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SCHOLARLY REVIEW

Resistance Exercise Training, a Simple Intervention to Preserve Muscle Mass and Strength in Prostate Cancer Patients on Androgen Deprivation Therapy

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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.

Keywords: strength training, hormonal therapy, lean body mass

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 (Cancer Today, n.d.). The high incidence of prostate cancer has been attributed to a combination of improved diagnostics and the aging of the population, with advanced age being a well-established risk factor for the development of prostate cancer (Rawla, 2019). Below the age of 50 years, 1.2 per 100.000 men are diagnoses with prostate cancer, while the incidence rate increases to 568 per 100.000 in European men aged 65 years and older (Cancer Today, n.d.). 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 (Cancer Today, n.d.); therefore, a substantial number of (older) men are living with prostate cancer (Rawla, 2019). 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 (Mottet et al., 2021). In metastatic disease, ADT is the first-line treatment, often combined with chemotherapy (Cornford et al., 2021).

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 (Huggins & Hodges, 1941). However, androgens also play key roles in maintaining skeletal muscle mass. As a result, ADT results in an accelerated loss of muscle mass (Haseen et al., 2010). This is accompanied by an increase in fat mass (Haseen et al., 2010), a reduction in insulin sensitivity (Smith et al., 2006), and an increased risk of developing diabetes (Wang et al., 2016) and cardiovascular disorders (Edmunds et al., 2020).

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 (Chodzko-Zajko et al., 2009), forms an established intervention to increase muscle mass and strength, and improve physical performance in older adults suffering from sarcopenia (Beckwée et al., 2019).

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 strove to include all relevant randomized controlled trials (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 ADT

Mechanism of Action of Androgens and ADT in Prostate Cancer

Prostate cancer is an androgen-dependent disease. Androgens, with testosterone as the major androgen, exert vital roles in normal

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prostate development and homeostasis via androgen receptor (AR) signaling (Zhou et al., 2015). However, when prostate cells mutate to cancerous cells, the role of AR signaling shifts from promoting cell differentiation to uncontrolled cell proliferation (Zhou et al., 2015). Interruption of the AR signaling pathway by either surgical (orchiectomy) or pharmaceutical interventions (ADT) impairs further tumor proliferation (Shafi et al., 2013). ADT may be comprised of anti-androgens and/or luteinizing hormone-releasing hormone (LHRH) analogs. Anti-androgens block the effect of androgens on a cellular level by competitively binding to the AR, and are used usually concomitantly with LHRH agonist (often temporary, to suppress the initial surge of testosterone) (Crawford et al., 2019). LHRH analogs affect the levels of circulating androgens by suppressing the hypothalamic–pituitary–gonadal axis, resulting in an inhibition of testicular testosterone production (Crawford et al., 2019). 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 (Crawford et al., 2019). As a result, serum testosterone reaches castration levels within 2–4 weeks after initiation of ADT (Klotz et al., 2008). 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 (Klotz et al., 2008). For more extensive information about the working mechanism of the different kinds of ADT, we refer to the review of Crawford et al. (2019).

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 (Saad et al., 2017). 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 (MacLean et al., 2008; Rana et al., 2014). In addition, testosterone induces nongenomic signaling pathways. Nongenomic signaling occurs independently of nuclear receptors and subsequent transcriptional responses, requires constant presence of androgens to maintain intracellular signaling, and occurs much faster than genomic signaling (within seconds to minutes instead of hours; Kraemer et al., 2020). Several nongenomic pathways have been described, among pathways increasing intracellular calcium concentrations (important for contractile properties) and activation of mammalian target of rapamycin pathway signaling (central link for the development of muscle hypertrophy; Basualto-Alarcón et al., 2013; Dent et al., 2012; Kraemer et al., 2020). It has been suggested that the crosstalk between genomic and nongenomic signaling is important for an orchestrated cellular response induced by testosterone (Basualto-Alarcón et al., 2013; Kraemer et al., 2020). Furthermore, testosterone might promote the differentiation of pluripotent stem cells toward the myogenic lineage instead of the adipogenic lineage (Herbst & Bhasin, 2004; Singh et al., 2003) and, as such, induce hypertrophy by increasing satellite cell number and myonuclear number (Herbst & Bhasin, 2004; Sinha-Hikim et al., 2003). Testosterone deficiency, on the other hand, results in the loss of muscle mass (Herbst & Bhasin, 2004). Testosterone deficiency is supposed to induce an imbalance between muscle protein breakdown and muscle protein synthesis pathways (Rossetti et al., 2017). Furthermore, testosterone deficiency potentially promotes differentiation of mesenchymal stem cells to adipocytes instead of myocytes (Singh et al., 2003).

