Original Article

Differential Impact of Family History on Age-Associated Increase in the Prevalence of Hypertension and Diabetes in Male Japanese Workers

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Family history and aging are independent risk factors for the development of hypertension as well as for the development of diabetes. However, it is unclear how the family histories influence the rate of age-associated increase in these diseases. Moreover, despite the fact that hypertension and diabetes often occur concomitantly, it is not known whether family history of hypertension increases the risk of diabetes or *vice versa*. To gain an insight into these questions, we investigated the cross-sectional prevalence and family history of hypertension and diabetes in 1,123 male subjects (mean age, 42.1 ± 12 years; range, 20–60 years) who participated in annual medical check-ups. The data were analyzed by 10-year age groups (20s, 30s, 40s and 50s). The prevalence of hypertension increased with age group either in the absence (12% in the 20s and 39% in the 50s) or in the presence (21% in the 20s and 59% in the 50s) of family history of hypertension, and thus the increasing rate of prevalence with age was not affected by family history. The prevalence of diabetes in the absence of family history of diabetes was low until the 40s (<1.2%) but it jumped in the 50s (4.3%). On the other hand, in the presence of family history, the prevalence was 4% in the 20s and progressively increased to 20% in the 50s. The impact of family history on the risk of diabetes was strong and appeared to increase with age. Family history of hypertension did not increase the risk of diabetes, and family history of diabetes did not increase the risk of hypertension. These results suggest that family history of hypertension has an additive impact on the age-associated increase in the risk of hypertension, whereas family history of diabetes has an exponential impact on aging-associated increase in the risk of diabetes. (*Hypertens Res* 2006; 29: 81–87)

Key Words: family history, hypertension, diabetes, epidemiology

Introduction

Family histories of hypertension and diabetes are established risk factors for development of the respective diseases (1–3). In addition to the familial predisposition, aging constitutes a

strong and independent risk factor for both hypertension and diabetes. However, it is not clear how much impact family history has on the onset of hypertension and diabetes (4, 5). To our knowledge, there is no epidemiological basis to predict the age of onset of hypertension and/or diabetes in individuals who are healthy but with familial predispositions.

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It has been increasingly recognized that both hypertension and insulin resistance, or diabetes, often occur concomitantly (6–8). Accumulation of these cardiovascular risk factors, along with visceral fat obesity, is an essential component of the metabolic syndrome (9, 10). However, the mechanism of the cardiovascular risk factor clustering is not well understood. If there is a genetic link among these cardiovascular risk factors, family history of hypertension may be associated with the occurrence of diabetes or, conversely, family history of diabetes may be associated with the occurrence of hypertension. If such interrelations are found, taking a family history may be helpful to predict the development of metabolic syndrome or cardiovascular disease. To date, there has been no study to determine whether family history of hypertension increases the risk of diabetes or *vice versa*.

The present study was designed to investigate the impact of family history/histories of hypertension and/or diabetes on the age of onset of these two diseases and to clarify possible interactions between the two family histories.

Methods

Study Design and Study Population

The study had a cross-sectional design and was performed in conjunction with the annual medical checkups conducted in four companies in Kure City, Hiroshima, Japan. The Industrial Safety and Health Law in Japan requires employers to arrange for annual health examinations to be conducted for all employees. In the fall of 2002, 1,211 male employees and 811 female employees of the four companies (age range, 20–71 years) were eligible for annual health checkups, and 1,191 male employees and 640 female employees (98.3% and 78.9%, respectively) underwent checkups. All of the male subjects who underwent checkups were asked to participate in our survey, and agreement for participation was obtained from all of the subjects. We excluded female subjects from our study because menopause, which is experienced by most females in their 40s and 50s, may confound the analysis of age-related change in the prevalence of hypertension and diabetes. Among the 1,191 subjects who participated in the present survey, 36 subjects whose blood data were incomplete and 32 subjects older than 60 years were excluded. Thus a total of 1,123 subjects participated in the study and were included in the final analysis.

The four companies were a shipyard company, a bank, an industrial parts manufacturer, and a food delivery company. The participants were divided into one of the following three occupational categories based on their self report in the questionnaire: manual laborer ($n=436$), office worker ($n=420$), and business salesperson with a primary responsibility of meeting customers outside the office ($n=229$). Thirty-eight subjects did not answer this question regarding occupation.

