Changes in blood glucose and cholesterol levels due to androgen deprivation therapy in men with non-metastatic prostate cancer

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Abstract

Objective: To investigate the effects of androgen deprivation therapy (ADT) on blood glucose and cholesterol over 12 months in a prospective matched cohort study.

Methods: English-speaking patients with non-metastatic prostate cancer attending the Princess Margaret Hospital were invited to participate in this study. Patients were divided into two cohorts: ADT users and controls. Androgen deprivation therapy users were frequency matched to controls on age, education and body mass index (BMI). The study consisted of two visits. Sociodemographic and clinical information, medication use, physical fitness, height and weight were collected before initiation of ADT. Twelve months later, fasting morning blood work was obtained to measure plasma glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides. Statistical analyses included univariate and multivariable linear regression.

Results: We recruited 75 patients (mean age 68.9), 38 of whom were undergoing ADT. Twelve patients with prior diabetes and 29 patients taking cholesterol-lowering medication at baseline were excluded from the glucose and cholesterol analysis, respectively. In adjusted analyses, ADT users had a significantly higher glucose level compared to controls (5.88 vs. 5.52 mmol/L, $p = 0.024$). Overall, ADT users had higher levels of total cholesterol, HDL, LDL, and triglycerides than controls, although none of the differences reached statistical significance.

Conclusion: One year of ADT use is associated with elevated fasting glucose levels and may increase all lipid fractions in men with prostate cancer.

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Résumé

Objectif : Examiner les effets d'un traitement antiandrogène sur la glycémie et la cholestérolémie pendant 12 mois dans une étude prospective de cohorte appariée.

Méthodologie : Des patients anglophones atteints d'un cancer de la prostate non métastatique traités à l'hôpital Princess Margaret ont été invités à participer à l'étude. Les patients ont été séparés en deux groupes : les utilisateurs de traitement antiandrogène et les témoins. Les utilisateurs de traitement antiandrogène ont été appariés aux témoins selon la fréquence en fonction de l'âge, de la scolarité et de l'indice de masse corporelle (IMC). Deux visites étaient prévues à l'étude. On a recueilli des données sociodémographiques et cliniques, des informations sur l'usage de médicaments, le niveau de forme physique, la taille et le poids avant l'instauration du traitement antiandrogène. Douze mois plus tard, on a procédé à des analyses de sang à jeun (le matin) afin de mesurer les taux de glucose, de cholestérol total, de cholestérol des lipoprotéines de haute densité (C-HDL), de cholestérol des lipoprotéines de basse densité (C-LDL) et de triglycérides dans le plasma. Les analyses statistiques incluaient des analyses de régression linéaire univariées et multivariées.

Résultats : Nous avons recruté 75 patients (âge moyen : 68,9 ans), dont 38 suivaient un traitement antiandrogène. Douze patients atteints de diabète et 29 patients sous traitement hypocholestérolémiant au départ ont été exclus de l'analyse du glucose et du cholestérol, respectivement. Dans les analyses ajustées, les utilisateurs de traitement antiandrogène affichaient des taux significativement plus élevés de glucose en comparaison avec les témoins (5,88 contre 5,52 mmol/L, p = 0,024). De façon globale, les utilisateurs de traitement antiandrogène présentaient des taux plus élevés de cholestérol total, de C-HDL, de C-LDL et de triglycérides que les témoins, même si aucune des différences notées n'a atteint le seuil de signification statistique.

Conclusion : Un an de prise d'un traitement antiandrogène est associé à des taux élevés de glucose à jeun et pourrait amener une hausse de toutes les fractions lipidiques chez les hommes atteints de cancer de la prostate.

Background

Prostate cancer is the most common cancer among men in the United States and Canada.[1,2] The 5-year disease-specific survival for men with all stages of prostate cancer combined is 98.8%.[3] Androgen deprivation therapy (ADT) using gonadotropin-releasing hormone (GnRH) agonists is now commonly prescribed for men with locally advanced or high-risk localized disease in addition to men with metastatic disease.[4,5] Androgen deprivation therapy has been to shown to improve survival for men in these disease groups, but long-term androgen deprivation has also been associated with important side effects in a variety of areas, including osteoporosis, diabetes, anemia and possibly cardiovascular disease.[6,7]

Although several large retrospective studies using administrative data have shown an increased risk of developing

diabetes with GnRH use,[8,9] these studies often lack detailed clinical information about patients; data from prospective studies have been limited. Findings by Dockery and colleagues demonstrated that ADT did not affect blood glucose levels over a 3-month period.[10] Another study reported an increase in fasting glucose and insulin requirements in diabetic patients undergoing ADT for a 2-year period.[11] The impact of longer-term ADT use on blood glucose levels in non-diabetic patients has not been reported.

