Blood Pressure in Young Adulthood and the Risk of Type 2 Diabetes in Middle Age

Sherita Hill Golden, MD, MHS1,2
Nae-Yuh Wang, PhD1
Michael J. Klag, MD, MPH1,2

Lucy A. Meoni, SCM1,4
Frederick L. Brancati, MD, MHS1,2

OBJECTIVE — Hypertension is known to accompany type 2 diabetes in middle age, but it is unknown how early in life blood pressure (BP) begins to rise among individuals who later develop diabetes. The objective of this study was to evaluate elevated BP as a long-term predictor of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a prospective cohort study of 1,152 white male medical students in The Johns Hopkins Precursors Study to longitudinally assess systolic BP (SBP) and diastolic BP (DBP) from young adulthood through middle age in men who went on to develop diabetes. Incident diabetes was identified by self-report through mailed questionnaires verified by medical record review.

RESULTS — During a median follow-up of 38 years, 77 cases of incident diabetes occurred. The mean age of diabetes diagnosis was 58 years. As early as age 30 years, mean SBP and DBP were significantly higher in men who developed diabetes during follow-up than in those who remained nondiabetic (SBP 122 vs. 119 mmHg, P = 0.009; DBP 78 vs. 75 mmHg, P = 0.0005). The rate of increase in SBP and DBP over time in men who developed diabetes was greater than the rate of increase in men who did not develop diabetes (SBP 0.49 vs. 0.27 mmHg/year, P < 0.00003; DBP 0.24 vs. 0.17 mmHg/year, P = 0.09). After adjustment for BMI and other risk factors for diabetes, SBP and DBP at age 30 years remained significantly higher in individuals who developed diabetes than in their nondiabetic counterparts, however, the difference in the rate of increase in SBP was no longer significant following multivariate adjustment.

CONCLUSIONS — BP elevations precede the development of type 2 diabetes in middle age by 20–25 years. Higher BP in the prediabetic state might contribute to the presence of vascular disease at the time of diagnosis of type 2 diabetes.

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Hypertension is known to accompany diabetes in middle age and is a risk factor for diabetic vascular complications. Less well appreciated is how many years before the onset of diabetes blood pressure (BP) begins to rise.

Previous studies show that even within the range of normal BP, prediabetic individuals have higher BP 3–16 years before diagnosis compared with individuals who remain nondiabetic (1). Many patients with new-onset type 2 diabetes have evidence of complications, such as retinopathy, nephropathy, and cardiovascular disease, at the time of diagnosis (2). Elevated BP is a risk factor for diabetes complications, and high BP before the onset of diabetes may explain the high prevalence of cardiovascular disease at the time of diabetes diagnosis. Therefore, high BP before the onset of type 2 diabetes is a potential target for the prevention of diabetes complications.

The presence of hypertension may also be an indicator of the pathogenesis of type 2 diabetes. According to the “Common Soil Hypothesis” (3), elevated BP could be an early sign of underlying insulin resistance, related to central adiposity. An alternative hypothesis is that elevated BP is a marker of endothelial dysfunction, which is itself a risk factor for the development of insulin resistance, type 2 diabetes, and vascular disease (4–7).

Literature on BP before the onset of type 2 diabetes is limited by relatively short-term follow-up (1) and lack of data on explanatory risk factors for BP changes in prediabetic individuals (8). We therefore conducted a prospective study of elevated BP as a long-term predictor of type 2 diabetes in the Johns Hopkins Precursors Study, which has longitudinal data on BP from young adulthood through middle age. Particular attention was paid to BMI as a possible explanatory factor underlying both the elevated BP and the subsequent risk of type 2 diabetes. We also evaluated data on vascular reactivity from the cold pressor test, which is an indirect measure of endothelial function (9–11).

RESEARCH DESIGN AND METHODS

Study population

The Johns Hopkins Precursors Study was designed and initiated by Caroline Bedell Thomas, MD, in 1947 to identify precursors for cardiovascular disease. It is an ongoing, longitudinal cohort study of 1,337 former medical students at Johns Hopkins University School of Medicine, Balti-
more, MD, in the classes of 1948–1964. Individuals with type 1 diabetes at baseline or during follow-up (n = 8), those who died in medical school (n = 5), and those who did not participate in follow-up since graduation (n = 10) were excluded. Women (n = 121) and men of non-European ancestry (n = 30) were also excluded due to small numbers. White men without baseline BP measurements were also excluded (n = 11) from the analysis, leaving a cohort of 1,152 white men at risk for incident diabetes.