Impact of ADT 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 36–52 weeks have shown decreases in lean body mass (LBM), a surrogate for muscle mass, ranging between 1.9% and 3.8% in prostate cancer patients on ADT (Berruti et al., 2002; Galvão et al., 2008; Østergren et al., 2019; Smith, 2004; Smith et al., 2002). The loss of LBM seems to start rapidly after initiation of ADT. After 3 months of ADT treatment, a significant decline in LBM has been observed (Smith et al., 2001). 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 1–1.5 years of ADT treatment. In the following 1–2 years the decline continued, but the rate at which this occurred was substantially lower (Smith et al., 2012; van Londen et al., 2008). In addition, Londen et al. showed that the loss of muscle 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 for a long time it has been recognized that aging can be accompanied by skeletal muscle mass loss. When severe, this can eventually result in sarcopenia, defined as a progressive and generalized skeletal muscle disorder that involves the accelerated loss of muscle mass and function. However, besides aging, it is nowadays recognized that many other causes can contribute to sarcopenia, like malnutrition, inactivity, diseases, and iatrogenic factors like drugs (e.g., ADT; Cruz-Jentoft & Sayer, 2019). Therefore, differentiating the relation between ADT-related muscle loss and sarcopenia—for example, to explore the impact of ADT on the occurrence and exacerbating of sarcopenia—receives more and more attention (Couderc et al., 2020, 2022; Owen et al., 2019).

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 (Beaudart et al., 2019). 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 (Beaudart et al., 2019).

Upper body muscle strength indeed seems to decrease during ADT. Two cross-sectional studies assessed strength by 1-repetition maximum (1-RM) measurements in prostate cancer patients on ADT, and compared this with age-matched control subjects (Basaria et al., 2002; Galvão et al., 2009). 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 (Galvão et al., 2009), for leg press 1-RM no differences between groups

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were observed (Basaria et al., 2002; Galvão et al., 2009). Results for handgrip strength have been inconsistent as well. Some studies found a decline in handgrip strength in patients on ADT (Alibhai et al., 2015; Girard et al., 2014; Gonzalez et al., 2016; Soyupek et al., 2008), while others failed to observe changes (Joly et al., 2006; Stone et al., 2000).

Patients on ADT subjectively experience a deterioration of their physical performance (Alibhai et al., 2010), 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, while others did not find differences (Alibhai et al., 2010; Bylow et al., 2011; Clay et al., 2007; Galvão et al., 2009; Gonzalez et al., 2016; Joly et al., 2006; Levy et al., 2008).

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 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 (Cruz-Jentoft & Sayer, 2019), and can even increase muscle mass (Peterson et al., 2011), muscle strength (Peterson et al., 2010), and physical performance (Beckwée et al., 2019). 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 whether RET can be (as) effective during ADT.

As previously discussed, 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 (Vingren et al., 2010). Testosterone administration in men with normal testosterone levels (eugonadal) has indeed been shown to increase muscle protein synthesis rates (Ferrando et al., 1998; Griggs et al., 1989). In line, testosterone replacement therapy in hypogonadal (older) men has been reported to increase muscle protein synthesis rates and augment muscle mass (Ferrando et al., 2002; Tenover, 1992; Urban et al., 1995). Following resistance exercise, testosterone is often considered the primary anabolic hormone for muscle adaptation (Gharahdaghi et al., 2020; Vingren et al., 2010). 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 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" versus "low" postexercise elevation in anabolic hormone concentration on the muscle adaptive response. They found no relation between the postexercise increases of any systemic anabolic hormone including testosterone, and changes in muscle protein synthesis rates or gains in muscle mass or strength (Morton et al., 2016; West et al., 2009, 2010). 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 (Hansen et al., 2001).

