Resistance Exercise Training in Patients With Genitourinary Cancers to Mitigate Treatment-Related Skeletal Muscle Loss

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Abstract: The use of targeted therapies in patients with genitourinary malignancies has significantly improved outcomes. For example, androgen receptor (AR) pathway inhibitors have improved outcomes for patients with prostate cancer, and antiangiogenic agents have improved outcomes for those with kidney cancer. However, these advances have been accompanied by musculoskeletal side effects that manifest as physical dysfunction. Although the effects of androgen deprivation therapy on skeletal muscle are well-known, an additional concern is that the muscle loss associated with these newer drugs—especially AR pathway inhibitors—may result in insulin resistance and metabolic syndrome, thus increasing the risk for cardiovascular events and diabetes. Antiangiogenic agents also may cause muscle loss, although this has been poorly described in the literature. As these targeted therapies begin to be used in the earlier stages of treatment, there will be a critical need to prevent treatment-related toxicities with nonpharmacologic interventions. Over the past decade, exercise training has emerged as a novel nonpharmacologic adjunctive method to address toxicities resulting from these targeted therapies. Despite numerous studies in patients with prostate cancer, there remains a large gap in our knowledge of the true efficacy of exercise therapy, as well as the best way to prescribe exercise programs. Here, we suggest that the central role of skeletal muscle in the development of side effects of AR pathway inhibitors and antiangiogenic agents may unlock a number of unique opportunities to study how exercise prescriptions can be used more effectively. Resistance training may be a particularly important modality.

Introduction

Over the past 5 to 10 years, targeted therapies have revolutionized the treatment of prostate cancer and kidney cancer, improving patient outcomes. Prostate cancer is the most common cancer in

Table 1. Treatment-Related Physical Dysfunction Associated With First-Line Targeted Therapies in mCRPC and mRCC[4,8-11,98,99]

Agent	Target	Asthenic Conditions[a]	Falls	Sarcopenia
Androgen receptor–directed				
Abiraterone	CYP17[b]	Fatigue, 39%-44% Asthenia, 13%	5.9%	3%-4%[c]
Enzalutamide	Androgen receptor	Fatigue, 36%-51%	6.4%	NR
VEGF-directed				
Pazopanib	VEGFR-1,2,3; c-KIT; PDGFR	Fatigue, 55%	NR	NR
Sunitinib	VEGFR-1,2,3; c-KIT; PDGFR	Fatigue, 63%	NR	At baseline predicts DLT

CYP17, cytochrome P-450 isoform 17; DLT, dose-limiting toxicity; mCRPC, metastatic castration-resistant prostate cancer; mRCC, metastatic renal cell carcinoma; NR, not reported; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

[a] Include fatigue and asthenia.

[b] Enzyme required for androgen biosynthesis.

[c] Retrospective analysis.

men and the second leading cause of cancer-related deaths in men in the United States. In 2015, prostate cancer was diagnosed in an estimated 220,800 men, and 27,540 men died of the disease.[1] Although kidney cancer is much less common than prostate cancer, it was diagnosed in an estimated 61,560 people in 2015, and approximately 14,080 people died of the disease that year.[1] Compared with patients who have metastatic kidney cancer, survival in patients who have advanced prostate cancer is relatively long. Survival in men with biochemically recurrent (nonmetastatic) prostate cancer is approximately 9 years, and the typical survival in men with metastatic castration-resistant prostate cancer (mCRPC) ranges from 19 to 32 months.[2-4] On the other hand, patients with metastatic renal cell carcinoma (mRCC) who were treated in the prior cytokine era had a median survival of 10 months and a 2-year overall survival of 20%.[5] In the current era of targeted therapy, these numbers have improved to 22 months and 47%, respectively.[6] Patients with favorable-risk mRCC now may survive as long as 4 or 5 years.[6]

The targeted therapies that have led to these improved outcomes include androgen receptor (AR) signaling inhibitors in prostate cancer and antiangiogenic agents in kidney cancer. Both of these classes of agents have significant side effects. Androgen deprivation therapy (ADT), arguably the first targeted therapy used for cancer, was pioneered in 1941.[7] This initially involved bilateral orchiectomy to reduce serum androgen levels and was further developed to include gonadotropin-releasing hormone (GnRH) agonists and antagonists to achieve the same effect. In 2011 and 2012, the androgen biosynthesis inhibitor abiraterone acetate (Zytiga, Janssen) and the AR inhibitor enzalutamide (Xtandi, Astellas/Medivation), respectively, were approved for mCRPC based on favorable results of phase 3 studies; these labels were subsequently expanded in 2012 and 2014.[4,8-10] Beginning in 2006, the vascular endothelial growth factor (VEGF) signaling pathway inhibitors sunitinib (Sutent, Pfizer), pazopanib (Votrient, Novartis), axitinib (Inlyta, Pfizer), sorafenib (Nexavar, Bayer/Onyx), and bevacizumab (Avastin, Genentech) were approved for mRCC.[11-16] Most of these targeted therapies are not commonly used in other types of cancer and have idiosyncratic side effects, many of which appear to be related to on- and off-target effects on the cardiovascular and musculoskeletal systems. Thus, musculoskeletal system side effects due to targeted therapies that result in physical dysfunction are common in patients treated with these agents for mRCC or mCRPC (Table 1).

