Attenuation of Resting but Not Load-Mediated Protein Synthesis in Prostate Cancer Patients on Androgen Deprivation

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Context: Androgen deprivation therapy (ADT) is a common prostate cancer (PCa) treatment but results in muscular atrophy. Periodic increases in muscle protein synthesis (MPS) that occur after resistance exercise or protein intake may ameliorate this muscle loss, but the impact of these anabolic stimuli during ADT is unclear.

Objective: To determine the acute MPS response to whey protein supplementation with and without resistance exercise during ADT.

Design: Acute response in PCa patients vs age-matched controls (CON).

Setting: Academic laboratory setting.

Participants: PCa patients on ADT (N = 8) and CON (N = 10).

Intervention: A standardized diet was consumed for 2 days prior to performing unilateral knee extension resistance exercise followed by ingestion of 40 g of whey protein.

Main Outcome Measures: Bilateral biopsies and stable isotope infusions were used to determine MPS rates at rest after protein ingestion with and without resistance exercise.

Results: Baseline MPS during ADT was suppressed relative to CON (P = 0.01). Protein consumption stimulated MPS in both groups (approximate twofold increase, both $P < 0.001$), but to a greater extent in CON ($P = 0.003$). Protein plus resistance exercise increased MPS (~3.4-fold increase, both $P < 0.001$) to a greater extent than did protein alone ($P < 0.001$), but with no difference between groups (P = 0.380).

Conclusions: ADT reduces basal and protein feeding-induced rises in MPS; however, combined protein ingestion with resistance exercise stimulated MPS to a similar degree as CON. Testosterone appears to play a role in maintaining muscle mass but is not necessary to initiate a robust response in MPS following resistance exercise when combined with protein ingestion. **(*J Clin Endocrinol Metab* 102: 1076–1083, 2017)**

Prostate cancer (PCa) is the most common non-dermatological form of cancer in US men and is the second leading cause of cancer-related death (1). Androgen deprivation therapy (ADT) is a common adjuvant treatment that slows tumor growth but is associated with adverse effects, notably significant declines in

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 5 October 2016. Accepted 13 January 2017.
First Published Online 19 January 2017

Abbreviations: ADT, androgen deprivation therapy; CON, controls; Ex-Fed, 40 g of whey protein ingestion combined with unilateral knee extension resistance exercise; Fed, 40 g of whey protein ingestion; MPB, muscle protein breakdown; MPS, muscle protein synthesis; PCa, prostate cancer; SD, standard deviation.

muscle mass, strength (2–4), and physical function (4, 5), which negatively impact health-related quality of life. The iatrogenic effects of ADT on musculoskeletal health are similar to sarcopenia, but they present at an accelerated rate (6, 7). Because age-related and ADT-induced reductions in health-related quality of life are treatable, therapies to offset these side effects are crucial to PCa patients undergoing hormone therapy.

During the past decade, exercise interventions have been used to reduce the side effects of PCa treatment. Resistance training during ADT improves muscle function, reduces fatigue, and enhances physical function and quality of life (7–14). Thus, repeated bouts of resistance exercise are beneficial during ADT and address some of the treatment-related side effects. However, whether significant muscle hypertrophy occurs with ADT following resistance training remains controversial. Some studies report no change in muscle mass (10, 13), whereas others showed increased mass compared with non-exercise controls (9, 11). Our most recent work (8) demonstrated muscle hypertrophy similar to healthy older adults (15), suggesting that the muscle's capacity to respond to a sufficient loading stimulus remains intact despite ADT.

Although the role of ADT on load-mediated hypertrophy is unclear, pharmacological manipulation of testosterone impacts skeletal muscle mass (16). Muscle protein synthesis (MPS) significantly increased in older men when testosterone was restored to that of young men (17), suggesting that testosterone ablation impairs resting MPS. Indeed, 10 weeks of ADT decreased whole-body protein synthesis, strength, and lean mass in young men (18). However, MPS has yet to be examined specifically in PCa patients, who may respond differently than young men due to differences in age, length of ADT, or other cancer-related treatments. To minimize muscle loss during ADT, it is necessary to shift the balance between MPS and muscle protein breakdown (MPB) to favor an anabolic environment. Resistance exercise and protein supplementation stimulate MPS, effects that are synergistic when used concurrently (19). Of the available protein supplements, whey protein produces the greatest increases in acute MPS (20) and augments lean muscle mass accretion with resistance training (21). Higher protein doses are needed to maximize MPS in older adults (22–24) whereas less is required in younger individuals (25, 26). Thus, this age-related "anabolic resistance" to feeding warrants consideration for interventions in clinical populations, including patients receiving ADT.

