Mid-life Blood Pressure Levels and the Eight-Year Incidence of Type 2 Diabetes Mellitus: The Rancho Bernardo Study

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Abstract

Type 2 diabetes mellitus (T2DM) and hypertension frequently occur together. We examined whether blood pressure (BP) levels predict eight-year incident diabetes. Participants were community-dwelling older adults who had BP measured twice and an oral glucose tolerance test at baseline and again 8.3 years later. At baseline, participants were classified as normotensive [systolic (SBP) <120 mmHg and diastolic (DBP) <80 mmHg; n=242]; prehypertensive (SBP 120 and <140 mmHg or DBP 80 and <90 mmHg; n=426); or hypertensive (SBP 140 mmHg or DBP 90 mmHg or using anti-hypertensive medication; n=457). There were 1125 participants (mean age 66.0 years; 44.3% men) who attended the baseline and follow-up visit, of whom 85 had new onset T2DM. Participants who developed T2DM had higher mean body mass index (BMI) and BP levels than those who did not develop diabetes. In logistic regression models adjusted for age, sex, BMI, and physical activity, the odds of incident T2DM was greater in prehypertensives (OR2.32 95%CI 1.05–5.1, P=0.03) and hypertensives (OR3.5 95%CI 1.50–8.0, P=0.002) compared to normotensives. Excluding participants who used anti-hypertensive medications did not change results. In conclusion, mid-life hypertension and prehypertension predicted future diabetes, independent of BMI. Glucose surveillance should be encouraged in adults with prehypertension or hypertension.

Keywords

blood pressure; diabetes; hypertension; obesity; prospective

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Introduction

Hypertension and type 2 diabetes mellitus (T2DM) are both associated with obesity and frequently occur together 1,2. Surprisingly few cohort studies have examined blood pressure (BP) as an independent risk factor for future T2DM. The large Women's Health Study 3 showed that self-reported BP was a strong predictor of self-reported T2DM in 38172 women; the MONICA/KORA study found that hypertension increased the risk for reported future T2DM in 11001 participants 4. Neither of these studies had the ability to fully exclude T2DM at baseline nor fully confirm a new diagnosis at follow up, because participants did not have an oral glucose tolerance test (OGTT) at both visits.

We present here the 8-year risk of new T2DM confirmed by OGTT according to baseline measured BP levels in community-dwelling mid-life adults, before and after adjusting for covariates.

METHODS

Study population

Participants were members of the Rancho Bernardo Study, a southern California community of middle to upper-middle class Caucasian adults established in 1972. These individuals were initially enrolled in a study of heart disease risk factors as part of the Lipid Research Clinics Prevalence Program. The health of these participants has been followed ever since with periodic clinic visits and yearly mailed questionnaires. The details of the initial study have been described previously5.

Between 1984 and 1987, 80% of surviving local community-dwelling participants attended a research clinic visit when they had an OGTT, along with measurement of classic heart disease risk factors. The 1125 participants without T2DM at baseline (fasting plasma glucose <7 mmol/L, 2-h post-challenge glucose <11.1 mmol/L, and no diabetes medication) were evaluated for incident T2DM 8.3 years later (SD ± 1.0, maximum 17 years) 6.

All participants provided written informed consent at both visits. The study was approved by the Human Research Protection Program at the University of California, San Diego.

Data collection

Height and weight were measured in participants wearing light clothing without shoes, using a regularly calibrated scale and stadiometer. Body mass index (BMI) was calculated as weight (kilograms)/height (meters)2. Waist circumference was measured midway between the inferior lateral margin of the ribs and the superior lateral border of the iliac crest. Systolic and diastolic BP (SBP, DBP) were measured twice in seated resting subjects by certified staff according to a standard protocol 7. Participants were seated quietly for at least 5 minutes prior to BP measurement in a chair, with feet on the floor, and arm supported at heart level. The auscultatory method of BP measurement with a properly calibrated and validated instrument was used.

