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Longitudinal patterns of occurrence and remission of erectile dysfunction in men with type 1 diabetes

Melody R. Palmer, PhD^a, Sarah K. Holt, PhD^a, Aruna V. Sarma, PhD, MHA^b, Rodney L. Dunn, MS^b, James M. Hotaling, MD, MS^c, Patricia A. Cleary, MS^d, Barbara H. Braffett, PhD^d, Patricia Gatcomb, APRN, MSN, CDE^e, Catherine Martin, MS, APRN, BC-ADM, CDE^f, William H. Herman, MD, MPH^{f,g}, Alan M. Jacobson, MD^h, and Hunter Wessells, MD^{a,i} the Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications Research Group

^aDepartment of Urology, University of Washington, 1959 NE Pacific St, Box 356510, Seattle, Washington, 98195

^bDepartment of Urology, University of Michigan, 1500 E Medical Center Drive, Ann Arbor, Michigan, 48109

^cDepartment of Urology, 50 N Medical Drive, Salt Lake City, Utah, 84132

^dThe Biostatistics Center, George Washington University, 6110 Executive Boulevard, Suite 750, Rockville, Maryland, 20852-3943

^eDepartment of Medicine, Yale University, 1 Long Wharf Dr, Ste 503, New Haven, Connecticut, 06511

^fInternal Medicine, University of Michigan, 1500 E Medical Center Drive, Ann Arbor, Michigan, 48109

^gDepartment of Epidemiology, University of Michigan, 1415 Washington Heights, 4667 SPH I, Ann Arbor, Michigan, 48109-2029

^hResearch Institute, Winthrop University Hospital, 222 Station Plaza N, Suite 300, Mineola, New York, 11501

ⁱDiabetes Research Center, University of Washington, 1959 NE Pacific St, Box 356510, Seattle, Washington, 98195

INTRODUCTION

Erectile dysfunction (ED) is a common problem among aging men. Men with diabetes have a 2-to 4-fold higher risk for ED [1], and experience greater severity, based on epidemiologic studies and pharmaceutical trials of phosphodiesterase 5 inhibitors [2]. Shared factors that

Corresponding author: Melody R. Palmer, 206-218-7220.

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influence ED risk in men with and without diabetes include aging, cigarette smoking, high blood pressure and high body mass index (BMI). A variety of diabetes-associated abnormalities, such as vascular and endothelial dysfunction, neuropathy, and hypertension, are major contributors to ED [3]. Better glycemic control in type 1 diabetes is associated with reduced prevalence of ED [4]; however, even men with well controlled diabetes remain at very high risk compared to men without diabetes.

ED is generally considered a permanent diagnosis, but several recent studies have shown that 21–29% of men experience remission from one assessment to another several years apart [5,6]. Younger men were more likely to experience remission of ED, consistent with psychological rather than organic factors, underlying its occurrence in youth. In contrast, men with diabetes (type 1 or type 2), dyslipidemia, angina, or lower urinary tract symptoms (LUTS) had a lower odds of remission [6]. However, no study has looked at a large population of men with diabetes using detailed longitudinal data. Diabetes complications such as peripheral neuropathy and nephropathy are thought to contribute to the earlier onset and greater severity of ED [3,7], but patterns and predictors for remission of ED are not well understood in this population because most cohorts have only a handful of patients with diabetes. Longer duration of diabetes is associated with an increase in degenerative neuropathy, which could affect reversibility of ED [8]. Verifying these findings in larger cohorts of men with diabetes is important; identifying factors that influence remission or reversibility of ED could lead to investigations of novel intervention or prevention strategies.

With up to 30 years of follow-up of the cohort in the Diabetes Control and Complications Trial (DCCT) and its observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), we were able to investigate the patterns and predictors of ED occurrence and remission. The consistent collection of standardized data over time in a large population of men with type 1 diabetes facilitated the study of the factors influencing remission. We hypothesized that the probability of regaining potency would be influenced by older age, poor glycemic control, and presence of other diabetes-related complications.