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, LBM and muscle strength after 10 weeks (Mauras et al., 1998). Furthermore, during RET, testosterone deprivation blocked the acute, postexercise rise in serum testosterone, prevented gains in muscle strength, and attenuated increases in lean mass, compared with the control group without testosterone deprivation (Kvorning et al., 2006, 2007). In agreement, in prostate cancer patients on ADT a reduction of basal muscle protein synthesis rates by 39% compared with healthy age-matched control subjects has been found (Hanson et al., 2017). 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 (Hanson et al., 2017). 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 ADT

For this review, RCTs examining the effects of a supervised exercise training intervention with a RET-component and with no other nonexercise 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., if two articles reported results based on the same primary study, this result was incorporated only once). Up to November 2022, nine RCTs matched these criteria (Alberga et al., 2012; Cormie et al., 2015; Galvão et al., 2010; Ndjavera et al., 2020; Newton et al., 2019, 2020; Nilsen et al., 2015; Segal et al., 2003; Winters-Stone, Dieckmann, et al., 2015; Winters-Stone, Dobek, et al., 2015). Four RCTs performed RET (Alberga et al., 2012; Nilsen et al., 2015; Segal et al., 2003; Winters-Stone, Dieckmann, et al., 2015; Winters-Stone, Dobek, et al., 2015). 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 (Alberga et al., 2012). Furthermore, four studies offered a combined resistance and aerobic exercise training program (Cormie et al., 2015; Galvão et al., 2010; Ndjavera et al., 2020; Newton et al., 2020). Finally, one study had a three-armed design with a resistance exercise arm, a combined resistance plus aerobic exercise arm, and a control group (Newton et al., 2019). More information about the study characteristics, including the exercise training programs, are summarized in Table 1.

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Table 1 Characteristics of the Included Studies

	Patient details	ADT treatment	Study intervention
RET 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; 3× per week 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; CON 111 ± 136 days Other treatments: All RTx	EX: RE, all sessions supervised, machine-based, whole body, progressive CON: Asked to maintain prestudy physical activity level and to not initiate exercise Duration and frequency: 24 weeks; 3× per week Training adherence[b]: 88% (median of completed sessions)
Winters-Stone, Dieckmann, 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, two of three sessions supervised. RE: Free weights (supervised) or resistance bands (home exercises); multijoint exercises which emphasized movements common to activities of daily living. IL: 50× two-footed jumps CON: Stretching and relaxation exercises Duration and frequency: 12 months; 3× per week 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 neoadjuvant ADT, and this RTx was followed by adjuvant ADT	EX: RE, two of three sessions supervised, machine-based, whole body, progressive CON: Encouraged to maintain habitual activity level and to not initiating RE Duration and frequency: 16 weeks; 3× per week Training adherence: 88% for lower body exercises, 84% for upper body exercises (excluding one outlier of 31%; average proportion of completed exercises)
RET 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 analog) 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: a. RE + IL, 2× per week supervised RE + IL and 2× per week home-based IL b. RE + AE, 2× per week supervised RE + AE AND encouraged to undertake home-based AE to accumulate 150 min per week 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)

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Table 1 *(continued)*

	Patient details	ADT treatment	Study intervention
Combined resistance and aerobic exercise training			
Galvão 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 analog) 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; 2× per week Training adherence: 94% (average completed exercise sessions)
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; 2× per week 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 2× AE + I and 1× RE + I, next week 2× RE + IL and 1× 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 3.4–5.2× body weight. Additional encouraged to 2× per week home-based training of AE (walking and cycling) and modified version of IL CON: Usual care Duration and frequency: 6 months, 3× per week (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 and 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: Six 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 3× per week. CON: Usual care. Duration and frequency: 12 weeks; 2× per week (followed by 12 weeks home-based training; data not included in this review) Training adherence: ≥70% (completed exercise sessions)

Note. Values are presented as mean ± *SD*, *n* of patients, or percentage of patients. AE = adverse events; 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; RET = resistance exercise training; RM = repetition maximum; RTx = radiation therapy; VO_2max = maximal oxygen uptake.

