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Association between changes in bodyweight and cardiovascular disease risk factors among obese Japanese patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: We aimed to assess the association between bodyweight reduction and cardiovascular disease risk factors, and to identify the minimum bodyweight reduction associated with significant improvement in cardiovascular disease risk factors among obese Japanese patients with type 2 diabetes.

Materials and Methods: The cohort comprised 1,753 patients with type 2 diabetes and body mass index ≥25 kg/m^2, who visited our clinic between 2013 and 2016. Multivariable linear regression analysis was carried out to assess the relationship between bodyweight changes and glycated hemoglobin A1c, serum lipids and blood pressure. Analyses of covariance were carried out to compare mean changes in cardiovascular disease risk factors across six groups of bodyweight change, <–5%, –5% to <–3%, –3% to <–1%, –1% to <1% (reference), 1% to <3% and ≥3%.

Results: Log-transformed bodyweight change had a significantly positive relationship with log-transformed glycated hemoglobin A1c, triglycerides, low-density lipoprotein cholesterol and systolic blood pressure changes, and a negative relationship with high-density lipoprotein cholesterol, after adjusting for sex, age, duration of diabetes, body mass index, use of glucose-lowering, lipid-lowering and antihypertensive agents, and changes in the use of these medications. A mean change in glycated hemoglobin A1c was significantly improved only in the <–5% group compared with the reference. Mean changes in triglycerides were improved in all groups, and significantly in the <–5% group.

Conclusions: Bodyweight change was significantly associated with cardiovascular disease risk factor changes, and >5% bodyweight reduction was associated with improved glycated hemoglobin A1c.

INTRODUCTION

Obesity has been frequently associated with cardiovascular disease (CVD) risk factors, including insulin resistance, impaired glucose tolerance, dyslipidemia and hypertension[1,2]. Obesity also worsens glycemic control in patients with type 2 diabetes mainly through insulin resistance[3]. However, classic glucose-lowering agents, such as insulin preparations, sulfonylureas, thiazolidinediones and glinides, effectively lower plasma glucose levels while increasing bodyweight[4–7]. According to the Japan Diabetes Clinical Database Management Study[8], approximately half of Japanese patients with type 2 diabetes were obese, with a body mass index (BMI) of ≥25 kg/m^2. Furthermore, the mean BMI in both men and women increased consistently from 2003 to 2013, then decreased in 2016[8]. Conversely, the mean glycated hemoglobin A1c (HbA1c) level generally decreased consistently from 7.4% in 2003 to 7.1% in 2019–2020[8]. This paradox of weight gain despite a decrease in HbA1c might be explained by the use of the aforementioned hypoglycemic agents associated with bodyweight gain.

We have previously reported that for obese Japanese individuals without diabetes, a 5% bodyweight reduction was significantly associated with a decrease in fasting plasma glucose and HbA1c levels in women, and with a decline in blood pressure and lipid levels in men[9]. The Japan Society for the Study of

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Obesity (JASSO) recommends a bodyweight reduction of ≥3% for obese persons (BMI ≥25 kg/m^2) and 5–10% for severely obese persons (BMI ≥35 kg/m^2)[10]. The American Diabetes Association (ADA) recommends diet and exercise designed to achieve and maintain weight reduction of ≥ 5% for most patients with type 2 diabetes who are overweight or obese and are ready to achieve weight reduction[11]. Although bodyweight reduction leads to improvement in CVD risk factors in patients with type 2 diabetes[12], there are few epidemiological studies examining the association between bodyweight reduction and changes in CVD risk factors among obese Japanese patients with type 2 diabetes. Furthermore, it is unknown to what extent bodyweight reduction is associated with a significant improvement in CVD risk factors among patients with type 2 diabetes. Therefore, we carried out the present historical observational study to examine the association between changes in bodyweight and those in CVD risk factors, independent of the effect of glucose-lowering agents that might affect the bodyweight. We also examined the extent to which bodyweight reduction is associated with significant improvement in CVD risk factors among obese Japanese patients with type 2 diabetes.

