Medical Oncology

# Weight Gain on Androgen Deprivation Therapy: Which Patients Are at Highest Risk?

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**OBJECTIVE** To identify factors associated with weight gain at 1 year from initiation of androgen deprivation therapy (ADT).

**METHODS** A retrospective review assessed weight change among 118 men with nonmetastatic prostate cancer treated with ADT for at least 6 months. Outcome associations were tested using 2-tailed *t* tests and linear regression.

**RESULTS** Men in our cohort had significant weight gain (+1.32 kg, $P = .0005$) in the 1 year after ADT initiation. Three risk factors for weight gain on ADT were identified as follows: age <65 years (2.72 kg gained, $P = .001$), body mass index (BMI) <30 (1.98 kg gained, $P = .00002$), and nondiabetic status (1.56 kg gained, $P = .0003$). Multivariable regression found both age <65 years (beta = 4.01, $P = .02$) and BMI <30 (beta = 3.57, $P = .03$) to be independently predictive of weight gain, whereas nondiabetic status was nonsignificantly predictive of weight gain (beta = 2.14, $P = .29$). Weight change was further stratified by the total number of risk factors present (risk score): scores of 0, 1, 2, and 3 risk factors corresponded to weight changes of −1.10, +0.41, +1.34, and +3.79 kg, respectively (*P-trend* = .0005).

**CONCLUSION** Age <65 years and BMI <30 were both independently associated with weight gain 1 year after starting ADT. Increasing weight gain was also strongly associated with increasing number of baseline risk factors present. Despite traditional concerns about ADT in unhealthy men, these data suggest younger, healthier patients may be at higher risk for gaining weight on ADT and should be counseled accordingly. UROLOGY ■: ■—■, 2014. © 2014 Elsevier Inc.

Androgen deprivation therapy (ADT) is increasingly used as an adjuvant therapy for the treatment of localized prostate cancer, and data suggest that nearly half of all patients with prostate cancer today will undergo ADT at some point in managment.[1] As the overall 5-year survival for all men with prostate cancer is very favorable,[2] an understanding of the adverse effects of ADT and their implications for long-term health is critical.

Along with decreased libido, fatigue, anemia, vasomotor flushing, gynecomastia, and osteoporosis, several adverse metabolic effects have been associated with ADT.[3] Noteworthy among these are body composition changes toward sarcopenic obesity[4] (increased fat mass and decreased lean body mass), decreased insulin sensitivity,[5] and adverse alterations in lipid profiles.[6] Although data are mixed about the definitive impact of ADT on cardiovascular morbidity and mortality,[3,7] each of these adverse metabolic effects are independent cardiovascular risk factors, and cardiovascular disease is the leading cause of death in older men with prostate cancer.[5]

Weight gain has been associated with ADT in several studies looking at body composition and metabolic changes because of hormonal therapy.[8] Of note, Kim et al[9] sought to characterize the natural history of ADT-related weight gain among 132 men on ADT for biochemical recurrence after prostatectomy and found an average weight gain of 2.2 kg, occurring primarily in the first year of therapy. Although baseline characteristics of patient age, pre-ADT body mass index (BMI), disease aggressiveness, and race were analyzed, none was found to be significantly predictive for risk or magnitude of weight gain. Alternatively, a recent study by Timilshina et al[10] showed a significant maximum weight gain of 2.6 kg among 85 men on ADT over 36 months but also found men younger than 65 years to gain significantly more weight than older men (4.7 vs 1.7 kg, respectively). A relationship between lower BMI and higher likelihood of weight gain was noted without supporting data, and both

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race and smoking status were also analyzed but not found to be predictive of weight gain.

Taken together, recent data support the growing body of evidence that ADT leads to significant weight gain. ADT may also differentially affect patients' body composition depending on their baseline health and demographic characteristics. Of note, more recent evidence suggests that exercise may prevent ADT-associated changes in body composition.[11,12] Therefore, a better understanding and identification of the risk factors for ADT-related weight gain would allow us to identify men who are at highest risk for this adverse effect and who might benefit most from prophylactic intervention.

On the basis of these considerations, we conducted a retrospective review of weight change in men after ADT initiation to better characterize a patient's risk of weight gain based on his baseline characteristics.

## MATERIALS AND METHODS

### Study Design

This was an institutional review board–approved review of a retrospectively assembled cohort of patients with nonmetastatic prostate cancer treated with ADT. The cohort was analyzed for the primary outcome of weight gain at 1 year after initiating ADT and the secondary aim to determine whether the baseline characteristics of age, BMI, and diabetic status were potential risk factors predisposing to weight gain on ADT.