Studies demonstrating lipid alterations with ADT have been somewhat contradictory. Early research showed that ADT caused an increase in total cholesterol, high-density lipoprotein (HDL), and triglyceride levels in 50 patients with benign prostatic hyperplasia.[12] Conversely, a large, recent study showed a decrease in HDL and an increase in low-density lipoprotein (LDL), triglycerides and total cholesterol with 12-month use of ADT.[13] Prior studies have generally featured small sample sizes, and have not consistently accounted for patient medication use, smoking history, body mass index (BMI) and previous diseases.[14] Independently, all of these factors have an effect on blood cholesterol levels, and need to be accounted for to understand the effects of ADT.

We sought to investigate the effects of ADT on blood glucose and blood cholesterol over a 12-month period in a prospective matched cohort study.

Materials and methods

We approached English-speaking patients with non-metastatic prostate cancer attending Princess Margaret Hospital, a tertiary care cancer centre in Toronto, Canada, to take part in this pilot study. Recruited patients were part of a larger, prospective longitudinal cohort study investigating side effects and quality of life in patients undergoing ADT. The ADT cohort consisted of men who were initiating continuous ADT for at least 12 months. A control group, consisting of men with prostate cancer but not on ADT, was also recruited. Men in the ADT cohort were frequency matched to controls on age, education and BMI. Patients with another active malignancy or major neuropsychiatric abnormalities were excluded. All patients provided written, informed consent. The study was approved by the institutional Research Ethics Board.

The study consisted of 2 visits. The baseline visit was done prior to patients initiating ADT. Sociodemographic information, smoking and alcohol use, medication use and other comorbidities were collected from patients and the patient's electronic health record by a trained research assistant. In addition, the health record was used to collect specific disease information. Height and weight were measured using standardized instruments at baseline to compute the BMI. Lastly, physical fitness was measured using a 6-minute walk test (a submaximal exercise test in which the distance a patient walks in 6 minutes is measured).[15]

Each patient was asked to return for a second visit after 12 months. Patients reported whether they had started taking any new medications, or had developed any new comorbidities over the course of the year. Fasting morning blood work was obtained to measure plasma glucose, HDL, LDL, triglycerides and total cholesterol. Samples were collected and analyzed immediately in a reference laboratory where possible, or else in commercial labs following standard procedures.

Statistical analyses

Baseline characteristics were described using means for continuous variables and counts for categorical variables. To compare the two cohorts, Student's t-tests and chi-square tests were used for continuous and categorical variables, respectively. To determine whether ADT use was associated with either glucose levels or total cholesterol levels, we performed univariate linear regression. Patients with prior or current diabetes were excluded from the glucose analysis, and patients taking cholesterol-lowering medication (including statins, fibric acid derivatives, binding resins, and ezetimibe) were excluded from the cholesterol analysis. We then built multivariable linear regression models for both outcome variables using a hybrid selection approach to minimize overfitting given the modest sample size.[16,17] Variables were included in the multivariable model if they were statistically significant in the univariate analysis with a less restrictive p value of 0.20.[16] Age and BMI were forced into the models based on prior studies demonstrating relationships with insulin resistance and hyperlipidemia. Variables were subsequently removed if their p value was >0.10 to create a more parsimonious model. Because of laboratory or administrative error, 8 subjects had 1 or more missing cholesterol fractions measured beyond total cholesterol. As such, only total cholesterol was examined in regression models. All statistical analyses were done using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

A total of 75 patients were recruited, 38 of whom initiated ADT. The mean overall age of the patients was 68.9 years (range 53-87). In general, the 2 groups were well-matched with respect to age, sociodemographic variables, BMI and fitness levels (Table 1). As anticipated, patients in the ADT cohort had higher stage disease with worse Gleason scores than controls (Table 1). Twelve patients (6 ADT users, 6 controls) had prior diabetes and were excluded from the glucose analysis. A total of 29 patients (17 ADT users, 12 controls) reported taking cholesterol-lowering medication at baseline, and were excluded from the cholesterol analysis. No patient