MATERIALS AND METHODS

Study participants

This was a single hospital-based historical observational cohort study, comprising 2,381 Japanese patients with type 2 diabetes and a BMI of ≥25.0 kg/m^2 who visited the Diabetes Center, Tokyo Women's Medical University in 2013 (baseline year). Patients aged <20 years (n = 1) and those with missing data (n = 112) were excluded. Those with weight-affecting illnesses, such as malignant tumors (n = 168), renal dysfunction, estimated glomerular filtration rate <30 mL/min/1.73 m^2, on dialysis and kidney transplantation (n = 113), endocrine diseases or steroid use (n = 19), severe infection (n = 1), bariatric surgery (n = 1), pregnant women (n = 2), and those who died (n = 3) or were lost to follow up (n = 208) were also excluded. The remaining 1,753 patients (664 women and 1,089 men) who repeatedly visited our hospital in 2015 or 2016 (follow-up years) and had complete medical records' data were included in the analysis. The mean observation period for this study was 2.9 ± 0.2 years. There were 96 patients with a 2-year observation period, and 1,657 patients with a 3-year observation period. Type 2 diabetes was diagnosed according to the position statement of the ADA[13].

Data on the duration of diabetes, anthropometric measurements, HbA1c, plasma lipids (triglycerides, low-density lipoprotein [LDL] cholesterol and high-density lipoprotein [HDL] cholesterol), blood pressure, use of oral hypoglycemic, lipid-lowering medications and antihypertensive agents were collected as below. In addition, glucagon-like peptide-1 receptor agonist and dosage of insulin were extracted from the patients' clinical records from the first visits in 2013 and subsequent visits in 2015 or 2016. For patients who had medical records from both 2015 and 2016, data from 2016 were used for the analysis.

Biochemical analysis

Data on HbA1c, triglycerides, LDL and HDL cholesterol levels were collected at the time of the visit, regardless of whether blood was drawn fasting or postprandially. HbA1c levels were measured by high-performance liquid chromatography using HA8190V (Arkley, Kyoto, Japan) and reported using the National Glycohemoglobin Standardization Program assigned values[14]. Serum levels of triglycerides and LDL cholesterol were measured using colorimetric enzymatic methods with a fully automated LABOSPECT008 High Technologies Clinical Analyzer (Hitachi, Tokyo, Japan).

Anthropometric and body composition measurements

Height was measured to the nearest 0.1 cm with bare feet, and in the standing position. Bodyweight was measured to the nearest 0.1 kg with outerwear and shoes taken off during an outpatient visit (BWB-200; Tanita, Tokyo, Japan). BMI was calculated as the weight in kg divided by the height squared in m^2. Blood pressure was measured in a sitting position at the outpatient visit (HBP-1300; Omron, Tokyo, Japan).

Measurements

Changes in the CVD risk factors, including bodyweight, BMI, HbA1c, triglycerides, LDL and HDL cholesterol, and blood pressure, were defined as follows: ([data in 2015 or 2016 (follow-up)] − [data in 2013 (baseline)])/(data in 2013 [baseline]).

Changes in bodyweight were classified into the following six groups: <–5% (n = 330), –5% to <–3% (n = 228), –3% to <–1% (n = 309), –1% to <1% (reference group) (n = 308), 1% to <3% (n = 241) and ≥3% (n = 337). These cut-off values were used in accordance with the recommendations of the JASSO[10] and ADA[11], as described above.

Next, the use of glucose-lowering (sulfonylureas, glinides, α-glucosidase inhibitors, biguanides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and insulin), lipid-lowering and antihypertensive agents were assessed according to the dates of addition, continuation or cessation of these agents. Compound agents were treated as classified into their respective components.

Statistical analysis

The Statistical Package for the Social Sciences for Windows (SPSS, Chicago, IL, USA) version 24.0 was used for the statistical analysis, and a P-value of <0.05 was set as the significant difference in two-sided tests.

Normally distributed data, presented as means and standard deviations, were compared using the paired t-test. Data that were not normally distributed were log-transformed to fit a normal distribution. McNemar's test was used to compare the percentage of each categorical variable between the baseline and follow-up periods. The least square mean changes and 95% confidence intervals were provided only for descriptive purposes, hence P-values were not calculated.

A multivariable linear regression model was used to test the linear relationship between changes in bodyweight as an independent variable, and changes in HbA1c, serum lipids and systolic blood pressure as the dependent variables, respectively. In the model, log-transformed values were used for changes in bodyweight, HbA1c, serum lipids and systolic blood pressure. Adjustments were made for sex and age, duration of diabetes, BMI, use of glucose- and lipid-lowering medications, and antihypertensive agents at baseline, and changes in the use of these medications.

