Research Article

Association between Body Weight Gain from 20 Years of Age and Diabetic Nephropathy in Japanese Patients with Type 2 Diabetes

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Keywords

Body weight gain · Nephropathy · Type 2 diabetes

Abstract

Background/Aims: It has been reported that the body mass index shows a U-shaped association with death from cardiovascular disease (CVD) in the Asian population. The relationship between body weight (BW) gain from early adulthood and diabetic nephropathy remains to be elucidated in Japanese patients with type 2 diabetes. Our aim was to investigate the association between BW gain from early adulthood and diabetic nephropathy in Japanese patients with type 2 diabetes. **Methods:** We assessed the BW of 471 consecutive patients with type 2 diabetes and calculated the change in BW from the age of 20 years to the lifetime maximum ($\Delta BW_{\text{max-20y}}$). We then evaluated the relationship of $\Delta BW_{\text{max-20y}}$ with the degree of urinary albumin excretion (UAE), which is a useful marker for CVD. **Results:** $\Delta BW_{\text{max-20y}}$ negatively correlated with the logarithm of UAE ($r = -0.160$, $p = 0.002$). Multiple regression analysis demonstrated that $\Delta BW_{\text{max-20y}}$ was independently correlated with the logarithm of UAE ($\beta = -0.112$, $p = 0.034$). **Conclusions:** BW gain from the age of 20 years is correlated with diabetic nephropathy in Japanese patients with type 2 diabetes.

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Introduction

Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in patients with type 2 diabetes, and several risk factors including smoking, hypertension, and dyslipidemia have been shown to accelerate the progression of CVD [1, 2]. Elevated albumin excretion rate, which is a useful marker for diabetic nephropathy, has also been reported to be associated with an increased risk of cardiovascular mortality and the progression of CVD [3, 4].

The prevalence of overweight and obesity, which have been increasing worldwide, are well-established risk factors for diabetes, hypertension, and CVD [5–10]. On the other hand, it has been reported that body mass index (BMI) shows a U-shaped association with death from CVD in the Asian population [11, 12]. Across BMI categories, the hazard ratio of CVD did not change significantly in the Asian population with diabetes [13]. Higher BMI might be a weak risk factor for mortality from CVD in the Asian population, for which a lower prevalence of overweight or obesity compared with Western populations has been reported [11]. A few studies have demonstrated the association between body weight (BW) status and CVD in diabetic patients. Carnethon et al. [14] found an association of BW status with CVD in adults with incident diabetes; they reported that adults of normal weight at the time of incident diabetes had higher cardiovascular mortality than those who were overweight or obese. Bello et al. [15] demonstrated that BW gain in the short term could exacerbate albuminuria. However, the relationship between BW gain from early adulthood and diabetic complications, including albuminuria, remains to be elucidated in Asian patients with type 2 diabetes. We evaluated the relationship between BW gain from early adulthood and albuminuria in Japanese patients with type 2 diabetes.

Methods

Patients and Study Design

We performed a cross-sectional study on 471 patients with type 2 diabetes recruited from the outpatient clinic at the Matsushita Memorial Hospital, Japanese Red Cross Kyoto Daini Hospital, and Kyoto Yamashiro General Medical Center from April 2014 to July 2017. Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [16]. BMI was calculated. Patients were classified as nonsmokers, past smokers, or current smokers based on information in a self-administered questionnaire. Patients with advanced renal dysfunction (serum creatinine [Cr] >2.0 mg/dL), malignancy, or a psychological disorder were excluded from the study. We then evaluated the relationship of BW gain from early adulthood to albuminuria in all patients.

Patients and Public Involvement

Our study participants were members of the general population with type 2 diabetes. The research questions and outcome measures were developed to guide future clinical practice and public management. No patients were involved in the design of, recruitment to, or conducting of the study. Patients at the Matsushita Memorial Hospital can assess results of the hospital's studies via the website.

Assessment of BW Gain from Early Adulthood and Data Collection

BW at 20 years and maximum lifetime BW were obtained from a database containing information from self-administered questionnaires. BW gain from early adulthood was defined as BW change from 20 years to maximum lifetime BW ($\Delta BW_{\text{max-20y}}$).

Table 1. Characteristics of patients

Total (male/female)	471 (295/176)
Age, years	66.4 (10.7)
Duration of diabetes, years	13.0 (9.6)
Body mass index	
Current	24.3 (3.8)
At 20 years	22.5 (3.7)
Lifetime maximum	27.7 (4.2)
Average systolic blood pressure, mm Hg	131.8 (18.6)
Hemoglobin A _{1c} , %	7.5 (1.3)
Total cholesterol, mmol/L	4.67 (0.82)
Triglyceride, mmol/L	1.69 (1.04)
Uric acid, μmol/L	321.2 (77.3)
Creatinine, μmol/L	72.7 (22.0)
Smoker, never/past/current	230/149/92
Excreted urinary albumin, mg/g Cr	14.6 (6.5–35.4)
Dipeptidyl peptidase-4 inhibitor, –/+	253/219
Antihypertensive drug, calcium channel blocker/ diuretic/RAS inhibitor	152/43/207
Statin, –/+	207/264

Data are expressed as *n*, mean (SD), or median (interquartile range).
RAS, renin-angiotensin system.

