Diabetic Complications Consortium

Application Title: **Testosterone Concentrations and Cardiovascular Disease in Men with Type 1 Diabetes**
Principal Investigator: **Sarma, Aruna V., Kim Catherine. University of Michigan**

1. Project Accomplishments:

The funded proposal resulted in 2 manuscripts all of which have been completed and are published.

2. Specific Aims

The finalized specific aims of the project were to use the DCCT/EDIC cohort to focus upon the relevance of testosterone concentrations among men with Type 1 diabetes on risk of CVD endpoints.

SPECIFIC AIM 1: ***To examine how absolute levels and changes in endogenous T are associated with absolute levels and changes in CVD risk factors among men with T1D.*** We hypothesize that lower T levels and decreases in T levels (both total and bioavailable) will predict increases in blood pressure, triglycerides, hemoglobin A1c, and decreases in high-density lipoprotein, before and after adjustment for age and obesity.

SPECIFIC AIM 2: ***To examine how endogenous T are associated with cardiac structure and function on cardiac MRI (CMR) among men with T1D.*** We hypothesize that lower T levels (both total and bioavailable) will predict lower values and greater change in values of left ventricular mass and end-diastolic volume, before and after adjustment for age, obesity, hemoglobin A1c, blood pressure, and lipid levels.

SPECIFIC AIM 3: ***To examine how absolute levels of endogenous T are associated with CVD events among men with T1D.*** We hypothesize that lower T levels (both total and bioavailable) will predict a greater incidence of CVD events, before and after adjustment for age, obesity, hemoglobin A1c, blood pressure, and lipid levels.

Initially we examined the relationship between endogenous testosterone concentrations and potential mediators of the increased risk of cardiovascular disease observed in numerous studies. First, we found that lower testosterone concentrations were more common in men with cardiovascular autonomic neuropathy (CAN) and components of CAN (see Table 1 below). However, once the older age of men with lower testosterone was considered, as well as their higher body mass index, these associations were not clinically significant. This work was published in the Journal of Sexual Medicine (see abstract and citation below). Although higher testosterone concentrations were associated with more favorable components of autonomic conduction, specifically the Valsalva ratio, consistent relationships with other components of autonomic conduction were not observed. These findings suggest that autonomic dysfunction is an unlikely mechanism for the increased risk of cardiovascular mortality in men with low testosterone concentrations.

Table 1 Sociodemographic/clinical and diabetes characteristics in men at EDIC year 10 by cardiovascular autonomic neuropathy status at EDIC year 16/17 (n = 615)

Characteristics at EDIC year 10	Overall N = 615	CAN* N = 231	No CAN N = 384	*P* value
Age (years)	44.5 ± 6.6	46.7 ± 6.2	43.2 ± 6.5	<0.0001
Current cigarette smoker (n,%)	83 (14)	43 (19)	40 (11)	0.004
BMI (kg/m^2)	28.1 ± 4.1	28.5 ± 4.6	27.9 ± 3.8	0.4
BMI category (n,%)				0.3
BMI < 25 kg/m^2	137 (22)	52 (23)	85 (22)	
BMI25–30 kg/m^2	310 (51)	109 (47)	201 (53)	
BMI ≥ 30 kg/m^2	163 (27)	69 (30)	94 (25)	
BMI change since EDIC baseline (kg/m^2)	1.8 ± 2.2	1.6 ± 2.2	1.9 ± 2.2	0.07
Waist circumference (cm)	95.4 ± 10.9	96.9 ± 12.4	94.4 ± 9.8	0.02
Randomization to intensive treatment (n,%)	305 (50)	106 (46)	199 (52)	0.2
Primary prevention cohort (n,%)	305 (50)	96 (42)	209 (54)	0.003
Duration of diabetes (years)	22.4 ± 4.8	23.4 ± 4.9	21.9 ± 4.7	0.0001
Time-weighted DCCT/EDIC HbA1c (%)	8.0 ± 1.0	8.3 ± 1.1	7.9 ± 0.9	<0.0001
Time-weighted DCCT/EDIC insulin dosage (units/kg/day)	0.66 ± 0.18	0.66 ± 0.18	0.65 ± 0.18	0.8
Peripheral neuropathy (n,%)†	217 (36)	103 (45)	114 (30)	0.0001
Hypertension (n,%)‡	349 (57)	155 (68)	194 (51)	<0.0001
Total testosterone (ng/dL)	595.5 ± 210.3	578.1 ± 216.1	606.0 ± 206.3	0.07
Bioavailable testosterone (ng/dL)	9.7 ± 2.5	9.4 ± 2.5	9.9 ± 2.4	0.06
Total testosterone <300 ng/dL (n,%)	39 (6)	20 (9)	19 (5)	0.07