Analysis of covariance (ANCOVA) was carried out to compare the mean changes in the CVD risk factors across the six bodyweight change groups, after adjustment for the aforementioned covariates, by carrying out multiple comparisons using the Dunnett–Hsu test with the reference group of '−1% to <1% bodyweight change.'

RESULTS

Characteristics of the obese Japanese patients with type 2 diabetes at baseline and follow up

Table 1 shows the characteristics of the study patients at baseline and follow up. The mean age at baseline was 62 years. The mean values of BMI, triglycerides, LDL cholesterol and diastolic blood pressure were significantly decreased, and the mean HbA1c and HDL cholesterol values significantly increased during the observation period ($P < 0.001$). The use of glinides ($P = 0.003$), dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, insulin and antihypertensive agents (all $P < 0.001$) increased at follow up compared with those at baseline, whereas the use of thiazolidinediones significantly decreased ($P = 0.003$). No patients were treated with sodium–glucose cotransporter-2 inhibitors at baseline, as this class of glucose-lowering agents has only been on the Japanese market since 2014.

Table S1 shows the mean values and 95% confidence intervals for BMI at baseline and follow up according to the addition, maintenance or cessation of a single glucose-, or lipid-lowering, or antihypertensive agent. There were no significant changes in the mean BMI with the addition or discontinuation of these agents.

Multivariable linear regression analysis to predict the changes in CVD risk factors based on bodyweight change

Multivariable linear regression analysis showed that the changes in the log-transformed bodyweight had a positive relationship with the changes in the log-transformed HbA1c, triglycerides, LDL cholesterol and systolic blood pressure, and a negative relationship with the log-transformed HDL cholesterol, after adjustment for sex and age, duration of diabetes, BMI, and the use of glucose- and lipid-lowering medications, and antihypertensive agents at baseline (model 1; Table 2). These results were consistent even after additional adjustments for the changes in the use of these agents (model 2; Table 2).

Table 1 | Characteristics of the obese Japanese patients with type 2 diabetes at baseline and follow up

	Baseline	Follow up	*P*-values
Age (years)	62 ± 12	65 ± 12	
Men (%)	62.1	62.1	
BMI (kg/m^2)	28.9 ± 3.7	28.6 ± 3.9	<0.001
Diabetes duration (years)	14.8 ± 9.6	17.7 ± 9.6	
HbA1c (%)	7.7 ± 1.3	7.9 ± 1.4	<0.001
Log triglycerides (mg/dL)†	5.0 ± 0.5	4.8 ± 0.5	<0.001
LDL cholesterol (mg/dL)	110 ± 25	105 ± 27	<0.001
HDL cholesterol (mg/dL)	54 ± 13	57 ± 17	<0.001
Systolic blood pressure (mmHg)	136 ± 17	135 ± 17	0.075
Diastolic blood pressure (mmHg)	77 ± 12	74 ± 12	<0.001
Glucose-lowering agents, % (*n*)	90.1 (1,579)	93.5 (1,639)	<0.001
Sulfonylurea, % (*n*)	39.1 (685)	38.4 (673)	0.432
Glinides, % (*n*)	1.5 (26)	3.0 (52)	0.003
α-GI, % (*n*)	18.1 (318)	19.1 (334)	0.221
Biguanide, % (*n*)	42.7 (748)	43.5 (763)	0.390
Thiazolidinedione, % (*n*)	15.9 (279)	13.9 (244)	0.003
DPP-4 inhibitors, % (*n*)	45.9 (804)	56.4 (988)	<0.001
SGLT2 inhibitors, % (*n*)	–	10.3 (180)	
GLP-1 receptor agonists, % (*n*)	2.3 (40)	6.7 (118)	<0.001
Insulin, % (*n*)	35.7 (626)	38.2 (670)	<0.001
Dose (unit/day)	13.7 ± 22.5	13.9 ± 22.0	
Lipid-lowering agents, % (*n*)	61.3 (1,075)	62.3 (1,092)	0.284
Antihypertensive agents, % (*n*)	64.3 (1,127)	68.7 (1,205)	<0.001

Values are shown as the mean ± standard deviations or medians (interquartile ranges) for triglycerides or proportions (numbers), as appropriate. *P*-values: baseline versus follow up. †This variable was log-transformed for the analyses. BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2, sodium–glucose cotransporter 2; α-GI, α-glucosidase inhibitor.

