

Extent of weight reduction necessary for minimization of diabetes risk in Japanese men with visceral fat accumulation and glycated hemoglobin of 5.6–6.4%

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Keywords

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ABSTRACT

Aims/Introduction: Weight reduction improves glycemic control in obese men with glycated hemoglobin (HbA1c) of 5.6–6.4%, suggesting that it can prevent the development of diabetes in these patients. The aim of the present study was to quantify the amount of weight reduction necessary for minimization of diabetes risk in Japanese men with visceral fat accumulation.

Materials and Methods: The study participants were 482 men with an estimated visceral fat area of ≥ 100 cm², HbA1c of 5.6–6.4%, fasting plasma glucose (FPG) of < 126 mg/dL or casual plasma glucose < 200 mg/dL. They were divided into two groups based on weight change at the end of the 3-year follow-up period (weight gain and weight loss groups). The weight loss group was classified into quartile subgroups (lowest group, 0 to $< 1.2\%$: second lowest group, ≥ 1.2 to $< 2.5\%$: second highest group, ≥ 2.5 to $< 4.3\%$: highest group, $\geq 4.3\%$ weight loss). The development of diabetes at the end-point represented a rise in HbA1c to $\geq 6.5\%$ or FPG ≥ 126 mg/dL, or casual plasma glucose ≥ 200 mg/dL.

Results: The cumulative incidence of diabetes at the end of the 3-year follow-up period was 16.2% in the weight gain group and 10.1% in the weight loss group (*P* not significant). The incidence of diabetes was significantly lower in the highest weight loss group (3.1%), but not in the second highest, the second lowest and the lowest weight loss groups (9.7, 10.1 and 18.3%), compared with the weight gain group.

Conclusions: Minimization of the risk of diabetes in Japanese men with visceral fat accumulation requires a minimum of 4–5% weight loss in those with HbA1c of 5.6–6.4%.

INTRODUCTION

The estimated number of people with type 2 diabetes mellitus worldwide in 2011 was approximately 366 million people, and that number should reach more than 552 million in 2030¹. In 2007, more than 22 million Japanese were estimated to have type 2 diabetes mellitus based on analysis by The Ministry of Health, Labor and Welfare (<http://www.mhlw.go.jp/houdou/>

2008/12/h1225-5a.html), with an increase of approximately 1.6-fold in the number of people with type 2 diabetes mellitus in the past decade. Thus, prevention of type 2 diabetes mellitus is a major challenge for public health professionals throughout the world.

Type 2 diabetes mellitus results from both genetic predisposition and environmental risk factors, such as obesity, visceral fat accumulation and physical inactivity. Therefore, lifestyle interventions, especially aimed at reducing weight, could prevent the development of this disease. In fact, several large-scale

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intervention trials have concluded that lifestyle intervention to reduce bodyweight successfully prevented or delayed the onset of type 2 diabetes mellitus in subjects with impaired glucose tolerance^{2–4}. We have also reported that weight reduction was closely associated with improvement of glycemic control in male patients with visceral fat accumulation and glycated hemoglobin (HbA1c) of 5.6–6.4%, but not in patients without visceral fat accumulation⁵. The results suggested that lifestyle intervention to reduce bodyweight should be provided, especially to patients with visceral fat in order to prevent the development of type 2 diabetes mellitus. However, there is virtually no information on how much these individuals need to reduce their weight to prevent the development of type 2 diabetes mellitus.

The present study was designed to determine the extent of weight reduction in Japanese men with visceral fat accumulation and HbA1c of 5.6–6.4%, necessary to prevent type 2 diabetes mellitus within a period of 3 years.

