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Obese frailty, physical performance deficits, and falls in older men with biochemical recurrence of prostate cancer on androgen deprivation therapy: a case-control study

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Abstract

Objectives—Early androgen deprivation therapy (ADT) has no proven survival advantage in older men with biochemical recurrence (BCR) of prostate cancer (PCa), and it may contribute to geriatric frailty; we tested this hypothesis.

Methods—We conducted a case-control study of men aged 60+ with BCR on ADT (n=63) versus PCa survivors without recurrence (n=71). Frailty prevalence, “obese” frailty, Short Physical Performance Battery (SPPB) scores and falls were compared. An exploratory analysis of frailty biomarkers (CRP, ESR, hemoglobin, albumin, and total cholesterol) was performed. Summary statistics, univariate and multivariate regression analyses were conducted.

Results—More patients on ADT were obese (BMI >30; 46.2% vs. 20.6%; p=0.03). There were no statistical differences in SPPB (p=0.41) or frailty (p=0.20). Using a proposed “obese” frailty criteria, 8.7% in ADT group were frail and 56.5% were “prefrail”, compared with 2.9% and 48.8% of controls (p=0.02). Falls in the last year were higher in ADT group (14.3% vs. 2.8%; p=0.02). In analyses controlling for age, clinical characteristics, and comorbidities, the ADT group trended toward significance for “obese” frailty (p = 0.14) and falls (OR = 4.74, p = 0.11). Comorbidity significantly increased the likelihood of “obese” frailty (p=0.01) and falls (OR 2.02, p = 0.01).

Conclusions—Men with BCR on ADT are frailer using proposed modified “obese” frailty criteria. They may have lower performance status and more falls. A larger, prospective trial is necessary to establish a causal link between ADT use and progression of frailty and disability.

Keywords

prostate cancer; biochemical recurrence; androgen deprivation therapy; frailty; older adults

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INTRODUCTION

Prostate cancer (PCa) is largely a disease of older men. Seventy-five percent of PCa incidence and greater than 90% of PCa mortality occurs in men aged 65 years or older.[1] Due to competing causes of death, a significant number of older men with PCa will die with, not as a result of, their disease. In fact, 61% of all men diagnosed with PCa after age 67 die of another cause.[2]

The standard therapy for PCa recurrence is ADT. While ADT provides survival advantages when used for overtly metastatic disease, it is well established that ADT can cause significant quality of life (QOL) lowering morbidity, including fatigue, anemia, osteoporosis and sarcopenia, occurring as early as 3 months after ADT initiation.[3,4] Patients on ADT for one year have a lower lean muscle mass, reduced upper limb strength, and worse self-reported physical function than those not on ADT.[4,5] Increased prevalence of fractures in PCa patients on ADT has also been reported, with a positive correlation between number of luteinizing hormone-releasing hormone (LHRH) agonist doses and fracture risk.[6]

Despite its potential toxicities and lack of proven survival advantage, ADT is widely used in men with biochemical cancer recurrence (BCR). The overall use of ADT has increased by 27% in less than a decade.[7] Although ADT is the standard treatment for BCR, the optimal time to start treatment in this setting remains uncertain.[8] To date, no overall survival benefit has been demonstrated with early versus late initiation of ADT in men with BCR that is low to moderate risk.[9] Older men who more often have indolent disease and limited life-expectancies due to other health problems provide an even bigger challenge; given the known toxicities of treatment, the long natural history of PCa, and the unproven survival benefit with early initiation, when to start ADT in these patient populations is even less clear.[10]

Since PCa largely affects older men, it is important to be mindful of age-associated physiological changes. Older age is associated with increased comorbidities, decreased organ function, and decreased functional reserve which can lead to an increased risk of adverse events such as hospitalization, loss of independence and death. *Frailty* is a term from geriatrics which describes older patients who are vulnerable to stressors and susceptible to adverse outcomes including falls, disability, hospitalization, and death.[11] A commonly accepted operational definition developed by Fried and colleagues is a clinical syndrome in which three or more of the following five criteria are present: unintentional weight loss, self-reported exhaustion, weakness, slow gait speed, and low physical activity.[11] Due to the increased awareness of the complex nature of frailty, more recent research has focused on identification of subtypes of frailty.[12] It is felt that identifying subtypes with different causal pathways and prognosis could offer insight into the development of specific interventions to prevent and treat frailty.[13]

In addition to the clinical definition, research has also increasingly focused on the identification of reliable biomarkers of frailty. While the pathophysiology of frailty is not completely understood, chronic inflammation has been proposed as an underlying biological mechanism, thus the use of inflammatory biomarkers have been proposed for predicting frailty. In particular, CRP, IL-6, hemoglobin, albumin and cholesterol have been associated with frailty.[14–16] Use of these biomarkers as early markers of frailty and physical decline in PCa patients has not been reported.