Data collection

At baseline during medical school, each participant underwent a detailed medical history and physical examination, including measurement of BP, height, and weight. Age range at baseline examination was 20–29 years. After medical school, follow-up data were collected using annual mailed questionnaires. In general, yearly response rates exceeded 70% and, during any 5-year interval, at least 85% of participants have responded at least once. In addition, ongoing mortality surveillance is conducted by review of alumni records and obituaries and by periodic National Death Index searches. A committee of internists reviews copies of the death certificates to assess cause of death and underlying medical conditions.

BP

BP was measured in medical school using a standard protocol on multiple occasions (median nine per participant); in contrast, BP after graduation was assessed by means of annual questionnaires (12). Participants were asked to measure their BP in the seated position. The average number of years that participants reported their BP was 11, with a range from 1 to 27 (median 16 per participant). Self-reports of BP in a subset of this cohort were remarkably accurate (13).

BMI

At baseline, height was measured with a stadiometer and weight with a balance-beam scale. BMI was calculated as weight in kilograms divided by the square of the height in meters. During follow-up, BMI was calculated from the weight participants reported on their annual questionnaires.

Vascular reactivity

The cold pressor test was performed on 1,068 white males using the Hines and Brown technique (14). After performing baseline measurements of BP and pulse, the right hand was immersed up to the wrist for 1 min in a bucket of ice water at 4°C. Blood pressure and pulse were measured in the left arm at 30 and 60 s and were recorded. The maximum change in systolic BP (SBP), diastolic BP (DBP), and heart rate from baseline was used as the measure of cold pressor reactivity. Details of this procedure have been described previously (15,16).

Covariates

Prevalence of diabetes in parents was assessed at baseline, and incidence of diabetes in parents was assessed prospectively annually after graduation. Physical activity was assessed in medical school, every 5 years after graduation until 1984, as well as in 1978, 1986, 1989, and 1993. Methods of assessment of physical activity varied over follow-up. Physical activity was assessed in medical school and over follow-up using the question, “How much physical training have you had in the past month?” Possible responses were “none,” “little,” “moderate,” and “much.” In 1978, 1986, 1989, and 1993, participants were asked the number of times per week that they engaged in physical activity vigorous enough to work up a sweat. This question was developed in the Harvard Alumni Study and has been validated in a number of populations (17). Based on data from years in which both questionnaires were administered, all responses were converted to a frequency–quantity scale based on number of episodes of vigorous physical activity per week. Responses to both questions show strong inverse relations to the incidence of hypertension in this cohort (18).

Information on cigarette smoking was obtained at baseline and during follow-up for physical activity (see above). Self-reports of smoking behavior have been validated in this cohort (13). The development of hypertension after graduation was assessed by means of annual questionnaires. Hypertension was defined as a reported BP ≥160/95 mmHg on one annual questionnaire, ≥140/90 mmHg on two or more annual questionnaires, or hypertension requiring drug therapy.

Data on the use of antihypertensive and cholesterol-lowering medication use were ascertained in a standardized fashion in 1991, a point by which 75% of person-years of follow-up was accrued. While data on specific classes of antihypertensives were collected, specific data on the type of cholesterol-lowering medications (i.e., statins versus other classes) were not collected. ACE-1 inhibitors and statins have recently been associated with a reduced incidence of diabetes (19,20). In this historical cohort, because relatively few individuals were using ACE inhibitors (4.2%) or any cholesterol-lowering medications (6%), the small numbers precluded us from considering use of these possibly protective drugs in our multivariate models.

The mean BMI, physical activity level, SBPs, and DBPs at age 50 years was determined by averaging each individual’s recorded data at or just before age 50 years. The percentage of smokers and cumulative incidence of hypertension were also determined at age 50 years for the cohort.

Outcome

Incident type 2 diabetes was defined as the occurrence of any one of the following conditions: report of pharmacologically treated diabetes on an annual mailed questionnaire (1), report of nonpharmacologically treated diabetes on two or more annual mailed questionnaires (2), physician diagnosis of diabetes in office or hospital records (3), report of a fasting plasma glucose level of at least 140 mg/dl or a nonfasting plasma glucose level of at least 200 mg/dl (4), and diagnosis of diabetes as an underlying or other condition on a death certificate (5). Between 1994 and 2000, a questionnaire was administered asking about a history of ketosis, immediate need for insulin therapy at diagnosis, or other features suggestive of type 1 diabetes. Individuals that met any of these criteria were considered to have type 1 diabetes and were excluded from the analysis. Of the 77 incident cases of diabetes used in this analysis, 21 (27%) were confirmed by medical records or death certificates and 36 (51%) of those who were still alive when the validation questionnaire was mailed) reported symptoms at presentation, elevated fasting glucose or glycohemoglobin levels, and/or antidiabetic medication use on the validation questionnaire.

