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Effects of androgen deprivation therapy on telomere length.

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Short title: androgen deprivation and telomeres

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Abstract

Objective: Recent evidence suggests that androgens either directly or via aromatisation to oestradiol may regulate telomere length, hence providing a mechanism whereby reproductive steroids are linked to biological aging in men. Using men with prostate cancer initiating androgen deprivation therapy (ADT), we tested the hypothesis that severe sex steroid deprivation would accelerate telomere shortening.

Design: We conducted a secondary analysis of a 2-year prospective controlled study among 65 men with non-metastatic prostate cancer newly commencing adjuvant ADT (n=40) and age- and radiotherapy-matched prostate cancer controls (n=25).

Methods: We measured leukocyte telomere length (LTL) expressed as telomeric/single copy control gene (T/S) ratio at baseline, 6, 12 and 24 months. Generalised linear models determined the mean adjusted difference (MAD) [95% confidence interval] between groups during follow-up.

Results: Compared to controls over 24 months, men receiving ADT had no change in LTL, MAD for T/S ratio (0.105 [-0.004; 0.213], p=0.235).

Conclusions: Using men with prostate cancer receiving ADT as a model we found no evidence that prolonged and profound sex steroid deprivation is associated with accelerated telomerase shortening. Larger studies will be required to confirm, or refute these findings.

Introduction

Telomeres are specialised hexanucleotide repeats complexed to proteins. They are located at ends of linear chromosomes and protect their structural integrity¹. Telomere length reduces with increasing chronological age and with accumulation of age-related comorbidities. Given that telomere shortening contributes to cellular senescence, telomere length represents a cellular marker of biological aging¹. Recent preclinical, observational and interventional studies suggest that androgens play a role in

preserving telomere length ²⁻⁵. However, whether this is an androgen receptor mediated effect, or whether androgens act indirectly, via aromatisation to oestradiol ^{6,7}, is unclear.

Because prostate cancer is an androgen responsive malignancy, androgen deprivation therapy (ADT, defined here as medical castration using gonadotropin-releasing hormone (GnRH) analogs) is an effective treatment. ADT reduces serum testosterone, but also oestradiol levels to castrate range. ADT is often prescribed for extended times (*e.g.* 3 years for high-risk prostate cancer with curative intent). Therefore, these patients offer a unique model of profound and global sex steroid deficiency over an extended period ⁸: ADT represents the only situation where an ethical requirement for T replacement is absent for prolonged periods. Given that ADT reduces both circulating testosterone and estradiol to near castrate levels, effects on telomere length -if testosterone indeed plays a role- should be evident irrespective of whether this occurs as a direct effect or via its aromatization to estradiol. Moreover, ADT also accelerates certain features associated with biological aging, such as loss of bone ⁹ and muscle mass ¹⁰, and increased insulin resistance ¹¹. We therefore conducted a secondary analysis of a 2-year, prospective case-control study in men with prostate cancer initiating ADT adjuvant to radiotherapy and age- and radiotherapy-matched prostate cancer controls to test the hypothesis that sex steroid deprivation accelerates telomere shortening.

Subjects and Methods

We conducted a prospective 24-month case-control study at a tertiary referral hospital (Austin Health, Melbourne, Australia). The study was approved by the Human Research Ethics Committee, Austin Health. All participants provided written informed consent. This is a secondary analysis assessing the effects of ADT on telomere length. The effects of ADT on muscle function, the primary outcome of the study are reported elsewhere ¹².

Participants were recruited from prostate cancer outpatient clinics. Inclusion criteria included age 55-85 years, localised non-metastatic prostate cancer (Stage T1-3, Nx, M0), and an Eastern Co-operative Oncology Group performance status of 0 (fully active and unrestricted in physical activity). Exclusion criteria included that any illnesses or other

factors predisposing them to androgen deficiency, previous ADT, or significant medical comorbidities including active renal, liver, cardiac, respiratory or joint or neuromuscular disease. Cases were newly commencing long-term ADT with different brands of GnRH agonists, including triptorelin, goserelin, eligard and lucrin, at the discretion of the treating physician. To assess the specific effects of ADT, cases and controls were matched for age, body mass index, medical co-morbidities, radiotherapy treatment and baseline testosterone level ¹².

