Differential Effect of Glycemia on the Incidence of Hypertension by Sex

The Epidemiology of Diabetes Complications study

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OBJECTIVE—Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications analyses demonstrated that intensive insulin therapy was inversely associated with incident hypertension. We thus sought to confirm these observations and, given sex differences in other type 1 diabetes complications and risk factors, assessed whether any such associations differ by sex.

RESEARCH DESIGN AND METHODS—Participants of a prospective cohort of childhood-onset type 1 diabetes, free of hypertension at study entry (baseline mean age, 28 years; diabetes duration, 19 years), were selected for study (n = 510). Hypertension incidence was defined as blood pressure >140/90 mmHg or use of hypertension medications in two consecutive visits. Intensive insulin therapy was defined as three or more injections (or pump) and four or more glucose tests daily. Baseline predictors of hypertension were examined using Cox proportional hazards models. Models with time-dependent updated means of baseline significant variables were also constructed.

RESULTS—Hypertension incidence over 18 years of follow-up was marginally higher in men than in women (43.2 vs. 35.4%, P = 0.07). A significant interaction was noted between sex and HbA_{1c}, and separate models were constructed by sex. Multivariably, elevated HbA_{1c} was a significant predictor only in men (hazard ratio 1.48 [95% CI 1.28–1.71]). In time-dependent models, although a significant effect of HbA_{1c} was also seen in women (1.21 [1.00–1.46]), the effect of glycemic control on hypertension development remained stronger in men (1.59 [1.29–1.97], P interaction <0.0001).

CONCLUSIONS—Although hyperglycemia is a risk factor for hypertension, its effect is stronger in men compared with women with type 1 diabetes.

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Hypertension is the number one attributable risk factor for death within the general population worldwide (1) and remains particularly prevalent among individuals with diabetes (2), despite the broad availability of effective treatment regimens (3). Among individuals with type 1 diabetes, the presence of hypertension has been associated with a significantly increased risk of both microvascular (4) and macrovascular (5) complications, and it also raises overall mortality risk (6). Given the increased incidence of cardiovascular and kidney complications in this population, the control of arterial blood pressure is of imminent importance, as is the management of risk factors for hypertension incidence itself.

Modifiable lifestyle factors, such as obesity and physical inactivity, and dietary factors, including excess alcohol consumption, increased dietary sodium intake, and inadequate fruit, vegetable, and potassium intakes, have been shown to significantly increase the risk of new-onset hypertension in the general population (3,7,8). Although, traditionally, individuals with type 1 diabetes were thought to be of normal or subnormal weight, the adoption of unhealthy lifestyle behaviors and/or intensive insulin therapy have led to an increasing prevalence of overweight and obesity in individuals with this diabetes type (9). Moreover, the presence of hyperglycemia has been suggested to further contribute to the excess risk of hypertension in these individuals by promoting vascular stiffness (10). Indeed, analyses of the Diabetes Control and Complications Trial (DCCT) and its observational follow-up study, Epidemiology of Diabetes Intervention and Complications (EDIC), demonstrated that hyperglycemia and intensive insulin therapy are associated with incident hypertension (11), although sex differences were not evaluated. Differences in the incidence of and/or risk factors for vascular complications associated with hypertension (i.e., kidney and heart disease) have been previously described by our group among individuals with type 1 diabetes (12–14). We therefore aimed to assess the association between glycemia (HbA_{1c}), glycemic control (intensive therapy), and the development of hypertension in a well-characterized cohort study of individuals with childhood-onset type 1 diabetes, to confirm whether findings from the DCCT/EDIC study are apparent in the general type 1 diabetes population, and to determine whether any association between glycemic control or intensive insulin treatment with incident hypertension varies by sex.

RESEARCH DESIGN AND METHODS

—Participants from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study with arterial blood pressure <140/90 at study initiation were selected for study (n = 510). The EDC is a historical cohort study based on incident cases of childhood-onset (prior to their 17th birthday) type 1 diabetes, diagnosed or seen within 1 year of diagnosis (1950–1980) at the Children's Hospital of Pittsburgh (15). This cohort has been previously shown to be epidemiologically representative of the type 1 diabetes population of Allegheny County, Pennsylvania (16). The first clinical assessment for the EDC study took place between 1986 and 1988, when the mean participant age

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and diabetes duration were 28 and 19 years, respectively. Subsequently, biennial examinations were conducted for 10 years, with a further examination at 18 years of follow-up. The University of Pittsburgh institutional review board approved the study protocol.

