Sexual Dysfunction as a Marker of Cardiovascular Disease in Males With 50 or More Years of Type 1 Diabetes

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OBJECTIVE—Vascular dysfunction is a major contributor to diabetes complications. It is also the primary physiologic cause of erectile dysfunction and considered an independent predictor of cardiovascular disease (CVD) in males over age 40. A cohort of individuals with 50 or more years of type 1 diabetes, Joslin Medalists, have low rates of small but not large vessel complications. This study aims to identify the prevalence and longitudinal association of sexual dysfunction (SD) with CVD in Joslin Medalists.

RESEARCH DESIGN AND METHODS—Description and association of self-assessment of SD in males of the Medalist cohort by self-reported sexual problems with CVD. SD is validated through the use of the abbreviated International Index of Erectile Dysfunction (IIEF).

RESULTS—Of 301 males in the Medalist Study, 69.8% reported a history of SD. Unadjusted risk factors included elevated glycated hemoglobin (HbA_{1c}) ($P = 0.02$), elevated BMI ($P = 0.03$), higher total cholesterol ($P = 0.02$), lower HDL ($P < 0.01$), and increased levels of interleukin-6 ($P = 0.03$). SD was independently associated with CVD (age-, HbA_{1c}-, and BMI-adjusted OR 1.9 [95% CI 1.0–3.5]). In adjusted analyses, retinal, neural, and renal complications were not associated ($P > 0.05$) with SD. Current report of SD (IIEF score ≤17) in a subset of Medalists was significantly correlated with self-reported longitudinal SD.

CONCLUSIONS—SD in those with extreme-duration type 1 diabetes is independently associated with CVD, representing a large vessel pattern. The findings suggest that SD may predict CVD in those with type 1 diabetes of long duration. These individuals have also been found to be relatively free of microvascular complications.

An increasing number of individuals are surviving to extreme durations of type 1 diabetes; therefore more individuals will be at risk for developing related complications (1–4). The Joslin 50-Year Medalists, individuals with an average duration of 55 years of type 1 diabetes, have been characterized with low levels of microvascular complications; although levels of macrovascular disease may not follow the same pattern (3,4). Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in those with diabetes. Multiple studies have shown that diabetes independently increases the risk for CVD up to 1.4-fold (5–7). The primary risk factors for heart disease associated with diabetes include dyslipidemia, elevated BMI, poor glycemic control, hypertension, insulin resistance, and history of smoking (8). However, individuals with type 1 diabetes are often leaner and have elevated HDL levels compared to those with type 2 diabetes, which, by standard risk scores, would place them at lower risk for CVD (9,10). For these individuals, a primary screening mechanism could be helpful for early intervention in the development of CVD. One proposed mechanism is screening for sexual dysfunction (SD) and its associated symptoms (5,11).

In this study, the relationship of reporting "lifetime sexual problems" with CVD in a large group of men with extreme duration of type 1 diabetes is examined. Identifying an early marker of CVD that a patient may be more likely to report, such as SD, could be helpful in interventions to alter the natural history of this disease.

RESEARCH DESIGN AND METHODS

Details of the Medalist Study have been described extensively elsewhere (3,4,12). Individuals who had documented 50 or more years of insulin use for type 1 diabetes were invited to participate in the study. Informed consent was obtained from all subjects prior to participation in the study. Individuals traveled to Joslin Diabetes Center (JDC) (Boston, MA) for physical and ophthalmic examination and biospecimen collection of urine and blood. Participants completed questionnaires regarding medical history, lifestyle, diet, and physical activity.

From 2005 to the time of analysis, 1,121 medals were awarded to residents in the United States who demonstrated 50 or more years of insulin-dependent type 1 diabetes. Of these Medalists, 800 participated in the study. Most Medalists (88%) received routine endocrine care outside JDC. The 12% who declined participation cited illness, time commitment, or financial issues. Glycated hemoglobin (HbA_{1c}) was determined by high-performance liquid chromatography (Tosoh G7 and 2.2, Tokyo, Japan). Lipid profiles were determined by standard enzymatic methods (kits from Roche Diagnostics, Indianapolis, IN; Denka Seiken, Tokyo, Japan; and AsahiKasei, Tokyo, Japan). Inflammatory markers interleukin-6 (IL-6), plasminogen activator inhibitor 1 (PAI-1), and vascular cell adhesion molecule (VCAM) and testosterone and sex hormone–binding globulin (SHBG) levels were assayed by human serum ELISA assays at the JDC Specialized Assay Core (R&D Systems,

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Received 4 February 2013 and accepted 16 April 2013.
DOI: 10.2337/dc13-0294
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-0294/-/DC1.