Overnight fasting blood samples were taken in the morning. Serum total cholesterol and triglyceride concentrations were assessed using standard enzymatic methods. Hemoglobin A_{1c} (HbA_{1c}) was assayed using high-performance liquid chromatography and expressed as the unit defined by the National Glycohemoglobin Standardization Program. Urinary albumin and Cr concentrations were determined in early morning spot urine. Urinary albumin excretion (UAE) was measured using an immunoturbidimetric assay.

Statistical Analysis

Means, medians, and frequencies of potential confounding variables were calculated. Because triglycerides and UAE showed skewed distributions, log transformation was carried out before performing correlation and regression analysis. The relationships between $\Delta BW_{\max-20y}$ and the logarithm of UAE, and between $\Delta BW_{\max-20y}$ and age or other variables were examined by Pearson's correlation analyses. To examine the effects of various factors on the logarithm of UAE, the following were considered simultaneously as independent variables for multiple regression analysis: age, sex, BMI, duration of diabetes, $\Delta BW_{\max-20y}$, average systolic blood pressure (SBP), HbA_{1c}, total cholesterol, the logarithm of triglyceride, uric acid, Cr, smoking status, the use of dipeptidyl peptidase-4 inhibitors, renin-angiotensin system (RAS) inhibitors, and statin. All continuous variables are presented as mean (standard deviation), median (interquartile range), or absolute number. A *p* value <0.05 was considered statistically significant.

Results

Characteristics of the 471 patients with diabetes enrolled in this study are shown in Table 1. Mean current BMI, BMI at 20 years, or maximum lifetime BMI were 24.3 (3.8), 22.5 (3.7), and 27.7 (4.2), respectively. The median UAE was 14.6 (6.5–35.4) mg/g Cr.

Table 2. Correlation between body weight gain from the age of 20 years and other variables

	Body weight gain; $\Delta BW_{\text{max-20y}}$	
	<i>r</i>	<i>p</i>
Age	-0.172	0.0002
Body mass index	0.445	<0.0001
Duration of diabetes	-0.131	0.004
Average systolic blood pressure	-0.035	0.448
Hemoglobin A _{1c}	-0.084	0.069
Total cholesterol	0.011	0.808
Logarithm of triglyceride	0.086	0.063
Uric acid	0.021	0.647
Creatinine	-0.064	0.134
Logarithm of urinary albumin excretion	-0.160	0.002

No significant correlations were found between current BMI, BMI at 20 years, or maximum lifetime BMI and the logarithm of UAE. Relationships between $\Delta BW_{\text{max-20y}}$ and other variables are shown in Table 2. No significant correlations were found between $\Delta BW_{\text{max-20y}}$ and average SBP, HbA_{1c}, total cholesterol, the logarithm of triglyceride, uric acid, or Cr. $\Delta BW_{\text{max-20y}}$ was positively correlated with BMI ($r = 0.445$, $p < 0.0001$). $\Delta BW_{\text{max-20y}}$ was negatively correlated with age ($r = -0.172$, $p = 0.0002$), duration of diabetes ($r = -0.131$, $p = 0.004$), and the logarithm of UAE ($r = -0.160$, $p = 0.002$).

Simple correlation and multiple regression analysis on the logarithm of UAE are shown in Table 3. Multiple regression analysis demonstrated that $\Delta BW_{\text{max-20y}}$ was independently correlated with the logarithm of UAE ($\beta = -0.112$, $p = 0.034$).

Discussion

The major finding of our study was that there were significant correlations between BW gain from early adulthood and albuminuria in Japanese patients with type 2 diabetes. BW gain from early adulthood was negatively correlated with the logarithm of UAE. The negative correlation between BW gain from early adulthood and albuminuria was unexpected. Our findings could reflect a higher UAE in patients who already had risk factors unrelated to diabetes. However, the findings persisted after adjustment for known risk factors such as duration of diabetes, hypertension, or smoking.

Although unintentional BW loss is common in patients with type 1 diabetes, it is also present in type 2 diabetes [17]. Guidelines recommend intentional BW loss for better glycemic control and an improvement in other CVD risk factors in type 2 diabetes patients [18]. Both scenarios are potentially controversial for describing the association between BW gain from early adulthood and albuminuria. Apparent β cell destruction might cause unintentional BW loss. In this study, we did not include patients with type 1 diabetes who had β cell destruction. However, we did not identify the exact type of diabetes in all patients owing to the difficulty of accessing the data on C-peptide or glutamic acid decarboxylase. Therefore, we could not determine whether patients with little change in BW had β cell destruction, e.g., latent autoimmune diabetes in adults [19]. Little change in BW from early adulthood might be caused by impaired insulin secretion. The duration of impaired glucose tolerance in patients who have little change in BW from early adulthood might be longer than patients who did not have little change in BW.