Due to the established adverse effect of ADT on body composition, muscle strength, and self-reported physical function, the relation of these changes to objective measures of physical performance and their relationship to PCa patients' risk of falls and fragility fractures has been suggested.[5,6] While it has been hypothesized that ADT could lead to

frailty in older men with PCa,[17] the specific impact from ADT on the development of frailty by formal criteria is not known.

Previously, we found that 56% of older men on ADT had abnormal scores on SPPB and 22% fell over the previous 3 months, although no control group was included.[5] Given this, a case-control study was designed to measure the specific contribution of ADT to frailty (as defined by Fried et al), objective physical performance measures, and falls in older PCa patients with BCR. Specifically, we compared two groups: men with BCR on ADT and a control group of men with a history of PCa status-post definitive local therapy with no current evidence of disease.

MATERIAL AND METHODS

Patients and Study Design

A cross-sectional study of men with PCa aged 60 and older was performed. Two groups were compared: men with BCR (asymptomatic rise in PSA with no radiographic evidence of metastatic disease) on ADT for 6 months or more and men with a history of PCa status-post surgery or radiation therapy not on ADT with no evidence of disease by PSA (controls). All patients had bone and CT scans of the chest, abdomen and pelvis to rule out metastatic disease. Patients were recruited from the University of Chicago and Medical College of Wisconsin medical oncology, urology and radiation oncology clinics. Patients completed a questionnaire and physical performance measures under the guidance of a trained research assistant. Biomarkers of frailty were also obtained. Patients with a known diagnosis of dementia or on medications for dementia were excluded.

Measurements

Socio-demographics, patient characteristics and PCa history were obtained from medical records and from patients. Self-reported comorbidities were measured with the Older Americans Resources and Service (OARS) comorbidity scale.[18]

Physical performance was measured using the validated Short Physical Performance Battery (SPPB), an objective, clinically-relevant measure of balance, lower extremity strength, and walking speed.[19] A score less than 10 (out of a possible 12) is abnormal, indicating worse physical performance and increased risk of incident disability and mortality.[19] Patients were asked if they had fallen in the last 6 months.

Frailty was measured using Fried's criteria. The five criteria (unintentional weight loss, self-reported exhaustion, weakness/grip strength, walking speed, and physical activity) were obtained and measured by a trained research assistant; positive criteria were assessed as described in detail by Fried et al.[11] Patient-reported weight loss greater than 10 pounds over the last year was recorded. Self-reported exhaustion was measured using two items from the Center for Epidemiological Studies depression (CES-D) scale. Grip strength was measured using the Jamar hydraulic hand dynamometer. Walking speed was measured using a timed 15 foot walk, adjusting for height and gender. Self-reported physical activity was assessed using weighted score of kilocalories expended per week. Patients meeting three of five Fried's criteria are considered frail; patients meeting 1–2 criteria are considered pre-frail.[11] Proposed biomarkers of frailty (IL-6, CRP, albumin, hemoglobin and lipids) were obtained at time of assessment. Additionally, PSA levels, testosterone levels, and fasting glucose levels at the time of the assessments were measured.

Previously, we noted that "subjective weight loss" might not apply to men on ADT because they are known to gain weight. The clear difference between our groups in BMI, with those on ADT being significantly heavier than controls, suggested a reassessment of this specific

frailty criterion. It is known that obesity is associated with an increased likelihood of prefrailty and frailty.[20,21] Therefore, based on this literature review, an analysis of "obese" frailty criteria was also performedby modifying Fried's frailty criteria, substituting the weight loss criterion with an "obesity" criterion, defined as BMI > 30.

