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Body composition changes during androgen deprivation therapy for prostate cancer: A 2-year prospective study

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Abstract

Background—Little is known about the long-term impact of androgen deprivation therapy (ADT) on body composition in men with prostate cancer. We compared body composition parameters in men with non-metastatic prostate cancer on or not on therapy with healthy, age-matched controls at baseline and monitored changes over a 2-year period.

Methods—We measured body fat mass and lean body mass in 81 men with prostate cancer on no ADT, 43 men on acute ADT (less than 6 months), 67 men on chronic ADT (more than 6 months) and 53 age-matched healthy controls. Measurements were performed every 6 months for 2 years.

Results—Men with prostate cancer on acute ADT (mean 3 months) had significant gains in body fat mass [1499.56 ± 322.28 g (mean ± S.E.) after 12 months, 2167.15 ± 676.45 g after 24 months, $p < 0.01$ for both] and losses in lean body mass (929.74 ± 296.36 g after 12 months, 1785.81 ± 501.31 g after 24 months, $p < 0.01$ for both) over 2 years. Men on chronic ADT (mean 31 months) had smaller but still significant body composition changes over 24 months. Changes in body composition in men on no ADT were small and healthy controls had no significant changes.

Conclusions—Men with prostate cancer on ADT have significant gains in body fat mass and losses lean body mass over 2 years. These changes are most pronounced with initiation of ADT.

Keywords

Prostate cancer; Androgen deprivation therapy; Body composition; Dual-energy X-ray absorptiometry

1. Introduction

Androgen deprivation therapy (ADT) has been the primary post-surgical treatment for metastatic prostate cancer since the 1940s [15]. Beginning in the early 1990s, men with non-metastatic prostate cancer were placed on ADT as an adjuvant therapy [6]. The use of ADT as a primary or neo-adjuvant therapy in non-metastatic prostate cancer patients has increased since then [1]. Androgens have important roles not only in the maintenance of bone mineral density [9,12], but also lean body mass. Several cross-sectional and retrospective studies demonstrate accelerated loss of lean body mass and gain in body fat in individuals on ADT for up to 1 year [2,3,5,25–28]. One controlled study compared men on ADT with healthy controls over a 6-month period and reported similar findings [4]. The effects of ADT on body

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composition for more than 1 year remain unknown. Therefore, we compared body composition parameters in men with non-metastatic prostate cancer on or not on ADT with healthy, age-matched controls at baseline and monitored changes over a 2-year period.

2. Materials and methods

2.1. Subjects

Men with non-metastatic prostate cancer who had previous surgery and/or radiation were recruited from the private practices of the University of Pittsburgh Physicians and cancer support groups as part of a study to examine changes in bone mass [13]. Normal healthy controls were recruited through local newspaper advertisements as previously reported [7]. All participants were community-dwelling men aged 50 years and older. Men with prostate cancer were grouped as having no androgen deprivation therapy (ADT), acute ADT (initiating ADT within the last 6 months prior to enrollment), and chronic ADT (treated with ADT for 6 months or longer). ADT constituted either orchiectomy, treatment with gonadotropin-releasing hormone (GnRH) agonists, treatment with anti-androgens, or combinations of these as previously described [13]. Because this study also involved examining bone loss in men on ADT, subjects were excluded if they had a disease or were taking any medication known to affect bone and mineral metabolism [13]. The protocol was approved by the Institutional Review Board at the University of Pittsburgh. Written informed consent was obtained from all subjects before their enrollment.

2.2. Outcome measures

2.2.1. Measures of body habitus—Measures of body habitus included height (cm), weight (kg), and body mass index (BMI, kg/m^2). Height was measured to the nearest centimeter using a Harpenden stadiometer (Holtain Ltd., Crymych Dyfed, UK). Weight was measured with a balance beam scale. Height, weight and BMI were measured at baseline, 12 months and 24 months. Percent body fat and lean body mass were measured using body composition software on a Hologic QDR-4500A bone densitometer (Hologic Inc., Bedford, MA). Body composition parameters were measured at each 6-month visit.