Comparison of the estimated mean changes in the CVD risk factors in the six groups of bodyweight change

Figure 1 shows the mean changes in HbA1c levels, serum lipids and systolic blood pressure according to the six groups of bodyweight change with the reference group of '−1 to <1% changes in bodyweight.' The mean change in HbA1c was higher in the ≥−5% of the bodyweight change groups, whereas lower only in the <−5% group compared with baseline. Significantly lower and higher mean changes in HbA1c were observed in the <−5% group ($P < 0.001$) and ≥3% group ($P = 0.010$), respectively, when compared with the reference group. Levels of triglycerides decreased in all the six groups. A significantly lower mean change in triglycerides was only observed in the <−5% group ($P = 0.001$). LDL cholesterol decreased and HDL cholesterol increased in all six groups compared with the baseline. In all groups, there were no significant changes in LDL and HDL cholesterol compared with those of the reference group. The changes in the systolic blood pressure were significantly greater in the 1% to <3% and ≥3% groups ($P = 0.003$ and $P = 0.010$, respectively).

Table 2 | Multivariable linear regression analysis to predict the changes in each risk factor for cardiovascular disease with changes in bodyweight

Dependent variables	Model 1				Model 2			
	B	SE	β	95% CI of *B*	*B*	SE	β	95% CI of *B*
HbA1c change	0.519	0.063	0.196	0.395 to 0.642	0.566	0.065	0.214	0.438 to 0.693
Triglyceride change	1.328	0.241	0.132	0.855 to 1.800	1.437	0.250	0.143	0.948 to 1.927
LDL cholesterol change	0.340	0.121	0.068	0.102 to 0.578	0.352	0.125	0.070	0.107 to 0.597
HDL cholesterol change	−0.349	0.126	−0.067	−0.595 to −0.102	−0.321	0.130	−0.062	−0.577 to −0.066
Systolic blood pressure change	0.183	0.058	0.076	0.069 to 0.298	0.171	0.060	0.071	0.052 to 0.289

Each dependent variable was logarithmically transformed before analysis. Model 1: Covariates incorporated in the model included age, sex, duration of diabetes, body mass index at baseline and use of medications (sulfonylurea, glinides, α-glucosidase inhibitors, biguanide, thiazolidinedione, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, insulin, and lipid-lowering and antihypertensive agents) at baseline. Model 2: Covariates incorporated in the model included age, sex, duration of diabetes, body mass index at baseline, medications used (sulfonylurea, glinides, α-glucosidase inhibitors, biguanide, thiazolidinedione, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, insulin, and lipid-lowering and antihypertensive agents) at baseline, and changes in the use of these medications. *B*, partial regression coefficient; BMI, body mass index; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error; SGLT2, sodium–glucose cotransporter-2; α-GI, α-glucosidase inhibitor; β, standardized partial regression coefficient.

DISCUSSION

The present hospital-based observational cohort study showed significant associations between changes in bodyweight and CVD risk factors, even after considering the effect of medications on patients with type 2 diabetes. To the best of our knowledge, this is the first study to evaluate the association between changes in bodyweight and changes in CVD risk factors among obese Japanese patients with type 2 diabetes.

According to the Look AHEAD study, a multicenter, randomized clinical trial, a mean bodyweight reduction of 8.6% by intensive lifestyle intervention was associated with significant improvement in glycemic control in obese patients with type 2 diabetes[15]. Subsequent observational analysis of the participants in the Look AHEAD study showed weight losses of 5 to <10% were associated with significant improvement in CVD risk factors[12]. The present observational study showed that the overall mean HbA1c increased from 7.7% to 7.9% over 3 years, and the only patients who reduced bodyweight >5% achieved decline in HbA1c after adjustments for covariates. Furthermore, when compared with patients whose bodyweight did not change, the decrease in HbA1c was significantly greater in patients who lost >5% of bodyweight, suggesting that at least 5% of bodyweight reduction might be effective in lowering HbA1c levels through presumably improving insulin resistance[16]. These results support the ADA's recommendation of dietary, physical activity and behavioral therapies intended to reduce bodyweight by ≥5% for patients with type 2 diabetes who are overweight or obese[11], even in Japanese patients.

