Impaired Fasting Glucose and the Risk of Hypertension in Japanese Men Between the 1980s and the 1990s

The Osaka Health Survey

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OBJECTIVE — To determine whether impaired fasting glucose (IFG) increased the risk for hypertension in two large Japanese cohorts during the different time periods.

RESEARCH DESIGN AND METHODS — We prospectively investigated two Japanese cohorts: a 1980s population, comprising 4,130 normotensive and nondiabetic men aged 35–60 years entered between 1981 and 1983, and a 1990s population, comprising 4,319 normotensive and nondiabetic men aged 35–60 years entered between 1991 and 1992. Data on lifestyle factors were obtained from questionnaires. IFG was defined as a fasting plasma glucose level ≥110 and <126 mg/dl.

RESULTS — During the 4-year observation period, 708 cases of hypertension were confirmed in the 1980s and 848 cases were confirmed in the 1990s. In both the 1980s and 1990s populations, IFG was associated with the risk of hypertension. The frequency of IFG in men in the 1990s group was twice as high as that in the 1980s group. The multivariate-adjusted odds ratio (OR) of hypertension was 1.54 (95% CI, 1.01–2.34) for men with IFG in the 1980s population and 1.73 (1.31–2.29) in the 1990s population, compared with those without IFG in the two populations. In the 1990s population, among lean men with a BMI ≤23 kg/m^2, men with IFG had a multivariate-adjusted OR of hypertension of 2.31 (1.46–3.65) compared with those without IFG.

CONCLUSIONS — This study demonstrated direct correlation between IFG and hypertension and greater incidence of this hypertension in the 1990s group than in the 1980s group.

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Impaired fasting glucose (IFG) (fasting plasma glucose ≥110 and <126 mg/dl), type 2 diabetes, and hypertension have emerged as major public health problems in Japan, and the prevalence of IFG and type 2 diabetes has increased over the past decade (1). IFG and type 2 diabetes often accompany hypertension. In the evaluation of patients with type 2 diabetes, hypertension can be largely classified into two types: renal hypertension due to diabetic nephropathy, and essential hypertension in patients without diabetic nephropathy. Diabetic nephropathy is closely associated with hypertension (2,3). The pathogenesis of hypertension in type 2 diabetes patients without nephropathy is similar to that in nondiabetic patients with essential hypertension. The prevalence of hypertension is higher in subjects with impaired glucose tolerance than in those without impaired glucose tolerance or type 2 diabetes (4–7). It is not known, however, whether IFG increases the risk of hypertension independent of known risk factors, such as age, obesity, alcohol consumption, and physical activity.

With few exceptions, epidemiological studies of the 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 (5,7,8), but prospective epidemiological data relating fasting glucose or impaired glucose tolerance test to hypertension are inconclusive (9–11). IFG was positively associated with the risk of hypertension in the Paris Prospective Study (9), but in no other prospective studies (10,11). These studies included subjects with borderline hypertension at study entry. Recently, diabetic patients with borderline hypertension have been encouraged to adopt lifestyle modification and to accept prompt pharmacological therapy (12).

In the present study, hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or taking antihypertensive medications. We prospectively examined the effects of IFG on the subsequent incidence of hypertension in a large Japanese cohort. This association was examined separately in the 1980s and the 1990s. We chose each observation period in the 1980s and the 1990s as 4 years because there was a rare occurrence of renal hypertension due to diabetic nephropathy for just those 4 years.

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Abbreviations: ADA, American Diabetes Association; IFG, impaired fasting glucose; JNC-VI, sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; OR, odds ratio.

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

RESEARCH DESIGN AND METHODS

Osaka Health Survey

The Osaka Health Survey is an ongoing cohort investigation designed to clarify the risk factors for major diseases, including hypertension and type 2 diabetes, among male employees of a company in Osaka, Japan. Japanese law requires employers to conduct annual health screenings of all employees. In addition to these annual screenings, all employees in this company aged ≥35 years undergo more detailed medical checkups, including questionnaires every 2 years on lifestyle characteristics. The present study includes subjects who have undergone detailed biennial checkups.

