Association between Duration of Obesity and Risk of Non-Insulin-Dependent Diabetes Mellitus

The Sotetsu Study

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The authors investigated the association between duration of obesity (ordinary obesity as body mass index (BMI) (kg/m²) ≥25.0 and extreme obesity as BMI ≥27.8) and the risk of diabetes mellitus. Male employees of a railway company, aged 30 years or older, observed for 10 years or more, free from serious disease conditions, with initial BMI <25.0, aged 30 years or more at the time diabetes was diagnosed, and with complete data, were examined by univariate and multivariate analyses (n = 1,598). Age-adjusted odds ratios for diabetes were significantly increased among males who were obese for 10-19.9 years and >20 years (odds ratios = 2.10 and 2.84 for ordinary obesity and 6.14 and 4.15 for extreme obesity, respectively). Additional adjustment for current obesity, physical activity, smoking, drinking, family history, and observation period did not change the findings remarkably. In conclusion, ≥10 years duration of ordinary obesity or ≥1 year of extreme obesity was an important predictor for diabetes independent of age, current obesity, physical activity, smoking, drinking, family history, and observation period. Am J Epidemiol 1999;149:256-60.

At present, there is a global epidemic of non-insulin-dependent diabetes mellitus with projected morbidity and mortality that are both of enormous magnitude (1). It is well known that several factors influence the development of non-insulin-dependent diabetes mellitus, such as obesity, overeating, and a sedentary life-style (2). Obesity has been most consistently and most strongly associated with an increased risk of diabetes (3), and it is generally accepted that both the degree and duration of obesity increase the risk of diabetes (4). Surprisingly, few studies have examined the association between the duration of obesity and diabetes (5, 6). There has been no epidemiologic study, to our knowledge, on the relation between the duration of obesity and diabetes in the Japanese general population.

The purpose of this study was to investigate the association between duration of obesity and non-insulin-dependent diabetes mellitus in middle-aged Japanese men.

MATERIALS AND METHODS

The subjects were recruited from the population of the Sotetsu Study, a prospective study conducted to examine the relation between life-style risk factors and chronic diseases, such as coronary heart disease, diabetes, hyperlipidemia, and hypertension. Details of this study have been described elsewhere (7).

The subjects of the present study comprised 2,322 male railway employees who underwent a health examination during the period February to May 1995. This health examination included anthropometric measurement (height and weight), blood pressure measurement, urinalysis, blood biochemistry, electrocardiogram, and chest and gastric x-rays. All of the subjects were interviewed by physicians, and data on newly diagnosed diseases and treatment were recorded. Family history of diabetes was recorded from 1994 to 1995. Data on physical activity, smoking status, and alcohol use, which may be associated with diabetes, were obtained from each individual’s self-reported
questionnaire and included the start and/or end point of drinking and/or smoking.

The subject's weight on joining the company was obtained as the primary data from the medical records. Subsequently, weights were measured at 5-year intervals starting from age 20 years to the current age for employees who joined as graduates. For employees who joined the company after age 20 years, weights were measured at 5-year intervals starting from the earliest age reached with the first digit of 0 or 5. A total of 588 males who were younger than age 30 years or whose observation period was insufficient (<10 years) were excluded. Height was also obtained from the records, but the authors used current height as the individual height parameter in adulthood because the mean difference between height at age 20 years and the current height was less than 0.6 cm. Body mass index (BMI) was calculated as body weight (kg)/height (m)^2. Ordinary obesity was defined as BMI ≥25.0 at any age, according to the World Health Organization criteria (8). In addition, extreme obesity was defined as BMI ≥27.8, according to the usual US criteria (9). Individuals who had a fasting plasma glucose level ≥6.1 mmol/liter (110 mg/dl) and/or who were positive for glucose by the urine stick test using an enzymatic method (Bayer Diagnostic, Tokyo) were tested further with a 75 g oral glucose tolerance test. Plasma glucose level before and 30, 60, and 120 minutes after a 75 g oral glucose tolerance test were measured by the glucose-oxidase method at an external laboratory (Health Science Research Institute, Yokohama).

Subjects with diabetes included: 1) males under treatment by diet, oral hypoglycemic agents, or insulin injection for physician-diagnosed non-insulin-dependent diabetes mellitus; 2) males who were classified as diabetic according to the World Health Organization criteria after a 75 g glucose load (2). Subjects with a fasting plasma glucose level ≥7.8 mmol/liter (140 mg/dl) and/or a 2-hour postload plasma glucose level ≥11.1 mmol/liter (200 mg/dl) were classified as diabetic, and the others were classified as non-diabetic.

