Original Article

Clinical Features of Normal Weight Japanese Patients with Type 2 Diabetes who had Formerly been Obese

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Aim: Although the mean body mass index (BMI) of Japanese patients with type 2 diabetes was within the normal range, we have previously shown that approximately half of all patients classified as normal weight had been formerly obese. The present study examined the clinical features of Japanese type 2 diabetic patients who are currently of normal weight but had formerly been obese (NWFO).

Methods: Body weight history with self-reported body weight was obtainable for 108 of 114 type 2 diabetic outpatients who had been regularly attending our department. Common carotid artery intima-media thickness (IMT) was also measured.

Results: At the time of the examinations, 5 (5%) and 36 (33%) of 108 type 2 diabetic patients were lean (BMI < 18.5 kg/m²) and obese (BMI ≥ 25 kg/m²), respectively, whereas normal weight (BMI ≥ 18.5-< 25 kg/m²) was found in 67 (62%) patients. Among 108 patients, 67 (62%) were normal weight, of which 32 (48%) were formerly obese (NWFO). NWFO patients with a mean age of 65 years old at the clinic visit had reached their lifetime maximum body weight at age 45 and became diabetic at age 51 years. Obese patients aged 62 years at the clinic visit became diabetic at age 50 and had reached their maximum weight at age 51 years. Diabetes duration was 11 years in patients who had never been obese. Thus, NWFO patients had been exposed to obesity-related metabolic abnormalities and/or hyperglycemia for 20 years on average whereas obese and never obese patients had been exposed for 11-12 years. Although obese patients had higher fasting TG and greater BMI than NWFO, both obese and NWFO patients had similarly lower HDL cholesterol levels than those who had never been obese; however, there was no difference among the 3 groups in diabetic treatment, diabetes duration, HbA1c levels, and prevalence of atherosclerotic risk factors, including smokers, users of statins and antihypertensive drugs. Carotid max IMT was thicker in NWFO type 2 diabetic patients (0.86 ± 0.04mm) than either obese patients (0.78 ± 0.03mm, p = 0.041) or those who had never been obese (0.78 ± 0.02mm, p = 0.046).

Conclusion: This report confirms that approximately half of 108 Japanese type 2 diabetic patients who are currently normal weight were formerly obese and shows that these patients had a thicker carotid IMT than either obese patients or those who had never been obese. Formerly obese diabetic patients who have lost weight and are currently normal weight might have been exposed to long-term obesity-related cardiometabolic abnormalities and/or hyperglycemia, resulting in increased common carotid IMT. We therefore suggest that an improved clinical screening tool would include the assessment of body weight history for all Japanese type 2 diabetic patients at their first clinic visit.


Key words: Weight history, Maximum BMI, Normal weight, Type 2 diabetics, Carotid IMT

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Introduction

Metabolic and epidemiological studies have revealed that obesity is causally related to type 2 diabetes⁴⁻⁵. In addition, weight gain after adolescence is also associated with an increased risk for type 2 diabetes⁴⁻⁵; however, the degree of obesity associated with
the risk for diabetes appears to be lower in Japanese than in Caucasians\(^6\). In addition, body mass index (BMI in kg/m\(^2\)) was much lower in Japanese than white patients with type 2 diabetes\(^7\). Moreover, the mean BMI of Japanese type 2 diabetic patients was normal (23.1 kg/m\(^2\)) and comparable to that of their non-diabetic counterparts (22.7 kg/m\(^2\))\(^8\), whereas the BMI of white diabetic patients (29.4 kg/m\(^2\)) was much greater than that reported for non-diabetics of the same ethnic origin (24.1 kg/m\(^2\))\(^9\).

We have previously reported the body weight history of Japanese type 2 diabetic patients\(^10\). Normal weight is defined as a BMI ranging from 18.5 to 24.9 kg/m\(^2\) and obesity as a BMI ≥ 25.0 kg/m\(^2\). In that retrospective analysis, we confirmed the previous findings that mean current BMI (23.8 kg/m\(^2\)) was within the normal range in diabetic patients with a mean age of 64 years and that 67% of the diabetic patients studied were classified as having normal weight; however, their mean BMI was 27.0 kg/m\(^2\) at a mean age of 45 years when they reached their lifetime maximum body weight. They lost on average 8 kg weight during the next 19 years. Roughly half of the normal weight Japanese patients with type 2 diabetes had been obese at their lifetime maximum body weight\(^10\). We examined the clinical features of Japanese type 2 diabetic patients who were currently normal weight but had formerly been obese (NWFO). We also measured common carotid artery intima-media thickness (IMT), a surrogate marker of early atherosclerosis\(^11\), in these patients with type 2 diabetes.

