



# Diabetic Peripheral Neuropathy and Urological Complications in Type 1 Diabetes: Findings From the Epidemiology of Diabetes Interventions and Complications Study

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## OBJECTIVE

To evaluate associations between diabetic peripheral neuropathy (DPN) and urological complications in men and women with type 1 diabetes (T1D).

## RESEARCH DESIGN AND METHODS

Measurements of DPN at Epidemiology of Diabetes Intervention and Complications (EDIC) years 1, 14, and 17 and urological complications at EDIC year 17 were examined in 635 men (mean age 51.6 years, diabetes duration 29.5 years) and 371 women (mean age 50.6 years, diabetes duration 29.8 years) enrolled in the Diabetes Control and Complications Trial (DCCT)/EDIC study. DPN was defined by symptoms, signs, and abnormal electrophysiology or by abnormal Michigan Neuropathy Screening Instrument (MNSI) examination or questionnaire scores.

## RESULTS

Erectile dysfunction (ED) in combination with lower urinary tract symptoms (LUTS) was reported in 15% of men and female sexual dysfunction (FSD), LUTS, and urinary incontinence (UI) in 16% of women. Adjusted for age, drinking status, BMI, depression, DCCT/EDIC time-weighted mean HbA<sub>1c</sub>, microalbuminuria, hypertension, triglycerides, and statin medication use, the odds of reporting ED and LUTS versus no ED or LUTS at EDIC year 17 were 3.52 (95% CI 1.69, 7.31) times greater in men with confirmed DPN at EDIC year 13/14 compared to men without confirmed DPN. Compared to men without DPN, men with DPN based on abnormal MNSI examination or questionnaire scores had significantly higher odds of reporting ED and LUTS versus no ED or LUTS at EDIC year 17. There were no significant differences in DPN between women reporting both FSD and LUTS/UI compared with those without FSD or LUTS/UI at EDIC year 17.

## CONCLUSIONS

In long-standing T1D, DPN is associated with the later development of urological complications in men.

Urological symptoms and complications are highly prevalent (1) and important causes of morbidity in individuals with diabetes (2). Among women with diabetes, female

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\*A complete list of the DCCT/EDIC Research Group can be found in the supplementary material online.

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sexual dysfunction (FSD), lower urinary tract symptoms (LUTS), and urinary incontinence (UI) have a significant negative impact on quality of life (2,3). Similarly, erectile dysfunction (ED) and LUTS are problems for many men >50 years of age, particularly in men with type 1 diabetes (T1D) (4,5).

Recently, the UroEDIC study, an ancillary study of urological complications in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study (5,6), reported that cardiovascular autonomic neuropathy (CAN) predicted the development of ED/LUTS in men with T1D phenotyped by high-quality, validated measures (7). A significant association between CAN and FSD/UI was also observed in women with T1D (8,9).

Distal symmetric sensorimotor polyneuropathy, the most common form of diabetic neuropathy (10), may also affect genital sensory and/or motor function (11). Furthermore, peripheral neuropathy is one of the most prevalent causes of reduced bladder sensation, including bladder dysfunction associated with diabetes (12,13). Our previous work in UroEDIC suggests a possible association between peripheral neuropathy and urological complications in individuals with T1D (1). However, systematic evaluations of these associations using sensitive and specific markers of DPN while also controlling for known risk factors are lacking. Consequently, the objective of this study was to comprehensively evaluate the associations between diabetic peripheral neuropathy (DPN) and urological complications in participants with long-standing T1D enrolled in the DCCT/EDIC study.

## RESEARCH DESIGN AND METHODS

### Population and Setting

The DCCT and EDIC studies have been described in detail (14,15). Briefly, 1,441

subjects with T1D for 1–15 years with no (primary prevention cohort) or minimal diabetic retinopathy (secondary intervention cohort) were enrolled in DCCT. Subjects were randomly assigned to receive either intensive or conventional treatment and followed for 3–9 years in DCCT (mean 6.5 years). At the end of DCCT in 1993, intensive therapy was recommended for all participants, and they were returned to their health care providers for ongoing diabetes care. Annual EDIC examinations began in 1994, with 1,375 (96%) former DCCT subjects consenting to participate in the follow-up study. A detailed description of EDIC study procedures and baseline characteristics has been published (14).

Of the original 761 men and 680 women enrolled in DCCT, 746 and 676 completed the study in 1993, and 720 (97%) and 655 (96%) elected to participate in the first annual examination in EDIC in 1994. UroEDIC, an ancillary study designed to examine urological complications of diabetes, included UroEDIC I evaluations in 2003 (EDIC year 10) and follow-up UroEDIC II evaluations in 2010 (EDIC year 17). At EDIC year 17, 644 (96%) of the 669 actively participating men and 580 (94%) of the 618 actively participating women agreed to participate in UroEDIC II, and among them, 635 men and 371 women had valid ED/LUTS and FSD/UI information available, respectively. Figure 1 summarizes the timeline for data collection of urological complications and neuropathy data during DCCT/EDIC. All DCCT/EDIC procedures were approved by institutional review boards at participating clinical centers. Written informed consent was provided by all participants.