MATERIALS AND METHODS

Participants

The study participants were male employees of the Amagasaki City Office, Hyogo, Japan, who had completed the annual health check-up in 2004 and revisited the annual health check-up, at least once, until 2007. Among these participants, 482 men with estimated visceral fat area (eVFA) of ≥ 100 cm², HbA1c of 5.6–6.4% and fasting plasma glucose (FPG) of < 126 mg/dL or casual plasma glucose of < 200 mg/dL in 2004, who were not taking any antidiabetic medications during the follow-up period, were included in this analysis. Because the data were obtained at the annual health check-up, we have either fasting or casual data on plasma glucose concentrations in each participant. FPG ≥ 126 mg/dL or casual plasma glucose ≥ 200 mg/dL is one of the criteria for the diagnosis of diabetes in Japan⁶. The HbA1c range of 5.6–6.4% is the cut-off criterion for screening subjects eligible to receive health guidance, which is designed to prevent type 2 diabetes mellitus, according to the report of the Japan Diabetes Society (JDS)⁶. Visceral fat accumulation was estimated by bioelectrical impedance analysis⁷, and defined as eVFA ≥ 100 cm², according to the Japanese criteria⁸. In addition, we excluded from the present study those subjects whose HbA1c was found to be $> 8.0\%$ in the following year; because they were considered to have reduced bodyweight not by the lifestyle intervention, but by deterioration of glucose tolerance. After the health check-up, the medical staff provided health guidance aimed at lifestyle change, which is a risk factor-oriented health promotion program encouraging a scientific understanding of the spectrum of metabolic syndrome from visceral fat accumulation to atherosclerotic cardiovascular diseases, as reported previously^{9–11}.

The study was approved by the human ethics committee of Osaka University, and a signed informed consent form was obtained from each participant. This trial was registered with the University hospital Medical Information Network (UMIN no. 000002391).

Laboratory Tests

HbA1c levels were determined by high-performance liquid chromatography (Rapidia Auto HbA1c-L; TFB, Tokyo, Japan). The value for HbA1c (%) represented the National Glycohemoglobin Standardization Program (NGSP) value (%). The following is the equation used for conversion of HbA1c (JDS) to HbA1c (NGSP): National Glycohemoglobin Standardization Program (%) = $1.02 \times$ Japan Diabetes Society (%) + 0.25%^{6,12}.

Determination of eVFA

The eVFA was determined by the bioelectrical impedance analysis method, as described previously⁷. The measurements of eVFA complied with the Guidelines of the ethical committees of Osaka University.

Statistical Analysis

In the present study, diabetes was set at HbA1c $\geq 6.5\%$ or FPG ≥ 126 mg/dL or casual plasma glucose ≥ 200 mg/dL. The incidence of diabetes was calculated by the person-year method. The cumulative incidence was compared between participants who gained and those who lost weight during the 3-year study period using the Kaplan–Meier product-limit method. Furthermore, the weight loss group was classified into quartile subgroups (lowest group, 0 to $< 1.2\%$: second lowest group, ≥ 1.2 to $< 2.5\%$: second highest group, ≥ 2.5 to $< 4.3\%$: highest group, $\geq 4.3\%$ weight loss). The cumulative incidence was compared with the weight gain group in each subgroup. The percent weight loss was calculated as $([\text{bodyweight in 2004}] - [\text{bodyweight in the last year of observation}] / [\text{bodyweight in 2004}])$. The incidence of diabetes judged by HbA1c $\geq 6.5\%$ or FPG ≥ 126 mg/dL or casual plasma glucose ≥ 200 mg/dL was used as the end-point.

In addition, we also divided the participants into subgroups based on waist circumference (WC) and eVFA change at end of the 3-year follow-up period, and analyzed the incidence of diabetes. The WC loss group was classified into quartile subgroups (lowest group, 0 to $< 1.7\%$: second lowest group, ≥ 1.7 to $< 3.3\%$: second highest group, ≥ 3.3 to $< 5.5\%$: highest group, $\geq 5.5\%$ WC loss). The eVFA loss group was classified into quartile subgroups (lowest group, 0 to $< 5.9\%$: second lowest group, ≥ 5.9 to $< 10.8\%$: second highest group, ≥ 10.8 to $< 20.0\%$: highest group, $\geq 20.0\%$ eVFA loss). The percent WC loss or eVFA loss was calculated as $([\text{WC or eVFA in 2004}] - [\text{WC or eVFA in the last year of observation}] / [\text{WC or eVFA in 2004}])$. The cumulative incidence was compared with the WC or eVFA gain group in each subgroup, respectively.

Data are presented as mean \pm standard deviation, and compared by the Student's *t*-test and log-rank test. A *P*-value < 0.05 denoted the presence of a statistically significant difference.