Study population

We enrolled 6,219 men aged 35–60 years at entry between 1981 and 1983. We excluded 1,008 men who did not undergo medical checkup for follow-up. We also excluded 1,081 men because they had physician-diagnosed hypertension, borderline hypertension, or type 2 diabetes at entry. The 1980s study sample totaled 4,130 men. We enrolled 6,797 men aged 35–60 years at entry in 1991 or 1992. Of these, we excluded 1,365 men because they had physician-diagnosed hypertension, borderline hypertension, or type 2 diabetes at entry. We also excluded 1,113 men who did not undergo a medical checkup during the follow-up period. The 1990s study sample totaled 4,319 men.

Diagnosis of hypertension

Hypertension was diagnosed by World Health Organization criteria as borderline hypertension (systolic blood pressure ≥140 and <160 mmHg or diastolic blood pressure ≥90 and <95 mmHg) or hypertension (systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥95 mmHg, or taking antihypertensive medications) since study entry (13). In the analysis of this study, hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or taking antihypertensive medication (12).

Diagnosis of IFG and type 2 diabetes

IFG was defined on the basis of American Diabetes Association (ADA) criteria (fasting plasma glucose level ≥110 and <126 mg/dl [≥6.1 and <7.0 mmol/l]), and type 2 diabetes was defined on the basis of the new ADA criteria (fasting plasma glucose ≥126 mg/dl [≥7.0 mmol/l]) or taking hypoglycemic medications. Normal fasting glucose was also defined on the basis of the new ADA criteria (fasting plasma glucose <110 mg/dl [≤6.1 mmol/l]) (14).

Biochemical measurements and questionnaires

The biennial clinical examination consisted of a medical history, a physical examination, blood pressure measurement, anthropometric measurements, and questionnaires on lifestyle characteristics, such as physical activity, number of cigarettes smoked, 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 >2 h before the examinations. After a 5-min rest in a quiet room, systolic and diastolic blood pressures were measured twice at an interval of a 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. The BMI was calculated as the weight in kilograms divided by the height in meters squared. Fasting blood samples were obtained for measurement of the fasting plasma glucose level, and this was done at every visit.

The questionnaire on physical activity elicited information on leisure-time physical activity. Subjects were asked about the type and weekly frequency of leisure-time physical activity. Vigorous exercisers were defined as those who engaged in any regular physical activity, such as jogging, bicycling, swimming, or tennis, long enough to work up a sweat at least once a week. Questions about alcohol intake included items about the type of alcoholic beverage, 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) using standard Japanese tables. Subjects were classified as smokers or nonsmokers according to whether they currently smoked at least one cigarette daily.

Statistical analyses

Baseline variables were compared for the 1980s population and the 1990s population by the unpaired *t* test for continuous variables and by the χ^2 test for categorical variables. Multiple logistic regression analysis was used to evaluate the simultaneous effects of IFG, age, BMI, daily alcohol consumption, physical activity (at least once per week or not), smoking status (smokers or nonsmokers), and weight change during the 4-year follow-up period (kilograms/4 years). The linear trends in risks were evaluated by entering indicators for each categorical level of exposure, using the median value for each category. We calculated the 95% CI for each odds ratio (OR), and all *P* values are two-tailed. Statistical analyses were performed using the SPSS 7.5J software package.

RESULTS

In the 1980s population, 708 (17.1%) of the 4,130 men eligible for analysis developed hypertension during the 4-year follow-up period. In the 1990s population, 848 (19.6%) of the 4,319 men eligible for analysis developed hypertension during the 4-year follow-up period.