Table 1. Baseline patient characteristics

Variable	ADT users (n = 38)	Controls (n = 37)	*p* value
Mean age, year (SD)	68.9 (7.7)	68.9 (6.7)	0.99
Mean education, year (SD)	14.2 (4.5)	15.3 (4.3)	0.27
Income			0.08
<$20K	14	7	
$20-$40K	3	12	
$40-$60K	10	8	
$60-$100K	2	1	
>$100K	8	8	
Work status			0.86
Still at work	14	14	
Retired	24	22	
Race			0.15
White	31	36	
Black	3	0	
Hispanic	1	0	
Oriental	3	1	
No. of current smokers	6 (15.8%)	6 (16.2%)	0.96
Alcohol use/day			0.05
None	13	6	
Less than 1 drink	11	22	
>1 drink	13	8	
Mean BMI (SD)	28.2 (5.8)	28.1 (3.7)	0.99
Mean 6-min walk, feet (SD)	1,560 (290)	1,600 (220)	0.535
Clinical stage			0.01
T1c	14	20	
T2a	6	12	
T2b	3	3	
T2c	5	1	
T3	10	1	
Mean Gleason score (SD)	7.3 (1.2)	6.4 (0.9)	0.004
Prior curative treatment			0.18
None	7	6	
Brachytherapy	2	5	
External beam RT	21	11	
RP	5	8	
RP + RT	2	3	
Prior comorbidities			
Diabetes	6	6	0.96
Hyperlipidemia	13	13	0.93
Hypertension	18	19	0.73
Myocardial infarction	0	0	-
PVD	1	0	0.32
Other cardiac illness	7	5	0.56
Renal failure	0	0	-
Medication use			
Diabetes	5	5	0.96
Antiplatelet agent	10	7	0.44
Cholesterol	17	12	0.27
Other heart	26	25	0.94

ADT: androgen deprivation therapy; BMI: body mass index; RT: radiotherapy; P: radical prostatectomy; PVD: peripheral vascular disease; SD: standard deviation.

developed diabetes or started taking cholesterol-lowering medication between baseline and the 12-month visit.

Table 2. Comparison of fasting glucose (after excluding diabetic patients) and cholesterol levels (after excluding patients taking cholesterol medication) among ADT users and controls

Variable	ADT users	Controls	*p* value
Glucose (mmol/L)	n = 29	n = 31	
Mean glucose (SD)	5.88 (0.56)	5.52 (0.61)	0.024
Range	4.80-7.10	4.50-7.10	
Cholesterol (mmol/L)	n = 20	n = 25	
Mean total cholesterol (SD)	5.31 (1.2)	4.93 (1.2)	0.31
Range	3.09-6.84	2.92-7.09	
Mean HDL (SD)	1.38 (0.52)	1.30 (0.35)	0.55
Range	0.80-2.65	0.79-2.28	
Mean LDL (SD)	3.40 (0.71)	3.10 (1.0)	0.36
Range	2.34-4.60	1.60-5.14	
Mean triglycerides (SD)	1.63 (0.89)	1.23 (0.63)	0.12
Range	0.43-2.78	0.69-3.17	

HDL: high-density lipoprotein; LDL: low-density lipoprotein; SD: standard deviation; ADT: androgen deprivation therapy.

Effect of ADT on blood glucose

In unadjusted analyses, ADT users had a significantly higher 12-month fasting glucose level compared to controls ($p = 0.024$). In univariate analyses, ADT use was the strongest statistically significant independent predictor of fasting glucose. Hypertension and smoking were weakly associated ($p < 0.20$) with fasting glucose. The remaining variables were not good predictors of fasting glucose (data not shown). In multivariable analyses, ADT use remained a statistically significant predictor of fasting glucose level ($p < 0.03$) when all of the variables were included (full model) and in a reduced model with the least significant predictors (alcohol use, hyperlipidemia and BMI) removed (Table 3).

Effect of ADT on cholesterol

In unadjusted analyses, ADT users tended to have higher levels of total cholesterol, HDL, LDL and triglycerides compared to controls, although none of the differences were statistically significant (Table 2).

In univariate analyses, only age and hypertension were significant predictors of total cholesterol ($p = 0.011$ and 0.015, respectively). These variables remained significant in both the full and reduced multivariable models. In the latter model, smoking had a trend towards significance ($p = 0.09$). All 3 aforementioned variables were negatively correlated with total cholesterol. Androgen deprivation therapy use was not a significant predictor in any of the cholesterol models (Table 4).