Diabetes Care Publish Ahead of Print, published online June 18, 2013

Minneapolis, MN; ALPCO Diagnostics, Salem, NH). C-reactive protein (CRP) was determined by nephelometric methods, and urine albumin-creatinine ratios (ACRs) were determined by turbidimetric methods (Quest Diagnostics, Wallingford, CT).

CVD status was based on self-reported history of coronary artery disease, angina, heart attack, prior cardiac or leg angioplasty, or bypass graft surgery. Renal status was defined as those with nephropathy (Chronic Kidney Disease Epidemiology Collaboration formula [CKD-EPI] estimated glomerular filtration rate [eGFR] $<$60 mL/min/1.73 m^2) versus those without (eGFR $\geq$60 mL/min/1.73 m^2). A dilated eye examination was performed and retinopathy status was graded using guidelines from the Early Treatment Diabetic Retinopathy Study (ETDRS). Proliferative diabetic retinopathy (PDR) was defined as an ETDRS $\geq$60 (13). The Michigan Neuropathy Screening Instrument was used to assess neuropathy; scores $>$2 were considered positive (14).

Lifetime SD was defined as an affirmative response to the question, "Please indicate if you have ever had any sexual problems" on a self-administered medical history questionnaire. The five-item International Index of Erectile Dysfunction (IIEF) questionnaire was used to assess current SD in a subset of the males. The IIEF was mailed, marked only with personal study identification number to ensure anonymity (15). An IIEF score $\leq$17 was considered significant erectile dysfunction (ED).

All variables were visually inspected and analyzed for distribution to determine the appropriate statistical methods. Comparisons were used depending on variable distribution (Kruskal-Wallis test, Student *t* test, and χ^2 [Fisher exact] test). SD was the outcome variable used in logistic regression models examining the relationship of both CVD and inflammatory markers. Logistic regression was used to estimate odds ratios (ORs) and 95% CIs and adjust for potential confounders, including comorbid conditions and sociodemographic and lifestyle factors.

All multivariate models were adjusted for age, HbA_{1c}, and BMI. A type 1 error $\leq$0.05 was considered significant. As SD was the primary outcome, a multiple comparison correction was not applied. STATA (v12 SE, College Station, TX) and Statistical Analysis Software v 9.2 (SAS v9.2, Cary, NC) were used.

RESULTS—Of all Medalists, 48.7% (n = 320) were male and 301 answered the question regarding a history of sexual problems; 69.8% of males reported experiencing SD over their lifetime. These individuals had a mean age, age at diagnosis, and duration of diabetes of 71.7 ± 8.5 years, 12.4 ± 7.0 years, and 59.3 ± 7.3 years, respectively. Mean BMI was 25.8 ± 3.6 kg/m^2, with mean insulin dose 0.49 ± 0.2 units/kg^2. Mean HbA_{1c} was 7.03% ± 0.89 (53 ± 6 mmol/mol). The lipid profile included a mean cholesterol of 152.0 ± 31.7 mg/dL, with HDL 57.3 ± 17.2 mg/dL and LDL 79.5 ± 22.8 mg/dL. Mean ACR was 28.3 ± 68.3 μg/mg, with 49.3% having PDR and 51.8% of males having CVD (Table 1).

