Dynamic Patterns of Testosterone Levels in Individuals and Risk of Prostate Cancer among Hypogonadal Men: A Longitudinal Study

Xiaohui Xu,* Xiao Zhang, Yan Zhong, Farid Saad,† Maria J. Perez-Patron, Karim Haider and Ahmad Haider

From the Department of Epidemiology and Biostatistics, School of Public Health (XX, XZ, MJP-P) and Department of Statistics (YZ), Texas A&M University, College Station, Texas, Global Medical Affairs Andrology, Bayer AG (FS), Berlin and Private Urology Practice, Bremerhaven (KH, AH), Germany, and Research Department, Gulf Medical University (FS), Ajman, United Arab Emirates

Purpose: We investigated whether dynamic patterns of testosterone levels contribute to risk of prostate cancer.

Materials and Methods: We used data on 376 untreated men with hypogonadism (testosterone 12.1 nmol/l or less) recruited from a urology office in Germany. Age at study entry served as a surrogate for age at the first detection of testosterone below 12.1 nmol/l. We derived 3 indicators, including the coefficient of variation, the ratio of the largest decline relative to the mean and the median of maximum declines, to measure the dynamic patterns of testosterone in an individual.

Results: Our findings suggest that the later that testosterone dropped below 12.1 nmol/l in a man, the less the lifetime risk of prostate cancer in that individual (HR 0.68, 95% CI 0.57–0.82). Further declines or dynamic variations of testosterone were associated with increased risk of prostate cancer (high vs low coefficient of variation HR 4.88, 95% CI 1.97–12.08, high vs low ratio of largest decline relative to mean HR 8.45, 95% CI 2.82–25.37 and high vs low median of maximum declines HR 2.70, 95% CI 1.15–6.35).

Conclusions: To our knowledge this study is the first to provide evidence of the association between dynamic patterns of testosterone and prostate cancer development. This may have substantial clinical impacts on prostate cancer prevention.

Key Words: prostatic neoplasms, testosterone, hypogonadism, prostate-specific antigen, risk factors

Abbreviations and Acronyms

AR = androgen receptor

BMI = body mass index

CV = coefficient of variation

MMD = median of maximum declines in 24-month screening window

MMDRM = ratio of maximum decline relative to mean

PCa = prostate cancer

T = testosterone

TTh = T therapy

Accepted for publication August 24, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* Correspondence: Department of Epidemiology and Biostatistics, School of Public Health Texas A&M University MS 1266 212 Adriance Lab Rd., College Station, Texas 77843 (telephone: 979-436-9500; FAX: 979-458-1877; e-mail: xiaohui.xu@sph.tamhsc.edu).

† Financial interest and/or other relationship with Bayer AG.

TESTOSTERONE and its derivative dihydrotestosterone are the most abundant androgens in males. Generally T levels begin to decrease by approximately 3.2 to 3.5 ng/dl per year in healthy middle-aged men.[1,2] As T levels decline with age, a subset of males with a significant T decline experience late onset hypogonadism, characterized by symptoms of diminished libido and erectile dysfunction.[3,4]

T has an essential role in prostate development, growth and function, and the relationship between T and PCa progression has been recognized since 1941, when Huggins and Hodges reported that PCa growth was driven by androgen and castration could effectively treat PCa.[5] However, the etiological role of T in the development of PCa remains unclear, although more than 75 years have passed. A recent review article evaluated 45 published studies of the relationships between T and PCa risk, of which 18 showed a negative

0022-5347/18/1992-0465/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2017.08.117
Vol. 199, 465-473, February 2018
Printed in U.S.A.

association between T levels and PCa, 17 showed a positive association and 10 demonstrated no association.[6] A pooled global study of prospectively collected data also revealed no relationship between PCa development and any of various hormone concentrations, including T.[7] These studies applied various models and statistical methods and yet none considered dynamic variations in T with time.

