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Fasting Insulin Level Is Positively Associated With Incidence of Hypertension Among American Young Adults

A 20-year follow-up study

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OBJECTIVE—Although hyperinsulinemia, a surrogate of insulin resistance, may play a role in the pathogenesis of hypertension (HTN), the longitudinal association between fasting insulin level and HTN development is still controversial. We examined the relation between fasting insulin and incidence of HTN in a large prospective cohort.

RESEARCH DESIGN AND METHODS—A prospective cohort of 3,413 Americans, aged 18–30 years, without HTN in 1985 (baseline) were enrolled. Six follow-ups were conducted in 1987, 1990, 1992, 1995, 2000, and 2005. Fasting insulin and glucose levels were assessed by a radioimmunoassay and hexokinase method, respectively. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CIs of incident HTN (defined as the initiation of antihypertensive medication, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg).

RESULTS—During the 20-year follow-up, 796 incident cases were identified. After adjustment for potential confounders, participants in the highest quartile of insulin levels had a significantly higher incidence of HTN (HR 1.85 [95% CI 1.42–2.40]; $P_{\text{trend}} < 0.001$) compared with those in the lowest quartile. The positive association persisted in each sex/ethnicity/weight status subgroup. A similar dose-response relation was observed when insulin-to-glucose ratio or homeostatic model assessment of insulin resistance was used as exposure.

CONCLUSIONS—Fasting serum insulin levels or hyperinsulinemia in young adulthood was positively associated with incidence of HTN later in life for both men and women, African Americans and Caucasians, and those with normal weight and overweight. Our findings suggested that fasting insulin ascertainment may help clinicians identify those at high risk of HTN.

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Hypertension (HTN), a leading cause of cardiovascular morbidity and mortality, has become an important public health burden worldwide (1). It has been well established that HTN tends to coexist with diabetes (2,3), either preceding or being the complication of

diabetes. In addition, the risk factors for HTN and diabetes are prone to cluster together, and it has been hypothesized that hyperinsulinemia, a surrogate measure of insulin resistance, might provide the pathophysiological mechanism underlying these observations (4).

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Some epidemiological studies, including both cross-sectional and longitudinal studies, have indicated that insulin levels are associated with blood pressure (BP) as well as incidence of HTN (5–7). However, inconsistent findings (8,9), especially in a specific sex or ethnic subgroup (10,11), made this topic a controversy. In addition, among the limited prospective studies on the association of insulin level with incidence of HTN (5,6,9,12–14), most have been conducted in only one sex or one ethnic group (9,12–14). Few studies have examined the association in both men and women, and African Americans (AAs) and Caucasians (5,6). Therefore, we prospectively examined fasting insulin level in relation to incidence of HTN in a large biracial cohort of American men and women over 20 years of follow-up using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study.

RESEARCH DESIGN AND METHODS

Study design

The CARDIA study is an ongoing, prospective, multicenter, observational study of the natural history of the development of cardiovascular disease risk from young adulthood to midlife. In 1985, 5,115 young adults between the ages of 18 and 30 years were randomly selected from four U.S. cities: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. The sampling scheme was designed to achieve a balance at each site by age (18–24 and 25–30 years), sex, ethnicity (AA and Caucasian), and education (high school degree or less and more than high school). To date, six follow-ups have been conducted at examination years 2, 5, 7, 10, 15, and 20. Follow-up rates averaged $>90\%$, and $\sim 70\%$ of the participants in the original cohort returned at year 20.

More details of the study design and recruitment protocol have been previously reported (15). The institutional review committee approval and informed consent was obtained for each examination.

Among those who had serum insulin measured at baseline ($n = 3791$), we excluded participants who had not fasted for at least 8 h ($n = 80$) or were pregnant at any examination ($n = 200$) or were diagnosed as HTN at baseline ($n = 98$) in a sequential manner. After all these exclusions, 3,413 participants remained in the sample.