RESULTS

The clinical characteristics of the study participants are presented in Table 1. The mean age of the entire group was 52.2 ± 8.1 years, with a mean HbA1c of $5.9 \pm 0.2\%$. There

Table 1 | Clinical characteristics of the study participants

	Total	Weight loss group	Weight gain group	P-value
<i>n</i>	482	277	205	
Age (years)	52.2 ± 8.1	52.8 ± 7.9	51.4 ± 8.3	NS
Body mass index (kg/m ²)	26.1 ± 2.5	26.2 ± 2.4	26.0 ± 2.5	NS
Obesity† (yes/no)	318/164	186/91	132/73	NS
WC (cm)	90.8 ± 5.6	91.2 ± 5.6	90.3 ± 5.5	NS
eVFA (cm ²)	132.5 ± 25.8	133.6 ± 25.6	131.0 ± 26.1	NS
Fasting plasma glucose (mg/dL)	101 ± 9 (76)	101 ± 9 (45)	101 ± 10 (31)	NS
Causal plasma glucose (mg/dL)	108 ± 22 (406)	110 ± 22 (232)	106 ± 23 (174)	NS
HbA1c (%)	5.9 ± 0.2	5.9 ± 0.2	5.9 ± 0.2	NS
Systolic blood pressure (mmHg)	135 ± 19	137 ± 20	133 ± 17	0.0157
Diastolic blood pressure (mmHg)	84 ± 13	85 ± 14	83 ± 11	NS
Total cholesterol (mg/dL)	213 ± 34	214 ± 35	213 ± 33	NS
Triglyceride (mg/dL)	213 ± 139	218 ± 153	206 ± 117	NS
LDL cholesterol (mg/dL)	121 ± 29	121 ± 29	121 ± 28	NS
HDL cholesterol (mg/dL)	52 ± 14	52 ± 14	51 ± 13	NS
Family history of diabetes (yes/no)	71/411	38/239	33/172	NS
WC change (%)	−0.9 ± 4.5	−2.9 ± 4.0	1.9 ± 3.6	<0.0001
eVFA change (%)	−4.4 ± 15.5	−11.1 ± 13.8	4.8 ± 12.8	<0.0001
Bodyweight change (%)	−0.7 ± 4.2	−3.3 ± 2.9	2.8 ± 3.0	<0.0001

Data are mean ± standard deviation or number of participants, numbers in parentheses represent available data. P-values represent comparison between weight loss and weight gain groups. †Obesity was defined as body mass index of ≥ 25 kg/m². Percent change in bodyweight was calculated by $([\text{bodyweight in the last year of observation}] - [\text{bodyweight in 2004}]) / (\text{bodyweight in 2004})$. eVFA, estimated visceral fat area; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant; WC, waist circumference.

were no significant differences in body mass index (BMI), WC, eVFA, and HbA1c between the weight loss and weight gain groups. In addition, the proportion of participants with a family history of diabetes was not different between the weight gain and weight loss groups. The weight change was $-0.7 \pm 4.2\%$ for the entire group, with $-3.3 \pm 2.9\%$ for the weight loss group and $2.8 \pm 3.0\%$ for the weight gain group. During the 3-year study, the cumulative incidence of diabetes was 16.2% in the weight gain group and 10.1% in the weight loss group, but the difference was not significant ($P = 0.0522$).

We also analyzed the cumulative incidence of diabetes for each subdivision group of the weight loss group. The clinical characteristics of the four subgroups are listed in Table 2. There were no significant differences in age, BMI, WC, eVFA, HbA1c, and family history of diabetes between each subgroup and the weight gain group. The casual plasma glucose in the ≥ 1.2 to 2.5% weight loss group and systolic blood pressure in the 0–1.2% weight loss group were significantly different from those of the weight gain group. The bodyweight changes were -0.7 ± 0.3 , -1.8 ± 0.4 , -3.4 ± 0.5 , and $-7.4 \pm 2.8\%$ in the 0 to <1.2, ≥ 1.2 to <2.5, ≥ 2.5 to <4.3 and $\geq 4.3\%$ weight loss groups, respectively. During the 3-year study period, the cumulative incidences of diabetes were 18.3, 10.1, 9.7, and 3.1% in the 0 to <1.2, ≥ 1.2 to <2.5, ≥ 2.5 to <4.3 and $\geq 4.3\%$ weight loss groups, respectively. Analysis of the incidence of diabetes relative to that in the weight gain group showed significant differences in $\geq 4.3\%$ group ($P = 0.006$), but not in the 0 to <1.2, ≥ 1.2 to <2.5

and ≥ 2.5 to <4.3% weight loss groups (Figure 1). Similar results were obtained when casual plasma glucose in the ≥ 1.2 to 2.5% weight loss group and systolic blood pressure in the 0 to <1.2% weight loss group were adjusted to those of the weight gain group. Among the weight loss subgroups, a significant difference was also observed in the incidence of diabetes between the ≥ 4.3 and 0 to <1.2% weight loss groups ($P = 0.004$).