Prior to each clinic visit, participants were sent questionnaires concerning demographic, health care, diabetes self-care, and medical history information. Leisure time physical activity was assessed by the Paffenbarger questionnaire (17), and a previously published algorithm (18) was used to calculate physical activity over the past week and over the past year based on the daily number of city block equivalents walked, the number of flights of stairs climbed, and the frequency and duration of leisure time activity. Three blood pressure measurements were taken by trained and certified personnel with a Hawksley random zero sphygmomanometer, after a 5-min rest in the sitting position according to the Hypertension Detection and Follow-up Program protocol (19). Hypertension was defined as ≥140/90 mmHg (mean of the second and third readings) or use of antihypertensive medications. For the present analyses, participants were only considered "hypertensive" if they were positive on two consecutive examination cycles. Intensive insulin therapy was defined as multiple (three or more) daily insulin injections or continuous subcutaneous insulin infusion in addition to frequent (at least four times daily) glucose testing. Stable glycosylated hemoglobin (HbA_1) was measured by ion-exchange chromatography (Isolab, Akron, OH) for the first 18 months, and the subsequent 10 years by automated high-performance liquid chromatography (Diamat; Bio-Rad, Hercules, CA); the two assays were highly correlated (r = 0.95). For follow-up beyond the 10 years, HbA_{1c} was measured with the DCA 2000 analyzer (Bayer,

Table 1—*Participant characteristics at study entry by incidence of hypertension during 18 years of follow-up*

	Men			Women		
	No HTN	Incident HTN		No HTN	Incident HTN	
Participant characteristics	*n* = 142	*n* = 108	*P* value	*n* = 168	*n* = 92	*P* value
Age (years)	24.6 (7.5)	27.7 (7.4)	0.001	25.9 (7.6)	28.2 (8.1)	0.02
Age at onset (years)	7.9 (4.3)	7.8 (4.2)	0.77	8.1 (3.7)	8.9 (4.2)	0.13
Diabetes duration (years)	16.7 (6.7)	20.0 (7.5)	0.0003	17.7 (7.4)	19.3 (7.8)	0.11
Follow-up time (years)	13.9 (6.0)	10.3 (5.4)	<0.0001	14.3 (6.1)	10.0 (5.1)	<0.0001
African Americans (%, *n*)	0.70 (1)	0.0 (0)	1.00	4.8 (8)	3.3 (3)	0.75
BMI (kg/m^2, *n* = 140; 108; 168; 92)	23.1 (3.2)	23.7 (3.0)	0.11	23.1 (3.4)	23.7 (3.2)	0.13
WHR (*n* = 142; 107; 166; 91)	0.86 (0.05)	0.87 (0.05)	0.01	0.77 (0.05)	0.78 (0.06)	0.14
Percent ever smoked (*n*)	32.4 (46)	46.3 (50)	0.02	34.5 (58)	31.5 (29)	0.62
HbA_{1c} (%, *n* = 141; 108; 167; 92)	8.5 (1.4)	9.2 (1.6)	0.001	8.6 (1.4)	8.9 (1.7)	0.14
Insulin dose per body weight (*n* = 135; 100; 164; 87)*	0.83 (0.68–0.98)	0.79 (0.65–0.96)	0.18	0.77 (0.59–0.92)	0.68 (0.58–0.90)	0.36
Multiple (≥3) daily insulin injections (*n* = 135; 100; 164; 87)	2.2 (3)	4.0 (4)	0.46†	11.0 (18)	4.6 (4)	0.10*
Glucose monitoring, once per week (*n* = 135; 99; 164; 87)	61.5 (83)	51.5 (51)	0.13	74.4 (122)	73.6 (64)	0.89
Intensive insulin therapy (%, *n* = 135; 100; 164; 87)	1.5 (2)	2.0 (2)	1.00†	11.0 (18)	3.4 (3)	0.05†
SBP (mmHg)	109.3 (9.2)	116.5 (10.9)	<0.0001	104.4 (8.7)	110.7 (11.6)	<0.0001
DBP (mmHg)	70.4 (8.5)	75.6 (8.9)	<0.0001	67.2 (7.8)	70.4 (8.3)	0.002
Pulse (beats per min)	75.1 (10.1)	79.0 (8.5)	0.002	77.5 (8.7)	81.1 (9.7)	0.003
HDL cholesterol (mmol/L, *n* = 141; 108; 167; 91)	1.3 (0.25)	1.3 (0.23)	0.31	1.6 (0.35)	1.5 (0.28)	0.01
Non-HDL cholesterol (mmol/L, *n* = 141; 108; 167; 91)	3.2 (0.83)	3.8 (1.3)	<0.0001	3.2 (0.91)	3.5 (1.1)	0.03
Serum creatinine (μmol/L, *n* = 141; 108; 167; 92)*	80.0 (62.0–88.0)	80.0 (71.0–97.0)	0.25	62.0 (53.0–80.0)	71.0 (53.0–80.0)	0.73
eGFR (mL/min/1.73 m^2)	115.8 (95.3–127.4)	109.8 (94.4–123.7)	0.10	114.0 (91.5–125.1)	103.0 (83.0–128.2)	0.28
AER (μg/min)*	9.8 (6.2–22.7)	34.3 (9.6–380.6)	<0.0001	9.7 (5.9–24.6)	20.4 (9.1–166.7)	<0.0001
WBC × 10^3/mm^2 (*n* = 141; 106; 168; 91)	6.1 (1.6)	6.6 (1.9)	0.02	6.4 (1.8)	6.9 (2.2)	0.05
Fibrinogen (μmol/L, *n* = 141; 106; 165; 91)*	7.1 (5.9–8.4)	7.9 (6.6–9.7)	0.001	7.9 (6.9–9.7)	8.4 (7.4–10.0)	0.13
Calories expended in physical activity (*n* = 135; 98; 156; 82)*	2,560 (1,184–4,072)	2,045 (756–3,876)	0.20	1,162 (546–2,364)	1,157 (552–2,212)	0.64