*Defined using autonomic testing completed in EDIC year 16/17 and abnormal finding defined as R–R variation < 15 or RR variation 15–20 in combination with Valsalva ratio ≤1.5 or a decrease of >10 mm Hg in diastolic blood pressure
†Defined at EDIC year 10 by the Michigan Neuropathy Screening Instrument >6 responses on the questionnaire or a score of >2 on the exam
‡Hypertension is defined as sitting systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or the use of antihypertensive medication
BMI = body mass index; CAN = cardiovascular autonomic neuropathy; DCCT = Diabetes Control and Complications Trial; EDIC = Epidemiology of Diabetes Interventions and Complications Study; HbA1c = hemoglobin A1c

Abstract

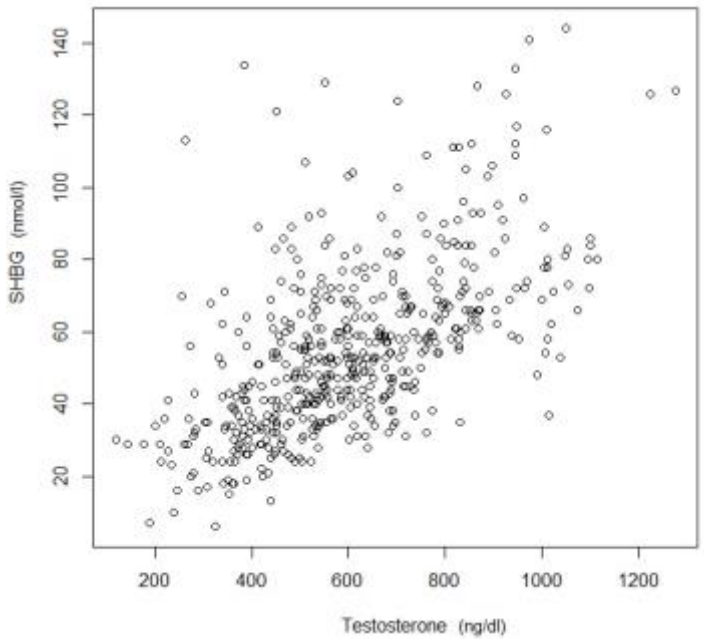
Introduction. Previous studies have reported that lower testosterone concentrations are associated with cardiovascular autonomic neuropathy (CAN), a risk factor for cardiovascular events. However, no studies have examined this relationship in men with type 1 diabetes, who are at high risk for CAN.
Aim. The aim of this study was to examine the associations between testosterone concentrations and measures of CAN in a large, well-characterized cohort of men with type 1 diabetes.
Methods. We conducted an analysis of men in the Diabetes Control and Complications Trial (DCCT), a randomized trial of intensive glucose control, and its observational follow-up the Epidemiology of Diabetes Intervention and Complications (EDIC) Study. Testosterone was measured by liquid chromatography mass spectrometry in stored samples from EDIC follow-up years 10 and 17. Regression models were used to assess the cross-sectional relationships between testosterone and CAN measures.
Main Outcome Measures. The main CAN measure from EDIC follow-up year 17 was a standardized composite of R–R variation with paced breathing < 15, or R–R variation 15–20 combined with either a Valsalva ratio ≤ 1.5 or a decrease in diastolic blood pressure > 10 mm Hg upon standing. Continuous R–R variation and Valsalva ratio were secondary outcomes.
Results. Lower total and bioavailable testosterone concentrations at follow-up years 10 and 17 were not associated with the presence of CAN at year 17. In analyses using Valsalva ratio as a continuous measure, higher total ($P = 0.01$) and bioavailable testosterone concentrations ($P = 0.005$) were associated with a higher (more favorable) Valsalva ratio after adjustment for covariates including age, body mass index, smoking status, hypertension, and glycemia.
Conclusions. Testosterone levels are not associated with CAN among men with type 1 diabetes. Although testosterone is associated with a higher Valsalva ratio, a more favorable indicator, the clinical significance of this association is not known. **Kim C, Pop-Busui R, Braffett B, Cleary PA, Bebu I, Wessells H, Orchard T, and Sarma AV, for the DCCT/E.D.I.C. Research Group. Testosterone Concentrations and Cardiovascular Autonomic Neuropathy in Men with Type 1 Diabetes in the Epidemiology of Diabetes Interventions and Complications Study (EDIC).**

We then examined whether higher testosterone concentrations were linked with greater cardiac mass, volume, and parameters of function. We found that higher total testosterone concentrations were associated with greater cardiac mass but not with measures of cardiac function (see Table 2 below). This work was published in Clinical Endocrinology (see abstract and citation below). However, bioavailable testosterone concentrations were not associated with many measures of volume and mass, suggesting that sex hormone binding globulin (SHBG) accounted for the association rather than testosterone. SHGB correlated with testosterone concentrations (see Figure), but SHGB is also recognized to correlate strongly with hepatic and visceral adiposity. These findings suggest that testosterone relationships with cardiovascular mortality are influenced by SHGB and possibly by adipose tissue.