### DPN Evaluations

DPN evaluations were performed at EDIC year 13 or 14 using assessments of

symptoms, clinical signs, and electrophysiology as previously described (Fig. 1) (16). Briefly, certified neurologists performed the clinical examinations, including neurological history and physical examination, to detect the presence of distal symmetrical polyneuropathy and identify potential causes of neuropathy, including diabetes. Nerve conduction studies were performed by trained and certified electromyographers on the dominant side median (motor and sensory), peroneal (motor), and sural (sensory) nerves using percutaneous nerve stimulation and surface recordings (16). In addition, the Michigan Neuropathy Screening Instrument (MNSI) (17), a validated instrument with high sensitivity and specificity for DPN comprising a 15-item symptom questionnaire, structured foot examination, and assessment of ankle reflexes and distal vibration perception, was administered annually during EDIC (18).

DPN was defined as either 1) confirmed DPN based on two or more positive responses among symptoms, sensory signs, and ankle reflex changes consistent with distal symmetrical polyneuropathy plus nerve conduction abnormalities involving two or more nerves among the median, peroneal, and sural nerves or 2) abnormal MNSI based on either a clinical examination score of  $\geq 2.5$  or  $\geq 4$  positive responses on the questionnaire using validated cut points developed in this cohort (19). We further defined sustained DPN as a persistent MNSI clinical examination score of  $\geq 2.5$  or  $\geq 4$  positive responses on the MNSI questionnaire for  $\geq 2$  consecutive years during EDIC years 1–17.

### Urological Complications Evaluations

Presence of ED was assessed with the International Index of Erectile Function, a reliable, validated instrument (20).

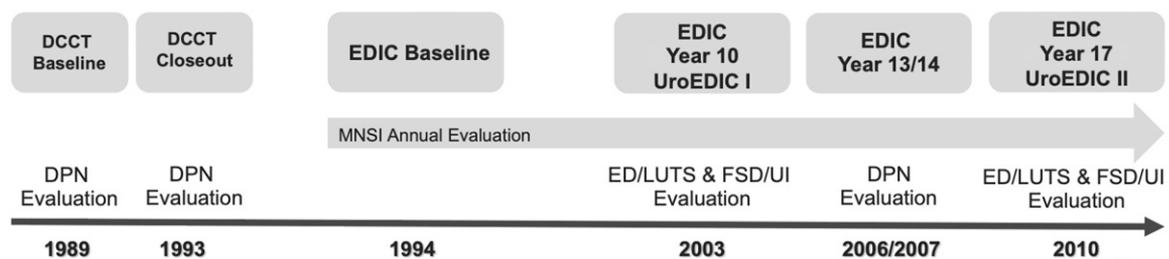


Figure 1—Flowchart of neurological and urological data collection in the DCCT/EDIC study.

Because 20% of participants responded “did not attempt intercourse” on questions in the erectile function (EF) domain, we created a proxy item to assess EF in the entire cohort, regardless of sexual activity and presence of a partner. A single question in the EF domain asks participants, “Over the past 4 weeks, how would you rate your confidence that you get and keep your erection?” Those who answered very low or low were classified as having ED. Those who answered moderate, high, or very high were classified as not having ED. Among the men who engaged in sexual intercourse during the preceding 4 weeks, this definition of ED correlated strongly with total EF domain scores ( $r = 0.77$ ,  $P < 0.001$ ) and ED bother ( $r = 0.80$ ,  $P < 0.001$ ).

FSD was evaluated by the abbreviated version of the Female Sexual Function Index (FSFI-R), a widely used, multidimensional, well-validated, self-reported measure that assesses sexual function across six domains, including sexual desire, arousal, lubrication, orgasm, satisfaction, and pain, among sexually active women (21). Presence of FSD among women who reported being sexually active was defined by a score  $\leq 22.75$  on the FSFI-R.

LUTS severity was determined in men and women during EDIC year 17 using the American Urological Association Symptom Index (22). This index includes a seven-item questionnaire that quantifies the presence and frequency of the following LUTS: nocturia, frequency, urgency, weak urinary stream, intermittency, straining, and sensation of incomplete emptying. Scores range from 0 to 35, and LUTS was defined with widely accepted validated cut points of 0–7 and 8–35 for none/mild and moderate/severe, respectively.

UI in women was determined on the basis of incontinence frequency and amount of urine lost per episode (drops, small splashes, more) using the validated Sandvik Severity Index (23). This index is calculated from frequency and amount of urine loss on a scale of 0–12 (dry/mild 0–2, moderate 3–6, severe 8–9, very severe 12). For the current study, presence of UI was defined as Sandvik Severity Index of 3–12 (moderate/very severe UI).

### Other Evaluations

Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was measured at baseline and quarterly during DCCT and annually in EDIC, as previously described (14). The time-weighted mean value for HbA<sub>1c</sub> during DCCT and EDIC was calculated by weighting each value by the time interval since the last measurement up to EDIC year 17. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured quarterly during DCCT and annually during EDIC. Hypertension was defined as sitting SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg or the use of antihypertensive medication. Fasting lipids (triglycerides, total and HDL cholesterol) were measured centrally on alternate years during EDIC. Retinopathy was assessed in one-quarter of the cohort annually during EDIC using fundus photographs that were graded centrally using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale (24). Proliferative diabetic retinopathy was defined by neovascularization observed on standardized stereoscopic seven-field fundus photography grading or evidence of scatter photocoagulation. Albumin excretion rate was measured in one-half of the cohort annually during EDIC, and kidney disease was defined as microalbuminuria (albumin excretion rate  $\geq 30$  mg/24 h at two consecutive visits). Depression symptoms were assessed using the Psychiatric Symptom Checklist 90-R (SCL-90R), a widely used and well-validated measure that provides an assessment of psychiatric symptoms and generates a total score on the global severity index and subscales, including depression T-scores that are derived from normative samples. Higher scores reflect more symptoms (25).