MATERIAL AND METHODS

Longitudinal data on ED status, diabetes and clinical parameters in DCCT/EDIC male participants were collected prospectively. The DCCT (1983–1993) enrolled 1441 patients with type 1 diabetes between the ages of 13 and 39, including 761 men. The DCCT was a randomized controlled clinical trial that examined the effects of intensive diabetes therapy compared with conventional therapy. The major outcomes were the development and progression of diabetes microvascular complications [9]. DCCT participants were enrolled into two cohorts, primary prevention or secondary intervention, based on diabetes duration and presence of existing complications. Intensive therapy was aimed at achieving glycemic control as close to the non-diabetic range as safely possible using multiple daily insulin injections or continuous subcutaneous insulin infusion with dose adjustment based on frequent daily blood glucose monitoring. Conventional therapy aimed at maintaining clinical well-being with 1–2 daily insulin injections and no specified glucose targets. The DCCT demonstrated major and consistent benefits of intensive therapy and intensive therapy was

recommended for all participants. Subsequently, 1375 (96%) of the subjects (n=720 men) agreed to participate in the EDIC follow-up study (1994-present).

The DCCT/EDIC annual exams included a single question assessing ED in men as follows: *'Has the patient experienced impotence/erectile dysfunction since the last completed annual visit?' Responses were Yes or No.* For purposes of the current study, the following exclusions were made: 1) men with fewer than 5 years of ED questionnaire responses over the entire 30-year study period; 2) men with fewer than 5 years of follow-up after the initial report of ED; and 3) men who never reported impotence and were not followed in EDIC past the age of 44. After the exclusions, there were no men reporting ED at DCCT entry. The men excluded have no systematic differences to the men included, other than age for men without ED who only had follow-up time at younger ages. The current report includes 600 men (83% of the original male cohort). (See Supplementary Material A for exclusion criteria sample sizes). The last exclusion criterion was applied since these men had not reached the median age of first report of ED and could not be considered a reliable reference group. In cases where ED data were missing but flanking years were present and congruent, ED status was imputed to the congruent value. Beginning at EDIC year 13 (~2004–2005), men were asked about their use of prescription medication to treat ED. For these analyses, if an individual reported use of ED medication but answered *No* on the annual impotence question or the answer was missing, their ED status was considered to be *Yes*. This resulted in a total of 79 ED status changes between 56 men. ED was also assessed using the International Index of Erectile Function at two time periods during EDIC.

We looked at concordance between IIEF and the *Yes/No* question at those two time points (Supplementary Materials, B, Figures S1 and S2). The following socio-demographic, clinical, and diabetes-related characteristics assessed annually from DCCT baseline to EDIC year 20 were examined in this study: age (years), smoking (current vs. former/never), education (high school graduate vs. some college or more), BMI (kg/m²), diastolic and systolic blood pressure (mm Hg), hypertension defined as use of hypertension medication, sbp $\geq$ 140, or dbp $\geq$ 90 [10], HbA1c (%) and duration of diabetes (years).

We examined patterns of ED over time by creating a heat map-style display, with a unit for each year of data for each participant, arranged by age of first report of ED. ED phenotype categories were assigned with a heuristic approach based on the patterns in the graph. Differences in clinical and socio-demographic variables at DCCT baseline by ED categories were tested using t-tests for continuous variables and chi-square tests for categorical variables. We examined associations between clinical and socio-demographic variables and ED categories using multivariable logistic models comparing participants in each of the ED categories to the reference group of participants who had never reported ED. We also compared variables at first report of ED between men in the two main ED categories.

The intermittent group included all patterns of Impotence *Yes/No* over the years, but we also looked at a more strictly defined group of men who experienced remission. This group included men with 2 or more years of Impotence=*Yes* followed by 2 or more years of Impotence=*No*. We then compared the characteristics of these men to men with persistent ED at their first year of ED with multivariable logistic regression.

All analyses were conducted in R (<https://www.R-project.org/>).