As patients with advanced prostate cancer and mRCC live longer, it becomes increasingly important to recognize and mitigate treatment-emergent adverse events. Although some adverse events can be reversed with discontinuation of the targeted therapy, others may persist after therapy is discontinued.[17] Finally, although these targeted therapies initially were approved for the treatment of advanced or metastatic disease in both cancers, they currently are being studied in earlier stages of disease,[18,19] when patients may be even more sensitive to treatment-emergent adverse events and long-term effects. This situation highlights the importance of strategies to prevent and mitigate the toxicities of these drugs.

One emerging commonality of AR-directed and anti-VEGF agents is that they can cause sarcopenia. Sarcopenia has been defined as a decrease in skeletal muscle or lean body mass; more recent definitions may also include loss of muscle function, such as decreased strength or mobility.[20,21] In patients with several types of solid tumors, sarcopenia—defined as an appendicular skeletal muscle index more than 2 standard deviations below the mean (<7.26 kg/m^2 for men and <5.45 kg/m^2 for women)—has been shown to be associated with decreased survival,[22,23] muscle strength,

physical functioning, and quality of life.[24,25] In patients with mRCC, one retrospective study suggested that the VEGF receptor tyrosine kinase inhibitor (TKI) sorafenib may cause a loss of 5% of muscle after 6 months of treatment.[26] A post hoc report demonstrated that single-agent abiraterone may cause a loss of 3% to 4% of muscle in patients with mCRPC after 6 months of treatment.[27] These results were bolstered by the observation that in a subset of patients for whom scans were available that had been obtained while they were on ADT alone, before starting abiraterone, cross-sectional muscle area was relatively stable. These results need to be prospectively validated. However, they do suggest that treatment-emergent sarcopenia may be an important and underrecognized issue, given the number of patients who continue to take AR-directed or anti-VEGF agents for many months.

This review focuses on the biology of AR- and VEGF-directed therapies related to skeletal muscle, the evidence demonstrating that resistance exercise training may mitigate skeletal muscle loss in patients living with cancer, and the gaps in research regarding optimal exercise prescriptions for patients with treatment-emergent sarcopenia.

Advanced Prostate Cancer

Importance of ADT-Induced Muscle Dysfunction

In patients who have prostate cancer treated with ADT, the central role of skeletal muscle in therapy-induced side effects is often overlooked. As serum testosterone is reduced by chemical or surgical castration, skeletal muscle—also known as lean body mass—is reduced. This reduction in turn leads to insulin resistance and a 44% increased risk for new-onset diabetes.[28] Indeed, insulin resistance in skeletal muscle is now recognized to be the primary defect in type 2 diabetes.[29] Insulin resistance in turn places the patient at increased risk for cardiovascular events.[28] Reduction in skeletal muscle also has effects on patient-centered outcomes; as fatigue increases, quality of life decreases.[30-32]

As will be expounded upon in this review, resistance exercise training with the goal of maintaining or increasing muscle mass must be dosed differently than resistance training for strength endurance, maximal strength, or other purposes. Furthermore, exercise training to improve work capacity (ie, peak oxygen consumption, or peak Vo_2) may compete with training to improve or maintain skeletal muscle mass. The competing goals of aerobic and resistance training are often referred to as the interference effect, in which aerobic exercise has the potential to deleteriously affect muscle hypertrophy (increase in lean muscle mass) and strength development, depending on its frequency and duration.[33] Although training to improve peak Vo_2 may separately improve insulin sensitivity, it may do nothing to improve or maintain muscle mass. Here, we critically review the strength training protocols that have been used to date in genitourinary cancer research and provide a possible path forward for resistance training research based on the existing literature on strength and conditioning in all populations.

Brief Introduction: Exercise Training

Over the past decade, an increasing number of clinical studies have investigated the effects of exercise in patients undergoing ADT for prostate cancer.[34-48] The primary rationale for these trials is the need to develop secondary measures to counteract the adverse effects of ADT without adding toxicity. It is not surprising that a nonpharmacologic approach, such as exercise, would be considered a logical intervention choice, given its beneficial pleiotropic effects, many of which counter the detrimental biological, physiologic, and psychosocial effects of ADT.[49] Against this background, a recent systematic review by Gardner and colleagues of more than 10 clinical studies suggested that exercise not only is safe in patients undergoing ADT for prostate cancer but also may help mitigate ADT-related adverse effects and symptoms without concomitant toxicity.[50] However, as initially noted in a follow-up commentary by Winters-Stone and Beer, few randomized controlled trials to date have been designed to address adequately the outcomes associated with exercise.[51] Thus, there remains a large gap in our knowledge regarding the true efficacy of exercise therapy, as well as the proper methods of tailoring exercise prescriptions in men who are undergoing ADT for advanced prostate cancer.

