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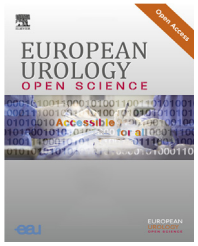

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Prostate Cancer

Profiling of Skeletal Muscle and Adipose Tissue Depots in Men with Advanced Prostate Cancer Receiving Different Forms of Androgen Deprivation Therapy

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Abstract

Background: Androgen deprivation therapy (ADT) is a common treatment modality for men with prostate cancer. Increases in adipose tissue mass and decreases in skeletal muscle mass are known on-target adverse effects of standard ADT. The effects of newer agents such as abiraterone acetate (ABI) and enzalutamide (ENZA) on body composition and how these compare with standard luteinizing hormone-releasing hormone agonists (aLHRHs) are unclear.
Objective: To assess the effects of different forms of androgen deprivation therapy on body composition in men with prostate cancer.
Design, setting, and participants: Using a retrospective design, 229 patients receiving aLHRHs alone (n = 120) or in combination with ABI (n = 53) or ENZA (n = 56) were studied.
Outcome measurements and statistical analysis: Muscle, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) were assessed at baseline, 6 mo, and 18 mo after initiating therapy using a cross-sectional densitometry analysis performed on standard of care computed tomography images. Response trajectories for all treatment groups were calculated via a two-way analysis of variance post hoc test, for both within-group and between-group differences.
Results and limitations: Treatment with aLHRHs, ABI, and ENZA was associated with a median muscle volume loss of –1.4%, –4.8%, and –5.5% at 6 mo, and –7.1%, –8.1%, and –8.3% at 18 mo, respectively. Therapy with aLHRHs was associated with minimal changes in VAT (0.3% at 6 mo and –0.1% at 18 mo). ABI therapy was associated with significant increases in VAT at 6 mo (4.9%) but not at 18 mo (0.5%), and ENZA therapy was associated with significant decreases in VAT (–4.6% at 6 mo and –5.4% at 18 mo). With respect to SAT, treatment with aLHRHs was associated with increases over time (8.6% at 6 mo and 4.7% at 18 mo), ABI was associated with

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decreases over time (–3.6% at 6 mo and –6.8% at 18 mo), and ENZA had no clear effects (1.7% at 6 mo and 3.3% at 18 mo).
Conclusions: ADT regimens cause significant short-term losses in muscle mass, with the most rapid effects occurring with ABI and ENZA. The three regimens have disparate effects on SAT and VAT, suggesting distinct roles of androgens in these tissues.
Patient summary: Androgen deprivation therapy alters body composition in men with prostate cancer. Abiraterone and enzalutamide are associated with losses in muscle mass compared with luteinizing hormone-releasing hormone agonists. These treatments impact subcutaneous and visceral fat mass, suggesting distinct roles of androgens in these tissues.

1. Introduction

Prostate cancer is the most common malignancy in American men, accounting for nearly 20% of all cancers in men, making it one of the most common cancers of this population [1]. Androgen deprivation therapy (ADT) is a common treatment modality for men with advanced prostate cancer. The biological basis of ADT lies in the fact that prostate cancers are highly enriched with androgen receptors, the stimulation of which drives the growth of these cancers. Androgens such as testosterone or dihydrotestosterone (DHT) are required for the growth and proliferation of prostate-derived cells. The production and release of these hormones are governed by the hypothalamic-pituitary-gonadal axis with the release of luteinizing hormone-releasing hormone (LHRH)-stimulating pituitary luteinizing hormone secretion and subsequent testosterone production from the testes. The prostate then converts testosterone to 5α-DHT, which then binds to the androgen receptor. The stimulation of the androgen receptor is critical to the growth and development of healthy and malignant prostate cells and is similarly important in slowing growth in malignant cells when these receptors are blocked [2].

