High Normal Blood Pressure, Hypertension, and the Risk of Type 2 Diabetes in Japanese Men

The Osaka Health Survey

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OBJECTIVE — To investigate the relationship between high normal blood pressure or hypertension and the risk of developing type 2 diabetes in a large Japanese cohort.

RESEARCH DESIGN AND METHODS — We enrolled 7,594 Japanese men aged 35–60 years who did not have diabetes or impaired fasting glucose at study entry. Type 2 diabetes was defined as a fasting plasma glucose level of ≥126 mg/dl or a 2-h postload plasma glucose level of ≥200 mg/dl. High normal blood pressure was defined as no history of hypertension and a systolic blood pressure of ≥130 and <140 mmHg or a diastolic blood pressure of ≥85 and <90 mmHg. Subjects were considered to have hypertension if they had a systolic blood pressure ≥140 mmHg, if they had a diastolic blood pressure ≥90 mmHg, or if they were taking antihypertensive medications.

RESULTS — We confirmed 600 cases of type 2 diabetes during the 72,946 person-years of follow-up. Both high normal blood pressure and hypertension were associated with the risk of type 2 diabetes. Compared with normotensive men, men with high normal blood pressure had a multiple adjusted relative risk (RR) of 1.39 (95% CI 1.14–1.69), and men with hypertension had a multiple adjusted RR of 1.76 (1.43–2.16). Even among lean men (BMI <22.7 kg/m^2), men with high normal blood pressure had a multiple adjusted RR of 1.71 (1.20–2.42), and men with hypertension had a multiple adjusted RR of 2.02 (1.34–3.05) compared with normotensive men.

CONCLUSIONS — High normal blood pressure and hypertension are associated with an increased risk of developing type 2 diabetes.

Diabetes Care 22:1683–1687, 1999

Type 2 diabetes and hypertension have emerged as major public health problems in Japan. Type 2 diabetes often accompanies hypertension. Impaired glucose tolerance, including impaired fasting glucose, is a strong predictor of type 2 diabetes. Recently, we reported (1) that impaired fasting glucose is an independent risk factor for hypertension. On the other hand, high normal blood pressure is a strong predictor of hypertension (2). Whether high blood pressure, including high normal blood pressure and hypertension, increases the risk of developing type 2 diabetes is not known.

With few exceptions, epidemiological studies of plasma glucose level and hypertension have been cross-sectional rather than prospective. Several cross-sectional studies have reported that hypertension and blood pressure are significantly associated with plasma glucose levels (3–5), but prospective epidemiological data relating hypertension to type 2 diabetes are inconclusive (6–9). Some studies have reported a positive association (6–8), but one study reported a null association (9). All of these studies classified subjects with borderline hypertension (which is now classified as hypertension) as normotensive at study entry. Recently, diabetic patients with high normal blood pressure have been encouraged to adopt lifestyle modifications and to undergo prompt pharmacological therapy (10). To our knowledge, there has been no study relating high normal blood pressure to type 2 diabetes.

In this study, the diagnosis of type 2 diabetes was made based on the new American Diabetes Association (ADA) criterion of a fasting plasma glucose level of ≥126 mg/dl (7.0 mmol/l) or an oral glucose tolerance test (OGTT) with a 2-h postload plasma glucose level of ≥200 mg/dl (11.1 mmol/l) (11). We prospectively examined the relationship between high normal blood pressure or hypertension and the development of type 2 diabetes during a 5- to 16-year observation period.

RESEARCH DESIGN AND METHODS

Osaka Health Survey

The Osaka Health Survey is an ongoing cohort investigation designed to clarify risk factors for chronic diseases, including hypertension and diabetes, among male employees of a gas company in Osaka, Japan. Japanese law requires that all employers conduct annual health screenings for all employees. For the purpose of the Osaka Health Survey, in addition to these annual screenings, all employees aged ≥35 years undergo more detailed biennial clinical examinations and complete questionnaires on health-related behaviors.

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Received for publication 12 March 1999 and accepted in revised form 28 June 1999.