Ascertainment of insulin and glucose

Fasting blood samples were collected according to standardized CARDIA procedures and processed at central laboratories (15). Fasting serum insulin was measured originally by a nonspecific insulin assay at baseline and in later examinations by a new radioimmunoassay (Linco Research Inc., St. Charles, MO). To assure comparability of insulin across visits, sera stored from baseline was re-measured by the new assay 8 years later (16). The Pearson correlation of log insulin values for baseline by the original (17) and the new method (18) was 0.81. Fasting glucose was detected by hexokinase method on a Cobas Mira Plus chemistry analyzer at each examination (16). On the basis of re-assays of glucose in 2006 and 2007 in ~200 samples per examination drawn at years 7, 10, 15, and 20, and of insulin in 100 samples stored since year 15, glucose and insulin were recalibrated to harmonize them with the previous measurements. Recalibrated glucose values were $6.98 + 0.94 \times \text{year 7 glucose concentration}$, $7.15 + 0.96 \times \text{year 10 glucose concentration}$, $6.99 + 1.01 \times \text{year 15 glucose concentration}$, and $4.06 + 0.97 \times \text{year 20 glucose concentration}$. Recalibrated insulin was $-0.36 + 0.93 \times \text{year 20 insulin concentration}$ (19). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as $\text{glucose (mmol/L)} \times \text{insulin (mU/L)} / 22.5$ (20).

Ascertainment of HTN

BP was measured at the first six examinations using the Hawksley random-zero sphygmomanometer (W.A. Baum Co., Copiague, NY) and at the seventh (examination year 20) using the OmRON HEM907XL by trained and certified technicians (21). Three BP measurements were taken from the right arm of each participant at 1-min intervals after a 5-min seated rest. Systolic BP (SBP) and diastolic

BP (DBP) were recorded as phase I and phase V Korotkoff sounds through examination year 15. Based on a study of ~900 participants, we estimated SBP (random zero) = $3.74 + 0.96 \times \text{observed OmRON SBP}$ and estimated DBP = $1.30 + 0.97 \times \text{observed OmRON DBP}$ at examination year 20 (22). The second and third of the measurements were averaged for all analyses.

HTN was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or taking antihypertensive medication at each examination. HTN incidence was defined as the percentage of nonhypertensive participants at baseline who developed HTN at the 20-year follow-up.

Measurement of covariates

Demographic variables, including age, sex, ethnicity, and education level, were collected using a self-administered questionnaire and verified during clinic examinations. Education level was classified as <12, 12, 13–15, and ≥ 16 years. Anthropometric measures were collected with participants wearing light clothing and no shoes. Body weight was measured to nearest 0.5 lb using a calibrated scale. Height was measured to the nearest 0.5 cm with a vertical ruler. BMI was calculated as weight in kilograms divided by height in meters squared.

Smoking status was determined by an interviewer-administered questionnaire and participants were categorized into three groups: nonsmokers, former smokers, and current smokers. Alcohol consumption was measured by the question, "Do you drink any alcoholic beverages in the past year?" If the answer was yes, it was followed by three questions on how many servings of wine, beer, and liquor. Total ethanol consumption in milliliters per day was estimated from the answers about individual alcoholic beverages using the formula $([\text{beer servings/week} \times 16.7] + [\text{wine servings/week} \times 17.02] + [\text{liquor servings/week} \times 19.09]) / 7$, and was categorized into six groups: 0 (never drink), 0.1–4.9, 5.0–9.9, 10–14.9, 15.0–29.9, and ≥ 30 mL/day. Physical activity was assessed using the CARDIA Physical Activity History Questionnaire, an interviewer-administered self-report of frequency of participation in 13 categories of recreational sports, exercise, leisure, and occupational activities over the previous 12 months. Physical activity score was calculated in exercise units (EU) based on the frequency and duration of activity over the previous year. A score of

100 EU is roughly equivalent to engaging in vigorous activity 2–3 h/week for 6 months of the year.

Dietary intakes of sodium, potassium, and magnesium were assessed by the CARDIA Diet History Questionnaire, an interviewer-administered quantitative food frequency questionnaire, which has been evaluated and discussed elsewhere (23). Diet assessment was conducted three times: at baseline and examination years 7 and 20.