ADT is commonly achieved by using LHRH agonists (aLHRHs) such as leuprolide or goserelin, or antagonists such as degarelix, resulting in low levels of serum testosterone, typically <20 ng/dl. Suppressing testosterone alters body composition greatly. In adult men, low testosterone levels results in lower muscle mass and strength, and these effects can be restored with testosterone replacement therapy [3]. In men with prostate cancer treated with aLHRHs, lean mass (predominantly skeletal muscle) decreases (–2.8%, 95% confidence interval [CI] –3.6 to –2.0, $p < 0.0001$) and fat mass increases (+7.7%, 95% CI 4.3–11.2, $p < 0.0001$) [4]. These changes in body composition have important implications on cancer-specific outcomes and quality of life. Low skeletal muscle mass is an independent adverse prognosticator for prostate cancer progression [5], and increased fat mass itself is an independent risk factor for increased mortality in patients with prostate cancer [6,7]. Furthermore, men with prostate cancer who are treated with ADT have an increased risk of adverse cardiovascular events and cardiovascular deaths [8]. Men with low muscle mass also have higher rates of frailty, falls, fractures, and depressed mood, which all reduces quality of life [9]. The risk of falls is compounded in these patients by ADT-induced osteopenia and osteoporosis [10].

Most research in prostate cancer and body composition changes has focused on aLHRHs; however, the landscape of prostate cancer treatment has changed dramatically in recent years. Novel agents that target the androgen axis can further suppress serum testosterone to very low level (<0.9 ng/dl) and completely block its effects at the level of the androgen receptor. For example, abiraterone (ABI) is a 17α-hydroxylase and 17,20-lyase inhibitor that blocks the early steps of androgen biosynthesis in the testes, adrenal gland, and prostate cancer cells [11]. ABI is associated with hypertension secondary to selective inhibition of CYP17 leading to hypermineralocorticoidism [12], and so ABI is combined with oral glucocorticoid replacement therapy (eg, prednisone). Another approach to block the effects of androgens is to directly target the androgen receptor. Enzalutamide (ENZA) is a nonsteroidal antiandrogen that blocks androgen receptor signaling by inhibiting its binding to androgens, nuclear translocation, and interactions with coactivators [13]. In recent times, ABI and ENZA are given in combination with aLHRHs in the setting of advanced castration-resistant and castration-sensitive prostate cancer, and have been shown to improve overall survival, time to biochemical progression, progression-free survival, and biochemical response rates [14,15].

Given the unique mechanisms of action of these ADT approaches, the effects on skeletal muscle and fat tissue may differ from single-agent aLHRHs. We hypothesized that ABI and ENZA would be associated with more severe losses in skeletal muscle but have disparate effects on adipose tissue when compared with patients treated with aLHRHs alone over the course of 18 mo.

2. Patients and methods

2.1. Study approval, patients, and setting

This is a single-center, retrospective study. Clinical data and imaging files were extracted from the medical records of patients with prostate cancer treated with aLHRHs alone or aLHRHs combined with ENZA or ABI who received diagnostic workup and/or treatment at Memorial

Sloan Kettering Cancer Center (MSKCC) between 2007 and 2015. Patients receiving ABI also received 5 mg of prednisone twice daily. Most of the patients treated with ABI 89% (50/56) and ENZA 54% (31/57) participated in clinical trials that included only patients with castrate-resistant prostate cancer. Changes in body composition were calculated without grouping by castration status. Clinical data were extracted from the medical record within 1 mo of a patient's recorded computed tomography (CT) scan corresponding to the start of therapy (aLHRH, ENZA + aLHRH, or ABI + aLHRH). These data included demographics, treatment course, pathology reports, and testosterone levels obtained from electronic records.

The study was approved by the institutional review board of MSKCC (protocol 16-586). Investigators from Weill Cornell Medicine received anonymized data for analysis under an exemption waiver from the institutional review board of Weill Cornell Medicine.