Data are mean (SD), median (interquartile range), or percent (*n*). eGFR, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI); HTN, hypertension. *The Wilcoxon two-sample test was used for non-normally distributed variables. †Fisher exact test P value.

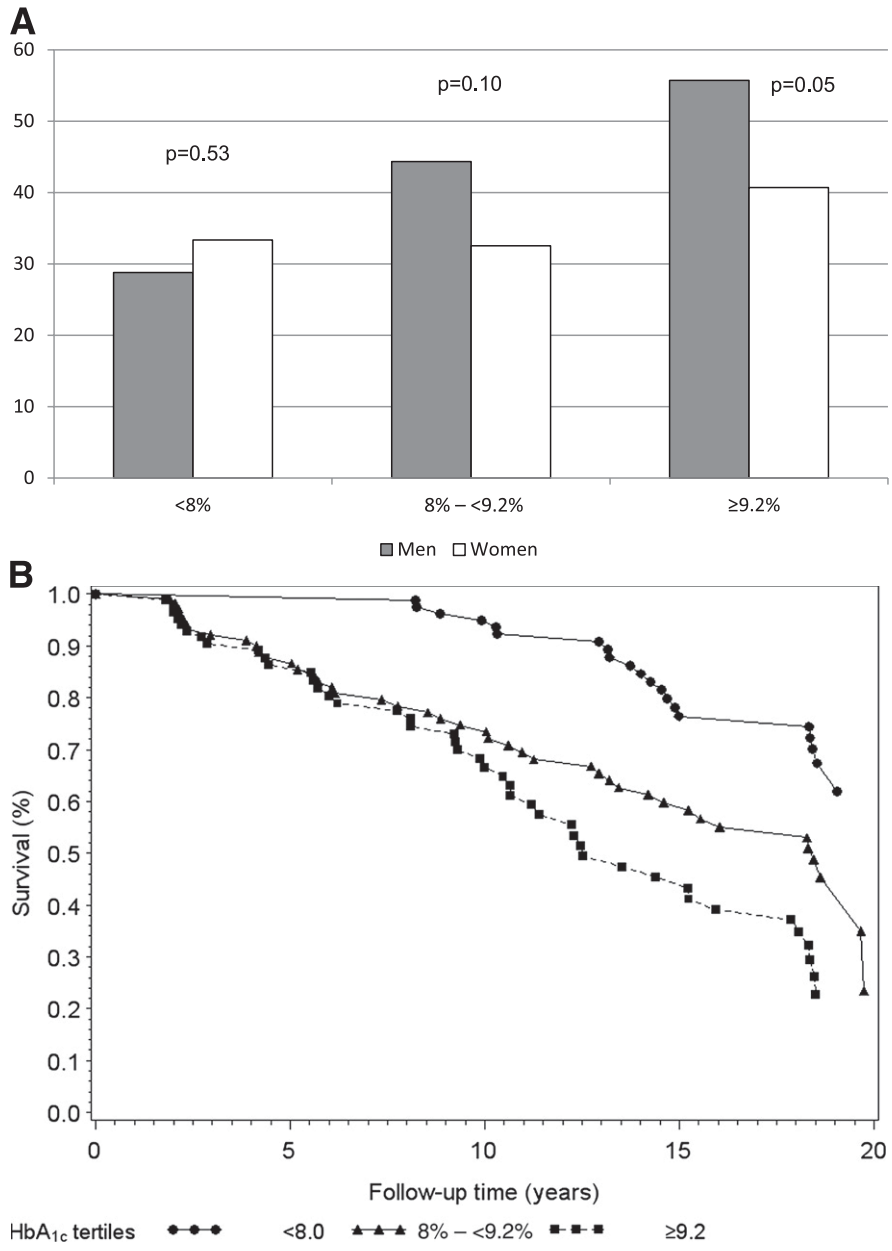

Figure 1—A: *Incidence of hypertension by sex and tertiles of HbA_{1c} at study entry. Among men,* P *value = 0.004 and* P *value for trend = 0.0008. Among women,* P *value = 0.47 and* P *value for trend = 0.31.* B: *Diabetes duration–adjusted survival curves for hypertension by tertiles of HbA_{1c} at study entry among men. The Pittsburgh EDC study (hazard ratio$_{8.0\ to\ <9.2}$ 2.42 [95% CI 1.43–4.10],* P *value = 0.0009; hazard ratio $_{\geq 9.2}$ 4.00 [2.35–6.80],* P *value <0.0001; log-rank* P *value <0.0001).* C: *Diabetes duration–adjusted survival curves for hypertension by tertiles of HbA_{1c} at study entry among women. The Pittsburgh EDC study (hazard ratio $_{8.0–<9.2}$ 1.18 [0.70–1.98],* P *value = 0.54; HR$_{\geq 9.2}$ 1.58 [0.97–2.58],* P *value = 0.07; log-rank* P *value = 0.22).*

Tarrytown, NY). The DCA and Diamat assays were also highly correlated (r = 0.95). Original HbA_1 (1986–1998) and HbA_{1c} values (1998–2004) were converted to DCCT-aligned standard HbA_{1c} values using regression formulae derived from duplicate assays (DCCT HbA_{1c} = [0.83 × Diamat HbA_1] + 0.14 and DCCT HbA_{1c} = [DCA HbA_{1c} − 1.13]/0.81). HDL cholesterol was determined enzymatically after precipitation with heparin and manganese chloride, with a modification (20) of the Lipid Research Clinics method (21). Cholesterol and triglycerides were measured enzymatically (22,23). Non-HDL cholesterol was calculated as total minus HDL cholesterol. White blood cell (WBC) count was obtained using a counter S-plus IV and fibrinogen using a biuret colorimetric procedure and a clotting method. Urinary albumin was measured by immunonephelometry (24), and creatinine was assayed by an Ectachem 400 Analyzer (Eastman Kodak Co., Rochester, NY). Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (25). It should, however, be noted that serum creatinine was not calibrated in this study. All assays were conducted during the cycle that samples were obtained, and thus, prolonged storage would not have affected measurements performed in this study.