Statistical analysis

BP measurements collected over the course of follow-up versus age at data collection were first visualized using scatter-
plot. The mean response profile of BP over time was explored using nonparametric regression spline estimation (21). The average rate of change in BP over time was determined for individuals who developed type 2 diabetes and for individuals who remained nondiabetic using the generalized estimating equations (GEE) approach developed by Liang and Zeger (22). GEE accounts for correlation of BP within individuals over time, allowing valid inferences from longitudinal data. The participants often reported more than one BP reading on an annual questionnaire, so the mean of all BPs reported was used in the analyses. Observations were censored once a participant was diagnosed as having diabetes.

The association between BP and type 2 diabetes was also investigated using survival analysis methodologies. Age was the time variable used in all survival analyses. The difference in diabetes incidence between BP changes to the cold pressor test was tested using the log-rank test (23). BP was also modeled as a time-dependent variable in Cox proportional hazards analysis (24) to determine how many years before the diagnosis of diabetes that BP differences were evident between individuals who developed diabetes and those who did not. In these analyses, the lag time before diagnosis was defined in 5-year intervals and the risk of developing diabetes was determined for each 10-mmHg increment in BP. Blood pressure with no years of lag time was defined by the level of most recent BP measure before the onset of diabetes among those with diabetes in comparison with BP at the same age among those without diabetes. Blood pressures with different lag times were defined in a similar fashion. Multivariate Cox proportional hazards models were developed to adjust for possible confounding variables including incidence of diabetes in parents as well as time-dependent data during follow-up on BMI, physical activity, and cigarette smoking. Individuals with missing data were excluded from the multivariate analysis. Estimates of relative risk and corresponding two-sided 95% CIs relating BP level to incidence of diabetes were computed from the Cox models. The cumulative incidence of subsequent diabetes associated with baseline cold pressor test was calculated for three categories of BP change (≥8 to 10, 11–20, and ≥21 mmHg) using Kaplan-Meier analysis (25). Differences in the mean baseline and follow-up variables at age 50 years were compared using a Student’s t test for continuous variables and a χ² test for categorical variables. All tests of significance were two-tailed with an α level of 0.05. Analyses were conducted using SAS statistical software (Version 8).

**RESULTS**

**Baseline characteristics**

Table 1 displays the baseline characteristics of the 1,152 initially nondiabetic white men included in the analysis. Individuals who developed type 2 diabetes over follow-up were, at baseline, less physically active, had higher BMI, were more likely to have a parental history of diabetes, and had higher SBPs and DBPs. However, men who developed diabetes did not show an elevated BP response to the cold pressor test at baseline; in fact, their DBP was lower than that of their nondiabetic counterparts.

**Incident type 2 diabetes**

Over a median follow-up of 38 years (interquartile range 34–44), 77 cases of incident diabetes occurred. The mean age at diabetes diagnosis was 58 years (32–77).

**BP before type 2 diabetes**

Figures 1A and B show the mean SBPs and DBPs, respectively, in diabetic and nondiabetic individuals versus age. Both SBPs and DBPs were higher in individuals who developed diabetes during follow-up than in those individuals who remained nondiabetic. As early as age 30 years, mean SBPs and DBPs were significantly higher in men who developed diabetes during follow-up than in those who remained nondiabetic (SBP 122 vs. 119 mmHg, P = 0.009; DBP 78 vs. 75 mmHg, P = 0.0005). After adjusting for time-dependent BMI, physical activity, and cigarette smoking, as well as parental history of diabetes, the differences in SBP and DBP remained statistically significant at age 30 years (SBP 124 vs. 121 mmHg, P = 0.03; DBP 80 vs. 77 mmHg, P = 0.01).

The rate of increase in SBP over time in men who developed diabetes was nearly twice as great as that in men who did not develop diabetes (0.49 vs. 0.27 mmHg/year, P = 0.0003). The rate of increase in DBP was marginally greater among the men who developed diabetes (0.24 vs. 0.17 mmHg/year, P = 0.09). However, differences in rates between individuals who developed diabetes and those who remained nondiabetic became statistically nonsignificant after multivariate adjustment (0.31 vs. 0.20 mmHg/year for SBP, P = 0.1; 0.07 vs. 0.07 mmHg/year for DBP, P = 0.92).