There are relatively few resistance training studies performed during ADT (14). None has examined the effects of resistance exercise or protein supplementation on MPS during PCa treatment, yet both appear to be attractive options to reduce muscle loss during ADT. Given the importance of muscle mass and strength on physical function and quality of life, strategies to minimize ADT-related detriments to musculoskeletal health must be further explored. Moreover, determining the acute response provides important information for designing future resistance exercise and dietary interventions to maximize the MPS and subsequent hypertrophic response. Therefore, the purpose of this study was to determine the acute MPS response to whey protein supplementation with (Ex-Fed) and without (Fed) resistance exercise in PCa patients on ADT relative to healthy age-matched men. It was hypothesized that baseline MPS would be suppressed with ADT but that diet- and resistance-induced increases in MPS would be independent of ADT.

Methods

Participants

Eight men (age 68 years [standard deviation (SD), 5 years]) with physician-diagnosed PCa on ADT for at least 3 months [559 days (331 days)] were recruited for this trial. Ten healthy men [age 70 years (4 years)] with no history of PCa that had previously completed an identical trial served as controls (CON), as published previously (23). Healthy age-matched CON were selected, as they represent the best case MPS response to Fed or Ex-Fed and provide context on the magnitude of the MPS changes from rest.

All participants were generally healthy and were not engaged in regular resistance training; their physical characteristics are described in Table 1. Most participants were low to moderately active. CON were all nonsmokers and had no history of diabetes. Men on ADT were currently nonsmokers, although several previously smoked, and one participant had controlled diabetes (managed via diet only). Men on ADT had approval from their physician to participate in the study. Participants were informed of the study procedures and the potential risks and all gave their written informed consent. The project was approved by the local ethics committees at the Peter MacCallum Cancer Centre, Victoria University, and McMaster University and was conducted in accordance with principles set out in the Declaration of Helsinki.

Design

Both groups of older men (ADT and CON) consumed 40 g of whey protein isolate immediately following a single session of unilateral knee extension exercises. Previously, 40 g of protein produced the highest MPS rates (23) and exceeded the 0.4 g/kg needed to observe a plateau in MPS in older adults (24). The unilateral model permits each participant to serve as his own resting control with muscle biopsies being obtained immediately and 240 minutes after resistance exercise (see "Muscle biopsies").

Preliminary assessments

Preliminary assessments for CON were described previously (23) and were followed exactly for the ADT group. Briefly, two

Table 1. Participant Characteristics

	CON (N = 10)	ADT (N = 8)	*P* Value
Age, y	70 (4)	68 (5)	0.372
Body mass index, kg/m^2	26.0 (2.2)	30.0 (3.5)	0.029
Height, m	1.75 (0.09)	1.71 (0.08)	0.309
Mass, kg	80.7 (12)	87.8 (9.7)	0.204
Lean mass, kg	56.0 (9)	58.0 (7.8)	0.685
% Fat	27.0 (8)	29.5 (5.1)	0.843
SPPB	11.6 (0.7)	11.6 (0.7)	0.942
KE 1RM, kg	56.5 (12.5)	49.0 (12.2)	0.221
Total testosterone, ng/dL	430.2 (146.0)	45.7 (4.9)	<0.001
PSA, ng/mL	2.8 (0.7)	2.6 (0.6)	0.732
Time since diagnosis, d	—	1498 (1546)	—
Length of ADT, d	—	559 (331)	—
Tumor stage	—	2 (1)	—
Gleeson score	—	8 (1)	—

Data are expressed as mean (SD).

Abbreviations: KE 1MR, knee extension maximal strength; PSA, prostate-specific antigen; SPPB, short physical performance battery.

weeks before the trial day, body composition was determined using dual-energy x-ray absorptiometry (Hologic, Waltham, MA). Participants performed a 5-minute cycling warm-up and were familiarized with the knee extension exercise before maximal unilateral strength was determined. Two submaximal warm-up sets were completed before a series of single repetitions with increasing resistance were performed until participants were unable to complete the full range of motion. One minute of rest separated each attempt. One week later, testing was repeated and the highest value was used to determine maximal strength. Physical function was assessed using the short physical performance battery, as described by Guralnik *et al.* (27), immediately prior to strength testing.

Dietary control

Three-day dietary food records were used to estimate normal macronutrient intake. Participants were instructed to record all food and drink, as described previously (23). Average daily caloric requirements and total protein intake were estimated using the Harris–Benedict equation and adjusted based on participant-reported activity levels after meeting with the study dietician. Standardized diets containing 1.0 g/kg/day of protein for the 2 days prior to the trial were administered to the participants by the study dietician. Participants were otherwise instructed to keep dietary and physical activity habits consistent throughout their study participation.