Statistical analysis

Analyses were conducted stratified by sex. Univariate associations were determined using the Student t test for normally distributed continuous variables or Wilcoxon two-sample test for nonnormally distributed continuous variables. The χ^2 or Fisher exact test, as appropriate, was used for univariate analysis of categorical variables. Cox proportional hazards models with backward elimination were constructed to assess independent predictors of hypertension incidence among traditional risk factors and univariately significant variables. Cox proportional hazards models were also constructed using time-dependent updated means of variables significant in models using baseline characteristics. Survival time was defined as the time in years from study entry to either incident hypertension or censorship during the 18-year follow-up. Nonnormally distributed variables were logarithmically transformed for entry into multivariable models. Statistical analyses were conducted using Statistical Analysis Software (SAS), version 9.2 (SAS Institute, Cary, NC).

RESULTS

Incidence and univariate predictors of hypertension in the entire cohort

During 18 years of follow-up, 39.2% (n = 200) of individuals developed incident hypertension, for an incidence rate of 31.2 per 1,000 person-years. Incidence was slightly lower in women (35.4%) than in men (43.2%, P = 0.07). Table 1 presents characteristics of male and female participants at study entry by incident hypertension. In both sexes, compared with participants whose arterial blood pressure remained within a normal range, those who subsequently developed hypertension were more likely to be older and have elevated baseline

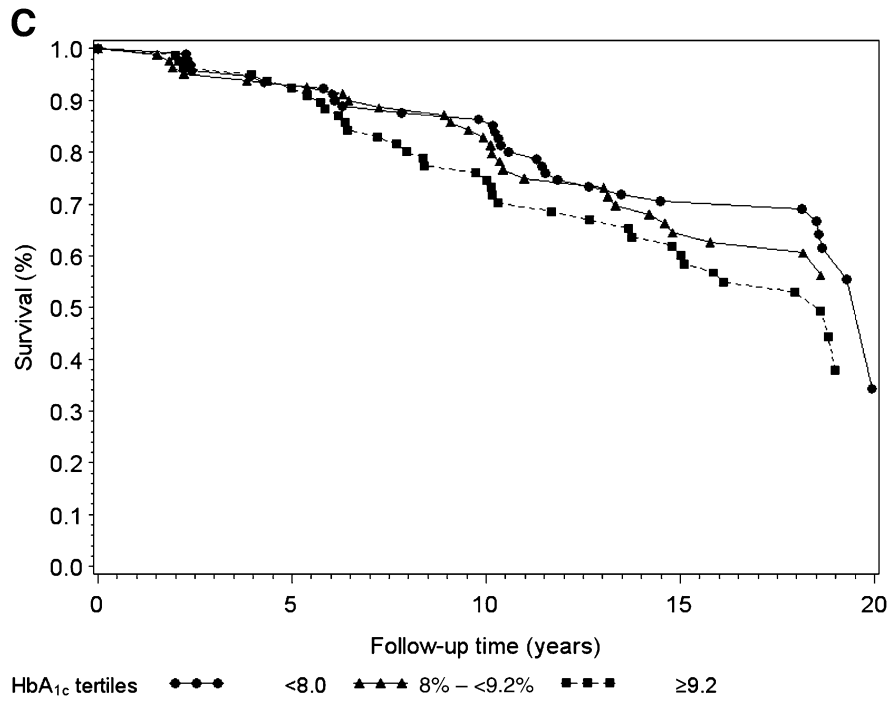

Figure 1—*Continued*

blood pressure, non-HDL cholesterol, albumin excretion rate (AER), and WBC count. In addition, male participants who developed hypertension were more likely to have a longer duration of type 1 diabetes, larger waist-to-hip ratio (WHR), and elevated HbA_{1c} and fibrinogen levels at study entry. Among women, those who subsequently developed hypertension had lower HDL cholesterol concentrations at study entry compared with women who maintained normal arterial blood pressure. No participant received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers at study baseline.