**Subjects and Methods**

We enrolled 117 consecutive Japanese patients with type 2 diabetes mellitus from January through June 2007. They had been regularly attending our department once a month for more than 12 months and had undergone carotid IMT measurements. We excluded patients with hepatitis B surface antigen or antibodies against hepatitis C virus. Patients who had aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of 100 U/L or greater, serum creatinine >177 μmol/L, proteinuria in the nephrotic range, or a history of cardiovascular events were also excluded. Three patients did not agree to participate in the study; therefore, we studied the remaining 114 patients. The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

For each subject, height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Current BMI was calculated from these measurements. Each subject was questioned by a physician (TK) about their body weight at age 20 years and maximum weight and age at the time of their lifetime maximum body weight. When ages and weights were reported as a range, not a single figure, the means of minimum and maximum values were used for analysis. The corresponding BMI was calculated from these recalled weights and heights. Of 114 patients, 6 patients did not recall their body weight at age 20 years and were excluded from further analyses. These 6 patients were older than the other patients; age averaged 76 years old. There was no difference in other clinical characteristics between the 2 groups (data not shown). Family history was considered negative for diabetes when the patients reported that none of their siblings and neither parents nor grandparents had diabetes.

IMT was measured using ultrasonic diagnosis equipment (SDU-2200; Shimadzu, Tokyo, Japan) programmed with IMT software (Intimascope; Media Cross Co. Ltd., Tokyo, Japan) as previously described\(^12\). This software allows us to recognize automatically the edge of the internal and external membranes of the blood vessels and to measure automatically the distance at a sub-pixel level (estimated to be 0.01 mm), using a three-dimensional polynomial measurement formula.

Carotid artery ultrasonography was performed using 10-MHz scanning frequency in B mode with the participant in the supine position with the neck slightly extended and the head rotated contralaterally to the side. Images were obtained in the 20 mm proximal to the origin of the bulb at the far wall of the right and left common carotid artery. In all subjects examined in this study, no plaque was observed in this segment. Thus, in this plaque-free region, computer-based IMT was evaluated by two methods: maximum and average evaluations. Maximum (max) evaluation was obtained by the IMT value at the maximal point of the region. Average IMT (aver-IMT) is the average value of 250 computer-based points in the region. Mean values of the right and left max IMT and aver IMT were used for statistical analysis.

Blood was withdrawn after overnight fasting. Plasma glucose, serum creatinine, TG, total and HDL cholesterol were measured using an autoanalyzer. A1C values were determined by high performance liquid chromatography. LDL cholesterol was calculated using Friedwald’s formula\(^13\).

Statistical analyses were performed with SPSS system 15.0 (SPSS Inc., Chicago, IL). Data are expressed as frequencies or the means ± SE. Two-tailed p values < 0.05 were considered significant.
Results

Table 1 summarizes the clinical features and weight history of 108 type 2 diabetic patients studied. Sixteen patients (15%) were treated with diet alone, 64 (59%) with sulphonylurea and/or metformin, and 28 (26%) with insulin. Statins were given to 46 patients (43%) and antihypertensive drugs to 59 patients (55%). A family history of diabetes was positive in 59 patients (55%).

Diabetic patients had gained 14 kg on average from 20 to 49 years old and BMI had increased from 21.3 to 26.8 kg/m$^2$ (Table 1). Since then they lost 7 kg and BMI had decreased to 24.1 kg/m$^2$ at age 65.

When 108 type 2 diabetic patients were 20 years old, 14% and 77% were lean and normal weight, respectively, whereas only 9% had grade I obesity (BMI: 25.0-30.0 kg/m$^2$) and none had grade II obesity (BMI: 30.0-35.0 kg/m$^2$) (Fig. 1). At age 49 years, when they reached their lifetime maximum body weight, 45% had grade I and 17% had grade II obesity, whereas only 1% were lean and 37% normal weight. The proportion of grade I obesity fell to 23% and grade II to 10%, and normal weight increased to 62% at the time of the examination when their age averaged 64 years.

Thirty-two (48%) of 67 normal weight patients were formerly obese. One hundred and eight type 2 diabetic patients were divided into 3 groups (Table 2): currently obese patients, NWFO and those who had never been obese (never-OB). Of 108 Japanese type 2 diabetic patients studied. 30% were NWFO Obese patients became diabetic at younger age and were currently younger as compared to never-OB patients. There was no difference among the 3 groups in diabetic treatment and diabetes duration. Also, no difference was found in the prevalence of smokers, or users of antihypertensive or statins. The 3 groups had a similar proportion of patients with a positive family history for diabetes.