Seventeen males were excluded because of serious disease conditions prior to the diagnosis of diabetes. Serious disease condition included a medical history of gastrectomy, neoplasm, coronary heart disease, apoplexy, liver cirrhosis, hyperthyroidism, and hyperlipidemia under treatment. Ninety males whose initial BMI was ≥25.0 were excluded because of lack of data on their obesity status prior to the initial examination. In order to avoid the inclusion of insulin-dependent diabetes mellitus, four males who were diagnosed as diabetic at an age of less than 30 years were excluded. In addition, 27 males who lacked two consecutive follow-up data were excluded to ensure reliability of the estimated duration of obesity. This left 1,598 males who were eligible for enrollment in this study.

Between the excluded men and the remainder, there was no statistically significant difference in current obesity (BMI = 23.7 vs. 23.6, p = 0.63) nor in the prevalence of diabetes (5.5 percent vs. 4.5 percent, p = 0.29).

In order to evaluate the association between duration of obesity and diabetes, the authors calculated the individual duration of ordinary obesity and extreme obesity by the person-years method in which one unit was 5 years. Duration of obesity was classified into 0 years (reference), 0.1–9.9 years (n = 252 and 92), 10.0–19.9 (n = 197 and 29), and ≥20.0 years (n = 100 and 16).

Age (30–39, 40–49, and 50–65 years of age) was used consistently as a potential confounding factor. Crude and age-adjusted odds ratios for diabetes were calculated using the Mantel-Haenszel method. Additional adjustment for other confounding factors, such as current obesity (BMI ≥25.0 for ordinary obesity and ≥27.8 for extreme obesity), physical activity, smoking status, alcohol use, family history of diabetes, and observation period, was made by means of multiple logistic regression analysis.

In order to evaluate themediated effect of plasma insulin on the association between obesity duration and diabetes, the authors examined the association between plasma insulin and obesity duration. Venipuncture was performed after overnight fasting and insulin was measured by a double-antibody radioimmunoassay method (10) (Phadeseph insulin RIA kit, Pharmacia & Upjohn, Tokyo) in an external laboratory (SRL, Tokyo). Because of a highly skewed distribution, plasma insulin was log-transformed in the following analysis.

All computations were performed using the Statistical Analysis System (SAS) (11). Reported p values were two-sided, and p values < 0.05 were regarded as statistically significant.

**RESULTS**

The characteristics of the study population are shown in table 1. Age, observation period, and obesity period were significantly greater among diabetic patients than among the controls. Current BMI was not different between the cases and controls. The proportion with a positive family history was significantly greater among cases compared with controls.

Crude and age-adjusted odds ratios for diabetes are shown in table 2. The odds ratio for diabetes among men whose duration of ordinary obesity was <10 years was increased by 40 percent compared with the reference group, but the difference was not statistically significant. The odds ratio for diabetes among men who
TABLE 1. Characteristics of the study subjects: case-control study of non-insulin-dependent diabetes mellitus (NIDDM) in male employees of a railway company in Japan, 1995 (n = 1,598)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NIDDM cases (n = 72)</th>
<th>Controls (n = 1,526)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD*)</td>
<td>51.3 (5.3)</td>
<td>45.5 (8.1)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Current body mass index (kg/m²), mean (SD)</td>
<td>23.7 (3.3)</td>
<td>23.6 (2.6)</td>
<td>0.78†</td>
</tr>
<tr>
<td>Observation period (years), mean (SD)</td>
<td>30.0 (6.1)</td>
<td>24.3 (7.5)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Obesity duration (years), mean (SD)</td>
<td>8.6 (9.9)</td>
<td>3.9 (7.1)</td>
<td>0.001§</td>
</tr>
<tr>
<td>Physical activity ≥2–3 days/week (%)</td>
<td>19.4</td>
<td>11.4</td>
<td>0.038§</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>69.4</td>
<td>60.9</td>
<td>0.15§</td>
</tr>
<tr>
<td>Drinkers (%)</td>
<td>80.6</td>
<td>80.1</td>
<td>0.93§</td>
</tr>
<tr>
<td>Family history of diabetes mellitus (%)</td>
<td>30.6</td>
<td>7.9</td>
<td>0.0001§</td>
</tr>
</tbody>
</table>

* SD, standard deviation.
† Student's t test.
‡ Wilcoxon's rank sum test.
§ Chi-square test.