2.2. Computed tomography image analysis

The imaging files were reviewed on commercially available PACS software (Centricity; GE Healthcare, Chicago, IL, USA) to ensure that there was no artifact distortion. Muscle volume was measured at the L3 level by two readers who were trained and was supervised by two consultant radiologists. Using iNtuition software (TeraRecon, Houston, TX, USA), the volumetric slabs were analyzed for the presence of skeletal muscle using a semiautomated technique, as described previously [16]. First, attenuation thresholds of –29 and 150 HU were applied to the entire image volume, and a color-coded map of voxels was generated to highlight the skeletal muscle. The nonmuscular soft tissues (abdominopelvic viscera, large blood vessels, spinal cord, and portions of the bone marrow) were excluded manually by drawing a region of interest around the identified tissue region. Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes were segmented from the L3 volumetric slab using a similar semiautomated approach with iNtuition.

2.3. Statistical measures

The clinical and demographic characteristics were analyzed by summary statistics (*N* [%], median, range). Two-way analysis of variance (ANOVA) was used to access the effect of treatment group and time for each therapy on muscle, subcutaneous fat, and visceral fat volumes at the three time points using both absolute values and values relative to baseline. An ANOVA Tukey's post hoc analysis was applied with Bonferroni correction where appropriate. Analyses were performed using Python (3.9.1) and R (4.1.1), and graphs were created in Prism.

3. Results

3.1. Patient population description

A total of 229 patients were identified from the electronic medical record as having received either leuprolide or goserelin (grouped together as aLHRHs) or aLHRHs in combination with ABI or ENZA over the course of 18 mo. One hundred and twenty (53%) patients received aLHRHs only, 53 (23%) received ABI + aLHRH, and 56 (24%) received ENZA + aLHRH (Table 1). Most patients in this study were identified as White (89%), with the remainder of patients identifying as Black or African American (7%), Asian or of Indian subcontinent (1%), or other/unknown (3%). Nearly all patients (98%) had a pathological diagnosis of adenocarcinoma, with 27% having distant metastasis, 25% having local nodal involvement, and the remaining with locally advanced disease without nodal involvement or metastasis. The majority of patients (55%) had a baseline testosterone level of <50 ng/dl, defined here as "castrate," and the remainder (10%) demonstrated a baseline testosterone level of >50 ng/dl, defined here as "noncastrate" or had unknown castrate status (34%). Of the castrate patients, the median testosterone level was <10 ng/dl. Volumetric skeletal muscle, SAT, and VAT measures were quantified using clinical diagnostic CT images at baseline, 6 mo, and 18 mo after the initiation of treatment (Table 2). There were no significant differences in the baseline skeletal muscle, SAT, and VAT values among groups. After 6 mo of treatment, patients treated with ABI had less skeletal muscle than the aLHRH group (p = 0.0009). There were no differences in the SAT or VAT volumes among groups at this time point. After 18 mo of treatment, the aLHRH group had significantly reduced muscle volume as compared with baseline (p = 0.02), and the ABI group had significantly less muscle than the aLHRH group.

3.2. Relative changes in skeletal muscle, visceral fat, and subcutaneous fat over time

The absolute levels of skeletal muscle, SAT, and VAT were highly variable within each group, so we next analyzed the percent change in skeletal muscle, SAT, and VAT over time (Fig. 1). In this analysis, it was shown that all patients experienced reductions in muscle volume, regardless of treatment group (Fig. 1A). Patients in the aLHRH group experienced the least amount of muscle loss at 6 mo (–1.4%, range: –14.4% to 12.3%) when compared with other arms (ABI: –4.8%, range: –25.1% to 0.9%; ENZA: –5.5%, range: –48.0% to 8.6%) and at 18 mo –7.1%, range: –24.3% to 14.4%, p < 0.001) compared with other groups (ABI: –8.1%, range: –33.3% to 7.6%, p < 0.001; ENZA: –8.3%, range: –27.0% to –1.6%, p < 0.001). However, the aLHRH group also experienced the greatest decrease in muscle volume between the 6- and 18-mo time points (–1.4% to –7.1%) compared with the other treatment groups (ENZA: –5.5% to –8.3%; ABI: –4.8% to –8.1%).