Measurements and Definitions

The health examinations included medical history, physical examination, measurements of body weight, height, and blood pressure, and laboratory tests, including serum levels of blood glucose and glycosylated hemoglobin (HbA1c). The subjects were regarded as having diabetes when they were so diagnosed by their family doctors and/or when they had an HbA1c level of more than 6.5% (11). Body mass index (BMI) was calculated by the following equation: body weight [kg]/(height [m])². Blood pressure was measured twice in a sitting position by nurses using a mercury sphygmomanometer after the participant had rested for 15 min in a quiet room. The average of the two measurements was used for analysis. Subjects with averaged values of systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg as well as subjects receiving treatment for hypertension by their family doctors were regarded as having hypertension.

Questionnaire on Family History

All participants completed a questionnaire with items on past disease, current disease, medication, alcohol consumption, smoking, and family history of hypertension and diabetes. The family history was taken by having each participant select “yes,” “no,” or “uncertain” in a table of questions on the presence of hypertension and diabetes in the grandfather, grandmother, father, mother, siblings, and children. Positive family history of hypertension and/or diabetes was defined as having at least one member in the group including the father, mother and siblings with hypertension and/or diabetes. To blind subjects to our major interest in the questionnaire (*i.e.*, family history of hypertension and diabetes), additional extraneous health questions were also included.

Statistical Analysis

Differences in clinical data among the 4 age-groups were analyzed by analysis of variance followed by Scheffé’s post-hoc test. Multiple logistic regression analysis was applied to examine the effects of age and family history on the prevalence of hypertension or diabetes adjusted for BMI and occupation. In the age-specific analysis of prevalence of hypertension or diabetes in those with and those without family history, significance was calculated by the χ^2 test. Differences with values of $p < 0.05$ were regarded as statistically significant.

Results

Table 1 shows the mean age and mean values of BMI, SBP, DBP, blood pressures, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, blood glucose, and HbA1c. There was an increasing trend in all of the parameters

Table 1. Mean Values of Body Mass Index (BMI), Blood Pressure, and Serum Parameters of Lipid and Glucose Metabolism in 10 Year-Age Groups

Group	Age range (years old)	n	Body mass index (kg/m ²)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Total cholesterol (mg/dl)	HDL cholesterol (mg/dl)	Triglyceride (mg/dl)	Glucose (mg/dl)	HbA1c (%)
20s	20–29	216	22.4±3.5 ^{†,§}	123.1±14 ^{†,§}	71.5±11 ^{†,§}	180.5±30 ^{†,§}	59.7±14	103±58.1 ^{†,§}	88.5±24 ^{†,§}	4.48±0.5 ^{†,§}
30s	30–39	221	23.6±3.6 ^{*,§}	123.7±15 [§]	75.2±11 ^{*,§}	199.1±34 ^{*,§}	59.9±15	140±104.1 ^{*,§}	94.1±24 [§]	4.64±0.7 ^{*,§}
40s	40–49	306	24.2±3.3 ^{*,†}	126.7±15 ^{*,†}	78.9±11 ^{*,†}	214.8±33 ^{*,†}	58.5±15	163±117.9 ^{*,†}	104.2±33 ^{*,†}	4.88±0.8 ^{*,†}
50s	50–60	380	23.1±2.9 ^{*,§}	133.4±17 ^{*,†,§}	82.1±11 ^{*,†,§}	210.2±34 ^{*,†}	62.1±16 [§]	142±96.8 ^{*,§}	107.7±38 ^{*,†}	5.03±1 ^{*,†,§}
Total		1,123								

Values are mean±SD. * $p<0.0001$ vs. 20s, $^{\dagger}p<0.0001$ vs. 30s, and $^{\S}p<0.0001$ vs. 40s. HDL, high-density lipoprotein.

Table 2. Multivariate-Adjusted Odds Ratios (OR) and 95% Confidence Interval (CI) of Hypertension

Factor	Unit	OR	95% CI	p value
Aging	10-year aging	1.86	(1.62–2.16)	<0.001
Family history of hypertension	present vs. absent	2.37	(1.72–3.25)	<0.001
Family history of diabetes	present vs. absent	0.97	(0.65–1.42)	ns
Body mass index	increase by 1 kg/m ²	1.20	(1.14–1.25)	<0.001
Occupation	manual labor vs. office work	1.50	(1.09–2.08)	<0.01
	sales work vs. office work	0.70	(0.44–1.08)	ns

Definition of hypertension: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or on anti-hypertensive medication. ns, not significant.