### Patients

Men in this cohort were diagnosed and treated at the Brigham and Women's Hospital in Boston, MA. To qualify for inclusion, men had to have a nonmetastatic prostate cancer diagnosis between 1993 and 2013, have 1 weight measurement within the year before ADT initiation (baseline weight), and 1 weight measurement within 6 and 18 months after initiation of ADT. All men included in the study were treated with leuprolide acetate for androgen deprivation, with length of treatment ranging from 6 months to indefinite duration.

### Data Extraction

The patient cohort was defined, and detailed data were obtained using a clinical data registry application of Partners Healthcare, the Research Patient Data Registry. Detailed data including vital signs (height and weight), medications (with dates of administration), and diagnosis (with dates of diagnoses) were extracted from medical records by the Research Patient Data Registry. Further details, such as metastatic status at diagnosis and indications for ADT initiation were extracted by individual medical record review.

### Outcome Measurements

For the primary outcome of weight change at 1 year from ADT initiation, a baseline weight was recorded for each patient by selecting the most recent weight within the year before the start of hormonal therapy. For weight at 1 year from ADT initiation, 1 weight value was recorded within the window of 6-18 months from ADT initiation, with the weight closest to 12 months selected for men with multiple recordings within this timeframe. Weight was recorded as a continuous variable, with change defined as the difference between the weight at 1 year and the baseline weight for each patient. The height of each patient was also extracted, and the BMI was calculated using the formula BMI = weight (kg)/height (m)$^{\wedge}$2. Pre-ADT weight was used for determining patient BMI values.

Next, the secondary aim of stratifying risk on the basis of baseline characteristics of age, BMI, and diabetic status was investigated. Given previous data delineating age <65 years as a risk factor for weight gain on ADT,[9] this cutoff was maintained in our study, and age was analyzed as a categorical variable stratified by <65 years vs 65 years or older. The commonly accepted definition of obesity is a BMI of 30 or greater, and so baseline BMI was also defined as a dichotomous categorical variable with nonobese, or BMI <30, compared with obese status, or BMI >30. Given the strong association between weight and diabetes,[13] diabetic vs nondiabetic status was analyzed as a third categorical variable. For supplemental analysis of the effect of both age and BMI, each was also analyzed on a 3-tiered categorical platform with ages <65, 65-75, and >75 years and BMI <25, 25-30, and >30, respectively.

### Statistical Analysis

Weights, pre- vs post-ADT, were compared by paired, 2-tailed *t* tests for each putative risk factor and for the proposed aggregate risk factor model. Statistical significance was defined as a *P* value of <.05, and all *P* values were 2 sided. Trend tests were performed by including BMI ranges, age ranges, and aggregate risk scores in regression models as ordinal variables, that is, 1 (age <65 years, BMI <25, or risk score of 1) to 3 (age >75 years, BMI >30, or risk score of 3). Multivariable analysis of the continuous, dependent variable of weight change was also analyzed by linear regression to account for multiple interactions among the independent variables of baseline age (continuous), BMI (continuous), and diabetic status (categorical). Fisher exact test was used to test the association between shorter duration of ADT (<12 vs >12 months) with baseline age (<65 or >65 years). *T* tests and chi-squared testing were implemented for comparisons of baseline or historical characteristics between weight gainers and weight losers.

## RESULTS

### Patient Demographics

The demographic characteristics of the 118 men in this cohort are described in Table 1. The cohort had a mean age of 70.6 years (standard deviation [SD] = 10.8) at the time of ADT initiation. Mean baseline weight within the cohort was 85.5 kg (or 188.2 lbs, SD = 16.6), and mean BMI was 28.9 (SD = 4.9). The minimum duration of ADT for all patients was 6 months, and over two-thirds had >12 months of ADT. One-year weights were recorded at a mean of 376 days (SD = 86) from ADT initiation. A comparison of demographic and historical characteristics between men who gained weight and men who lost weight yielded no statistically significant differences (Table 1). ADT duration <12 months was found to be more common among men <65 years with a prevalence of 50% (15 of 30) compared with 28% (23 of 82) for men age <65 years ($P = .042$).