Table 2. Associations between testosterone and sex hormone binding globulin (SHBG) and cardiac magnetic resonance imaging measures, β-coefficients (standard errors) and *P*-values*

	Left ventricular mass (g/m^2)	End-diastolic volume (ml/m^2)	End-systolic volume (ml/m^2)	Stroke volume (ml/m^2)	Ejection fraction (%)	Cardiac output ($l/min/m^2$)	Left ventricular mass/end-diastolic volume (mg/ml)
Total testosterone (ng/dl)	**0·0070 (0·0028)**	**0·0093 (0·0032)**	**0·0048 (0·0019)**	**0·0045 (0·0019)**	−0·0015 (0·0015)	1·52e−05 (0·0001)	0·0001 (1·75e−04)
P	**0·014**	**0·003**	**0·012**	**0·023**	0·339	0·879	0·568
Bioavailable testosterone (ng/dl)	**0·578 (0·253)**	0·063 (0·274)	0·164 (0·169)	−0·10 (0·173)	−0·145 (0·134)	−0·0094 (0·013)	**0·0075 (0·0034)**
P	**0·023**	0·818	0·332	0·563	0·279	0·470	**0·026**
SHBG (nmol/l)	0·0196 (0·0252)	**0·076 (0·027)**	**0·037 (0·017)**	**0·039 (0·017)**	−0·014 (0·013)	0·0004 (0·0013)	**0·0008 (0·0003)**
P	0·437	**0·005**	**0·030**	**0·022**	0·300	0·758	**0·025**

*Covariates include age, randomization arm, cohort, alcohol use, cigarette use, macroalbuminuria, HbA1c, insulin dose, body mass index, lipids, systolic blood pressure and use of antihypertensive medications.
Bolded values indicate statistical significance at $p < 0.05$.



Abstract

Objective Low testosterone concentrations have been reported to be associated with increased risk of congestive heart failure, but the mechanisms are unclear. Our objective was to examine the relationship between endogenous testosterone and measures of cardiac mass and function among men with type 1 diabetes.

Design Secondary analysis of a prospective observational study. Participants Men (n = 508) in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the observational follow-up of the Diabetes Control and Complications Trial (DCCT).

Measurements Testosterone assessed by liquid chromatography mass spectrometry at EDIC year 10 and cardiac magnetic resonance imaging (CMR) measures at EDIC years 14/15. Linear regression models were used to assess the relationship between testosterone, sex hormone binding globulin (SHBG) and left ventricular (LV) mass, volume, ejection fraction and cardiac index before and after adjustment for age, randomization arm, alcohol and cigarette use, macroalbuminuria, haemoglobin A1c, insulin dose, body mass index, lipids, blood pressure, use of antihypertensive medications and microvascular complications.

Results In fully adjusted models, total testosterone concentrations were significantly associated with LV mass (P = 0 014), end-diastolic volume (P = 0 002), end-systolic volume (P = 0 012) and stroke volume (P = 0 022), but not measures of LV function after adjustment for cardiac risk factors. Bioavailable testosterone was associated with LV mass, but not volume or function, while SHBG was associated with volume, but not mass or function.

Conclusions Among men with type 1 diabetes, higher total testosterone was associated with higher LV mass and volume, but not with function. The clinical significance of this association remains to be established.

Finally, we have not found that testosterone concentrations correlate with carotid intima media thickness after adjustment for age and other covariates. The relationship between endogenous testosterone and outcomes including incident CVD events such as mortality could not be completed due to EDIC embargo of CVD event data due to limited sample size.

3. Publications

1) Catherine Kim MD, MPH, Rodica Pop-Busui MD, PhD, Barbara Braffett PhD, Patricia A. Cleary MS, Ionut Bebu PhD, Hunter Wessells MD, Trevor Orchard MD, and Aruna V. Sarma PhD for the DCCT/EDIC Research Group. *Testosterone Concentrations and Cardiovascular Autonomic Neuropathy in Men with Type 1 Diabetes in the Epidemiology of Diabetes Interventions and Complications Study (EDIC).* Journal of Sexual Medicine, 12:2153-2159, 2015.

2) Catherine Kim MD, MPH, Ionut Bebu PhD, PhD, Barbara Braffett PhD, Patricia A. Cleary MS, Valerie Arends MS, Michael Steffes MD PhD, Hunter Wessells MD, Trevor Orchard MD, and Aruna V. Sarma PhD for the DCCT/EDIC Research Group. *Testosterone and Cardiac Mass and Function in Men with Type 1 Diabetes in the Epidemiology of Diabetes Interventions and Complications Study (EDIC).* Clinical Endocrinology, 84(5):693-9, 2016.