### Statistical Analysis

Descriptive analyses examined the distribution of sociodemographic and clinical characteristics, markers of diabetes control and treatment, BP control, diabetic complications, and neuropathy measures by ED/LUTS status in men and FSD/LUTS/UI status in sexually active women. The Kruskal-Wallis test was used to assess differences in continuous variables and the  $\chi^2$  test for differences in categorical variables. For men and women separately, multivariable logistic regression models were used to evaluate the associations between

measures of neuropathy at EDIC years 1, 14, and 17 and the presence of ED/LUTS or FSD/LUTS/UI at EDIC year 17. Variables that were significant at the  $P < 0.05$  level in the bivariate analyses, with no adjustment for multiple comparisons, were entered into the multivariable models as covariates. For men, adjustments were made for age, drinking status, BMI, SCL-90R depression T-score, DCCT/EDIC time-weighted mean HbA<sub>1c</sub>, microalbuminuria, hypertension, triglycerides, and statin medication use. For women, adjustments were made for age, menopausal status, SCL-90R depression T-score, SBP, and statin medication use. All analyses were performed using SAS 9.3 statistical software (SAS Institute, Cary, NC).

### RESULTS

At EDIC year 17, 30% of men reported ED only, 10% LUTS only, and 15% both ED and LUTS, while 25% of women reported FSD only, 18% LUTS/UI only, and 16% both FSD and LUTS/UI. Table 1 summarizes the sociodemographic, clinical, and diabetes-related characteristics of the study participants by ED and LUTS status and FSD and LUTS/UI status. Compared with men without ED and LUTS, men with ED and LUTS were significantly older, with higher time-weighted mean HbA<sub>1c</sub>, SBP, and triglyceride levels; prevalence of hypertension and self-reported use of BP medication; statin use; depression T-scores; and prevalence of microalbuminuria. Although women reporting both FSD and LUTS/UI were significantly older, were more likely to be postmenopausal, had higher depression T-scores, and had higher reported use of statins compared with women without FSD and LUTS/UI, the risk factor profile for women was not similar to men. Most notably, a significant difference in HbA<sub>1c</sub> between categories of FSD and LUTS/UI was not observed (Table 1). A large number ( $n = 198$ ) of women were excluded from analyses because of reporting no sexual activity. Importantly, there were no significant differences in covariates examined or in the associations observed between women who were excluded versus those included in the current analysis (data not shown).

The prevalence of DPN by ED/LUTS and FSD/LUTS/UI status is shown in Table 2. In unadjusted analyses, men with ED and LUTS at EDIC year 17 had a