Next, we also separately analyzed data of patients with high levels of HbA1c (6.0–6.4%). Their clinical characteristics are presented in Table 3. There were no significant differences in age, BMI, and family history of diabetes between each weight loss group and the weight gain group. The WC and eVFA of the 0 to <1.2% weight loss group, casual plasma glucose of the ≥ 1.2 to <2.5% weight loss group and HbA1c of the $\geq 4.3\%$ weight loss group were significantly different from those of the weight gain group. During the 3-year study period, the cumulative incidences of diabetes were 50.0, 29.3, 20.5, and 0% in the 0 to <1.2, ≥ 1.2 to <2.5, ≥ 2.5 to <4.3 and $\geq 4.3\%$ weight loss groups, respectively. Analysis of the incidence of diabetes relative to that in the weight gain group (38.3%) showed that the difference was significant for the $\geq 4.3\%$ weight loss group ($P = 0.004$), but was not significant for the other three groups (Figure 2). Similar results were obtained when WC and eVFA in the 0 to <1.2% weight loss group, casual plasma glucose in the ≥ 1.2 to <2.5% weight loss group and HbA1c in the $\geq 4.3\%$ weight loss group were adjusted to those of the weight gain group. Among the weight loss subgroups, a significant

Table 2 | Clinical characteristics of the four subgroups of participants who showed weight loss at study end

	Bodyweight loss (%)			
	≥4.3%	≥2.5 to <4.3%	≥1.2 to <2.5%	0 to <1.2%
<i>n</i>	69	69	69	70
Age (years)	52.3 ± 8.3	52.5 ± 7.5	53.2 ± 7.6	53.2 ± 8.3
Body mass index (kg/m ²)	26.3 ± 2.1	26.3 ± 2.8	25.8 ± 2.3	26.6 ± 2.3
Obesity† (yes/no)	47/22	44/25	44/25	51/19
WC (cm)	91.6 ± 5.3	90.6 ± 5.7	90.5 ± 4.6	91.9 ± 6.6
eVFA (cm ²)	137.3 ± 24.9	129.4 ± 24.5	129.0 ± 19.8	138.5 ± 30.9
Fasting plasma glucose (mg/dL)	98 ± 10 (14)	100 ± 7 (8)	101 ± 8 (10)	105 ± 9 (13)
Causal plasma glucose (mg/dL)	109 ± 23 (55)	109 ± 18 (61)	113 ± 26* (59)	108 ± 21 (57)
HbA1c (%)	5.8 ± 0.2	5.9 ± 0.2	5.9 ± 0.3	5.9 ± 0.2
Systolic blood pressure (mmHg)	136 ± 19	137 ± 19	137 ± 22	139 ± 18*
Diastolic blood pressure (mmHg)	85 ± 14	86 ± 12	84 ± 15	85 ± 13
Total cholesterol (mg/dL)	217 ± 31	215 ± 37	211 ± 39	214 ± 31
Triglyceride (mg/dL)	212 ± 123	227 ± 173	205 ± 98	226 ± 199
LDL cholesterol (mg/dL)	127 ± 28	119 ± 31	120 ± 30	120 ± 29
HDL cholesterol (mg/dL)	50 ± 13	52 ± 14	54 ± 15	53 ± 15
Family history of diabetes (yes/no)	7/62	11/58	7/62	13/57
WC change (%)	-6.4 ± 4.2	-3.4 ± 3.1	-1.6 ± 2.9	-0.4 ± 3.2
eVFA change (%)	-23.4 ± 13.8	-10.9 ± 10.9	-6.5 ± 10.2	-3.8 ± 11.2
Bodyweight change (%)	-7.4 ± 2.8	-3.4 ± 0.5	-1.8 ± 0.4	-0.7 ± 0.3

Data are mean ± standard deviation or number of participants, numbers in parentheses represent available data. * $P < 0.05$, compared with the weight gain group. †Obesity was defined as body mass index of ≥ 25 kg/m². eVFA, estimated visceral fat area; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WC, waist circumference.