Fig. 1. Effects of aging and family history of hypertension on the prevalence of hypertension. The prevalence of hypertension increased with age both in those with and without a family history of hypertension. A family history of hypertension increased the risk of hypertension by approximately 1.5–2 fold in all age groups. FH, family history.

except HDL cholesterol with aging. The proportions of subjects who drank alcohol more than 4 days a week and current smokers were 49% and 54%, respectively.

Prevalence of Hypertension

The prevalence of hypertension in all of the subjects was

28.7%. When analyzed by age group, the prevalence was 12.5% in the 20s, 16.3% in the 30s, 29.7% in the 40s, and 44.5% in the 50s, indicating an increasing trend with aging.

Multiple logistic regression analyses revealed that the risk of hypertension was significantly associated with age group, family history of hypertension, BMI, and work as a manual laborer. Notably, family history of diabetes did not increase the risk of hypertension. Table 2 shows the multivariate-adjusted odds ratios of hypertension according to 10-year age group, family history of hypertension, BMI, and kind of work. There was a significant difference in the risk of hypertension between office work and manual labor.

To elucidate the impact of family history of hypertension on age of onset, the prevalence of hypertension was compared according to the presence or absence of family history in each age group. The proportion of subjects with positive family history of hypertension was 23.5% (16.2% in the 20s, 20.7% in the 30s, 30.5% in the 40s, and 24.1% in the 50s). Seven percent of all subjects responded that they were “uncertain” whether one or more of their family members had hypertension. The prevalences of hypertension in the absence of family history of hypertension were 11% in the 20s, 14% in the 30s, 22% in the 40s, and 39% in the 50s (Fig. 1). Among subjects with a family history of hypertension, the prevalences of hypertension were 22% ($p=0.08$ vs. those without family history) in the 20s, 26.7% ($p<0.05$) in the 30s, 44.7% ($p<0.0001$) in the 40s, and 59.3% ($p<0.001$) in the 50s. Thus, when a family history was present, the prevalence rates

Table 3. Multivariate-Adjusted Odds Ratios (ORs) and 95% Confidence Interval (CI) of Diabetes

Factor	Unit	OR	95% CI	<i>p</i> value
Aging	10-year aging	2.49	(1.65–3.97)	<0.001
Family history of diabetes	present vs. absent	5.79	(2.95–11.4)	<0.001
Family history of hypertension	present vs. absent	1.00	(0.46–2.00)	ns
Body mass index	increase by 1 kg/m ²	1.18	(1.08–1.30)	<0.001
Occupation	manual labor vs. office work	0.91	(0.44–1.98)	ns
	sales work vs. office work	1.53	(0.58–3.83)	ns

Definition of diabetes: HbA1c $\geq 6.5\%$ or being treated as diabetes. ns, not significant.

Fig. 2. Effects of aging and family history of diabetes on the prevalence of diabetes. The occurrence of diabetes was strongly associated with the presence of a family history of diabetes, and age had an exponential impact on the expression of the genetic trait. FH, family history.

were approximately 1.5 to 2-fold higher than when it was absent in all age groups (Fig. 1). The age-related increase in the prevalence of hypertension was similar between subjects with and those without a family history of hypertension.

Prevalence of Diabetes

The prevalence of diabetes in all of the subjects was 3.6%. When analyzed by age group, the prevalence was 0.9% in the 20s, 1.8% in the 30s, 2.9% in the 40s, and 6.6% in the 50s, indicating an exponential increase with aging.

Multiple logistic regression analysis revealed that the risk of diabetes was significantly associated with age group, family history of diabetes, and BMI (Table 3). Similar to the finding that family history of hypertension did not increase the risk of diabetes, family history of diabetes did not increase the risk of hypertension. Table 3 shows the multivariate-adjusted odds ratios of diabetes according to 10-year age group, family history of hypertension, and BMI. Notably, the presence of a family history of diabetes increased the risk of diabetes by approximately 5 fold.

