Risk of new-onset diabetes mellitus and worsening glycaemic variables for established diabetes in men undergoing androgen-deprivation therapy for prostate cancer

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OBJECTIVE

To investigate the incidence of new-onset diabetes mellitus (NODM) and of worsening glycaemic control in established DM after starting androgen-deprivation therapy (ADT) for prostate cancer, as ADT is associated with altered body composition, potentially influencing insulin sensitivity.

PATIENTS AND METHODS

We retrospectively reviewed patients receiving ADT for prostate cancer at our institution between January 1989 and July 2005; those with incomplete information and those receiving only neoadjuvant ADT were excluded. Variables examined included age, race, body mass index (BMI), pretreatment prostate-specific antigen, Gleason sum, clinical stage, ADT type (medical vs surgical) and schedule (continuous vs intermittent), presence of pre-existing DM, serum glucose and glycosylated haemoglobin (HbA1c) levels before and after ADT, and receipt of vitamin D or bisphosphonate supplementation. Data were analysed statistically and $P < 0.05$ considered to indicate significance.

RESULTS

In all, 396 patients (median age 73.2 years; median BMI of 26.7 kg/m^2 at ADT initiation) were analysed. Of these, 59.1% were African-American and 40.9% were Caucasian/other. At a median follow-up of 60.1 months, 36 (11.3%) patients developed NODM. In 77 patients with pre-existing DM, there was an increase of ≥10% in serum HbA1c or fasting glucose levels in 15 (19.5%) and 22 (28.6%), respectively. On multivariate analysis, a BMI of ≥30 kg/m^2 was associated with an increased risk of developing NODM (odds ratio 4.65, $P = 0.031$). Receipt of vitamin D had a protective effect (odds ratio 5.75, $P = 0.017$).

CONCLUSIONS

Patients receiving ADT for prostate cancer with or with no history of DM should have routine surveillance of glycaemic control, particularly when their BMI is ≥30 kg/m^2, with appropriate preventive and treatment measures.

KEYWORDS

prostatic neoplasm, GnRH, diabetes mellitus, castration, male, risk factors

INTRODUCTION

Prostate cancer is the most common malignancy in men in the USA, with an expected 218 890 new cases and 27 050 deaths estimated in 2007 [1]. Since recognizing the utility of androgen deprivation therapy (ADT) in treating prostate cancer, ADT has become a widespread treatment for men with clinically localized as well as advanced-stage disease. Current applications of ADT include neoadjuvant and adjuvant therapy in men undergoing primary external-beam radiotherapy (EBRT) or brachytherapy for clinically localized cancer, adjuvant therapy in men with lymph node metastases, salvage therapy in men with an increasing PSA level after primary surgical or radiation treatment for localized cancer, reducing the prostate before prostate cryosurgery, and primary palliative therapy in selected patients [2].

Common adverse effects of ADT include decreased libido, vasomotor flushing, fatigue, anaemia, osteoporosis and altered body composition, and are well documented [2–7]. Growing evidence supports an association between sex hormones and the risk for developing diabetes mellitus (DM); specifically, serum testosterone concentrations have an inverse relationship with insulin resistance [8,9].

ADT has been associated with insulin resistance and abnormal glucose tolerance in several small series [5,6,10,11]. Recent investigations further supported a link between ADT and incident DM and/or metabolic syndrome [12]. Herein, we report our investigation into the association between ADT for prostate cancer and the development of new-onset DM (NODM) and worsening glycaemic control in patients with known DM before starting ADT.

PATIENTS AND METHODS

After obtaining institutional review board approval, we retrospectively reviewed all patients receiving ADT for prostate cancer at one centre at our institution (Veterans Affairs Medical Center, VAMC) between January 1989 and June 2005. Patients receiving

Variable	Value
Mean (median, range):	
age at ADT initiation, years	71.7 (73.1, 46.7–89.3)
serum PSA level pre-ADT, ng/mL	130.8 (15.4, 0.4–6031.0)
Gleason grade sum	6.9 (7.0, 3.0–10.0)
primary Gleason grade	3.4 (3.0, 2.0–5.0)
secondary Gleason grade	3.5 (3.0, 1.0–5.0)
BMI, kg/m^2	26.9 (26.7, 12.5–52.4)
N (%):	
Race,	
African-American	234 (59.1)
Caucasian/Other	162 (40.9)
Castration type	
medical	371 (93.7)
surgical	25 (6.3)
ADT type	
primary	132 (33.3)
salvage	264 (66.7)
EBRT/brachytherapy	199 (50.3)
RP	32 (8.1)
TCAP	13 (3.3)
EBRT/TCAP	2 (0.5)
RP/EBRT	18 (4.5)
ADT administration schedule	
continuous	360 (90.9)
intermittent	36 (9.1)
Clinical stage	
T1a/b	15 (3.8)
T1c	163 (41.1)
T2a	42 (10.6)
T2b/c	22 (5.6)
T3a/b/c	7 (1.8)
N+	8 (2.0)
M+	14 (3.5)
Unknown	125 (31.6)
Vitamin D supplementation	
Yes	11 (2.8)
No	385 (97.2)
Bisphosphonate therapy	
Yes	18 (4.5)
No	378 (95.5)
Follow-up, months	
Mean (median, range)	66.1 (60.1, 10.7–208.2)

