial Center Maastricht.

Study design

This study was a multicenter partly randomized controlled trial, comparing two exercise intervention groups with a separately recruited usual care control group. Both exercise intervention groups performed 20 weeks of supervised, progressive resistance exercise training in combination with protein or placebo supplementation. Upon completion of the exercise training program, patients were encouraged to autonomously continue regular exercise training at home or in their neighborhood, but no formal intervention was offered. Patients in the usual care control group only received usual care. These patients were asked to participate in a study about the effects of ADT and were not informed about the exercise intervention nor encouraged to perform regular exercise. An experimental test day was planned at baseline (T0), after completion of 20 weeks of intervention or usual care (T1) and 1 year after study enrollment (T2). The effects of the 20-week resistance exercise training and protein *vs* placebo supplementation in PCa patients receiving ADT have been published earlier (7).

Interventional period

The intervention (exercise with protein or placebo supplementation) has been previously described in detail (7). In brief, patients in both exercise training groups performed an identical, supervised, progressive whole-body resistance exercise training program (60 min, twice a week) for 20 weeks. The main program consisted of training on the leg press and leg extension (2 warm-up sets and 4 working sets all of 10 repetitions) separated by two upper body exercises (1 warm-up set and 3 working sets). In cycles of 3 weeks, workload was increased from 65% to 70% one-repetition maximum (1RM) followed by a reduction in workload to 60% in every 4th week to allow for proper recovery and minimize the risk of injury. After the 4th, 8th, 12th and

16th week of training, indirect 1RM-measurements were performed in order to progressively adjust the workload. In addition, patients in the exercise intervention groups were randomly assigned to ingest a protein or placebo supplement directly after every exercise session and each night before sleep.

Outcome measurements

For a detailed description of the assessment of the outcome measurements, we refer to our previous paper (7). Below, the main aspects for the outcome parameters are described.

Body composition

Body weight was measured using a digital scale to the nearest 0.1 kg. Height was measured by a fixed stadiometer to the nearest 0.5 cm. Body mass index (BMI) was calculated as kilograms per square meter. Waist circumference was measured at the midpoint between the top of the iliac crest and the lower margin of the lowest palpable rib at the end of a normal expiration. The average of two measurements with ≤1 cm difference was rounded up to the nearest 0.5 cm. Whole body and regional lean mass and fat mass were measured with whole body dual-energy X-ray absorptiometry (DXA: Discovery A; Hologic, Marlborough, MA, USA [MUMC+ and Máxima Medical Centre (MMC)] or LUNAR iDXA; GE Healthcare, Chicago, IL, USA and Horizon A; Hologic, Marlborough, MA, USA [both Jeroen Bosch Hospital (JBZ)]). Within-subject comparisons were only performed over results obtained by the same DXA scan.

Skeletal muscle mass

Skeletal muscle mass was assessed with a single-slice computed tomography (CT) scan (SOMATOM Definition Flash; Siemens, München, Germany [MUMC + and JBZ] or Ingenuity CT, Philips Medical Systems, Eindhoven, The Netherlands [MMC]) to determine the anatomic cross-sectional area (CSA) of the quadriceps muscle, as described previously (24). A single-slice image was made 15 cm proximal to the top of the patella of both legs. Quadriceps muscle CSA of the dominant leg was calculated by manual tracing using ImageJ software (version 1.52p, National Institute of Health, Bethesda, MD, USA).

Muscle strength

Maximal muscle strength was assessed by 1RM strength tests on the leg press and leg extension machines (Technogym, Milan, Italy). Patients started with a short warm up on a cycle ergometer, after which proper lifting technique was demonstrated and practiced, and a specific warming-up of 10 and 5 repetitions on ~50 and 70% of the predicted 1RM was performed. The 1RM was determined by increasing the load after each successful single lift until failure. A repetition was valid if the entire lift was completed in a controlled manner without assistance.

Habitual physical activity

During the 48h before all experimental test days, patients were instructed to refrain from any exhaustive physical activity and to arrive at the study location by car or public transportation after an overnight fast. To assess habitual physical activity, patients were instructed to wear

a small-sized triaxial accelerometer (ActiGraph wGT3X-BT; ActiGraph, Pensacola, FL, USA) on the waist during wakefulness for seven days prior to the test days. Accelerometer data were analyzed with ActiLife (version 6.13.4; ActiGraph, Pensacola, FL, USA) and average daily step count, percentage of time spent sedentary and in light, moderate, and (very) vigorous activity intensity were calculated. Data were included if patients wore the accelerometer for ≥5 days and ≥10 h per day.

Statistical analyses

Data were expressed as means ± standard deviation (SD) (normally distributed), median and interquartile range (not-normally distributed), or as frequency and percentages. For all analyses the two interventions groups were merged resulting in one exercise intervention group (EX). Baseline characteristics between EX *vs* the usual care control group (CON) and between patients who completed the 1-year measurements *vs* patients loss to follow-up, were compared using independent samples t-tests (for continuous variables) or chi-square tests (for categorical variables). As primary analysis, the differences between baseline and 1 year were assessed by a two-way repeated-measures ANOVA with time (baseline *vs* 1 year) as within subject factor and group (EX *vs* CON) as between subject factor. Effect sizes were calculated using partial eta squared ($\eta^2_{partial}$). In case of a significant time x treatment interaction, a paired-sample t-test was performed to detect within group changes over time. For muscle strength, absolute 1RM values could not be compared due to slight differences in leg press and leg extension equipment at the different study locations. Therefore, percentage changes over the 1-year period were calculated and compared between groups with independent samples t-test.

As secondary, explorative analysis, changes over time during the intervention period (baseline *vs* 20 weeks) and follow-up period (20 weeks *vs* 1 year) were described to obtain more insight into the changes during the different periods.

Data were analyzed on an intention-to-treat basis. Significance was set at $P<0.05$. All analyses were performed with the use of IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY).

Results

The results of the 20-week training intervention were reported previously (7) and are combined with the 1-year follow-up data in this article.

Patients

Ninety-six patients completed the first 20 weeks of the study. In 68 patients the 1-year follow-up measurements were performed. Twenty-eight patients could not perform the 1-year follow-up measurements due to the COVID-19-induced lockdown (EX *n*=16, CON *n*=2), medical problems (EX *n*=5, CON *n*=2) or death (EX *n*=2, CON *n*=1).

Baseline characteristics are presented in **Table 1**. Included patients were on average 71±6 years old, slightly overweight (BMI 27.1±3.4 $kg \cdot m^{-2}$) and treated with ADT for 82±186 days. Compared to patients who completed all measurements, patients loss to follow-up had less appendicular lean mass, a lower quadriceps CSA, and a lower habitual physical activity level at baseline ($P \leq 0.05$). At T2, 83% of the patients from EX reported to have autonomously performed exercise training with a resistance-type component during the follow-up period.

Table 1 Baseline patients' characteristics

	One-year follow-up completed				Loss to follow-up		
	Total (*n*=68)	**EX (*n*=37)**	**CON (*n*=31)**	***P*-value[a]**	**Total (*n*=28)**	**EX (*n*=23)**	**CON (*n*=5)**
Age (y)	71 ± 6	71 ± 6	71 ± 6	0.909	72 ± 8	73 ± 8	67 ± 10
Time since PCa diagnosis (months)	21 ± 39	18 ± 36	25 ± 42	0.464	30 ± 43	35 ± 46	11 ± 17
Gleason score	8 ± 1	8 ± 1	8 ± 1	0.340	8 ± 1	8 ± 1	9 ± 1
ADT duration (days)	82 ± 186	117 ± 243	40 ± 52	0.068	166 ± 242	199 ± 257	16 ± 5
Bone metastase, *n* (%)	27 (41.5)	11 (32.4)	16 (51.6)	0.116	17 (63.0)	14 (63.6)[b]	3 (60)
Number of comorbidities				0.248			
0	14 (21.2)	5 (13.9)	9 (30.0)		4 (14.3)	3 (13.0)	1 (20.0)
1	22 (33.3)	14 (38.9)	8 (26.7)		11 (39.3)	9 (39.1)	2 (40.0)
≥ 2	30 (45.5)	17 (47.2)	13 (43.3)		13 (46.4)	11 (47.8)	2 (40.0)
Body weight (kg)	84.0 ± 12.2	84.0 ± 11.3	84.0 ± 13.4	0.998	81.2 ± 12.9	82.3 ± 13.9	76.3 ± 4.8
BMI ($kg \cdot m^{-2}$)	27.1 ± 3.4	27.2 ± 3.0	26.9 ± 3.9	0.645	26.6 ± 3.7	26.9 ± 4.0	25.4 ± 2.2
Fat percentage (%)	30.1 ± 5.6	29.0 ± 4.5	31.4 ± 6.5	0.089	30.9 ± 4.8	30.7 ± 5.0	31.6 ± 4.2
Whole body lean mass (kg)	56.8 ± 6.8	57.8 ± 6.8	55.7 ± 6.8	0.218	53.9 ± 6.7	54.5 ± 7.0	51.0 ± 3.8
Appendicular lean mass (kg)	24.8 ± 3.1	24.9 ± 3.2	24.7 ± 3.1	0.788	23.1 ± 3.2[b]	23.2 ± 3.4	22.5 ± 2.1
Quadriceps muscle CSA (cm^2)	65.3 ± 9.4	63.6 ± 9.9	67.4 ± 8.4	0.098	59.6 ± 8.8[b]	59.7 ± 8.8	59.0 ± 9.6[b]
Steps per day	6652 ± 2582	6332 ± 2785	7004 ± 2333	0.298	5474 ± 2627[b]	5178 ± 2794	6776 ± 1132
% per day sedentary (%)	75 ± 7	76 ± 7	73 ± 7	0.107	78 ± 7[b]	80 ± 6[b]	71 ± 4

Values are mean ± SD, or number and (%). EX, exercise intervention group; CON, usual care control group; PCa, prostate cancer; ADT, androgen deprivation therapy; BMI, body mass index; CSA, cross-sectional area.

Not all data are available for all patients. Data available in 'total completed group': time since PCa diagnosis, Gleason score, quadriceps muscle CSA, *n*=67; number of comorbidities, *n*=66; bone metastase, steps per day, % per day sedentary, *n*=65. Data available in 'completed EX': number of comorbidities *n*=36; bone metastase, steps per day, % per day sedentary, *n*=34. Data available in 'completed CON': time since PCa diagnosis, Gleason score, number of comorbidities, quadriceps muscle CSA, *n*=30. Data available in 'total loss to follow up': bone metastase, quadriceps muscle CSA, steps per day, % per day sedentary, *n*=27. Data available in 'loss to follow up EX': bone metastase, quadriceps muscle CSA, steps per day, % per day sedentary, *n*=22.

[a]*P*-value of baseline value of EX compared to CON of patients who completed the 1-year follow-up assessments. [b]Significantly different from patients in corresponding group who completed the study (all $P \leq 0.05$).