In persons without diabetes, there were positive associations between body size indices (BMI, waist circumference, waist : hip ratio, etc.) and triglyceride and LDL cholesterol levels, and a negative association between these indices and HDL cholesterol. The most striking associations with body size were triglycerides and HDL cholesterol[17]. Look AHEAD analysis showed that a bodyweight reduction of 5 to <10% had a great impact on improving abnormalities of triglycerides and HDL cholesterol, but not on LDL cholesterol[12]. In the present study, dyslipidemia generally improved during the observation period with no cut-off point for bodyweight change. As lipid metabolism might be influenced by genetic predisposition, such as primary dyslipidemia (familial hypercholesterolemia)[18,19], bodyweight reduction might not necessarily contribute to the improvement of serum lipid levels. However, a change in triglycerides was significantly greater in the <−5% group than in the group wherein there was no bodyweight change, suggesting improvements in lifestyle factors, such as exercise and diet.

The overall mean systolic blood pressure remained unchanged for 3 years, and multivariable regression analysis showed a significant association between bodyweight change and systolic blood pressure. In the six groups of bodyweight change, the systolic blood pressure elevated in the weight gain group, and dropped in the weight unchanged and reduction groups. The degree of the change was constant, even if the weight reduction increased; hence, there was no cut-off point for bodyweight reduction associated with decreased systolic blood pressure. This might be because systolic blood pressure is affected by the diet (salt reduction), sympathetic nervous system[20,21] and other disorders (heart disease, kidney disease, etc.).

In the present study, there were discrepancies in the relationship between the change in bodyweight, and the change in lipid profiles and systolic blood pressure by the two analytic methods used, namely, ANCOVA and the linear regression analysis. This might be because of the difference in the treatment of the data. Log-transformed values were used in the linear regression model, and raw values were used in the ANCOVA analysis. Furthermore, using ANCOVA, the change in bodyweight was