Table 1 shows the baseline characteristics of the two-phase cohort. The proportion of IFG was higher in the 1990s than in

Table 1—*Baseline clinical characteristics in the 1980s and 1990s populations*

	1980s population	1990s population	*P* value
n	4,130	4,319	
Age (years)	43.6 ± 5.7	44.5 ± 6.2	<0.0001
Body weight (kg)	62.1 ± 8.0	65.1 ± 8.5	<0.0001
BMI (kg/m^2)	22.6 ± 2.6	23.1 ± 2.6	<0.0001
Systolic blood pressure (mmHg)	120.3 ± 10.8	122.9 ± 10.3	<0.0001
Diastolic blood pressure (mmHg)	65.9 ± 10.3	69.2 ± 9.3	<0.0001
Heart rate (beat/min)	71.7 ± 10.7	70.8 ± 10.4	<0.0001
Daily alcohol consumption (ml/day)	26.4 ± 22.6	38.4 ± 31.9	<0.0001
Cigarette smoking (%)	61.4	56.7	<0.0001
Vigorous physical activity (%)	33.3	33.7	0.73
Impaired fasting glucose (%)	3.2	6.1	0.011

Data are means ± SD except for impaired fasting glucose, physical activity, and smoking habits. Vigorous physical activity is defined as leisure-time physical activity long enough to work up a sweat at least once a week.

Table 2—*Baseline age- and BMI-specific prevalence of IFG in the 1980s and 1990s populations*

	1980s population		1990s population		
	n	IFG (%)	*n*	IFG (%)	*P* value
Age-groups (years)					
35–39	1,121	2.9	1,191	2.9	0.89
40–44	1,251	2.5	1,100	6.5	<0.0001
45–49	982	3.9	892	7.5	0.01
50–60	776	3.9	1,136	8.1	<0.0001
BMI groups (kg/m^2)					
≤20.0	664	2.0	512	3.1	0.2
20.1–22.0	1,047	2.7	948	4.5	0.025
22.1–24.0	1,249	3.0	1,364	5.9	<0.0001
24.1–26.0	813	4.2	946	7.8	0.002
>26.0	357	5.6	549	9.3	0.044

P values are based on χ^2 test.

the 1980s. The 1990s population had a higher mean of body weight, BMI, systolic blood pressure, and daily alcohol consumption than the 1980s population. The proportion of vigorous physical activity did not differ between the two populations.

The prevalence of IFG by age was higher in the 1990s than in the 1980s, except for the lowest age category. The prevalence of IFG by BMI was also higher in the 1990s than in the 1980s, except for the lowest BMI category (Table 2). Furthermore, we investigated the incidence of IFG during the 4-year follow-up period both in the 1980s population and in the 1990s population among men who were free of type 2 diabetes, IFG, and hypertension at study entry. The incidence of IFG was higher in the 1990s population than in the 1980s population ($P < 0.001$). In the 1980s population, 347 men (8.7%) developed IFG during the 4-year follow-up period, and in the 1990s population, 458 men (11.3%) developed IFG during the 4-year follow-up period

IFG was significantly and positively associated with the risk of hypertension in both the 1980s and 1990s populations (Table 3). After data were adjusted for age, BMI, weight change during the 4-year follow-up period, daily alcohol consumption, leisure-time physical activity, and smoking habits, the OR of hypertension was 1.54 (95% CI, 1.01–2.34) among men with IFG in the 1980s and 1.73 (1.31–2.29) among men with IFG in the 1990s, compared with those with normal fasting glucose in the two populations (Table 3).

To examine whether baseline BMI modified the relation between the IFG and the risk of hypertension in the1990s population, we stratified the data by two levels of BMI between 1991 and 1992 (Table 4). After data were adjusted for multiple confounders, even among lean men with a BMI ≤23.0 kg/m^2, IFG was associated with an increased risk of hypertension (OR 2.34 [1.46–3.65]) compared with men with normal fasting glucose. Among men with a higher BMI (>23.0 kg/m^2), those with fasting plasma glucose ≥100 and <110 mg/dl had a multivariate-adjusted OR of hypertension of 1.33 (1.06–1.68) compared with those with a fasting plasma glucose <100 mg/dl.