Trial protocol

Between 7:00 and 7:30 AM, participants reported to the laboratory in the fasted state. Bilateral intravenous catheters were inserted for (1) stable isotope infusion and (2) repeat blood sampling with a 0.9% saline drip to keep the catheter patent. Priming doses of L-[*ring*-$^{13}C_6$]-phenylalanine (2 mmol/kg; 99 atom percent; Cambridge Isotopes, Tewksbury, MA) were delivered followed by continuous infusion (0.05 mmol/kg/minute) throughout the trial. Arterialized blood samples were obtained at regular intervals by warming the arm using a custom-built heater for 10 minutes prior to sampling or using a heat blanket, as described previously (23). After 2.5 hours of infusion, participants completed three sets of unilateral knee extensions using a predetermined load (70% of maximal strength) that was set at their 10-repetition maximum, separated by 2 minutes of rest. Participants were verbally encouraged to complete as many repetitions as possible until fatigue ensued. This resistance exercise protocol has demonstrated large increases in MPS (23, 28). Immediately following exercise, participants consumed 40 g of whey protein isolate (General Nutrition Company, Pittsburgh, PA) dissolved in 400 mL of water. The protein beverage was enriched to 8% L-[*ring*-$^{13}C_6$]-phenylalanine to minimize disturbances to the isotopic steady-state, as validated previously (29).

Muscle biopsies

Muscle samples were obtained from the *vastus lateralis* using a 5-mm Bergstrom needle (modified for manual suction), under 2% local anesthesia. Bilateral biopsies were obtained immediately and 240 minutes after protein consumption. All samples were blotted dry and any visible fat or connective tissue was removed prior to freezing in liquid nitrogen.

Muscle analyses

Myofibrillar-enriched protein fractions and intracellular amino acids were isolated from separate ~30 mg and ~20 mg of wet muscle, respectively, as described previously (23, 28).

Blood analyses

L-[*ring*-$^{13}C_6$]-phenylalanine enrichments from plasma were determined as described previously (23). Blood amino acid concentrations were analyzed by HPLC as previously described (23). Total testosterone (Immulite 2000; Siemens Immulite, Erlangen, Germany) and prostate-specific antigen levels (Sigma-Aldrich, Oakville, ON, Canada) were measured at the McMaster University Core Laboratory Facility. Within-assay coefficient of variation was less than 5% and between assay variability <7%. The minimum detectable concentration of total testosterone was 5 ng·dL^{-1} and prostate specific antigen was 0.1 mg/mL.

Protein synthesis calculations

MPS for myofibrillar proteins was calculated using the standard precursor-product method: MPS (%/hour) = $(E_{p2} - E_{p1})/E_{ic} \times 1/t \times 100$, where E_{p2} and E_{p1} are the protein-bound enrichments from biopsies obtained at 240 minutes and baseline plasma proteins, respectively. The difference represents the change in bound protein enrichment between time points. E_{ic} is the mean intracellular phenylalanine enrichment from biopsies taken from both legs at t = 240 minutes, and t is the exact tracer incorporation time in hours. Tracer-naive participants allowed for the use of preinfusion blood samples (*i.e.*, a mixed plasma protein fraction) as a surrogate baseline enrichment of muscle protein, as previously described (23, 28, 30) and validated (29).

Statistical analyses

Differences between groups were analyzed using a mixed model analysis of variance. Following the observation of a significant F ratio by analysis of variance, Bonferroni-adjusted

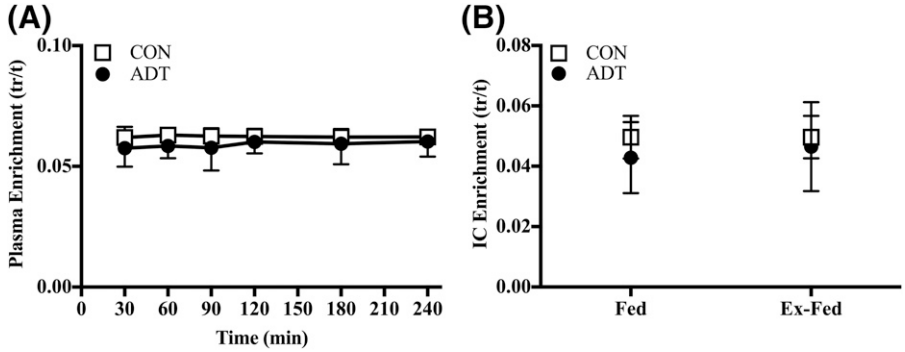

Figure 1. (A) $^{13}C_6$-phenylalanine enrichment measured and shown at tracer (tr)-to-tracee (t) ratio in the in plasma was stable, as shown from 30 to 240 minutes after exercise. (B) $^{13}C_6$-phenylalanine intracellular (IC) pool enrichment as determined from the 240 minute biopsy samples from the nonexercised (Fed) and exercised (Ex-Fed) legs. Data are expressed as mean (SD).

t tests were used for *post hoc* analyses. Localization of significant interaction was determined using simple main effect analyses. Correlations were used to examine the relationship between ADT length and resting MPS. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS 20 for MacIntosh. Data are reported as mean (SD).