### Outcome Measures

At 1 year from ADT initiation, men in our cohort gained an average of 1.32 kg compared with their baseline

**Table 1.** Patient characteristics

| Variable | Total | Gainer | Loser | *P* |
|---|---|---|---|---|
| Number of patients, n (%) | 118 (100) | 74 (63) | 44 (37) | |
| Mean (SD) | | | | |
| Weight change, kg | 1.31 (4.0) | 3.7 (2.7) | −2.7 (2.1) | |
| Baseline age, y | 71 (11) | 70 (10) | 71 (12) | .657* |
| Baseline weight, kg | 85.5 (16.5) | 85.1 (17.3) | 86.2 (15.4) | .732* |
| Baseline BMI, kg/m$^2$ | 29.0 (4.9) | 28.3 (4.8) | 29.9 (4.9) | .098* |
| Race, n (%) | | | | .238 |
| White | 89 (75) | 59 (80) | 30 (68) | |
| Black | 17 (14) | 10 (14) | 7 (16) | |
| Other | 12 (10) | 5 (7) | 7 (16) | |
| ADT indication, n (%) | | | | .705 |
| High risk disease | 60 (59) | 40 (56) | 20 (56) | |
| Local recurrence | 33 (33) | 23 (32) | 10 (28) | |
| Primary treatment | 14 (14) | 8 (11) | 6 (17) | |
| Pathologic Gleason, n (%) | | | | .406 |
| ≤6 | 16 (16) | 13 (20) | 3 (9) | |
| 3 + 4 | 24 (25) | 15 (23) | 9 (28) | |
| ≥4 + 3 | 57 (59) | 37 (57) | 20 (63) | |
| Primary therapy, n (%) | | | | .551 |
| RT | 74 (65) | 47 (65) | 27 (66) | |
| RP | 6 (5) | 3 (4) | 3 (7) | |
| RT + RP | 14 (12) | 11 (15) | 3 (7) | |
| ADT only | 19 (17) | 11 (15) | 8 (20) | |
| Pathology for RP, n (%) | | | | |
| ECE, n (%) | | | | .893 |
| Positive | 9 (53) | 7 (54) | 2 (50) | |
| Negative | 8 (47) | 6 (46) | 2 (50) | |
| Surgical margins, n (%) | | | | .154 |
| Positive | 4 (24) | 2 (15) | 2 (50) | |
| Negative | 13 (76) | 11 (85) | 2 (50) | |
| SVI, n (%) | | | | .659 |
| Positive | 3 (18) | 2 (15) | 1 (25) | |
| Negative | 14 (82) | 11 (85) | 3 (75) | |

ADT, androgen deprivation therapy; BMI, body mass index; ECE, extra capsular extension; RP, radical prostatectomy; RT, radiation therapy; SD, standard deviation; SVI, seminal vesicle invasion.
*P* value from Chi-squared except where noted.
* *P* value from *t* test.

weights (SD = 4.0, $P = .0005$). Furthermore, Table 2 shows that significant weight gain occurred in men of ages <65 years (2.72 kg, SD = 3.6, $P = .001$), men who were nonobese by BMI <30 (1.98 kg, SD = 3.8, $P = .00002$), and men who did not have a diagnosis of diabetes (1.56 kg, SD = 4.0, $P = .0003$). These are contrasted by no significant changes in weight among men aged 65 years or older (0.74 kg, SD = 4.0, $P = .09$), men who were obese by BMI >30 (0.10 kg, SD = 4.0, $P = .87$), and men with a diagnosis of diabetes (0.26 kg, SD = 3.6, $P = .74$).

Both age and BMI were further stratified into 3-tiered categorical variables of age <65, 65-75, and >75 years and BMI <25, 25-30 and >30 to better characterize the effect of each variable on weight gain (Table 3). Weight gain significantly decreased with both increasing baseline age (2.72, 1.43, 0.12 kg gained for age <65, 65-75, >75 years respectively, *P-trend* = .004) and increasing baseline BMI (2.42, 1.77, and 0.10 kg gained for BMI <25, 25-30, and >30 respectively, *P-trend* = .013).

As most patients in this cohort (64%) had 2 or more of the 3 identified risk factors for weight gain (age <65 years, BMI <30, nondiabetic), a risk scoring system was contrived by assigning one point to each risk factor present per patient and stratifying patients by aggregate risk score (Table 4). Weight gain on ADT was strongly associated with increasing risk score (*P-trend* = .0005). Men with 0 risk factors present (ie, patients who were obese, diabetic, and age >65 years) had a weight change of −1.10 kg (SD = 4.0, $P = .43$), whereas men with 1 risk factor had a weight gain of 0.41 kg (SD = 4.0, $P = .56$), men with 2 risk factors had a weight gain of 1.34 kg (SD = 3.8, $P = .01$), and men with 3 risk factors had a weight gain of 3.79 kg (SD = 3.5, $P = .0001$).