2.2.2. Measures of gonadal status—Total testosterone was measured by competitive immunoassay (ng/dl; Diagnostic Products Corp., Los Angeles, CA) with intra-assay CV of 2.4–8.3%. Free testosterone was measured by tracer equilibrium dialysis (pg/ml; Nichols Institute, San Juan-Capistrano, CA) with an intra-assay CV of 4.2–11.6%. Prostate-specific antigen (PSA) was measured by chemiluminance (ng/ml; Bayer Diagnostics, Tarrytown, NY).

2.3. Statistical analysis

This was a secondary analysis of a study designed to examine changes in bone mass in men with prostate cancer. All data analyses were performed using SAS® software, version 9.1 (SAS Institute, Inc., Cary, NC, USA). Descriptive statistics were used to characterize the four groups in the study sample. Analysis of variance (ANOVA) was used to compare baseline characteristics among the groups. Analysis of covariance (ANCOVA) was used to make adjusted comparisons of both absolute and percent changes in body composition across the groups. These adjusted comparisons were controlled for the baseline value of the change measure and age. In addition, the significance of within-group changes between baseline and follow-up assessments were examined using paired samples *t*-tests.

3. Results

Of the prostate cancer subjects enrolled, 81 were not on ADT, 43 had been on ADT for less than 6 months (acute ADT, mean duration 3.0 ± 0.3 months), and 67 had been on ADT for

over 6 months (chronic ADT, mean duration 30.7 ± 3.8 months). Fifty-three healthy controls also participated in the study (Table 1). Subjects with prostate cancer on ADT were older than those not on ADT or healthy controls ($p < 0.0001$). Body fat mass and percentage of body fat were lowest in the healthy controls and greater in the prostate cancer patients. Subjects on chronic ADT had the lowest and healthy controls had the highest lean body mass and percentage of lean mass ($p = 0.0092$ and $p < 0.0001$ across all groups, respectively). Body mass index (BMI) followed the trends seen in body fat across groups but was not significant across the four groups ($p = 0.3352$).

Changes in body composition were observed as early as 6 months in men on acute ADT (Figs. 1 and 2). Subjects on acute ADT at 6 months had significant gains in body fat mass (1332.10 ± 276.69 g (mean ± S.E.M.), $p < 0.0001$) and percent body fat (1.16% ± 0.23, $p < 0.0001$) as well as losses in percent lean body mass (1.17 ± 0.26%, $p < 0.0001$). At 12 months, subjects on acute ADT showed the greatest losses in lean body mass (929.4 ± 296.4 g, $p = 0.0035$) and percent lean mass from baseline (1.71 ± 0.34%, $p < 0.0001$) and the highest gains in body fat mass (1499.6 ± 322.3 g, $p < 0.0001$) and percent body fat (1.63 ± 0.31%, $p < 0.0001$) from baseline. Subjects on chronic ADT had a smaller but still significant increase in body fat mass (1162.9 ± 423.4 g, $p = 0.0088$), percent body fat (0.80 ± 0.31%, $p = 0.0131$) and a decrease in the percent lean body mass (0.67 ± 0.30%, $p = 0.0313$) compared to baseline. The healthy controls also had small but significant increases in body fat mass (607.77 ± 280.59 g, $p = 0.0359$) and percent body fat (0.45 ± 0.22%, $p = 0.0419$). Prostate cancer patients on no ADT had non-significant increases in body fat and decreases in lean body mass parameters over 12 months.

At 24 months, all men with prostate cancer had lost lean body mass and gained body fat mass. Men on acute ADT had the greatest differences in body fat mass (2167.15 ± 676.45 g, $p = 0.0035$), percent body fat (2.11 ± 0.62%, $p = 0.0021$), lean body mass (−1785.81 ± 501.31 g, $p = 0.0014$), and percent lean body mass (−2.27 ± 0.61%, $p = 0.001$) from baseline. Men on chronic ADT and no ADT also had smaller but significant increases in the percent body fat mass and decreases in percent lean body mass (all $p < 0.05$). BMI did not significantly change for all groups at both the 12- and 24-month time points, except in the chronic ADT group at 12 months (0.44 ± 0.18, $p = 0.0184$).