Results

No group differences existed for age, height, body mass, functional status, or knee extension strength; men on ADT had a significantly greater body mass index ($P = 0.029$, Table 1). Men on ADT had suppressed total testosterone, which was below the clinical definition of low testosterone (<50 ng/dL), with levels significantly less than those of CON ($P < 0.001$). The average duration of ADT was 18 months.

Plasma $^{13}C_6$-phenylalanine enrichment remained constant following protein intake and resistance exercise and throughout the trial [Fig. 1(A)]. The tracer added to the protein drink resulted in an unaltered tracer-to-tracee ratio, indicating that isotopic equilibrium was present throughout the infusion. Plasma [Fig. 1(A)] and intracellular phenylalanine [Fig. 1(B)] enrichment levels with ADT were similar to CON, with no differences between Fed and Ex-Fed or between groups.

Blood leucine concentration increased 4.2-fold after protein consumption in ADT patients at 90 minutes [$P < 0.001$, Fig. 2(A)] and remained elevated above baseline (−180 minutes) throughout the trial ($P < 0.05$). A similar pattern was observed for branched chain amino acid concentration, with a 3.2-fold increase over baseline ($P < 0.001$) at 90 minutes that also remained elevated throughout the trial [$P < 0.05$, Fig. 2(B)].

For MPS, there was a significant group × time interaction [$P < 0.001$, Fig. 3(A)]. Compared with CON [0.0250 (0.004%/hour)], men on ADT had a 0.7-fold decrease in MPS at rest ($P = 0.001$) and a 0.5-fold decrease at 240 minutes in Fed ($P < 0.001$), but the group difference in Ex-Fed did not reach significance ($P = 0.054$). At 240 minutes, MPS was 1.7-fold higher for ADT and 2.3-fold higher for CON compared with baseline in Fed (both $P < 0.001$), but there was a greater change in CON [ΔADT, 0.0118 (0.0062%/hour); ΔCON, 0.0314 (0.0148%/hour); $P = 0.003$]. In Ex-Fed, MPS for ADT and CON was 3.5- and 3.3-fold higher than baseline and 2.1- and 1.5-fold higher than Fed, respectively (all $P < 0.001$), but the absolute change from baseline was not different between groups [ΔADT, 0.0451 (0.0083%/hour); ΔCON, 0.0584 (0.0271%/hour); $P = 0.380$]. ADT length did not appear to influence resting MPS rates [$r = 0.152$, $P = 0.720$, Fig. 3(B)].

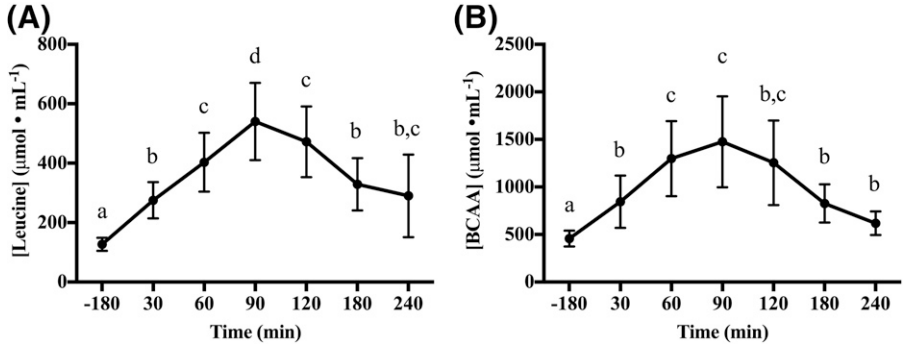

Figure 2. Blood amino acid profiles in men on ADT across the trial for (A) leucine and (B) total branched chain amino acids (BCAA). Time points with different letters were significantly different ($P < 0.05$) from each other. All data are presented as mean (SD).