With respect to changes in VAT (Fig. 1B), there was no significant difference over time in the aLHRH group (0.3% at 6 mo and –0.1% at 18 mo). There was a statistically significant reduction in the ENZA group at 6 mo (–4.6%, p = 0.004) and 18 mo (–5.4%, p = 0.005) as compared with baseline, and a reduction at both times compared with aLHRHs (p = 0.007 and p = 0.009, respectively). There was a significant increase in VAT in the ABI group as compared with baseline (4.9%, p = 0.004) and the aLHRH group at 6 mo (p = 0.01), but not at 18 mo.

With respect to changes in SAT (Fig. 1C), the aLHRH group increased at 6 mo (8.6%, p < 0.0001) and at 18 mo (4.7%, p = 0.09) as compared with baseline. The ABI group lost SAT at both 6 mo (–3.6%, p = 0.16) and 18 mo (–6.8%, p = 0.02) as compared with baseline. There were no significant changes in SAT in the ENZA group over time (1.7% at 6 mo and 3.3% at 18 mo). At 6 mo, both ABI (p < 0.0001) and ENZA (p = 0.04) had less SAT change than aLHRHs. At 18 mo, the ABI group had lost more SAT than the aLHRH (0.0002) and ENZA (0.05) groups.

Table 1 – Patient characteristics

Number	Total	aLHRH	ABI	ENZA
Total, *n* (%)	229 (100)	120 (52)	53 (23)	56 (24)
Age at treatment start (yr), median (IQR)	68 (62–75)	67 (61–73)	73 (67–77)	67 (61–75)
Race, *n* (%)				
White	203 (89)	100 (83)	51 (96)	52 (93)
Black or African American	17 (7)	12 (10)	2 (4)	3 (5)
Asian—Far East/Indian	2 (1)	2 (2)	0 (0)	0 (0)
Other	2 (1)	2 (2)	0 (0)	0 (0)
Unknown	5 (2)	4 (3)	0 (0)	1 (2)
Histological description, *n* (%)				
Adenocarcinoma	228 (98)	119 (99)	52 (98)	56 (100)
Infiltrating duct carcinoma	1 (0.3)	0 (0)	1 (2)	0 (0)
T stage, *n* (%)				
TX	16 (7)	9 (8)	4 (8)	3 (5)
T0	0 (0)	0 (0)	0 (0)	0 (0)
T1	98 (43)	51 (43)	25 (47)	22 (39)
T2	44 (19)	17 (14)	13 (25)	14 (25)
T3	49 (21)	34 (28)	6 (11)	9 (16)
T4	8 (3)	6 (5)	0 (0)	2 (4)
Unknown	14 (6)	3 (3)	5 (9)	6 (11)
N stage, *n* (%)				
NX	16 (7)	5 (4)	6 (12)	5 (9)
N0	144 (63)	76 (63)	34 (69)	34 (61)
N1	57 (25)	37 (31)	9 (18)	11 (20)
Unknown	12 (5)	2 (2)	4 (8)	6 (11)
M stage, *n* (%)				
MX	6 (3)	1 (1)	2 (4)	3 (5)
M0	150 (66)	77 (64)	35 (66)	38 (68)
M1	61 (27)	40 (33)	12 (23)	9 (16)
Unknown	12 (5)	2 (2)	4 (8)	6 (11)
Castrate status, *n* (%)				
Castrate (testosterone <50 ng/dl)	126 (55)	35 (29)	41 (77)	50 (89)
Noncastrate (testosterone >50 ng/dl)	22 (10)	19 (16)	3 (6)	0 (0)
Unknown	81 (35)	66 (55)	9 (17)	6 (11)

aLHRH = luteinizing hormone-releasing hormone agonist; ABI = abiraterone; ENZA = enzalutamide; IQR = interquartile range.