Other cardiovascular risk factors including family history of T2DM, current cigarette smoking, and physical activity (exercise 3 times/week) were self-reported using standard questionnaires. Medication was validated by a nurse who examined pills and prescriptions brought to the clinic for that purpose.

Fasting total, HDL, and LDL cholesterol and triglyceride levels were measured in a Center for Disease Control Certified Lipid Research Clinic Laboratory in morning blood samples collected after an overnight, usually 12-hour, fast. Total cholesterol and triglyceride levels were measured by enzymatic techniques using an ABA-200 biochromatic analyzer (Abbott Laboratories, Irving, TX). HDL was measured after precipitation of the other lipoproteins with heparin and manganese chloride. LDL was estimated using the Friedewald formula 8. Plasma glucose levels were measured by the glucose oxidase method, plasma insulin by double-antibody RIA, and serum creatinine by the Jaffe reaction method. Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was used to estimate insulin resistance according to the formula: insulin (mU/l) $\times$ glucose (mmol/l))/22.5 9.

Statistical analyses

T2DM (incident and baseline) was defined as fasting plasma glucose 7 mmol/L and/or 2-h post-challenge glucose 11.1 mmol/L and/or diabetes previously diagnosed by a physician and/or use of diabetes specific medication 6.

BP was considered as a continuous and categorical variable. For the latter, baseline BP was divided into 3 groups: 1) Normotensives: SBP <120 mm Hg and DBP <80 mm Hg; 2) Prehypertensives: SBP 120 and <140 mm Hg or DBP 80 and <90 mm Hg; 3) Hypertensives: SBP 140 mm Hg or DBP 90 mm Hg or current use of anti-hypertensive medication 1.

Variables with normal distribution were presented as means ± standard deviation (SD) and those with non-normal distribution as medians and inter-quartile range. Variables with non-normal distribution were log-transformed for analysis. In univariate analyses, clinical characteristics were compared by BP classification using analysis of variance (for continuous variables) or Chi-square (for categorical variables).

Logistic regression models were used to examine the likehood for incident T2DM by BP levels and were adjusted for known covariates in four separate models. Three models included age, sex, physical activity, and measures of obesity/insulin resistance (BMI, waist circumference or HOMA-IR--each separately). A fourth model added baseline fasting plasma glucose and family history of diabetes. All covariates were chosen based on a univariate association with the outcome. Significant collinearity between independent variables and significant interactions were not observed. The Hosmer and Lemeshow test was applied to evaluate whether the estimates of the model fit the data at an acceptable level (P >0.05). Receiver-operating characteristic (ROC) curves were constructed to calculate sensitivity and specificity of BP levels in identifying incident T2DM.

All analyses were performed using SPSS (version 13.1, SPSS, Inc., Chicago, IL). P values (two tailed) <0.05 were considered statistically significant.

Results

Among the 1125 older adults without diabetes at baseline (mean age 66.0 ± 10.7 years; 44.3% male), 21.5% were normotensive (n = 242), 37.9% were prehypertensive (n = 426), and 40.6% were hypertensive (n = 457). As shown in Table 1, BP categories were positively and linearly associated with age BMI, waist girth, fasting plasma glucose, triglycerides, and HOMA-IR.

During follow up (mean 8.3 ± 1.0 years, maximum 17 years), there were 85 new cases of T2DM (9, 32, and 44 among normotensive, prehypertensive, and hypertensive, respectively). Participants who developed T2DM had higher baseline BMI (26.4 ± 4.0 vs. 24.9 ± 3.5 kg/m^2, P <0.001) and BP levels (systolic: 139 ± 18 vs. 131 ± 19 mm Hg, P <0.001; diastolic: 78 ± 9.4 vs. 76 ± 9 mm Hg, P = 0.02) compared with those who did not develop T2DM. Pulse pressure did not differ by T2DM incidence (no-T2DM: 58.6 ±18.4 mm Hg vs. 60.3 ± 14.7 mm Hg in those who developed T2DM, P = 0.32). The proportion of normotensives, prehypertensives, and hypertensives among those who developed T2DM and those who did not was 10.6%, 37.6%, 51.8%, and 29.1%, 42.7%, 28.3%, respectively (P for trend <0.001).