4. Discussion

Our results demonstrate that body fat mass and percentage of body fat increased and lean body mass and percentage of lean mass decreased in men with prostate cancer on androgen deprivation therapy. Duration of ADT correlated with higher body fat and lower lean body mass parameters. The greatest change in body composition occurred in the first 12 months of therapy in subjects in the acute ADT group. These changes continued after 12 months. Subjects on chronic ADT also had significant changes in body composition after 24 months. Men on no ADT had smaller but significant changes in body fat and lean mass. In comparison, body composition in the control group remained stable over 24 months.

In healthy aging men, declining androgen levels correlate with increasing body fat mass and a decreasing lean body mass [22,29]. The increased adiposity in turn may contribute to the androgen deficiency, primarily due to decreased sex hormone binding globulin levels [8]. Decreased muscle mass leads to diminished strength and a higher risk for frailty endpoints such as falls and fractures [17]. Androgen replacement in men with acquired hypogonadism reverses these changes [16]. Men with actively treated prostate cancer do not have this option. Instead, ADT in this population accelerates these effects on body composition and significantly lowers physical function and general health when compared to healthy, aging men [7].

Our results support the accelerated body composition changes during the first year of ADT reported in previous studies. The mean duration of ADT in the acute group at enrollment to our study was 3 months. One study found significant changes after only 3 months of ADT [6]. Our findings may be an underestimate of actual body composition changes in the first year of therapy.

We also found continued smaller but still significant increases in body fat mass and decreases in lean body mass over 24 months. Support for this continued effect is lacking due to limited ADT-associated outcome data after 1 year. A cross-sectional study in men with prostate cancer up to 5 years ADT had significantly higher weight and body fat percentage than healthy controls [24]. Information on bone health with chronic ADT usage is more robust. In a small, prospective study, lumbar spine and femoral neck bone mineral density (BMD) declined at each 6-month time point up to 18 months [20]. Although the BMD loss at 18 months was significant, the rate of loss between each 6-month time point remained non-significant [20]. In a recent large retrospective analysis of 50,613 men with prostate cancer, 19.4% of surviving patients on ADT had a fracture after 5 years compared to 12.6% of patients not on ADT ($p < 0.001$) [23].

We observed that men with prostate cancer on no ADT had small increases in body fat and decreases in lean body mass over 24 months. The reasons for these changes are unclear. Several studies have suggested that obesity and metabolic syndrome are associated with prostate cancer [11,14,18]. However, the relationship is complex and may be related to the grade of prostate cancer. Further studies are needed to clarify this relationship.

Because this was a secondary analysis for a study on skeletal health, subjects with low bone mass or who were using skeletal anti-resorptive agents were not recruited or were discontinued from the study [13]. Men with low BMD and high fracture risk often have reduced muscle mass and higher percentage of body fat [19]. Subjects enrolled in our study may have been healthier than the general population of men with prostate cancer on ADT. Also, free and total testosterone levels were not drawn at the 24-month visit. Therefore, biochemical confirmation of continued chemical castration was not available. However, continued suppression of androgen levels after 2 years of ADT has been demonstrated in another study [21].

Our study has many important strengths. It is the largest study to examine changes in body composition with ADT. It is also the first to prospectively observe body composition changes after 1 year of ADT. Two different control groups (age-matched healthy control subjects and prostate cancer patients not on ADT) were used for comparisons. Finally, we used a single dual-energy X-ray absorptiometry machine for all body composition measurements.

In summary, androgen deprivation therapy for men with prostate cancer has profound effects on body composition. Much of this effect occurs in the first year of therapy. However, significant increases in body fat and decreases in lean body mass continue after 1 year. Interventions such as resistance training have been shown to improve muscle strength and functional performance in older men who have received ADT for prostate cancer [10]. Future studies are needed to determine if these interventions should be considered at initiation of ADT and continued for the duration of therapy.

