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Blood pressure, anti-hypertensive medication use and risk of erectile dysfunction in men with type I diabetes

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Abstract

Objective: To gain insight into the effect of blood pressure on the pathophysiology of diabetic erectile dysfunction, we determined the onset, severity and treatment of hypertension and risk of incident erectile dysfunction in men with type I diabetes.

Methods: This prospective cohort study included 692 men without prevalent erectile dysfunction in the Epidemiology of Diabetes Interventions and Complications study. Erectile dysfunction was assessed yearly for 16 years with a single question querying presence of impotence. Multivariable cox proportional hazards models examined associations of hypertension variables with risk for incident erectile dysfunction.

Results: Over 7,762 person-years of follow-up, 337 of 692 men reported incident erectile dysfunction representing an unadjusted rate of 43.4 cases per 1000 person-years. Risk of erectile dysfunction significantly increased with each 10mmHg of systolic blood pressure elevation for those not taking anti-hypertensive medications, after adjustment for age, cigarette smoking and HbA1c levels (RR=1.21, 95% CI=1.04, 1.41). This relationship disappeared among those reporting

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anti-hypertensive medication use (RR=0.96, 95% CI=0.84, 1.10) and the interaction between SBP and medication use was statistically significant ($p=0.02$). Anti-hypertensive medication did not confer any reduction of ED risk, with similar rates across all measures of blood pressure and hypertension.

Conclusion: Among men with type 1 diabetes not using antihypertensive medications, higher systolic blood pressure is associated with increased risk of developing erectile dysfunction. These findings provide evidence to support further investigation into the potential benefit of early blood pressure control on risk of ED in men with diabetes regardless of age, blood pressure level, or glycemic control.

Keywords

Erectile Dysfunction; Diabetes; Blood Pressure; Hypertension; Anti-Hypertensive Medications; Risk Factors

INTRODUCTION

Erectile Dysfunction (ED) is an important problem for men over the age of 50, estimated to affect as many as 30 million men in the United States.[1,2] A link between cardiovascular risk factors, including hypertension (HTN), and ED is well established and may result from generalized endothelial dysfunction.[3-5] Men with type 1 diabetes (T1DM) are at particular risk for ED because of the high prevalence of microangiopathy, endothelial dysfunction, neuropathy, and other risk factors.[6,7] Surprisingly, relationships between hypertension and more specifically, blood pressure levels, and the risk of developing ED in type 1 diabetes populations have not been comprehensively examined. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy type 1 diabetes cohort, untreated hypertension increased the odds of ED, but this and other reports relied solely on cross sectional data.[8,9] We hypothesized that men with T1DM and pre-hypertension, as well as those with hypertension, are at increased risk for ED. Thus, we examined the relationship between blood pressure levels and hypertension and the risk of developing incident ED over 16 years in a cohort of men with T1DM who participated in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study, the observational follow up of participants of the Diabetes Control and Complications Trial (DCCT).

METHODS

Population and Setting

DCCT/ EDIC has been described in detail.[10] Briefly, DCCT was a multicenter, randomized, controlled clinical trial designed to compare the effects of intensive and conventional diabetes therapy on the development and progression of early microvascular complications of T1DM.[11] From 1983-1989, 1441 patients (including 761 men) were enrolled at 29 centers. DCCT included a primary prevention cohort and a secondary intervention cohort. The primary prevention cohort included 378 men with no retinopathy, a urinary albumin excretion rate <40 mg/24 h, and diabetes duration of 1-5 years at baseline. The secondary intervention cohort included 383 men who, at baseline, had nonproliferative retinopathy, urinary albumin excretion rate ≥ 200 mg/24 h, and diabetes duration of 1-15

years. Individuals were excluded if they had hypertension (defined by SBP ≥ 140 or DBP ≥ 90 mmHg) or were taking anti-hypertensive medication, symptomatic ischemic heart disease, or symptomatic peripheral polyneuropathy requiring therapy. The intensive therapy regimen was designed to achieve glycemic control as close to the non-diabetic range as safely possible with 3 or more daily insulin injections or an insulin pump, with dose selection guided by frequent self-monitoring of blood glucose. Conventional therapy consisted of 1-2 daily insulin injections without stipulated target glucose levels.