Abbreviations: ADA, American Diabetes Association; OGTT, oral glucose tolerance test; RR, relative risk.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics according to blood pressure level at study entry*

	Blood pressure			
	Normotension	High normal blood pressure	Hypertension	*P* for trend
Subjects (*n*)	4,538	1,824	1,232	
Age (years)	41.6 ± 6.4	41.0 ± 6.6	43.7 ± 7.3	<0.001*
BMI (kg/m^2)	22.4 ± 2.6	23.2 ± 2.6	23.6 ± 2.7	<0.001*
Systolic blood pressure (mmHg)	116.9 ± 8.4	133.6 ± 3.7	148.5 ± 11.1	<0.001*
Diastolic blood pressure (mmHg)	65.0 ± 9.1	73.6 ± 9.5	82.5 ± 12.7	<0.001*
Heart rate (beats/min)	70.5 ± 11.3	74.8 ± 11.7	78.5 ± 12.9	<0.001*
Smoking habit (%)				
Lifelong nonsmokers	20.6	21.2	19.6	NS*
Former smokers	17.2	18.4	18.8	NS*
Current smokers	62.1	60.4	61.6	NS*
Cigarettes per day	24.5 ± 9.8	24.2 ± 10.0	24.0 ± 9.9	NS*
Drinking habit (%)	80.6	86.0	88.0	<0.001†
Daily alcohol consumption (ml)	35.5 ± 25.1	41.6 ± 28.0	40.8 ± 26.1	<0.001*
Regular physical exercise (%)‡	31.4	32.0	31.7	NS†
Fasting plasma glucose (mmol/l)	4.99 ± 0.46	5.06 ± 0.48	5.09 ± 0.47	<0.001*
Parental history of type 2 diabetes (%)	11.8	12.4	10.4	NS†

Data are means ± SD or %. *Multiple regression model adjusted for age; †logistical regression model adjusted for age; ‡engaging in regular physical exercise at least once weekly.

Study population

We enrolled 8,410 men aged 35 to 61 years at entry between 1981 and 1991. We excluded 648 men because they had diabetes or impaired fasting glucose at study entry. We excluded 168 men who did not undergo a medical checkup during the follow-up period. The study population thus consisted of 7,594 men.

Measurements

The biennial clinical examination consisted of a medical history, a physical examination, blood pressure measurements, anthropometric measurements, fasting plasma glucose measurements, and questionnaires on lifestyle characteristics such as physical activity, smoking habit, and daily alcohol consumption. Trained nurses took all measurements. Participants were asked to fast for 12 h and to avoid smoking and heavy physical activity for more than 2 h before the examinations. After a 5-min rest in a quiet room, systolic and diastolic blood pressures were measured twice every few minutes on the right arm with a standard mercury sphygmomanometer, and the subject's blood pressure was defined as the average of two readings. Anthropometric measurements included height and body weight, which were measured while the subject was wearing light clothing without shoes. BMI was calculated as the weight in kilograms divided by the height in meters squared.

A questionnaire elicited information on leisure-time physical activity. Participants were asked about the type and weekly frequency of leisure-time physical activity. Regular physical exercise was defined as participation in any regular physical activity, such as jogging, bicycling, swimming, and tennis, long enough to work up a sweat at least once a week. The questions about regular physical exercise have been validated as a measure of physical exercise (12).

Questions about alcohol intake included items about the type of alcoholic beverage consumed, the weekly frequency of alcohol consumption, and the usual amount consumed daily. Alcohol intake was converted to total alcohol consumption (in milliliters of ethanol per day) by using standard Japanese tables. Current and past smoking habits were classified according to the type and quantity of cigarettes smoked daily. Participants were classified as current, past, or nonsmokers.

Diagnosis of type 2 diabetes

All subjects underwent medical screenings by a physician at least once annually, and cases of type 2 diabetes were diagnosed by physicians according to a fasting plasma glucose level of ≥140 mg/dl (7.8 mmol/l) or an OGTT with a 2-h postload plasma glucose level of ≥200 mg/dl (11.1 mmol/l) since study entry. We could not perform the OGTT in all cases. Therefore, in the analyses for this study, we redefined type 2 diabetes by using the new ADA criterion of a fasting plasma glucose level of ≥126 mg/dl (7.0 mmol/l) or an OGTT with a 2-h postload plasma glucose level of ≥200 mg/dl (11.1 mmol/l) (11). Impaired fasting glucose was defined when subjects had no history of diagnosed type 2 diabetes and when the fasting plasma glucose level was ≥110 and <126 mg/dl (≥6.1 and <7.0 mmol/l) (the new ADA criterion).

Diagnosis of high normal blood pressure and hypertension

Hypertension was diagnosed according to World Health Organization criteria as borderline hypertension (no history of hypertension and a systolic blood pressure ≥140 and <160 mmHg or a diastolic blood pressure ≥90 and <95 mmHg) or hypertension (subjects with a systolic blood pressure of ≥160 mmHg, a diastolic blood pressure of ≥95 mmHg, or who were taking antihypertensive medications) since study entry (13). In the analyses for this study, hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medications (10). High normal blood pressure was defined as no history of hypertension and a systolic blood pressure ≥130 and <140 mmHg or a diastolic blood pressure ≥85 and <90 mmHg (10). Normal blood pressure was defined as no history of hypertension, a systolic blood pressure <130 mmHg, and a diastolic blood pressure <85 mmHg (10).