TABLE 1
The clinicopathological and demographic data for 396 patients with prostate cancer treated with ADT

TCAP, targeted cryoablation of the prostate.

only neoadjuvant ADT were excluded. Clinicopathological variables examined included age at ADT initiation, race, body mass index (BMI), pretreatment serum PSA level, Gleason grade, clinical stage (TNM 1992), type of ADT (medical vs surgical), ADT schedule (continuous vs intermittent), and receipt of vitamin D or bisphosphonate therapy. Patients undergoing ADT were diagnosed with NODM according to the WHO/American Diabetes Association (ADA) recommendations with two separate fasting blood glucose (FBG) measures of ≥126 mg/dL [13]. Further, treatments (diet, insulin or oral therapy) implemented in patients with NODM were recorded.

Patients with a diagnosis of DM and undergoing targeted therapy (diet, insulin therapy, oral therapy) before starting ADT were designated as having pre-existing DM; in these men glycaemic control was determined by comparing mean FBG and glycosylated haemoglobin (HbA1c) levels before and after treatment. At least three separate values for FBG and HbA1c were averaged to obtain mean values before and after ADT for comparison. Subsets were analysed to determine the percentage of patients with a ≥10% rise in mean FBG or mean HbA1c after starting ADT. ADT was defined as receipt of a GnRH agonist (goserelin acetate depot, AstraZeneca PLC, London, UK), combined androgen blockade (CAB, GnRH agonist and antiandrogen), or bilateral orchidectomy.

Data were analysed using the chi-square and Kruskal–Wallis ANOVA (where appropriate), and univariate and multivariate logistic regression, with all potential explanatory covariates incorporated into models. Variables showing an association with NODM or worsening DM were considered for multivariate analysis. Independent variables were modelled as both continuous and categorical variables as follows: age ≥70 vs <70 years, Gleason grade sum ≥7 vs <7, PSA level ≥10 vs <10 ng/mL, and BMI ≥30 vs <30 kg/m^2. All P values were based on two-sided tests of significance, with $P < 0.05$ considered to indicate statistically significant differences. The Hosmer-Lemeshow test eliminated models that fitted poorly.

RESULTS

The demographic data and disease characteristics are outlined in Table 1; after exclusions, 396 patients were analysed (median age at ADT initiation 73.1 years, range 46.7–89.3; median follow-up 60.1 months, range 10.7–208.2). Of these, 234 (59.1%) were African-American and 162 (40.9%) were Caucasian/other. In all, 371 (93.7%) men received medical castration ADT while 25 (6.3%) had bilateral orchidectomy; 264 (66.7%) men had salvage ADT for an increasing PSA level after primary treatment, 132 (33.3%) received primary ADT, and 360 (90.9%) received continuous ADT (surgical or medical), while 36 (9.1%) received intermittent ADT.

Table 2 shows rates of DM and glycaemic variables; in all, 113 (28.5%) patients with DM were identified, of whom 77 (19.4%) had pre-existing DM at ADT induction and 319 (80.6%) had no evidence of previous DM. Of the latter patients, 36 (11.3%) were diagnosed with NODM, and of these, four (11%) required insulin supplementation, 19 (53%) required oral hypoglycaemic therapy,

TABLE 2 A comparison of serum HbA1c and FBG levels, and of clinical variables, before and after ADT for prostate cancer