Table 3. Multivariable analysis of fasting glucose (n = 60)

Variable	Full model		Reduced model	
	β-coeff. (SE)	value	β-coeff. (SE)	*p* value
ADT Use	0.33 (1.55)	0.039	0.33 (0.15)	0.034
Hypertension	0.28 (0.17)	0.11	0.23 (0.16)	0.14
Hyperlipidemia	-0.21 (0.17)	0.24	-	-
Age (per year)	0.01 (1.04)	0.81	0.002 (0.01)	0.85
Smoking	-0.30 (0.22)	0.18	-0.28 (0.21)	0.19
Alcohol use	0.09 (0.19)	0.65	-	-
BMI	0.01 (0.02)	0.69	-	-

ADT: androgen deprivation therapy; BMI: body mass index. For the reduced model, variables marked with a dash were excluded. See text for more details.

Discussion

We compared fasting blood glucose and total cholesterol levels in a group of ADT users and a matched group of controls. We found that 12 months of ADT use was associated with higher fasting glucose levels than among controls. However, although cholesterol levels tended to be higher in ADT users, these were not statistically significant. We found no other predictor of fasting glucose among the variables analyzed, whereas increasing age and hypertension were associated with slightly lower total cholesterol levels in adjusted models.

The fasting glucose results demonstrated in our study build on past studies. Dockery and colleagues demonstrated there was no change in fasting glucose within 3 months after starting ADT.[10] However, they had a small sample size (n = 16) and only followed patients for 3 months. A longer follow-up period may have yielded more conclusive results. Research by Basaria and colleagues demonstrated that the degree of insulin resistance and hyperglycemia are directly related to the duration of ADT.[18] Once again, this study had a very small sample size (n = 18), there was no control group, and patients had been on ADT for varying periods of time. Our results build on these prior findings by demonstrating that ADT use for 1 year is associated with an increase in fasting glucose levels. These findings are likely due to ADT use as opposed to prostate cancer or other factors, as all of our controls had prostate cancer and were matched on age and BMI with ADT users. The finding of increased fasting glucose levels is also supported by large studies using administrative data to demonstrate an increased risk of diabetes with ADT use over time.[8,9]

The cholesterol results obtained in our study are less conclusive due to the small sample size, but add to the published literature. In a recently published systematic review of this area, 3 studies analyzing the effect of ADT on lipid fractions were identified.[14] The average sample sizes of these studies was small (n = 24-40) and the studies had varying time points of follow-up, ranging from 24 weeks to 1 year. In all 3 studies, total cholesterol and HDL were found to increase with ADT use. Inconsistencies were reported with LDL and triglyceride values, with studies reporting either an increase or no change in the values. Furthermore, a recent large randomized trial found a decrease in HDL levels and no increase in total cholesterol with ADT use.[13] Further study with appropriate controls is thus needed to understand the effect of ADT on different lipid fractions.

What is the clinical relevance of our findings? It is important for a clinician starting a patient on ADT to obtain fasting blood glucose and lipid levels prior to initiating treatment. For patients with frank diabetes, which remains underdiagnosed,[19] they should be managed by their primary care physician or diabetic specialist according to standard guidelines.[20] For those with impaired fasting glucose (IFG), consideration should be given to lifestyle modification and/or initiation of metformin to prevent progression to diabetes.[21] For these patients and for those with normal fasting blood glucose, our results, combined with prior studies, suggest that repeat glucose levels should be measured to screen for the development of diabetes at least once yearly while men remain on ADT. Although the difference in blood glucose between men on ADT and controls may seem small (0.36 mmol/L), it is likely clinically significant for 2 reasons. First, in the setting of IFG, glucose levels range from 6.1 to 7.0 mmol/L. Thus, a rise of about 0.4 mmol/L would shift almost half these patients into the category of diabetes, with obvious prognostic and therapeutic implications. Second, intensive lifestyle modifications, metformin and rosiglitazone have been shown to decrease progression to diabetes from IFG by 30% to 60% in large randomized trials.[21,22] In these trials, the average decrease in blood glucose level was in the range of 0.3 to 0.5 mmol/L, similar to our observed difference. These data would suggest the effect of ADT on developing diabetes is particularly relevant for men who are already at risk (i.e., men with IFG).

For men with elevated cholesterol levels, management should be dictated by cardiovascular risk factors. It remains unclear whether we should monitor or manage these patients differently because of concomitant ADT use.

Our study did have a number of limitations. The 2 key ones were lack of blood measurement at baseline and small sample size. Our study began in 2004, at which time little was known about the impact of ADT on glucose or lipids. Partway through our study, we added measurements of fasting glucose and lipids, but could only obtain 12-month measurements at that point. It is possible that ADT users had elevated blood glucose levels prior to starting ADT, although other cardiovascular risk factors, BMI, other comorbidity, age, educational level and physical fitness were similar among ADT users and controls, making this unlikely.