Body composition and skeletal muscle mass

Results for body composition and skeletal muscle mass at baseline and after 1 year, are presented in **Table 2**. For body composition, only results of patients whose T0 and T2 assessment were performed on the same DXA scanner are included. In this subgroup, whole body fat mass and fat percentage were at baseline significantly lower in EX compared to CON ($P<0.05$). After 1 year, significant differences over time between groups were found for body weight, BMI, waist circumference and whole body fat mass (time x treatment interaction, all $P<0.05$). Body weight, BMI and waist circumferences increased over time in CON, with no significant changes over time in EX, while fat mass gains were significantly attenuated in EX compared to CON. For fat percentage, whole body lean mass and appendicular lean mass, no significant differences between groups over time were observed. However, in the total population, fat percentage increased, while whole body lean mass and appendicular lean mass decreased over time (1.6±2.1%, -0.7±2.3 kg, -0.5±1.1 kg respectively; time effect, all $P<0.05$). For quadriceps muscle CSA, no significant baseline differences were found between EX and CON. Over the 1-year period, quadriceps muscle CSA decreased in the total population (-2.2±2.9 cm^2, time effect, $P<0.001$), with no significant differences between groups.

Muscle strength

Over the 1-year period, muscle strength increased in EX (leg press 4±11%, leg extension 5±16%) and decreased in CON (leg press -10±9%, leg extension -11±13%), resulting in significant differences between groups (both $P<0.001$).

Habitual physical activity

No baseline differences between groups were found for habitual physical activity. Between baseline and 1 year, average daily step count and percentage of time in moderate activity intensity significantly decreased ($-9.7 \cdot 10^2 \pm 2.2 \cdot 10^3$ steps and -1.1±2.5% respectively; time effect, both $P<0.001$), while percentage of time sedentary showed a strong trend toward an increase (1.3±5.6%, time effect, $P=0.059$), with no differences between group. No differences between groups or over time were found for percentage time in light and in (very) vigorous activity intensity.

Table 2 Changes in body composition and muscle mass over time

		Baseline	1 year	Time effect	Time x treatment interaction	Within-group changes over 1 year	
	n	Mean ± SD	Mean ± SD	*P*-value	*P*-value ($\eta^2_{partial}$)	Mean ± SD	*P*-value
Body weight (kg)				<0.001	0.019 (0.086)		
EX	37	84.0 ± 11.3	84.6 ± 10.7			0.6 ± 3.3	0.297
CON	27	85.7 ± 12.7	88.0 ± 13.3			2.4 ± 2.3	<0.001
BMI (kg·cm^{-2})				<0.001	0.020 (0.085)		
EX	37	27.2 ± 3.0	27.4 ± 2.6			0.2 ± 1.1	0.339
CON	27	27.2 ± 3.9	27.9 ± 4.1			0.8 ± 0.7	<0.001
Waist circumference (cm)				0.008	0.022 (0.079)		
EX	37	104.3 ± 10.3	104.5 ± 9.2			0.2 ± 4.4	0.783
CON	29	103.7 ± 10.5	106.4 ± 11.0			2.7 ± 4.1	0.001
Whole body fat mass (kg)[a]				<0.001	0.032 (0.099)		
EX	31	25.4 ± 6.5	26.7 ± 5.3			1.2 ± 2.6	0.011
CON	16	30.9 ± 8.2	33.7 ± 8.9			2.8 ± 1.9	<0.001
Fat percentage (%)[a]				<0.001	0.176 (0.040)		
EX	31	29.3 ± 4.8	30.6 ± 3.5			1.3 ± 2.2	
CON	16	33.9 ± 4.9	36.1 ± 5.0			2.2 ± 1.8	
Whole body lean mass (kg)				0.049	0.950 (<0.001)		
EX	31	57.9 ± 6.7	57.2 ± 6.5			-0.8 ± 2.5	
CON	16	57.7 ± 6.5	57.0 ± 6.5			-0.7 ± 2.0	
Appendicular lean mass (kg)				0.004	0.832 (0.001)		
EX	31	24.9 ± 3.2	24.4 ± 3.1			-0.5 ± 1.2	
CON	16	25.1 ± 2.9	24.5 ± 2.8			-0.6 ± 1.0	
Quadriceps muscle CSA (cm^2)				<0.001	0.066 (0.054)		
EX	37	63.6 ± 9.9	62.0 ± 9.7			-1.6 ± 2.9	
CON	26	66.8 ± 8.0	63.8 ± 8.3			-3.0 ± 2.9	

Values are mean ± SD. For DXA measurements, results are only included when the baseline and 1-year assessment of a patient were performed on the identical scanner. CON, usual care control group; EX, exercise intervention group; BMI, body mass index; CSA, cross-sectional area. [a]Significantly different between groups at baseline ($P<0.05$).

Changes during the intervention and follow-up period (explorative)

Figure 1 shows the percentage changes of outcome measures during the intervention and follow-up period separately. For fat mass, gains were attenuated during the intervention period in EX compared to CON. During the follow-up period, EX could maintain this obtained benefit, resulting in a still existing between-group difference after 1 year. Lean mass and muscle mass was maintained respectively increased during the intervention period in EX, while both decreased in CON. However, after cessation of the exercise program, the loss of lean and muscle mass in EX was this large, that after 1 year no between-group differences existed anymore. In accordance, muscle strength increased in EX during the intervention period, followed by a decrease during the follow-up period, while in CON a gradual decrease over the entire year was observed. For muscle strength however, there was still a benefit present in EX compared to CON after 1 year.

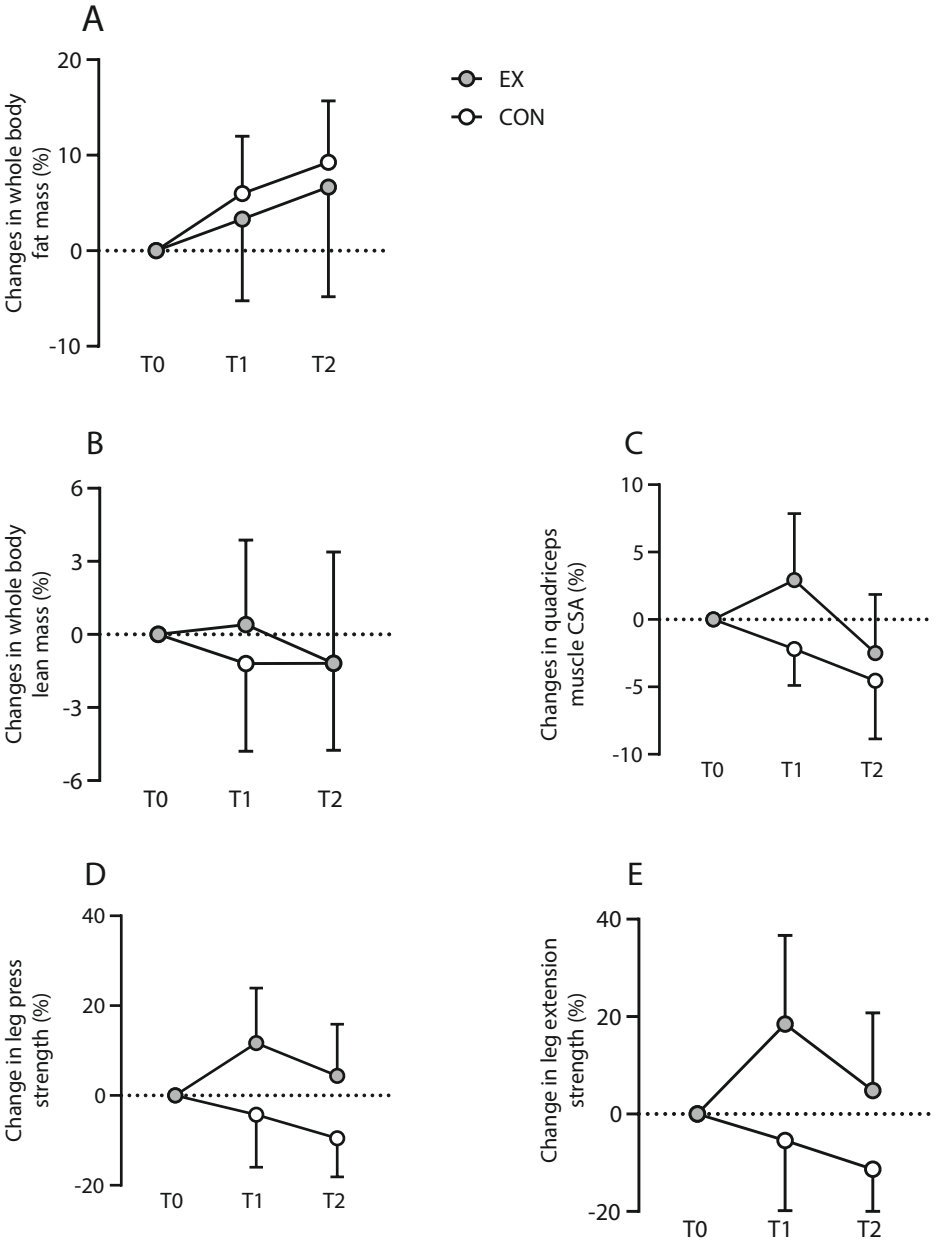

Figure 1 Percentages changes compared to baseline in whole body fat mass (A), whole body lean mass (B), quadriceps muscle cross-sectional area (C), leg press (D) and leg extension muscle strength (E) after 20 weeks and 1 year. EX, exercise intervention group; CON, usual care control group; T0, baseline; T1, after 20 weeks; T2, after 1 year; CSA, cross-sectional area.

Discussion

We have previously shown that a 20-week supervised resistance exercise training program is effective to combat the adverse effects of ADT in PCa patients. The exercise training program resulted in positive effects on fat mass, muscle mass and muscle strength, compared to usual care only (7). In the current study, we assessed whether these beneficial effects are maintained after discontinuation of the supervised intervention. Results showed that 1 year after inclusion - 7 months after cessation of the supervised exercise intervention - the exercise training effects were not preserved, though some outcomes were still improved compared to baseline. Fat mass accretion was still attenuated in EX compared to CON, with an accompanying lower increase in waist circumference in EX than in CON. Muscle strength in EX was still ~5% higher than at baseline, and this significantly differed from CON, in which a ~10% decline over the 1-year period was seen. For muscle mass however, no sustained exercise training benefits were observed. Both lean mass as surrogate for muscle mass, and quadriceps muscle CSA declined in EX after cessation of the supervised exercise program to levels lower than at baseline, with no differences between EX and CON after 1 year (**Table 2**).

Up till now, studies in healthy older adults (14-22) or older adults with stable chronic diseases (23), provide some insight in the sustainability of gains in muscle mass and muscle strength obtained during an exercise program, showing rapid declines after termination of the intervention. We are the first to explore the long-term sustainability of the benefits of a supervised exercise program in PCa patients on ADT. Our results revealed that both muscle mass and strength declined following cessation of the supervised exercise program. For muscle strength, these declines were smaller than the initial exercise training-induced gains, resulting in a small positive net result after 1 year, significantly different from the decline in CON. For muscle mass, however, the declines in the follow-up period were larger than the initial obtained improvements, resulting in a net decline after 1 year that was no longer different from the decline in CON. This discrepancy between changes in muscle mass and strength seems to be in agreement with previous findings (14, 16, 17, 21-23), showing a larger decline of muscle mass compared to muscle strength after cessation of an exercise intervention. Probably this is caused by neuromuscular adaptations (25) that persist longer than the more temporary gains in muscle tissue mass. For whole body fat mass, the exercise training-induced attenuation of fat mass gain was maintained during the follow-up period in EX. Snijders *et al*. (22) published one of the few studies assessing the sustained exercise training effects on whole body fat mass as well. However, in their study the exercise training-induced decline in fat mass was dissipated one year after cessation of the supervised intervention.