Statistical analysis

Participants were divided into quartiles according to insulin levels ($\mu\text{U/mL}$). Baseline characteristics of participants were expressed as mean (SD), median (interquartile range), or proportion and were compared across quartiles by using ANOVA, Kruskal-Wallis test, or χ^2 test as appropriate. We used Cox proportional hazards models to evaluate associations of serum insulin levels, insulin-to-glucose ratio (IGR), and HOMA-IR with incidence of HTN. Follow-up time was calculated as the difference between the baseline examination and the year in which HTN was first identified, year 20, or the year a participant was censored. We used nonparametric splines to examine whether there was a nonlinear relation of exposure of interest with incidence of HTN. We used generalized estimating equations (GEEs) with identity linkage under exchangeable correlation structure assumption to examine exposures of interest in relation to continuous SBP and DBP.

To reduce measurement error caused by within-person variation and to best represent long-term insulin level (IGR or HOMA-IR) prior to HTN, we used cumulative average values of the exposures of interest (24). For example, we related the insulin levels (IGR or HOMA-IR) measured at baseline to new HTN cases identified at examination years 2, 5, and 7, and the average of insulin levels (IGR or HOMA-IR) detected at baseline and years 7, 10, and 15 to new cases identified at year 20. To explore whether the duration of follow-up would affect the associations, we also used the baseline exposure model and the most recent exposure model in the sensitivity analyses (24).

We categorized exposures of interest into quartiles based on their distributions. The initial analysis (model 1) was adjusted for age, sex, ethnicity, and study center. In model 2, we further adjusted for BMI, education, smoking status, alcohol consumption, physical activity, baseline systolic BP,

Fasting insulin and incidence of hypertension

and family history of HTN, and in model 3, we additionally adjusted for dietary intakes of sodium, potassium, and magnesium. Glucose was also adjusted in the final model when insulin was used as exposure. Ordinal variables using the median value in each quartile were created for trend tests. As antihypertensive medication information was used to define incident cases of HTN, we did not include it in Cox models and only included it for GEE analysis.

In addition, we investigated whether sex, ethnicity, and overweight/obese status modified the relations between insulin level and incidence of HTN. These analyses were performed by creating interaction terms of exposure of interest with these potential modifiers. The *P* values for interaction were calculated from likelihood ratio test by comparing models with and without the interaction terms.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). *P* ≤ 0.05 was considered statistically significant.

RESULTS—Table 1 shows the baseline characteristics of 3,413 participants according to quartiles of serum insulin level. The cumulative median levels of insulin were 7.8, 9.8, 12.3, and 18.0 μU/mL across quartiles. At baseline, the mean

age of study population was 25.0 ± 3.6 years and the mean BMI was 24.4 ± 4.8 kg/m². Compared with participants in the lowest quartile of insulin level, those in the highest quartile were slightly younger, more likely to be females, AAs, and non-current smokers, and had relatively lower education level and lower alcohol consumption. They were less likely to be active and lean.

A total of 796 incident cases of HTN were identified (incident rate = 13.7/1,000 person-years) during 57,920 person-years of follow-up. As illustrated in Table 2, insulin levels were positively and significantly associated with incidence of HTN. Participants in the highest quartile of insulin level had a significantly higher incidence of HTN (hazard ratio [HR] 1.85 [95% CI 1.42–2.40]; *P*_{trend} < 0.001) compared with those in the lowest quartile, after adjustment for potential confounders. Nonparametric spline analysis did not suggest any nonlinear association such as a “threshold” relation. Every unit increase of fasting insulin was associated with a 1.03-fold higher risk of incident HTN (95% CI 1.02–1.04). A similar significant dose-response relation was observed for IGR (Q4 vs. Q1: HR 1.78 [95% CI 1.35–2.37]; *P*_{trend} < 0.001) and HOMA-IR (Q4 vs. Q1: 1.27 [1.00–1.63]; *P*_{trend} < 0.001). When we further stratified

data by sex or ethnicity, the observed positive associations remained consistent in each subgroup and none of the tests for interactions was statistically significant. Moreover, to test whether the observed positive association was solely driven by overweight/obese status, we did a fully stratified analysis by creating different quartiles within the stratum of normal weight and overweight/obese, and the similar positive associations were documented within each subgroup.