RESULTS

Among men reporting at least one year of ED ($n=368$, 61.3%), the age at the first report of a single year of ED ranged from 18 to 63 years (mean = 43.3, standard deviation [SD] = 7.0 years). The mean number of assessments for each subject was 23.4. We identified four categories in this population over time: 232 (38.7%) men never reported ED (Never), 40 (6.7%) reported ED one or two consecutive years only (Isolated), 251 (41.8%) changed status from ED to no ED and back to ED at least one time (Intermittent), and 77 (12.8%) reported ED continuously after the first report of impotence (Persistent). There was no difference in the mean or median years measured between the ED phenotype categories. One hundred and fifty-one men (41.0% of all ED cases) reported treatment for ED. Longitudinal patterns of ED by age are presented in Figure 1.

We compared demographic and clinical variables at DCCT baseline between those never reporting ED vs. each ED category separately (Table 1). At DCCT baseline, men in the Isolated group resembled men who never reported ED. At DCCT baseline, compared to men never reporting ED, men in the Intermittent group were more likely to be older ($p=0.00014$), overweight or obese ($p=0.0014$), have higher HbA1c ($p=0.00061$), and have been in the conventional treatment group during the DCCT ($p=0.013$). Men with Persistent ED were also older ($p<0.0001$), with higher BMI ($p<0.0001$) and HbA1c ($p=0.0034$), and were more often current smokers ($p=0.04$) compared to men in the No ED group. Report of oral ED medication use was most common in the Persistent group (Supplementary Materials, C, Table S1).

We investigated whether men in the Intermittent and Persistent categories differed at their first year reporting ED (Table 2). Age at first report of ED was modestly but significantly lower in Intermittent (43.7 ± 6.3 years), compared to Persistent (46.8 ± 6.8 ; $p=0.009$). HbA1c was not significantly different between Intermittent and Persistent ED ($p=0.14$). In a multivariable logistic model of variables at the first year of ED, men in the Persistent category were older and had higher HbA1c levels than men with Intermittent ED when adjusted for BMI, diabetes duration, smoking, hypertension, education, and DCCT treatment group and primary or secondary intervention cohort.

In the current study, 291 of 368 men who ever reported ED (79.1%) subsequently reported at least one year of remission. Within a three-year window after intervals of 1 to 5 consecutive years of ED following the initial reporting, the remission rates ranged from 59.9% to 23.7%. A subset of 85 (23.1% of ED-reporting men) men fit a more strict definition of remission, requiring 2 consecutive years answering “No.”

Some men in the intermittent group had multiple switches in ED status, but none of both or either at two consecutive years. Due to our concern that these apparent single year remission events were due to issues unrelated to the men’s physiologic function, we extracted a more strictly defined group of men who reported remission intervals of two or more consecutive years. The remitters group contained 85 men. In a multivariable logistic model comparing 68

of these men (those with no missing demographic and clinical data at their first year of ED), men who were older had lower odds of remission and men who were in the Conventional DCCT treatment group had higher odds of remission (Table 2).

DISCUSSION

A large proportion of men with type 1 diabetes and ED experienced one or more periods of remission over a mean follow-up of 26.9 years. We discovered distinct longitudinal patterns of ED, which highlights the importance of assessing ED over time versus at a single point in time. Our results showed that younger men with better glycemic control and earlier ED onset were more likely to be in the group with Intermittent ED, suggesting younger men may have more modifiable risk factors than men who initially present with ED at an older age.

Comparing subjects in the Remission and Persistent groups, men in the Conventional DCCT treatment group were more likely to experience remission. This was surprising to us because overall ED risk is higher in the Conventional group. Men in the Persistent group are older at their first ED, thus likely to be farther from DCCT, where men in the Conventional group had greater variation in their glycemic control. Our theory is that younger men in the Conventional group who first had ED in DCCT were more likely to remit once they entered ED and their glucose levels stabilized.

In the DCCT/EDIC study, the overall ED risk was influenced by commonly known factors such as age, BMI, and smoking, but older age and poor glycemic control during the first year following initial reporting of ED were most predictive of persistent ED. Several studies have examined ED remission in population cohorts, comparing two time points. In the first stage of the Massachusetts Male Aging Study (MMAS), age and BMI were associated with progression (as measured by occurrence or increasing severity) and remission, while smoking and self-assessed health status were associated with progression [11]. Only age was significant in multivariable models of remission and progression in population samples from a follow-up study in MMAS and in the Men's Attitudes to Life Events and Sexuality (MALES) [5]. In the Florey Adelaide Male Ageing Study (FAMAS) age, diabetes (both types), dyslipidemia, angina, and voiding lower urinary tract symptoms (LUTS) were all associated with lower odds of remission after adjustment for employment status, anxiety, and obstructive sleep apnea [6].