Blood was drawn in the morning and in the fasted state at 0, 6, 12 and 24 months. Serum total testosterone was measured with a electrochemiluminescence immunoassay using Cobas C8000, Roche Diagnostics (minimum detection 0.4 nmol/l, inter-assay variation 5.0-6.9%), as described ¹². Oestradiol was measured by electrochemiluminescence immunoassay using the same system (minimum detection 19.0 pmol/l, inter-assay variation 1.9-3.5%).

Leukocyte telomere length (LTL) was measured from leukocyte DNA samples by a multiplex quantitative PCR method as described ⁵. We optimized a PCR-based methodology for accurate measurement of LTL using the protocol described by Cawthon ¹³ which we have further developed ⁵. Briefly, telomere lengths of leukocyte DNA samples were measured by a multiplex quantitative PCR method. Each sample was amplified for telomeric DNA and for beta globin, a single-copy control gene, which was used as an internal control to normalize the starting amount of DNA. The K562 cell line was used as a standard ¹⁴. A four-point standard curve derived from the K562 cell line was included in each run to assess and compensate for interplate variations in PCR efficiency. The mean PCR efficiencies for telomeric DNA and beta globin are 94.5% and 92.4% respectively. Two quality-control samples were also included in each run to assess interplate and intraplate variability of threshold cycle (Ct) values. Furthermore, 5% of the test samples were repeated on a different run to account for interplate variability. Periodic reproducibility experiments were performed to confirm adequate normalization. All samples, standards, and controls were run in triplicate and the median value used for analyses. A standard curve derived from K562 cell line was used to transform the cycle threshold into nanograms of DNA. The amount of telomeric DNA (T) was divided by the amount of single-copy control gene DNA (S), producing a relative

measurement of the telomere length (T/S ratio), representing the normalised quantity of telomeric DNA. The coefficient of variation for the quantitative PCR across batches was <10%.

Statistical analysis

Data were not normally distributed and are presented as median and interquartile range (IQR). Comparisons of baseline characteristics were made using Wilcoxon rank sum test for continuous variables or chi square test for frequencies. Two sided p values <0.05 were considered significant. Repeated measurements were compared between groups using a linear mixed model¹⁵. The effect of interest was the interaction of time points and group, incorporating baseline values as a fixed covariate and repeated measure by subject as random effect. The model is also robust against regression to the mean. As a quantitative measure, mean adjusted difference (MAD) plus 95% CI between the groups from baseline to 24 months is provided. Statistical analyses were performed using R statistical package (version 3.3.2 for Mac)¹⁶.

Results

Baseline characteristics of the study subjects

Study participants were matched for age, body mass index, medical co-morbidities, radiotherapy and baseline testosterone level (Table 1). Given ADT is added to radiotherapy as treatment for high-risk disease, whereas radiotherapy alone is indicated for intermediate risk disease, baseline Gleason scores and PSA levels were higher in cases compared to controls. At baseline, all men were clinically eugonadal and had age-appropriate normal testosterone levels. There was no difference in baseline LTL, measured by the T/S ratio between cases and controls (Table 1).

While serum total testosterone and oestradiol levels remained stable in controls, both were decreased to castrate levels in men receiving ADT over the course of the study (Figure 1). Only men recruited relatively early in the study had assessments at 24 months, because men recruited at later time points were not followed beyond 12 months due to funding limitations.

Change in leukocyte telomere length over time

There was no difference in the LTL, measured by the T/S ratio and presented as mean adjusted differences at each time point of follow-up (6, 12 and 24 months) between men receiving ADT and the age- and radiotherapy-matched prostate cancer, overall $p=0.235$ (Table 2, Figure 2).

Discussion

In this controlled prospective study, using men with prostate cancer receiving ADT as a model, we found no evidence that severe sex steroid deprivation over 2 years is associated with shorter telomere length.