Exercise Interventions in Men Undergoing ADT

Exercise interventions in men undergoing ADT for prostate cancer have included increased general physical activity consisting of individualized, home-based aerobic exercise, stretching, and light resistance movements, in addition to prescriptions for supervised aerobic training and supervised resistance training according to the American College of Sports Medicine (ACSM) recommendations.[37,46,47] Several studies and reviews have presented these data comprehensively and in detail.[50] The current available evidence suggests that resistance training alone or in combination with aerobic training modestly increases muscular endurance or strength. Surprisingly few data, however, support the idea that supervised aerobic training alone can improve cardiorespiratory fitness (assessed with peak Vo_2), fatigue, or patient-reported measures of quality of life.[50]

Effects of ADT on Skeletal Muscle

ADT may impact numerous aspects of the cardiovascular reserve, both directly and indirectly. It is likely that the direct effects of ADT on skeletal muscle are a major

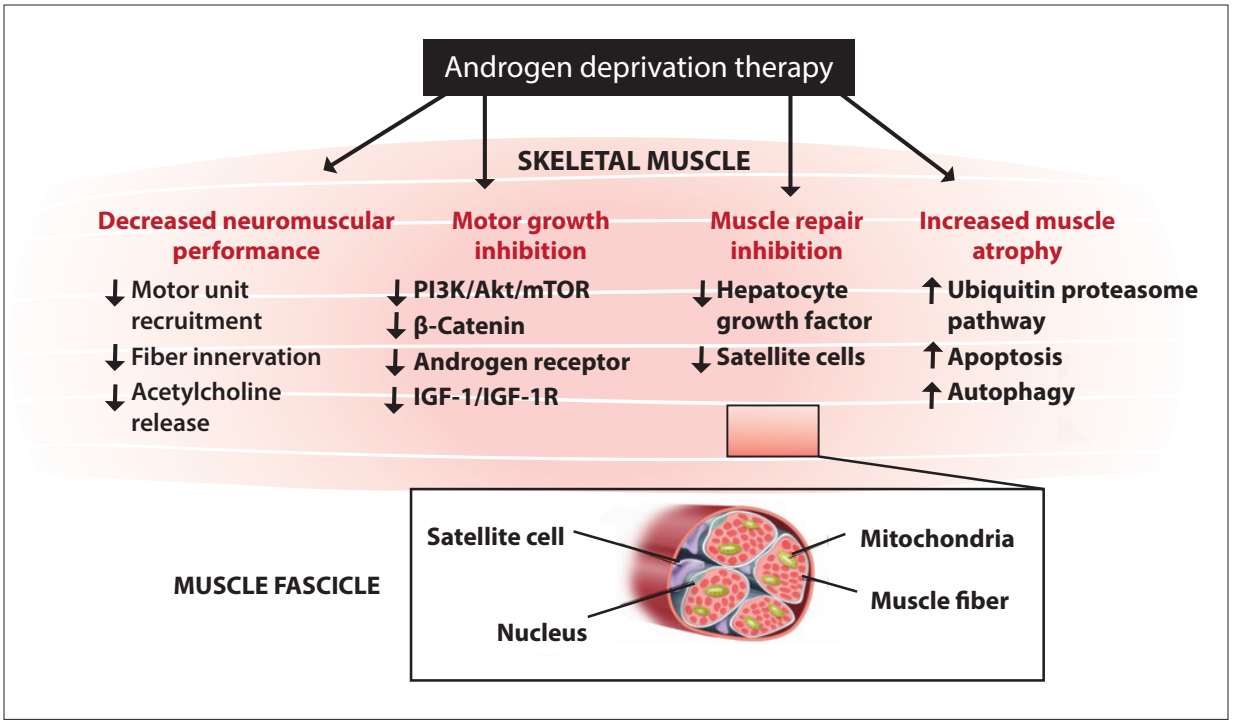

Figure 1. The pro–muscle atrophy phenotype induced at the initiation of androgen deprivation therapy. Androgen deprivation therapy has effects on numerous aspects of skeletal muscle physiology that contribute to overall muscle atrophy, including a decrease in neuromuscular performance, a decrease in muscle growth, a decrease in muscle repair, and an increase in muscle atrophy. Each of these effects is related to changes in cell-specific and biological pathway–specific mechanisms within skeletal muscle that result in muscle atrophy. Some of the underlying postulated mechanisms are represented in this figure.

IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

contributor to the inconsistencies seen in randomized trials of exercise capacity and additional outcomes associated with changes in skeletal muscle. Although the underlying biological mechanisms are poorly understood, ADT-mediated reductions in sex steroids are hypothesized to lead to the following:

1. activation of skeletal muscle atrophy–related genes and proteins via apoptosis, autophagy, and the ubiquitin-proteasome pathway;
2. inhibition of anabolic muscle growth through reduced activation of the AR, β-catenin, insulin-like growth factor 1 (IGF-1), and Akt/mammalian target of rapamycin (mTOR) pathways; and
3. inhibition of muscle repair mechanisms via reduced production of hepatocyte growth factor (HGF) and dysregulation of satellite cells in skeletal muscle.

