A positive family history of hypertension might be associated with an accelerated onset of type 2 diabetes: Results from the National Center Diabetes Database (NCDD-02)

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Abstract. Type 2 diabetes, which is characterized by a combination of decreased insulin secretion and decreased insulin sensitivity, can be delayed or prevented by healthy lifestyle behaviors. Therefore, it is important that the population in general understands their personal risk at an early age to reduce their chances of ever developing the disease. A family history of hypertension is known to be associated with insulin resistance, but the effect of a family history of hypertension on the onset of type 2 diabetes has not well been examined. We performed a retrospective study examining patient age at the time of the diagnosis of type 2 diabetes by analyzing a dataset of 1,299 patients (1,021 men and 278 women) who had been diagnosed as having type 2 diabetes during a health checkup. The mean ± standard deviation of the patient age at the time of the diagnosis of diabetes was 49.1 ± 10.4 years for patients with a family history of hypertension and 51.8 ± 11.4 years for patients without a family history of hypertension (p < 0.001). A multivariate linear regression analysis showed a significant association between a family history of hypertension and a younger age at the time of the diagnosis of type 2 diabetes, independent of a family history of diabetes mellitus and a male sex, suggesting that a positive family history of hypertension might be associated with the accelerated onset of type 2 diabetes.

Key words: Type 2 diabetes, Family history of hypertension, Age at the onset of diabetes
approximately 29% of the 9.5 million people with diabetes had never been treated, and another 11.0 million people were at a high risk of developing diabetes [3]. Type 2 diabetes, which is characterized by a combination of decreased insulin secretion and decreased insulin sensitivity [4-6], can be delayed or prevented by healthy lifestyle behaviors [7, 8]. Therefore, it is important that the population in general understands their personal risk at an early age to reduce their chances of ever developing the disease.

An elevation in blood pressure, even within a high normal level, is associated with insulin resistance [9, 10], and a high normal blood pressure and hypertension are associated with an elevated risk of developing type 2 diabetes [11-13]. Moreover, Kim et al. reported that in addition to subjects with hypertension at the time of registration, subjects who later developed prehypertension or hypertension were also at risk for developing type 2 diabetes [14]. This observation showed that subjects at risk for developing hypertension are candidates for lifestyle interventions for the prevention of type 2 diabetes.

Families share genetic factors as well as a variety of lifestyle factors, such as food preferences, activities of daily life, and health beliefs. It is well known that a family history of hypertension is associated with insulin resistance [15, 16], but the effect of a family history of hypertension on the onset of type 2 diabetes has not been well examined.

In the present study, we tried to estimate the effect of a family history of hypertension on the patient age at the time of the onset of type 2 diabetes. For this purpose, we examined the age at the time of the diagnosis of type 2 diabetes among patients registered in the National Center Diabetes Database.

**Materials and Methods**

**Population included in the analysis**

The National Center Diabetes Database collected data on diabetic outpatients. The structure of the database has been previously described in detail [17]. The criteria used for the diagnosis of diabetes were defined by the Japan Diabetes Society [18-20]; these criteria are almost identical to the criteria of the World Health Organization [21]. The presence or absence of a self-reported family history of diabetes and hypertension of the individual’s grandparents, parents, siblings, children, or grandchildren was obtained from medical records and was entered into the database [17]. The situation at the time of the first diagnosis of diabetes was categorized as 1) at a health checkup, 2) during a hospital visit for the treatment of another disease, 3) at the time of the appearance of signs and symptoms of diabetes, 4) other situations, or 5) not described in the medical records [17]. Self-reported information about body weight at the age of 20 years was obtained from the patient’s medical records. We first extracted data for 1,469 type 2 diabetes patients whose diabetes had been diagnosed at the time of a health checkup and for whom the year at the time of the diagnosis of diabetes had been registered. Among these 1,469 patients, 143 subjects who developed diabetic retinopathy within five years of the diagnosis of diabetes were excluded from the analyses. We also excluded 27 patients because their family histories of diabetes and hypertension had not been registered. After these exclusions, data for 1,299 patients (1,021 men and 278 women) were finally selected for this study. This research conformed to the “Ethical Guidelines for Medical and Health Research involving Human Subjects” issued by the Ministry of Health, Labour and Welfare of Japan and was approved by the National Center for Global Health and Medicine Research Ethics Committee.