The effect of glycemic control on the development of hypertension

To evaluate whether a dissimilar distribution of HbA_{1c} between male and female participants at study entry was responsible for the observed discrepancy in its association with hypertension incidence by sex, we assessed incidence by HbA_{1c} tertiles. As shown in Fig. 1*A*, the proportion of incident cases was similar by sex within the first HbA_{1c} tertile but appeared to be slightly increased among men compared with women within the second and third tertiles. Moreover, although hypertension incidence appeared to increase linearly with increasing HbA_{1c} tertile among men (*P* value for trend = 0.0008), a similar increase in risk was not apparent among women (*P* value for trend = 0.31). Figure 1*B* and *C* depicts the diabetes duration–adjusted 18-year survival free of hypertension for men and women, respectively, by tertiles of HbA_{1c} at study entry. These graphs clearly show a strong association between HbA_{1c} and hypertension incidence among men but a much weaker, nonsignificant relationship among women. Thus, compared with men with HbA_{1c} <8%, the estimated relative hazard of developing hypertension was 2.42 (95% CI 1.43–4.10) times higher among those with HbA_{1c} between 8 and 9.2% and four (2.35–6.80) times higher among men whose levels were >9.2%. Among women, however, even levels >9.2% were only associated with a borderline significantly increased hazard compared with HbA_{1c} levels <8% (*P* = 0.07).

The presence of effect modification of HbA_{1c} by sex was confirmed with the results of a significant interaction term (*P* = 0.009) in a Cox proportional hazards model that included variables for sex, HbA_{1c}, and the interaction term. Thus, separate multivariable models (with backward elimination) were constructed for male and female participants. Since only 4 men and 21 women followed an intensive insulin therapy protocol at study entry, this variable was not included in multivariable models of baseline predictors. Among men (Table 2), elevated HbA_{1c}, systolic blood pressure (SBP), and AER predicted hypertension development. In women, elevated SBP and AER were also predictors, along with non-HDL cholesterol. HbA_{1c}, however, was not an independent predictor in women.

To better understand the modification of the effect of HbA_{1c} by sex, we also performed separate Cox proportional hazards models by HbA_{1c} tertile (Table 3). Interestingly, these analyses revealed the presence of an over twofold significantly increased risk for hypertension incidence in women compared with men among those in the lowest HbA_{1c} tertile (hazard ratio 2.24 [95% CI 1.17–4.27]). No difference in risk by sex was noted in the second tertile of HbA_{1c} (1.30 [0.77–2.18]), whereas a significantly lower risk for women compared with men was observed in the third HbA_{1c} tertile (0.53 [0.32–0.86]). These findings could not be attributed to sex differences in the distribution of HbA_{1c} within each tertile (the *P* value for a difference by sex was 0.81, 0.60, and 0.47 for the first, second, and third tertile, respectively).

A significant interaction between sex and HbA_{1c} ($P < 0.0001$) was also noted when analyses were repeated using time-dependent updated means of baseline independent predictors of hypertension incidence. Thus, although a significant effect of HbA_{1c} was seen even among female participants (hazard ratio 1.21 [95% CI 1.00–1.46]), the effect of glycemic control on hypertension development was stronger in men (1.59 [1.29–1.97]) (data not shown). As intensive insulin therapy became more prevalent past study entry, this variable was allowed for in time-dependent models; however, intensive insulin therapy was not associated with incident hypertension in either sex. Although surprising, this finding is likely attributed to the fact that >60% of incident hypertension cases had developed by the sixth examination cycle (1996–1998), whereas intensive insulin therapy appears to have been largely adopted after that time period in this population.

CONCLUSIONS—In this cohort of individuals with long-standing type 1 diabetes, the effect of hyperglycemia, as measured by greater HbA_{1c} levels at study entry, on new-onset hypertension was much stronger in men compared with women. The very small number of men and women following intensive insulin therapy at study entry (4 and 21,

Table 2—*Cox proportional hazards models for the prediction of hypertension among male and female participants during 18 years of follow-up in the Pittsburgh EDC study*