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Biographies

Gijsberta van Londen, M.D., is a senior, clinical geriatric hematology–oncology fellow at the University of Pittsburgh. She is pursuing a Master of Science degree in 'Clinical Trials of the Aging Population'.

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Joel B. Nelson, M.D., is the Frederic N. Schwentker Professor and Chairman, Department of Urology at the University of Pittsburgh School of Medicine. He has been collaborating with the Principal Investigator on studies involving men with prostate cancer suffering from cancer related bone loss. He has expertise in surgical treatment of prostate cancer and will continue to collaborate with Dr. Greenspan.

Susan L. Greenspan, M.D., Principal Investigator, is board-certified in internal medicine, geriatrics, and endocrinology and metabolism, and currently holds joint appointments in the Division of Endocrinology and Metabolism and the Geriatrics Division of the University of Pittsburgh Medical Center (UPMC). Dr. Greenspan is Professor of Medicine at University of Pittsburgh School of Medicine and Director of the Osteoporosis Prevention and Treatment Center at UPMC. She is also Program Director of UPMC's Clinical Translational Research Center located in UPMC Braddock Hospital, Pittsburgh, PA. Dr. Greenspan has published numerous papers on topics in bone and mineral metabolism including maintenance of skeletal integrity in elderly men and women, assessments of new techniques and devices for

classification of bone status, new biochemical markers of bone turnover for therapeutic assessment, and cancer treatment related bone loss.