Among those with and without SD, age, age at diagnosis, and duration of type 1 diabetes were not significantly different (P = 0.93, P = 0.61, and P = 0.69, respectively) (Table 1). Mean BMI (26.1 ± 3.8 vs. 25.1 ± 3.0 kg/m^2) was higher in those reporting SD (P = 0.03), as were ever smoking (51.7 vs. 39.3%, P = 0.05) and HbA_{1c} (P = 0.02). Total cholesterol levels were significantly higher (159.3 ± 32.1 vs. 150.1 ± 30.6 mg/dL, P = 0.02) and HDL levels (55.1 ± 16.2 vs. 62.1 ± 17.8 mg/dL, $P < 0.01$) were significantly lower in those without SD. The percentage of those with PDR was slightly higher in Medalists reporting SD (54.0 vs. 39.1%, P = 0.04); however, no relationship was found with neuropathy (P = 0.23). Of those males without SD, 44.3% had CVD, compared with 56.5% with SD (P = 0.05) (Table 1).

Levels of IL-6 (median [Q1–Q3]: 0.09 pg/mL [0.04–0.19] vs. 0.1 pg/mL [0.06–0.3], P = 0.03) were significantly higher in those reporting SD. Other inflammatory markers, including PAI-1 and CRP, were not significantly different between groups (P = 0.08 and P = 0.45). Total testosterone and SHBG did not vary between those with and without SD (P = 0.9 and P = 0.3) (Table 2).

There was a significant difference in the use of lipid-lowering agents (57.1% no SD vs. 74.3% SD, P = 0.003) and platelet medications (23.1% no SD vs. 35.2% SD, P = 0.04) but not in the use of blood pressure medication or adrenergic, beta, or calcium channel blockers (Supplementary Table 1). Use of phosphodiesterase type 5 (PDE5) inhibitors was reported as 1.8% tadalafil, 2.5% sildenafil, and 0.7% vardenafil; penile implants were reported by 3.6% (Supplementary Table 2). There was no relationship between insulin pump use or current self-rated blood glucose control ($P > 0.05$) and SD. There

Table 1—*Clinical characteristics of male Medalists by SD status*

	Overall (n = 301)	No dysfunction (n = 91)	Dysfunction (n = 210)	P
Age (years)	71.7 ± 8.5	71.6 ± 9.1	71.7 ± 8.2	0.93
Age at diagnosis (years)	12.4 ± 7.0	12.0 ± 7.0	12.4 ± 7.0	0.61
Duration (years)	59.3 ± 7.3	59.6 ± 7.9	59.2 ± 7.1	0.69
BMI (kg/m^2)	25.8 ± 3.6	25.1 ± 3.0	26.1 ± 3.8	0.03
Smoking (ever) (%)	48.0	39.3	51.7	0.05
HbA_{1c} (%)	7.0 ± 0.9	6.8 ± 0.8	7.1 ± 0.9	0.02
HbA_{1c} (mmol/mol)	53.0 ± 6.8	51.0 ± 6.0	54.0 ± 6.8	0.02
Insulin dose/kg (units/kg^2)	0.49 ± 0.18	0.48 ± 0.18	0.50 ± 0.20	0.41
Systolic BP (mmHg)	126.2 ± 12.8	123.6 ± 13.5	127.3 ± 12.7	0.07
Diastolic BP (mmHg)	66.3 ± 8.2	65.6 ± 8.7	67.1 ± 7.5	0.23
Cholesterol (mg/dL)	152.0 ± 31.7	150.1 ± 30.6	159.3 ± 32.1	0.02
HDL (mg/dL)	57.3 ± 17.2	62.1 ± 17.8	55.1 ± 16.2	$<$0.01
LDL (mg/dL)	79.5 ± 22.8	79.7 ± 22.2	79.2 ± 23.2	0.87
Triglycerides (mg/dL)	79.1 ± 43.8	80.6 ± 47.2	79.0 ± 43.3	0.77
Hypertension (%)	71.4	67.0	75.7	0.12
CVD* (%)	51.8	44.3	56.5	0.05
PDR (%) (ETDRS $>$60)§	49.3	39.1	54.0	0.04
ACR (μg/mg)	28.3 ± 68.3	24.5 ± 62.5	26.7 ± 62.0	0.5
Neuropathy (%) (MNSI $>$2)	48.9	43.1	51.6	0.23

Data are presented as mean ± SD or %. MNSI, Michigan Neuropathy Screening Instrument. *CVD, history of coronary artery disease, angina, MI, cardiac/leg angioplasty, or bypass graft surgery. §This relationship is no longer significant with adjustment for antihypertensives.