On multiple variable regression analysis, age <65 years significantly predicted weight gain (beta = 4.01, $P = .02$), as did nonobese status (beta = 3.57, $P = .03$), although nondiabetic status was nonsignificantly predictive of weight gain (beta = 2.14, $P = .29$).

## COMMENT

This retrospective study revealed significant weight gain among a cohort of men with nonmetastatic prostate cancer over the year after initiation of ADT. We also demonstrated that patients who were aged <65 years, nonobese, or nondiabetic each had significant weight

**Table 2.** Risk factors for weight gain on ADT

| Risk Factor | n | Weight Change, kg (SD) | *P* |
|---|---|---|---|
| Age, y | | | |
| <65 | 34 | 2.72 (4.0) | .0001 |
| >65 | 84 | 0.74 (4.0) | .09 |
| BMI | | | |
| <30 | 76 | 1.98 (3.8) | .00002 |
| >30 | 42 | 0.10 (4.0) | .87 |
| Nondiabetic | 96 | 1.56 (4.0) | .0003 |
| Diabetic | 22 | 0.26 (3.6) | .74 |
| All patients | 118 | 1.31 (4.0) | .0005 |

Abbreviations as in Table 1.

**Table 3.** Effect of baseline age and BMI on weight gain, demonstrating increasing weight gain with decreasing age or BMI

| Demographic | n | Weight Change, kg (SD) | *P* |
|---|---|---|---|
| Age, y | | | |
| <65 | 34 | 2.72 (4.0) | .0001 |
| 65-75 | 40 | 1.43 (4.5) | .048 |
| >75 | 44 | 0.12 (3.5) | .82 |
| | | *P-trend* = .004 | |
| BMI | | | |
| <25 | 24 | 2.42 (3.9) | .005 |
| 25-30 | 42 | 1.77 (3.8) | .001 |
| >30 | 42 | 0.10 (4.0) | .87 |
| | | *P-trend* = .013 | |

Abbreviations as in Table 1.

gain at 1 year that was higher in magnitude than weight gained by patients without these factors. Patients age >65 years and those with obesity or diabetes did not exhibit significant weight changes at 1 year. Multivariable regression identified both age and baseline BMI as independently predictive of weight gain on ADT, although nondiabetic status did not reach independent significance. We also designed a weight change prediction model by attributing 1 point per risk factor present per patient and found a stepwise increase in weight gain for each increase in aggregate risk score. Most men had more than 1 risk factor at ADT initiation, and significant weight gain was found only among men with 2 or more baseline risk factors. To our knowledge, younger age has been the only risk factor significantly associated with increased weight gain on ADT in the literature,[10] and the relationships between obesity or diabetic status and ADT-related weight gain are novel findings.

One parsimonious theory for a relationship between the identified risk factors is that men in each of these risk categories of young, slender, and nondiabetic (compared with older, obese, or diabetic men) are likely to have higher baseline serum testosterone and therefore a larger magnitude of testosterone decline on androgen deprivation. Studies show that older men have decreased total and free serum testosterone and increased sex hormone–binding globulin relative to younger men.[14,15] Obesity is also associated with lower free testosterone among an age-controlled population in the European Male Aging

**Table 4.** Aggregate risk score and weight gain on ADT

| Risk Score | n | Weight Change, kg (SD) | *P* |
|---|---|---|---|
| 0 | 9 | −1.10 (4.0) | .4322 |
| 1 | 32 | 0.41 (4.0) | .562 |
| 2 | 57 | 1.34 (3.8) | .0102 |
| 3 | 20 | 3.79 (3.5) | .0001 |
| | | *P-trend* = .0005 | |

Abbreviations as in Table 1.

Study.[16] Moreover, an association between diabetes and decreased testosterone was confirmed by an extensive 43-study meta-analysis.[17] The mechanisms by which each condition interacts with testosterone decline are only partially characterized and beyond the scope of this analysis. However, it is possible that some element of testosterone-mediated protection against weight gain is already compromised in these groups of patients, leaving a less observable effect on androgen deprivation.