All of these contribute to the activation of an overall pro-atrophy phenotype at the initiation of ADT (Figure 1).[52-54] Pro-atrophy phenotypes generally have been associated with numerous aspects of skeletal muscle dysfunction, which recently has emerged as an important prognostic factor in the oncology setting.[55] Although muscle dysfunction can be defined as any impairment related to muscle strength or composition, the underlying reduction of total lean muscle mass, decrease in muscle strength, and impairment of mitochondrial function all contribute to overall muscle dysfunction (Figure 2).[55,56] ADTs, which lower serum testosterone levels, have been suggested to be a major causal factor in mitochondrial dysfunction.[56] A study of 60 Swedish men with hypogonadism and testosterone levels mimicking the levels of patients on ADT found impaired mitochondrial function in skeletal muscle and decreased expression of oxidative phosphorylation genes in these subjects. Oxidative phosphorylation genes are necessary for aerobic respiration and serve as important biomarkers of overall exercise capacity.[57] In addition, the importance of skeletal muscle–based mitochondrial function in overall exercise capacity has become increasingly evident in recent studies investigating exercise capacity in patients with heart failure. Abnormalities in skeletal muscle, specifically a shift in muscle fiber type toward muscle fibers less dense in mitochondria, are a major contributor to exercise intolerance and decline in physical functioning.[58,59] Because physical

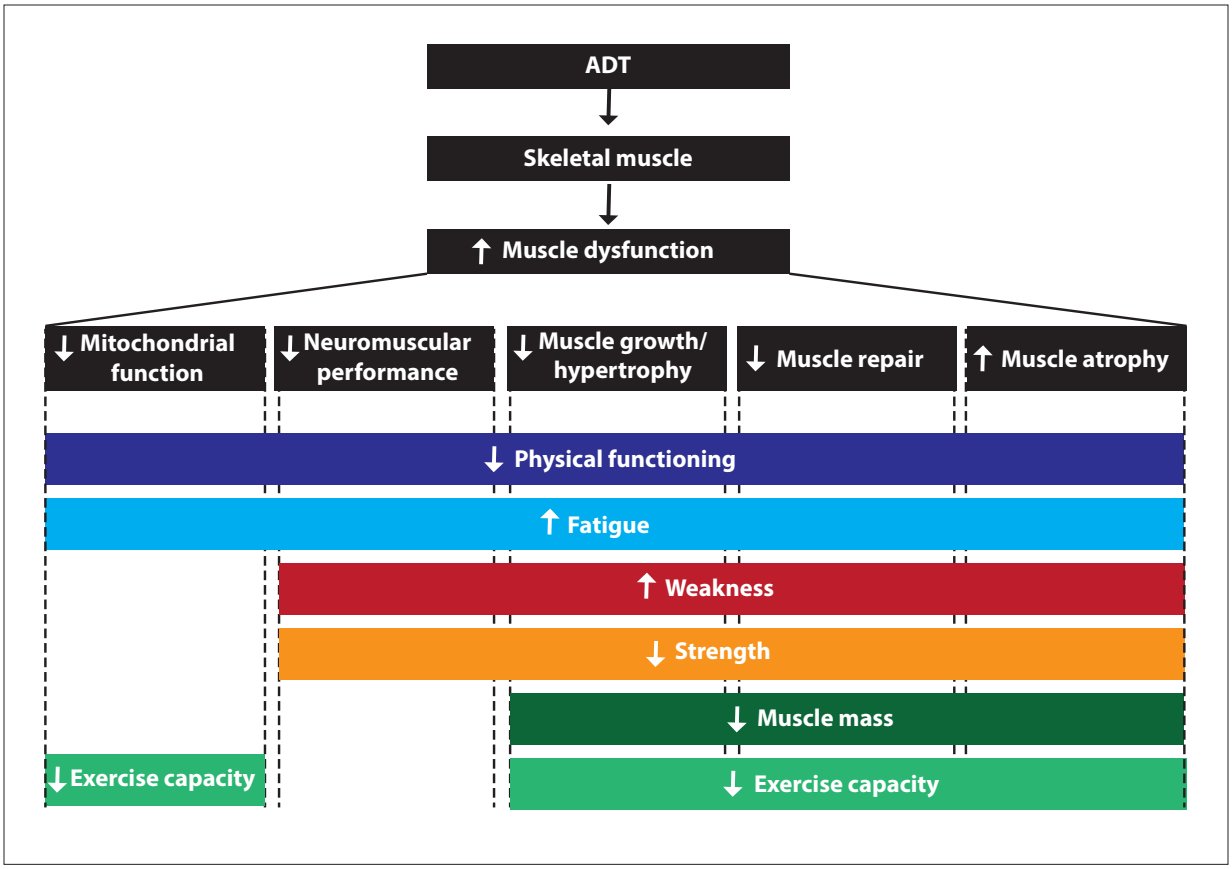

Figure 2. Skeletal muscle dysfunction induced by androgen deprivation therapy (ADT): mechanisms of effects on measures of skeletal muscle–based and patient-reported outcomes. Skeletal muscle dysfunction is a central component of the musculoskeletal effects of ADT that may negatively impact patient-reported outcomes and additional, clinically relevant measurements of health and fitness.