Variable	Group			P
	pre-existing DM	NODM	No DM	
N (%)	77 (19.4)	36 (11.3)	283 (71.5)	
Mean (range): serum HbA1c				
before ADT	7.14 (4.9–7.23)	–	–	
after ADT	7.23 (5.4–12.7)	6.92 (5.4–9.4)		
P	0.29	–	–	
n (%) with increase ≥10%	15 (19.5)	–	–	
FBG				
before ADT	127.6 (79.0–364.5)	–	–	
after ADT	135.5 (74.5–750.0)	171.3 (77.5–407.0)	–	
P	<0.001	–	–	
n (%) with increase ≥10%	22 (28.6)	–	–	
Clinical variables				
Mean (median, range):				
age at ADT, years	70.6 (71.5, 46.7–86.1)	72.0 (73.2, 47.8–83.0)	71.9 (73.3, 47.8–89.2)	0.41*
BMI, kg/m^2	29.9 (28.3, 17.3–52.3)	28.1 (28.3, 15.2–39.0)	26.2 (25.7, 12.5–44.4)	<0.001*
PSA before ADTm ng/mL	46.5 (13.6, 0.4–448.0)	18.8 (13.0, 0.9–73.6)	160.6 (16.6, 0.5–6031.0)	0.183*
N (%):				
Race				0.261†
African-American	47 (61.0)	25 (69.4)	162 (57.2)	
Caucasian/other	30 (39.0)	11 (30.6)	121 (42.8)	
Castration type				0.229†
medical	71 (92.2)	36 (100)	266 (94.0)	
surgical	6 (7.8)	0 (0)	17 (6.0)	

**Comparison by ANOVA; no DM vs pre-existing DM, P < 0.001; NODM vs pre-existing DM, P = 0.27; NODM vs no DM, P = 0.77. †Comparison by chi-square analysis.*

and 13 (36%) initiated an ADA recommended diet.

In the 77 patients with pre-existing DM the mean (range) serum HbA1c levels before and after treatment were 7.14 (4.9–16.9) and 7.23 (2.8–12.7), respectively, and remained unchanged with ADT ($P = 0.29$). However, 15 (20%) patients in this subset had a mean rise in HbA1c levels of ≥10%, the mean being 19.7%. In men with established DM there were significantly higher mean FBG levels after ADT than before ADT, at 135.5 (74.5–750.0) and 127.6 (79.0–364.5) mg/dL ($P < 0.001$); 22 (29%) in this subset had an increase in mean FBG of ≥10%, the mean being 30.3%.

Univariate and multivariate logistic regression analysis was used to identify factors predictive of worsening glycaemic variables including age, BMI, pretreatment serum PSA level, race, castration schedule, and vitamin D or bisphosphonate supplementation (data not shown). While race was found to be predictive of developing a ≥10% rise in mean HbA1c ($P = 0.008$) in the univariate analysis, this was not significant on multivariate analysis when adjusting for the remaining variables. No other variables had predictive value in univariate or multivariate analysis.

Table 2 also compares patients with no DM, NODM and pre-existing DM for age, BMI, race, pretreatment PSA level and type of ADT (medical vs surgical). All variables were similar between groups, except for BMI. Patients with pre-existing DM had a significantly higher mean (SD) BMI than those with no history of DM, at 29.9 (6.67) vs 26.2 (5.32) kg/m^2, respectively ($P < 0.001$). There was no significant difference between pretreatment BMI values between patients with NODM and pre-existing DM ($P = 0.27$). Patients with NODM also had a similar pretreatment BMI to those with no DM, at 28.1 (5.89) and 26.2 (5.32) kg/m^2, respectively ($P = 0.77$).

Logistic regression analysis was used to identify factors predictive for or protective against developing NODM in these patients (Table 3). When adjusting for other variables, multivariate analysis showed that a BMI of ≥30 kg/m^2 (vs <30) was predictive of developing NODM, with an odds ratio (OR, 95% CI) of 4.65 (4.608–4.686; $P = 0.031$). By contrast, vitamin D supplementation was protective against developing NODM (OR 5.75, 5.111–6.385, $P = 0.017$).

DISCUSSION

Since identifying the androgen dependency of prostate cancer, ADT has become a common treatment for selected patients with localized or advanced disease, and has shown survival benefits when administered as adjuvant therapy after EBRT or in the presence of nodal metastases discovered at the time of radical prostatectomy (RP) [2]. Cooperberg *et al.* [14] found significant increases in the use of primary ADT between 1999 and 2001 when compared with the previous decade, with 14.2%, 19.7% and 48.2% of men receiving primary ADT for low-, intermediate-, and high-risk prostate cancer, respectively. Furthermore, 7.8% of patients having RP,

TABLE 3 Predictive and protective factors for developing NODM on multivariate analysis