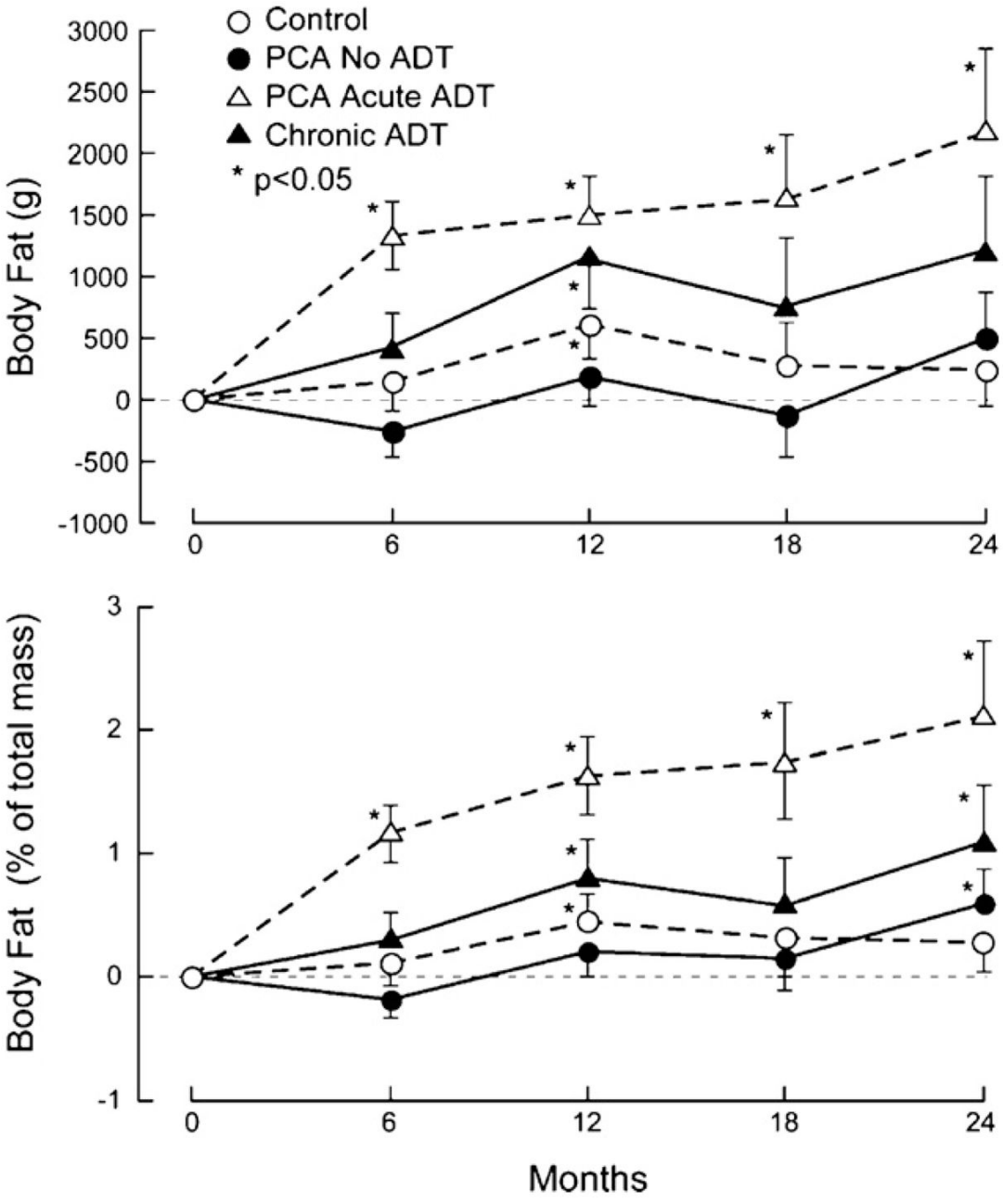

Fig. 1.

Changes from baseline in (a) total body fat mass (g) and (b) percent body fat over 24 months. Results are shown as mean ± S.E. (a) $p = 0.0024$ across all groups at 24 months. (b) $p < 0.0001$ across all groups at 24 months. Abbreviations: ADT, androgen deprivation therapy.