HDL cholesterol levels were lower and fasting TG levels were higher in obese patients than in those with never-OB. HDL cholesterol levels were also lower in NWFO patients than in those with never-OB in the face of similar fasting TG levels and a similar proportion of smokers. BMI was slightly greater in NWFO than never-OB patients; thus, both obese and NWFO patients had similar HDL cholesterol levels despite large differences in BMI and fasting TG.

The 3 groups of type 2 diabetic patients showed similar patterns of fluctuations in body weights (Table 3); weight gain from early adulthood to mid-life, followed by a weight loss to their sixties. Weight gain, however, was greatest in the obese group [22 kg], intermediate in the NWFO group [14 kg] and least in the never-OB group [8 kg]. In contrast, weight loss from mid-life to their sixties was twice as great in the NWFO group [11 kg] as in the other 2 groups [5-6 kg].

Table 1. Clinical characteristics, weight history and biochemical data in 108 type 2 diabetic patients studied

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SE or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>62</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>at max BMI</td>
<td>49 ± 1</td>
</tr>
<tr>
<td>at diabetes onset</td>
<td>53 ± 1</td>
</tr>
<tr>
<td>at the present time</td>
<td>64 ± 1</td>
</tr>
<tr>
<td>Diet/Oral drugs/Insulin (%)</td>
<td>15/59/26</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Users of statins (%)</td>
<td>43</td>
</tr>
<tr>
<td>Users of anti-hypertensive drugs (%)</td>
<td>55</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>31</td>
</tr>
<tr>
<td>Positive family history of diabetes (%)</td>
<td>55</td>
</tr>
<tr>
<td>BMI (kg/m$^2$): at 20 years old</td>
<td>21.3 ± 0.3</td>
</tr>
<tr>
<td>maximum</td>
<td>26.8 ± 0.4</td>
</tr>
<tr>
<td>current</td>
<td>24.1 ± 0.4</td>
</tr>
<tr>
<td>Weight change (kg):</td>
<td></td>
</tr>
<tr>
<td>from age 20 to maximum BMI</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>from max BMI to the present time</td>
<td>−7 ± 1</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.8 ± 0.1</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>140 ± 5</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>184 ± 3</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>105 ± 3</td>
</tr>
<tr>
<td>Fasting triglycerides (mg/dL)</td>
<td>127 ± 6</td>
</tr>
</tbody>
</table>

Fig. 1. Weight distribution when type 2 diabetic patients were 20 years old, when they reached their maximum BMI and at the present time.
NWFO patients with a mean age of 65 years at the clinic visit had reached their lifetime maximum body weight at age 45 with a mean BMI of 27.1 kg/m² and became diabetic at age 51 years (Table 3); however, obese patients aged 62 years became diabetic at age 50 and had reached their maximum weight at age 51 years with a mean BMI of 30.9 kg/m². Although there was no difference in diabetes duration between the 2 groups, NWFO patients were exposed for 20 years to obesity-related cardiometabolic abnormalities and/or hyperglycemia, whereas obese patients were exposed to diabetes (hyperglycemia) for 12 years ($p<0.001$). Mean diabetes duration was 11 years in never-OB patients. Thus, NWFO patients had been exposed to obesity-related cardiometabolic abnormalities and/or hyperglycemia for a longer time period than obese and never-OB patients.

Although the 3 groups of type 2 diabetic patients were lean in early adulthood, BMI in obese and NWFO patients was slightly but significantly greater...
than in those with never-OB. In addition, current BMI was slightly greater in patients with NWFO than in never-OB patients, although BMI in the 2 groups was within the normal range.

As shown in Fig. 2, NWFO type 2 diabetic patients (0.86 ± 0.04 mm) had a thicker carotid max IMT than obese patients (0.78 ± 0.03 mm, \( p = 0.041 \)) and patients who had never experienced obesity (0.78 ± 0.02 mm, \( p = 0.046 \)). Results with average IMT were similar to those with max IMT. Although never-OB patients were older than obese patients, there was no difference in age between NWFO and never-OB or obese patients. NWFO patients had type 2 diabetes for a somewhat longer time period but there was no significant difference among the 3 patient groups.

![Fig. 2](image-url)

**Fig. 2.** Maximum and average carotid IMT in patients who never been obese (never-OB), normal weight patients who had formerly been obese (NWFO) and currently obese patients (Obese).

\( *p < 0.05 \) vs. the other 2 groups, \( *p < 0.05 \) vs. obese.