TABLE 2. Crude and age-adjusted odds ratios (OR) and 95% confidence intervals (CI) for non-insulin-dependent diabetes mellitus according to the duration of obesity: case-control study in male employees of a railway company in Japan, 1995 (n = 1,598)

<table>
<thead>
<tr>
<th>Obesity duration (years)</th>
<th>Duration of ordinary obesity*</th>
<th>Crude OR</th>
<th>95% Cl</th>
<th>Age-adjusted OR</th>
<th>95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1.41</td>
<td>0.70–2.81</td>
<td>1.31</td>
<td>0.65–2.66</td>
</tr>
<tr>
<td></td>
<td>0.1–9.9</td>
<td>2.36</td>
<td>1.26–4.41</td>
<td>2.10</td>
<td>1.12–3.96</td>
</tr>
<tr>
<td></td>
<td>≥20.0</td>
<td>5.01</td>
<td>2.74–9.17</td>
<td>2.84</td>
<td>1.50–5.38</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Obesity duration (years)</th>
<th>Duration of extreme obesity*</th>
<th>Crude OR</th>
<th>95% Cl</th>
<th>Age-adjusted OR</th>
<th>95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>2.88</td>
<td>1.42–5.86</td>
<td>2.95</td>
<td>1.43–6.07</td>
</tr>
<tr>
<td></td>
<td>0.1–9.9</td>
<td>8.45</td>
<td>3.98–17.93</td>
<td>6.14</td>
<td>2.85–13.24</td>
</tr>
<tr>
<td></td>
<td>≥20.0</td>
<td>6.13</td>
<td>1.98–18.95</td>
<td>4.15</td>
<td>1.21–14.28</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* Ordinary obesity was defined as body mass index (BMI) (kg/m²) ≥25.0 and extreme obesity as BMI ≥27.8.
† No obesity (0 years duration) was defined as the reference group.

Fully adjusted odds ratios for diabetes were presented in table 3. The risk of diabetes was increased with increasing duration of ordinary obesity independent of age, current obesity, physical activity, smoking status, alcohol use, family history, and observation period. Compared with non-obese subjects, risk of diabetes among subjects who had experienced ordinary obesity for 0.1–9.9 years was about threefold higher, while risk in subjects who had experienced ordinary obesity for ≥20 years was ninefold higher. In regard to extreme obesity, the risk of diabetes was higher for any level of obesity duration compared with no obesity, although we failed to find a dose-response relationship. The

TABLE 3. Fully adjusted* odds ratios (OR) and 95% confidence intervals (CI) for non-insulin-dependent diabetes mellitus according to the duration of obesity: case-control study in male employees of a railway company in Japan, 1995 (n = 1,598)

<table>
<thead>
<tr>
<th>Obesity duration (years)</th>
<th>Ordinary obesity†</th>
<th>95% CI</th>
<th>Extreme obesity†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.98</td>
<td>0.01</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>0.1–9.9</td>
<td>2.98</td>
<td>1.31–6.77</td>
<td>7.61</td>
</tr>
<tr>
<td></td>
<td>10.0–19.9</td>
<td>5.59</td>
<td>2.41–13.00</td>
<td>58.63</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.0001</td>
<td></td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, current obesity, physical activity, smoking, drinking, family history of diabetes mellitus, and observation period by means of multiple logistic regression analysis.
† Ordinary obesity was defined as body mass index (BMI) (kg/m²) ≥25.0 and extreme obesity as BMI ≥27.8.
‡ No obesity (0 years duration) was defined as the reference group.
increase in risk of diabetes after adjustment for current obesity suggested that current obesity was an effect modification in the association between obesity duration and diabetes, even though there was no significant effect modification of current obesity in the association between duration of obesity and diabetes ($p = 0.38$ for ordinary obesity and $p = 0.18$ for extreme obesity).

The association between plasma insulin and diabetes risk factors (as mentioned above) was examined. Whether adjusted for confounding factors or not, plasma insulin level did not show a significant association with the duration of obesity (data not shown).