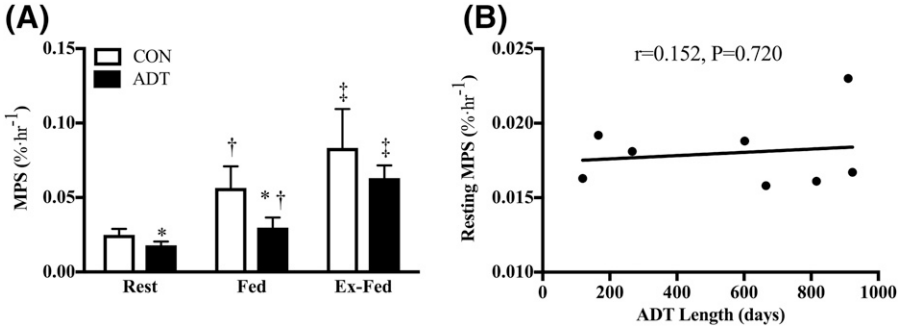

Figure 3. (A) Myofibrillar MPS (%/hr) at rest and 240 minutes after consumption of 40 g of protein (Fed) or 40 g of protein combined with resistance exercise (Ex-Fed) in CON vs ADT. (B) The association between length of ADT and resting MPS during PCa treatment. Data are presented as mean (SD). *Significantly different from CON at the specific time point ($P < 0.01$); †significantly different from baseline value ($P < 0.001$; ‡Significantly different from baseline and Fed condition ($P < 0.001$).

Discussion

The primary findings from this study were that men with PCa on ADT had reduced basal and protein feeding–induced rises in MPS, indicating a role for testosterone in maintaining these rates. However, when protein ingestion followed resistance exercise, increases in MPS in men on ADT exceeded those seen in protein alone and were of a similar magnitude and were not statistically significantly different from the optimal response seen in healthy elderly men. This suggests that ADT reduces resting MPS and in response to a protein-containing meal; however, men receiving ADT are still able to initiate a robust response in MPS following resistance exercise and consumption of an effective dose (0.4 to 0.5 g/kg) of whey protein (23, 24). This supports our previous work showing significant muscle hypertrophy is possible following high-intensity resistance training in men with PCa on ADT (8).

Testosterone's role in muscle hypertrophy is complex. Evidence from older adults strongly indicates that testosterone administration increases MPS and lean mass accretion (16, 17). Moreover, androgen suppression reduced resting MPS by 39%, as shown in this study, and whole-body protein synthesis by 12.5% (18). This decrease in MPS likely contributes to the 1% to 2% reduction in lean mass seen during the first 6 to 12 months of ADT (2–4). Muscle atrophy that accompanies ADT is insidious, persisting even after 24 to 36 months of treatment with little muscle mass change in non-ADT PCa patients or controls (2, 3). Resistance training is an attractive lifestyle choice to mitigate muscle loss, given its success in other clinical populations, but data are ambiguous when ADT and resistance training are combined. Early studies in PCa patients on ADT indicated no change in body composition and little evidence of muscle hypertrophy following resistance training (10, 31). This was supported by a recent year-long study combining moderate intensity resistance training and impact training (13). Other studies have shown modest (0.5 to 0.7 kg) muscle hypertrophy with resistance training during ADT (9, 11) compared with nonexercising controls, but that training responses may be compromised by ADT (32). Finally, our group has demonstrated a 1.8 kg increase in lean mass following high-intensity resistance training (8) that exceeded all other studies using PCa patients on ADT, and we have shown that the gains in knee extensor strength (28% vs 28%), knee extensor power (15% vs 16%), and total body lean mass (2.7% vs 1.9%) were similar to healthy men of similar age performing an identical training routine (15). Interestingly, only PCa patients showed a tendency to improve lean mass whereas all other types of cancer survivors demonstrated little change in a recent systematic review of resistance training following treatment (12). Collectively, these data suggest that muscle hypertrophy is possible during treatment of PCa; however, differences in study methodologies may preclude a clear effect.

Exercise oncology is an emerging field and initial studies used relatively conservative exercise interventions because the risk of potential adverse events was unknown (10, 31). We hypothesize that the heterogeneous hypertrophic responses previously reported after resistance training in PCa patients are most likely due to reduced training intensities or volumes used during ADT that were insufficient to stimulate MPS and lean mass accretion. We propose that this thesis is more likely as opposed to an inherent muscle-related deficit due to testosterone deficiency. In support of this thesis, we report in this study that men on ADT demonstrated robust increases in MPS and that the absolute change from baseline was similar to CON in Ex-Fed. Although admittedly not hypertrophy, MPS increases are indicative that the capacity of the muscle to respond to a loading stimulus is intact. In the present study, resistance exercises were performed to volitional fatigue, and this may be a critical element driving the increased MPS, regardless of

concentrations of testosterone, training volume, or intensity. For example, three sets of knee extension to failure induced a 3.1-fold increase in MPS whereas a single set elevated MPS 2.1-fold in healthy individuals (28). The absolute load may also not be critical, as light (30% of maximum) and heavy (90% of maximum) resistance exercise to fatigue increases myofibrillar MPS to the same degree (33). In our previous work, men on ADT performed 15 repetitions, beginning at a load equivalent to their five repetition maximum (8). When muscle failure ensued, slightly reducing the load several times permitted the fatigued muscle to complete all 15 repetitions in each set. A common theme between the present study, our previous work (8), and other investigations (28, 33) was completing work to fatigue. This may be an important consideration when seeking to induce muscle hypertrophy to preserve or enhance physical function in older oncology patients while simultaneously reducing the absolute load required in patients with disabilities or limitations.