In MALES, MMAS, and FAMAS, remission rates among men with and without diabetes were 25%, 29%, and 21% for 3, 5, and 7 year follow-up intervals, respectively [5,6]. In a study of men with type 1 or 2 diabetes, 11 of 128 men with ED (8.6%) reported remission in a 5-year follow up [12]. In a population-based cohort of men with type 1 diabetes in Wisconsin, 9 of 53 men with ED (17.0%) reported remission of ED at a 10-year follow up [13]. In a study of men with type 2 diabetes using an 18-month mean follow-up, 22.6% of men who reported ED in the initial visit reported improvement [14]. Our remission rates for similar time ranges do fall within the range of previous studies, but annual assessment and longer overall follow-up time in the DCCT/EDIC allowed us to capture a more refined view of ED occurrence and remission than has been possible before. Differences in remission

rates between our study and others could be due to the age of the cohort, measures used to assess ED, and lower sampling frequency resulting in different temporal resolution of the data.

The pathophysiology of younger men with ED may be more modifiable than the irreversible complications that come with age and longer diabetes duration. We observed that younger men were more likely to experience a return to potency after reporting ED, even after adjusting for multiple risk factors. In men with diabetes, the presence of other diabetes complications may influence ED risk. The accumulation of advanced glycation endproducts (AGEs) leads to autonomic neuropathy in a nitric oxide dependent manner, and nitric oxide is a key component of erectile function [8]. Remission has been observed in other diabetes complications. For example, Perkins et al. found that regression of microalbuminuria in type 1 diabetes was common in people who were younger and had lower HbA1c, total cholesterol, and triglycerides [15]. Improvement in HbA1c levels in men with type 2 diabetes have been shown to lead to better IIEF scores[16]. The results of the current study could be used to motivate behavioral changes for intervention in men at first onset of ED.

EDIC participants experiencing remission of ED provides a unique opportunity to investigate whether men with persistent versus remitting ED have similar or different pathophysiological mechanisms. From a diabetes practice perspective, these findings strongly suggest that at the first signal of ED, clinicians should review all potential risk factors, and identify potential interventions (e.g. improved glycemic control, weight loss, smoking cessation) that might delay or prevent the development of irreversible ED.

Longitudinal data collection on other health conditions and diabetic complications is ongoing in EDIC. Future work should examine the timing of the onset of these complications relative to ED and potential differences in pathophysiology between the categories. Our theory is that there is a reversible and irreversible phase of diabetes-related ED, but we should also investigate an alternative hypothesis: that ED in younger men is more often psychogenic and thus more likely to be transient, while later onset ED is more likely to be organic and irreversible. An annual question about psychiatric events could be compared to ED status, as well as more detailed measures of mental health and quality of life that were surveyed at EDIC year 17 [17]. Additional work should look at the differences in ED risk between men with type 1 and type 2 diabetes, given the differing ED mechanisms observed in animal models of each diabetes type[18].

A primary limitation of our study is the *Yes/No* binary definition of ED based on the term “impotence”, which has a potentially pejorative connotation. It does not provide severity information. However, we expect that men respond consistently over the years, and comparison with IIEF measures at selected years showed good concordance (Supplemental Figures S1 and S2). In contrast, other studies have based remission on a reduction in severity (IIEF for FAMAS, single question for MALES and MMAS). Adding PDE5-I use as part of the ED definition improved detection of men who were sexually active but reported no ED because their treatment is successful. EDIC annual data collection beginning in 2010 includes an additional question that will better approximate severity. The question is “*How*

would you rate your confidence that you get and keep your erection?" and the answer choices are *Very Low, Low, Moderate, High, or Very High*.