Table 2 shows that prehypertension and hypertension increased the risk for incident T2DM compared to the normotensive reference group in analyses adjusted for age, sex, physical activity, measures of obesity/insulin resistance (BMI, waist circumference and HOMA-IR separately), fasting plasma glucose, and family history of diabetes. The same pattern was observed using BP as a continuous variable: each increment of 10 mm Hg in systolic BP increased the risk for future T2DM by approximately 13% in all models (see Figure 1), each increment of 5 mm Hg in diastolic BP increased the risk of incident T2DM by approximately 15% in age-adjusted models and in model 3, and each 10 mm Hg increment in pulse pressure increased the risk of incident T2DM by 20% in all models. Because diuretics and beta-blockers have been associated with an increased risk of diabetes, we repeated the analyses excluding the 181 participants taking anti-hypertensive medication; this did not materially change any of the results. Further adjustments for smoking status and alcohol intake did not change any of the results.

Figure 2 shows the ROC curve for T2DM. As shown, the negative predictive value (NPV) of SBP level of 130.5 mm Hg was 92.5% (sensitivity 67.1% and specificity 45.1%), and for DBP level of 90.5 mm Hg 93.6% (sensitivity 14.1% and specificity 93.6%). Pulse pressure value less than 38.5 mm Hg had a NPV of 92.8% (sensitivity 91% and specificity 13%).

In a sensitive analysis (adjusted for age, sex, and physical exercise) stratified by BMI (<25 kg/m^2 and 25 kg/m^2), we determined whether BP levels predicted T2DM only among overweight/obese participants. Compared to the normotensive group, being prehypertensive or hypertensive increased the risk for incident T2DM in the overweight/obese group (prehypertensive OR 3.4 95%CI 1.00–12, P = 0.049; hypertensive OR 7.1 95%CI 2.0–25, P = 0.002) but not in the normal-weight group (prehypertensive: OR 1.2 95%CI 0.4–3.5, P = 0.73; hypertensive: OR 2.2 95%CI 0.8–6.7, P = 0.13).

Discussion

In this population-based study, higher baseline BP levels evaluated both as categories (prehypertension and hypertension) and as continuous values were strong and independent predictors of incident T2DM in men and women. Furthermore a BP below 130.5/90.5 mm Hg had a high NPV for future T2DM (~ 94%).

Previously The Women's Health Initiative Study (38172 women followed for 10.2 years) demonstrated that being prehypertensive and hypertensive increased the risk for incident T2DM by 45% and 100%, respectively, in age-adjusted analysis3. The MONICA/KORA study (11001 men and women followed for 12.5 years) replicated these results in a general population: hypertension was associated with a 2-fold risk for future diabetes in adjusted models 4. These reports of an association between hypertension *per se* and incident T2DM were based on self-reported incident diabetes. Our paper is the first to demonstrate that measured BP levels predict T2DM defined at baseline and follow up by OGTT.

A recent report of 1754 Italian men with hypertension showed that men with uncontrolled hypertension had a higher risk of new diabetes compared to men who had controlled hypertension 10. The present study also demonstrates that the higher the baseline BP, the greater risk for subsequent T2DM. Also, our results demonstrated that the lowest BP levels (130.5/90.5 mm Hg) were associated with very small likelihood for incident diabetes (NPV 92.3%).