Of the original 761 men enrolled, 746 completed the DCCT in 1993 and then in 1994, 741 enrolled in EDIC, an observational extension of the DCCT. During EDIC, the cohort has been followed annually. Of the 741 men, 734 provided information on blood pressure and hypertension and ED in the period from EDIC entry to EDIC year 16. Of these, 41 men who reported ED at EDIC entry and 1 man who did not report impotence data during EDIC were excluded. Thus, 692 men with 7,762 person-years of follow-up were included in the current study. The EDIC study was reviewed and approved by the institutional review board of each participating center and the Federal Government issued a Certificate of Confidentiality.

Erectile Dysfunction Measurements

ED was assessed annually in EDIC with a single item question that asked the participants: *“Have you experienced impotence in the last year?”* Those who answered ‘yes’ were considered to have ED. This item was assessed during each EDIC year, allowing for longitudinal assessment of ED status. We assessed the performance of this single question versus the validated and universally accepted International Index of Erectile Function (IIEF) Erectile Function (EF) domain and two individual items of the IIEF that are commonly used for clinical assessments of ED (question 3 “how often were your erections hard enough for penetration” and question 4 “how difficult was it to maintain your erection to completion of intercourse”) collected at EDIC year 10.[12] EF domain was dichotomized as Severe/Moderate ED vs. Mild/None ED. The single-item question had strong agreement with the EF domain, question 3, and question 4 (87.3%, 88.3%, and 87.7%, respectively). In order to further test the accuracy of the single item question, we computed its specificity and sensitivity, respectively, with the EF domain (92%, 70%), question 3 (91%, 71%), and question 4 (92%, 64%). Information regarding phosphodiesterase type 5 (PDE5) inhibitor use was not collected until EDIC year 13. Adding PDE5 inhibitor use to the definition of ED beginning with EDIC year 13 did not alter results due to the low frequency of their use (n=5); therefore, the results presented used a definition of ED that did not incorporate PDE5 inhibitor use.

Hypertension Measurements

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured annually during EDIC[13] and participants were categorized based on the Joint National Committee (JNC) 7 Report on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[14] as normotensive (SBP<120 and DBP<80 mmHg), prehypertensive (120 $\leq$ SBP<140 or 80 $\leq$ DBP<90 mmHg), or hypertensive (SBP ≥ 140 or DBP ≥ 90 mmHg). Blood pressure was measured using digital manometers by trained observers, with participants comfortably seated in a quiet room at a comfortable temperature for at least 5

minutes, the arm slightly flexed, and the forearm supported at heart level. Participants were queried annually on use of antihypertensive medications. The anti-hypertensive medication regimen was further classified as monotherapy (taking only one medication) or multiple drug therapy (≥ 2 medications). Any antihypertensive medication used by patients was included in the initial analysis but only four classes of antihypertensive medication use, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta blockers (BB), and thiazide diuretics, had sufficient numbers for individual analysis. For this study, at each EDIC assessment, blood pressure measurements over the previous 3 years were averaged and used as time-dependent covariates in relation to the onset of ED at each visit. This smoothing method for these hypertension variables was explored to reduce the impact of extreme high or low blood pressure values on a single day that may not be reflective of a subject's normal blood pressure levels, as well as to account for the possibility that the hypertension impact on ED may occur some time after the rise in hypertension is first noted. The final decision of a 3-year window was selected based on preliminary modeling of permutations of the relationship between time averaged blood pressure variables and ED, with time spans ranging from 1 to 10 years explored (data not shown).