From a clinical and patient perspective, sustained improvements of muscle strength and attenuation of fat mass gains are relevant profits. Strength is important to independently perform activities of daily living and is associated with survival (26), while being overweight and obese are associated with the development of multiple comorbidities like cardiovascular diseases (27, 28). However, despite a partial preservation of muscle strength after 1 year,

substantial decreases in both muscle strength and mass were observed during the follow-up period. This is remarkable, as our patients had experienced the benefits of training during the intervention period and were strongly encouraged to autonomously continue training. In fact, a large number of our patients (83%) reported to have continued exercise training with a resistance-type component. Apparently, most PCa patients are not capable to autonomously perform exercise at an intensity sufficient to preserve or further improve exercise training-induced gains during ADT. This is in agreement with studies in free-living healthy and older adults with chronic disease (22, 23). These studies showed that one year after termination of the supervised program, autonomous continuation of resistance exercise only resulted in attenuation of the decline of muscle mass (22) or muscle strength, and improvements in waist circumference (23). Therefore, performing a supervised and structured training program as long as ADT is prescribed (often ≥2 years) would probably be most ideal. Though it seems likely that this would lead to maintenance of training gains, this still needs to be confirmed. Besides physiological factors, other aspects like motivation will determine the long-term efficiency. Furthermore, practical issues, costs, staffing aspects and the extra pressure on the health care system should be taken into account as well. Therefore, a broad focus on ways to increase sustainability of exercise regimes is needed, for example on maintenance training programs, hybrid training regimes (partly autonomously, partly supervised), the use of digital technologies to support home training or educational strategies to teach patients how to exercise effectively and achieve long-term behavioral changes.

Our study has been hampered by the COVID-19-induced lockdown from March 2020 onwards. The follow-up period of 10 out of 37 (27%) patients in the exercise intervention group fell within this lockdown, considerably restricting the possibilities to continue exercise training. However, a sensitivity analysis without these patients showed similar results.

We conclude that the beneficial effects of a 20-week supervised resistance exercise training program in PCa patients treated with ADT, are not effectively preserved over a longer time period. One year after start of the intervention, exercise training benefits are only (partly) preserved for fat mass and muscle strength, but have completely dissipated for muscle mass. Although a high number of patients reported to have continued exercise training, the impact was insufficient to preserve the benefits of the supervised exercise intervention and stress the importance for more guided long-term strategies. Therefore, in order to offset the detrimental adverse effects of ADT on the long-term and to maintain body composition and performance benefits, more focus on the sustainability of the effects of exercise programs is required.

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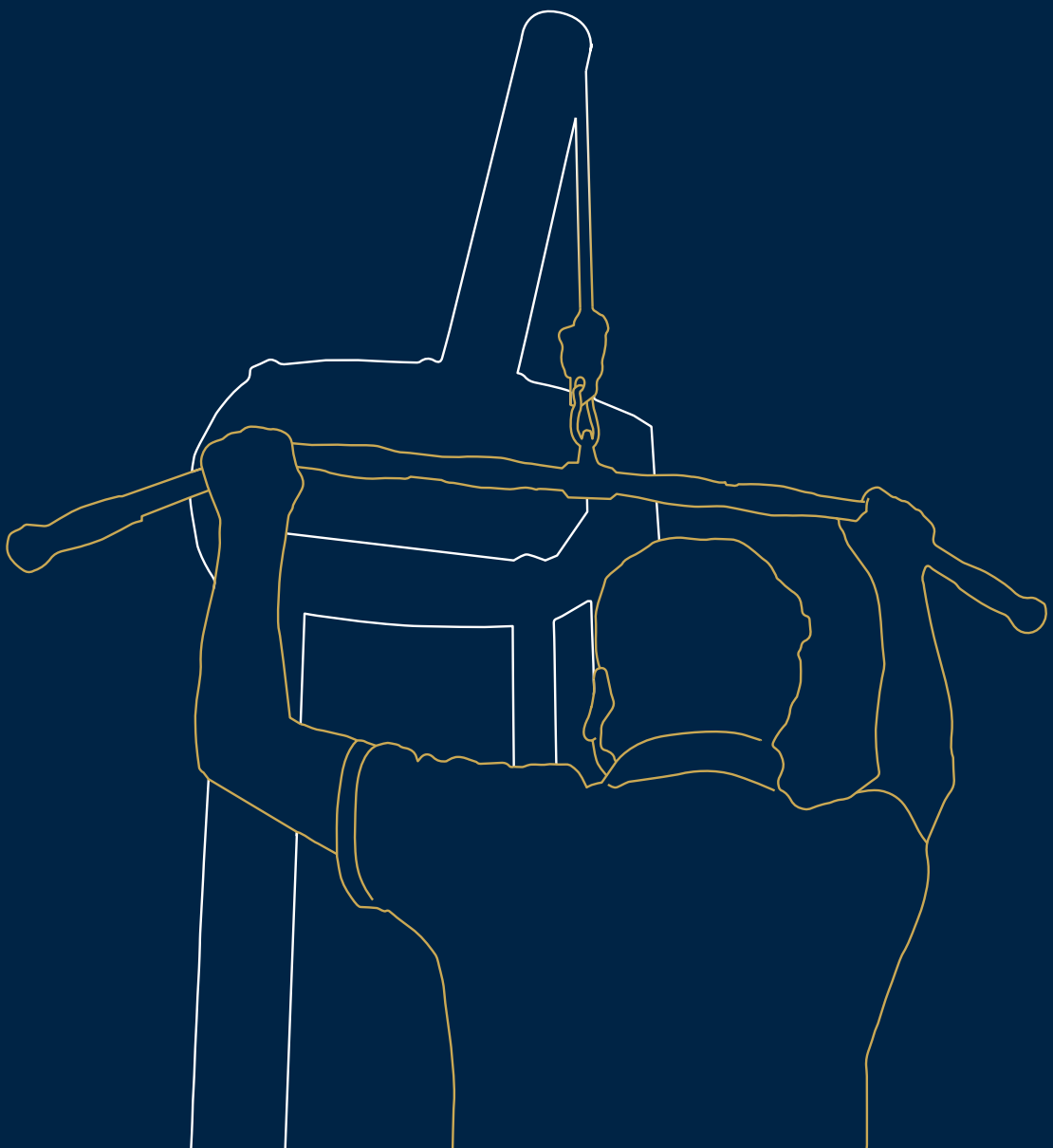

CHAPTER 7

A low or high physical activity level does not modulate prostate tumor tissue protein synthesis rates

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Abstract

Introduction: Physical activity level has been identified as an important factor in the development and progression of various types of cancer. Furthermore, changes in physical activity level may modulate tumor growth. In this study, we determined the impact of a low versus high physical activity level on skeletal muscle, healthy prostate, and prostate tumor protein synthesis rates *in vivo* in prostate cancer patients.

Methods: Thirty prostate cancer patients (age: 66±5 y, BMI: 27.4±2.9 kg per m^2) were randomized to a low (<4000 steps per day, *n*=15) or high (>14000 steps per day, *n*=15) physical activity level for seven days prior to their scheduled radical prostatectomy. Daily deuterium oxide administration was combined with the collection of plasma, skeletal muscle, non-tumorous prostate, and prostate tumor tissue during the surgical procedure to determine tissue protein synthesis rates throughout the intervention period.

Results: Daily step counts averaged 3610±878 and 17589±4680 steps in patients subjected to the low and high physical activity level, respectively (P<0.001). No differences were observed between tissue protein synthesis rates of skeletal muscle, healthy prostate, or prostate tumor between the low (1.47±0.21, 2.74±0.70, and 4.76±1.23 % per day, respectively) and high (1.42±0.16, 2.64±0.58, and 4.72±0.80 % per day, respectively) physical activity group (all P>0.4). Tissue protein synthesis rates were 1.9±0.6 higher in prostate tumor tissue compared with non-tumorous prostate tissue.

Conclusions: A short-term low or high physical activity level does not modulate prostate or prostate tumor protein synthesis rates *in vivo* in prostate cancer patients.

Introduction

Prostate cancer is the second most common cancer and the fifth leading cause of death in men worldwide (1). Lifestyle modifications are rapidly becoming recognized as important adjunct therapeutic approaches to slow cancer development and enhance treatment efficacy. Epidemiological data suggest that physical activity protects against the development and/or progression of several types of cancer (2, 3), including prostate cancer (4-11). Furthermore, emerging pre-clinical evidence in animal models indicates that increased physical activity (e.g., wheel running, swimming) can strongly reduce tumor growth (12, 13).

Tumor growth is regulated by the balance between tumor protein synthesis and breakdown rates. Evidence suggests that physical activity modulates translational signaling involved in the regulation of tumor protein synthesis (14-16). Several exercise-mediated mechanisms have been proposed that may elicit tumor-growth inhibiting effects, including modulation of hormonal/growth factors (e.g., insulin/insulin growth factor (IGF), testosterone) (17), release of myokines (12), improved immune function (17), and changes in tumor vascularization (18). However, despite the compelling pre-clinical data, the anti-carcinogenic effects of increasing physical activity level have not been established *in vivo* in humans.

Recently, we applied peri-operative intravenous stable isotope amino acid infusions with tumor tissue sample collection during resection surgery in pancreatic cancer patients as a means to quantify pancreatic tissue and pancreatic tumor tissue protein synthesis rates (19). This approach allowed us to assess tumor tissue protein synthesis rates over a 4-8 hour timespan prior to resection. Though this provides us with important insight in the dynamics of tumor protein metabolism, it precludes the assessment of potential tumor-growth inhibiting effects to lower tumor protein synthesis rates. The recent re-introduction of the use of deuterium oxide (^2H_2O) administration provides a stable isotope tracer labeling methodology that allows us to assess tissue protein synthesis rates over a more extended period of several days or even weeks (20). Such expanded assessment periods provide us with the opportunity to assess the impact of lifestyle interventions on tissue protein synthesis rates. So far this approach has been successfully applied to assess the impact of more (20) or less (21, 22) physical activity on muscle tissue protein synthesis rates. To date, this approach has not been applied to assess the impact of physical activity level on tumor protein synthesis rates *in vivo* in (prostate) cancer patients.

In the present study, 30 prostate cancer patients scheduled for radical prostatectomy were subjected to either a low or high level of daily physical activity level. In the week prior to surgery, patients performed either less than 4000 steps per day (low physical activity) or more than 14000 steps per day (high physical activity). Deuterium oxide was provided per os throughout the intervention period with saliva, blood, muscle, non-tumorous prostate and prostate tumor tissue sampling to allow subsequent assessment of skeletal muscle, healthy prostate, and prostate tumor protein synthesis rates.

Methods

Participants and ethical approval

A total of thirty prostate cancer patients were recruited to participate in the present study between June 2020 and June 2021. Patients were eligible for participation when they were scheduled for a robot-assisted radical prostatectomy with curative intent because of prostate cancer. Furthermore, patients needed capable to perform walking activities required to participate in the physical activity intervention program. Potential subjects were identified by the urologist at the outpatient clinic of the Department of Urology of the Jessa Hospital, Hasselt, Belgium. All patients were informed of the nature and potential risks of the experimental procedure before informed written consent was obtained. The study was approved by the Ethical Review Committee (Ethische Toetsingscommissie) Jessa Hospital, Hasselt, Belgium (reference: B243202042677) and conformed to standards for the use of human participants in research as outlined in the declaration of Helsinki. All patients provided written informed consent before participating in this study. The study was registered at Netherlands Trial Register as Trial NL8768.