Table 2 – Absolute median body composition volumes

	Skeletal muscle (cm^3)				SAT (cm^3)				VAT (cm^3)			
	aLHRH	ABI	ENZA	ANOVA (group) *p* value	aLHRH	ABI	ENZA	ANOVA (group) *p* value	aLHRH	ABI	ENZA	ANOVA (group) *p* value
Baseline	486.5 (275–684)	435.0 (304–687)	478.0 (362–730)	**<0.0001**	28.2 (6.84–62.2)	26.55 (8.82–59.4)	27.15 (7.72–48.3)	**0.007**	116.5 (68.7–204)	119.5 (71.8–215)	114.5 (66.9–200)	**0.04**
6 mo	480.5 (279–683)	**407.5[a] (300–620)**	447.5 (297–675)		29.55 (6.53–62.3)	25.1 (7.89–56.3)	27.85 (3.79–49.9)		113 (55.3–201)	123.5 (69.8–210)	103 (57–184)	
18 mo	**451.5[b] (252–664)**	**400.5[a] (295–689)**	442 (309–598)		27.55 (5.92–56.6)	22.9 (5.75–53)	27.3 (8.4–51.9)		114.5 (69.4–205)	120.5 (59.5–213)	105 (77.9–168)	
ANOVA (time) *p* value		**<0.0001**		0.65		0.66		0.8		0.74		0.68

aLHRH = luteinizing hormone-releasing hormone agonist; ANOVA = analysis of variance; ABI = abiraterone; ENZA = enzalutamide; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.
ANOVA (time) compares differences in means in body composition with respect to time. ANOVA (group) compares differences in means in body composition with respect to treatment.
Bolded values are associated with a significant p-value ($p < 0.05$).
[a] Denotes a significant change as compared with an aLHRH.
[b] Denotes a significant change from baseline.

4. Discussion

Adverse changes in body composition are well established in men with advanced prostate cancer receiving ADT; however, such changes have been assessed using modalities that cannot directly measure skeletal muscle mass such as body mass index, waist and thigh circumference, and dual-energy x-ray absorptiometry [5–7,9,10]. Here, we use direct volumetric measures of tissue abundance from CT images to describe the effects of aLHRHs, ABI, and ENZA on skeletal