Statistical Analysis

Participants who did not report having ED at EDIC entry (n=692) were considered at risk for incident ED from EDIC entry until they reported being impotent. Unadjusted incidence rates of ED were calculated as the number of cases of incident ED divided by the person-years at risk. Rates are expressed as the number of cases per 1000 person-years. Associations of blood pressure and hypertension over the previous 3 years with risk of incident ED were tested using Cox proportional hazard models. Separate multivariable models were built with each of the blood pressure and hypertension measurements as the primary exposures; these variables were included in the model as time-dependent covariates. Models for each of the blood pressure and hypertension variables were determined using a backwards model-building process. Candidate covariates included age, DCCT treatment arm, DCCT cohort (primary or secondary), DCCT/EDIC time weighted mean HbA1c[15] (per HbA1c%), smoking status, marital status, alcohol intake status and body mass index (BMI). Age, BMI, HbA1c, marital status, smoking status, and alcohol intake status were included in the models as time-dependent covariates. Final models included only those variables that were nominally significant at the p 0.05 level (age, smoking status, HbA1c). An interaction term defined by the cross-product of the blood pressure/hypertension variable and antihypertensive medication use was included in models to examine the potential for differences in the associations between blood pressure/hypertension and ED risk by antihypertensive medication use. Significance of interaction terms were examined using the Likelihood Ratio test. All analyses were performed using SAS® version 9.4.

RESULTS

Baseline characteristics of the 692 men who comprise the study cohort are presented in Table 1. Median age at baseline was 35.7 years and 451 men (69%) reported being married. Twenty one percent of men reported smoking while 46% reported drinking alcohol at least once per week. Over 60% of the population was overweight or obese at baseline with

median BMI measuring 25.9 kg/m². Median DCCT/EDIC HbA1c was 7.9% (range 4.4-13.9). Seventeen men (2.5%) met JNC criteria for hypertension while 45% of the cohort at baseline were considered prehypertensive. At baseline, 6.7% of men reported antihypertensive medication use with a majority of those men reporting ACEi/ARB use.

Over 16 years of follow-up (7,762 person-years at risk), a total of 337 men reported incident ED representing an overall unadjusted incidence rate of 43.4 cases per 1000 person-years. Incidence of ED increased with elevated systolic and diastolic blood pressure levels over the previous 3 years (Table 2). Similarly, unadjusted rates of ED were 33.4 per 1000 person-years for normotensive men and 48.0 per 1000 person-years for prehypertensive men compared to 70.1 per 1000 person-years for hypertensive men based on JNC hypertension classification. Finally, unadjusted risk of ED was 2-fold greater in men reporting anti-hypertensive medication use (66.1/1000 person-years) compared to men not taking anti-hypertensive medications over the past 3 years (33.3/1000 person-years). Rates differed by type of anti-hypertensive medication with the highest incidence of ED reported in men on beta blockers only (128.2/1000 person-years). Consistent with unadjusted analyses, overall, increased blood pressure was associated with increased risk of ED after adjustment for age, cigarette smoking and HbA1c levels. Prehypertensive and hypertensive men had 27% and 39% increased risk of ED respectively compared to normotensive men, albeit the results did not reach statistical significance. Risk of ED significantly increased with report of any anti-hypertensive medication use (RR=1.33, 95% CI=1.05, 1.69) and was observed for all categories of anti-hypertensive medication use with the strongest association observed for men reporting use of beta blockers only (RR=2.49, 95% CI=1.02, 6.11).

Absolute rates and adjusted risk of incident ED by various blood pressure and hypertension measures are shown stratified by anti-hypertensive medication use in Table 3 in order to examine the potential for differences in effect of medication use on the associations between blood pressure/hypertension and ED risk (interaction). Incidence of ED increased with increased systolic and diastolic blood pressure levels over the previous 3 years among those not taking antihypertensive medications. After adjusting for age, cigarette smoking and HbA1c levels, a 10mmHg increase in mean SBP was significantly associated with a 21% increase (95% CI 4%, 41%) in incident ED risk. Similar increases were noted for DBP (25% increased risk) albeit these results did not reach statistical significance. Unadjusted rates of ED in untreated men were 25.1 per 1000 person-years for normotensive men compared to 67.4 per 1000 person-years for hypertensive men based on JNC hypertension classification. There was a significant increase in the adjusted risk of incident ED relative to normotensive men in men with pre-hypertension (RR=1.40, 95% CI=1.01, 1.92) and a greater than two-fold increased risk in men with hypertension (RR=2.19, 95% CI=1.20, 4.01).

