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

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

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George L. King, MD
Hillary A. Keenan, PhD

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 years. 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 (HbA1c) (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–HbA1c, 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.

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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/m², with mean insulin dose 0.49 ± 0.2 units/kg². Mean HbA1c 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/m²) was higher in those reporting SD (P = 0.03), as were ever smoking (51.7% vs. 39.3%, P = 0.05) and HbA1c (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 = 0.03) (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, β, 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

<table>
<thead>
<tr>
<th>Overall</th>
<th>No dysfunction (n = 301)</th>
<th>Dysfunction (n = 210)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>71.7 ± 8.5</td>
<td>71.6 ± 9.1</td>
<td>71.7 ± 8.2</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>12.4 ± 7.0</td>
<td>12.0 ± 7.0</td>
<td>12.4 ± 7.0</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>59.3 ± 7.3</td>
<td>59.6 ± 7.9</td>
<td>59.2 ± 7.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 3.6</td>
<td>25.1 ± 3.0</td>
<td>26.1 ± 3.8</td>
</tr>
<tr>
<td>Smoking (ever) (%)</td>
<td>48.0</td>
<td>39.3</td>
<td>51.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.0 ± 0.9</td>
<td>6.8 ± 0.8</td>
<td>7.1 ± 0.9</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>53.0 ± 6.8</td>
<td>51.0 ± 6.0</td>
<td>54.0 ± 6.8</td>
</tr>
<tr>
<td>Insulin dose (units/kg²)</td>
<td>0.49 ± 0.18</td>
<td>0.48 ± 0.18</td>
<td>0.50 ± 0.20</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>126.2 ± 12.8</td>
<td>123.6 ± 13.5</td>
<td>127.3 ± 12.7</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>66.3 ± 8.2</td>
<td>65.6 ± 8.7</td>
<td>67.1 ± 7.5</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>152.0 ± 31.7</td>
<td>150.1 ± 30.6</td>
<td>159.3 ± 32.1</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>57.3 ± 17.2</td>
<td>62.1 ± 17.8</td>
<td>55.1 ± 16.2</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>79.5 ± 22.8</td>
<td>79.7 ± 22.2</td>
<td>79.2 ± 23.2</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>79.1 ± 43.8</td>
<td>80.6 ± 47.2</td>
<td>79.0 ± 43.3</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>71.4</td>
<td>67.0</td>
<td>75.7</td>
</tr>
<tr>
<td>CVD (%)*</td>
<td>51.8</td>
<td>44.3</td>
<td>56.5</td>
</tr>
<tr>
<td>PDR (%) (ETDRS &gt;60)</td>
<td>49.3</td>
<td>39.1</td>
<td>54.0</td>
</tr>
<tr>
<td>ACR (µg/mg)</td>
<td>28.3 ± 68.3</td>
<td>24.5 ± 62.5</td>
<td>26.7 ± 62.0</td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>48.9</td>
<td>43.1</td>
<td>51.6</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean ± SD or %.

MNSI, Michigan Neuropathy Screening Instrument.

*History of coronary artery disease, angina, MI, cardiac/leg angioplasty, or bypass graft surgery.

§This relationship is no longer significant with adjustment for antihypertensives.
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 overall self-report question (χ² = 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 HbA₁c (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 m² [P < 0.001]) and higher rate of PDR (61.3 ± 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 HbA₁c (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 HbA₁c.

### 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 middle part 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 HbA₁c 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 Eeden 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 HbA₁c 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 cutoff 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.
Duration, glycemic control, age, and lipid profile did not correlate with microvascular complications; however, CVD showed a significant relationship with Hba1c, 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 absence of the typical risk profile of glycemic control, BMI, and dyslipidemia in patients with type 1 or type 2 diabetes.

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