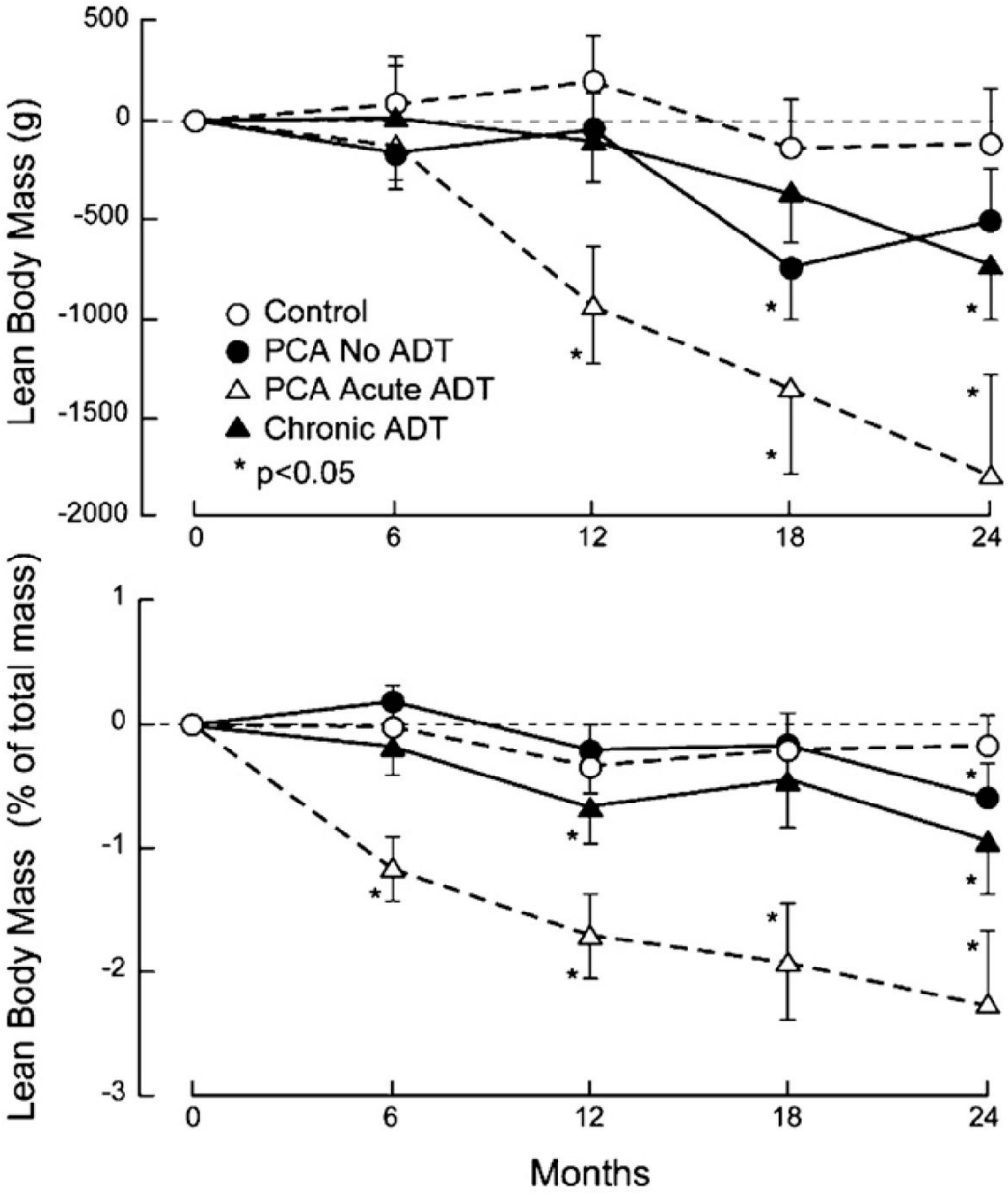

Fig. 2.

Changes from baseline in (a) total lean body mass (g) and (b) percent lean mass over 24 months. Results are shown as mean ± S.E. (a) $p = 0.0630$ across all groups at 24 months. (b) $p < 0.0001$ across all groups at 24 months. Abbreviations: ADT, androgen deprivation therapy.

Table 1

Baseline body composition characteristics (mean ± S.E.)

Parameters	Controls (*n* = 53)	No ADT (*n* = 81)	Acute ADT (*n* = 43)	Chronic ADT (*n* = 67)	*p*-Value (across groups)
Age (years)	62.55 ± 1.59	66.70 ± 0.81	70.86 ± 1.19	71.07 ± 1.07	<0.0001
Duration of ADT (months)			2.95 ± 0.25	30.67 ± 3.78	
Body mass index (kg/m^2)	27.62 ± 0.47	28.26 ± 0.41	28.43 ± 0.88	29.12 ± 0.61	0.3352
Body fat (g)	21629.25 ± 930.57	23606.34 ± 895.82	23999.39 ± 1240.08	27469.28 ± 1129.24	0.0013
Body fat % (% of total mass)	25.14 ± 0.71	26.74 ± 0.66	27.08 ± 0.83	31.43 ± 0.65	<0.0001
Lean body mass (g)	60157.05 ± 884.79	60238.66 ± 771.04	59881.70 ± 1147.27	56482.19 ± 1014.13	0.0092
Lean body mass % (% of total mass)	71.62 ± 0.67	70.25 ± 0.62	69.92 ± 0.79	65.86 ± 0.63	<0.0001
Testosterone (ng/dl)	421.88 ± 24.64	345.5 ± 18.90	81.69 ± 30.65	34.7 ± 12.87	<0.0001
Free testosterone (pg/ml)	66.47 ± 5.00	55.4 ± 3.21	11.64 ± 6.69	2.2 ± 0.38	<0.0001
PSA (ng/ml)	1.8 ± 0.2	1.6 ± 0.3	3.0 ± 1.2	6.2 ± 2.1	0.0219

Abbreviations: ADT, androgen deprivation therapy, PSA, prostate specific antigen.