The reason why higher BP levels predict an increase risk of T2DM is not clear, but several hypotheses are reasonable. An association between hyperinsulinemia the primary metabolic derangement of T2DM pathogenesis--and hypertension has been known for more than two decades 11,12. Insulin has been associated with several potential mechanisms that could increase BP levels, such as sodium retention, sympathetic nervous system overactivity, disturbed membrane ion transport, and proliferation of vascular smooth muscle cells 12. However, a previous cross-sectional report from the Rancho Bernardo Study did not show that insulin was independently associated with hypertension 13. Another potential explanation is that high BP levels cause microvascular dysfunction that precede islet cell failure as shown in animal models 14; in epidemiological studies, biomarkers of endothelial dysfunction independently predict T2DM 15,16. Alternatively BP and T2DM could share a common gene polymorphism; for example, the renin-angiotensin system gene polymorphism associated with essential hypertension 17 has also been associated with increased risk for T2DM 18,19, although these results were not replicated in other studies20,21.

The present study has the strengths of a well-characterized prospective cohort study. Baseline BP was measured twice by certified staff, medication use was validated, and diagnosis of baseline and outcome diabetes included an OGTT. Despite the older age of the cohort at the baseline visit, there was an 80% survival rate to the second visit. However, some study limitations should be noted. The participants are middle- to upper-class Caucasians, mainly of European origin, who moved to Rancho Bernardo in midlife; results may not be generalizeable to other populations. Another possible limitation is the relatively

small number of incident T2DM that did not permit further BP stratification (e.g., normal vs. high normal) because of power analysis issues.

Although the current clinical guideline for high BP treatment (from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) in the United States recommends obtaining a panel of laboratory tests to evaluate the cardiovascular risk profile of individuals with hypertension defined as SBP 140 mm Hg or DBP 90 mm Hg) 1, the present study shows that prehypertension doubles the risk for future diabetes, suggesting that glucose surveillance is important not only in hypertensives but also in prehypertensives.

In conclusion, BP defined as categorical (prehypertension and hypertension) and continuous variables is an independent predictor of incident diabetes. These results highlight the potential value of glucose surveillance in adults with hypertension or prehypertension.

Summary table

What is known about topic

- Hypertension and type 2 diabetes mellitus (T2DM) are both associated with obesity and frequently occur together.

- Previous cohort studies have shown that hypertension is an independent risk factor for future self-reported T2DM

What this study adds

- This study shows that mid-life hypertension and prehypertension predict future T2DM independent of body mass index and blood pressure medication in community-dwelling adults with new T2DM confirmed by an oral glucose tolerance test at baseline and follow- up visits.

- Blood pressure levels increase the risk of future T2DM also as a continuous variable (each increment of 10 mmHg in systolic blood pressure and/or 5 mm Hg in diastolic blood pressure levels increase the risk of T2DM by ~ 13% in multivariate models).

- Low blood pressure levels such as levels below 130.5/90.5 mm Hg had a high negative predictive value for future T2DM (~ 94%).