[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.

Muscle Mass

Six of the included studies examined LBM by dual-energy X-ray absorptiometry scans (Alberga et al., 2012; Cormie et al., 2015; Galvão et al., 2010; Newton et al., 2019; Nilsen et al., 2015; Winters-Stone, Dieckmann, et al., 2015; Table 2). For appendicular LBM, positive exercise effects were found with adjusted differences of 0.3–0.8 kg between the exercise and control group (Cormie et al., 2015; Galvão et al., 2010; Newton et al., 2019;

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Table 2 Results of the Included Studies for Muscle Mass, Muscle Strength, and Physical Performances

	Muscle mass	Muscle strength	Physical performances
RET only			
Segal et al. (2003)	N.A.	↑ 1RM LP (EX + 11.8, CON −1.6 kg; $p < .001$)[a] ↑ 1RM CP (EX + 13.1, CON −2.6 kg; $p = .009$)[a]	N.A.
Alberga et al. (2012)[b]	↑ Total LBM (2.76 kg; $p = .005$)	↑ 8RM LE (+23.3; $p = .001$) ↑ 8RM BP (+14.1; $p < .001$)	N.A.
Winters-Stone, Dieckmann, et al. (2015) Winters-Stone, Dobek et al. (2015)	↔ Total LBM	↑ 1RM LP ($p = .01$,[c] $p = .03$[d]) ↑ 1RM BP ($p = .03$,[c] $p = .01$[d])	(↑) 5-time sit-to-stand test ($p = .09$[c], $p = .07$[d]) 4-m usual walk speed ($p = .37$[c], $p = .97$[d]) 4-m fast walk speed ($p = .31$[c], $p = .13$[d]) ↑ Self-reported physical function (EORTC QLQC30; $p < .01$)[c,d]
Nilsen et al. (2015)	↔ Total LBM ↑ LBM lower extremities (+0.49 kg; $p = .002$)[e] ↑ LBM upper extremities (+0.15 kg; $p < .05$)[e] ↑ Appendicular LBM (+0.64 kg; $p = .001$)[e]	↑ 1RM LP (+42 kg; $p < .001$)[e] ↑ 1RM CP (+6 kg; $p < .001$)[e] ↑ 1RM SP (+5 kg; $p < .001$)[e]	↑ = 30-s chair stand test (+2 reps; $p < .001$)[e] ↑ Stair climbing test, loaded (−0.27 s; $p = .024$)[e] ↑ Stair climbing tests, unloaded (−0.23 kg; $p = .047$)[e] (↑) Shuttle walk test (+39 m; $p = .064$)[e]
RET only + combined resistance and aerobic exercise training			
Newton et al. (2019)	RE + IL vs. CON: ↔ LBM ↑Appendicular LBM (+0.3 kg; $p = .045$) RE + AE vs. CON: ↔ LBM ↔ Appendicular LBM	RE + IL vs. CON: ↑ 1RM LP (+12.7 kg; $p = .012$) ↑ 1RM LE (+7.9 kg; $p < .001$) ↑ 1RM CP (+3.4 kg; $p = .003$) ↑ 1RM SR (+6.1; $p < .001$) RE + AE vs. CON: ↑ 1RM LP (+18.6 kg; $p = .001$) ↑ 1RM LE (+7.9 kg; $p < .001$) ↑ 1RM CP (+3.2 kg; $p = .002$) ↑ 1RM SR (+5.5; $p < .001$)	N.A.
Combined resistance and aerobic exercise training			
Galvão et al. (2010)	↑ Total LBM (+0.76 kg; $p = .047$) ↑ Upper limb LBM (+0.26 kg; $p < .01$) ↑ Lower limb LBM (+0.54 kg; $p = .019$) ↑ Appendicular LBM (+0.80 kg; $p = .03$)	↑ 1RM LP (+30.8 kg; $p < .001$) ↑ 1RM LE (+11.5 kg; $p < .001$) ↑ 1RM CP (+2.8 kg; $p = .018$) ↑ 1RM SR (+ 5.1 kg; $p < .001$)	↑ 6-m usual walk test (−0.31 s; $p = .024$) ↑ 6-m backward walk test (−4.1 s; $p = .039$) (↑) 5-time sit-to-stand test (−1.0 s; $p = .074$) (↑) 400-m walk test (−7.0 s; $p = .080$) ↔ 6-m fast walk test
Cormie et al. (2015)	(↑) Total LBM (+0.7 kg; $p = .078$) ↑ Appendicular LBM (+0.4 kg; $p = .019$)	↑ 1RM LP (+25.9 kg; $p < .001$) ↑ 1RM CP (+4.8 kg; $p = .004$) ↑ 1RM SR (+4.0 kg; $p = .026$)	↑ 5-time sit-to-stand test (−1.1 s; $p < .001$) ↔ Stair climb test ↔ 6-m walk (usual and fast pace)
Newton et al. (2020)	N.A.	↑ 1RM LP (+19.9 kg, $p < .001$) ↑ 1RM CP (+4.3 kg; $p < .001$) ↑ 1RM SR (+5.6 kg, $p < .001$)	↑ 5-time sit-to-stand test (−1.0 s; $p < .001$) ↑ Stair climb test (−0.4 s: $p < .001$) ↑ 6-m fast walk test (−0.2 s; $p < .001$) ↑ 400-m walk test (−9.7 s; $p < .001$) ↔ 6-m usual walk test ↔ 6-m backward tandem walk test
Ndjavera et al. (2020)	↔ Fat-free mass[f]	↔ Handgrip strength	N.A.