**Statistical analysis**

From the database, we obtained the presence or absence of a self-reported family history of diabetes and hypertension, the patients’ age at the time of the diagnosis of type 2 diabetes, and their body weight at the age of 20 years. We also obtained the patients’ height and body weight at the time of registration. Weight (in kilograms) was divided by the square of height (in meters) to calculate the body mass index (BMI), and the values were rounded to three significant digits. Subjects were divided according to smoking status into never smokers and ever smokers.

Patients in the present cohort were divided into 2 groups for comparison: a group with or without a family history of hypertension. The data analysis was performed using R version 3.2.1 [22]. Continuous variables were summarized as the mean ± standard deviation. Differences in the values of factors and the frequency of subjects were examined using the Student t-test and the chi-square test, respectively. p values less than 0.05 were considered to be statistically significant. To examine whether a family history of
hypertension affected the age at the time of the diagnosis of type 2 diabetes independently of the family history of diabetes and sex, we performed a multivariate linear regression analysis using the presence (converted to a dummy variable of 1) or absence (converted to a dummy variable of 0) of a family history of diabetes, the presence (converted to a dummy variable of 1) or absence (converted to a dummy variable of 0) of a family history of hypertension, and sex (a male sex was converted to a dummy variable of 1) as independent variables and the age at the time of the diagnosis of type 2 diabetes as the dependent variable.

**Results**

The demographics of patients stratified according to their family histories of hypertension are presented in Table 1. The patient age at the time of the diagnosis of diabetes was lower in the group with a positive family history of hypertension than in the group with a negative family history of diabetes. In the group with a positive family history of hypertension, the proportion of patients with a positive family history of diabetes were larger than those in the group with a negative family history of hypertension.

In the present cohort, the patient age at the time of the diagnosis of diabetes was lower in the group with a positive family history of diabetes (48.9 ± 10.7 years; n = 759) than in the group with a negative family history of diabetes (52.2 ± 11.1 years; n = 540; p < 0.001, Table 2) and was also lower in men (mean ± SD, 49.4 ± 10.8 years; n = 1,021) than in women (mean ± SD, 53.6 ± 11.2 years; n = 278; p < 0.001). Accordingly, we performed a multivariable linear regression analysis using the presence or absence of a family history of hypertension (% converted to a dummy variable of 1) or absence (converted to a dummy variable of 0) of a family history of hypertension, and sex (a male sex was converted to a dummy variable of 1) as independent variables and the age at the time of the diagnosis of type 2 diabetes as the dependent variable.

### Table 1  Clinical characteristics of type 2 diabetic patients with or without a family history of hypertension

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Family history of hypertension (+) (n = 702)</th>
<th>Family history of hypertension (-) (n = 597)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the diagnosis of diabetes (years, mean ± standard deviation)</td>
<td>49.1 ± 10.4</td>
<td>51.8 ± 11.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.9%</td>
<td>20.7%</td>
<td>0.660</td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
<td>64.2%</td>
<td>51.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index at an age of 20 years (kg/m², mean ± standard deviation, n = 1,033)</td>
<td>22.2 ± 3.3</td>
<td>22.0 ± 3.4</td>
<td>0.406</td>
</tr>
<tr>
<td>Body mass index at registration (kg/m², mean ± standard deviation, n = 1,185)</td>
<td>25.1 ± 4.1</td>
<td>24.2 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking status at registration (%) (%, n = 1,271)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>34.5</td>
<td>36.7</td>
<td>0.443</td>
</tr>
<tr>
<td>Ever</td>
<td>65.5</td>
<td>63.3</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2  Clinical characteristics of type 2 diabetic patients with or without a family history of diabetes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Family history of diabetes (+) (n = 759)</th>
<th>Family history of diabetes (-) (n = 540)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the diagnosis of diabetes (years, mean ± standard deviation)</td>
<td>48.9 ± 10.7</td>
<td>52.2 ± 11.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women (%)</td>
<td>24.0%</td>
<td>17.8%</td>
<td>0.007</td>
</tr>
<tr>
<td>Family history of hypertension (%)</td>
<td>59.4%</td>
<td>46.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index at an age of 20 years (kg/m², mean ± standard deviation, n = 1,033)</td>
<td>22.0 ± 3.2</td>
<td>22.3 ± 3.6</td>
<td>0.092</td>
</tr>
<tr>
<td>Body mass index at registration (kg/m², mean ± standard deviation, n = 1,185)</td>
<td>24.5 ± 4.0</td>
<td>25.0 ± 4.0</td>
<td>0.031</td>
</tr>
<tr>
<td>Smoking status at registration (%) (%, n = 1,271)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>37.0</td>
<td>33.5</td>
<td>0.191</td>
</tr>
<tr>
<td>Ever</td>
<td>63.0</td>
<td>66.5</td>
<td></td>
</tr>
</tbody>
</table>
The present study had several limitations. First, we examined a retrospective cohort of type 2 diabetes patients. Using this method, we cannot compare the incidence of diabetes among adults with or without a family history of hypertension. Second, the use of self-reported information regarding family history is susceptible to error. Third, a retrospective study design is inferior to a prospective study in terms of the accuracy of the patient age at the time of the onset of type 2 diabetes. The data we obtained consisted of self-reported information on the age at the time of the diagnosis of diabetes at a health checkup.