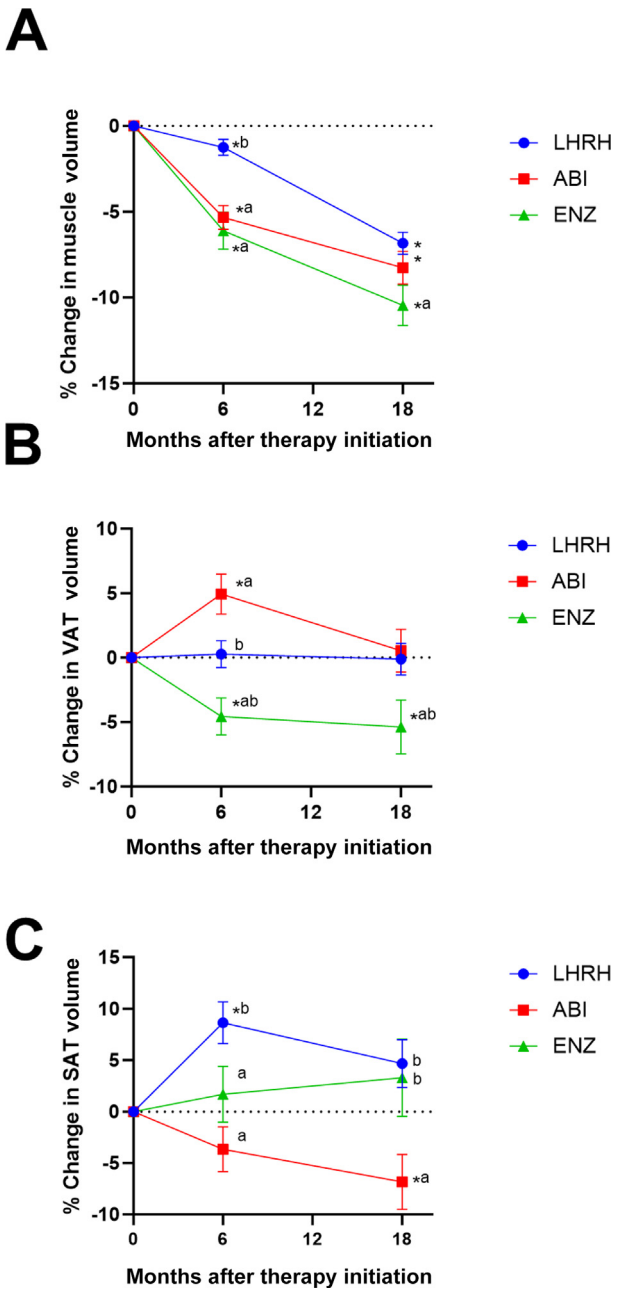

Fig. 1 – Percent changes in tissue volume over time. Percent change in (A) skeletal muscle, (B) visceral adipose tissue (VAT), and (C) subcutaneous adipose tissue (SAT) over time in patients with prostate cancer treated with LHRH agonists (aLHRHs), abiraterone (ABI), and enzalutamide (ENZ). Significant changes ($p < 0.05$ by two-way ANOVA post hoc test) are indicated by * for within-group comparisons compared with baseline, letter a for between-group differences compared with aLHRHs, and letter b for between-group differences compared with ABI. LHRH = luteinizing hormone-releasing hormone.

muscle and adipose tissue over time. Our data provide unique insight into the disparate effects of these agents on body composition over time.

We find that both ABI and ENZA induce a more rapid loss of skeletal muscle with significant differences at 6 mo, as compared with aLHRHs. These differences are attenuated at 18 mo because the aLHRH group experiences a large drop in muscle mass from 6 to 18 mo. We suspect that these early changes are due to the rapid and potent effects of ABI and ENZA on testosterone levels and androgen receptor activity, as compared with aLHRHs. At 18 mo, the ENZA group continues to have lost more muscle mass than the aLHRH group, suggesting that inhibition of the androgen receptor reduces muscle mass more effectively than lowering testosterone levels.

Our data expand those of Fischer et al [17] who used cross-sectional imaging to analyze body composition changes after a median time of about 11 mo. In a cohort of 54 individuals, they found that ENZA and ABI induce losses of skeletal muscle compared with baseline (ENZA: −5.2%, $p < 0.0001$, and ABI: −3.0%, $p = 0.02$). In agreement with our data, they found that the loss of skeletal muscle with ENZA occurred early and was already apparent after 3–6 mo on treatment. Our data quantify this finding and compare its magnitude with those of patients treated with aLHRHs alone.

Our work also agrees with other groups who find an increase in fat mass in patients treated with aLHRHs [18,19]. We find that this increase is due exclusively to changes in SAT volume and not VAT. Interestingly, the addition of ABI to aLHRHs reverses this effect completely, and leads to an early and sustained loss of SAT volume. SAT is an energy storage depot, and its loss may be due to changes in energy balance, such as reduced food intake or increased energy expenditure in the setting of advancing cancer. We cannot rule out a direct effect of ABI or a steroid precursor on SAT.

We find that ENZA has distinct effects on VAT, causing an early and sustained loss in tissue volume that is not observed with aLHRHs or ABI. This result suggests that the androgen receptor plays a distinct role in this tissue. Androgen receptors are more prominent in VAT than in SAT [20]. In rodents, selective knockdown of the androgen receptor in adipocytes reduces VAT mass by regulating insulin action and rates of lipolysis [21]. Given the importance of VAT in the normal physiological balance of adipokines, insulin resistance, and endothelial dysfunction [22], we speculate that patients treated with ENZA would have improved metabolic outcomes as compared with those treated with ABI. Indeed, ABI is associated with new diagnosis of diabetes (hazard ratio [HR], 1.37), while ENZA was associated with a reduced risk of diabetes (HR, 0.66) in men with prostate cancer [23].