It has been well documented that to maximize MPS in older adults, greater protein doses are required. Older men require ~0.4 g of protein/kg/meal (22, 23) to achieve anabolic effects similar to their younger counterparts consuming only 0.25 g of protein/kg/meal (24, 25). In the present study, men on ADT exceeded this threshold (0.46 g of protein/kg/meal), yet a diminished response was observed relative to CON for Fed. This suggests that age-related anabolic resistance to protein intake may be greater during PCa treatment. Previous research showing no difference in MPS rates between young men and women, where testosterone differences are substantial (30), indirectly supports the notion that androgenic hormones (*i.e.*, testosterone) are not a primary driver of meal-induced increases MPS. We propose that these observations suggest that other factors such as disease state, ADT length, or habitual physical activity are also playing a role in determining protein-stimulated increases in MPS. Surprisingly, ADT length did not influence resting MPS rates in the present study, which does not support previous finding where PCa patients on acute (<6 months) ADT experienced greater muscle atrophy than did those on chronic ADT (>6 months) (2, 3). Although the attenuated rise in MPS with Fed raises the possibility that with ADT greater doses of protein may be required to maximally stimulate MPS, the MPS response appears to be independent of length of time since ADT onset under the current conditions.

Protein supplementation during ADT is limited, and we are not aware of any data examining MPS, MPB, or lean mass accretion during testosterone suppression. Given the attenuated Fed response, future studies should consider higher protein doses for men undergoing ADT for PCa and advocating for resistance training to prevent adverse changes in body composition. Doses may even need to exceed the 40 g (~0.46 g/kg) used in the present study to maximize MPS and attenuate MPB to induce hypertrophy (26).

Indicators of MPB were not measured in the present study due to limited muscle sample. Therefore, we were unable to assess changes in MPB during ADT. Hyperaminoacidemia and testosterone independently increase MPS with no change in MPB (34, 35), whereas resistance exercise increases both MPS and MBP (36). The net result is an improvement in fasting net protein balance (34–36). In hyperaminoacidemia, testosterone reduces MBP and enhances MPS efficiency (37). It is possible that changes in inward and outward amino acid transport occurred in the older men undergoing ADT, and thus with protein ingestion there may have been a reduction in the amino acid pool available to stimulate MPS (37), but we are unable to account for this.

This study had limitations. The sample sizes used were adequate to determine within-group changes but may be slightly underpowered to detect between-group differences for Ex-Fed ($1 - \beta = 0.556$). The original protein source from the CON (23) was no longer available. The source used in the ADT group had no substantial differences in leucine (4.0 g vs 4.2 g), branched chain amino acids (3.5 g vs 3.5 g), or essential amino acids (18.4 g vs 18.2 g) and individual amino acid concentration that did not vary by >1.25% per 40-g serving (Supplemental Table 1). The design of this study included healthy men and compared the Fed and Ex-Fed responses during ADT in a best case scenario. In this initial study, we sought to examine the effects in the population most affected by ADT and to see if the response was normal. Although the effects of resistance exercise only were not included, current best practice is to consume protein shortly after exercise (38) and was used in this study.

In summary, the MPS response in older men following resistance exercise in the Fed state does not appear to be significantly influenced by systemic concentrations of testosterone. ADT resulted in a reduced MPS at rest and with feeding, but structured resistance training with planned protein ingestion may be advantageous in men undergoing ADT for PCa by helping alleviate muscle atrophy. In planning resistance training programs during ADT, working to fatigue may be a critical factor because we observed a robust stimulation of MPS in the Fed state, and this training style has demonstrated significant muscle hypertrophy during ADT (8). Future studies should explore mechanisms underpinning ADT-induced reductions in MPS at rest and after protein feeding. It will be important to delineate the amount and timing of protein consumption that will minimize the side effects of

ADT to preserve muscle mass, function, and ultimately quality of life in men being treated for PCa.