To elucidate the impact of family history of diabetes on the age of onset, the prevalence of diabetes was compared

between subjects with and without a family history in each age group. The proportion of subjects with a positive family history of diabetes was 15.0% (11.7% in the 20s, 11.9% in the 30s, 20.1% in the 40s, and 14.6% in the 50s). Six percent of all subjects responded that they were “uncertain” whether one or more of their family members had diabetes. As shown in Fig. 2, the prevalence of diabetes in the absence of a family history of diabetes was 0.5% in the 20s, 1.0% in the 30s, 1.2% in the 40s, and 4.3% in the 50s, with the greatest increase occurring between the 40s and 50s. In subjects with a family history of diabetes, the prevalence of diabetes was 4% ($p=0.08$ vs. those without a family history) in the 20s, 7.7% ($p<0.05$) in the 30s, 9.7% ($p<0.001$) in the 40s, and 20% ($p<0.0001$) in the 50s. Thus the rates of prevalence were much higher among those with than among those without a family history of diabetes (Fig. 2). In addition, the pattern of exponential increase in the rate of diabetes with age appeared to be enhanced by the presence of a family history of diabetes (Fig. 2).

Effect of Clustering of Family Histories of Hypertension and Diabetes

We next used multiple regression analysis to investigate whether clustering of family histories of hypertension and diabetes conferred additional risk for the occurrence of hypertension and/or diabetes. As shown in Table 4, the clustering of family histories of hypertension and diabetes had no additional impact on the risk of hypertension or diabetes compared to the effects of having a family history of either hypertension or diabetes alone. Likewise, as already described above, the presence of a family history of hypertension did not increase the risk of diabetes, and a family history of diabetes did not increase the risk of hypertension (Tables 2 and 3). However, these findings do not mean that hypertension and diabetes occur independently of each other. The prevalence of diabetes in the presence vs. absence of hypertension was 7.4% vs. 2%, and the prevalence of hypertension in the presence vs. absence of diabetes was 64% vs. 27% ($p<0.001$ by the χ^2 test), suggesting that these two diseases are likely to occur concomitantly in the same individuals.

Table 4. Odds Ratios (OR) and 95% Confidence Interval (CI) of Hypertension and Diabetes by Association of Family Histories of Hypertension and Diabetes

Factor	<i>n</i>	OR	95% CI	<i>p</i> value
Hypertension				
No family history	858	1.00	—	—
Family history of hypertension alone	208	2.40	(1.70–3.40)	<0.001
Family histories of hypertension and diabetes	57	2.25	(1.24–4.02)	<0.01
Diabetes				
No family history	954	1.00	—	—
Family history of diabetes alone	112	5.83	(2.67–12.4)	<0.001
Family histories of hypertension and diabetes	57	5.70	(2.08–14.2)	<0.001

Definition of hypertension: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or on anti-hypertensive medication. Definition of diabetes: HbA1c $\geq 6.5\%$ or being treated as diabetes.

Discussion

In the present study, we demonstrated different patterns of age-associated increase in the prevalence of hypertension and diabetes. At the same time, we found differential impacts of family history on the onset age of these two diseases. The prevalence of hypertension increased almost linearly with age, and family history of hypertension increased the risk of hypertension by approximately 1.5–2 fold in all age groups. The rates of age-associated increase in the prevalence of hypertension in subjects with a family history and those without a family history of hypertension were similar, suggesting that familial predisposition and aging have independent and comparable impacts on the incidence of hypertension. On the other hand, the prevalence of diabetes was exponentially increased in the older age groups, and this tendency was much more pronounced in those with a family history of diabetes, indicating that the incidence of diabetes depends largely on familial predisposition, the expression of which is relatively suppressed during the earlier half of life.

There are sex-related differences in the mechanisms of hypertension and/or diabetes, and these differences are associated with differences in the prevalence of these diseases (12–14). Menopause has been linked to an increase in the occurrence of hypertension and obesity (15, 16). In the present study, we used only male subjects in order to exclude confounding effects due to such sex-related differences, and thereby simplify our interpretation of the outcomes. In a future study, however, it would be of interest to clarify the interactions of sex, age, and familial predisposition in the mechanisms of development of hypertension and/or diabetes.

In the present study, we defined a positive family history as having at least one parent or sibling with the diseases. However, it has been reported that family history of hypertension (2, 4, 5) and that of diabetes (17, 18) are both quantitatively associated with the prevalences of the respective diseases. In the present study, however, the sample size was not large enough to allow a valid comparison among subgroups divided

by the number of family members with hypertension or diabetes. The proportion of subjects with family history of either hypertension or diabetes increases with age of the family member, causing an underestimation of the effect of family history during the earlier half of life. This is, however, a limitation of cross-sectional studies in which the family history of any age-related disease is investigated on the basis of questionnaires or interviews. Uncertainty about the diseases of family members may also cause a bias of the outcome. In the present study, the proportions of subjects who were “uncertain” about the family history in the questionnaire were only 7% for hypertension and 6% for diabetes, percentages that should not greatly affect the results of this study.