Table 4. Multivariable analysis of total cholesterol (n = 45)

Variable	Full model		Reduced model	
	β-coeff. (SE)	*p* value	β-coeff. (SE)	*p* value
ADT Use	0.31 (0.36)	0.39	0.35 (0.33)	0.30
Hypertension	-0.81 (0.37	0.04	-0.71 (0.34)	0.041
Age (per year)	-0.05 (0.02	0.05	-0.05 (0.02)	0.038
Smoking	-0.66 (0.34	0.14	-0.74 (0.43)	0.09
BMI	0.03 (0.03)	0.92	-	-
Alcohol use	0.04 (0.40)	0.47	-	-

ADT: androgen deprivation therapy; BMI: body mass index. For the reduced model, variables marked with a dash were excluded. See text for more details.

However, prospectively collected blood measurements over multiple time points would clearly be helpful. We also recognize that our sample size is fairly small (75 patients). After excluding diabetic patients (n = 12) and patients on cholesterol medications (n = 29) the sample sizes for the 2 groups were reduced further. Thus, it is likely that this is the reason why statistically significant differences were not observed in the lipid fractions between ADT users and controls.

Furthermore, due to laboratory and administrative errors, some patients did not have several lipid fractions measured. Despite this, differences in fasting glucose were statistically significant. Generalizability may also be an issue, as only English-speaking patients from a single tertiary care centre were recruited. Thus, further longitudinal studies with a larger sample and more diverse population of prostate cancer patients are required to confirm these results. Further longitudinal analyses examining changes in other lipoprotein components (e.g., apolipoprotein B100) among ADT users and controls, as well as following patients for a longer time period to assess changes in lipid fractions, could also provide valuable information and a greater understanding of the possible adverse cardiovascular and metabolic effects of ADT.

Conclusion

We demonstrated that 1 year of ADT use increased serum fasting glucose; however, the effects on serum total cholesterol, HDL, LDL and triglyceride levels are less clear in men with non-metastatic prostate cancer.

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ADT and the metabolic syndrome: no good deed goes unpunished

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Although androgen deprivation therapy (ADT) has been used for more than half a century to treat prostate cancer, its mechanism and associated side effects are continuously updated. Androgens are key players in glucose homeostasis and lipid metabolism. In fact, lower total testosterone predicts a higher incidence of the metabolic syndrome, a cluster of risk factors predisposing patients to late onset diabetes mellitus, atherosclerosis and cardiovascular (CVS) morbidity and mortality.[1] Since CVS disease is the most common competing cause for mortality, we should make all efforts to minimize our iatrogenic contribution to the metabolic syndrome and familiarize ourselves with the growing body of evidence linking ADT to the metabolic syndrome.[2,3] Mohamedali and colleagues present their experience with the impact of long-term ADT on blood glucose levels in non-diabetic prostate cancer patients. The authors demonstrated that 1 year of ADT use is associated with elevated fasting glucose levels.[4] This data is in line with a recent review of the ADT/metabolic syndrome which showed a clear casual association between ADT and diabetes mellitus, but the causal association is not as strong with CVS morbidity.[5] The link needs to be better explored as novel ADT strategies are about to change our practice. In recent years it has become clear that current modes of castration are far from optimal in achieving complete androgen deprivation in prostate cancer cells. Multiple pre-clinical evidences suggest that prostate cancer cells can produce androgens which activate the androgen receptor already in concentrations lower than those traditionally defined as castrated serum testosterone levels (<20 ng/dL). Accordingly, although not completely validated, clinical observations suggest the lower the testosterone level under ADT, the longer the survival;[6] it is possible that even lower levels of testosterone within and it is possible that even transient events of testosterone break through within the framework of ADT can accelerate disease progression.[7] Hence, the current trend in ADT is a more strict deprivation of androgens in castrate resistant prostate cancer, and what we used to define as maximal androgen blocked (MAB) will certainly be expanded with the introduction of novel products, such as arbiraterone and MDV3100. It is reasonable to expect that novel therapeutic strategies that induce more effective testosterone suppression will reciprocally accentuate the metabolic side effect profile of ADT. Data comparing the long-term metabolic side effect of different modes of castration is currently limited,[8] but once available, should better guide us in treating patients with known risk factors for CVS disease. We should incorporate routine baseline and follow-up assessments of metabolic measurements (fasting glucose levels, lipids, BMI) and advocate lifestyle modification for our ADT patients. We should also stay tuned for potentially more detrimental metabolic side effects with more strict MAB regimens.

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