To explore the role of dynamic patterns of T in PCa development and find possible explanations of the previous conflicting findings we proposed a dynamic model.[8] In this model we speculated that normal prostate cells may have a normal range of T and this range varies among individuals. When significant decreases or abnormal variations of T levels develop in an individual, we hypothesize that these changes in a stable environment in the prostate could have significant impacts on normal prostate cells and make cells more susceptible to mutations. Our hypothesized dynamic model was supported by the age patterns and racial disparities of PCa, and indicated that males with an earlier and significant decrease in T levels were at a higher risk for PCa.[8] However, it is difficult to obtain longitudinal and repeat measurements of T in an individual. To our knowledge this dynamic model has not been tested and confirmed using research data, and relevant measures assessing the dynamic patterns have never been reported.

In this study we used data on a prospective cohort of 376 untreated hypogonadal men from a single center urology office in Germany to achieve certain aims. These aims were to 1) examine whether males with an early life significant T drop were at higher risk for PCa than those without such a drop and 2) test whether further declines, great variations or significant T drops increase the risk of PCa.

METHODS

Study Population

We recruited 376 hypogonadal men with T 12.1 nmol/l or less who elected against T replacement therapy from a urology office in Bremerhaven, Germany in 2004 and followed them through 2016. Those with androgen dependent carcinoma of the prostate or of the male mammary gland and past or current liver tumors were excluded from analysis. The study followed the ethical guidelines as formulated by the German Medical Association. All subjects consented to be included in study. The research protocol was approved by the institutional review board office.

Testosterone Monitoring and Prostate Cancer Diagnosis

Total testosterone in serum was measured by immunoassay. Intra-assay and interassay CVs were 4.0% and 5.6%, respectively. The PCa diagnosis was confirmed by biopsy. If prostate specific antigen increased to more than 4 ng/ml or by more than 0.75 ng/ml within 12 months, or if there were suspicious findings on imaging, biopsies were performed to determine whether PCa was present.[9] Prostate specific antigen and T levels were monitored semiannually or annually.

Indicators Describing Testosterone Dynamic Patterns

Study Entry Age. Males with abnormal reproductive organ function (below average) would seek consultation from a physician, who thus obtained information on T levels. If T was 12.1 nmol/l or less, the men would be enrolled in the study after signing the informed consent sheet. Therefore, we considered study entry age as an important indicator of the earliest time when T dropped below 12.1 nmol/l, although the actual time of the decrease below 12.1 nmol/l might have developed before the age at study entry.

To address whether further dynamic T variations or declines would have an impact on the risk of PCa after a diagnosis of late onset hypogonadism we obtained all T measurements during followup for each subject. We analyzed the dynamic patterns of T in each individual using statistical indicators as described.

Coefficient of Variation. CV is the ratio of the SD to the mean of T levels of an individual. It measures the variation in individual T levels with time. We used the 75th percentile of CVs to classify subjects into a high variation group (CV 0.1 or greater) and a low variation group (CV less than 0.1).

Maximum Magnitude of Decline Relative to Mean. Figure 1 shows MMDRM, which indicates how many times more the largest decrease was than the average T level. The formula used to derive the MMDRM indicator is $\max_{t\geq 5}$ (mean $[X_1$ to $X_{t-1}] - X_t)$/(mean $[X_1$ to $X_{t-1}]$, where X_t is the T level at time t. We selected $t = 5$ as the starting point of t for a relatively stable estimation of the mean. We used the 75th percentile of MMDRMs to classify subjects into a high decline group (MMDRM 0.2 or greater) and a low decline group (MMDRM less than 0.2).

Median Maximum Decline. We first measured the maximum decrease within a 24-month screening window starting at time zero when the participant entered the study and moving it to the end of the study (fig. 1). We then calculated the median of these maximum decreases. This indicator reflected the average largest drop of T in a short period window in an individual. We used the 75th percentile of MMDs as a cutoff point to classify participants into a high MMD group (MMD 1.4 or greater) and a low MMD group (MMD less than 1.4).

Confounders

Information on family history of PCa, alcohol use and smoking status were collected at baseline. BMI was calculated using baseline height and weight. Considering the small sample size, we only included the most important confounders to ensure statistical power. All covariates were selected a priori based on previous research.[10,11]