The prevalence of hypertension in all subjects was 28.7%, a value comparable with the results of similar surveys performed in Japan (5, 19, 20), China (21) and the United States (22). However, the prevalence of hypertension may be greatly influenced by various factors, including characteristics of the subjects (race, age, and sex) (21, 22), types of survey (work place or community) (19, 20), and methods of blood pressure measurement (home or ambulatory, length of resting time before measurement, and number of measurements) (23). Considering that our survey was conducted during working hours, it is possible that blood pressure, and thus the prevalence of hypertension, may have been overestimated. However, according to the report of the Fifth National Survey on Cardiovascular Disease by the Ministry of Health, Labour and Welfare of Japan (24), in which blood pressure was measured just once in randomly selected subjects from several different communities, the proportions of male subjects having SBP and/or DBP of more than 140/90 mmHg were 23.1% in the 30s, 40.4% in the 40s, 51.3% in the 50s and 51.7% in the entire groups, proportions higher than those found in our study. Thus, the prevalence of hypertension in the present study is not likely to have been exaggerated by the physical activities of the subjects.

The overall prevalence of diabetes was 3.6%, which is relatively low compared with previously reported prevalences (11, 25–28). According to the report of the Japanese Commit-

tee on the Classification and Diagnostic Criteria of Diabetes (11), the prevalence of "diabetic type" hyperglycemia in Japanese health check examinees was 7.8% when it was identified by fasting plasma glucose level of more than 126 mg/dl, and the prevalence was 12% when it was identified by glucose level 2 h after 75 g glucose load of more than 200 mg/dl. In the present study, we identified diabetes by HbA1c because reliable data of fasting glucose level or glucose level 2 h after 75 g glucose load were not available. The cutoff line we used in the present survey (HbA1c $\geq 6.5\%$) was relatively strict, and this might have been the reason for the low prevalence of diabetes in the present study. However, this cutoff line, *i.e.*, HbA1c $\geq 6.5\%$, is generally accepted as appropriate for a convincing diagnosis of diabetes (11). Consistent with our data, the survey conducted by the Japanese Ministry of Health, Labour and Welfare (29) showed that the proportions of individuals with HbA1c of more than 6.1% were 0.9% in the 20s, 1.6% in the 30s, 5.8% in the 40s and 10% in the 50s, which are close to the values in our study. The small difference between the prevalence rates in that survey and those in our survey is consistent with the difference in the cutoff line of HbA1c.

Both environmental and genetic factors play a major role in the mechanisms of hypertension and diabetes. Lifestyle modification is strongly recommended for those at increased risk for these diseases. The present observations provide a guide for identifying those at high risk. For example, healthy men in their 40s with a positive family history of diabetes should be encouraged to keep their lifestyle healthy, since one out of five such individuals may develop diabetes in their 50s. Similarly, it was surprising that the prevalence of hypertension in men in their 20s with a family history of hypertension was as high as 20%. On the other hand, the prevalence of diabetes was very low in the 20s regardless of family history. To our knowledge, there has been no report linking the risk of hypertension and diabetes with family history in an age-specific fashion.

In the present study, we tested the hypothesis that hypertension and diabetes develop from a common genetic basis by examining the impact of family history of hypertension on the prevalence of diabetes and *vice versa* (Tables 2 and 3). We found that family history of hypertension did not increase the risk of diabetes, and family history of diabetes did not increase the risk of hypertension. Furthermore, clustering of family histories of hypertension and diabetes had no effect on the prevalence of either disease (Table 4). These results support the notion that hypertension and diabetes are genetically independent. However, these findings do not contradict the recent concept of metabolic syndrome (30). In our subjects, the prevalence of diabetes in the presence of hypertension and the prevalence of hypertension in the presence of diabetes were significantly high, indicating that hypertension and diabetes are likely to be associated with each other. Taken together, the results suggest that hypertension and diabetes share a common pathogenesis but are derived from indepen-

dent genetics.

In summary, we demonstrated different patterns of interaction between aging and familial predisposition in terms of the risk of hypertension and diabetes. Our results indicate that the combination of age and family history, both of which are simple and easy to obtain, provides useful and important information for selecting high-risk individuals and for deciding appropriate treatment.

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