Table 2 shows the relative hazard (RH) of developing diabetes for a 10-mmHg higher SBP or DBP by years before diagnosis of diabetes. As early as 25 years before the onset of diabetes, the risk of developing diabetes was associated with higher SBP (RH 1.57, 95% CI 1.26–1.96) and DBP (1.64, 1.14–2.36). Adjustment for BMI, parental history of diabetes, and physical activity attenuated the risks somewhat, but for almost all time points studied the RHs remained statistically significant.

Treatment for hypertension before the diagnosis of diabetes might obscure the relation between BP and incident dia-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Developed diabetes</th>
<th>Did not develop diabetes</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>77</td>
<td>1,075</td>
<td></td>
</tr>
<tr>
<td>Mean age at graduation (years)</td>
<td>27 (2)</td>
<td>26 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Parental history of diabetes (%)</td>
<td>38</td>
<td>23</td>
<td>0.003</td>
</tr>
<tr>
<td>Exercise (times/week)†</td>
<td>0 (1)</td>
<td>1 (1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking (cigarette/day)†</td>
<td>10 (13)</td>
<td>9 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119 (12)</td>
<td>116 (9)</td>
<td>0.02</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73 (8)</td>
<td>70 (7)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cold pressor test SBP change (mmHg)†</td>
<td>12 (9)</td>
<td>12 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Cold pressor test DBP change (mmHg)†</td>
<td>12 (9)</td>
<td>15 (9)</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 (4)</td>
<td>23 (2)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data for continuous variables, summary statistic is mean (SD), for categorical variables, summary statistic is percentage of individuals with a given characteristic. †P for Student’s t test for continuous variables and for χ² for categorical variables. ‡Available on a subset of 967–1,135 of 1,152 individuals.
Type 1 diabetes occurring in middle age could also be misclassified as type 2 diabetes. We therefore conducted a subsidiary analysis where individuals with hypertension or diabetes diagnosed before age 50 years were excluded. These results were similar to the main analysis, showing that mean SBP and DBP as early as age 35 years were significantly higher in men who later developed diabetes compared with those who remained non-diabetic (SBP 123 vs. 120 mmHg, \( P < 0.008 \); DBP 77 vs. 75 mmHg; \( P < 0.02 \)). Also, compared with their nonhypertensive counterparts, men with hypertension before age 50 years were three times more likely to develop diabetes (RH 3.2, 95% CI 1.8–5.7).

Changes in related variables across the lifespan

To provide a context, we characterized other variables related to BP and diabetes at age 50 years. Compared with men who did not develop diabetes, those who developed diabetes were less physically active (exercise 2.6 vs. 1.8 times/week, \( P < 0.001 \)), had higher BMI (26.9 vs. 24.3 kg/m\(^2\), \( P < 0.0001 \)), and higher SBP (131 vs. 124 mmHg, \( P < 0.001 \)) and DBP (82 vs. 78 mmHg, \( P < 0.001 \)) at age 50 years. The cumulative incidence of hypertension by age 50 years was higher for men who developed diabetes than for those who did not (26 vs. 11%). There was no difference in the percentage of smokers at age 50 years between men who developed diabetes and those who did not.

Vascular reactivity before type 2 diabetes

Contrary to our hypothesis, the DBP response to the cold pressor test appeared lower in individuals who went on to develop diabetes compared with their non-diabetic counterparts. However, this apparent effect was markedly attenuated in a longitudinal Kaplan-Meier analysis (\( P = 0.21 \)). SBP response to the cold pressor test showed no difference between diabetic and nondiabetic men at baseline or in longitudinal analyses.

Table 2—RH of incident type 2 diabetes per 10-mmHg higher BP by year of BP measurement before the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Years before type 2 diabetes diagnosis</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td></td>
<td>DBP</td>
<td></td>
</tr>
<tr>
<td>0*</td>
<td>1.47 (1.25–1.72)</td>
<td>1.25 (1.05–1.48)</td>
<td>1.37 (1.02–1.83)</td>
<td>1.12 (0.84–1.50)</td>
</tr>
<tr>
<td>5</td>
<td>1.42 (1.20–1.67)</td>
<td>1.19 (0.99–1.43)</td>
<td>1.61 (1.28–2.02)</td>
<td>1.29 (0.99–1.67)</td>
</tr>
<tr>
<td>10</td>
<td>1.60 (1.35–1.89)</td>
<td>1.33 (1.11–1.60)</td>
<td>1.82 (1.35–2.46)</td>
<td>1.37 (1.01–1.88)</td>
</tr>
<tr>
<td>15</td>
<td>1.58 (1.32–1.90)</td>
<td>1.32 (1.09–1.60)</td>
<td>2.02 (1.48–2.74)</td>
<td>1.56 (1.14–2.13)</td>
</tr>
<tr>
<td>20</td>
<td>1.53 (1.25–1.88)</td>
<td>1.34 (1.06–1.68)</td>
<td>2.32 (1.70–3.17)</td>
<td>1.93 (1.39–2.69)</td>
</tr>
<tr>
<td>25</td>
<td>1.57 (1.26–1.96)</td>
<td>1.42 (1.11–1.82)</td>
<td>1.64 (1.14–2.36)</td>
<td>1.42 (0.96–2.09)</td>
</tr>
</tbody>
</table>