Using GEE, we found that insulin level was positively associated with both SBP and DBP. The multivariable-adjusted β coefficients comparing the highest to the lowest quartiles of insulin levels were 3.64 mmHg (95% CI 2.82–4.46 mmHg; *P*_{trend} < 0.001) and 2.34 mmHg (1.65–3.03 mmHg; *P*_{trend} < 0.001) for SBP and DBP, respectively. A similar significant dose-response relation was also observed for the association of IGR or HOMA-IR with SBP and DBP (data not shown). When we examined the associations among normotensive individuals, the positive associations were essentially the same.

Sensitivity analyses were conducted to test the robustness of our main findings. First, we used the baseline exposure model and the most recent exposure model to explore the possible effect of

Table 1—Baseline characteristics by quartile of fasting insulin level (CARDIA study, 1985–2005*)

Baseline characteristic	Quartile of insulin level				Total (n = 3,413)	<i>P</i> value
	1 (n = 795)	2 (n = 849)	3 (n = 921)	4 (n = 848)		
Insulin level, μU/mL	7.8 (7.0–8.3)	9.8 (9.3–10.3)	12.3 (11.5–13.0)	18.0 (16.0–22.7)	11.0 (9.0–14.3)	—
Glucose level, mg/dL	84.2 (80.8–88.6)	86.0 (82.5–90.0)	87.7 (83.4–91.8)	90.2 (85.4–95.2)	87.0 (82.8–91.6)	—
IGR, (μU/mL)/(mg/dL)	0.09 (0.08–0.10)	0.11 (0.11–0.12)	0.14 (0.13–0.15)	0.20 (0.18–0.24)	0.13 (0.10–0.16)	—
HOMA-IR	1.6 (1.4–1.8)	2.1 (1.9–2.2)	2.6 (2.5–2.9)	4.0 (3.5–5.3)	2.4 (1.9–3.1)	—
SBP, mmHg	108.2 (10.5)	109.7 (10.0)	110.3 (9.7)	112.2 (10.1)	110.1 (10.1)	<0.001
DBP, mmHg	67.1 (9.2)	68.2 (8.5)	68.5 (9.0)	69.3 (9.4)	68.3 (9.0)	<0.001
Age, years	25.5 (3.3)	25.1 (3.6)	24.6 (3.7)	24.9 (3.7)	25.0 (3.6)	<0.001
Female, %	52.8	50.5	50.0	57.3	52.6	0.009
AA, %	33.1	40.3	50.6	63.2	47.1	<0.001
Education, years	14.2 (2.3)	14.0 (2.3)	13.9 (2.2)	13.6 (2.2)	13.9 (2.3)	<0.001
Current smokers, %	31.3	29.5	26.4	27.4	28.6	0.016
Alcohol consumption, mL/day	7.2 (0.0–19.2)	5.1 (0.0–16.9)	4.8 (0.0–15.0)	2.4 (0.0–10.2)	4.8 (0.0–15.0)	<0.001
Physical activity, EU	433 (245–642)	404 (236–638)	366 (208–568)	296 (155–496)	372 (208–589)	<0.001
BMI, kg/m ²	21.9 (2.7)	23.0 (3.1)	24.4 (4.1)	28.1 (6.0)	24.4 (4.8)	<0.001
Family history of HTN, %	44.0	47.1	50.0	55.1	49.1	<0.001
Dietary intake, mg/1,000 kcal/day						
Sodium	1,503.9 (311.4)	1,500.0 (302.1)	1,497.7 (275.3)	1,490.4 (299.4)	1,497.9 (296.6)	0.821
Potassium	1,423.4 (410.5)	1,395.1 (409.9)	1,321.5 (359.7)	1,269.4 (337.4)	1,350.6 (384.3)	<0.001
Magnesium	157.1 (58.5)	149.2 (55.3)	138.8 (45.3)	130.0 (41.1)	143.5 (51.3)	<0.001

*Data are mean (SD), median (interquartile range), or proportion as appropriate. *P* values for difference across all quartiles of insulin level were calculated with ANOVA, Kruskal-Wallis test, or χ² test as appropriate.