Statistical analysis

The incidence of type 2 diabetes between 1981 and 1997 was computed according to the blood pressure level at entry. For each subject, person-years of follow-up were counted from the date at entry (1981–1991) to the date of diagnosis of diabetes or 1 April 1997, whichever came first. The follow-up rate was 94% of total potential person-years of follow-up. The rate of type 2 diabetes was obtained by dividing the number of cases by the number of person-years in each category of blood pressure level. Relative risk (RR) was calculated as the rate of occurrence of type 2 diabetes in a specific category of blood pressure level divided by the incidence rate in the lowest category of blood pressure. Multivariate Cox proportional hazards regression analysis was used

to evaluate the simultaneous effects of blood pressure levels, age, BMI, leisure-time physical activity (regular physical exercise at least once weekly or less than once weekly), parental history of diabetes (yes or no), smoking habit (current smokers, past smokers, or nonsmokers), and daily alcohol consumption. The linear trends in risks were evaluated by entering indicators for each categorical level of exposure.

We calculated the 95% CIs for each RR. *P* values are two-tailed. Statistical analyses were performed with the SPSS 8.0 software package (SPSS, Chicago, IL).

RESULTS — During the 5- to 16-year follow-up period (72,946 person-years), 600 men developed type 2 diabetes. Age was highest among men with hypertension. BMI, fasting plasma glucose level, daily alcohol consumption, and the proportion of alcohol drinkers increased significantly with increases in blood pressure level (Table 1). No significant relationship was evident between blood pressure level and the proportion of regular physical exercise, smoking habit, or parental history of type 2 diabetes.

High normal blood pressure, hypertension, and the risk of type 2 diabetes

In this study, high normal blood pressure and hypertension were associated with an increased risk of type 2 diabetes (Table 2). Compared with normotensive men, men with high normal blood pressure had an age-adjusted RR of developing type 2 diabetes of 1.52 (95% CI 1.25–1.85), and men with hypertension had an age-adjusted RR of developing diabetes of 2.05 (1.67–2.51). These associations persisted even after multivariate adjustment for age, BMI, daily alcohol consumption, smoking habit, leisure-time physical activity, and parental history of diabetes.

To quantify further the effect of blood pressure level on type 2 diabetes, we modeled blood pressure level as a continuous variable (Table 2). The results suggested that the multiple adjusted RR for systolic blood pressure was 1.18/10 mmHg (1.12–1.25), and the multiple adjusted RR for diastolic blood pressure was 1.14/10 mmHg (1.06–1.22).

To exclude the effect of antihypertensive medications on the effect of blood pressure level on the risk of type 2 diabetes, we excluded subjects taking such medications from the analysis (Table 2). The results were almost the same. Compared with normotensive men, men with high normal blood pressure had a multiple adjusted RR of developing type 2 diabetes of 1.39 (1.14–1.70), and men with hypertension had a multiple adjusted RR of developing type 2 diabetes of 1.62 (1.28–2.05). When we modeled blood pressure level as a continuous variable, the multiple adjusted RR for systolic blood pressure was 1.17/10 mmHg (1.09–1.26), and the multiple adjusted RR for diastolic blood pressure was 1.09/10 mmHg (1.01–1.20).

Table 2—*Relative risk of type 2 diabetes according to blood pressure level*

	Total person-years	Cases (*n*)	Age-adjusted	Multiple adjusted*
Model 1†				
Normotension	45,384	300	1.00	1.00
High normal blood pressure	16,632	156	1.52 (1.25–1.85)	1.39 (1.14–1.69)
Hypertension	10,930	144	2.05 (1.67–2.51)	1.76 (1.43–2.16)
P for trend			<0.0001	<0.0001
Continuous (per 10 mmHg)				
Systolic blood pressure			1.23 (1.17–1.30)	1.18 (1.12–1.25)
Diastolic blood pressure			1.24 (1.16–1.32)	1.14 (1.06–1.22)
Model 2‡				
Normotension	45,384	300	1.00	1.00
High normal blood pressure	16,632	156	1.52 (1.25–1.85)	1.39 (1.14–1.70)
Hypertension	6,516	79	1.84 (1.45–2.33)	1.62 (1.28–2.05)
P for trend			<0.0001	<0.0001
Continuous (per 10 mmHg)				
Systolic blood pressure			1.23 (1.15–1.32)	1.17 (1.09–1.26)
Diastolic blood pressure			1.19 (1.10–1.30)	1.09 (1.01–1.20)
Model 3§				
Study entry (third examination)				
Normotension				
Normotension	31,272	138	1.00	1.00
High normal blood pressure	8,744	59	1.46 (1.08–1.99)	1.35 (0.99–1.83)
Hypertension	2,266	25	2.20 (1.43–3.40)	1.93 (1.25–2.99)
High normal blood pressure				
Normotension	5,410	32	1.60 (1.09–2.35)	1.46 (0.99–2.15)
High normal blood pressure	6,148	40	1.65 (1.16–2.36)	1.54 (1.08–2.20)
Hypertension	3,546	35	2.22 (1.52–3.23)	1.89 (1.29–2.76)