While the incidence of ED was significantly greater in men reporting anti-hypertensive medication use overall, among men using anti-hypertensive medications, there was no significant difference in the incidence of ED observed by blood pressure or hypertension measures. (Figure 1) All associations observed between blood pressure and hypertension status and ED in men not taking antihypertensive medication were attenuated or disappeared among men reporting antihypertensive medication use suggesting antihypertensive medication use modifies the effect of blood pressure and hypertension on ED risk. A

statistically significant interaction between SBP and antihypertensive medication use was observed ($p=0.02$). (Table 3)

DISCUSSION

The 692 men in DCCT/EDIC represent the largest cohort of people with T1DM followed longitudinally for the development of ED. Comprehensive patient characterization, including standardized annual blood pressure measurements and annual assessment of impotence, allowed us to quantify the long-term relationship between blood pressure, hypertension and the risk of incident ED. We found that in men not treated for hypertension, the risk of ED increased significantly with higher systolic blood pressure levels and according JNC hypertension classification (normal, prehypertensive, hypertensive). While a significant increased risk of ED was also observed for men who reported anti-hypertensive medication use relative to those who reported no anti-hypertensive medication use, the association of blood pressure levels with ED were modified by anti-hypertensive medication use such that the associations between blood pressure and hypertension classification and the risk of ED observed among men taking anti-hypertensive medication disappeared among men reporting no anti-hypertensive medication use. All associations observed were independent of age, smoking status and glycemic control as assessed by mean updated HbA1c and suggest that a relationship between vascular pressure experienced by the end cavernosal arteries/sinusoids and systemic blood pressure operates independently of these other factors to affect ED risk.

This is the first study to quantify the association between longitudinal assessments of blood pressure levels, hypertension classification, and ED risk in T1DM men. Among men not reporting anti-hypertensive medication use, we observed that every 10mmHg increase in SBP and increased the risk of developing incident ED by 21% and 25%, respectively. An association at the lower range of blood pressures has been described previously in men with type 2 diabetes (T2DM) by the LOOK Ahead Study. Rosen et al[16] demonstrated that every 10mmHg increase in SBP was associated with a 30% increased prevalence of ED and every 10mmHg increase in DBP was associated with a 10% increased risk. The magnitudes of the increased risks are similar to our results, although their analyses were cross sectional. While our findings only reached statistical significance for continuous SBP, our analyses underscore the potential benefit early blood pressure control might provide.

Among the cohort of men who were taking anti-hypertensive medications, we observed that prevailing blood pressure was not associated with risk of ED. This is consistent with findings from Rosen et al[16] in men with T2DM. While overall this study demonstrated an association between hypertension status and ED risk, authors observed antihypertensive medications did not significantly influence the odds of ED conferred by HTN despite 80% of the men reporting treatment. There are multiple potential explanations for the lack of association among treated men. First, it is possible that any reduction in risk as a result of decreased blood pressure associated with anti-hypertensive medication use was offset by the increased risk of ED associated with medication side effects[1,17,18]. Beta blockers and thiazide diuretics are widely acknowledged to worsen ED. However, data from animal models of hypertension show a protective effect of blood pressure reduction with other classes of antihypertensive medications, e.g. calcium channel blockers and ACEi.[19]

Because 80% of men taking antihypertensive medications were using ACEi, the class of medications least likely to cause erectile dysfunction, we do not believe that medication side effects are the only explanation for the lack of increased ED risk associated with blood pressure among treated men. A second possibility is that among men treated with antihypertensive medications, the biological processes leading to ED have already started and cannot be interrupted by treatment. This suggests that blood pressure itself is not causally related to ED but rather is a marker for the processes (endothelial dysfunction, arterial stiffness or calcification) that also contribute to ED development.