**Table 1—Characteristics of DCCT/EDIC men and women by categories of urological complications at EDIC year 17**

	Men			Women			P	
	No LUTS or ED (n = 284)	ED only (n = 193)	LUTS only (n = 61)	ED and LUTS (n = 97)	No FSD or LUTS/UI (n = 153)	FSD only (n = 92)		LUTS/UI only (n = 65)
<b>Sociodemographic/clinical</b>								
Attained age (years)	49.3 ± 6.3	52.9 ± 6.2	51.4 ± 6.7	55.7 ± 5.7	47.3 ± 7.0	52.5 ± 7.0	48.7 ± 5.8	50.7 ± 7.2
Married/remarried	220 (77)	142 (74)	47 (77)	78 (80)	111 (73)	76 (84)	51 (78)	51 (84)
Current smoker	26 (9)	26 (14)	7 (11)	18 (19)	20 (13)	7 (7)	8 (12)	7 (11)
Current drinker	134 (47)	105 (55)	41 (67)	45 (46)	66 (43)	40 (44)	25 (38)	25 (41)
BMI (kg/m <sup>2</sup> )	28.5 ± 4.5	29.5 ± 4.9	28.0 ± 3.5	28.9 ± 5.6	28.1 ± 5.8	27.5 ± 5.3	28.8 ± 6.0	29.2 ± 5.4
BMI ≥30 kg/m <sup>2</sup>	93 (33)	84 (44)	17 (28)	32 (34)	42 (28)	21 (24)	26 (41)	19 (32)
Postmenopausal	—	—	—	—	60 (41)	59 (66)	27 (42)	35 (59)
Hysterectomy	—	—	—	—	23 (16)	16 (18)	9 (14)	11 (19)
Parity (n live births)								
0	—	—	—	—	74 (49)	58 (63)	33 (51)	36 (59)
1	—	—	—	—	29 (19)	15 (16)	13 (20)	12 (20)
≥2	—	—	—	—	49 (32)	19 (21)	19 (29)	13 (21)
Urinary tract infection (within past year)	—	—	—	—	25 (17)	12 (14)	14 (23)	11 (18)
SCL-90R depression T-score*	45.7 ± 12.2	50.1 ± 12.7	52.5 ± 16.6	58.5 ± 18.1	47.0 ± 10.5	50.3 ± 11.5	51.4 ± 13.4	57.4 ± 16.7
<b>Diabetes control and treatment</b>								
Primary prevention cohort	149 (52)	87 (45)	37 (61)	42 (43)	85 (56)	43 (47)	32 (49)	35 (57)
Intensive treatment group	144 (51)	96 (50)	29 (48)	46 (47)	69 (45)	48 (52)	37 (57)	34 (56)
DCCT/EDIC time-weighted HbA <sub>1c</sub> (%)	7.8 ± 0.9	8.2 ± 1.0	7.8 ± 1.0	8.1 ± 1.0	8.0 ± 0.9	8.0 ± 0.9	7.9 ± 1.0	8.0 ± 1.0
<b>Diabetes-related complications</b>								
Proliferative diabetic retinopathy	44 (15)	45 (23)	12 (20)	25 (26)	18 (12)	16 (17)	10 (15)	14 (23)
Microalbuminuria	33 (12)	52 (28)	13 (22)	30 (32)	15 (10)	10 (11)	8 (12)	2 (3)
<b>BP control (mmHg)</b>								
SBP	119.7 ± 12.9	125.1 ± 14.0	124.7 ± 13.5	125.9 ± 16.5	115.8 ± 13.7	121.1 ± 16.6	121.1 ± 14.5	120.7 ± 15.5
DBP	73.3 ± 9.1	73.3 ± 9.1	74.9 ± 8.9	71.3 ± 9.4	70.0 ± 9.1	70.9 ± 8.9	71.1 ± 9.0	70.8 ± 8.7
Hypertension†	183 (64)	150 (78)	39 (64)	78 (80)	79 (52)	61 (56)	39 (60)	37 (61)
<b>Antihypertensive medication use</b>								
β-Blockers	21 (7)	30 (16)	2 (3)	18 (19)	11 (8)	11 (13)	7 (11)	9 (15)
ACE inhibitors or ARBs	155 (55)	131 (68)	32 (54)	66 (69)	65 (45)	38 (44)	32 (51)	31 (51)
Calcium channel blockers	15 (5)	21 (11)	6 (10)	13 (14)	7 (5)	6 (7)	5 (8)	6 (10)
<b>Lipids</b>								
Total cholesterol (mg/dL)	166.4 ± 35.7	164.2 ± 37.5	177.3 ± 46.6	164.7 ± 37.5	178.5 ± 31.7	184.5 ± 38.9	176.3 ± 39.9	182.9 ± 29.7
HDL-C (mg/dL)	54.9 ± 15.6	54.2 ± 14.8	56.0 ± 14.3	54.8 ± 16.6	68.2 ± 19.6	67.2 ± 16.6	67.1 ± 17.9	67.8 ± 16.8
LDL-C (mg/dL)	95.4 ± 31.2	91.9 ± 30.0	96.8 ± 30.1	91.2 ± 33.8	97.0 ± 25.4	99.8 ± 31.5	94.6 ± 32.5	100.7 ± 26.4
Triglycerides (mg/dL)	80.7 ± 47.2	88.5 ± 64.8	121.8 ± 188.7	93.9 ± 57.4	66.6 ± 36.2	81.3 ± 53.1	73.2 ± 45.8	72.2 ± 38.5
Statin medication use	167 (59)	146 (76)	42 (71)	74 (78)	52 (36)	45 (52)	29 (46)	32 (52)

Data are mean ± SD or n (%). P values are based on the Kruskal-Wallis test for quantitative variables or the  $\chi^2$  test for qualitative variables for differences between any of the four groups. Boldface indicates significance at P < 0.05. ARB, angiotensin receptor blocker; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol. \*Based on SCL-90R scores that are converted to standard T-scores by referring to the appropriate population-based norm tables. †Hypertension defined as sitting SBP ≥140 mmHg and/or DBP ≥90 mmHg or the use of antihypertensive medication.

**Table 2—Frequency of DPN measures by category of urological complications at EDIC year 17**

	No ED or LUTS (n = 284)	ED only (n = 193)	LUTS only (n = 61)	ED and LUTS (n = 97)	P
<b>Men</b>					
EDIC year 1					
MNSI examination score $\geq 2.5$	45 (16)	54 (29)	10 (17)	37 (40)	<b>&lt;0.0001</b>
MNSI questionnaire score $\geq 4$	46 (17)	45 (24)	15 (25)	35 (38)	<b>0.0005</b>
EDIC year 14					
Confirmed DPN*	59 (22)	77 (41)	17 (31)	54 (62)	<b>&lt;0.0001</b>
MNSI examination score $\geq 2.5$	72 (28)	83 (44)	13 (23)	50 (56)	<b>&lt;0.0001</b>
MNSI questionnaire score $\geq 4$	60 (22)	67 (36)	19 (33)	55 (61)	<b>&lt;0.0001</b>
EDIC year 17					
MNSI examination score $\geq 2.5$	90 (32)	85 (45)	19 (33)	56 (59)	<b>&lt;0.0001</b>
MNSI questionnaire score $\geq 4$	71 (25)	75 (40)	23 (40)	59 (62)	<b>&lt;0.0001</b>
EDIC years 1–17					
Sustained MNSI examination score $\geq 2.5$	127 (45)	119 (62)	21 (34)	70 (72)	<b>&lt;0.0001</b>
Sustained MNSI questionnaire score $\geq 4$	14 (5)	23 (12)	7 (11)	36 (37)	<b>&lt;0.0001</b>
<b>Women</b>					
EDIC year 1					
MNSI examination score $\geq 2.5$	26 (19)	16 (18)	12 (19)	7 (11)	0.6056
MNSI questionnaire score $\geq 4$	29 (21)	21 (24)	14 (22)	14 (22)	0.9374
EDIC year 14					
Confirmed DPN*	24 (17)	21 (25)	9 (15)	11 (20)	0.3948
MNSI examination score $\geq 2.5$	54 (38)	19 (22)	15 (25)	16 (28)	0.0588
MNSI questionnaire score $\geq 4$	35 (24)	21 (24)	20 (33)	25 (44)	<b>0.0319</b>
EDIC year 17					
MNSI examination score $\geq 2.5$	47 (33)	34 (40)	14 (23)	22 (36)	0.1615
MNSI questionnaire score $\geq 4$	41 (29)	31 (36)	23 (37)	24 (40)	0.3521
EDIC years 1–17					
Sustained MNSI examination score $\geq 2.5$	73 (48)	46 (50)	26 (40)	26 (43)	0.5738
Sustained MNSI questionnaire score $\geq 4$	12 (8)	12 (13)	8 (12)	8 (13)	0.5001