Table 3. Correlation between logarithm of urinary albumin excretion and other variables

	<i>r</i>	<i>p</i>	β	<i>p</i>
Age	0.178	0.0006	0.041	0.418
Sex	–	–	–0.189	0.001
Body mass index	–0.028	0.590	0.011	0.851
Duration of diabetes	0.193	0.0002	0.080	0.104
Body weight gain ($\Delta BW_{\text{max-20y}}$)	–0.160	0.002	–0.112	0.034
Average systolic blood pressure	0.166	0.001	0.213	<0.0001
Hemoglobin A _{1c}	0.065	0.209	0.013	0.800
Total cholesterol	–0.121	0.019	–0.084	0.094
Logarithm of triglyceride	0.049	0.346	0.034	0.508
Uric acid	0.139	0.010	–0.040	0.456
Creatinine	0.042	<0.0001	0.470	<0.0001
Smoking status	–	–	0.101	0.062
Dipeptidyl peptidase-4 inhibitor	–	–	0.145	0.003
RAS inhibitors	–	–	–0.024	0.632
Statin	–	–	–0.053	0.283

Sex was defined as female (= 0) or male (= 1), smoking status was defined as nonsmoker (= 0), past smoker (= 1), or current smoker (= 2), and medication for renin-angiotensin system (RAS) inhibitors or dyslipidemia was defined as without (= 0) or with (= 1).

On the other hand, we did not evaluate lean-muscle mass in our study. Little change in BW might be the result of less lean-muscle mass, which is associated with less insulin sensitivity and consequently an unfavorable metabolism. It is well known that the Asian population has less insulin sensitivity than the Western population [20]. Unmeasured insulin sensitivity might be an important residual confounder among patients with little change in BW from early adulthood.

Nonalcoholic fatty liver disease (NAFLD) is a known risk factor for albuminuria [21]. We previously reported the impact of NAFLD on incident type 2 diabetes in nonoverweight individuals [22]. Nonoverweight individuals with NAFLD had a higher risk of incident type 2 diabetes than overweight individuals without NAFLD. Moreover, the nonoverweight individuals with NAFLD who developed type 2 diabetes showed little change in BW from baseline to the time of incident type 2 diabetes. The presence of NAFLD in patients with little change in BW from early adulthood might have affected our findings.

There were several limitations to this study. First, this study had a cross-sectional design with retrospective components. More specifically, it took into account the difference between the reported BW at the age of 20 years and maximum BW that was reached through lifetime at some point until this study was conducted. The correlation analysis between UAE (the biological effect of processes that develop over time) and risk factors took only 1-point measurements into account. Second, it has been reported that weight loss can reverse renal pathology. The relationship between weight changes and changes in UAE maybe explained by the effect of weight change on blood pressure and cholesterol. Unfortunately, however, we had no information about the age of the patient and the duration of the maximum weight. Third, sarcopenia, which is associated with a loss of lean-muscle mass, could result in a lower BW; unfortunately, there was no data about sarcopenia. Fourth, the study population consisted only of Japanese men and women. Populations of Asian origin are reported to have lower BMI than those of European origin [23]; therefore, it is not certain whether our findings can be generalized to other ethnic groups. Fifth, medication adherence or medication for diabetes can affect UAE; we unfortunately had insufficient data on medication adherence and type of diabetes control medication. Finally, the number

of patients available for analysis was not large enough. The BW information in this study was self-reported. Large prospective trials are needed to better assess the relationship between BW gain from early adulthood and albuminuria in patients with type 2 diabetes.

In conclusion, BW gain from the age of 20 years may be associated with diabetic nephropathy in Japanese patients with type 2 diabetes. Taking the potential effects of BW gain from the age of 20 years into consideration could be helpful in daily clinical practice.

Statement of Ethics

This study was approved by the local Research Ethics Committee. This study was performed according to the ethics statement by the Japanese Ministry of Health, Labor and Welfare, and was conducted the study in accordance with the Declaration of Helsinki. We provided information about the study, including aims, methods and handling of personal information, to patients based on the ethics statement by the Japanese Ministry of Health, Labor and Welfare, and patients provided verbal informed consent to participate. Data cannot be shared publicly. Data are available from the Ethics Committee (contact via Matsushita Memorial Hospital) for researchers who meet the criteria for access to confidential data.

Disclosure Statement

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Author Contributions

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content.

H.O. researched data and wrote the manuscript. G.H., H.N., M.K., M.T., and Y.O. contributed to the discussion. K.N. and T.Y. researched data and contributed to the discussion. M.F. reviewed and edited the manuscript. H.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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