Note. Values are presented as adjusted mean group differences. 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; RET = resistance exercise training; ↑ = significant increase (for body composition or muscle strength outcomes), or significant improvement (for physical performance outcomes), in EX versus CON ($p < .05$); (↑) = tendency to increase in EX versus CON; ↔ = no significant difference between EX versus CON.
[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.

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Nilsen et al., 2015). 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 ($p < .001$; Cormie et al., 2015). 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 (Newton et al., 2019). 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 RET induced hypertrophic response (Newton et al., 2019).

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 (Galvão et al., 2010), and one study showed a positive trend ($p = .078$; Cormie et al., 2015), 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 (Newton et al., 2019). In the studies performing RET only, three of four studies assessing total LBM found no exercise effect (Newton et al., 2019; Nilsen et al., 2015; Winters-Stone, Dieckmann, et al., 2015). 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 ($p < .001$) in the control group, with no significant changes over time in the exercise group (–0.3 kg, $p = .685$; Alberga et al., 2012).

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 (Ndjavera et al., 2020), and two of the included studies did not assess muscle mass (Newton et al., 2020; Segal et al., 2003). Furthermore, none of the included studies assessed muscle mass with more direct measures than dual-energy X-ray absorptiometry, 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 with a control group (Alberga et al., 2012; Cormie et al., 2015; Galvão et al., 2010; Newton et al., 2019, 2020; Nilsen et al., 2015; Segal et al., 2003; Winters-Stone, Dobek, et al., 2015). Within-groups analysis by Alberga et al. and Cormie et al., showed (nearly) significant ($p \leq .055$) 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; Alberga et al., 2012; Cormie et al., 2015). Ndajvera et al. found no differences in muscle strength between groups (Ndjavera et al., 2020). However, this was most likely because muscle strength was measured by handgrip strength. Although handgrip strength correlates well with measures of leg muscle strength, it is not a valid measure to evaluate changes in muscle strength over time during RET in older people (Buckner et al., 2019; Tieland et al., 2015).