Data are n (%). P values are based on the Kruskal-Wallis test for quantitative variables or  $\chi^2$  test for qualitative variables for differences between any of the four groups. Boldface indicates significance at  $P < 0.05$ . \*Confirmed DPN defined as two or more positive responses among symptoms, sensory signs, and ankle reflex changes consistent with distal symmetrical polyneuropathy plus nerve conduction abnormalities involving two or more nerves among the median, peroneal, and sural nerves.

higher prevalence of DPN at all time points, defined as either confirmed DPN at EDIC year 13/14 or as abnormal MNSI examination and questionnaire scores at EDIC years 1, 14, and 17, compared with participants without ED or LUTS. The highest DPN prevalence was observed among men reporting both ED and LUTS, with 62% with confirmed DPN at EDIC year 13/14 and 72% with sustained DPN based on examination vs. 22% and 45% among those with no ED or LUTS, respectively ( $P < 0.0001$  for both). There were no significant differences in DPN prevalence between women reporting both FSD and LUTS/UI and those without FSD or LUTS/UI at EDIC year 1 or 17. However, among women, there was a significant difference in prevalence of symptomatic DPN reported at EDIC year 14 based on abnormal scores on the MNSI questionnaire ( $P = 0.03$ ).

The odds of reporting ED and LUTS and FSD and LUTS/UI by measures of DPN adjusted for sex-specific risk factors are shown in Table 3. Adjusted for potential confounders, among men the odds of ED and LUTS versus no ED or LUTS at EDIC year 17 were 3.52 (95% CI 1.69, 7.31) times greater in those with confirmed DPN at EDIC year 13/14 than in those without confirmed DPN. Additionally, men with abnormal MNSI examination or questionnaire scores at EDIC years 1, 14, and 17 had significantly higher odds of ED and LUTS versus no ED or LUTS at EDIC year 17 than men without DPN. Finally, men with sustained DPN based on abnormal MNSI questionnaire scores at two or more consecutive visits had significantly higher odds of ED and LUTS versus no ED or LUTS at EDIC year 17 than those without sustained DPN (odds ratio [OR] 4.24 [95% CI 1.68, 10.69]).

Among women, there were no statistically significant associations between any measures of DPN at EDIC years 1 and 17 and reports of FSD and UI at EDIC year 17 after adjustment for potential confounders. At EDIC year 14, women with abnormal MNSI examination scores had a decreased odds of FSD only versus no FSD or LUTS/UI at EDIC year 17 than women without DPN (OR 0.33 [95% CI 0.16, 0.69]).

## CONCLUSIONS

This study examined the association between measures of DPN and ED/LUTS and FSD/UI among a large and well-phenotyped cohort of men and women with T1D participating in the DCCT/EDIC study. These data provide strong evidence that DPN is associated with ED and LUTS in men and are in concert with our prior reports demonstrating an association of ED/LUTS with peripheral

**Table 3—Association of DPN measures and urological complications at EDIC year 17**

	ED only vs. no ED or LUTS	LUTS only vs. no ED or LUTS	ED and LUTS vs. no ED or LUTS
<b>Men</b>			
EDIC year 1			
MNSI examination score $\geq 2.5$	1.61 (0.93, 2.78)	1.10 (0.45, 2.64)	<b>2.67 (1.26, 5.64)</b>
MNSI questionnaire score $\geq 4$	1.29 (0.75, 2.23)	1.31 (0.60, 2.86)	<b>2.09 (1.01, 4.31)</b>
EDIC year 14			
Confirmed DPN*	1.42 (0.86, 2.35)	1.17 (0.52, 2.63)	<b>3.52 (1.69, 7.31)</b>
MNSI examination score $\geq 2.5$	1.59 (0.99, 2.55)	0.74 (0.34, 1.64)	<b>2.10 (1.06, 4.14)</b>
MNSI questionnaire score $\geq 4$	1.25 (0.76, 2.05)	1.69 (0.83, 3.44)	<b>3.62 (1.81, 7.24)</b>
EDIC year 17			
MNSI examination score $\geq 2.5$	0.95 (0.59, 1.53)	0.68 (0.33, 1.40)	1.57 (0.82, 3.00)
MNSI questionnaire score $\geq 4$	1.34 (0.84, 2.15)	<b>2.21 (1.10, 4.44)</b>	<b>2.37 (1.22, 4.59)</b>
EDIC years 1–17			
Sustained MNSI examination score $\geq 2.5$	1.35 (0.85, 2.15)	0.54 (0.26, 1.12)	1.97 (1.00, 3.87)
Sustained MNSI questionnaire score $\geq 4$	1.41 (0.61, 3.24)	1.32 (0.37, 4.75)	<b>4.24 (1.68, 10.69)</b>
<b>Women</b>			
	FSD only vs. no FSD or LUTS/UI	UI only vs. no FSD or LUTS/UI	FSD and UI vs. no FSD or LUTS/UI
EDIC year 1			
MNSI examination score $\geq 2.5$	0.86 (0.38, 1.96)	0.92 (0.40, 2.13)	0.60 (0.22, 1.66)
MNSI questionnaire score $\geq 4$	1.03 (0.46, 2.30)	1.06 (0.46, 2.43)	1.02 (0.41, 2.51)
EDIC year 14			
Confirmed DPN*	1.39 (0.64, 3.00)	0.64 (0.26, 1.59)	1.17 (0.46, 2.95)
MNSI examination score $\geq 2.5$	<b>0.33 (0.16, 0.69)</b>	0.48 (0.23, 1.01)	0.71 (0.33, 1.54)
MNSI questionnaire score $\geq 4$	0.76 (0.36, 1.59)	1.11 (0.54, 2.28)	1.58 (0.73, 3.41)
EDIC year 17			
MNSI examination score $\geq 2.5$	1.07 (0.56, 2.05)	0.52 (0.24, 1.12)	1.25 (0.60, 2.62)
MNSI questionnaire score $\geq 4$	1.13 (0.59, 2.18)	1.25 (0.63, 2.45)	1.30 (0.62, 2.75)
EDIC years 1–17			
Sustained MNSI examination score $\geq 2.5$	0.86 (0.46, 1.59)	0.60 (0.31, 1.15)	0.72 (0.35, 1.47)
Sustained MNSI questionnaire score $\geq 4$	1.24 (0.46, 3.34)	1.48 (0.55, 4.00)	1.39 (0.47, 4.07)