Study design

This study was a two-armed, randomized controlled trial. A graphic overview of the study design is presented in **Figure 1**. The study protocol consisted of 9 consecutive days. The first experimental procedures were conducted on the morning of day 1 at the patients' homes. After obtaining informed consent, a fasting serum and saliva sample were collected, body weight was measured, and the deuterium oxide (^2H_2O) dosing protocol was initiated. Patients were then randomised to perform either the low (*n*=15) or high (*n*=15) physical activity intervention. The randomisation was performed by an independent researcher who used computer-generated random numbers in permuted blocks of 6.

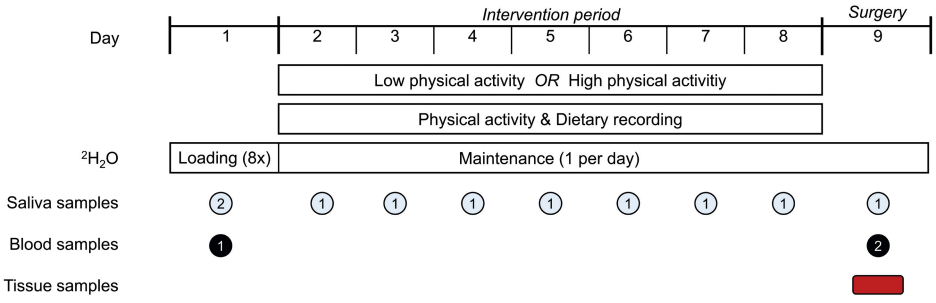

Figure 1 Graphic overview of the study design. Tissue samples of vastus lateralis muscle, healthy prostate, and prostate tumor tissue. ^2H_2O, deuterated water.

The intervention period ran from day 2 until day 8. During this period, patients in the low physical activity group were instructed to perform no more than 4000 steps per day, and patients in the high physical activity group were instructed to perform 14000 steps or more per day. Other physical activities (e.g., cycling) were allowed in the high physical activity group if they were additional to the 14000 steps a day. Patients in the low physical activity group refrained from other physical activities besides the limited step count. Patients tracked their physical activity throughout the intervention period and recorded their food intake for three days. The researchers had daily telephone contact with the patients to provide constant guidance and ensure compliance to the $^{2}H_{2}O$ dosing protocol. During surgery, blood, *vastus lateralis* muscle, non-tumorous prostate and prostate tumor tissue samples were collected.

Physical activity

Patients were instructed to refrain from strenuous exercise in the 48 h before start of the study. On the first experimental day, patients were provided with an accelerometer, a physical activity diary and a pedometer. The accelerometer (Actigraph wGT3X-BT; ActiGraph, Pensacola, FL, USA) and physical activity diary were used to objectively track all physical activities during the intervention period (23, 24). From day 2 until day 8, patients continuously wore the accelerometer during waking hours on the right hip. In addition, patients simultaneously tracked their physical activities in a 7-day physical activity diary. The pedometer (Yamax Digi-Walker SW-200; Yamasa Tokei Keiki Co. Ltd., Tokyo, Japan) was worn on the left hip during waking hours and was used to provide patients with real-time feedback on their step count. The Yamax Digi-Walker SW-200 is an often used pedometer in (clinical) studies (21, 25-30), which provides a valid and reliable step count and performs well during a range of walking speeds (27, 31-33). Before use, each pedometer was checked for accuracy by walking a short distance at normal walking pace and simultaneously counting the actual steps taken (34). Each evening before sleep the displayed daily step count was recorded by the patient.

Dietary intake

Patients were instructed to maintain their habitual diet as consistently as possible in the 48 h prior to the start of the study. During the study period, no dietary restrictions were imposed. Dietary intake was monitored by a 3-day food diary, filled in by the patient on two weekdays and one weekend day. Food diaries were analysed for average energy and macronutrients intake using web-based software (Eetmeter; Voedingscentrum, Den Haag, The Netherlands).

Deuterated water-dosing protocol

The $^{2}H_{2}O$-dosing protocol consisted of one loading day and eight maintenance days. The dosing protocol was identical to previously published studies that administered $^{2}H_{2}O$ in human participants (20-22, 35, 36). On day 1 (loading day), one background serum and one saliva sample were collected following an overnight fast. Thereafter, patients ingested 8 x 50 mL boluses of 70% $^{2}H_{2}O$ (Cambridge Isotopes Laboratories, Andover, MA, U.S.A.) separated by 1.5 h to minimize the risk of side effects (e.g. dizziness or vertigo). Although ten patients reported light feelings of dizziness possibly related to the loading protocol, this was very mild, not

disabling and had completely disappeared the next day. After completing the loading protocol, a second saliva sample was collected in the course of the evening. From day 2 until day 8, patients consumed one $^{2}H_{2}O$ dose of 50 mL each morning upon waking. Each evening, patients collected a saliva sample at least 30 min after consuming dinner or evening snack. During surgery, an arterial serum sample was taken at the moment of the actual prostate resection.

Blood, saliva and tissue collection and processing

Blood samples were collected in evacuated tubes (ST II Advance Tube, BD Vacutainer, United Kingdom) and allowed to coagulate for at least 90 min before centrifugation at 1,000*g* for 15 min at 21°C. Aliquots of serum were frozen in liquid nitrogen and stored at -80°C. Saliva samples were collected using cotton dental swabs (Celluron, Hartmann, Germany). Patients lightly chewed on a cotton swab until saturated with saliva (at least 2 min). The swab was then removed and refrigerated in a sealed tube until collection on day 9. Saliva was extracted, frozen in liquid nitrogen, and stored at -80 °C until subsequent analyses.

Muscle, healthy prostate and prostate tumor tissue sampling took place during the surgical procedure. The muscle biopsy was obtained under general anesthesia prior to the start of the prostatectomy procedure. The muscle biopsy was obtained from the middle region of the *vastus lateralis* muscle (about 15 cm above the patella) and about 3 cm below entry through the fascia, using a modified Bergström needle (37) with manual suction. Muscle biopsy samples were dissected carefully and freed from any visible non-muscle material before being frozen in liquid nitrogen and stored at -80°C until further analysis. During the surgery, the prostate was resected, immediately fixed in formaldehyde 4% and transferred to the pathology laboratory. The prostatectomy resection specimen tissue was subsequently macroscopically evaluated and further handled in accordance with the regular pathological procedures. Eventually, the formalin-fixed and paraffin-embedded tissue was cut into slices and stained with haematoxylin and eosin, and if necessary immunohistochemical stains. The slices were carefully examined by the pathologist using light microscopy. Subsequently, samples of confirmed non-tumorous prostate and viable prostate tumor tissue without signs of necrosis or ischemia were collected for further stable isotope analyses (**Figure 2**).

Body water deuterium enrichments

Body water enrichment was analysed using the saliva samples collected throughout the experimental protocol as described previously (20). Briefly, samples were diluted 70-fold and reacted in sealed vials to undergo deuterium equilibration with hydrogen gas. The deuterium enrichment of the hydrogen gas was then measured in duplicate by isotope ratio mass spectrometry (IRMS; DELTA V Advantage IRMS fitted with a GasBench II system and PAL system auto injector; Thermo Fisher Scientific, Bremen, Germany). Standard regression curves were applied from a series of known standard enrichment values against the measured values to assess the linearity of the mass spectrometer and to account for deuterium loss during equilibration.

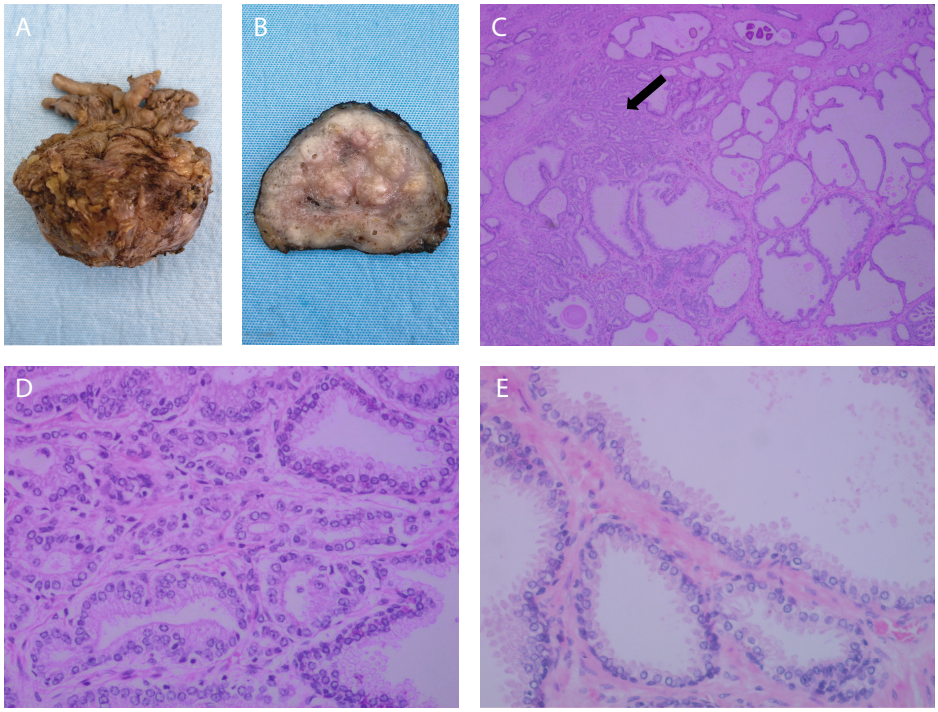

Figure 2 Prostate tumor biopsy. (A) Macroscopy of the prostatectomy specimen. (B) Macroscopy of cross-section of prostatectomy specimen. (C) Microscopy of coupe stained with haematoxylin and eosin, confirming the presence of adenocarcinoma (left, arrow) and healthy tissue (right), two times enlarged. (D) Microscopy confirming adenocarcinoma, twenty times enlarged. (E) Microscopy confirming healthy prostate tissue, twenty times enlarged.

Serum free [^{2}H]alanine enrichments

Serum free [^{2}H]alanine enrichments were determined by gas chromatography-mass spectrometry analyses, as described previously (20). Briefly, serum samples were deproteinized and purified before free amino acids were converted into *tert*-butyldimethylsilyl (*tert*-BDMS) derivatives with MTBSTFA before analysis by gas chromatography-mass spectrometry (GC-MS; Agilent 5975C MSD & 7890A GC, Wilmington, DE, U.S.A.). The plasma free alanine mass isotopomers (M and M+1) were determined using selective ion monitoring at *m/z* 232 and 233. Standard regression curves were applied from a series of known standard enrichment values against the measured values to assess the linearity of the mass spectrometer and to account for any isotope fractionation.

Muscle, prostate and prostate tumor tissue protein bound [^{2}H]alanine enrichments
For measurement of muscle protein bound [^{2}H]alanine enrichments, 30-60 mg wet muscle tissue was freeze dried. Collagen, blood, and other non-muscle fiber material were removed from the muscle fibers under a light microscope. The isolated muscle fiber mass (5-10 mg) was weighed, and 35 volumes (35 times dry weight of isolated muscle fibers wet:dry ratio) of ice-cold 2% perchloric acid were added. The tissue was then sonicated and centrifuged. The protein pellet was washed with three additional 1.5-mL washes of 2% perchloric acid, dried, and hydrolyzed in 6 M HCl at 120°C for 15-18 h.