functioning continues to decline over 2 years following continuous ADT, with no apparent recovery, the use of targeted exercise to improve exercise capacity, strength, lean muscle mass, and other skeletal muscle–based outcomes is necessary to decrease the long-term adverse effects of ADT on muscle dysfunction.[32]

Pathophysiology of Skeletal Muscle

Type 1 muscle fibers. The skeletal muscles are the largest system in the human body. Skeletal muscle is composed of multiple fiber types, each of which serves a unique physiologic function that ranges from postural support to forceful voluntary contraction.[60] Type 1 muscle fibers (also called *slow-twitch* muscle fibers) are found in greater numbers in endurance athletes, appear red owing to large amounts of myoglobin, are densely populated with capillaries and mitochondria, and are responsible for long-duration muscle contractions.[61] The abundant mitochondria found within type 1 muscle fibers play a critical role in determining exercise capacity through their ability to reduce available oxygen during the final step of oxidative phosphorylation, the primary mechanism of producing energy in the form of adenosine triphosphate (ATP) in muscle cells.[62] The number of mitochondria found in skeletal muscle is an important determinant of exercise capacity, measured by maximal oxygen consumption (Vo_2 max); reduction in mitochondrial density within type 1 muscle fibers, total number of type 1 muscle fibers, or cross-sectional area of type 1 muscle fibers can lead to an overall whole-body reduction in exercise capacity.[62-64] Emerging clinical data have shown a trend toward a decreased cross-sectional area of type 1 muscle fibers in patients undergoing ADT for prostate cancer.[48] Although a decrease in the cross-sectional area of type 1 muscle fibers typically occurs through a decrease in lean muscle mass due to muscle atrophy, these clinical data suggest that a reduction in exercise capacity or an increase in fatigue in a patient receiving ADT for prostate cancer may be attributed either to a loss of type 1 muscle fibers or to a reduction in the number or function of mitochondria within type 1 muscle fibers.

In addition, interest has been emerging in the role of the AR in directly regulating mitochondrial density in skeletal muscle beyond the effect of AR signaling on skeletal muscle size and strength. Although preclinical data in rats have indicated that AR blockade can significantly suppress exercise-induced hypertrophy in skeletal muscle, transgenic mouse models have indicated that the AR also may be an important regulator of mitochondrial biogenesis in skeletal muscle.[65,66] Blocking activation of the AR through ADT may reduce the effectiveness of aerobic training to facilitate increases in mitochondrial density in type 1 muscle fibers because both act through a peroxisome proliferator-activated receptor γ coactivator 1α (PGC1-α)–dependent mechanism.

In light of this evidence, exercise studies using aerobic training may be more effective before continuous ADT is initiated or during the pharmacologic nondosing intervals of intermittent ADT delivery seen in recent clinical trials, in order to prevent opposing effects on synonymous biological mechanisms.[67] In addition, patients with prostate cancer who have a history of cardiovascular disease and are at increased risk for a cardiovascular event within the first 6 months of ADT may be a population that should be specifically targeted with this approach, to prevent further damage to their cardiac reserve.[68] Certainly, preserving exercise capacity in patients at high risk should be a key objective during the nondosing segments of ADT therapy.

Type 2 muscle fibers. In contrast to type 1 fibers, type 2 muscle fibers (also called *fast-twitch* muscle fibers) appear white owing to significantly less myoglobin and fewer capillaries. They rely primarily on anaerobic glycolysis, are more abundant in muscle biopsy specimens of strength and power athletes, and generate high-velocity muscle contractions.[69] Recent evidence suggests that resistance training specifically targeting type 2b muscle fibers increases muscle hypertrophy, muscle mass, and strength but reduces running endurance, supporting a phenotype of short, high-velocity contractions.[70] Resistance training alone, or in combination with aerobic training, in patients undergoing ADT for prostate cancer has been shown to increase muscle mass, volume, endurance, power, and strength, with associated improvements in physical functioning and quality of life and a reduction in fatigue.[44] A recent investigation of the effects of strength training on cross-sectional area in patients undergoing ADT for prostate cancer showed a significant increase in type 2 muscle fibers with no measurable change in type 1 fibers, indicating that resistance training with high relative loads targets specific muscle fibers.[48] However, many of the muscular effects reported to date in numerous studies of patients undergoing ADT for prostate cancer have been demonstrated only in a subset of the total number of muscle groups trained, suggesting that improvements in muscular strength and endurance may not be axiomatic or that the selection of movement patterns was less than optimal.[48] It is possible that the heterogeneous patient responses to prescribed resistance training or the nonuniform distribution of the effects of ADT on skeletal muscle groups may account for the less-than-universal benefits of resistance training on skeletal muscle function.