Data are RRs (95% CIs) or *n*. *Adjusted for age, BMI, daily alcohol consumption, smoking habits (current, past, or nonsmokers), leisure-time physical activity (regular physical exercise at least once weekly or less than once weekly), and parental history of diabetes (yes or no); †based on data on blood pressure level at study entry (1981–1991) and including cases of hypertension from 1981 to 1997; ‡based on data on blood pressure level at study entry (1981–1991) and excluding subjects using antihypertensive medication at study entry and including cases of hypertension from 1981 through 1997; §based on data on blood pressure level at study entry (1981–1990) and the third examination 4 years later (1985–1994) and excluding cases of hypertension during the first 4-year follow-up period.

The change of blood pressure level during the first 4-year follow-up period

Because blood pressure level may change over time, additional analyses were performed on the basis of both the data at study entry (1981–1990) and at the third examination (1985–1994) and excluded cases of type 2 diabetes during the first 4-year follow-up period (Table 2). As a reference category, we used men with normotension at both examinations. The multiple adjusted RR of developing type 2 diabetes was 1.93 (1.25–2.99) among men with normotension at study entry and hypertension at the third examination, 1.54 (1.08–2.20) among men with high normal blood pressure at both examinations, and 1.89 (1.29–2.76) among men with high normal blood pressure at study entry and hypertension at the third examination. The age-adjusted RR of developing type 2 diabetes was 1.46 (1.08–1.99) among men with normotension at study entry and high normal blood pressure at the third examination and 1.60 (1.09–2.35) among men

Table 3—*Relative risk of type 2 diabetes according to blood pressure level and BMI*

	Total person-years	Cases (*n*)	Model 1		Model 2	
			Age-adjusted	Multiple adjusted*	Age-adjusted	Multiple adjusted*
BMI <22.7 kg/m² (*n* = 3,797)						
Normotension	25,542	103	1.00	1.00	1.00	1.00
High normal blood pressure	7,370	50	1.78 (1.25–2.52)	1.71 (1.20–2.42)	1.80 (1.27–2.55)	1.81 (1.28–2.57)
Hypertension	3,998	31	2.12 (1.41–3.19)	2.02 (1.34–3.05)	2.07 (1.38–3.10)	2.10 (1.40–3.15)
P for trend			<0.0001	<0.0001		
BMI ≥22.7 kg/m² (*n* = 3,797)						
Normotension	19,842	197	1.00	1.00	2.54 (1.99–3.24)	2.52 (1.97–3.21)
High normal blood pressure	9,262	106	1.27 (1.00–1.60)	1.28 (1.01–1.63)	3.14 (2.38–4.15)	3.15 (2.38–4.16)
Hypertension	6,932	113	1.68 (1.33–2.12)	1.70 (1.34–2.15)	4.25 (3.23–5.60)	4.23 (3.21–5.58)
P for trend			<0.0001	<0.0001	<0.0001	<0.0001

Data are RRs (95% CIs) or *n*. In model 1, normotensive men among each BMI group were the reference category, and in model 2, normotensive men with a BMI <22.7 kg/m² were the reference category. *Adjusted for age, daily alcohol consumption, smoking habits (current, past, or nonsmokers), leisure-time physical activity (regular physical exercise at least once weekly or less than once weekly), and parental history of diabetes (yes or no).

with high normal blood pressure at study entry and normotension at the third examination. After adjustment for age, BMI, daily alcohol consumption, smoking habit, leisure-time physical activity, and parental history of diabetes, these associations were attenuated (RRs 1.35 [0.99–1.83] and 1.46 [0.99–2.15], respectively).