**Discussion**

This report confirms our previous study\(^6\) that approximately half of normal weight type 2 diabetic patients were formerly obese and that the mean BMI of type 2 diabetic patients was within the normal range with a mean BMI of 24.1. The present study also showed that NWFO patients had a thicker carotid IMT than either obese or never-OB patients. NWFO patients were exposed to obesity-related metabolic abnormalities and/or hyperglycemia longer than obese patients or those who had never been obese. Although many studies have evaluated the relationship between weight change and the risk of type 2 diabetes\(^1\)–\(^5\), few studies have examined body weight changes in type 2 diabetic patients and, to our knowledge, the relationship between weight fluctuations and vascular complications in type 2 diabetic patients has not been investigated.

In the present study, carotid IMT was thicker in NWFO type 2 diabetic patients than either in obese patients or patients who had never been obese. Weight loss from mid-life to their sixties was twice as great in the NWFO group as in the other 2 groups. Although weight loss may be part of dietary therapy, it has been demonstrated repeatedly that dietary therapy fails to achieve weight loss maintenance [see Ref. 14 for literature]. On the contrary, weight loss, in addition to thirst, polydipsia and polyuria, is one of the typical symptoms of diabetes, a condition characterized by chronic hyperglycemia, and chronic hyperglycemia is one of the most important causes of vascular complications in diabetes. In addition, NWFO patients did not differ from obese or never-OB patients in risk factors for atherosclerosis: age, diabetes duration, HbA1c, the prevalence of smokers, and users of antihypertensive drugs and statins. Further, the maximum BMI of NWFO patients was lower than that of obese patients (27.1 vs. 30.9 kg/m\(^2\)). We therefore, speculated that NWFO diabetic patients had been exposed for a longer time period to obesity-related cardiometabolic abnormalities and/or hyperglycemia than obese and never-OB patients, and hence they had a thicker carotid IMT.

In a study sample of second-generation Japanese-American men\(^5\), the relationships of current and maximum BMI with type 2 diabetes were more apparent in men without a family history of diabetes than in those with a family history. In men without a family history, diabetic men had higher current and maximum lifetime BMI than nondiabetic men\(^5\). In contrast, no significant difference in current and maximum BMI was found between diabetic and nondiabetic men with a positive family history. These findings suggest that environmental factors that lead to increased adiposity are more important in the genesis of type 2 diabetes if a family history of diabetes is negative than if it is positive. The results found in second-generation Japanese-American men\(^5\) concur with studies by Kuzuya and Matsuda who reported that Japanese subjects with type 2 diabetes and obesity in the past had a lower prevalence of a positive family history of diabetes\(^10\). In the present study, however, the proportion of a positive family history of diabetes in type 2 diabetic patients with obesity in the past was similar to that in currently obese and never-OB patients.

Although the mean BMI of type 2 diabetic patients studied in the present report was within the normal range, as previously reported\(^7\)–\(^10\), our patients...
had gained 14 kg on average from 20 to 49 years old. Weight gain from early adulthood to the age at the lifetime maximum body weight was somewhat greater in our 64-year-old patients (14 kg) than in male Japanese railway-company employees aged 50 years (9.9 kg)\textsuperscript{3}.

In the present study, BMI was calculated from recalled weights divided by the current height. A small but statistically significant decrease in height with aging has been reported\textsuperscript{17}. For Caucasian men (45-49 years old), the mean decrease was 4 mm on remeasurement after 5 years while for men 65 years old or older, it was 6 mm. Errors introduced by using the current height are probably small. In addition, because age distributions among the comparison groups are similar, any errors introduced by the use of the current height to calculate past BMI are probably similar. Self-reported weight at age 20 might have introduced some misclassification. In a validation study in the Nurses' Health Study II, however, the difference between measured and self-reported body weight at age 18 was, on average, only 1.4 kg\textsuperscript{18}. The correlation coefficient between recalled weight at age 18 and measured weight in physical examination records at age 18 has been reported to be 0.87. Other limitations included underreporting of past weight in obese participants and overreporting in underweight participants\textsuperscript{19,20}. These might have introduced some misclassification.

In summary, this study confirms our previous study that roughly half of normal weight Japanese patients with type 2 diabetes had formerly been obese at their lifetime maximum body weight. In addition, formerly obese diabetic patients who have lost weight and are currently normal weight might have been exposed to long-term obesity-related cardiometabolic abnormalities and/or hyperglycemia, resulting in increased common carotid IMT. We therefore suggest that an improved clinical screening tool would include the assessment of body weight history among all Japanese type 2 diabetic patients at their first clinic visit.

Because diabetic patients in the present study had a mean BMI of 20-22 kg/m\textsuperscript{2} when they were 20 years old, and given that more and more Japanese are surviving to older age and, at the same time, gaining weight, maintaining a healthy weight throughout adulthood might be particularly important with respect to clinical or public health policies and our findings deserve further investigation and confirmation in additional studies.

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