Table 2—Multivariable-adjusted HRs (95% CIs) of incidence of HTN by serum levels (quartiles) of insulin, IGR, or HOMA-IR (CARDIA study, 1985–2005*)

	Quartile of exposure of interest				<i>P</i> _{trend}
	1 (lowest)	2	3	4 (highest)	
Insulin level, μU/mL	<9.0	9.0–10.9	11.0–14.2	\geq 14.3	—
HTN cases	113	144	209	330	—
Person-years	13,836	14,714	15,523	13,847	—
Incidence (per 1,000 person-years)	8.2	9.8	13.5	23.8	—
Model 1	1.00	1.11 (0.87–1.42)	1.44 (1.14–1.81)	2.33 (1.87–2.90)	<0.001
Model 2	1.00	1.03 (0.80–1.32)	1.28 (1.00–1.64)	1.54 (1.19–1.98)	<0.001
Model 3	1.00	1.13 (0.87–1.45)	1.48 (1.15–1.90)	1.85 (1.42–2.40)	<0.001
IGR, (μU/mL)/(mg/dL)	<0.103	0.103–0.125	0.126–0.160	\geq 0.161	—
HTN cases	124	143	202	326	—
Person-years	14,930	14,971	14,567	13,627	—
Incidence (per 1,000 person-years)	8.3	9.6	13.9	23.9	—
Model 1	1.00	1.15 (0.90–1.46)	1.47 (1.17–1.85)	2.46 (1.99–3.05)	<0.001
Model 2	1.00	1.19 (0.93–1.52)	1.40 (1.10–1.78)	1.80 (1.40–2.31)	<0.001
Model 3	1.00	1.18 (0.92–1.51)	1.39 (1.09–1.77)	1.78 (1.39–2.29)	<0.001
HOMA-IR	<1.88	1.88–2.37	2.38–3.13	\geq 3.14	—
HTN cases	129	148	197	321	—
Person-years	14,408	14,920	14,536	14,051	—
Incidence (per 1,000 person-years)	9.0	9.9	13.6	22.8	—
Model 1	1.00	1.01 (0.80–1.29)	1.28 (1.02–1.60)	1.99 (1.62–2.45)	<0.001
Model 2	1.00	0.98 (0.77–1.25)	1.07 (0.84–1.35)	1.27 (1.00–1.62)	0.013
Model 3	1.00	0.99 (0.77–1.26)	1.06 (0.84–1.35)	1.27 (1.00–1.63)	0.013

*Cox proportional hazards models were used to calculate HRs and 95% CIs. Continuous variables using medians in each quartile were created for the trend tests. Model 1, adjusted for age, sex, ethnicity (AA or Caucasian), and study center. Model 2, same as model 1 but with additional adjustment for BMI (quartiles), physical activity (quartiles), education (<12, 12, 13–15, 16, or >16 years), smoking status (non, former, or current smokers), alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, or \geq 30 mL/day), baseline SBP (continuous), and family history of HTN (yes or no). Model 3, same as model 2 but with additional adjustment for dietary intakes (quartiles) of sodium, potassium, and magnesium. Glucose (quartiles) was only additionally adjusted when using insulin levels as exposure.

follow-up time on the observed associations (Table 3). No material differences were found between long-term and short-term exposures. Second, when we further excluded 120 participants with baseline SBP/DBP \geq 130/85 mmHg, the multivariable adjusted HR of participants in the highest quartile was 1.83 (95% CI 1.38–2.42; *P*_{trend} < 0.001), as compared with those in the lowest quartile. Third, we additionally excluded 249 participants who were diagnosed as incident HTN only by antihypertensive medication; the results were similar (1.81 [1.30–2.52]; *P*_{trend} < 0.001). In addition, as insulin levels were unavailable at examination years 2 and 5, we re-examined three exposures of interest in relation to incidence of HTN using examination year 7 as baseline. After adjustment for the same covariates listed for model 3 in Table 2, the results remained (data not shown).