The effect of RET on physical performance during ADT is yet unclear. Despite patients subjectively reporting improvements in physical function (Winters-Stone, Dobek, et al., 2015), 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 s increased (Nilsen et al., 2015) or the time to perform five repetitions significantly decreased (Cormie et al., 2015; Galvão et al., 2010; Newton et al., 2020; Nilsen et al., 2015), or tended to decrease (Winters-Stone, Dobek, et al., 2015; Table 2). For the stair climb test[4] and the different walk tests[5] results were heterogeneous and no conclusion can be drawn (Cormie et al., 2015; Galvão et al., 2010; Newton et al., 2020; Nilsen et al., 2015; Winters-Stone, Dobek, et al., 2015; Table 2).

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. RET 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% (Alberga et al., 2012; Cormie et al., 2015; Galvão et al., 2010; Ndjavera et al., 2020; Newton et al., 2019, 2020; Nilsen et al., 2015; Segal et al., 2003; Winters-Stone, Dieckmann, et al., 2015; Winters-Stone, Dobek, et al., 2015). 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% (Alberga et al., 2012; Ndjavera et al., 2020; Newton et al., 2019, 2020; Nilsen et al., 2015; Segal et al., 2003; Winters-Stone, Dieckmann, et al., 2015; Winters-Stone, Dobek, et al., 2015), and two studies even reported excellent attendance rates of more than 90% (Cormie et al., 2015; Galvão et al., 2010; 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 (Reale et al., 2021).

Another aspect requiring attention is the sustainability of the exercise benefits after cessation of a supervised program. As ADT is often prescribed for several years, supervised exercise programs will only cover a set time period. Up until 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

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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 (Snijders et al., 2019).

Safety

A resistance exercise program can be performed safely during ADT. First, 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 (Vingren et al., 2010). Following an exercise program during ADT, no exercise-induced changes in serum testosterone, nor in the tumor progression marker "prostate specific antigen," have been observed (Cormie & Zopf, 2020; Gardner et al., 2014). Second, hardly any exercise-related adverse events 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 (Nilsen et al., 2015). In addition, in the study reported by Alberga et al., one patient experienced chest pain during exercise, however, subsequent cardiologic investigation was negative (Alberga et al., 2012). 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 (Alberga et al., 2012; Cormie et al., 2015; Galvão et al., 2010; Ndjavera et al., 2020; Newton et al., 2019), one excluded patients with metastases in the hip or spine (Winters-Stone, Dieckmann, et al., 2015; Winters-Stone, Dobek, et al., 2015), one excluded patients with unstable bone lesions (Segal et al., 2003), and one did not report whether these patients were included, or not (Nilsen et al., 2015). In clinical practice, ∼70% of men with prostate cancer will develop bone metastases throughout the course of their disease (Coleman, 2006). Cormie et al. were the first to publish a small pilot RCT investigating the safety and affectivity of RET in prostate cancer patients with bone metastases (Cormie et al., 2013). 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 (Galvão et al., 2018) and a pilot study performing remote resistance or aerobic exercise training in metastatic castrate-resistance prostate cancer patients (Kenfield et al., 2021), 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 3 months with twice weekly training sessions has been proven beneficial (Cormie et al., 2015; Galvão et al., 2010). 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 (Newton et al., 2020; Taaffe et al., 2019).

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 RET session until fatigue, followed by protein consumption, was effective to strongly increase muscle protein synthesis rates (Hanson et al., 2017). 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 (Mitchell et al., 2012; Starkey et al., 1996), 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 (ACSM, 2009). 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 (ACSM, 2009). 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 of 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, RET program with a minimum of twice weekly training sessions for at least 3 months would already be effective. Implementation of RET 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, RET is feasible and can be safely performed by prostate cancer patients during ADT. Consequently, we strongly

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advise a widespread implementation of RET in the standard clinical care for prostate cancer patients starting and receiving ADT.

Notes

1. Chair Stand Test, measures how many times in 30 s (30-s 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-time sit-to-stand test records the time to complete five sit-to-stand maneuvers (Beaudart et al., 2019).

2. Timed Up and Go, measures the time it take to stand up from a chair, walk 3 m, turn around, return and sit down, by that assessing gait and dynamic balance (Beaudart et al., 2019).

3. Short Physical Performance Battery, test battery consisting of a balance test, walking speed test, and 5-time sit-to-stand (Beaudart et al., 2019).

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-m 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).

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