Data are OR (95% CI) from six separate multivariable logistic regression models. The ORs were evaluated according to the presence or absence of confirmed DPN. For men, adjustments were made for age, drinking status, BMI, SCL-90R depression T-score, DCCT/EDIC time-weighted mean HbA<sub>1c</sub>, microalbuminuria, hypertension, triglycerides, and statin medication use. For women, adjustments were made for age, menopausal status, SCL-90R depression T-score, SBP, and statin medication use. Boldface indicates significance at  $P < 0.05$ . \*Confirmed DPN defined as two or more positive responses among symptoms, sensory signs, and ankle reflex changes consistent with distal symmetrical polyneuropathy plus nerve conduction abnormalities involving two or more nerves among the median, peroneal, and sural nerves.

neuropathy (1) and CAN (7), strengthening the pathogenetic link between neuropathic and urological complications in men with T1D. Consistent with our previous reports (1,8), we observed little to no impact of DPN on FSD/UI in women.

Prior studies have reported associations between ED and DPN, but the results have been inconsistent. For instance, in a small study that included 49 men with ED who were phenotyped for DPN on the basis of nerve conduction and quantitative sensory testing, DPN was not associated with ED (26). In contrast, the opposite was true in another small study of 30 subjects with type 2 diabetes (T2D) with symptomatic ED and 30 subjects without ED who were matched for age. In that study, DPN was most common in patients with ED (27). Finally, in a large cross-sectional study that included >2,000 men across 143 health care practices in Italy, a

history of diabetic neuropathy was associated with an increased risk of ED (28). The pathogenesis of ED in diabetes is multifactorial, but experimental evidence suggests an important role for neuropathy. Male erectile function is sustained by vascular and neuronal feedback loops. The sensory nervous system likely plays a role in these loops by mediating feedback through impaired nitric oxide release and nitric oxide synthase function of nonadrenergic noncholinergic neurons, decreased smooth muscle relaxation of the corpus cavernosum, impaired sensation of the glans, and abnormal motor function of skeletal muscles participating in erection (9).

Compared with ED, there are limited studies on predictors of FSD in diabetes. Although FSD that is due to diabetes is likely multifactorial, a neurogenic component has been proposed, albeit mostly autonomously mediated. A small study

found that women with diabetes had reduced reflexive capillary engorgement measured by vaginal photoplethysmography in response to erotic stimuli compared with control subjects without diabetes (29). Consistent with our findings, another study evaluated biothesiometric (vibratory) sensation of multiple genital and extragenital sites among 30 women with diabetes and 20 control subjects (11). Although women with diabetes showed significantly higher mean FSFI-R scores and higher biothesiometric values (reduced sensation) at each genital and extragenital site, there was no significant difference in biothesiometric values between women with diabetes with and without FSD. While we largely observed little to no impact of DPN on FSD in our cohort overall, we did find a significant decreased odds of FSD only in women with abnormal MNSI examination scores at EDIC year 14. These findings suggest

that denervation of peripheral nerves associated with DPN may involve, beyond the classical stocking-and-glove neuropathy, sensation of the genital areas. As pain with intercourse is a component of FSD, women with DPN may report less FSD because of general loss of sensation and decreased pain intensity.

Several explanations can be offered to account for the different pattern of urological complications, specifically sexual dysfunction, in men and women. It is possible, for example, that these differences in sex risk factor profiles are due to differences in the underlying physiological mechanisms (e.g., differences in neurotransmitter involvement) of sexual response in men and women (30,31). Additionally, it has been suggested that diabetes-related vasculopathy or neuropathy might be less readily perceived by women and that women with diabetes might not be aware of a relative decreased lubrication response and therefore not likely to report it (32), in contrast to men who readily experience and report ED. Alternatively, it has been proposed that in general, cultural and/or psychosocial factors may play a larger role in female sexuality and that depression is a more prevalent and potentially more impactful factor in women (33).