Acknowledgments

The authors thank the participants for their involvement and for the research staff of Jessica Meilak, Colleen Steward, and Samantha Cassar at Victoria University for invaluable assistance with trial day preparations, and Todd Prior and Tracy Rerecich at McMaster University for coordinating sample transfers and for obtaining the MPS data.

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This work was supported by funding from the following sources: E.D.H. was supported by a research development grant scheme from Victoria University and the Oded Bar-Or International Scholar Award from the American College of Sports Medicine. D.W.D.W. was supported by a Canadian Institutes for Health Research doctoral award. S.M.P. was supported by grants from the National Science and Engineering Research Council of Canada (RGPIN-04613), the Canadian Institutes for Health Research, and the Canada Research Chairs Program. A.H. was supported by Collaborative Research Network funding from the Department of Industry, Innovation and Science of Australia.

Disclosure Summary: The authors have nothing to disclose.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;**65**(1):5–29.
2. Smith MR, Saad F, Egerdie B, Sieber PR, Tammela TL, Ke C, Leder BZ, Goessl C. Sarcopenia during androgen-deprivation therapy for prostate cancer. *J Clin Oncol*. 2012;**30**(26):3271–3276.
3. van Londen GJ, Levy ME, Perera S, Nelson JB, Greenspan SL. Body composition changes during androgen deprivation therapy for prostate cancer: a 2-year prospective study. *Crit Rev Oncol Hematol*. 2008;**68**(2):172–177.
4. Galvão DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, Rowling C, Prince R. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int*. 2008;**102**(1):44–47.
5. Gonzalez BD, Jim HS, Small BJ, Sutton SK, Fishman MN, Zachariah B, Heysek RV, Jacobsen PB. Changes in physical functioning and muscle strength in men receiving androgen deprivation therapy for prostate cancer: a controlled comparison. *Support Care Cancer*. 2016;**24**(5):2201–2207.
6. Bylow K, Mohile SG, Stadler WM, Dale W. Does androgen-deprivation therapy accelerate the development of frailty in older men with prostate cancer?: a conceptual review. *Cancer*. 2007; **110**(12):2604–2613.
7. Hanson ED, Hurley BF. Intervening on the side effects of hormone-dependent cancer treatment: the role of strength training. *J Aging Res*. 2011;903291.
8. Hanson ED, Sheaff AK, Sood S, Ma L, Francis JD, Goldberg AP, Hurley BF. Strength training induces muscle hypertrophy and functional gains in black prostate cancer patients despite androgen deprivation therapy. *J Gerontol A Biol Sci Med Sci*. 2013;**68**(4): 490–498.
9. Nilsen TS, Raastad T, Skovlund E, Courneya KS, Langberg CW, Lilleby W, Fosså SD, Thorsen L. Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. *Acta Oncol*. 2015;**54**(10):1805–1813.
10. Galvão DA, Nosaka K, Taaffe DR, Spry N, Kristjanson LJ, McGuigan MR, Suzuki K, Yamaya K, Newton RU. Resistance training and reduction of treatment side effects in prostate cancer patients. *Med Sci Sports Exerc*. 2006;**38**(12):2045–2052.
11. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*. 2010;**28**(2):340–347.
12. Hanson ED, Wagoner CW, Anderson T, Battaglini CL. The independent effects of strength training in cancer survivors: a systematic review. *Curr Oncol Rep*. 2016;**18**(5):31.
13. Winters-Stone KM, Dieckmann N, Maddalozzo GF, Bennett JA, Ryan CW, Beer TM. Resistance exercise reduces body fat and insulin during androgen-deprivation therapy for prostate cancer. *Oncol Nurs Forum*. 2015;**42**(4):348–356.
14. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. *J Clin Oncol*. 2014;**32**(4):335–346.
15. Hanson ED, Srivatsan SR, Agrawal S, Menon KS, Delmonico MJ, Wang MQ, Hurley BF. Effects of strength training on physical function: influence of power, strength, and body composition. *J Strength Cond Res*. 2009;**23**(9):2627–2637.
16. Bhasin S, Woodhouse L, Storer TW. Proof of the effect of testosterone on skeletal muscle. *J Endocrinol*. 2001;**170**(1):27–38.
17. Urban RJ, Bodenburg YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, Ferrando A. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am J Physiol*. 1995;**269**(5 Pt 1):E820–E826.
18. Mauras N, Hayes V, Welch S, Rini A, Helgeson K, Dokler M, Veldhuis JD, Urban RJ. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. *J Clin Endocrinol Metab*. 1998;**83**(6):1886–1892.
19. Breen L, Phillips SM. Nutrient interaction for optimal protein anabolism in resistance exercise. *Curr Opin Clin Nutr Metab Care*. 2012;**15**(3):226–232.
20. Burd NA, Yang Y, Moore DR, Tang JE, Tarnopolsky MA, Phillips SM. Greater stimulation of myofibrillar protein synthesis with ingestion of whey protein isolate v. micellar casein at rest and after resistance exercise in elderly men. *Br J Nutr*. 2012;**108**(6):958–962.
21. Cribb PJ, Williams AD, Carey MF, Hayes A. The effect of whey isolate and resistance training on strength, body composition, and plasma glutamine. *Int J Sport Nutr Exerc Metab*. 2006;**16**(5): 494–509.
22. Pennings B, Groen B, de Lange A, Gijsen AP, Zorenc AH, Senden JM, van Loon LJ. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. *Am J Physiol Endocrinol Metab*. 2012;**302**(8): E992–E999.
23. Yang Y, Breen L, Burd NA, Hector AJ, Churchward-Venne TA, Josse AR, Tarnopolsky MA, Phillips SM. Resistance exercise enhances myofibrillar protein synthesis with graded intakes of whey protein in older men. *Br J Nutr*. 2012;**108**(10):1780–1788.
24. Moore DR, Churchward-Venne TA, Witard O, Breen L, Burd NA, Tipton KD, Phillips SM. Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. *J Gerontol A Biol Sci Med Sci*. 2015; **70**(1):57–62.
25. Moore DR, Robinson MJ, Fry JL, Tang JE, Glover EI, Wilkinson SB, Prior T, Tarnopolsky MA, Phillips SM. Ingested protein dose response of muscle and albumin protein synthesis after resistance exercise in young men. *Am J Clin Nutr*. 2009;**89**(1):161–168.