To examine the effect of IFG in relation to hypertension over a 14-year observation period among 4,130 men of the 1980s cohort, we performed additional analysis. Even after adjustment for multivariate confounders such as age, BMI, daily alcohol consumption, leisure-time physical activity, weight change during the 14-year follow-up period, and smoking habits, IFG was associated with an increased risk of hypertension. The multivariate-adjusted OR of hypertension was 1.75 (1.14–2.71) among men with IFG compared with those with normal fasting glucose.

CONCLUSIONS

— This prospective study demonstrated that IFG was positively associated with the development of hypertension in both the 1980s and the 1990s populations. This association persisted even after adjustments for several known or suspected predictors of hypertension, including age, BMI, weight change during the 4-year follow-up period, daily alcohol consumption, leisure-time physical activity, and smoking habits. After stratifying the 1990s population according to BMI, even among lean men with a BMI ≤23.0 kg/m^2, the association between IFG and risk of hypertension was significant. Among men with a BMI ≥23.1 kg/m^2, men with a fasting plasma glucose ≥100 and <110 mg/dl were at significant risk for hypertension compared with those with fasting plasma glucose <100 mg/dl.

Previous epidemiological findings on the association between fasting glucose or impaired glucose tolerance testing and the risk of hypertension have been inconclusive (9–11). One prospective study has reported a positive association (9), but others have reported no association (10,11). In a study of 4,149 men followed by the Paris Prospective Study for 3 years, fasting plasma glucose was a strong predictor of hypertension after adjustment for obesity (9). In the San Antonio Heart Study, Haffner et al. (11) showed that after adjustment for age, obesity, body fat distribution, and fasting plasma insulin level, impaired glucose tolerance was not associated with risk of hypertension among men and women and that type 2 diabetes was associated with risk of hypertension only among men (11). Vaccaro et al. (10) showed a strong association at baseline between impaired glucose tolerance and blood pressure, but this association was not found in a prospective analysis. Incomplete exclusion of subjects with hypertension at study entry, incom-

Table 3—*OR of hypertension according to IFG in the 1980s and 1990s populations*

			OR (95% CI)	
	n	Cases (%)	Age-adjusted	Multivariate-adjusted*
1980s				
Normal fasting glucose	3,998	675 (16.9)	1.00	1.00
IFG	132	33 (25.0)	1.60 (1.06–2.42)	1.54 (1.01–2.34)
1990s				
Normal fasting glucose	4,054	764 (18.8)	1.00	1.00
IFG	265	84 (31.7)	1.87 (1.42–2.45)	1.73 (1.31–2.29)

*Adjusted for age, BMI, daily alcohol consumption, smoking habits, vigorous activity (at least once a week or sedentary), and weight variation during the 4-year follow-up period.

Table 4—*OR of hypertension according to IFG and BMI in the 1990s population*

	OR (95% CI)	
	Age-adjusted	Multivariate-adjusted*
BMI ≤23.0 (*n* = 2,159)		
Model 1		
FPG <110 mg/dl	1.00	1.00
IFG	2.33 (1.48–3.67)	2.31 (1.46–3.65)
Model 2		
FPG <100 mg/dl	1.00	1.00
100 ≤FPG <110 mg/dl	1.15 (0.84–1.57)	1.08 (0.79–1.49)
IFG	2.40 (1.52–3.80)	2.35 (1.48–3.74)
P for trend	0.002	0.01
BMI >23.0 (n = 2,160)		
Model 1		
FPG <110 mg/dl	1.00	1.00
IFG	1.48 (1.05–2.09)	1.50 (1.06–2.13)
Model 2		
FPG <100 mg/dl	1.00	1.00
100 ≤FPG <110 mg/dl	1.34 (1.07–1.68)	1.33 (1.06–1.68)
IFG	1.62 (1.14–2.30)	1.64 (1.14–2.34)
P for trend	0.0008	0.001

*Adjusted for age, BMI, daily alcohol consumption, smoking habits, vigorous activity (at least once a week or sedentary), and weight variation during the 4-year follow-up period. FPG, fasting plasma glucose.

plete control for confounders like alcohol consumption and physical activity, or a limited number of study populations may explain the inconclusive associations.