Exercise Prescriptions: Resistance Training

Based on evidence regarding resistance training in patients undergoing ADT for prostate cancer, it can be hypothesized that the choice of resistance training exercises and modalities may become increasingly important when overall improvements in patients' muscular strength, hypertrophy, and endurance are evaluated. Resistance exercises that recruit large areas of muscle tissue, such as squats and dead lifts, may elicit greater skeletomuscular changes than accessory movements, such as arm curls and seated rows. Full-body movements, especially when performed with free weights instead of machines, can have a larger effect on muscle recruitment.[71] Synonymous recruitment of a greater number of type 2 muscle fibers through full-body compound movements may bring about a larger release of myokines, important signaling molecules released from contracted skeletal muscle that can alter body composition.[72] It is also important to note that not all resistance training exercise prescriptions are equivalent, and caution should be exercised when the outcomes of resistance training as a general methodology are interpreted because protocols can vary significantly. Different types of exercises, percentages of one-repetition maximum (1RM), numbers of repetitions and sets, and amounts of rest time between sets can elicit different physiologic effects and adaptations in skeletal muscle by targeting different energy systems and muscle fibers (Table 2).[73,74]

This is most evident in the physical and functional manifestations of various bodybuilders or Olympic weight lifters, who use defined resistance training protocols to achieve either muscle hypertrophy and definition or muscle power and strength, respectively. For example, although both Galvao and colleagues and Segal and colleagues used a 12-week, 2- or 3-times-weekly resistance training intervention in patients undergoing ADT for prostate cancer, with a 16- to 24-repetition training volume per exercise, the targeted muscular effects were quite different.[37,42] According to ACSM resistance training guidelines, the prescription of Segal and colleagues of 60% to 70% of 1RM with a 16- to 24-repetition training volume would be classified as a *muscular endurance* prescription. In contrast, the prescription of Galvao and colleagues of 60% to 85% of 1RM promotes a combination of *muscular strength*, *hypertrophy*, and *endurance*. Thus, the prescription of Segal

Table 2. Considerations for Resistance Training Prescriptions: American College of Sports Medicine Resistance Training Guidelines for Muscular Phenotypes in Healthy Adults[73,74]

	Strength	Power	Hypertrophy	Endurance
Load	60%-70% of 1RM	30%-60% of 1RM upper body; 0%-60% of 1RM lower body	70%-85% of 1RM	≤70% of 1RM
Repetitions	8-12	3-6	8-12	10-25
Sets	1-3	1-3	1-3	2-4
Total volume repetition range	8-36	3-18	8-36	20-100
Rest interval between sets, min	1-3	1-2	1-2	0.5-1

1RM, one-repetition maximum.

and colleagues primarily increased muscle endurance with regard to musculoskeletal outcomes, and that of Galvao and colleagues increased muscle strength, muscle endurance, and quadriceps thickness, aligning the measured outcomes with the intent of the prescription.

However, not all randomized trials have consistently shown a direct association between the resistance training exercise prescription and the intended type of musculoskeletal outcome, which may highlight not only the heterogeneity of patients' muscular and neuromuscular adaptations to exercise but also the importance of physiologic recovery from frequent acute bouts of resistance training. Resistance training protocols in which identical physiologic movement patterns consistently targeting the same muscle groups are performed in succession can lead to overtraining.

Although the underlying biological mechanisms of overtraining are still being investigated, the concept of overtraining is defined as a maladaptive response to exercise stimulus due to excessive training load or volume without adequate recovery.[75] The negative effects of overtraining may include activation of catabolic processes in skeletal muscle as well as neurologic, immunologic, and endocrine perturbations throughout the body, and these can decrease the body's ability to adapt positively to exercise stimuli.[76] Physiologic and musculoskeletal recovery from exercise is an area of research that has received little attention in the context of oncology and should be especially considered in patients undergoing ADT and AR pathway inhibitor therapy. The reason is that ADT and AR pathway inhibitor therapy may significantly affect muscle growth and repair processes during rest intervals or the period of inactivity between continuous acute exercise sessions, which are critical for adaptations to exercise.

A key type of cell in muscle that is necessary for muscle repair and recovery is the *satellite cell.* Satellite cells have been shown to be essential stem and progenitor cells that can undergo myogenic differentiation to fuse and restore damaged muscle following exercise.[54] A recent study investigated the effects of exercise on satellite cells in muscle biopsy specimens from patients undergoing ADT for prostate cancer and found no significant changes in satellite cells following 16 weeks of strength training.[48] However, the muscle biopsy specimens were taken 72 to 96 hours after the last training session, which may be well beyond the period in which muscle repair from satellite cells can be detected. Within 24 hours after the last resistance training or exercise session may be a better period during which to measure changes in satellite cell numbers and function. In future studies, it will become increasingly important to ensure proper recovery from a previous acute bout of resistance training through measurement of circulating creatine kinase before the next resistance training session is initiated. This will ensure maximal muscle adaptation and the prevention of neuromuscular fatigue.