There was a 4-yr difference in the average age of participants between the ABI group and the ENZA and aLHRH groups. This discrepancy did not cause a difference in the body composition parameters at baseline (Table 2). However, age is associated with a decrease in skeletal muscle and a shift from subcutaneous fat to visceral fat, so we cannot exclude a contribution [24,25]. Additionally, age decreases metabolic rate, reduces hepatic and renal clearance, and increases sensitivity to pharmacological agents [26]. Another confounding variable that may have impacted body composition was the coadministration of prednisone with ABI. Prednisone induces a state of insulin resistance in skeletal muscle and limits muscle repair and contractility [27]. Additionally, prednisone leads to redistribution of subcutaneous fat to visceral fat [28]. This effect mimics the

unique changes in VAT and SAT seen in the ABI arm: an initial rise in VAT and a greater sustained decrease in SAT. It is possible that the effects of age and corticosteroid use combined help explain some of the changes in the fat depots we saw in the ABI group.

Owing to difficulty in acquiring complete data regarding castration status, changes in body composition were calculated without grouping by castration status. It is possible that due to the unbalanced nature of the groups with respect to castration status, the differences between treatment groups may be skewed by a differential response to treatment. Low testosterone is associated with decreased lean mass and increased adiposity [4]. Additionally, advanced disease itself is associated with decreases in lean mass [5]. However, as there is no difference in the baseline muscle or fat volumes, it may be safe to assume that at the outset the groups are relatively homogenous. Although the ENZA and ABI groups had similar castration rates, the VAT and SAT results were different between the two groups. This suggests that the effects of castration are not easily observable.

Our study has several limitations. The retrospective nature predisposes to a selection bias and confounding due to risk factors that were not measured. We tried to assess the major clinical factors contributing to changes in body composition in this population to limit potential confounding. One feature that we could not control is the timing of CT scanning, and this variable may have contributed to small changes in measures over time. Furthermore, the retrospective chart review is limited by a lack of blinding and randomization. The latter likely contributed to variability among groups in our study. For example, the majority of patients in the ABI and ENZA groups failed aLHRH therapy, were castrate resistant, and participated in clinical trials by the start of the trial as opposed to those in the aLHRH group. Therefore, it is possible that the effects we observed could partly be due to (1) the cumulative ADT effect in the ABI and ENZA groups compared with the aLHRH group and (2) the differences in the castration status between the ABI and ENZA groups compared with the aLHRH group. We believe that these effects may help explain why we see an initial difference in skeletal muscle at the 6-mo time point between the two dual-agent groups compared with the single agent group, but no difference in the skeletal muscle between all three groups at 18 mo when all three groups have been on aLHRHs for an extended period of time. However, the stark differences in VAT and SAT between ABI and ENZA indicate that the changes in body composition are due to more than just differences in the population. Lastly, due to the limitations of randomly collected testosterone data and the poor sensitivity of the clinical assay (lower limit of detection 10 ng/dl), conclusions about the effectiveness of different ADT agents could not be assessed.

Despite these limitations, this manuscript provides an overview of the body composition changes that occur in men with prostate cancer following the induction of pharmacological hypogonadism using agents with disparate mechanisms of action. This data may help interpret the distinct metabolic effects that occur with these agents.

5. Conclusions

ABI, ENZA, and aLHRHs universally lead to decreases in skeletal muscle volume in men with prostate cancer. However, the changes in VAT and SAT are varied by time on treatment and by agent. Both lean mass and adiposity are key prognostic factors in patients with prostate cancer, and to our knowledge, no other study has examined the effects of these agents head to head on body composition. Therefore, the results of this study may help inform treatment decisions in patients with prostate cancer.

***Author contributions*:** Marcus D. Goncalves had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jones, Goncalves.
Acquisition of data: Blow, Murthy, Grover, Schwitzer.
Analysis and interpretation of data: Blow, Murthy, Nanus, Halpenny, Plodkowski, Jones, Goncalves.
Drafting of the manuscript: Blow, Murthy, Nanus, Goncalves.
Critical revision of the manuscript for important intellectual content: Blow, Murthy, Nanus, Plodkowski, Jones, Goncalves.
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Other: None.

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