In considering the literature surrounding ADT-related weight gain, it is important to note that ADT is associated with the development of "sarcopenic obesity," a relatively recent concept signifying a simultaneous decrease in lean body mass with a corresponding increase in adiposity.[18] The most comprehensive support of this phenomena can be found in a recent meta-analysis of body composition changes related to ADT that included 7 trials all showing both an increase in percentage fat mass and a decrease in percentage lean body mass.[8] Of note, the fat accumulation of androgen deprivation tends to predominate in a subcutaneous distribution, contrary to the visceral compartmentalization of fat typical of age-related sarcopenic obesity or obesity as seen within the metabolic syndrome.[19,20] In looking specifically at sarcopenia, a recent study showed that older men lose more lean body mass than younger men on ADT.[20] This finding could also partially explain the significant difference in weight gain across age categories seen in both this study and the initial study by Timilshina et al.[10] Of interest, although it might have been postulated that older men had shorter courses of ADT, thus resulting in less weight gain, we alternatively found that in our cohort, there were significantly more men <65 years undergoing short courses of ADT (<12 months) than men age 65 years or older.

With respect to clinical implications, there are a variety of comorbidities associated with excess weight and obesity. Although an absolute weight gain of 1.3 kg (the average weight gain in this cohort) may not be clinically or aesthetically significant to a given patient, data suggest that increases in adiposity far exceed total weight gain given the concurrent loss of lean body mass on ADT.[4,20] Furthermore, the primary objective of this study was to identify those men who gain the most weight on ADT, such as the men in our highest risk category who gained an average of 3.8 kg. Perhaps most importantly, body composition changes may play a role in the increased risk of cardiovascular disease (including coronary artery

disease and myocardial infarction) attributed to ADT in certain studies.[5,21,22] Furthermore, most weight gain is consistently reported within the first 1-2 years after initiating ADT,[9,10,23] with the start of significant body composition changes seen within the first few months of therapy.[24] Taken together, the comorbidity associated with weight gain and obesity and the natural history of early ADT-related changes both support the necessity of adequately predicting which patients are at highest risk of body composition change on ADT. Exercise, particularly in the form of resistance training, has been shown to increase quality of life[25] and possibly attenuate or even reverse body composition changes.[11,12]

Limitations of this study include the relatively small size and lack of non-ADT control group. It should be noted that although body composition changes have been well-documented in the literature, BMI and weight measurements discussed here do not discern between relative fat, muscle, and bone for each patient. BMI can occasionally misrepresent an athletic patient as being overweight because of a large lean body mass (muscular) component of their habitus. In addition, the large majority of patients treated at this institution were excluded because of the absence of a baseline weight measured before therapy or within the 6-18 month window necessary for outcome measures. Owing to the modest number of patients meeting inclusion criteria, we selected just 1 representative weight value for use in calculations, similar to the method used by Kim et al, as few patients had multiple measurements within the period of interest. However, the cohort was sufficiently large to detect a significant weight change and the corresponding risk factors. Also, ADT-related weight gain has been repeatedly well-documented in prospective studies compared with both men with prostate cancer (without ADT) and healthy controls.

Our risk scoring system might also be more precise if point values were weighted by corresponding coefficients in the regression model, but we believe that this simplified format should prove more clinically practical. Of note, although diabetic status was associated with weight gain on univariate analysis, it was not statistically proven to be independently predictive by multivariable regression, and it could be argued that this risk factor should be left out of the aggregate risk prediction model. Our testing of the independent influence of a diabetes diagnosis was likely obscured by both the small number of diabetic patients ($n = 22$) and the high prevalence of coincident baseline risk factors. This phenomenon of coincident risk is highlighted by the absence of a significant weight change among the smaller subpopulation ($n = 32$) of men with just 1 risk factor at ADT initiation. However, the highly significant trend of the composite risk score analysis (including nondiabetic status), coupled with the significant association between weight gain and nondiabetic status on univariate analysis, allows for its reasonable inclusion in our clinical prediction model with due understanding that it represents the weakest of 3 predictors and may be dependent on other characteristics.

Finally, we could not adjust for extrinsic factors such as potentially more intensive counseling for men with comorbidities and resultant variation in exercise between groups. It is likewise possible that medication regimens outside of leuprolide, such as metformin for men with diabetes, affected the weight gain of comparison subgroups. Finally, although we propose magnitude of testosterone decline as an explanatory theme in these data, our observation is indirect, and future research is needed among patients with measured baseline testosterone to confirm this hypothesis.

## CONCLUSION

Understanding the risk factors of weight gain on ADT will better inform the metabolic assessment and management of patients on hormonal therapy. Previous studies have suggested that men older than 65 years[21,26] or those with higher levels of comorbidity[27,28] may be the ones at greatest risk of cardiovascular harm from ADT and that increased caution should be used when offering ADT to these men. This study proposes that with respect to weight gain on ADT, younger and healthier men may be the ones at highest risk and serves as a reminder that judicious use of ADT with attention to metabolic side effects and encouragement of exercise is also essential in this population.

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