Acknowledgments

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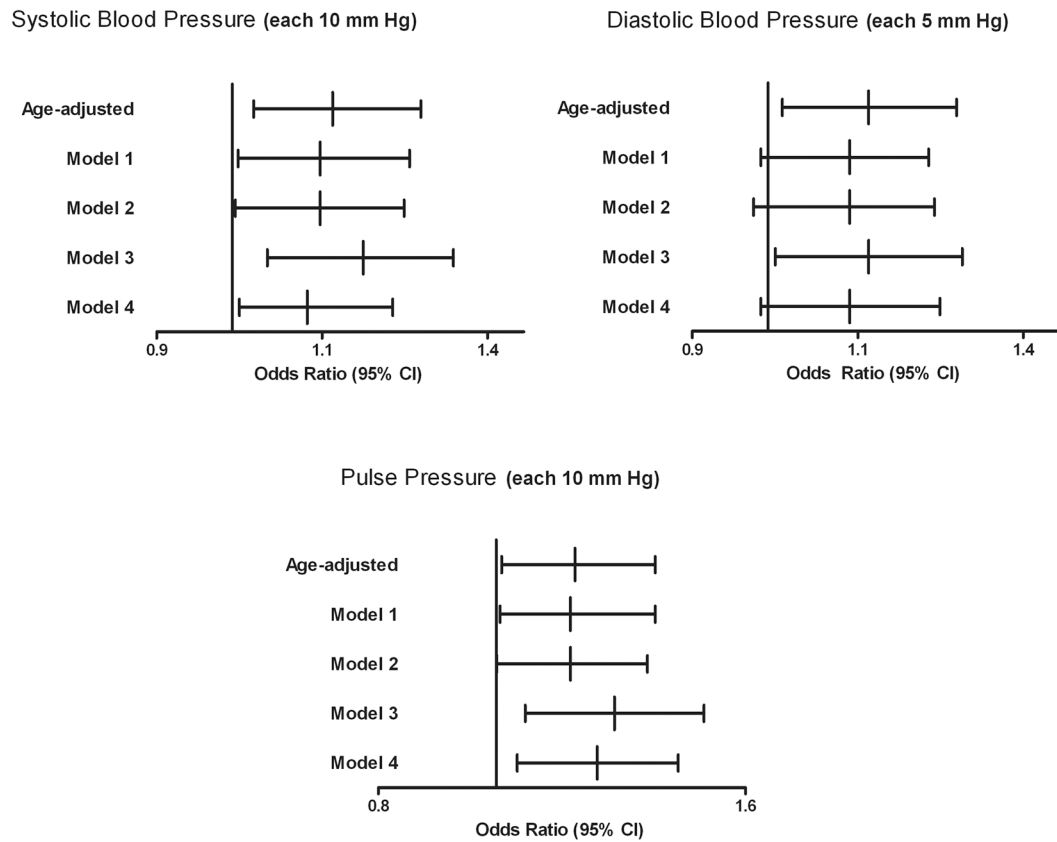
Systolic Blood Pressure **(each 10 mm Hg)**

Diastolic Blood Pressure **(each 5 mm Hg)**

Pulse Pressure **(each 10 mm Hg)**

Figure 1.
Age-adjusted and multivariate-adjusted odds ratio for type 2 diabetes mellitus incidence and blood pressure levels. Model 1: adjusted for age, sex, physical exercise and body mass index; Model 2: adjusted for age, sex, physical exercise and waist circumference; Model 3: adjusted for age, sex, physical exercise and HOMA-IR; Model 4: adjusted for age, sex, physical exercise, body mass index, fasting plasma glucose and family diabetes history.
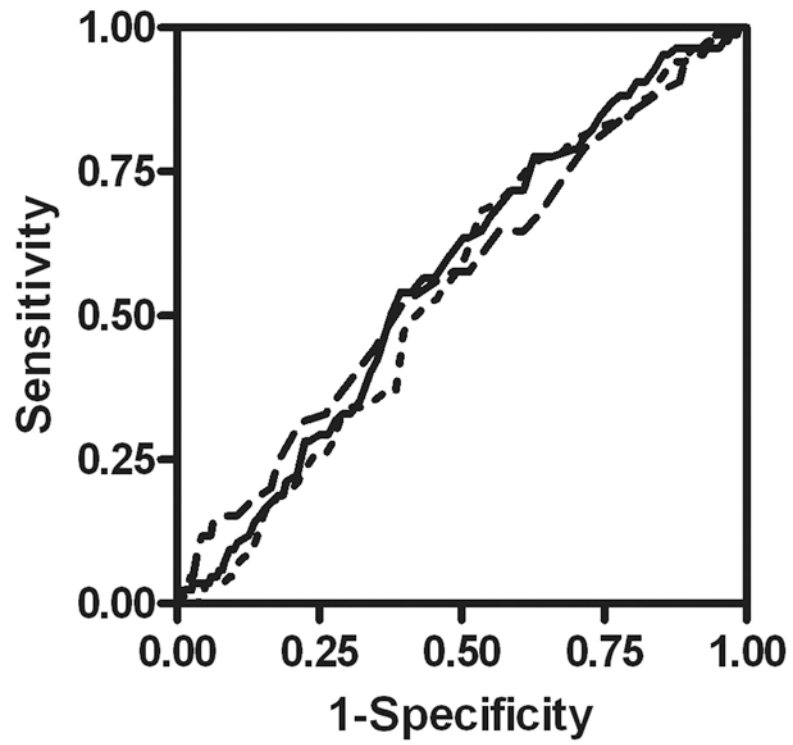
Figure 2.
Receiver-operating characteristic of systolic blood pressure (—), diastolic blood pressure (–
–), and pulse pressure (- -) for incident diabetes.