Another limitation is the generalizability of this cohort to other men with type 1 diabetes. Men in the DCCT/EDIC were selected and self-selected, and patients with hypertension and dyslipidemia at DCCT baseline were excluded. A cross section of the population of men with type 1 diabetes may have higher prevalence of ED and a wider range of glycemic control, suggesting a greater opportunity for identification and early intervention. These results can inform providers and patients that maintaining a healthy weight and tight glycemic controls are the best ways to manage ED.

CONCLUSIONS

Age, glycemic control, and BMI were important longitudinal predictors of ED. We have described a more complex ED phenotype, with variation in remission patterns, which may offer insight into differing mechanisms or opportunities for intervention. If validated in other cohorts, such findings could be used to establish more accurate prognostication of outcomes for patients with ED to guide individualized interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Longitudinal patterns of ED in DCCT/EDIC. Each box is a single year for a single participant, arranged by age on the x axis. White squares represent missing data. The participants are grouped by ED subphenotype, and within groups arranged by censor age (Never ED men) or age of first ED (Isolated, Intermittent, and Persistent ED men). Men in the intermittent group have 2 to 8 changes in ED status.

Table 1

Demographic and clinical variables at DCCT baseline by phenotype category of ED as shown in Figure 1. P-values refer to t-test or chi-squared test for each ED category compared with Never ED. Data are mean $\pm$ SD or n (%). Bold indicates $p < 0.05$ between Never and ED category (t-test or chi-square).

Variables DCCT baseline	Never N=232	Isolated N=40	Intermittent N=251	Persistent N=77
Age (years)	27.1 $\pm$ 5.7	27.7 $\pm$ 5.2 p=0.53	29.2 $\pm$ 6.3 p=0.000141	30.6 $\pm$ 6.0 p<0.0001
BMI (kg/m ²)	23.2 $\pm$ 2.5	23.1 $\pm$ 2.5 p=0.80	24.2 $\pm$ 2.9 p<0.0001	24.8 $\pm$ 2.6 p<0.0001
BMI category				
Normal BMI <25 kg/m ²	181 (78.0)	32 (80.0)	158 (62.9)	45 (58.4)
Overweight BMI 25–30 kg/m ²	47 (20.3)	8 (20.0)	84 (33.5)	30 (39.0)
Obese BMI $\geq$ 30 kg/m ²	4 (1.7)	0 (0) p=0.70	9 (3.6) p=0.001	2 (2.6) p=0.003
Diabetes Duration (years)	5.5 $\pm$ 4.0	4.9 $\pm$ 4.0 p=0.43	5.6 $\pm$ 4.1 p=0.61	4.9 $\pm$ 3.7 p=0.26
HbA1c (%) (mmol/mol)	8.7 $\pm$ 1.4 (72 $\pm$ 15.3)	8.5 $\pm$ 1.5 (69 $\pm$ 16.4) p=0.53	9.1 $\pm$ 1.5 (76 $\pm$ 16.4) p=0.0006	9.3 $\pm$ 1.6 (78 $\pm$ 17.5) p=0.003
Smoking				
Never	184 (79.3)	30 (75.0)	178 (70.9)	53 (68.8)
Former	4 (1.7)	1 (2.5)	7 (2.8)	0 (0)
Current	44 (19.0)	9 (22.5) p=0.76	66 (26.3) p=0.07	24 (31.2) p=0.04
Systolic blood pressure (mm Hg)	117.7 $\pm$ 11.3	115.1 $\pm$ 12.0 p=0.21	118.5 $\pm$ 10.5 p=0.43	118.6 $\pm$ 11.7 p=0.55
Education				
High school graduate	35 (15.1)	8 (20.0)	41 (16.3)	11 (14.3)
Some college	197 (84.9)	32 (80.0) p=0.58	210 (83.7) p=0.80	66 (85.7) p=0.99
Treatment Group				
Conventional	105 (45.3)	19 (47.5)	143 (57.0)	40 (51.9)
Intensive	127 (54.7)	21 (52.5) p=0.93	108 (43.0) p=0.01	37 (48.1) p=0.37
Enrollment Cohort				
Primary	117 (50.4)	18 (45.0)	121 (48.2)	42 (54.5)
Secondary	115 (49.6)	22 (55.0) p=0.64	130 (51.8) p=0.69	35 (45.5) p=0.62

Table 2

Variables at first report of ED comparing the Persistent ED group to the Intermittent and a subgroup of Intermittent with 2 or more years of consecutive remission. Values reported are mean $\pm$ SD or n (%), p-values refer to comparison of Intermittent or Remission to Persistent. Bold indicates $p < 0.05$. Hypertension defined as use of hypertension medication, sbp ≥ 140 , or dbp ≥ 90 . All values may not add up to total due to missing data.