For measurement of [^{2}H]alanine enrichment in healthy prostate and prostate tumor tissue proteins, visible paraffin was carefully removed from the samples. The isolated healthy prostate and prostate tumor tissue was weighed and 30-60 g was hydrolysed in 6M HCl at 120°C for 15–18 h. After hydrolysation muscle, healthy prostate, and prostate tumor samples were dried under a nitrogen stream while being heated at 120°C. Samples were then dissolved with a 25% acetic acid solution before being passed over Dowex exchange resin (AG 50W-X8, 100–200 mesh hydrogen form; Bio-Rad, Hercules, CA, U.S.A.) by using 2 M NH_4OH. Thereafter, the eluate was divided into 2 screw cap tubes and dried under a nitrogen stream for 24-36 h, and the purified amino acids were derivatized to their N(O,S)-ethoxycarbonyl ethyl esters (38). The derivatized samples were measured using a gas chromatography-isotope ratio mass spectrometer (MAT 253+; Thermo Fisher Scientific, Bremen, Germany) equipped with a pyrolysis oven using a 60-m DB-17MS column and 5-m precolumn (No. 122–4762; Agilent) and GC-Isolink. Ion masses 2 and 3 were monitored to determine the ^{2}H/^{1}H ratios of muscle protein bound alanine. A series of known standards were applied to assess linearity of the mass spectrometer and to control for the loss of tracer.

Calculations
Tissue protein synthesis rates were calculated as fractional synthetic rate (FSR), expressed as %·day^{-1}. FSR was determined using the incorporation of [^{2}H]alanine into tissue proteins and the mean body water deuterium enrichment corrected by a factor of 3.7 based on the deuterium labeling during de novo alanine synthesis. Secondly, we repeated the calculations using mean free [^{2}H]alanine enrichment in arterial serum instead of body water enrichment. The standard precursor-product method was used to calculate FSR:

$$\mathrm{FSR}(\% \cdot \mathrm{day}^{-1}) = \left(\frac{\mathrm{E_{p2}} - \mathrm{E_{p1}}}{\mathrm{E_{precursor}} \mathrm{x\ t}}\right) \mathrm{x} 100\%$$

where E_{p1} and E_{p2} are the protein bound enrichments measured in the basal mixed serum protein and tissue samples (muscle, healthy prostate, prostate tumor tissue), respectively (single biopsy approach). $E_{precursor}$ represents mean body water deuterium enrichment corrected by a factor 3.7, or mean free [^{2}H]alanine enrichment in serum. *t* represents the ^2H_2O incorporation time.

Statistical analyses

All data are expressed as means ± standard deviation (SD) or as frequency and percentages. Baseline characteristics were compared between groups using independent samples t-tests (for continuous variables) or chi-square tests (for categorical variables). Physical activity and dietary intake data were compared between groups using independent samples t-tests. Internal consistency between accelerometer and pedometer-derived average step count was assessed with Cronbach's alpha. Tissue-specific protein synthesis rates, expressed as fractional synthesis rates (FSR, %·day^{-1}), were compared between groups using independent samples t-tests for *vastus lateralis* muscle samples, prostate tissue and prostate tumor tissue. For explorative purposes, FSR values were compared between the different tissues using repeated measures ANOVA with tissue as within subject factor and group as between subject factor. Statistical significance was set at $P<0.05$. All analyses were performed using IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY).

Results

Thirty prostate cancer patients scheduled for a radical prostatectomy with curative intent because of proven localised intermediate to high risk prostate cancer were included in the study. Patients' characteristics are presented in **Table 1.** Patients were on average 66±5 y old and were slightly overweight (BMI 27.4±2.9 kg·m^{-2}). All prostate tumors were histopathological classified as adenocarcinomas with 90% graded as ISUP (International Society of Urological Pathology) 2 or 3. No differences were observed between the low and high physical activity group.

Table 1 Patients' characteristics

	Patients (*n*=30)
Age (y)	66 ± 5
Height (m)	1.77 ± 0.06
Weight (kg)	85.5 ± 10.6
BMI (kg·m^{-2})	27.4 ± 2.9
PSA, pre operative	7.8 ± 3.3
Histopathological diagnosis	
Adenocarcinoma	30 (100)
Other	0 0
Gleason Score	
7	27 (90.0)
8	1 (3.3)
9	2 (6.7)
Grade group (ISUP)	
2	16 (53.3)
3	11 (36.7)
4	1 (3.3)
5	2 (6.7)

Values are mean ± SD, or number and (%) of patients. BMI, body mass index; PSA, prostate-specific antigen; ISUP, International Society of Urological Pathology.

Physical activity

The physical activity intervention was successful (**Figure 3**), with an average daily step count of 3610±878 and 17589±4680 performed in the low and high physical activity group, respectively (P<0.001). Self-reported pedometer-derived step count was 3477±905 and 17127±4725 steps per day, respectively (P<0.001), and strongly correlated with the accelerometer-derived data (Cronbach's alpha=0.972).

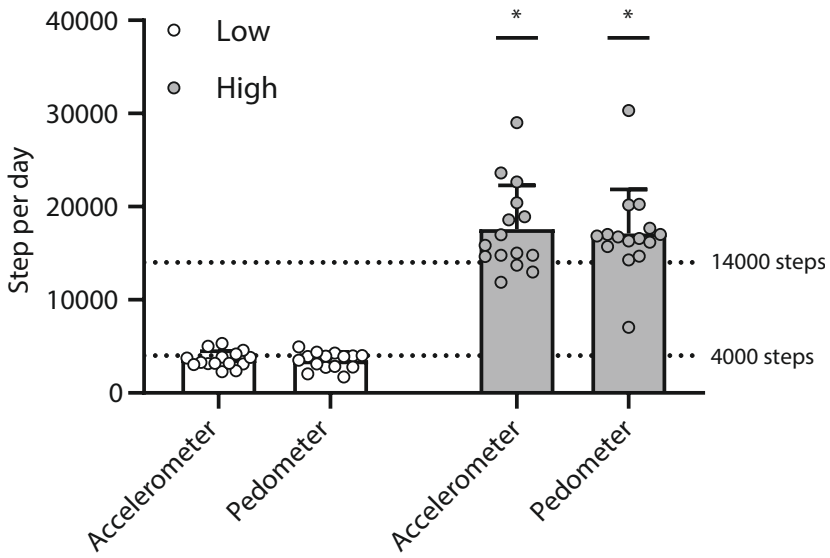

Figure 3 Average daily step count as derived with the accelerometers and with the pedometers. *Significantly different from average daily step count in the low habitual physical activity group. Low, low physical activity group; High, high physical activity group.

Dietary intake

Dietary intake data during the intervention are presented in **Table 2**. Due to apparent underreporting the data from one patient were excluded from analyses. Energy intake was higher in the high compared to the low physical activity group (10.7±1.6 and 9.1±1.4 MJ·day-^{1}, respectively, P=0.008). Energy intake was for 17±3% provided by protein, 41±9% by carbohydrate and 36±6% by fat, with no differences between groups. Daily protein intake was not different between groups and averaged 1.1±0.3 and 1.2±0.3 g·kg body weight·day-1 in the low and high physical activity group, respectively.

Table 2 Interventional dietary intake

	Without outlier		All patients		Between group difference (*P*-value)	
	n	**Mean ± SD**	***n***	**Mean ± SD**	**Without outlier**	**All patients**
Energy intake ($MJ \cdot day^{-1}$)					0.008	0.078
Low	15	9.1 ± 1.4	15	9.1 ± 1.4		
High	14	10.7 ± 1.6	15	10.3 ± 2.2		
Protein intake ($g \cdot kg\ BW^{-1} \cdot day^{-1}$)					0.285	0.461
Low	15	1.1 ± 0.3	15	1.1 ± 0.3		
High	14	1.2 ± 0.3	15	1.2 ± 0.4		
Protein intake (% of energy)					0.502	0.527
Low	15	17.4 ± 3.3	15	17.4 ± 3.3		
High	14	16.5 ± 3.3	15	16.6 ± 3.2		
Carbohydrate intake (% of energy)					0.081	0.062
Low	15	43.4 ± 8.3	15	43.4 ± 8.3		
High	14	37.6 ± 8.9	15	37.4 ± 8.6		
Fat intake (% of energy)					0.109	0.081
Low	15	34.4 ± 7.7	15	34.4 ± 7.7		
High	14	38.2 ± 4.0	15	38.5 ± 4.1		

Values are mean ± SD. Low, low physical activity group; High, high physical activity group; BW, body weight.

Precursor pool

After completion of the $^{2}H_{2}O$-dosing protocol (day 1), body water deuterium enrichment reached 0.57±0.07 and 0.56±0.07% in the low and high physical activity group, respectively. Over the study period, body water enrichment slightly increased and averaged 0.67±0.07 and 0.65±0.07% in the low and high physical activity group, respectively. Body water enrichment resulted in a serum free [^{2}H]alanine enrichment of 3.01±0.33 and 2.96±0.38 mole percent excess (MPE) on the day of surgery (day 8) in the low and high physical activity group, respectively. No differences between groups were found for body water or serum free enrichments.

Tissue protein synthesis rates

Following protein extraction, tissue protein synthesis rates were assessed (**Figure 4**). In *vastus lateralis* muscle tissue, protein synthesis rates averaged 1.47±0.21 and 1.42±0.16%·day^{-1} in the low and high physical activity group, respectively. In healthy prostate tissue, protein synthesis rates averaged 2.74±0.70 and 2.64±0.58%·day^{-1}, respectively. In prostate tumor tissue, protein synthesis rates averaged 4.76±1.23 and 4.72±0.80%·day^{-1}, respectively. **Table 3** presents the tissue protein synthesis rates calculated with body water enrichment and with serum free [^{2}H] alanine enrichment as precursor pool. For both methods, no differences in muscle, healthy prostate, or prostate tumor tissue protein synthesis rates were observed between groups. For explorative purposes, protein synthesis rates of different tissues were compared, only showing a main effect of tissue. Protein synthesis rates in prostate tumor tissue were 1.9±0.6 and 3.3±0.8 times higher than protein synthesis rates in healthy prostate tissue and skeletal muscle tissue, respectively (both P<0.001).

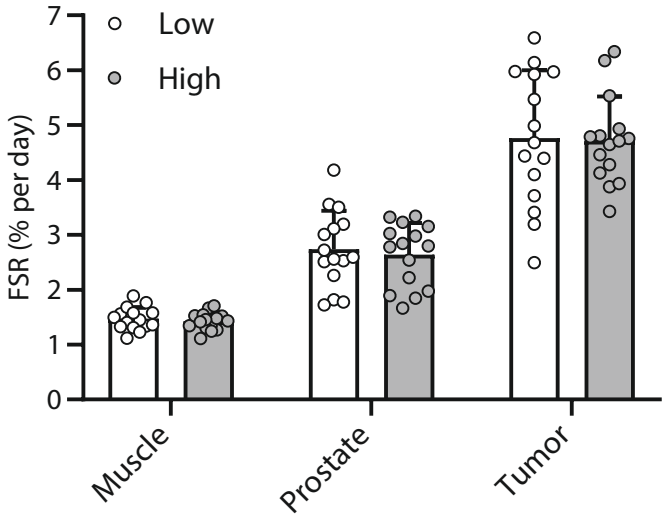

Figure 4 Tissue protein synthesis rates of vastus lateralis muscle, healthy prostate, and prostate tumor tissue, calculated with body water deuterium enrichments. No differences between groups were found. Protein synthesis rates of healthy prostate tissue were 1.9-fold higher than muscle protein synthesis rates (P<0.001). Protein synthesis rates of prostate tumor tissue, were 1.9-fold higher than healthy prostate protein synthesis rates (P<0.001) and 3.3-fold higher than skeletal muscle protein synthesis rates (P<0.001). FSR, fractional synthetic rate; Low, low physical activity group; High, high physical activity group.