Statistical Analysis

Univariate—The ADT and control groups were compared across all socio-demographic and clinical variables using t-tests and non-parametric tests (Fisher's exact, Chi-square categorical and ordinal) as appropriate. Three separate analyses of the hypothesized predictors were run for the outcome variables of modified Fried's criteria (ordinal scale 1 to 5), SPPB < 10, and having experienced a fall within the previous six months (yes or no).

Multivariate—Three separate regressions were run, with pre-defined independent variables selected based on clinical relevance, with being on ADT as the independent variable of primary interest. The outcome variables were "obese" frailty, SPPB score less than 10, and falls in the last 6 months. Because the majority of patients scored in the lower categories on the "obese" frailty criteria, a negative log-log ordinal regression analysis was performed to assess which variables were associated with higher values on the modified criteria. For both the SPPB<10 and the falls outcome variables, independent variables were tested in a binary logistic regression. For all three outcomes, the same independent variables were entered into the model in one block: treatment with ADT, age, current PSA, Gleason Score at diagnosis, primary treatment type (radiation or surgery), and comorbidity index. Emphasis was placed on testing coefficents, considered significant at p<.05, while controlling for the other variables mentioned rather than the "fit" of the overall models. All analyses were conducted using Stata.

RESULTS

Patient Characteristics

Between September 2006 and June 2009 (n=134), 63 men with BCR on ADT and 71 control patients meeting entry criteria were enrolled (Table 1). Patients in both groups were not significantly different by age, education, income, ethnicity or comorbidity score. PSA was no different between groups at the time of assessment. Median time on ADT was 41.7 (±. 40.6 months) for BCR group. Consistent with treatment goals, testosterone levels were significantly lower in the ADT exposure group. Consistent with the literature, the ADT exposure group had a higher prevalence of osteoporosis (14.3 vs 4.2; p=0.04), defined using the World Health Organization definition of T-score less than −2.5 from standard of care DEXA.

Univariate Associations

Frailty: Prevalence of frailty by formal Fried's criteria and modified "obese frailty" criteria was measured as described above (Table 2). There was no significant difference in frailty between groups using original Fried's criteria. BMI was significantly higher in ADT group compared to controls with 46.2% of ADT group meeting obesity or greater criteria (BMI > 30) compared to 20.6% of controls (p=0.03). When using criteria modified for obesity, men on ADT were significantly more frail than controls (8.7% vs. 2.9% frail, 56.5% vs. 48.8% prefrail; p = 0.02).

Physical performance: Mean SPPB scores were not statistically significantly different in men with BCR on ADT compared to controls (10.3 vs 10.0, p=0.41; Table 2). 32% of patients in the ADT group had SPPB score less than 10 compared to 24% of controls (p = 0.67).

Falls: Incident falls over 6 months were higher in ADT group when compared to controls, with 14.3% of ADT group reporting falls in last 6 months, compared to 2.8% of controls (p=.02) (Table 2).

Multivariate regressions—In multivariate regressions, comorbidity (as measured by the OARS comorbidity scale) significantly increased the likelihood of falls in logistic regression analysis (OR 2.02, p=0.01). Exposure to ADT appeared to increase likelihood of falling in multivariate regression analysis, although this did not quite reach statistical significance (OR = 4.74, p=0.11; Table 3).

Biomarkers of Frailty: Previously identified inflammatory frailty biomarkers (including IL-6, CRP, and cholesterol) were not significantly different between groups (Table 2). Those on ADT had significantly lower hemoglobin levels (12.7 in ADT group vs. 14.4 g/dl in controls, p< .01).