CONCLUSIONS—In this unique 20-year follow-up longitudinal study, we found that fasting insulin level and its two derived indices (i.e., IGR and HOMA-IR) were positively associated with incidence

of HTN as well as SBP and DBP in a dose-response manner among young AAs and Caucasians. Sex, ethnicity, and BMI status did not significantly modify the observed associations.

The findings of our study are generally in accordance with the results of previous studies. Serum insulin was found to be positively associated with incident HTN in 3,513 middle- or elder-aged individuals with a 5-year follow-up in Multi-Ethnic Study of Atherosclerosis (MESA) (6). Likewise, the positive association was found in 377 middle-aged participants with a 7-year follow-up from the Baltimore, MD, Clinical Center of Trials of HTN Prevention, Phase 1 (5). There were still a number of other supportive studies (9,12–14,25), although they were either relatively short-term (9,13), using a retrospective design (12,14,25), or only focusing on one sex or ethnic group (9,12,14).

However, unlike in our study, the positive association was not consistently observed in some ethnicity/sex subgroups in other studies. For example, positive association of fasting insulin level with SBP and DBP was documented in non-Hispanic whites but not in Mexican

Americans in 8-year follow-up San Antonio Heart Study (26). The racial difference was also found in another study, in which positive association was only found in Caucasians but not in AAs and Pima Indians (11). In National Health and Nutrition Examination Survey (NHNES) 1999–2002, higher fasting insulin >12.2 mU/mL or HOMA-IR \geq 2.6 was found to be positively associated with pre-HTN in men but not in women. In addition, sex difference in insulin-HTN relation was reported in 527 AAs aged 18–55 (10). Moreover, some studies reported findings contrary to our observations. Acute physiological increases in plasma insulin did not elevate arterial pressure of 13 borderline hypertensive young adults (27). In a double-blind crossover study, administration of insulin exerted a small BP-lowering effect on 23 nondiabetic, untreated patients with essential HTN (28). Of note, both of these small-sized studies investigated the short-term effect of insulin on pre-HTN or HTN. By contrast, our present study is elucidating a long-term association of insulin with incident HTN among normotensive participants.

Table 3—A sensitivity analysis of multivariable-adjusted HRs (95% CIs) of incidence of HTN by quartiles of exposure of interest (CARDIA study, 1985–2005*)

	Quartile of exposure of interest				P for trend
	1 (lowest)	2	3	4 (highest)	
Baseline model					
Insulin level, $\mu\text{U}/\text{mL}$	1.00	1.13 (0.91–1.41)	1.03 (0.80–1.32)	1.50 (1.20–1.87)	<0.001
IGR, ($\mu\text{U}/\text{mL}$)/(mg/dL)	1.00	1.09 (0.86–1.54)	1.22 (0.98–1.54)	1.50 (1.19–1.90)	<0.001
HOMA-IR	1.00	1.02 (0.82–1.28)	0.98 (0.78–1.23)	1.27 (1.02–1.58)	0.014
Most recent model					
Insulin level, $\mu\text{U}/\text{mL}$	1.00	1.41 (1.08–1.84)	1.74 (1.32–2.30)	1.99 (1.50–2.64)	<0.001
IGR, ($\mu\text{U}/\text{mL}$)/(mg/dL)	1.00	1.60 (1.21–2.11)	1.79 (1.36–2.35)	2.21 (1.67–2.92)	<0.001
HOMA-IR	1.00	1.25 (0.96–1.64)	1.32 (1.01–1.72)	1.43 (1.09–1.88)	0.027

*Cox proportional hazards models were used to calculate HRs and 95% CIs. Continuous variables using medians in each quartile were created for the trend tests. The adjusted covariates in the models were the same as those listed for model 3 in Table 2.