In the present cohort study, we did not identify why IFG increased the risk of hypertension. Insulin resistance and hyperinsulinemia have been thought to be common factors underlying the link between type 2 diabetes, obesity, and hypertension (15,16). However, associations between insulin resistance or hyperinsulinemia and hypertension have not been conclusively established (17–19). In our study, after adjustment for multivariate confounders, including BMI, IFG was associated with the risk of hypertension. Furthermore, even among lean men with a BMI ≤23.0 kg/m^2, the association between IFG and the risk of hypertension was significant. Therefore, this association between IFG and the risk of hypertension was independent of obesity. Recently it has been suggested that because increased serum superoxide generation correlates with glucose and glycated protein plasma levels in diabetic subjects, the increased prevalence of hypertension in diabetic patients might be related to this increased generation of free radicals (20). Several observations support this idea: free radicals abolish endothelium-dependent vasodilatation in diabetic and hypertensive rats (21,22), an antioxidant deficiency in diet contributes to the etiology of hypertension (23), antioxidant drugs improve the abnormal arterial vasomotor control in diabetic patients (24), and these drugs also show a blood pressure-lowering effect in both diabetic and hypertensive subjects (25).

All subjects underwent medical screening by a physician at least once annually, and cases of hypertension were diagnosed by the physician. Therefore, the data were not biased by a misdiagnosis of hypertension from a single measurement not typical for the patient. According to the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) (12), even patients who have high-normal blood pressure (systolic blood pressure ≥130 and <140 mmHg or diastolic blood pressure ≥85 and <90 mmHg) in addition to diabetes should be considered for prompt pharmacological therapy and appropriate lifestyle modifications. Impaired glucose tolerance is reported to be an independent cardiovascular risk factor. Therefore, in the analysis of this study, we defined hypertension as a systolic blood pressure ≥140, a diastolic blood pressure ≥90 mmHg, or treatment with antihypertensive medications (12). Furthermore, when we prospectively investigated the effect of IFG with respect to the subsequent risk of hypertension, we wanted to distinguish between hypertension that occurred in patients without nephropathy and renal hypertension accompanied by diabetic nephropathy. Each follow-up period in the 1980s and the 1990s lasted 4 years, and we excluded men with type 2 diabetes at study entry. Therefore, it was not likely that men with renal hypertension accompanied with diabetic nephropathy were confused with men who developed hypertension during the 4-year follow-up periods.

All subjects in the present study were registered employees of the company and thus are not representative of the general Japanese population. However, 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 were unlikely to be confounding.

We could not include several confounding variables in this study, such as the history of food intake, visceral adiposity (waist-to-hip ratio), and the fasting insulin level. First, it is well known that consumption of salt is associated with hypertension (26). Fat intake is reported to be associated with fasting insulin level (27). In the 1990s in Japan, consumption of salt was not different, but fat intake increased (1). Second, considerable attention has recently been focused on the pattern of fat distribution. The central pattern of distribution, with its increased waist-to-hip ratio, is associated with more insulin resistance than is the peripheral pattern of distribution (28,29). Individuals with the central pattern are more likely to have glucose intolerance, hypertension, hyperlipidemia, and vascular disease, a constellation of features that has been termed "syndrome X" (15). Therefore, history of food intake, visceral adiposity (waist-to-hip ratio), and fasting insulin level should be included in future studies.

In conclusion, IFG was a strong and independent risk factor for hypertension both in the 1990s and in the 1980s. The best approach for the control of hypertension in the general population is to follow the primary preventive recommendations of the JNC-VI (12). We believe that men with IFG should be encouraged to adopt lifestyle modifications.

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