Data are RH (95% CI). *Time 0 BP was defined as the most recent BP before the onset of diabetes among those with diabetes in comparison with BP at the same age among those without diabetes; †adjusted for parental history of diabetes, time-dependent BMI, time-dependent cigarette smoking, and time-dependent physical activity.
CONCLUSIONS — We found that BP elevations in young adulthood precede the development of diabetes in middle age by 20–25 years. These BP differences are only partially explained by greater adiposity in prediabetic individuals and are independent of other risk factors for type 2 diabetes, including family history of diabetes, physical activity, and smoking. We also demonstrated a greater risk of developing diabetes in individuals with hypertension. However, we found no difference in the BP response to the cold pressor test and subsequent development of diabetes.

Strengths of this study include long-term follow-up beginning in young adulthood, availability of longitudinal data on a variety of relevant covariates, and validity of BP and diabetes self-report in this cohort of physicians. Nonetheless, several limitations should be kept in mind in interpreting our data. First, data collection beyond baseline relied entirely on self-report. However, over 90% of incident diabetes cases were confirmed by review of other sources, and self-report of chronic diseases in this cohort of physicians has been shown to have a high degree of validity. Second, detailed data on lipoproteins, insulin, blood glucose levels, and other predictors of diabetes were not available. Third, we lacked power to evaluate the protective effects of ACE inhibitors and statins on the development of diabetes. Fourth, our data included only white men because the number of women and other ethnicities was too small to allow subgroup analyses. Fifth, the BP response to the cold pressor test may not have been an adequate assessment of endothelial function so early in the course of the prediabetic state, which might explain our finding of a lack of association between the cold pressor response and incident diabetes. The cold pressor test, however, is still used to measure coronary artery vasomotion, and an abnormal response to this test (i.e., coronary artery vasoconstriction) has been demonstrated in individuals with the metabolic syndrome (considered to be a prediabetic state) (26), hypertension (9,11), and atherosclerosis (10,27).

Paffenbarger et al. (8) published one of the earliest studies showing higher BP in individuals who subsequently developed diabetes. In this study of Harvard and Penn alumni, those who developed diabetes during follow-up had higher SBP (121.8 mmHg) at baseline (mean age 18 years) than those who remained nondiabetic (120.3 mmHg). There was no difference in DBP between these two groups. In addition, individuals with baseline SBP >130 mmHg had a 25% increased risk of developing diabetes compared with those with baseline SBP <130 mmHg, and 82% of adults who developed diabetes had hypertension before the diagnosis. No attempt was made to determine whether these relations were explained by adiposity or other shared risk factors. More recently, several studies have demonstrated a BP-diabetes relation (1, 28–33), some independent of adiposity (1). However, these studies were limited to middle-aged individuals and lacked data on BP in young adulthood (28,31).

At least three alternative hypotheses have been discussed as possible biological explanations for the relation of BP to diabetes risk. One hypothesis is that high BP is simply a marker for underlying insulin resistance, which constitutes a “common soil” for BP, diabetes, and cardiovascular disease (34).

A second hypothesis is that pharmacological treatment of hypertension promotes glucose intolerance; however, one recent study suggests that antihypertensive therapy is not a major risk factor for subsequent diabetes (33). A third alternative hypothesis is that elevated BP is an indicator of vascular dysfunction, which, in turn, leads to insulin resistance via impaired glucose and nutrient delivery to skeletal muscle (35–37). In our study, there was no important difference in baseline endothelial function between individuals who became diabetic and those who remained nondiabetic, despite higher BP in the prediabetic individuals. The exact role, if any, of hypertension in the development of diabetes remains controversial, and our study had limited data to explore these hypotheses.

Mounting evidence suggests that cardiovascular disease is present at or before the diagnosis of diabetes (38). A possible implication of our study is that elevated BP in the prediabetic state may be a contributing factor. Whether identification and treatment of high BP in young adulthood might prevent diabetic vascular complications or even diabetes itself requires further study.

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References