Clinical variable	OR (95% CI)	P
BMI (≥30 vs <30 kg/m^2)	4.65 (3.797–5.642)	0.031
Vitamin D supplementation	5.75 (5.688––6.507)	0.015
Bisphosphonate supplementation	0.29 (0.249–10.73)	0.615
Age (≥70 vs <70 years)	0.85 (0.399–1.824)	0.680
Race (African-American vs Caucasian/other)	2.61 (2.370––3.742)	0.090
Gleason score sum (≥7 vs <7)	1.97 (0.847–3.830)	0.130
PSA (≥10 vs <10 ng/mL)	1.08 (0.555–2.468)	0.680
Clinical stage	0.74 (0.400–1.769)	0.650
ADT schedule (continuous vs intermittent)	0.85 (0.157–1.949)	0.360

24.6% undergoing brachytherapy and 74.6% receiving EBRT received neoadjuvant ADT. With the expanded role of ADT in the treatment of contemporary prostate cancer, the importance of understanding and preventing ADT-associated morbidity is paramount.

Androgens are important factors in determining body composition. GnRH agonists reduce serum testosterone and oestradiol levels by down-regulating LH receptors at the level of the anterior pituitary gland, resulting in diminished release of sex hormones by the testicles [2]. Low serum testosterone levels associated with age-related or ADT- induced hypogonadism have been associated with loss of lean body mass, increased percentage of body fat composition, and development of insulin resistance [4–9]. Conversely, testosterone replacement in hypogonadal men has shown an improvement in insulin sensitivity [15]. While alterations in insulin sensitivity and glucose metabolism have been documented in patients receiving ADT, data are limited, with a preponderance of anecdotal reports and small series [5,6,10,11].

In a prospective study of 22 patients with newly diagnosed prostate cancer who were to receive ADT, Smith *et al.* [5] identified increases in the median serum insulin levels from 11.8 to 15.1 mU/L after 1 month of ADT, and to 19.3 mU/L by 3 months of treatment ($P = 0.02$). During the 3-month study, serum glucose levels remained unchanged despite the significant rise in serum insulin, implying the development of reduced insulin sensitivity even during short-term ADT. Similarly, Smith *et al.* [6] prospectively studied the effects of CAB in 25 men with locally advanced or recurrent prostate cancer and no history of DM. During the 12-week study there were no changes in FBG levels but significant increases in both mean HbA1c levels ($P < 0.001$) and fasting plasma insulin levels ($P = 0.04$), coupled with decreased insulin sensitivity measured by a homeostasis model assessing insulin resistance ($HOMA_{IR}$, $P = 0.02$). One patient in this cohort was diagnosed with DM at the completion of the study.

Basaria *et al.* [11] reported a cross-sectional analysis of 53 men, i.e. 18 with a history of prostate cancer and who received ≥12 months of ADT, 17 age-matched patients with prostate cancer treated with RP or EBRT (but no ADT), and 18 age-matched men with no history of prostate cancer (control group). They found significant increases in FBG levels ($P < 0.01$) and serum insulin levels ($P = 0.02$) in men receiving ADT, and which remained significant after adjusting for age and BMI. In addition, patients receiving ADT had a significantly higher insulin resistance by $HOMA_{IR}$ ($P = 0.01$). Inaba *et al.* [10] reported two patients with prostate cancer who developed hyperglycaemia after ADT initiation; the first had a history of well-controlled type 2 DM and had increases in both HbA1c and FBG levels after 3 weeks of CAB, requiring insulin supplementation and a thiazolidinedione agent to achieve glycaemic control. The second patient had no history of previous DM and developed hyperglycaemia and elevated HbA1c levels after only 4 weeks of ADT monotherapy with leuprolide, requiring hospitalization with administration of both insulin and thiazolidinedione therapy for glycaemic control. When compared to a control group of 144 men with no DM, the study patients had lower pancreatic β-cell function and reduced insulin sensitivity by $HOMA_{IR}$ evaluation.

Recently, Keating *et al.* [12] reported on 73 196 men with local/regional prostate cancer, from the Surveillance, Epidemiology and End Results database. In the 36.3% of patients receiving medical ADT, they found a greater incidence of DM, with a hazard ratio of 1.44 ($P < 0.001$), than in those not currently receiving ADT. Further, the duration of ADT increased the risk of incident DM, even with as little as 1–4 months of ADT. Moreover, they found that orchidectomy also led to increased rates of incident DM.

In the present series of 396 men receiving ADT for prostate cancer, of whom 319 were not diabetics on starting ADT, 36 (11.3%) were diagnosed with NODM and started appropriate medical management. Also, in 77 patients with pre-existing DM, ADT was associated with an increase in serum HbA1c and FBG levels of ≥10% in 15 (19.5%) and 22 (28.6%), respectively. Furthermore, this group had a significant increase in mean FBG levels, although HbA1c remained unchanged (Table 2).