Likewise, beyond studies of bladder dysfunction and prevalence, there are limited data on mechanisms and predictors of bladder dysfunction in diabetes, particularly in women. Mechanistically, alterations in bladder innervation, detrusor smooth muscle function, and urothelial dysfunction may contribute to overall bladder dysfunction and UI (13,34). Physiological evaluation of neuropathy in diabetes as a marker of bladder dysfunction has been explored in two previous studies (35,36). In a study of 52 men with diabetes, Bansal et al. (35) reported an association between autonomic and peripheral neuropathy and diabetic cystopathy. Sympathetic skin response and motor and sensory nerve condition studies of the hands and feet were moderately predictive of urodynamic profiles consistent with diabetic cystopathy. Similarly, Ueda et al. (36) found an association between decreased sympathetic skin response and cystometrogram findings in 23 patients with diabetes and 10 control subjects without diabetes. Although the mechanisms are still

debated, reduced bladder sensation in diabetes is attributable to lesions involving peripheral afferent fibers, particularly A $\delta$  (myelinated)/C (unmyelinated) small-diameter distal fibers, with additional damage of the mechanosensitive afferent nerves and impaired transmission to the spinal cord (12). Some earlier human studies reported that vesicourethral dysfunction is highly correlated with abnormal nerve conduction velocity in diabetes (37). In addition, the autonomic nervous system plays a central role in the regulation of the urinary bladder function (38). Experimental evidence suggests that sympathetic stimulation regulates urine storage, whereas parasympathetic activation predominates during voiding (39). More recent data from human studies support a continuous interplay between sympathetic and parasympathetic innervation, with complex, mutually interacting mechanisms involving muscarinic and adrenoceptors that control bladder smooth muscle reactivity and bladder afferent signaling (38).

Our study has several limitations. The lack of ED/LUTS and FSD/UI assessments concomitant with the full battery of confirmed DPN assessments is a notable limitation. However, during EDIC, both the full battery of confirmed DPN assessments and the MNSI were done concomitantly at years 13 and 14 and validated the use of the MNSI as an appropriate alternative to assess DPN annually (19). Furthermore, the confirmed DPN assessments at year 13/14 conducted before the assessment of urological complications is consistent with our hypothesis that neuropathy may be a predictor/potential cause of urinary and sexual dysfunction. We view this temporal sequence as a strength rather than as a limitation. Additionally, there were notable differences in exclusion criteria between men and women. While the use of the proxy item to assess erectile function allowed for the inclusion of men regardless of sexual activity, the FSFI-R was specifically validated to be used only in sexually active women. As a result, women who reported no sexual activity ( $n = 198$ ) were excluded from the analyses. Importantly, there were no significant differences in the covariates examined or in the associations observed between women who were excluded and those who were included in the current analysis (data not shown). Finally, the lack

of racial diversity of this cohort of men and women with T1D limits the generalizability of our results to other races or to patients with T2D.

Strengths of this study include the large sample size of men and women with T1D, the comprehensive DPN assessments performed by highly trained personnel using standardized procedures, and assessment of ED, LUTS, FSD, and UI using standardized and validated questionnaires. Additionally, patients T1D within DCCT/EDIC have been carefully evaluated for a vast array of risk factors besides glycemia that could affect both urological complications and DPN, including BP, lipids, obesity, smoking, alcohol consumption, other microvascular and macrovascular complications, medications, and quality of life.

In conclusion, in men with T1D participating in DCCT/EDIC, we found that the presence of DPN substantially increased the risk for ED and LUTS, even after extensive adjustments for other established and putative risk factors for DPN and urological complications. The association with FSD and LUTS/UI in women was inconsistent and observed for symptomatic DPN alone. Sex-related variation in these urological complications and their underlying mechanisms may explain some of these divergent findings. Future studies confirming the associations between DPN and development and progression of sexual and urinary dysfunction in other cohorts with T1D and T2D are warranted.

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**Author Contributions.** R.P.B., B.H.B., and A.V.S. designed the study, drafted the initial manuscript, and reviewed and edited subsequent versions of the manuscript. B.H.B. conducted the statistical analyses. H.W., W.H.H., C.L.M., and A.M.J. reviewed and edited the manuscript. B.H.B. 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.

**Data and Resource Availability.** Data collected for the DCCT/EDIC study through 30 June 2017 are available to the public through the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository (<https://repository.niddk.nih.gov/studies/edic>). Data collected in the current cycle (July 2017–June 2022) will be available within 2 years after the end of the funding cycle.