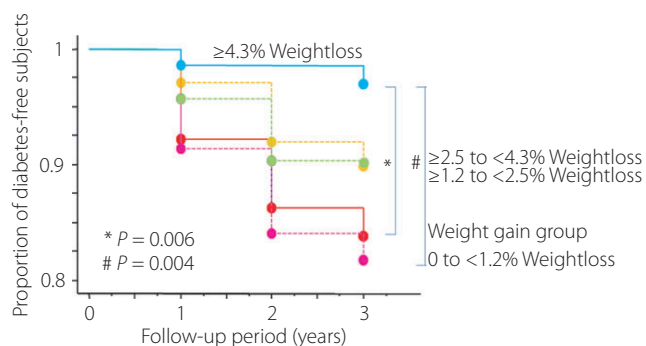


Figure 1 | Proportion of diabetes-free participants during the 3-year follow-up period among 482 male subjects who presented in 2004 with an estimated visceral fat area of ≥ 100 cm², glycated hemoglobin of 5.6–6.4% and fasting plasma glucose of < 126 mg/dL or casual plasma glucose of < 200 mg/dL. Analysis of differences in the proportion of diabetes-free participants among those who showed the indicated weight gain and weight loss using the Kaplan–Meier product-limit method. In this analysis, the end-point was set as the progression to glycated hemoglobin of $\geq 6.5\%$ or fasting plasma glucose ≥ 126 mg/dL, or casual plasma glucose ≥ 200 mg/dL. Note the significant differences in the incidence of diabetes between participants of the $\geq 4.3\%$ weight loss group ($P = 0.006$), but not those of the 0 to $< 1.2\%$, ≥ 1.2 to $< 2.5\%$ and ≥ 2.5 to $< 4.3\%$ weight loss groups, and the weight gain group. Comparison of data of the weight loss subgroups only showed a significant difference between the ≥ 4.3 and 0 to $< 1.2\%$ weight loss groups ($P = 0.004$).

difference was also observed in the incidence of diabetes between the ≥ 4.3 and 0 to $< 1.2\%$ weight loss groups ($P = 0.001$).

We also divided participants with HbA1c of 5.6–6.4% into subgroups based on WC and eVFA change at the end of the 3-year follow-up period, and analyzed the incidence of diabetes. During the 3-year study period, the cumulative incidences of diabetes were 20.2, 12.9, 11.9, and 3.2% in the 0 to < 1.7 , ≥ 1.7 to < 3.3 , ≥ 3.3 to < 5.5 and $\geq 5.5\%$ WC loss groups, respectively. Analysis of the incidence of diabetes relative to that in the WC gain group (13.3%) showed significant differences in the $\geq 5.5\%$, but not in the other WC loss groups. Furthermore, the cumulative incidences of diabetes were 9.4, 21.2, 10.3, and 4.5% in the 0 to < 5.9 , ≥ 5.9 to < 10.8 , ≥ 10.8 to < 20.0 and $\geq 20.0\%$ eVFA loss groups, respectively. Analysis of the incidence of diabetes relative to that in the eVFA gain group (14.6%) showed significant differences in $\geq 20.0\%$, but not in the other eVFA loss groups.

DISCUSSION

The Diabetes Prevention Program, a randomized clinical trial to prevent the development of diabetes, showed that intensive lifestyle intervention to reduce bodyweight could help in the prevention of type 2 diabetes mellitus, especially in patients with impaired glucose tolerance⁴. In that trial, the incidence of type 2 diabetes mellitus was reduced by 58% after 2.8 years, with an average weight reduction of 5.6 kg (loss of approximately 6% of bodyweight) in the intensive lifestyle

Table 3 | Clinical characteristics of participants with glycated hemoglobin of 6.0–6.4%