COMMENT AND CONCLUSIONS

We evaluated (obese) frailty, physical performance, and falls in men with BCR on ADT compared to men with a history of PCa not on ADT in a case control study. Our hypothesis was that older men with PCa on ADT would exhibit a higher prevalence of frailty, abnormal physical performance, and falls compared to controls. We did not find a significant difference between groups using the original Fried's criteria for frailty. There are two possible explanations for this finding – either those on ADT are insignificantly frailer than the controls or Fried's criteria do not capture the frailty that's present. Either or both may be true. We found men with BCR on ADT for a minimum of 6 months are less frail than hypothesized. We have postulated an alternative theoretical model of the development of frailty in ADT patients involving decreased energy leading to decreased activity, which leads to muscle loss and increased BMI.[22] We believe that increased BMI due to body composition changes is an integral part of the frailty syndrome for patients on ADT. Consequently, we propose that Fried's original criteria, do not accurately represent the mechanism of action by which older men with PCa on ADT become frail. Proposing a modified "obese frailty" criteria that includes high BMI in place of subjective weight loss, we found a greater likelihood of this phenotype in men on ADT. We also found that men on ADT exhibited significantly more falls when compared with controls, with 14.3% of men on ADT reporting falls in the last six months, confirming a mechanism for increased fractures in these men. This is important because recurrent falls increase the risk of morbidity, mortality and loss of independence in older adults.[23] Interestingly, we found in multivariate analysis that increased comorbidity significantly increased the likelihood of positive modified frailty criteria and falls, possibly suggesting that increased vulnerability contributes to clinically meaningful toxicity from ADT exposure.

Our reconsideration of the frailty criteria was made after the conception and design of the study in response to these findings and others in the recent literature. As we and others have done more work it this area, it has become apparent that the original criteria for frailty do not apply well to this population. Although patients are almost certain to lose muscle mass, ADT leads to total weight gain, not weight loss, and Fried's commonly used biologic syndrome model likely underestimates frailty in older men on ADT due to its weight loss criteria. It has been suggested that lean weight loss, or sarcopenia, rather than overall weight loss, is the relevant factor in the development of frailty.[22] In addition, it is known that obesity is also associated with increased likelihood of prefrailty and frailty.[20,21] Recent research has brought called attention to several subtypes of frailty, each with its own specific pathway to the end state of "frailty" and poorer prognoses.[13] Some have argued that "weight loss" is not a necessary component of frailty, since obesity has been shown to be associated

with the frailty syndrome, including its negative outcomes.[20] Thus, it seems reasonable to hypothesize that induction of obesity in men on ADT would put them at risk for "obese frailty". Therefore, we created a modified frailty criteria for men on ADT, substituting "obesity" for the original "unintentional weight loss" criteria, keeping the same number of needed positive criteria as the original definition. We suggest that future studies of frailty in men with PCa on ADT account for both the lean muscle mass lost and the adiposity that these men gain.

A preliminary analysis of proposed biomarkers of frailty previously identified in the general geriatrics population (CRP, IL-6, hemoglobin, albumin, and total cholesterol) was performed. We did not find that inflammatory biomarkers correlated with frailty by either criteria in these older men with BCR on ADT. This suggests that the primary underlying mechanisms of frailty typically identified in the general geriatrics population – i.e. low-level inflammation – differs from the mechanism leading to obese frailty in older men on ADT. As ADT causes adverse body composition changes through an endocrine pathway and not through chronic inflammation, it is likely that these markers measure the wrong pathway. Better biomarkers would measure sarcopenia and adiposity. Mild anemia, which has been associated with both androgen-depletion and frailty, is more prevalent in men on ADT.

We have previously proposed that ADT can induce frailty in patients with PCa,[22] and others have similarly discussed the development of "Androgen Deprivation Syndrome."[24] It is well-established that men with PCa experience sarcopenia, weakness, osteoporosis and increased risk of fragility fractures. Our previous work showed that men with low-volume PCa on ADT exhibited a higher than expected prevalence, compared with community-dwelling older men, of physical performance deficits and falls.[5,25] In the Medicare Current Beneficiary Survey (MCBS), a previous diagnosis of PCa was associated with falls,[26] and older men on ADT have a high prevalence of physical performance deficits.[27–29] This is the first study we know of specifically assessing the prevalence of frailty, physical performance, and falls in older men with BCR on ADT compared to appropriate controls.