Rates of ED overall were higher in this study of T1D than reported in other cohorts of similar age from the general population.[20] Further, rates of ED among those with hypertension in the DCCT/EDIC T1D cohort were double what has been reported in the general population, overall and by treatment status.[21] Nevertheless, most other risk factors for incident ED identified in this study are consistent with our previous work as well as those described elsewhere.[2,22] Increased age and HbA1c% were significant predictors of increased risk of incident ED in SBP, DBP and hypertension models.[23] Furthermore, non-smoking status exerted a protective effect consistent with prior studies[24,25]. Other risk factors such as DCCT treatment arm and BMI were not independently associated with ED during the model building process and were dropped from the final model. (data not shown) Autonomic neuropathy has been hypothesized to be involved, along with the endothelial dysfunction, in the pathogenesis of ED and hypertension. Measures of cardiovascular autonomic neuropathy were not available longitudinally and prior to the onset of ED to include in the current analyses. However, in a cross sectional study of this cohort, we demonstrated that men in whom ED developed during the study had a significantly lower respiratory rate variation and Valsalva ratio compared to those reporting no sexual dysfunction after adjusting for blood pressure[26]. Finally, while the lipid profile may influence the relationship between blood pressure/hypertension on ED, previously published work in this cohort demonstrated that total cholesterol and triglyceride levels were not independently associated with blood pressure[27] or ED risk[24] after adjustment for well recognized risk factors and therefore were not included in the current analysis.

This study has several limitations. The first is reliance on a binary single item definition of ED for our repeated measures analysis. The term impotence lacks specificity, could lead to under-reporting, and has a potentially pejorative connotation, but its availability annually over a 16-year period of time provides a unique opportunity to evaluate onset of ED in this population. The high level of agreement and calculated specificity between the impotence question and the IIEF EF domain provides reassurance that the single-item assessment used in this study was understood and provided reliable results that would have been very similar to those found if the multi-item IIEF had been used. Additionally, the study population is limited to Caucasian men with T1D. Results may not be generalizable to men of other races, men with type 2 diabetes, or men treated outside a long-term clinical trial setting.

CONCLUSION

Among men with T1DM not treated with antihypertensive medications, continuous systolic blood pressure and JNC classification of prehypertension and hypertension are

independently associated with risk of incident ED. Men with treated hypertension are at significantly increased risk of ED, however, attained blood pressure is not associated with risk of ED, potentially reflecting a medication effect or structural effects of longstanding hypertension on the penile vasculature (e.g. remodeling). These data provide a compelling argument for further investigation of the potential benefit of early blood pressure monitoring and treatment on risk of ED in men with T1DM regardless of their age, current blood pressure level, or glycemic control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Incidence Rates (95%CI) of ED by JNC Classification and Antihypertensive Medication Use
in Men with Type 1 Diabetes
Note: Incidence rates of ED are per 1000-person years.

Table 1.

Characteristics of the Study Population at EDIC Baseline (n=692)

Current Sociodemographic/Clinical	
Age (years) Median (Range)	35.7 (19.4, 50.9)
Married No. (%)	451 (69.2%)
Cigarette Smoker No. (%)	139 (21.1%)
Current Drinker No. (%)	305 (46.2%)
Body Mass Index (BMI) (kg/m ²) Median (Range)	25.9 (16.7, 49.8)
BMI Category (kg/m ²) No. (%)	
Normal (<25)	251 (38.3)
Overweight (25-29)	320 (48.9)
Obese (30+)	84 (12.8)
Diabetes Control and Treatment	
DCCT cohort No. (%)	
Primary Prevention	350 (50.6)
Secondary Intervention	342 (49.4)
Treatment Arm No. (%)	
Conventional	349 (50.4)
Intensive	343 (49.6)
DCCT/EDIC Weighted Hemoglobin A1c (%) Median (Range)	7.9 (4.4, 13.9)
Blood Pressure/Hypertension	
Systolic Blood Pressure (mmHg) Median (Range)	117 (96, 154)
Diastolic Blood Pressure (mmHg) Median (Range)	76 (57, 104)
JNC Classification No. (%)	
Normotensive (SBP<120 and DBP<80)	362 (52.3)
Prehypertensive (120 ≤ SBP<140 or 80 ≤ DBP<90)	313 (45.2)
Hypertensive (SBP ≥ 140 or DBP ≥ 90)	17 (2.5)
Anti-hypertensive Medication Use No. (%)	
No	646 (93.4)
Yes	46 (6.7)
ACEi/ARB only	37 (5.4)
Beta blockers only	4 (0.6)
Thiazide diuretics only	2 (0.3)
Multiple drug therapy (≥ 2)	3 (0.4)

Table 2.