Our analysis was prompted by recent evidence that sex steroids may modulate telomere length, a marker of cellular senescence, hence providing a potential mechanisms linking decreasing levels of circulating sex steroids to biological aging in men. In a recent cross-sectional study of community dwelling men, we reported that circulating levels of the testosterone metabolites dihydrotestosterone (DHT) and oestradiol, but not testosterone itself, correlate with LTL independently of age⁵. In experimental studies using a variety of cultured cells, testosterone³, synthetic androgens² and oestradiol^{2,6,7} have been reported to up-regulate telomerase activity, the enzyme that counters telomere shortening. This occurs by sex steroids increasing the expression of *TERT*, the gene expressing the catalytic subunit of telomerase^{2,6,7}. This effect may involve the activation of an estrogen-responsive element in the reporter region of the telomerase gene^{2,6}. Therefore, based on these preclinical studies, it has been assumed that the aromatisation of androgens to oestradiol is important for telomerase up-regulation. This is consistent with our observational Mendelian randomisation study reporting an association between aromatase gene polymorphisms reducing serum oestradiol and shorter LTL in community dwelling men⁵. However, in a recent phase 1-2 prospective study, danazol treatment, a non-aromatisable androgen that cannot be converted to oestradiol¹⁷, has been reported to prevent telomerase shortening in patients with genetic defects in telomere maintenance and repair⁴. This suggests that aromatization to an estrogen capable of activating an estrogen receptor does not appear to be necessary for the effect of danazol on telomere length¹⁸. Given that either androgens, oestrogens or both may be involved in the regulation of telomere length, we studied men receiving ADT, as ADT reduces both testosterone and its metabolites DHT and

oestradiol to castrate levels. Moreover, ADT promotes the development of sarcopaenia ¹⁰, of structural bone decay ⁹ and of insulin resistance ¹¹, all features associated with biological aging in men. Given the negative findings of our study, further work is required to determine whether telomere shortening plays a role, if any, in promoting ADT-associated adverse effects resembling that of accelerated aging.

To date, clinical studies assessing the effects of sex steroids in telomere length have been limited to cross-sectional studies among community dwelling men ^{5,19}. This study, to our knowledge, constitutes the first longitudinal controlled study examining the effects of changes in circulating sex steroids on telomere length. Only ADT-naïve men without clinical androgen deficiency who had, prior to commencing ADT, normal circulating testosterone levels were recruited. The focus on men receiving ADT ensured that both testosterone and oestradiol were reduced to castrate levels. In addition, the inclusion of an age- and radiotherapy and comorbidity- matched control group facilitated the delineation of specific effects of ADT. In addition, men were relatively healthy, living in the community without functional impairment receiving adjuvant ADT with curative intent, and all participants maintained undetectable prostate specific antigen levels throughout the study ¹².

The main limitation of the study is its relatively small sample size, especially with regards to the 2 year time point, and hence this study lacks the power to detect modest effects on telomere length. Indeed, this is a secondary analysis of a study powered to detect the effect of ADT on biomechanical leg muscle function ¹². In addition, 2 years is a relatively short time frame, and a longer duration may well be necessary to detect a significant effect of sex steroid deprivation. However, the severe reduction of sex steroid levels following ADT is much more rapid and profound in magnitude than the age-related decline in testosterone levels among community dwelling men not receiving ADT ²⁰. The study was not powered to assess whether changes in telomere length during ADT are associated with accelerated clinical features of aging observed during ADT, such as loss of muscle mass and function ^{10,12}, loss of bone mass ⁹ or metabolically unfavourable changes in body composition^{11,21}.

While we did not use Southern-blot based quantification of telomere length, the qPCR-based methodology used here has been reported to be strongly correlated to Southern-blot methodology with reported correlation coefficients of ranging from $r = 0.84$ to >0.9 ^{13,22}. To minimize measurement error of LTL over time, care was taken to ensure that all samples were extracted and processed by the same technician using the same protocol in one laboratory.

Exposure to significant ionizing radiation has been reported to be inversely correlated with LTL²³. In the absence of a control group not receiving radiation, we cannot discount possible effects of pelvic irradiation on telomere length. However, given that our objective was to assess the effects of sex steroid deprivation on telomere length, inclusion of a radiotherapy-matched control group should have eliminated possible confounding effects of radiation treatment.