There are limitations to this study. First, this is a cross-sectional design, so we are unable to establish a temporal relationship between initiation of ADT and outcomes. Second, patients were not specifically matched on some other characteristics that could impact outcomes such as age, race, marital status and income, although no significant differences were noted between the groups. We did, however, carefully select a control group to avoid "cancer burden" as a possible source of differences. In addition, we used multivariate approaches and measured known confounders. There may be selection factors that are different, and relevant to the outcomes, between the groups. Physicians may be reluctant to place older men with BCR who appear frailer on ADT making finding differences between our groups more difficult; thus we believe our estimates are conservative. Third, this study included men aged 60 and older, a relatively "young-old" cohort. Sarcopenia is associated with increasing age, thus older patients would be more likely to have sarcopenia upon initiation of ADT, and would be more likely to be vulnerable to its effects. Older men are also likely to have more comorbidities. It is possible that the younger men in our sample have enough reserve to compensate for ADT-related sarcopenia. Thus, significant differences in physical performance and frailty would be more difficult to identify in this smaller study with younger men. Fourth, we note that significantly more men in the BCR group underwent prostatectomy rather than radiation therapy and were significantly less likely to smoke compared to controls, suggesting that this group was healthier to begin with; as a result, they could be less vulnerable to overt frailty from ADT toxicities, again making finding differences more difficult in a cross-sectional study. Finally, we did not directly measure lean body mass in this study, relying on BMI to assess body composition. Although Fried's original criteria uses total body mass loss as one of the five contributors to frailty, lean body

mass loss is the relevant contributing factor to frailty. Because men on ADT gain adiposity as a result of their treatment, total body mass loss is not an appropriate frailty criterion for this group. We therefore adjusted the frailty criteria to include BMI in place of "subjective weight loss", consistent with work elsewhere on "obese frailty."[20] We believe it more accurately reflects the way in which ADT causes vulnerability.

This study is the first to report the higher prevalence of a specific type of frailty – namely obese frailty -- and falls in older men with BCR of PCa on ADT compared to cancer-survivor controls. Within the limits of a smaller, observational, cross-sectional study, it modestly supports the hypothesis that initiation of ADT might predispose older patients to "obese" frailty, performance deficits, and falls. Our data also supports the growing evidence that older men with comorbidities may be especially vulnerable to ADT toxicities . Thus, it is becoming increasingly important for practitioners to pay close attention to the potential toxicities of ADT when deciding if and when to treat their older patients.[30] It is likely that there is a large subset of older men who do not need to be treated for their PCa. More studies are needed to identify those who can be spared the potentially harmful toxicities of ADT.

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Table 1

Patient Characteristics for Older Men on Androgen Deprivation Therapy for Biochemical Recurrence of Prostate Cancer versus Controls (n = 118)

		ADT for BCR (n=63)	Control (n=71)	P-value
		Mean ± SD or %		
Age		72.1 ± 7.0	70.5± 6.3	0.21
Ethnicity	African American	31.7	45.1	0.25
	White	66.7	46.2	
	Other	1.6	4.2	
Marital Status	Married/Partner	82.6	76.1	0.26
	Single/Never Married	3.2	11.3	
	Divorced/Widowed	12.8	5.6	
	Other	1.6	4.2	
Education	High School or less	27.0	36.6	0.07
	College	41.2	45.1	
	Post-graduate	31.7	18.3	
Income	< $50,000	37.8	44.6	0.85
	$50–100,000	32.8	26.2	
	$100–200,000	19	18.5	
	Over $200,000	5.2	7.7	
	Unknown	5.2	3.1	
Local Therapy	Surgery	62.8	38.6	< 0.01
	Radiation	37.2	61.4	
PSA	At assessment	0.60 ± 1.84	0.69 ± 1.80	0.92
Gleason Score	< 7	14.9	52.9	< 0.01
	7	48.1	44.3	
	8–10	37.1	2.8	
Time on ADT (mo.)		41.7 ± 40.6		
Testosterone (ng/mL)		21.2 ± 30.9	377.9 ± 146.9	< 0.01
OARS Comorbidity Index	0	26.1	28.2	0.21
	1	32.8	47.9	
	2	17.4	15.5	
	3	15.2	7.0	
	4	6.5	1.4	
	5	2.2	0.0	
Tobacco Use (y/n)		41.3	62.0	0.02

ADT: Androgen deprivation therapy; PSA: Prostate-specific antigen; BCR: Biochemical Recurrence; OARS: Older Americans Resources and Service