## References

- Wessells H, Braffett BH, Holt SK, et al.; DCCT/EDIC Study Group. Burden of urological complications in men and women with long-standing type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Diabetes Care* 2018;41:2170–2177
- Jacobson AM, Braffett BH, Cleary PA, et al.; DCCT/EDIC Research Group. Relationship of urologic complications with health-related quality of life and perceived value of health in men and women with type 1 diabetes: the Diabetes Control and Complications Trial/Epidemiology of Interventions and Complications (DCCT/EDIC) cohort. *Diabetes Care* 2015;38:1904–1912
- Pontiroli AE, Cortelazzi D, Morabito A. Female sexual dysfunction and diabetes: a systematic review and meta-analysis. *J Sex Med* 2013;10:1044–1051
- Wessells H. Insights and interventions in diabetes associated erectile dysfunction. *J Urol* 2013;190:15–16
- Wessells H, Penson DF, Cleary P, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive glycemic therapy on erectile function in men with type 1 diabetes. *J Urol* 2011;185:1828–1834
- Sarma AV, Kanaya AM, Nyberg LM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Urinary incontinence among women with type 1 diabetes—how common is it? *J Urol* 2009;181:1224–1230; discussion 1230
- Pop-Busui R, Hotaling J, Braffett BH, et al.; DCCT/EDIC Research Group. Cardiovascular autonomic neuropathy, erectile dysfunction and lower urinary tract symptoms in men with type 1 diabetes: findings from the DCCT/EDIC. *J Urol* 2015;193:2045–2051
- Hotaling JM, Sarma AV, Patel DP, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Cardiovascular autonomic neuropathy, sexual dysfunction, and urinary incontinence in women with type 1 diabetes. *Diabetes Care* 2016;39:1587–1593
- Kempler P, Amarencu G, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Management strategies for gastrointestinal, erectile, bladder, and sudomotor dysfunction in patients with diabetes. *Diabetes Metab Res Rev* 2011;27:665–677
- Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136–154
- Erol B, Tefekli A, Sanli O, et al. Does sexual dysfunction correlate with deterioration of somatic sensory system in diabetic women? *Int J Impot Res* 2003;15:198–202
- Tsunoyama K, Sakakibara R, Yamaguchi C, et al. Pathogenesis of reduced or increased bladder sensation. *NeuroUrol Urodyn* 2011;30:339–343
- Daneshgari F, Liu G, Birder L, Hanna-Mitchell AT, Chacko S. Diabetic bladder dysfunction: current translational knowledge. *J Urol* 2009;182(Suppl.):S18–S26
- Shamoon H, Cleary P, Barnie A, et al. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care* 1999;22:99–111
- The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): results of feasibility study. *Diabetes Care* 1987;10:1–19
- Albers JW, Herman WH, Pop-Busui R, et al. Effect of prior intensive insulin treatment during the DCCT on peripheral neuropathy in type 1 diabetes during the EDIC study. *Diabetes Care* 2010;33:1090–1096
- Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care* 1994;17:1281–1289
- Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* 2014;37:31–38
- Herman WH, Pop-Busui R, Braffett BH, et al.; DCCT/EDIC Research Group. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. *Diabet Med* 2012;29:937–944
- Rosen RC, Cappelleri JC, Gendrano N 3rd. The International Index of Erectile Function (IIEF): a state-of-the-science review. *Int J Impot Res* 2002;14:226–244
- Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multi-dimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;26:191–208
- Barry MJ, Fowler FJ Jr, O'Leary MP, et al.; The Measurement Committee of the American Urological Association. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol* 1992;148:1549–1557; discussion 1564
- Sandvik H, Hunskaar S, Vanvik A, Bratt H, Seim A, Hermstad R. Diagnostic classification of female urinary incontinence: an epidemiological survey corrected for validity. *J Clin Epidemiol* 1995;48:339–343
- Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. *Ophthalmology* 1991;98(Suppl.):741–756
- Derogatis L, Rickels K, Rock A. The SCL-90-R: Administration, Scoring and Procedures Manual II. Baltimore, MD, Clinical Psychometric Research, 1983
- Hecht MJ, Neundörfer B, Kiesewetter F, Hilz MJ. Neuropathy is a major contributing factor to diabetic erectile dysfunction. *Neurol Res* 2001;23:651–654
- De Angelis L, Marfella MA, Siniscalchi M, et al. Erectile and endothelial dysfunction in type II diabetes: a possible link. *Diabetologia* 2001;44:1155–1160
- Parazzini F, Menchini Fabris F, Bortolotti A, et al. Frequency and determinants of erectile dysfunction in Italy. *Eur Urol* 2000;37:43–49
- Wincze JP, Albert A, Bansal S. Sexual arousal in diabetic females: physiological and self-report measures. *Arch Sex Behav* 1993;22:587–601
- Basson R. Human sex-response cycles. *J Sex Marital Ther* 2001;27:33–43
- Chivers ML, Bailey JM. A sex difference in features that elicit genital response. *Biol Psychol* 2005;70:115–120
- Schreiner-Engel P, Schiavi RC, Vietorisz D, Smith H. The differential impact of diabetes type on female sexuality. *J Psychosom Res* 1987;31:23–33
- Enzlin P, Rosen R, Wiegel M, et al.; DCCT/EDIC Research Group. Sexual dysfunction in women with type 1 diabetes: long-term findings from the DCCT/EDIC study cohort. *Diabetes Care* 2009;32:780–785
- Frimodt-Møller C. Diabetic cystopathy. A review of the urodynamic and clinical features of neurogenic bladder dysfunction in diabetes mellitus. *Dan Med Bull* 1978;25:49–60
- Bansal R, Agarwal MM, Modi M, Mandal AK, Singh SK. Urodynamic profile of diabetic patients with lower urinary tract symptoms: association of diabetic cystopathy with autonomic and peripheral neuropathy. *Urology* 2011;77:699–705
- Ueda T, Yoshimura N, Yoshida O. Diabetic cystopathy: relationship to autonomic neuropathy detected by sympathetic skin response. *J Urol* 1997;157:580–584
- Mitsui T, Kakizaki H, Kobayashi S, Morita H, Matsumura K, Koyanagi T. Vesicourethral function in diabetic patients: association of abnormal nerve conduction velocity with vesicourethral dysfunction. *NeuroUrol Urodyn* 1999;18:639–645
- Ochodnický P, Uvelius B, Andersson KE, Michel MC. Autonomic nervous control of the urinary bladder. *Acta Physiol (Oxf)* 2013;207:16–33
- Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiol Rev* 2004;84:935–986