Table 2—*Laboratory characteristics of male Medalists by SD status*

	Overall	No dysfunction	Dysfunction	*P*
Total testosterone (ng/mL)	3.2 ± 2.6	3.1 ± 2.2	3.2 ± 2.6	0.9
SHBG (nmol/L)	64.8 ± 33.6	68.1 ± 38.3	62.7 ± 29.7	0.3
PAI-1 (pg/mL)	169.0 (106.2–229.7)	160.0 (99.0–203.5)	204.1 (106.4–246.5)	0.08
IL-6 (pg/mL)	0.12 (0.06–0.24)	0.09 (0.04–0.19)	0.1 (0.06–0.3)	0.03
CRP (mg/L)	3.3 ± 11.5	0.94 ± 5.1	1.03 ± 13.7	0.45

Data are presented as mean ± SD or median (Q1–Q3).

was also no relationship with the number of times a day blood sugars were checked, level of education, or self-rated quality of life ($P > 0.05$) (Supplementary Table 3).

The five-item IIEF questionnaire was completed and returned by a subset of 63% (n = 197) of males, with 85.3% reporting a significant degree of ED (IIEF score ≥17), in agreement with the original self-report question (χ^2 = 256.0, $P < 0.001$) (15). Demographic and basic clinical characteristics did not vary significantly between the subsets of men who did and did not complete the IIEF.

Male Medalists with CVD (51.8%) were older and had a longer type 1 diabetes duration than males without CVD (73.3 ± 8.5 vs. 70.0 ± 8.0 years [P = 0.005] and 60.5 ± 7.8 vs. 57.9 ± 6.4 years [P = 0.003], respectively), as well as higher HbA_{1c} (7.2 ± 0.9 vs. 6.9 ± 0.8%; 55 ± 6.8 vs. 52 ± 6 mmol/mol [P = 0.002]). Individuals with CVD had higher total cholesterol, higher LDL, and higher HDL than those without CVD ($P <$ 0.01). Males with CVD had a lower mean eGFR (61.7 ± 19.7 vs. 72.7 ± 18.7 mL/min/1.73 m^2 [$P < 0.001$]) and higher rate of PDR (61.3 vs. 37.2%, $P < 0.001$). There was no difference in inflammatory markers, including CRP, IL-6, PAI-1, or VCAM, between those with and without CVD ($P > 0.05$) (Table 3). There was no significant difference in the use of PDE5 inhibitors by CVD disease; however, the frequency of men with a penile implant who have CVD (80 vs. 20%, P = 0.04) is higher than those without CVD.

The association of lifetime SD and CVD remained with adjustment for age, BMI, cholesterol, HDL, smoking, IL-6, antihypertensive medication, and HbA_{1c} (OR 3.7 [95% CI 1.5–9.0]). Additionally, lower inflammatory levels of IL-6 are associated with protection from reporting SD (0.4 [0.2–0.95]) when adjusted for age, BMI, HDL, smoking, and HbA_{1c}.

CONCLUSIONS—Several studies have established the connection between ED and CVD in men starting the fourth decade of life (11,16–18). The hypothesized etiology is that vessels feeding the penis are smaller than those feeding the heart and therefore show clinical symptoms earlier. The physiologic mechanism is endothelial dysfunction resulting from the inhibition of the nitric oxide cascade, thus preventing dilation of the arteries impairing the blood flow imperative for rigidity (19). The etiology of endothelial dysfunction may be different, or synergistic, depending on endogenous risk between those with and without diabetes due to the inherent damaging effects of the hyperglycemic exposure. Importantly for type 1 diabetic patients, this relationship may be independent of previously identified risk factors for CVD, as used in the Framingham Index (20). This is supported by the independent relationship of CVD and SD from other risk factors, including age and BMI, among this group of extreme-duration type 1 diabetic patients.