It is also possible that neuromuscular fatigue may occur during exercise prescriptions of increased resistance loading that can reduce the force production capacity of skeletal muscles and prevent the intended benefits of the exercise prescription, leading to 1RM measurements lower than actual 1RM capabilities.[77] Allowing more than 24 to 36 hours between training sessions should provide optimal recovery. However, much of the musculoskeletal recovery likely will depend on the type and dose of ADT and AR pathway inhibitor therapy, as well as the inherent genetic potential of each patient.[78] Taking into account the abilities and performance of each patient will become increasingly important for maintaining and improving musculoskeleton-based outcomes in patients with prostate cancer who are undergoing ADT either alone or in combination with AR pathway inhibition.

Metastatic Renal Cell Carcinoma

Significance of Muscle Loss in RCC

As mentioned earlier, skeletal muscle loss is associated with decreased physical functioning and poor overall survival in patients who have solid tumors.[22,79] The clinical implications of muscle loss in mRCC are unknown and currently under investigation. Nonetheless, decreased muscle mass may be a biomarker predictive of the development of treatment-related toxicities in patients with mRCC. In one retrospective series, patients who had

sarcopenia at the start of treatment with sunitinib, determined by cross-sectional area on computed tomography, were significantly more likely to experience dose-limiting toxicities such as fatigue and gastrointestinal adverse events than were patients who had normal muscle mass at the beginning of treatment.[80] Patients in the highest (>75th) percentile for muscle mass experienced dose-limiting toxicities 57% of the time, whereas patients in the lowest (<25th) percentile for muscle mass experienced dose-limiting toxicities 92% of the time.

Targeted Therapy in Patients With RCC and Muscle Loss

Cancer cachexia is a biologically complicated syndrome characterized by the tumor production of cytokines and inflammatory signals that result in decreased appetite, a catabolic state, and muscle loss, which ultimately lead to physical impairment.[81] An underrecognized concern is that treatments themselves may contribute to skeletal muscle toxicity, with clinical consequences that have not yet been explored. For example, in one retrospective analysis of patients with mRCC, skeletal muscle declined by 4.9% after 6 months and by 8% after 12 months of treatment with sorafenib, compared with no significant muscle loss after the administration of placebo.[26] Sorafenib is theorized to inhibit the Ras/Raf pathway, which facilitates muscle proliferation.[81] Several other targeted agents have been approved by the US Food and Drug Administration (FDA) for the treatment of mRCC, yet data on the effects of these drugs on skeletal muscle are lacking. For instance, everolimus (Afinitor, Novartis) and temsirolimus (Torisel, Pfizer) work by blocking the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, which is known to be important in muscle protein synthesis.[81] Furthermore, a variety of VEGF inhibitors used in mRCC treatment, including sunitinib, pazopanib, axitinib, and cabozantinib (Cometriq, Exelixis), have slightly different mechanisms of action and generally different toxicity profiles. The potentiation and magnitude of the antiangiogenic effects of VEGF inhibitors and TKIs on skeletal muscle toxicity have yet to be explored.

Pathophysiology of VEGF Inhibitor–Related Muscle Loss

A critical knowledge gap in the field, especially given that VEGF inhibitors are the most widely used agents in the treatment of mRCC today, is the lack of characterization of skeletal muscle changes and the degree to which they occur as a result of VEGF blockade. Many of the toxicities of VEGF inhibitors, such as renal dysfunction and hypothyroidism, have been closely tied to their effects on capillary angiogenesis.[82] Whether VEGF inhibitors cause a clinically meaningful degree of reduction in skeletal muscle angiogenesis is unclear because not all the evidence is consistent. For example, an organ analysis in mice after 1 to 3 weeks of VEGF receptor signaling inhibition indicated that capillary regression in skeletal muscle was extremely limited to undetectable (ie, no significant change in vascular density was evident).[83,84]

Many studies do, however, suggest that VEGF signaling is critical to muscle growth and generation.[85,86] In cardiac muscle, VEGF signaling is shown to be essential for ventricular remodeling.[87,88] Capillary growth in the heart is mediated through the stress-induced activation of hypoxia-inducible factor 1-alpha (HIF1A), which results in VEGF receptor activation. Furthermore, blocking VEGF receptors in the heart results in an inhibition of angiogenesis that prevents stress-induced compensatory hypertrophy, leading to dilated cardiomyopathy. Clinically, it is thought that in approximately 10% to 15% of patients the cardiac ejection fraction may decline during treatment with various VEGF inhibitors and TKIs.[11,89] Preclinical studies also have suggested that VEGF signaling plays an important role in initiating skeletal muscle myogenesis and terminal differentiation.[85,86] Mouse models of selective skeletal muscle VEGF receptor gene knockouts show a 50% reduction in muscle capillary density and an 80% decrease in exercise capacity compared with controls.[90] Given the preclinical evidence regarding the role of VEGF signaling in skeletal muscle growth, VEGF inhibitor treatment may prevent skeletal muscle regeneration in generally sedentary patients with cancer, who already have a tendency to lose muscle mass as part of the cancer cachexia syndrome.