	Model 1	Model 2	Model 3	Model 4	Model 5
Baseline participant characteristics	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Men (*n* = 227; 96 incident hypertension cases)					
Diabetes duration (years)	1.04 (1.01–1.07)	1.06 (1.03–1.09)	1.04 (1.01–1.07)	1.03 (1.00–1.06)	NS
WHR (per SD)	1.42 (1.07–1.89)	1.36 (1.01–1.84)	NS	NS	NS
HbA_{1c} (%)	NA	1.53 (1.34–1.75)	1.59 (1.39–1.83)	1.47 (1.27–1.70)	1.48 (1.28–1.71)
Insulin dose per weight	NA	NS	0.45 (0.18–1.12)	NS	NS
SBP (mmHg)	NA	NA	1.04 (1.01–1.07)	1.03 (1.00–1.06)	1.04 (1.02–1.06)
DBP (mmHg)	NA	NA	1.03 (1.00–1.07)	1.03 (0.997–1.07)	NS
Non-HDL (mmol/L)	NA	NA	NA	1.007 (1.002–1.01)	NS
AER (μg/min)	NA	NA	NA	NA	1.48 (1.33–1.66)
AIC	912.634	879.522	856.408	850.814	823.138
Women (*n* = 243; 84 incident hypertension cases)					
Diabetes duration (years)	1.02 (0.997–1.05)	NS	NS	NS	NS
Diagnosed in 1965–1980	NS	0.63 (0.40–0.99)	NS	NS	NS
WHR (per SD)	1.31 (1.01–1.69)	1.27 (0.98–1.66)	NS	NS	NS
HbA_{1c} (%)	NA	1.13 (0.99–1.29)	NS	NS	NS
SBP (mmHg)	NA	NA	1.06 (1.04–1.08)	1.06 (1.04–1.08)	1.06 (1.04–1.08)
DBP (mmHg)	NA	NA	1.03 (1.00–1.07)	1.03 (0.996–1.06)	NS
Non-HDL (mmol/L)	NA	NA	NA	1.008 (1.003–1.01)	1.006 (1.00–1.01)
AER (μg/min)	NA	NA	NA	NA	1.26 (1.13–1.41)
AIC	828.053	827.011	794.734	788.523	776.540

AIC, Akaike information criterion; DBP, diastolic blood pressure; HR, hazard ratio; NA, not applicable; NS, not selected. HRs for WHR are reported per 1 SD (0.068) increase. Model 1 allowed for diabetes duration, diabetes diagnosis cohort (1950–1964 vs. 1965–1980), and WHR. Model 2 allowed for variables in model 1, in addition to HbA_{1c} and insulin dose per weight. Model 3 allowed for variables in model 2, in addition to SBP and DBP. Model 4 allowed for variables in model 3, in addition to HDL and non-HDL cholesterol. Model 5 allowed for variables in model 4, in addition to AER, WBC count, and fibrinogen.

respectively) hindered assessment of such practice in multivariable models. When included in time-dependent analyses, intensive insulin therapy did not predict hypertension in either sex, potentially because such therapy was largely adopted in the later examination cycles, by which time hypertension would have developed in a large proportion of participants.

Similar findings of a more prominent role of hyperglycemia in the incidence of hypertension in male compared with female participants were also noted when mean HbA_{1c} levels throughout follow-up were considered. Moreover, the observed protective effect of insulin dose per kilogram body weight against hypertension incidence was also restricted to men in these analyses. The weaker relationship between glycemia and hypertension in women did not appear to be explained by a different distribution of HbA_{1c} by sex.

Table 3—*Cox proportional hazards models for hypertension incidence stratified by tertile of HbA_{1c} at study entry*

	HbA_{1c} <8.0%	8.0%< HbA_{1c} <9.2%	HbA_{1c} ≥9.2%
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1			
Sex			
Males	Referent	Referent	Referent
Females	2.67 (1.41-5.05)	1.22 (0.74–2.01)	0.61 (0.38–0.98)
AIC	398.816	657.428	667.120
Model 2			
Sex			
Males	Referent	Referent	Referent
Females	2.24 (1.17–4.27)	1.30 (0.77–2.18)	0.53 (0.32–0.86)
AIC	388.490	617.583	656.124

AIC, Akaike information criterion; HR, hazard ratio. Model 1 also allowed for diabetes duration, HbA1c, SBP, and DBP. Model 2 allowed for variables included in model 1 in addition to diabetes diagnosis cohort, insulin dose per weight, HDL and non-HDL cholesterol, AER, WBC count, and fibrinogen.