The 50-Year Medalists are a group of individuals who have had type 1 diabetes for 50 or more years and resultant prolonged hyperglycemic exposure. An onset of diabetes in the early to midpart of the last century meant that blood glucose management consisted of weekly testing with once-daily injections, resulting in frequent bouts of diabetic ketoacidosis or hypoglycemia and the potential for significant endothelial damage. Previous literature on Medalists documented a lower than expected prevalence of microvascular complications, including PDR (50.6%), neuropathy (60.6%), and nephropathy (13.1%) (3,4,12,21–24). As reported, the prevalence of CVD among male Medalists is 51.8%. At an index age of 75 years, in the Framingham Health Study, the adjusted lifetime (up to 95 years of age) risk estimate for men is 54.5% (95% CI 52.2–56.9), demonstrating that there is no increased prevalence of CVD among Medalists (10). This is in contrast to the ancillary study of the Epidemiology of Diabetes Interventions and Control (uroEDIC) Study on urologic symptoms, which assessed the prevalence of SD among their participants who had a mean type 1 diabetes duration of 22.1 years, average age of 44.6 ± 6.6 years, and time-weighted average HbA_{1c} of 8.07%, finding an overall prevalence of 58% ED (IIEF 0–20); they did not assess correlation with CVD (25). Our finding of no difference in testosterone levels in those with SD is consistent with the findings of Van Den Edeen et al. (25).

Klein et al. (26) in the Wisconsin Epidemiology Study of Diabetic Retinopathy examined markers of SD and found a cumulative incidence of 25% in men 21 years of age or older with 10 or more years of type 1 diabetes (mean age 34.4 ± 8.4 years and duration 20.5 ± 7.0 years) and mean HbA_{1c} of 9.7%. Those 40 years of age and older had the highest overall incidence at 48.6%. Primary risk factors other than age in this population included untreated hypertension (OR 5.0 [95% CI 2.05–12.3]) and smoking status (current OR 2.4 [1.09–5.30]), established risk factors for CVD. No significant relationship was found with microvascular complications with adjustment for age, smoking, and untreated hypertension. No contemporary association was found with CVD; however, total cholesterol was associated with SD but not HDL (26). In similarly aged nondiabetic men, the Massachusetts Male Aging Study documented a complete impotence rate of 67% by 70 years, and the National Health and Nutrition Examination Survey (NHANES) reported a prevalence of 77.5% for those 75 years of age and older (27,28).

In this study, we examined prevalence of SD and its relationship to CVD. A limitation of the self-reporting of "lifetime sexual problems" is that it may capture those with a history of SD due to social, economic, or lifestyle factors instead of progressive endothelial pathology, which may precede larger vessel disease. Close agreement of SD with IIEF scores suggests that the SD question may be capturing ED in our sample. Additionally, the IIEF cut-off was associated with cardiovascular risk factors, as well as CVD, the outcome of interest. Neurogenic, pharmacologic, and quality of life factors did not confound or influence the observed association of IIEF scores and CVD.