High normal blood pressure and hypertension in relation to BMI

To examine whether BMI modified the association between high normal blood pressure and hypertension and the risk of type 2 diabetes, we stratified subjects according to the median of BMI (Table 3). After data were adjusted for age, daily alcohol consumption, smoking habit, leisure-time physical activity, and parental history of diabetes, even among lean men (BMI <22.7 kg/m²), high normal blood pressure was associated with an increased risk of type 2 diabetes (RR 1.71 [1.20–2.42]), and hypertension was also associated with an increased risk of type 2 diabetes (RR 2.02 [1.34–3.05]) compared with men with normal blood pressure. Among men with a higher BMI (≥22.7 kg/m²), men with high normal blood pressure had a multiple adjusted RR of developing type 2 diabetes of 1.28 (1.01–1.63), and men with hypertension had a multiple adjusted RR of developing type 2 diabetes of 1.70 (1.34–2.15) compared with men with normal blood pressure.

To examine the effects of clustering risk factors such as blood pressure and BMI on the risk of type 2 diabetes, we used men with normotension and a BMI <22.7 kg/m² as a reference category (Table 3). Men with high normal blood pressure and a BMI ≥22.7 kg/m² had an age-adjusted RR of developing type 2 diabetes of 3.14 (2.38–4.15), and hypertensive men with a BMI ≥22.7 kg/m² had an age-adjusted RR of developing type 2 diabetes of 4.25 (3.23–5.60). Even after adjustment for other confounders, these associations did not change.

CONCLUSIONS — These prospective data demonstrate that both high normal blood pressure and hypertension are positively associated with the development of type 2 diabetes. These associations persisted even after adjustments for several known or suspected predictors of type 2 diabetes, including age, BMI, smoking habit, leisure-time physical activity, parental history of type 2 diabetes, and daily alcohol consumption.

We considered the possibility that there could be bias due to misclassification if the proportion of diagnoses of type 2 diabetes by OGTT differed across levels of blood pressure. In this study, 600 men developed type 2 diabetes during the 72,946 person-years of follow-up. A total of 100 men (16.7%) were diagnosed by a 2-h postload plasma glucose level of ≥200 mg/dl. However, the proportion of diagnoses by OGTT did not differ across levels of blood pressure (data not shown). All subjects in this study were registered employees of the same company. Thus, they may not always be representative of the general Japanese population; however, these relationships likely apply to most white-collar urban workers in Japan. The relative homogeneity of the cohort may actually enhance the study's internal validity. Because of the relatively uniform educational background and socioeconomic status of the men in this cohort, these variables do not likely represent confounding factors.

Previous epidemiological findings on the association between hypertension and the risk of type 2 diabetes are inconclusive (6–9). These prospective studies have reported a positive association (6–8), but one reported a null association (9). Hypertension was positively associated with the risk of type 2 diabetes in a cohort of male alumni from the University of Pennsylvania, in the Physicians' Health Study, and in a cohort in the Netherlands (6–8). In those studies, either subjects with borderline hypertension were classified as having normotension at study entry, the definition of hypertension was not clear, or control for confounders such as lifestyle factors was not complete. Morales et al. (9) in the San Antonio Heart Study showed that, after adjustment for age, sex, ethnicity, obesity, body fat distribution, and levels of fasting plasma glucose and insulin, hypertension was not associated with the risk of developing type 2 diabetes. In that study, incomplete exclusion of subjects with hypertension at study entry or a small study population may explain the null association.

Some antihypertensive medications such as thiazides and β-blockers have been reported to reduce glucose tolerance and increase the risk of type 2 diabetes (14–16), but others such as ACE inhibitors and α-blockers have been reported to increase

insulin sensitivity (16). Even after excluding subjects taking antihypertensive medications, the effect of both high normal blood pressure and hypertension on the risk of type 2 diabetes was not altered.

In this cohort study, we did not identify why high normal blood pressure and hypertension increase the risk of type 2 diabetes. Insulin resistance and hyperinsulinemia have been thought to be common factors underlying the link among type 2 diabetes, obesity, and hypertension (17,18). In this study, after adjustment for multivariate confounders including BMI, high normal blood pressure and hypertension were associated with the risk of type 2 diabetes. Furthermore, even among lean men (BMI <22.7 kg/m^2), the association between high normal blood pressure or hypertension and the risk of type 2 diabetes was significant. Therefore, this association was independent of obesity, although among nonobese men, the pattern of fat distribution such as visceral fat may be overlooked as possibly playing an important role in the relationship between high normal blood pressure or hypertension and the risk of type 2 diabetes. Some nonobese people with hypertension have been reported to have insulin resistance (19), which can lead to type 2 diabetes. The pattern of distribution of body fat such as visceral fat and fasting insulin level should be included in further studies.

In conclusion, our results provide evidence that high normal blood pressure and hypertension are associated with an increased risk of type 2 diabetes. We believe that men with high normal blood pressure or hypertension should be encouraged to modify their lifestyles.

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