In conclusion, the findings of the present retrospective cohort study suggest that a positive family history of hypertension might be associated with an accelerated onset of type 2 diabetes. Subjects with a family history of hypertension should be informed of their personal risk at an early age accompanied by information on preventive health behaviors to reduce their chances of ever developing type 2 diabetes.

**Discussion**

The purpose of the present study was to examine whether a family history of hypertension accelerates the onset of type 2 diabetes. A family history of disease reflects a genetic susceptibility, shared behaviors within the family, and as yet undetermined risk factors [23-26]. A positive family history of hypertension is associated with insulin resistance [15, 16], and insulin resistance increases the risk of developing type 2 diabetes [27, 28]. In the present cohort comprised of patients with type 2 diabetes, the presence of a family history of hypertension significantly affected the patient age at the time of the diagnosis of type 2 diabetes independently of a family history of diabetes and sex, suggesting that the presence of a family history of hypertension affected the patient age at the onset of type 2 diabetes. Is this result applicable to the general population? Ranasinghe et al. [29] and van der Sande et al. [30] compared cohorts of young adults with or without a family history of hypertension. While no significant difference in the fasting blood glucose level was observed between the two groups in either study [29, 30], the glucose level after a 2-hour, 75-gram oral glucose tolerance test was higher among the adults with a family history of hypertension than among the adults without such a family history [30]. Mitsumata et al. examined the subjects who participated in the longitudinal Tanno-Sobetsu Study [31] and reported that the fasting blood glucose level in adults with a parental history of hypertension was 0.3 mmol/L higher than that in adults without such a history [32]. Shirakawa et al. examined male workers who participated in a longitudinal study and reported that a family history of hypertension did not increase the risk of diabetes when analyzed according to 10-year age groups [33]. Thus, further study is warranted to examine the extent to which a family history of hypertension affects the development of diabetes in the general population.

**Table 3** Results of multivariate linear regression model examining factors affecting age at the time of the diagnosis of type 2 diabetes

<table>
<thead>
<tr>
<th>Regression Coefficient (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>52.5 (51.5 - 53.6)</td>
</tr>
<tr>
<td>Sex (men, 0; women, 1)</td>
<td>4.47 (3.05 - 5.88)</td>
</tr>
<tr>
<td>Family history of diabetes (no, 0; yes, 1)</td>
<td>-3.27 (-4.46 - -2.08)</td>
</tr>
<tr>
<td>Family history of hypertension (no, 0; yes, 1)</td>
<td>-2.35 (-3.52 - -1.18)</td>
</tr>
</tbody>
</table>

Adjusted $R^2 = 0.05853$, $F = 27.9$ on 3 and 1295 DF, $p$ value < 0.001.

The present study had several limitations. First, we examined a retrospective cohort of type 2 diabetes patients. Using this method, we cannot compare the incidence of diabetes among adults with or without a family history of hypertension. Second, the use of self-reported information regarding family history is susceptible to error. Third, a retrospective study design is inferior to a prospective study in terms of the accuracy of the patient age at the time of the onset of type 2 diabetes. The data we obtained consisted of self-reported information on the age at the time of the diagnosis of diabetes at a health checkup.

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