Table 3—*Clinical characteristics of male Medalists with and without CVD*

	No CVD	CVD	*P*
Age (years)	70.0 ± 8.0 (147)	73.3 ± 8.5 (158)	0.005
Age at diagnosis (years)	12.0 ± 6.7 (147)	12.9 ± 7.2 (158)	0.29
Duration (years)	57.9 ± 6.4 (147)	60.5 ± 7.8 (158)	0.003
BMI (kg/m^2)	26.1 ± 3.9 (144)	25.6 ± 3.3 (156)	0.21
Smoking (ever) (%)	45.2 (66)	52.0 (80)	0.24
HbA_{1c} (%)	6.9 ± 0.8 (147)	7.2 ± 0.9 (158)	0.002
HbA_{1c} (mmol/mol)	52.0 ± 6.0 (147)	55.0 ± 6.8 (158)	0.002
Insulin dose/kg (units/kg^2)	0.5 ± 0.19 (68)	0.5 ± 0.17 (86)	0.58
Systolic BP (mmHg)	127.5 ± 12.5 (95)	124.9 ± 13.1 (95)	0.16
Diastolic BP (mmHg)	67.2 ± 7.8 (95)	65.4 ± 8.5 (95)	0.14
Cholesterol (mg/dL)	160.9 ± 31.4 (147)	145.1 ± 29.0 (158)	<0.001
HDL (mg/dL)	60.7 ± 18.1 (147)	54.0 ± 15.7 (158)	0.001
LDL (mg/dL)	83.8 ± 23.3 (147)	75.0 ± 21.0 (157)	0.001
Triglycerides (mg/dL)	78.2 ± 41.8 (147)	81.4 ± 46.6 (158)	0.52
Testosterone (ng/mL)	3.1 ± 2.8 (113)	3.3 ± 2.4 (130)	0.61
SHBG (nmol/L)	66.0 ± 30.3 (86)	64.4 ± 35.6 (120)	0.74
EPI eGFR (mL/min/1.73 m^2)	72.7 ± 18.7 (146)	61.7 ± 19.7 (158)	<0.001
ACR (μg/mg)	24.5 ± 47.8 (130)	31.8 ± 82.9 (141)	0.38
Microalbuminuria (%)	13.9 (18)	14.9 (21)	0.8
PDR (%)	37.2 (42)	61.3 (65)	<0.001
Neuropathy (%)	48.3 (55)	47.9 (57)	0.96
Inflammatory markers			
PAI-1 (pg/mL)	190.4 (124.5–242.3) (65)	155.5 (95.0–197.4) (73)	0.35
IL-6 (pg/mL)	0.12 (0.05–0.22) (53)	0.12 (0.05–0.3) (67)	0.6
CRP (mg/L)	0.9 (0.5–1.8) (144)	1.1 (0.5–2.9) (153)	0.12
VCAM (ng/mL)	1,833.4 ± 105.7 (64)	2,034.33 ± 924.6 (76)	0.27
Medication use			
Blood pressure drug	42.6 (83)	57.4 (112)	0.01
Adrenergic blocker	40.0 (2)	60.0 (3)	0.7
Beta blocker	22.6 (23)	77.5 (79)	<0.001
Calcium channel blocker	42.6 (26)	57.4 (35)	0.33
Lipid-lowering drug	40.4 (86)	59.6 (127)	<0.001

Data are presented as mean ± SD, % (*n*), or median (Q1–Q3).

Duration, glycemic control, age, and lipid profile did not correlate with microvascular complications; however, CVD showed a significant relationship with HbA_{1c}, age, duration, lipid profile, and inflammatory markers. In studies of those with type 2 diabetes, the relationship of ED and CVD is thought to begin with the damage caused by the milieu of metabolic changes associated with the metabolic syndrome, established as a direct predecessor of CVD (29–33). However, as the Medalists do not have the same lipid profile (total cholesterol levels <200 mg/dL, HDL levels >35 mg/dL, and a triglyceride level <70 mg/dL), increased weight, and insulin resistance characteristic of type 2 diabetes (insulin dose, 0.5 units/kg [0.37–0.57]), the same early warning signs for CVD are not present. Of the Medalists that have died, 58.6% died of CVD, demonstrating a significant mortality from this disease risk that necessitates early detection (29–33). Findings of this analysis indicate that history of SD provides an important screening tool in the absence of the typical risk profile of glycemic control, BMI, and dyslipidemia in patients with type 1 or type 2 diabetes.

Acknowledgments—This research was funded by the Juvenile Diabetes Research Foundation (8-2005-358, nPOD 25-2008-383, and 18-2008-363), the Beatson Foundation, the Brehm Foundation, the National Institutes of Health (1R24-DK-090961-01 and DP3-DK-094333-01), and the Peabody Foundation.

J.K.S. provided research support to Boston Micromachines and Genentech, was on the scientific advisory board for Abbott Laboratories, and was a consultant for Novartis. G.L.K. provided research support for Sanofi. No other potential conflicts of interest relevant to this article were reported.

S.J.T., S.M.H., and H.A.K. researched, collected, and analyzed data and wrote and reviewed the manuscript. J.K.S. collected and analyzed data and reviewed the manuscript. G.L.K. reviewed and edited the manuscript. S.J.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank Varant Kupelian, PhD, for his insight and advice in the preparation of this manuscript.

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