**DISCUSSION**

Duration of obesity was found to be an important predictor of non-insulin-dependent diabetes mellitus, independent of age, current BMI, physical activity, smoking status, alcohol use, family history, and observation period.

The association of diabetes with either current obesity or past obesity has been examined in a number of cross-sectional, retrospective, or prospective studies (12-14). Surprisingly, to our knowledge, only two reports (5, 6) have examined the association between the duration of obesity and diabetes. Biermann et al. (5) suggested a strong association between the duration of obesity and glucose intolerance. However, they did not define obesity clearly nor explain their method of calculating the duration of obesity. Everhart et al. (6) examined the effect of the duration of obesity in Pima Indians by estimating the duration from the first time of BMI ≥30.0 up to the last examination or onset of diabetes. They demonstrated that the duration of obesity was a significant risk factor for diabetes independent of the current degree of obesity. However, their assumption that the subjects had consistently been obese since those subjects first became obese left open the possibility that the individual’s duration of obesity was overestimated.

The present study has several advantages compared with the previous studies. The authors estimated the duration of obesity considering weight reduction. Our study design was based on a case-control study and the authors were able to evaluate the effect of prolonged duration of obesity over 10 years on the risk of diabetes. An interesting feature of this study was how long the duration of obesity showed an effect on diabetes. If the least duration of obesity can be identified, the risk of diabetes may be decreased by intervention with the duration of obesity. Our finding that a duration of ordinary obesity of ≥10 years increased the risk of diabetes confirms the finding of Everhart et al. (6). Furthermore, the risk of diabetes increased when the duration of extreme obesity was at ≥1 year. In addition, the authors adjusted for several important confounding factors, such as physical activity, smoking, drinking, and family history of diabetes, in order to evaluate the independent effect of the duration of obesity, although these adjustments were not made in the previous study. The duration of extreme obesity indicated a higher risk of diabetes for any duration category compared with ordinary obesity. These findings suggest that more obese males require a shorter duration of obesity to develop diabetes. Although the authors failed to find a dose-response relationship between duration of extreme obesity and risk of diabetes, the number of the subjects was not sufficient to analyze the association ($n = 7$).

The biologic mechanism that underlies the association between the duration of obesity and diabetes has not yet been clarified. Everhart et al. (6) observed that two possible deleterious effects of prolonged duration of obesity on glucose homeostasis would be increased resistance to glucose disposal and decreased secretion of insulin. Barrett-Connor (4) suggested that fat cell hypertrophy, which is a main cause of adult obesity, induced elimination of insulin receptors and decreased the function of secreted insulin. If this hypothesis is correct, a positive association between the duration of obesity and plasma insulin will be found among non-diabetic individuals. Although current obesity was associated with insulin level (15), no report, to our knowledge, has examined this association except for one (6). Among Pima Indians, the duration of obesity and fasting insulin were found to be associated, but the direction of the association was dependent on the fasting plasma glucose concentration. Unfortunately, the authors failed to find any significant association between the duration of obesity and insulin concentration with or without adjustment for age, current BMI, physical activity, smoking status, alcohol use, and family history of diabetes and whether or not a separate model (fasting plasma glucose ≥ or <6.1 mmol/liter) was used (unpublished data). This discrepancy may be explained by the current degree of obesity which was strongly associated with the plasma insulin concentration.

Several limitations of this study should be mentioned. Our subjects were Japanese males aged 30 years or more. It is not clear whether or not these findings can be generalized to other races and to females. Although the prevalence of diabetes in our population (4.5 percent) was less than that of US males (5.0-14.0 percent), it was comparable with that of English and Japanese males (3.4-8.9 percent) (16-19). Because this study was of case-control design, factors such as death, resignation, or retirement from the railway company may have biased our results. Furthermore, it cannot be
overlooked that diabetes falling outside of our criteria may have been included in the reference group. Although the mean value of BMI among our subjects was less than that found in white subjects (20), the constitution of our population was not different from that of the general Japanese male population (21). Although the cut-off point of obesity in this study was lower than that of the previous study, the duration of extreme obesity, which was added as another cut-off point (BMI = 27.8), increased the risk of diabetes as well as the duration of ordinary obesity.

In conclusion, the duration of obesity, either ordinary or extreme, was associated with a significantly high risk of non-insulin-dependent diabetes mellitus compared with no obesity, independent of age, current obesity, smoking, alcohol use, family history of diabetes, and observation period.

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REFERENCES