We attempted to identify factors that would predict the development of either NODM or worsening glycaemic control in those with pre-existing DM. While the mean BMI was significantly higher in those with pre-existing DM than those with no DM, all other intergroup comparisons were similar (Table 2).

In patients developing NODM after starting ADT, only a BMI of ≥30 kg/m^2 was predictive of NODM ($P = 0.031$) after adjusting for other variables (Table 3), while African-American race approached significance ($P = 0.09$). As noted, BMI has shown clear associations with the risk of developing DM. Also there are data supporting the view that African-Americans are at higher risk of DM than other ethnic groups [16]. From that study it can be extrapolated that the interaction between race and BMI might be significant in identifying patients at higher risk of developing NODM or worsening DM during ADT for prostate cancer, although further investigation is needed. The significant protective effect of vitamin D (OR 5.75, $P = 0.015$, Table 3) against developing NODM during ADT is consistent with findings related to vitamin-D associated DM prevention seen in both animal and human studies [17–19].

There are several limitations to the present study. First, it was a retrospective review and is subject to the inherent biases of this type of

analysis. The lack of a control group (i.e. patients undergoing surveillance protocols or those receiving only primary therapy for localized disease) and potential selection bias for the time of starting ADT remain major methodological factors that limit the strength of our findings. While the electronic medical records system of the VAMC enables access to comprehensive medical management records across all specialities and VAMC localities, medical care provided outside the VAMC system was not included in our analysis. To an uncertain degree, these study limitations potentially underestimate the effects of long-term ADT on glycaemic control. Also, while comprising 396 patients, relatively few patients developed NODM (36) or had pre-existing DM (77). As such, our analysis is limited in its ability to detect all potential relationships between variables and the endpoints of the study. Furthermore, as patients were not evaluated prospectively and uniformly, it is possible that more patients developed NODM but went undetected. Nonetheless, we feel that the present results are supported by the size of the study group and the duration of follow-up. To our knowledge, this is the largest single-centre series reported to date of patients evaluated for NODM and worsening glycaemic control in those receiving ADT for prostate cancer. The mean follow-up of 66.1 months at an equal-access healthcare centre (VAMC) is substantial [20,21]. Age and disease characteristics in the present patients are representative of the larger population with prostate cancer in the USA, while race, lifestyle, and general health characteristics might reflect regional trends [22]. Ideally, a prospective analysis directly comparing matched controls to those receiving ADT would be ideal to show all the potential relationships.

Despite these limitations, we feel that these findings should at least prompt physicians administering ADT to patients with prostate cancer to adopt a regimen of close monitoring of serum FBG and HbA1c levels, particularly in obese patients (with a BMI of ≥30 kg/m^2) and if long-term therapy is planned; we have implemented a surveillance plan for patients treated at our institution in this regard. Given that hyperglycaemia is associated with increases in pro-inflammatory cytokines, oxidative stress, and increased free fatty acids [23–25], we hypothesise that the iatrogenic hypogonadism due to prolonged ADT for prostate cancer will lead to eventual insulin resistance, with subsequent up-regulation of these pro-inflammatory cytokines. As such, future studies should aim to prospectively evaluate patients with prostate cancer both before and during ADT, with particular attention to the effects on glycaemic and lipaemic indices, and levels of pro-inflammatory and anti-inflammatory cytokines. In addition, prospective, randomized trials evaluating the role of vitamin D supplementation as a chemopreventive agent against the development of NODM should be considered.

In conclusion, this study detected NODM in 11.3% of men receiving ADT for prostate cancer. Furthermore, there was worsening glycaemic control, as measured by a ≥10% increase in mean serum HbA1c and FBG levels, in 19.5% and 28.6% of patients with pre-existing DM, respectively. Patients with a BMI of ≥30 kg/m^2 had 4.6 times the risk of developing NODM, while vitamin D supplementation had a protective effect. While further investigation is required these data support close monitoring of serum HbA1c and FBG levels in men undergoing ADT, both in those with pre-existing DM and those with no DM but a history of obesity (BMI ≥30 kg/m^2).

CONFLICT OF INTEREST

None declared.

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Abbreviations: **ADT**, androgen deprivation therapy; **EBRT**, external-beam radiotherapy; **(NO)DM**, (new-onset) diabetes mellitus; **VAMC**, Veterans Affairs Medical Center; **BMI**, body mass index; **ADA**, American Diabetes Association; **FBG**, fasting blood glucose; **HbA1c**, glycosylated haemoglobin; **CAB**, combined androgen blockade; **RP**, radical prostatectomy; **$HOMA_{IR}$**, homeostasis model assessing insulin resistance.