In conclusion, in this 2-year prospective case controlled study we found no evidence that severe sex steroid deprivation accelerates telomerase shortening in men who have been diagnosed with prostate cancer. However larger, longer term studies are required to confirm, or to refute these findings.

Declaration of interest:

There was no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author Contribution statement:

A.S. researched data and wrote the manuscript, R.H. researched data, contributed to the discussion and reviewed/edited the manuscript. B.B.Y. researched data and reviewed/edited the manuscript. J.H. researched data and reviewed/ edited the manuscript J.P.B. researched data and reviewed/ edited the manuscript. M.G. designed the study, researched data and wrote the manuscript. A.S. and M.G. are the guarantors for the study.

Figure Legends

Figure 1. Circulating total testosterone and oestradiol levels in men receiving ADT and matched controls

Shown are serum total testosterone (Figure 1a) and oestradiol levels (Figure 1b) (adjusted mean, 95% CI) in men with prostate cancer receiving ADT (continuous line) and aged and radiotherapy matched prostate cancer controls (dashed line).

In cases where sex steroids levels were undetectable, levels were set at the lower limit of detection, 0.4 nmol/l for total testosterone, and 19 pmol/l for oestradiol respectively. P values refer to the overall significance of the change between groups during follow-up.

Figure 2. Leukocyte telomere length in men receiving ADT and matched controls

Shown are leukocyte telomere lengths, expressed as T/S ratio (adjusted mean, 95% CI) in men with prostate cancer receiving ADT (continuous line) and aged and radiotherapy matched prostate cancer controls (dashed line). The P value refers to the overall significance of the change between groups during follow-up.

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Table 1. Baseline characteristics

Baseline Characteristic	ADT group N=40	Control group N=25	p value
Age	67.0 [61.3; 73.3]	70.6 [65; 73.3]	0.21
Prostate Cancer Gleason Score	9 [7; 9]	7 [7; 7]	<0.01
Concurrent radiotherapy treatment	91.2%	88.9%	0.74
Previous prostatectomy	54.3%	77.8%	0.06
Total testosterone (nmol/L)	13.2 [9.2; 18.5]	15.5 [11.1; 17.0]	0.55
PSA (ug/L)	2.0 [0.16; 12.8]	0.07 [0.03; 0.35]	<0.01
Charlson co-morbidity index	2 [2; 3]	3 [2; 3]	0.17
Medical comorbidities			
Ischaemic heart disease	26.5%	14.8%	0.30
Diabetes mellitus	17.6%	18.5%	0.89
Liver disease	0%	0%	>0.99
Chronic kidney disease	0%	0%	>0.99
Hypertension	55.9%	59.3%	0.70
LTL, T/S ratio	1.01 [0.89;1.13]	0.94 [0.86;1.04]	0.106

PSA = prostate specific antigen; LTL = leukocyte telomere length; T/S = telomeric DNA/ single-copy control gene. Data presented are median [interquartile range] or proportions (%). Gleason score <7 = low-moderate risk, 7= intermediate risk, 8-10 = high risk prostate cancer.

Table 2. Leukocyte Telomere Length

LTL, T/S ratio	ADT Group	n	Controls	n	Mean adjusted difference [95% CI]	p value
0 months	1.01 [0.89;1.13]	40	0.94 [0.86;1.04]	25		
6 months	1.05 [0.92;1.19]	35	0.95 [0.90;1.10]	25	-0.006 [-0.077;0.069]	
12 months	1.07 [0.96;1.22]	28	1.03 [0.94;1.10]	22	0.003 [-0.072;0.078]	
24 months	1.06 [0.99;1.33]	7	0.99 [0.93;1.11]	12	0.105 [-0.004;0.213]	0.235

Medians [interquartile ranges] are presented. Mean adjusted difference refers to the change over 12 months across groups (mixed model). n denotes the number of study subjects at each time point in each group. The P value refers to the overall significance of the change between groups during follow-up.

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