Incidence of ED Over Time by Blood Pressure and Hypertension Classification

	N events	Person-years	Incidence Rate (per 1000 person-years)	Hazard Ratio* (95%CI)
All participants	337	7762	43.4	
Systolic Blood Pressure (mmHg)				
<120	124	3599	34.5	1.00 (ref)
120-139	183	3695	49.5	1.22 (0.96, 1.54)
140	25	351	71.2	1.18 (0.75, 1.85)
per 10mmHg increase	--	--	--	1.09 (0.98, 1.20)
Diastolic Blood Pressure (mmHg)				
<80	201	4949	40.6	1.00 (ref)
80-89	109	2407	45.3	1.14 (0.90, 1.45)
90	22	289	76.1	1.64 (1.02, 2.62)
per 10mmHg increase	--	--	--	1.14 (0.98, 1.33)
JNC Classification				
Normotensive (SBP<120 and DBP<80)	106	3169	33.4	1.00 (ref)
Prehypertensive (120 SBP<140 or 80 DBP<90)	191	3977	48.0	1.27 (1.00, 1.62)
Hypertensive (SBP 140 or DBP 90)	35	499	70.1	1.39 (0.93, 2.09)
Anti-hypertensive Medication Use				
No	179	5371	33.3	1.00 (ref)
Yes	158	2391	66.1	1.33 (1.05, 1.69)
ACEi/ARB only	127	1942	65.4	1.34 (1.05, 1.72)
Beta blockers only	5	39	128.2	2.49 (1.02, 6.11)
Thiazide diuretics only	1	22	45.5	1.05 (0.15, 7.56)
Multiple drug therapy (2)	25	388	64.4	1.14 (0.73, 1.78)

* Separate Cox proportional hazards models built for each blood pressure and hypertension variable adjusted for time-dependent versions of age, cigarette smoking, and time-weighted HbA1c

Table 3.

Incidence of ED Over Time by Antihypertensive Medication Use

Characteristic	No Antihypertensive Use		Antihypertensive Medication Use		p-value ^{***}
	Incidence Rate (per 1000 person-years)	Hazard Ratio [*] (95%CI)	Incidence Rate (per 1000 person-years)	Hazard Ratio [*] (95%CI)	
Systolic Blood Pressure (per 10mmHg increase)	--	1.21 (1.04, 1.41)	--	0.96 (0.84, 1.10)	0.02
Diastolic Blood Pressure (per 10mmHg increase)	--	1.25 (0.99, 1.59)	--	1.00 (0.82, 1.24)	0.16
Systolic Blood Pressure (mmHg)					0.23
<120	27.5	--	58.7	--	
120-139	38.1	1.22 (0.90, 1.66)	69.0	1.10 (0.77, 1.56)	
140	70.9	1.83 (0.91, 3.69)	71.4	0.81 (0.44, 1.46)	
Diastolic Blood Pressure (mmHg)					0.40
<80	30.8	--	68.4	--	
80-89	37.1	1.22 (0.88, 1.70)	58.5	0.97 (0.69, 1.37)	
90	63.1	2.14 (0.99, 4.63)	84.3	1.23 (0.68, 2.23)	
JNC Classification					0.08
Normotensive (SBP<120 and DBP<80)	25.1	--	63.2	--	
Prehypertensive (120 SBP<140 or 80 DBP<90)	38.6	1.40 (1.01, 1.92)	65.7	1.01 (0.70, 1.46)	
Hypertensive (SBP 140 or DBP 90)	67.4	2.19 (1.20, 4.01)	71.9	0.87 (0.50, 1.49)	

* Separate Cox proportional hazards models built for each blood pressure and hypertension variable adjusted for time-dependent versions of age, cigarette smoking, and time-weighted HbA1c

** p-value for interactions between blood pressure and hypertension variable and antihypertensive medication use using the Likelihood Ratio Test