Table 3 Tissue-specific protein synthesis rates

		Saliva	Serum	Between group differences (*P*-value)	
	n	**Mean ± SD**	**Mean ± SD**	**Saliva**	**Serum**
Muscle FSR (%·day^{-1})					
Low	15	1.47 ± 0.21	1.21 ± 0.17	0.484	0.379
High	15	1.42 ± 0.16	1.16 ± 0.10		
Total	30	1.45 ± 0.18	1.19 ± 0.14		
Prostate FSR (%·day^{-1})					
Low	15	2.74 ± 0.70	2.25 ± 0.60	0.685	0.623
High	15	2.64 ± 0.58	2.16 ± 0.46		
Total	30	2.69 ± 0.63	2.20 ± 0.52		
Prostate tumor FSR (%·day^{-1})					
Low	15	4.76 ± 1.23	3.89 ± 0.97	0.905	0.885
High	15	4.72 ± 0.80	3.85 ± 0.55		
Total	30	4.74 ± 1.02	3.87 ± 0.77		

Values are mean ± SD. The columns 'Saliva' and 'Serum' presents the tissue-specific protein synthesis rates as calculated with body water enrichment respectively serum free [^{2}H]alanine enrichment as precursor pool. FSR, fractional synthetic rate; Low, low physical activity group; High, high physical activity group.

Discussion

In the present study, we observed that physical activity levels (i.e., <4000 vs > 14000 steps per day during 1 week in the low and high activity group, respectively) did not modulate muscle, healthy prostate, or prostate tumor tissue protein synthesis rates. Furthermore, we showed that prostate tumor tissue protein synthesis rates are nearly twofold higher when compared to prostate tissue protein synthesis rates.

Following $^{2}H_{2}O$ loading, we successfully subjected patients to a low or high daily physical activity level for seven days prior to prostate tumor resection. We aimed to decrease daily step count to less than 4000 steps or to increase it to more than 14000 steps. Our intervention was successful with an average of 3610±878 and 17589±4680 steps made per day in the low and high activity group, respectively (**Figure 3**). As a reference, healthy people aged 50-94 y perform between 2000 to 9000 steps per day, with men being generally more active than women and activity levels declining with more advanced ages (39). The 4000 steps per day in the present study represents a more sedentary lifestyle, while 14000 steps per day is well above the normal physical activity level of our population. The greater activity level did not result in higher muscle protein synthesis rates, with averages of 1.47±0.21 and 1.42±0.16% per day in the low and high activity group, respectively. This seems to be in contrast with previous studies, showing robust changes in daily muscle protein synthesis rates following changes in physical activity level (20-22). However, in these previous studies changes in physical activity were much greater, with the application of: resistance-type exercise training (24% higher muscle protein synthesis rates in exercised compared to non-exercised leg) (20), limb immobilisation (36% lower muscle protein synthesis rates in immobilized compared to control leg) (22), or a severe step reduction protocol of >90% to on average <1200 steps per day (27% lower muscle protein synthesis rates during step reduction) (21). It could be speculated that the physical activity intervention implemented in the present study was insufficient to modulate translational signaling involved in the regulation of muscle protein synthesis rates. In line, no differences in protein synthesis rates were found between the low and high activity group for healthy prostate (2.74±0.70 and 2.64±0.58% per day, respectively) and prostate tumor (4.76±1.23 and 4.72±0.80% per day, respectively) tissue. Despite compelling pre-clinical data on the tumor-growth inhibiting effects of increasing physical activity level, our data indicate that a short-term low or high physical activity level does not directly modulate tumor protein synthesis rates. The possibility exists that more intense exercise applied over a more prolonged period is required to elicit tumor-growth inhibiting effects, by for example modulating hormonal/growth factors (17), release of myokines (12), improved immune function (17), and changes in tumor vascularization (18). Furthermore, the potential inhibitory effects of exercise on prostate and prostate tumor protein synthesis rates could have been offset by the accompanying higher daily energy intake in the high vs the low physical activity group (**Table 2**). However, this is speculative as we are still unaware of clinical evidence of the impact of energy intake and physical activity patterns on protein balance in healthy organ tissue and tumor tissues.

Despite the fact that a short-term low or high physical activity level does not seem to modulate prostate or prostate tumor protein synthesis rates, our findings provide novel insights into prostate and protate tumor metabolism. As far as we know, there are no data available on prostate and / or prostate tumor protein synthesis rates *in vivo*.

Prostate tumor protein synthesis rates were 1.9±0.6 fold higher when compared to protein synthesis rates of the surrounding healthy prostate tissue. Though the higher protein synthesis rates in prostate tumor versus healthy prostate tissue could suggest that there is net tumor tissue accretion, this is not *per se* the case. Tissue protein accretion is determined by the dynamic balance between tissue protein synthesis and breakdown rates. Interestingly, findings from other studies show that tumor protein synthesis rates are not typically higher than protein synthesis rates of the organ tissue in which the tumor is embedded. For example, we have previously reported lower protein synthesis rates in pancreatic tumor tissue when compared with healthy pancreatic tissue (19). Studies in gastrointestinal and colorectal cancers however, showed higher FSRs in the cancerous tissue compared to the corresponding healthy tissue (40, 41).

The apparent difference between healthy prostate and prostate tumor protein synthesis rates may provide us with indications for preferred intervention strategies to reduce tumor tissue accretion, e.g. to intervene on the molecular pathways of tumour tissue synthesis or breakdown. For example, the higher protein synthesis rates in prostate tumor than in healthy prostate tissue, could indicate that interventions (like physical activity, nutritional or pharmacological interventions) should focus on inhibiting tumor protein synthesis. This directly highlights the potential of the $^{2}H_{2}O$-methodology as applied in this study. It enables us to assess protein synthesis rates in cancerous and non-cancerous tissue, as well as the effect of several interventions on tumor protein synthesis rates *in vivo* in free-living patients.

There is repeated discussion about the influence of changes in physical activity on tumor metabolism. However, as we did not measure baseline physical activity levels, our data do not allow to draw conclusions over the effect of a change in physical activity. A second limitation is the lack of data on dietary intake at baseline. As a consequence, it was not possible to verify whether dietary intake had changed during the intervention period.

In conclusion, a short-term low or high physical activity level does not influence prostate tumor protein synthesis rates. More studies on the efficacy of short and long-term exercise interventions to lower tumor protein synthesis rates and attenuate tumor progression are warranted to understand the impact of lifestyle as an adjuvant therapy in the prevention and treatment of cancer.

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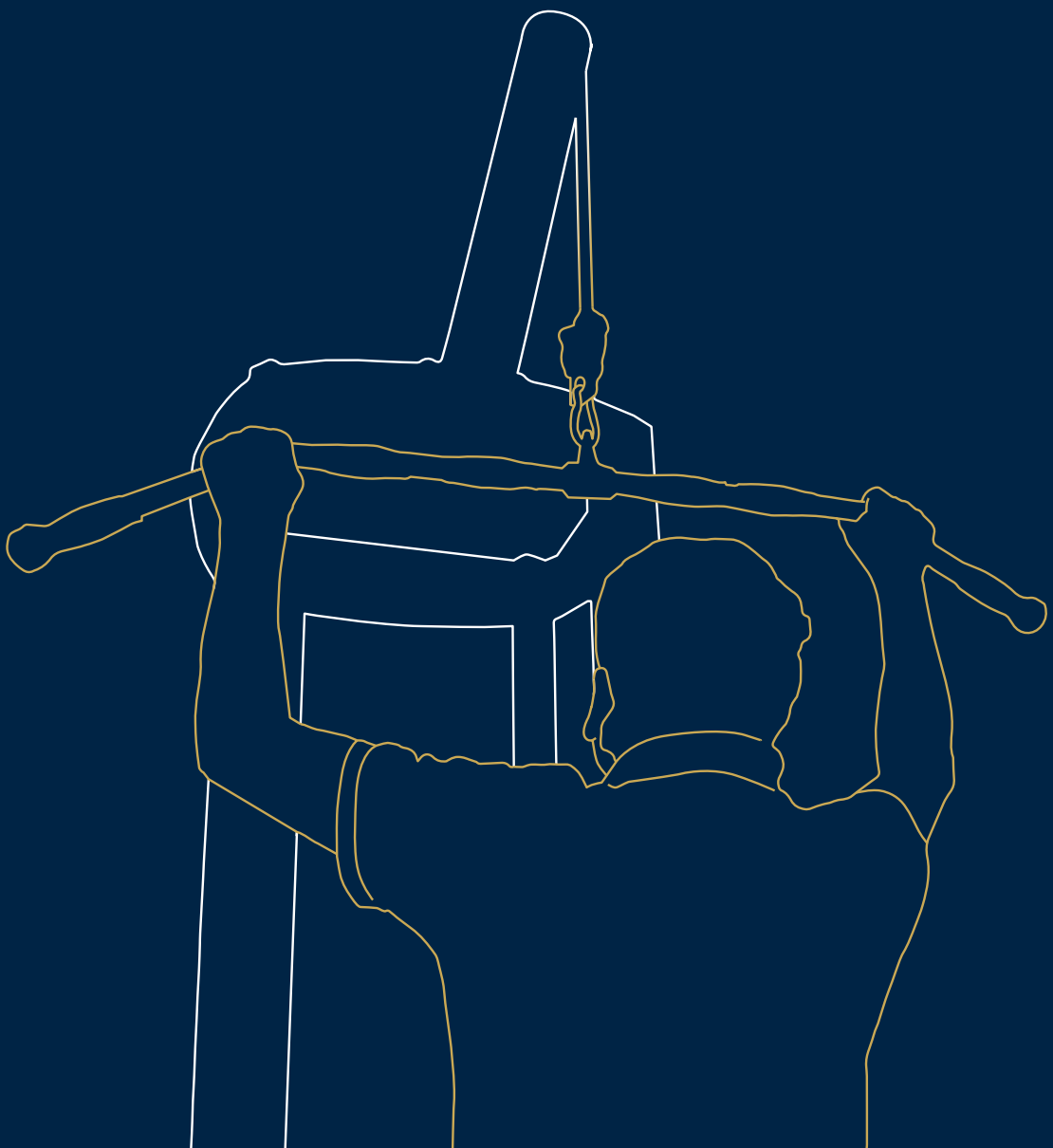

CHAPTER 8

General discussion

Importance of resistance exercise training during androgen deprivation therapy for prostate cancer

In this thesis, we examined the effects of resistance exercise training in prostate cancer patients on androgen deprivation therapy (ADT). ADT is an important treatment option in (locally) advanced prostate cancer, and can substantially improve survival. However, the decline in androgen levels results in numerous adverse effects, including loss of muscle mass, gain of fat mass, and a decline in both functional and metabolic health (**chapter 3**). We showed that resistance exercise training during ADT was capable of preventing many of these adverse effects. Moreover, resistance exercise training was even able to increase muscle mass and muscle strength despite the decline in circulating androgen levels. In addition, resistance exercise training attenuated the increase in fat mass and the decrease in aerobic capacity due to ADT (**chapter 4**). These positive effects strongly support the implementation of resistance exercise training as part of the standard care for prostate cancer patients receiving ADT.