Variables at index ED year	Intermittent n=206	Remission subgroup N=68	Persistent n=71
Age (years)	43.7 $\pm$ 6.3	42.6 $\pm$ 5.6 p=0.001	46.8 $\pm$ 6.8 p=0.009
BMI category			
Normal BMI <25	55 (26.7)	23 (33.8)	14 (19.7)
Overweight BMI 25–30	88 (42.7)	31 (45.6)	28 (39.4)
Obese BMI ≥ 30	55 (26.7)	13 (19.1) p=0.05	28 (39.4) p=0.14
Diabetes Duration (years)	20.1 $\pm$ 6.3	19.1 $\pm$ 5.8 p=0.22	20.4 $\pm$ 6.1 p=0.72
HbA1c (%)	8.4 $\pm$ 1.2	8.6 $\pm$ 1.3 p=0.95	8.6 $\pm$ 1.3 p=0.25
Smoking			
Never/Former	165 (80.1)	55 (80.9)	54 (76.1)
Current	41 (19.9)	13 (19.1) p=0.62	17 (23.9) p=0.58
Hypertension			
No	93 (45.1)	33 (48.5)	31 (43.7)
Yes	113 (54.9)	35 (51.5) p=0.68	40 (56.3) p=0.94
Education			
High school graduate	22 (10.6)	4 (5.9)	5 (7.0)
Some college	179 (86.9)	62 (91.2) p=0.34	66 (93.0) p=0.48
Treatment Group			
Conventional	119 (57.8)	51 (75.0)	35 (49.3)
Intensive	87 (42.2)	17 (25.0) p=0.003	36 (50.7) p=0.27
Enrollment Cohort			
Primary	107 (51.9)	31 (45.6)	39 (54.9)
Secondary	99 (48.1)	37 (54.4) p=0.35	32 (45.1) p=0.77

Table 3

Multivariable logistic models for variables at first report of ED comparing the Persistent ED group to the Intermittent and a subgroup of Intermittent with 2 or more years of consecutive remission. Intermittent and Remission are the reference groups in their respective columns. Bold indicates $p < 0.05$.

Variables at index ED year	Persistent v. Intermittent OR (CI)	Persistent v. Remission OR (CI)
Age (years)	1.07 (1.02–1.13) p=0.001	1.09 (1.01–1.18) p=0.03
BMI category		
Normal BMI <25	ref	Ref
Overweight BMI 25–30	1.30 (0.61–2.86) p=0.50	1.39 (0.54–3.63) p=0.50
Obese BMI ≥30	1.81 (0.82–4.11) p=0.15	2.55 (0.87–7.74) p=0.09
Diabetes Duration (years)	0.99 (0.93–1.06) p=0.85	1.01 (0.92–1.10) p=0.85
HbA1c (%)	1.29 (1.01–1.66) p=0.04	1.25 (0.91–1.76) p=0.18
Smoking		
Never/Former	ref	Ref
Current	1.54 (0.74–3.15) p=0.24	1.34 (0.49–3.71) p=0.56
Hypertension		
No	ref	Ref
Yes	1.01 (0.55–1.86) p=0.97	0.96 (0.43–2.13) p=0.92
Education		
High school graduate	0.70 (0.42–1.38)	1.35 (0.26–7.28)
Some college	ref p=0.53	Ref p=0.72
Treatment Group		
Conventional	0.79 (0.46–1.36)	0.38 (0.17–0.83)
Intensive	ref p=0.37	Ref p=0.02
Enrollment Cohort		
Primary	ref	Ref
Secondary	0.86 (0.43–1.71) p=0.66	0.53 (0.21–1.29) p=0.17