Poor Glycemic Control is Associated with Reduced Prostate Specific Antigen Concentrations in Men with Type 1 Diabetes

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Abbreviations and Acronyms

AER = albumin excretion rate

BMI = body mass index

DCCT = Diabetes Control and Complications Trial

EDIC = Epidemiology of Diabetes Interventions and Complications study

HbA1c = hemoglobin A1c

PCa = prostate cancer

PSA = prostate specific antigen

T1DM = type 1 diabetes mellitus

T2DM = type 2 diabetes mellitus

TT = total testosterone

UroEDIC = Urologic Complications of Diabetes Study

Purpose: Previous studies have revealed lower prostate specific antigen concentrations in men with type 2 diabetes, paralleling the reported lower prevalence of prostate cancer in diabetic men. Data are lacking on prostate specific antigen in men with type 1 diabetes whose insulin and obesity profiles differ from those with type 2 diabetes mellitus. In this study we examined the relationship between long-term glycemic control and prostate specific antigen in men with type 1 diabetes mellitus.

Materials and Methods: Total prostate specific antigen was measured at one time in 639 men in the EDIC, the observational followup of participants in the DCCT. The relationship between DCCT/EDIC weighted mean hemoglobin A1c and log prostate specific antigen was assessed using linear regression modeling after adjusting for age, body mass index, total testosterone, statin and thiazide medication use, diabetes duration, and DCCT randomization arm and cohort.

Results: Median subject age was 52 years, body mass index was 28.4 kg/m^2 and DCCT/EDIC time-weighted hemoglobin A1c was 7.9%. Median prostate specific antigen was 0.64 ng/ml (IQR 0.43, 1.05). Prostate specific antigen increased significantly with age ($p < 0.0001$) and with lower time-weighted hemoglobin A1c

Accepted for publication August 27, 2014.

The DCCT/EDIC has been supported by U01 Cooperative Agreement grants (1982-1993, 2011-2016) and contracts (1982-2011) with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (current Grants U01 DK094176 and U01 DK094157), and the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program (1993-2007) and Clinical Translational Science Center Program (2006-present), Bethesda, Maryland.

Additional support for this DCCT/EDIC collaborative study (UroEDIC) was provided by a R01 grant (2009-2013) from the National Institute of Diabetes and Digestive and Kidney Diseases (5R01DK083927-03).

Study received institutional review board approval.

Trial Registration: clinicaltrials.gov NCT00360815 and NCT00360893.

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† Financial interest and/or other relationship with SpermDx, Andro360 and Simple Circ.

‡ Nothing to disclose.

§ Financial interest and/or other relationship with NIH/NIDDK.

‖ A complete list of participants in the DCCT/EDIC Research Group can be found in The DCCT/EDIC Research Group: Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011; **365:** 2366.

Editor's Note: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1072 and 1073.

0022-5347/15/1933-0786/0
THE JOURNAL OF UROLOGY®
© 2015 by American Urological Association Education and Research, Inc.
http://dx.doi.org/10.1016/j.juro.2014.08.115
Vol. 193, 786-793, March 2015
Printed in U.S.A.

($p < 0.0001$). Each 10% increase in hemoglobin A1c was accompanied by an 11% reduction in prostate specific antigen ($p=0.0001$).

Conclusions: Prostate specific antigen decreases as hemoglobin A1c increases in men with type 1 diabetes mellitus. This relationship is independent of age, body mass index, androgen levels, medication use and measures of diabetes severity, which suggests that factors related to glycemia may directly affect prostate specific antigen levels.

Key Words: blood glucose, diabetes mellitus, prostate-specific antigen

Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer related death in men in the United States. An estimated 238,590 new cases of PCa were diagnosed in 2013 with an associated mortality of 29,720 cases.[1] Although controversial,[2] increases in PSA concentrations are commonly used as an initial step in screening for PCa.[3] PSA is a glycoprotein secreted by the prostate gland, and on average, men with prostate malignancy, inflammation or enlargement have a higher total PSA than men with lesser degrees of pathology.

While studies have shown that individuals with diabetes may have a higher risk of specific malignancies than those without diabetes,[4] a recent meta-analysis demonstrated that patients with diabetes have a statistically significant decreased risk of PCa.[5] This is paralleled by the inverse relationship reported between glucose levels and PSA. Specifically, previous studies have revealed a lower PSA in men with type 2 diabetes mellitus, and inverse associations between poor glycemic control, as assessed by hemoglobin A1c, and PSA.[6–9] There are several possible explanations why PSA may be lower in men with T2DM than in men without T2DM, including greater obesity and more frequent use of medications to treat dyslipidemia and hypertension. Men with a higher BMI have a lower mean total PSA than men with a lower BMI,[10–12] possibly due to hemodilution from increased plasma volume in larger men,[13] or lower androgen levels that characterize more obese and insulin resistant men.[14] PSA has been reported to decrease in response to statins, which are more commonly used in individuals with T2DM.[15–17] PSA concentrations also are lower in men who use thiazide diuretics to treat hypertension.[16] Finally, the vascular disease that characterizes diabetes might lead to prostate ischemia and subsequently lower PSA, although there is no direct evidence to support this hypothesis.[18]

These reports have focused on men with T2DM. The relationship between HbA1c and PSA in men with type 1 diabetes mellitus has not been reported but could inform the discussion in several ways. As opposed to men with T2DM, men with T1DM have increases in glycemic levels due to beta cell destruction and the subsequent lack of insulin secretion. Obesity and insulin resistance are less common at initial diagnosis. The prevalence of other cardiovascular risk factors, particularly dyslipidemia, tends to be lower in individuals with T1DM vs T2DM. Thus, the examination of men with T1DM offers the opportunity to focus on the role of hyperglycemia in PSA increase apart from other potential confounders.

In this study we examine the distribution of PSA concentrations in men with T1DM, and the relationship between long-term glycemic control and PSA, adjusted for body size, androgen levels, diabetes treatment and medication use. We hypothesized that poor glycemic control in T1DM may result in a lower PSA.

MATERIALS AND METHODS

Subjects

The DCCT randomly assigned 761 men with T1DM to intensive or conventional diabetes therapy with a mean of 6.5 years of treatment during 1983 to 1993.[19] At baseline the 378 men in the primary prevention cohort had no retinopathy or nephropathy and had 1 to 5 years of diabetes. The 383 men in the secondary intervention cohort had mild to moderate nonproliferative retinopathy, with albuminuria (AER as much as 200 mg per day) and 1 to 15 years of diabetes. Individuals with hypertension, symptomatic ischemic heart disease or symptomatic peripheral neuropathy requiring treatment were excluded from participation in the DCCT.

Figure 1 shows the flow of participants from enrollment into the DCCT, longitudinal followup in the EDIC and an ancillary study to examine urological complications, UroEDIC. Of the 761 men originally enrolled in the DCCT 639 (84%) provided serum for onetime measured PSA testing in 2010/2011 and are included in the current study. This sample represented 96% of the men who were active in the study during that period. The institutional review board of each participating center approved the study and the federal government issued a certificate of confidentiality.

DCCT Intervention and Other Therapies

Intensive therapy during the DCCT was aimed at achieving glycemic levels as close to the nondiabetic

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