Considerations for Exercise Prescriptions

Elucidating the biological mechanisms of VEGF inhibitor toxicities in skeletal muscle may have very important clinical implications. To date, no available clinical studies have prospectively looked at changes in skeletal muscle as a result of VEGF inhibitor treatment in patients with cancer. The relationship between VEGF signaling and skeletal muscle angiogenesis, growth, and functioning needs to be better elucidated to determine the types and timing of exercise prescriptions that may be of optimal clinical efficacy in patients. For instance, one concern is that resistance exercise might be less effective during VEGF inhibitor therapy. Several studies suggest that VEGF pathways are upregulated as a result of exercise and may be important for muscle angiogenesis, proliferation, and remodeling.[90-94] However, it may also be possible that exercising during VEGF inhibitor treatment is still effective in building skeletal muscle density because pathways such as angiopoietin, transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), and thrombospondin may compensate for the deficiencies in muscle angiogenesis that result

from VEGF inhibition.[90,95] These types of relationships between exercise and the biology of skeletal muscle are important for determining the optimal frequency, duration, and types of exercise required to benefit patients treated for mRCC with VEGF inhibition. As an example, sunitinib is often given on a 4-weeks-on, 2-weeks-off schedule or a 2-weeks-on, 1-week-off schedule. By contrast, pazopanib typically is administered continuously. It is unclear whether exercise prescriptions would be more effectively administered during on-treatment or off-treatment periods, and whether there is a greater benefit of aerobic vs resistance exercise under different treatment schedules. By characterizing the biological changes in skeletal muscle that are associated with VEGF inhibitor treatment and exercise training, and by correlating these with clinical outcomes, we can begin to design optimal exercise strategies.

Future Directions

In light of the current literature and evidence, a number of opportunities are available to enhance exercise studies of patients undergoing ADT and/or AR pathway inhibition treatment for advanced prostate cancer, as well as studies of patients who have mRCC and are being treated with VEGF inhibitors. First, the analysis of skeletal muscle biopsy specimens will provide a useful method to further characterize the direct and indirect effects of these therapies on skeletal muscle biology and function. Metabolomics, proteomics, genomic profiling, muscle fiber type analysis, and satellite cell analysis of biopsy specimens may help to determine the extent to which ADT, AR pathway inhibitors, and VEGF inhibitors affect particular outcomes of interest, and when these particular events may occur during the treatment process. Second, neuromuscular programming should be prioritized before resistance training protocols are initiated, with a focus on movements that support daily functional tasks. Ideally, these would include compound full-body exercises such as dead lifts, squats, and bench presses. Third, "smarter" resistance training protocols based on ACSM recommendations and combinations of protocols that match outcomes of interest should be used instead of a catch-all protocol (Table 3). For instance, if the outcome of interest is to prevent or decrease cancer cachexia, a resistance training prescription geared toward increasing lean muscle mass should be used, not one designed to improve muscular endurance.

Furthermore, evidence suggests that a block periodization protocol, which allows the synergistic progression of training to optimize peak performance through workload progression, may elicit greater improvements in outcomes than a nonperiodization, or linear, model; this should be considered when the schedule of ADT or treatment with AR pathway inhibitors or VEGF inhibitors in combination with resistance training is evaluated.[96] For example, block periodization encompasses a block, or defined training period (eg, 6-12 weeks) dedicated to muscle hypertrophy; this then leads to the next block for maximal strength and finally to the last block for power and explosive strength.[97] Lastly, recovery from the repeated acute bouts of exercise over the course of a protocol will need to be monitored more effectively to ensure that patients are getting adequate rest with time for muscle repair before the next exercise session is initiated.

In summary, there is convincing evidence that prescriptions for resistance training may mitigate the adverse effects of ADT, and additional studies are warranted in the context of AR pathway– and VEGF inhibition–targeted therapies. A critical step forward in achieving greater efficacy of exercise in future clinical trials of patients with genitourinary cancers will be to unravel the direct and indirect effects of cancer and cancer treatment on skeletal muscle.

Table 3. Considerations for Resistance Training Prescriptions: Correlative Outcomes Associated With Muscular Phenotype Categories[a]

	Strength	Power	Hypertrophy	Endurance
Physical functioning	+	+	+	+
Lean muscle mass			+	
Strength	+	+		
Fatigue	+	+	+	+
Exercise capacity	+	+	+	+
Quality of life	+	+	+	+
Type 2 muscle fibers	+	+	+	+
Type 1 muscle fibers				+

[a] Plus sign indicates that the outcome is associated with the muscular phenotype category.

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