The findings from this study are biologically plausible. Insulin can increase BP through all primary components that determine BP, including cardiac output, blood volume, and vascular flexibility. Insulin, a well-established inotropic agent (29), can increase cardiac output. Insulin can increase blood volume through stimulating secretion of vasopressin (an anti-diuretic) (30) and renal sodium retention (31). Insulin can increase vascular tone through several mechanisms. First, it can increase basal level of calcium in cytosol of vascular smooth muscle cells by promoting the voltage-dependent Ca^{2+} influx and inhibiting $\text{Na}^+/\text{Ca}^{2+}$ exchanger-dependent Ca^{2+} extrusion, leading to increased vascular tone (32). Second, it can stimulate the rennin-angiotensin system (33). Third, it can stimulate the secretion of endothelin-1 (34), a vascular constrictor. Therefore, insulin can increase BP in many different ways. However, this primary role of insulin in increasing BP has not been fully appreciated due to the popular perception that insulin is not functional in the presence of insulin resistance, which is tightly linked to increased BP. Nevertheless, studies have shown that insulin is functional at an increased basal level in the presence of insulin resistance and hyperinsulinemia (35).

Some researchers argued that the relation between insulin resistance and HTN is probably not unidirectional (36). However, the likelihood of high BP causing elevated insulin levels is presumably very low, because changes in insulin level usually precede the presence of obvious HTN in metabolic diseases (37). In addition, a large body of evidence lends credence to the increase of BP by insulin (38,39), but no existing evidence,

especially in mechanism, supports that HTN might cause hyperinsulinemia.

There are several strengths that need to be emphasized in this study. First, although randomized, placebo-controlled trials are the best approach to establish causal inference, it may not be feasible to conduct one on this topic, which makes the results from a well-designed prospective cohort study with relatively large sample size and long-term follow-up highly valuable. Second, the BP of our participants was measured by trained personnel using standardized procedures rather than self-reported, which may substantially reduce possible measurement error in BP. Importantly, the participants were young (at their ages of 18–30 years) at baseline, which enables us to investigate the evolution of cardiovascular disease risk by following the course of BP and the appearance of incident HTN in young adulthood.

Our study also has several limitations. First, insulin levels were not obtained at examination years 2 and 5. However, our results were unlikely to be biased substantially because we used accumulative models to approach the long-term exposure. Of note, when we used examination year 7 as baseline, the results were consistent. Another concern is that the assays of baseline insulin were measured again 7 years later. However, this would not materially alter our results. In one study, no significant change was detected in repeated assays of 34 samples stored at -20°C over an 8-year period (40). Also, the correlation between log insulin values from these two methods was high ($r = 0.81$) and would have little effect on the association between insulin levels and incident HTN. In fact, the re-assay of

baseline insulin levels with the same method used in later examinations may reduce the measurement error and strengthen our study. Third, the CARDIA cohort represents young AAs and Caucasians recruited from four metropolitan areas in the U.S. and was not nationally representative, which may limit the generalizability of our findings.

In conclusion, this prospective study suggests that fasting serum insulin levels are positively and longitudinally associated with BP and incidence of HTN in apparently healthy American young adults, including both men and women, and AAs and Caucasians. The findings from the current study may help clinicians identify those who are at high risk of HTN, and support that lifestyle modification to decrease insulin concentrations may be of great importance for HTN prevention.

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P.X. researched data, contributed to discussion, wrote the draft, and reviewed and edited the manuscript. K.L., S.S., and O.D.W. contributed to discussion and reviewed and edited the manuscript. W.C. contributed to discussion, wrote the draft (mechanism part), and reviewed and edited the manuscript. K.H. created the concept and design, contributed to discussion, wrote the draft, and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. K.H. 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.

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