Table 1

Baseline characteristics by blood pressure classification

	Normotensive (n = 242)	Prehypertensive (n = 426)	Hypertensive (n = 457)	P value[*]
Mean age (yrs)	58.8 ± 9.7	65.3 ± 8.8	69.6 ± 8.0	<0.001
Men (%)	37.3	43.5	39.4	0.71
Regular exercise (%)	84.6	80.4	83.3	0.31
Alcohol intake 3 times/week (%)	42.9	42.9	38.5	0.38
Current smoking (%)	16.6	9.6	10.4	0.04
Body mass index (kg/m^2)	24 ± 2.9	25.1 ± 3.6	25.0 ± 3.5	<0.001
Waist girth (cm)	80.2 ± 11.6	84.7 ± 11.8	84.6 ± 11.5	<0.001
Systolic blood pressure (mm Hg)	109 ± 7	128 ± 6	153 ± 16	<0.001
Diastolic blood pressure (mm Hg)	69 ± 6	75 ± 7	81 ± 10	<0.001
Pulse pressure (mm Hg)	40 ± 7	54 ± 9	74 ± 16	<0.001
Fasting plasma glucose (mmol/L)	5.22 ± 0.5	5.30 ± 0.5	5.45 ± 0.5	<0.001
Fasting insulin (pmol/L)	75.6 ± 47.4	81.0 ± 61.2	85.2 ± 56.4	0.05
Total cholesterol (mmol/L)	5.63 ± 1.08	5.67 ± 0.93	5.73 ± 1.00	0.28
LDL-c (mmol/L)	3.46 ± 1.03	3.48 ± 0.88	3.46 ± 0.92	0.97
HDL-c (mmol/L)	1.60 (0.64)	1.52 (0.64)	1.65 (0.62)	0.53
Triglycerides (mmol/L)	0.98 (0.80)	1.08 (0.72)	1.15 (0.85)	0.03
HOMA IR[**]	2.8 ± 1.4	3.0 ± 1.9	3.1 ± 2.0	0.04
Creatinine (μmol/L)	88.4 ± 19.4	88.4 ± 17.7	97.3 ± 17.7	0.24

Mean ± standard deviation or median (range interquartile).

[*] p for trend for continuous variables (ANOVA) and p value for difference between categorical variables (Chi-square).

[**] Homeostasis Model Assessment for Insulin Resistance--available for n = 205, 306, and 248

Table 2

Age-adjusted and multivariate-adjusted odds ratio (95% confidence intervals) for incident Type 2 Diabetes Mellitus by baseline prehypertension and hypertension status compared to normal blood pressure at baseline (reference group)

	Prehypertensive			Hypertensive		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Age-adjusted	2.4	1.1–5.3	0.02	5.1	2.3–11.2	<0.001
Model 1: adjusted for age, sex, physical exercise and body mass index	2.32	1.05–5.1	0.03	3.5	1.5–8.0	0.002
Model 2: adjusted for age, sex, physical exercise and waist circumference	2.4	1.1–5.4	0.02	3.7	1.6–8.4	0.002
Model 3: adjusted for age, sex, physical exercise and HOMA-IR	2.5	1.07–5.8	0.03	4.6	1.9–10.0	0.001
Model 4: adjusted for age, sex, physical exercise, body mass index, fasting plasma glucose and family diabetes history	2.28	1.03–5.0	0.04	3.7	1.7–8.5	0.002