Current clinical practice for prostate cancer patients treated with ADT

In the Dutch guidelines for the treatment of prostate cancer (1), ADT is indicated as the treatment of first choice in metastatic disease, and as treatment option in locally advanced disease. The guideline pays some attention to some ADT-related adverse effects, but hardly any attention to the adverse effects on body composition or skeletal muscle function. In the guideline, only the section on non-metastatic bone fractures describes that "*Obesity and sarcopenia are common adverse effects that occur soon after initiation of ADT. A 10% increase in fat mass and a decrease of up to 3% in 'tissue' mass is observed. Both changes can contribute to an increased risk of bone fractures*". The subsequent impact on physical function is not discussed. Furthermore, the importance of exercise to counteract these side effects, remains underexposed as well. In sections about the side effects on the cardiovascular system, bone health, and lipid and insulin profiles, the guideline mentions that patients should be advised to ensure an adequate physical activity level, and a proper body composition/body mass index, without giving further advice. In addition, in a separate chapter about *'(after)care for ADT*', it is mentioned that ADT might result in an increase of body weight and body mass index of ~2% in the first year, without any advice about (exercise) intervention to prevent this. Accordingly, exercise programs are not presented as part of the standard care for prostate cancer patients on ADT in the Netherlands.

Key elements for an effective exercise training program during ADT

The findings in this thesis strongly advocate the incorporation of resistance exercise training as part of standard prostate cancer care. To optimize patient engagement and effectivity of the program, a couple of conditions need to be fulfilled. First, training sessions should be supervised by a physical therapist, exercise physiologist or fitness trainer with prostate cancer specific expertise. Supervision is important for: a) ensuring correct execution of the exercises and thereby preventing injuries, b) correctly adapting the training load, taking into account the concept of progressive resistance exercise training and the actual health and fitness status of the patient (which can be influenced by factors like adjuvant therapies or complications), c) motivational aspects to achieve optimal commitment, adherence, and effort. Literature confirms

the importance of supervision and shows superior effects for supervised versus unsupervised exercise training interventions (2, 3). Additional to the supervision, patient engagement and enjoyment will be boosted by the implementation of group-based exercise training (4). We also experienced that our group-based training enabled social interaction, increased pleasure and provided unconstrained peer support. A final important factor influencing patient engagement and adherence is the training location (5). Patients prefer a convenient, easily accessible location, and a short travel distance to reach it.

Concerning the exercise prescription, resistance exercise training should form the major component of the program, as we and others clearly demonstrated the substantial impact of resistance exercise training on the increase in muscle mass and strength. Although we also observed an attenuation of both fat mass gains and aerobic capacity declines, the addition of an aerobic exercise component may provide even more pronounced effects on these outcomes (6). In addition, adding an impact-loading component could be considered to counteract the adverse effects of ADT on bone mineral density (7). A frequency of twice weekly training sessions will already be sufficient to induce significant training effects, as shown in our study and by others (8-11). Although more frequently training sessions may (theoretical) further augment the health benefits, this also increases the burden on patients - who often already have many clinical commitments – and may result in compromised compliance and adherence. With regard to the best timing of the program, it is important to realize that both patients starting with ADT as patients already receiving ADT will benefit from exercise training. However, whenever possible it is advised to start training immediately at onset of ADT or even before initiating ADT, in order to prevent the ADT-related side effects.

Finally, for proper exercise training adaptations, an adequate nutritional status is required, with specific attention for protein intake. As we found no surplus benefits of protein supplementation in our study population who already had an adequate protein intake (**chapter 4**), protein supplementation may not be required. However, we do advise screening for nutritional status to identify patients with or at risk for malnutrition and to provide them with nutritional support to achieve optimal nutritional intake with a particular focus on protein intake.

Challenges for implementation

To implement exercise training in standard prostate cancer care, a number of barriers need to be overcome. First, the infrastructure should be created within the current prostate cancer care, with clear descriptions of everyone's responsibilities. Who is going to inform patients, how to ensure that the program is offered to all patients, who is going to guide the exercise training? Related with this, financial, staffing, and practical aspects should be addressed. Health insurance companies should be involved to arrange reimbursements, and staff and facilities are required to perform the training program, which is challenging in a time of increasing burden on healthcare resources and professionals. Additional, patients need to be motivated to participate. During our study, we experienced that part of the patients was intrinsically very motivated to participate. In these patients, only mentioning the possibility to engage in an

exercise training program was enough to involve them. However, for less motivated patients, a clear explanation about the side effects of ADT and the potential of exercise training to prevent or overcome these side effects, will be necessary to convince them to participate. Indeed, many people are not aware of the potential of exercise training to improve health status and negate the adverse effects of ADT.

This last point brings us to a key element for successful implementation: education. Education of healthcare professionals and subsequently patients will ensure that they understand, acknowledge, and advocate the importance of resistance exercise training during ADT. Thereafter, it will be much easier to convince third parties such as insurance companies to release (financial) resources to support more widespread implementation of exercise training in standard care for prostate cancer patients.

Future research

Taken together, exercise training likely forms one of the most effective adjuvant therapies during ADT. To facilitate and optimize exercise implementation, more research is preferred. First of all, research to further elucidate the optimal exercise training program: the ideal combination of the different exercise modalities (resistance-, aerobic-, impact loading-type exercise), the optimal training variables (number of repetition and sets, intensity of exercise, length of intervals) and the potential benefits of other training modalities such as High Intensity Interval Training (HIIT). In addition, a broad focus on long-term sustainability of exercise effects, and strategies to improve sustainability, are warranted. As described in **chapter 6**, patients are not capable to autonomously preserve the gains in muscle mass and strength after cessation of the supervised exercise training program. It would be preferred to continue supervised and structured exercise training programs as long as ADT is being prescribed, but other strategies may proof to be effective to support effective (home-based) exercise training programs with alternative ways of personalized supervision. To reduce the burden on healthcare, the potential for alternative exercise programs should be explored, like hybrid training regimes (partly autonomously, partly supervised), home-based trainings, and the usefulness of support by digital technologies. Next to the efficacy of these different options, the costs should be taken into account as well. Research in cost-efficacy should focus on both short-term and long-term costs and benefits, as it is plausible that an exercise training program saves healthcare costs and/ or costs for society on the long-term by counteracting treatment related adverse effects and optimizing health status.

Conclusions

Implementation of exercise training should be recommended within the standard care for prostate cancer patients on ADT. A supervised resistance exercise training program, offered in small groups on an easily accessible location should be provided to all patients. Resistance exercise training should represent the major component of such an exercise program, with the addition of an aerobic and/or impact-loading component based on personal goals set by the patient and his medical support team. To achieve successful implementation of such and

exercise program in daily routine, education of both healthcare professionals and patients is essential, and ongoing research in this area is strongly encouraged.

The benefits of exercise extend well beyond the prevention of muscle loss in prostate cancer patients on ADT. Exercise provides benefits in the prevention, treatment, and recovery from many medical conditions and can improve functional capacity and overall health in both patients and healthy men and women. Benefits of exercise are evident throughout the entire lifespan, in both health and disease. Therefore, ***exercise is definitely medicine***, and we hope our work contributes to an increased attention for its clinical application.

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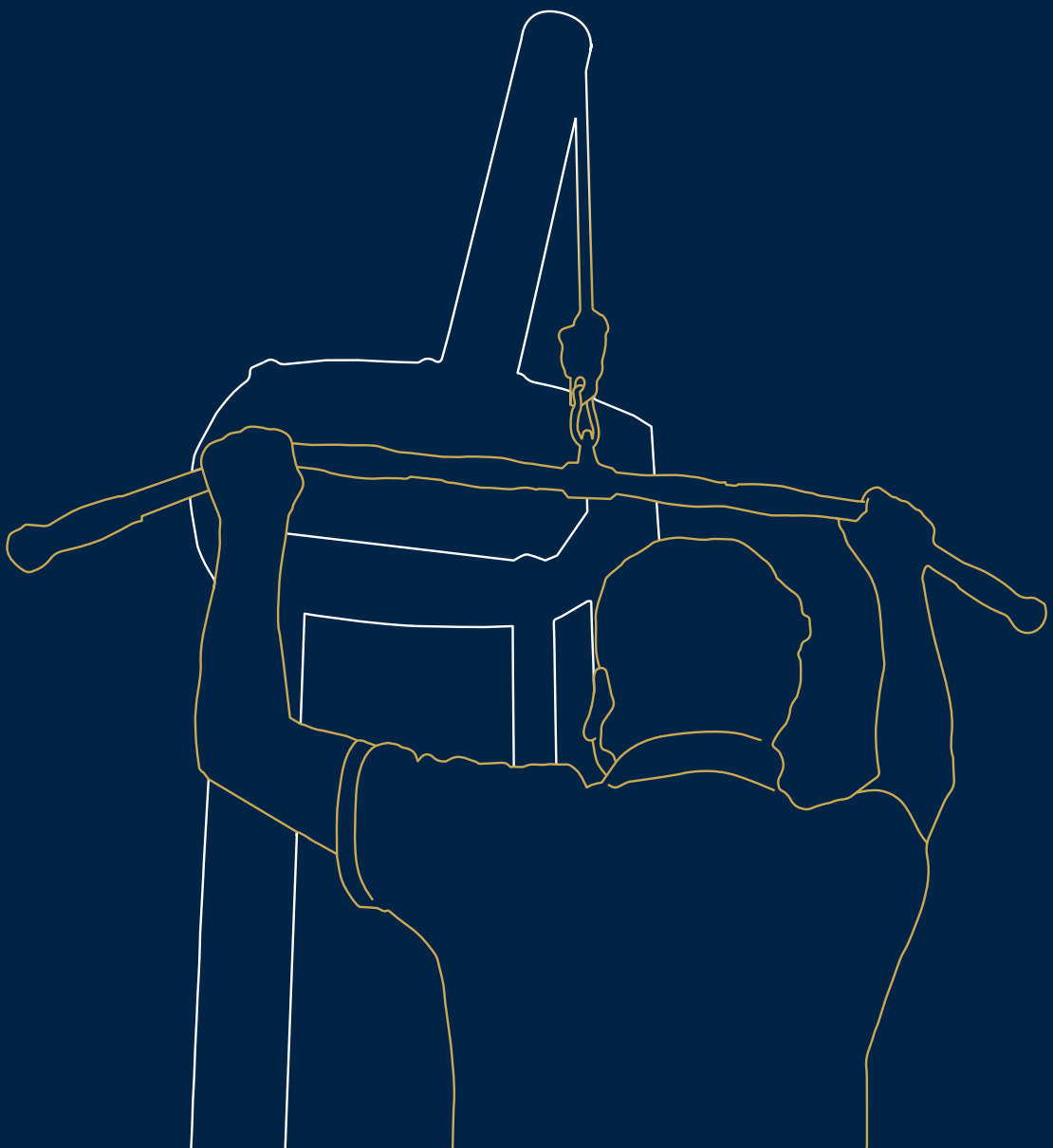