In the current analyses, hypertension incidence was slightly higher in men than in women. Male sex per se was also associated with increased hypertension risk in the DCCT/EDIC study of individuals with type 1 diabetes (11), as well as in the biracial cohort of the Coronary Artery Risk Development in (Young) Adults (CARDIA) study (26) and the Framingham Heart Study (27), among many others in the general population. Although not all reports concur that risk is greater among men, blood pressure has generally been reported to be higher in men than in women within the general population (28), with women exhibiting a lower risk for hypertension especially in the years prior to menopause, whereas risk becomes comparable between age-matched

men and postmenopausal women (29). This sex dimorphism and the observation of an important role of menopause have led to the hypothesis that sex hormones may act as modulators of vascular function and the pathogenesis of hypertension (30). Interestingly, a previous report also suggested that sex hormone–binding globulin and total testosterone are higher in male, but not female, children and young adults with diabetes compared with nondiabetic siblings, a finding apparently related to the absence of endogenous insulin (31). Whether such differences may account for the differential association between HbA_{1c} and hypertension incidence by sex could, unfortunately, not be evaluated, as hormone data are not available for EDC study participants. Moreover, as the associations reported in this manuscript were derived from a population where the majority of women are premenopausal, any conclusions made should be restricted to younger and middle-aged adults, as deviations from these relationships may be noted with longer follow-up, when more women would have reached menopause.

It has been suggested that the presence of hyperglycemia contributes to the excess risk of hypertension in individuals with diabetes by promoting vascular stiffness (10). Indeed, considerable evidence links hyperglycemia with increased flux through the polyol pathway and the reduction of glucose to sorbitol, increased formation of advanced glycosylation end products, and, importantly, generation of reactive oxygen species, which lead to vascular damage (10). Interestingly, our results suggest that the incidence of new-onset hypertension is higher in women compared with men among participants at better glycemic control but higher in men compared with women among those at worse glycemic control. The reason why glycemic stress may differentially affect a person's risk for developing hypertension based on their sex is currently unclear. As HbA_{1c} has improved over follow-up, it is possible that the impact of male predominance for hypertension at high HbA_{1c} has diminished in time, in a similar manner to what we have reported for renal disease (13) where the elimination of the male excess in advanced renal disease in the more recently diagnosed cohort may be potentially linked to improved glycemic control. A large body of literature has provided evidence that in addition to structural differences, developmental/environmental stressors may provoke a distinctive physiological response by sex (32). Thus, as here, although only a weak difference in hypertension incidence exists by sex, the pathogenesis of blood pressure elevation is likely to differ between men and women. This is consistent with our earlier observation of similar coronary artery disease incidences between men and women despite differences in risk factors by sex (12) and our recent report that HDL cholesterol shows a different relationship to coronary artery disease in women (U shaped) compared with men (inverse linear) in the EDC study, potentially explaining some of the loss of female protection against heart disease seen in type 1 diabetes (14).

Despite previously reported associations between BMI and hypertension incidence in the general population (26,27) as well as in type 1 diabetes (11), measures of body fatness (WHR and, in separate models, BMI) were not selected in the final prediction models in this study. However, AER, as measured at baseline and also as a time-dependent updated mean over the follow-up period, was significantly associated with increased risk for hypertension in both sexes. The categorization of study participants into normo- or microalbuminuric at the baseline assessment was also associated with increased risk of hypertension in both men (almost fourfold increased risk) and women (twofold increased risk). AER was strongly associated with the incidence of hypertension also in the report from the DCCT/EDIC study (11). A direct association between plasma lipid concentrations and hypertension incidence was also observed among women, although similarly strong associations were not seen among men.

In conclusion, the results of this study suggest that although hyperglycemia contributes to the development of hypertension, this effect is much stronger in men compared with women with type 1 diabetes. The reasons for this difference are not clear but merit further investigation as sex differences appear to be common in the natural history of type 1 diabetes complications, including coronary artery disease and kidney disease, both of which are closely related to hypertension.

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T.C. researched and analyzed data and wrote the manuscript. T.J.O. researched data, contributed to the discussion, and reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript. T.C. 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.

Preliminary analyses of this study were presented at the Scientific Sessions of the American Heart Association, Orlando, Florida, 14–18 November 2009.

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