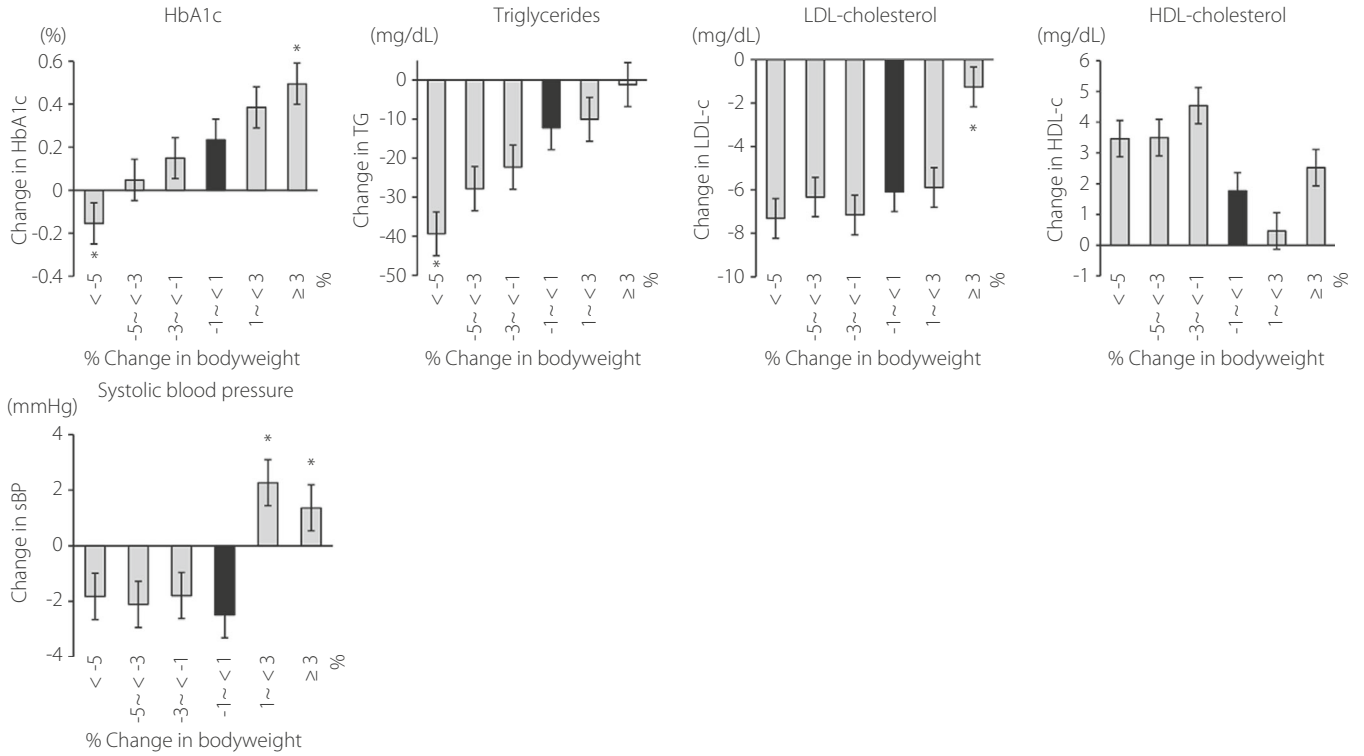

Figure 1 | Comparison of the estimated mean change in various cardiovascular risk factors among the six groups of bodyweight change. Statistical difference was tested by comparison with a reference group (−1 to <+1%). <−5%: patients with >5% of bodyweight reduction; −5% to <−3%: patients with 3–5% of bodyweight reduction; −3% to <−1%: patients with 1–3% of bodyweight reduction; −1% to <1%: patients with <1% of bodyweight reduction or gain; 1% to <3%: patients with 1–3% of bodyweight gain; ≥3%: patients with >3% of bodyweight gain. The dependent variables included age at baseline, sex, duration of diabetes at baseline, body mass index at baseline, medications used (sulfonylurea, glinides, α-glucosidase inhibitors, biguanide, thiazolidinedione, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, insulin, and lipid-lowering and antihypertensive agents) at baseline, and the changes in the use of these medications. HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; HDL-c, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; sBP, systolic blood pressure; TG, triglycerides.

stratified into six groups, and this might have reduced the statistical power. Nevertheless, use of ANCOVA was required to examine the clinical question of 'What bodyweight reduction is associated with significant improvement in CVD risk factors'.

According to the data based on a nationwide intervention targeting individuals with obesity disease (condition of obesity associated with various health disorders) or metabolic syndrome, metabolic factors gradually improved with weight reduction, and the minimum weight reduction required for improvement in CVD risk factors was reported to be 3% in obese or overweight Japanese individuals without medicated hypertension, dyslipidemia or diabetes[22]. Based on these results, regardless of the presence or absence of type 2 diabetes, the JASSO has recommended >3% bodyweight reduction in persons with a BMI of 25–30 kg/m^2, and 5–10% bodyweight reduction in persons with a BMI ≥35 kg/m^2[28]. Although our observational study was unable to show the causal relationship between bodyweight reduction and change in CVD risk factors, the present findings might support the recommendations from the JASSO and ADA.

The present study had several limitations. First, the study was observational and retrospective from a single facility, and thus could not prove a causal relationship between the change in bodyweight and change in CVD risk factors. In addition, our data might include patients with unintentional weight loss, such as malignancy and inflammatory diseases, and this affected the result. However, a previous observational study had reported the relationship of bodyweight loss and improvement of CVD risk factors[23], and these results are consistent with those of the present study. Furthermore, there were no data based on such a large-scale clinical practice for Japanese patients with type 2 diabetes. Second, the diet and exercise of individual patients were not evaluated, and we also could not evaluate the status of their smoking and alcohol intake, which are risk factors of CVD, due to lack of information from the medical records. The relationship between each of these factors and bodyweight change remains unclear.

In conclusion, bodyweight change had significant associations with changes in CVD risk factors. A bodyweight reduction of 5% was associated with improvement in glycemic control among obese Japanese patients with type 2 diabetes.

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DISCLOSURE

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Approval of the research protocol: The study protocol was approved by the institutional review board of Tokyo Women's Medical University. All clinical investigations were carried out in accordance with the tenets of the Declaration of Helsinki.

Informed consent: As this was a historical study using routine laboratory investigations, the requirement to obtain written informed consent was waived by the Committee.

Registry and the registration no. of the study/trial: 9 January 2019. No. 5043.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Mean body mass index between the baseline and follow-up period according to the addition, maintenance or cessation of a single glucose-, lipid-lowering or antihypertensive agent.