26. Churchward-Venne TA, Holwerda AM, Phillips SM, van Loon LJ. What is the optimal amount of protein to support post-exercise skeletal muscle reconditioning in the older adult? *Sports Med*. 2016; **46**(9):1205–1212.
27. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;**49**(2):M85–M94.
28. Burd NA, Holwerda AM, Selby KC, West DW, Staples AW, Cain NE, Cashaback JG, Potvin JR, Baker SK, Phillips SM. Resistance exercise volume affects myofibrillar protein synthesis and anabolic signalling molecule phosphorylation in young men. *J Physiol*. 2010; **588**(Pt 16):3119–3130.
29. Burd NA, West DW, Rerecich T, Prior T, Baker SK, Phillips SM. Validation of a single biopsy approach and bolus protein feeding to determine myofibrillar protein synthesis in stable isotope tracer studies in humans. *Nutr Metab (Lond)*. 2011;**8**:15.
30. West DW, Burd NA, Churchward-Venne TA, Camera DM, Mitchell CJ, Baker SK, Hawley JA, Coffey VG, Phillips SM. Sex-based comparisons of myofibrillar protein synthesis after resistance exercise in the fed state. *J Appl Physiol*. 2012;**112**(11): 1805–1813.
31. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, Venner PM, Quinney HA, Jones LW, D'Angelo ME, Wells GA. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2003;**21**(9):1653–1659.
32. Kvorning T, Andersen M, Brixen K, Madsen K. Suppression of endogenous testosterone production attenuates the response to strength training: a randomized, placebo-controlled, and blinded intervention study. *Am J Physiol Endocrinol Metab*. 2006;**291**(6): E1325–E1332.
33. Burd NA, West DW, Staples AW, Atherton PJ, Baker JM, Moore DR, Holwerda AM, Parise G, Rennie MJ, Baker SK, Phillips SM. Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. *PLoS One*. 2010;**5**(8):e12033.
34. Volpi E, Ferrando AA, Yeckel CW, Tipton KD, Wolfe RR. Exogenous amino acids stimulate net muscle protein synthesis in the elderly. *J Clin Invest*. 1998;**101**(9):2000–2007.
35. Ferrando AA, Tipton KD, Doyle D, Phillips SM, Cortiella J, Wolfe RR. Testosterone injection stimulates net protein synthesis but not tissue amino acid transport. *Am J Physiol*. 1998;**275**(5 Pt 1): E864–E871.
36. Biolo G, Maggi SP, Williams BD, Tipton KD, Wolfe RR. Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. *Am J Physiol*. 1995;**268**(3 Pt 1): E514–E520.
37. Ferrando AA, Sheffield-Moore M, Wolf SE, Herndon DN, Wolfe RR. Testosterone administration in severe burns ameliorates muscle catabolism. *Crit Care Med*. 2001;**29**(10):1936–1942.
38. Morton RW, McGlory C, Phillips SM. Nutritional interventions to augment resistance training-induced skeletal muscle hypertrophy. *Front Physiol*. 2015;**6**:245.