APPENDICES

Summary

Androgen deprivation therapy (ADT) forms the cornerstone in the treatment of advanced prostate cancer (PCa). By suppressing testosterone to castration levels, tumor progression is inhibited. However, ADT also results in adverse effects like a decrease in muscle mass and an increase in fat mass. In **chapter 2**, we elucidate on the working mechanism of ADT during prostate cancer, and its adverse effects on skeletal muscle mass. In addition, resistance exercise training is introduced as potential strategy to combat these adverse effects, including an overview of the literature on this topic. In chapter 3 to chapter 6, we describe de results of our studies on the effects of resistance exercise training, with or without protein supplementation, during ADT. In **chapter 3,** we first assessed the adverse effects of ADT. Initiation of ADT results in increases in body fat mass and insulin levels, and decreases in skeletal muscle mass, muscle strength, aerobic capacity, physical activity and health-related quality of life. In **chapter 4**, the effect of resistance exercise training on these adverse effects is examined. A supervised resistance exercise program of 20 weeks not only preserved, but even increased muscle mass and strength. Furthermore, resistance exercise training attenuated the increase in fat mass and the decline in aerobic capacity. In addition, we examined whether protein supplementation could enhance the effect of the resistance exercise training. We found no additional effect of the protein supplementation, probably because habitual protein intake in our population was already sufficient (>1.0 g per kg body weight per day). In **chapter 5**, we zoomed in on the effects of ADT and resistance exercise training on skeletal muscle fiber characteristics. We found that ADT results in a decrease in type I and type II-muscle fiber size and capillarization. Resistance exercise training, counteracted this decrease and resulted in an increase in type I and type II muscle fiber size and type I muscle fiber capillarization. In **chapter 6,** we examined whether the exercise-obtained benefits were preserved on the long term. For that, we reassessed outcome measures 1 year after study enrollment - about 7 months after cessation of the supervised exercise training intervention. Despite the high percentage of patients (83%) reporting exercise continuation, the obtained effects following supervised exercise training were not well preserved. After 1 year, no differences in fat percentage and muscle mass were found between the former exercise training and control group. For fat mass and muscle strength, still some differences existed in favor of the former exercise trained group.

In **chapter 7**, we shift our focus to exercise training as potential strategy to attenuate tumor progression. For that, we requested prostate cancer patients scheduled for a radical prostatectomy, to pursue a low or high daily step count in the week before surgery. No differences in tissue protein syntheses rates of prostate tumor, healthy prostate, or skeletal muscle tissue were found between the groups with the low and high daily step count. Probably our intervention was either not intense, or not long enough. We did find that the tissue protein synthesis rates were almost twofold higher in prostate tumor tissue when compared to the surrounding healthy prostate tissue.

We conclude this thesis with a discussion about the implications of our study results for clinical practice (**chapter 8**). Given the proven effectivity of resistance exercise training during ADT, we advocate implementation of resistance exercise training as part of the standard prostate cancer care. Therefore, we give advises regarding the training program, discuss challenges, and give suggestions for further research.

Samenvatting

Androgeen deprivatie therapie (ADT) is de hoeksteen in de behandeling van (lokaal) gevorderde prostaatkanker. Door het reduceren van testosteron tot castratieniveau, wordt de tumorprogressie geremd waardoor de overleving verbetert. ADT veroorzaakt echter ook bijwerkingen zoals een afname van spiermassa en een toename van vetmassa. In **hoofdstuk 2** gaan we dieper in op het werkingsmechanisme van ADT bij prostaatkanker en de bijwerkingen op skeletspierweefsel. Tevens wordt in dit hoofdstuk krachttraining geïntroduceerd als mogelijke strategie om deze bijwerkingen tegen te gaan, inclusief een uiteenzetting van de literatuur daarover. In hoofdstuk 3 tot en met hoofdstuk 6 beschrijven we de verschillende resultaten van ons onderzoek naar de effecten van krachttraining, al of niet gecombineerd met eiwitsuppletie, om de bijwerkingen van ADT tegen te gaan. Ten eerste hebben we in **hoofdstuk 3** de bijwerkingen van ADT in kaart gebracht. We vonden dat initiatie van ADT leidt tot toename van lichaamsvetmassa en insulinespiegels, en afname van skeletspiermassa, spierkracht, aerobe capaciteit, fysieke activiteit en gezondheidsgerelateerde kwaliteit van leven. In **hoofdstuk 4** wordt het effect van krachttraining op deze bijwerkingen onderzocht. Een gesuperviseerd krachttrainingsprogramma gedurende 20 weken zorgde ervoor dat spiermassa en spierkracht niet alleen behouden bleven, maar zelfs toenamen. Verder verminderde krachttraining de toename van vetmassa en de afname van aerobe capaciteit. Tevens hebben we bekeken of eiwitsuppletie het effect van de training kon versterken. Dit was niet het geval, mogelijk doordat de patiënten al voldoende eiwit innamen via hun dagelijkse voeding (>1.0 g per kg lichaamsgewicht per dag). In **hoofdstuk 5** hebben we ingezoomd op de effecten van ADT en krachttraining op skeletspiervezelkarakteristieken. Hierbij zagen we dat ADT leidt tot een afname van type-I- en type–II-spiervezelgrootte en -capillarisatie. Krachttraining daarentegen ging deze afname tegen en zorgde zelfs voor een toename van type-I- en type-II-spiervezelgrootte en type-I-spiervezelcapillarisatie. In **hoofdstuk 6** hebben we gekeken in hoeverre de effecten van het trainingsprogramma ook op de lange-termijn behouden blijven. Daartoe hebben we 1 jaar na start van de studie, dus ongeveer 7 maanden na het beëindigen van de gesuperviseerde training, de metingen herhaald. Ondanks het hoge percentage patiënten (83%) die aangaven het sporten zelfstandig te hebben gecontinueerd, bleken de eerder behaalde resultaten niet behouden te zijn. Na 1 jaar werden er geen verschillen meer gevonden in vetpercentage en spiermassa tussen de voormalige trainings- en controlegroep. Voor vetmassa en spierkracht werden nog wel enige verschillen gezien, ten gunste van de voormalige trainingsgroep.

In **hoofdstuk 7** hebben we onze focus verlegd naar beweging als strategie om tumorprogressie te remmen. Daartoe hebben we prostaatkankerpatiënten welke een prostatectomie moesten ondergaan, gevraagd om in de week vooraf aan de operatie, weinig of juist veel stappen te zetten. We vonden geen verschil in de eiwitopbouwsnelheid van prostaattumor-, gezond prostaat- of skeletspierweefsel tussen de groepen met weinig en veel stappen. Mogelijk was onze beweeginterventie niet krachtig of lang genoeg. Wel vonden we dat

de eiwitopbouwsnelheid in prostaattumorweefsel bijna twee keer zo hoog was als in het omliggende gezonde prostaatweefsel.

We sluiten het proefschrift af met het bespreken van de implicaties van ons onderzoek voor de klinische praktijk (**hoofdstuk 8**). Gezien de aangetoonde effectiviteit van krachttraining tijdens ADT, pleiten we ervoor dat krachttraining wordt opgenomen als onderdeel van de reguliere prostaatkankerzorg. Dit is momenteel nog niet het geval. Daarom geven we adviezen ten aanzien van de invulling van een dergelijk programma, bespreken we de uitdagingen die tijdens het implicatieproces zullen moeten worden overwonnen, en geven we suggesties voor verder onderzoek.

Valorization

Prostate cancer is the most frequently diagnosed type of cancer in European men. Due to an increasing incidence and decreasing mortality risk, it is expected that prostate cancer prevalence will further increase the upcoming years (1), resulting in a substantial number of men living with prostate cancer for several years. This puts increasing pressure on the healthcare system and society. Therefore, from the patients', healthcare, and societal perspective, strategies are warranted to prevent prostate cancer and its progression, and to counteract treatment-related adverse effects.

Many patients with prostate cancer will be treated with androgen deprivation therapy (ADT), the cornerstone in advanced prostate cancer treatment. Though ADT can substantially improve survival, it causes serious adverse effects. In our exercise training study, we showed that resistance exercise training effectively counteracts many of these adverse effects. Furthermore, we showed that resistance exercise training is feasible and can be performed safely in this population. As we included a broad range of prostate cancer patients on ADT, including patients with (bone) metastases, our results are representative for actual clinical practice. Therefore, we recommend implementation of resistance exercise training in standard prostate cancer care. To achieve implementation, our results have been or will be published in international, peer-reviewed journals. Furthermore, we started and will continue to inform healthcare professionals about our results at local meetings, conferences and symposia, as well as patients via the prostate cancer patients' organization. An extensive description regarding the preferred implementation of exercise training during ADT, including recommendations, is already provided in the general discussion (**chapter 8**) of this thesis.

Despite the impressive results of the supervised resistance exercise training program, we showed that the exercise-obtained benefits were not effectively preserved after cessation of the program. Although a large number of patients reported exercise continuation, patients were unable to maintain the obtained effects. This is an important finding for science as well as clinical practice, as many studies only evaluate the acute effects of a fixed exercise training intervention, whereas ADT is often prescribed for many years. Our findings highlight the importance of more research to develop more effective and feasible long-term exercise intervention strategies in prostate cancer patients during ADT.

Next to the ability of exercise training to counteract treatment-related side effects, we made a first attempt to elucidate whether physical activity level has the potential to influence prostate cancer progression. Our intervention, one week with a relatively low versus high daily physical activity level, did not result in differences between groups on prostate tumor protein synthesis rates, nor on healthy prostate or skeletal muscle protein synthesis rates. Studies with a more vigorous or longer exercise intervention are possibly required to actually induce an effect. However, our study does provide first insight in tissue protein metabolism of tumor and healthy prostate tissue. In addition, we showed that it is actual possible to assess the effect of a lifestyle

intervention on tumor metabolism in cancer patients outside a laboratory setting. This prompts further research in this interesting, and from many perspectives relevant, area.

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Curriculum Vitae

Lisanne H.P. Houben was born on February 28, 1991 in Meerssen, the Netherlands. In 2009, she completed secondary school with honors at Stella Maris College in Meerssen. In the same year, she started studying Medicine at Maastricht University. In 2010, she was awarded with the Maastricht University Top 3% Award (academic year 2009-2010). In 2012 she obtained her bachelor's degree with honors, followed by her master's degree in 2015. During her study, she already had a special interest for Rehabilitation and Sports Medicine, and attended internships in both fields. After finishing her Medicine study, she worked as a medical doctor (ANIOS) within the Spinal Cord Injury Rehabilitation department at Adelante Zorggroep, Hoensbroek, and continued within the Intensive Care Unit at Zuyderland Medical Centre, Heerlen, to broaden her clinical experience. In 2017, Lisanne started her PhD project at the department of Human Biology at Maastricht University, in collaboration with the Netherlands Comprehensive Cancer Organisation, Utrecht. Here research focused on the effects of exercise and nutrition in oncology patients. More specifically, she studied the adverse effects of androgen deprivation therapy on body composition and physical performance in prostate cancer patients, and the efficacy of resistance exercise training and protein supplementation to counteract these side effects. Additionally, she studied the impact of physical activity levels on prostate tumor tissue synthesis. In 2022 Lisanne was awarded with the runner-up NUTRIM Poster Prize, in 2023 with the VoedingNL Poster Prize for the best scientific poster / pitch, and nominated for the Push braces Prize for Sports Medicine for the best scientific article of 2023.

In 2022, Lisanne returned to the rehabilitation clinical practice, and worked as a medical doctor (ANIOS) within the department of Rehabilitation Medicine at the Sint Maartenskliniek, Nijmegen. In September 2023 she has started her specialty training (AIOS) in Rehabilitation Medicine at the Sint Maartenskliniek.

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Exercise training in prostate cancer patients on androgen deprivation therapy

Lisanne H.P. Houben | 2024