Table 2

Outcomes Comparing Men on ADT for BCR versus Controls

		Mean ± SD or %		P-value
Clinical Characteristics		**ADT for BCR**	**No ADT**	
		(n = 63)	**(n = 71)**	
Body Mass Index (BMI)	Underweight (< 18.5)	0.0	0.0	0.04
	Normal (18.5 to 25)	13.5	20.6	
	Overweight (25 to 30)	40.4	58.8	
	Obese I & II (30 to 40)	40.4	19.1	
	Severely obese (40 to 45)	5.8	1.5	
Osteoporosis		14.3	4.2	0.04
Traditional Fried's Components	Low Physical activity	20.6	8.7	0.51
	Exhaustion	21.0	16.9	0.55
	Weak grip strength	27.0	18.6	0.25
	Slow gait	4.8	4.4	0.91
	Weight loss (subjective)	4.8	12.7	0.11
Traditional Fried's Total Score	0 "Robust"	49.2	56.3	0.20
	1 "Prefrail"	34.9	33.8	
	2 "Prefrail"	9.5	7.0	
	3+ "Frail"	6.4	2.8	
Modified Fried's Total Score	0 "Robust"	34.8	48.5	0.02
(0 – 5)	1 "Prefrail"	32.6	38.5	
	2 "Prefrail"	23.9	10.3	
	3+ "Frail"	8.7	2.9	
Short Physical Performance Battery (SPPB)				
	Total Score	10.0 ± 2.2	10.3 ± 2.1	0.41
	Balance	3.7 ± 0.85	3.8 ± 0.7	0.42
	Walk	3.7 ± 0.6	3.8 ± 0.7	0.51
	Chair Stand	2.6 ± 1.3	2.8 ± 1.2	0.43
	% < 10 on SPPB	31.9	23.9	0.67
Had at least 1 fall, 6 months		14.3	2.8	0.02
Number of Falls, 6 months	0 falls	85.7	97.2	0.06
	1 fall	7.9	2.8	
	2+ falls	6.3	0.0	
Biomarkers				
	IL-6	3.8 ± 1.5	5.2 ± 5.4	0.18
	CRP	4.3 ± 3.5	4.8 ± 4.9	0.62
	Albumin	4.3 ± 0.2	4.3 ± 0.2	0.37
	Hemoglobin	12.8±1.5	14.4±1.5	<0.01
	Glucose	107.4 ± 24.9	101.4 ± 24.3	0.21

		Mean ± SD or %		P-value
Clinical Characteristics		**ADT for BCR**	**No ADT**	
		(n = 63)	**(n = 71)**	
	Total Cholesterol	173.9 ± 48.6	179.1 ± 40.9	0.56
	LDL	96.4 ± 35.4	104.0 ± 33.0	0.39
	HDL	51.7 ± 12.8	52.7 ± 15.6	0.79
	Triglycerides	122.6 ± 69.6	98.7 ± 39.2	0.11

ADT: Androgen deprivation therapy; BCR: Biochemical recurrence; SD: Standard deviation; IL-6: Interleukin-6; CRP: C-reactive protein; LDL: Low density lipid; HDL: High density lipid

Table 3

Multivariate assessments of effect of ADT on "Obese" frailty, SPPB, and falls in the last 6 months, controlling for age and clinical characteristics.

	Frailty[1]		SPPB[2,3] < 10		Falls[2]	
Characteristic	**Co-eff**	**P-value**	**OR**	**P-value**	**OR**	**P-value**
Age	0.01	0.75	1.08	0.08	1.12	0.08
PSA[4]	−0.02	0.22	0.74	0.33	1.23	0.26
Gleason	0.04	0.86	0.57	0.06	0.83	0.84
Radiation	0.43	0.29	0.82	0.72	0.61	0.57
OARS Comorbidity[5]	0.38	0.01	1.40	0.08	2.02	0.01
ADT[6]	0.59	0.14	1.85	0.23	4.74	0.11

[1] Ordinal regression with increasing score for modified Fried's frailty from 0 to 5, with positive coefficients indicating greater likelihood of increasing frailty by 1.

[2] Logistic regressions with coefficients interpretable as odds ratios (OR).

[3] SPPB Short Physical Performance Battery.

[4] PSA Prostate-specific antigen

[5] OARS Comorbidity Older Americans Resources and Services comorbidity scale

[6] ADT Androgen deprivation therapy