	Bodyweight loss (%)				Bodyweight gain (%)
	≥4.3%	≥2.5 to <4.3%	≥1.2 to <2.5%	0 to <1.2%	
<i>n</i>	17	22	20	21	67
Age (years)	55.3 ± 4.6	52.5 ± 7.4	53.2 ± 5.7	54.1 ± 7.7	53.2 ± 7.0
Body mass index (kg/m ²)	25.9 ± 1.8	26.4 ± 3.7	26.1 ± 2.8	27.2 ± 2.7	26.1 ± 2.4
Obesity† (yes/no)	12/5	14/8	11/9	16/5	42/25
WC (cm)	91.7 ± 4.5	92.1 ± 7.3	90.7 ± 5.5	94.6 ± 7.4*	91.0 ± 5.4
eVFA (cm ²)	138.7 ± 22.9	135.7 ± 33.8	130.6 ± 24.5	147.3 ± 34.1*	133.0 ± 24.2
Fasting plasma glucose (mg/dL)	110 ± 9 (4)	104 (2)	109 ± 6 (3)	113 ± 6 (5)	107 ± 8 (9)
Causal plasma glucose (mg/dL)	118 ± 23 (13)	114 ± 20 (20)	127 ± 31* (17)	108 ± 21 (16)	111 ± 25 (58)
HbA1c (%)	5.7 ± 0.1*	5.8 ± 0.1	5.8 ± 0.2	5.8 ± 0.2	5.8 ± 0.1
Systolic blood pressure (mmHg)	139 ± 19	140 ± 21	140 ± 19	141 ± 16	133 ± 24
Diastolic blood pressure (mmHg)	87 ± 13	85 ± 13	86 ± 13	87 ± 11	85 ± 9
Total cholesterol (mg/dL)	215 ± 27	225 ± 44	207 ± 38	212 ± 32	218 ± 36
Triglyceride (mg/dL)	209 ± 109	279 ± 260*	211 ± 99	205 ± 151	194 ± 119
LDL cholesterol (mg/dL)	123 ± 26	122 ± 38	114 ± 29	119 ± 30	126 ± 32
HDL cholesterol (mg/dL)	52 ± 14	54 ± 16	52 ± 15	54 ± 19	54 ± 10
Family history of diabetes (yes/no)	1/16	3/19	4/16	3/18	18/49
WC change (%)	−7.1 ± 3.3	−3.3 ± 3.5	−1.6 ± 3.3	−0.8 ± 3.0	1.9 ± 3.5
eVFA change (%)	−26.6 ± 12.4	−8.6 ± 12.8	−8.8 ± 10.9	−2.4 ± 12.6	5.1 ± 11.6
Bodyweight change (%)	−7.5 ± 2.4	−3.4 ± 0.6	−1.8 ± 0.4	−0.7 ± 0.3	2.8 ± 2.6

Data are mean ± standard deviation, numbers in parentheses represent available data. * $P < 0.05$, compared with the weight gain group. †Obesity was defined as body mass index of ≥ 25 kg/m². eVFA, estimated visceral fat area; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WC, waist circumference.

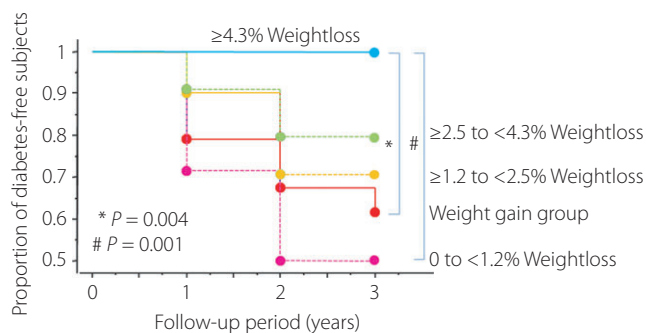


Figure 2 | Proportion of diabetes-free participants during the 3-year follow-up period among 147 male subjects who presented in 2004 with estimated visceral fat area ≥ 100 cm², glycated hemoglobin of 6.0–6.4% and fasting plasma glucose of < 126 mg/dL or casual plasma glucose of < 200 mg/dL. Differences in the proportion of diabetes-free participants among participants who showed the indicated weight gain and weight loss were compared using the Kaplan–Meier product-limit method. In this analysis, the end-point was set as progression to glycated hemoglobin of $\geq 6.5\%$ or fasting plasma glucose ≥ 126 mg/dL or casual plasma glucose ≥ 200 mg/dL. The incidence of diabetes was significantly different between the $\geq 4.3\%$ weight loss group ($P = 0.004$), but not between the other three groups, and the weight gain group (38.3% cumulative incidence). Analysis of data of the weight loss groups only showed a significant difference between the ≥ 4.3 and 0 to $< 1.2\%$ weight loss groups ($P = 0.001$).

intervention group compared with the placebo group, with an average weight reduction of 0.1 kg. The placebo group was provided with standard lifestyle recommendations including written information and an annual 20–30 min individual session that emphasized the importance of a healthy lifestyle. In another study by the same group¹³, they estimated that a 5-kg weight loss (approximately 5% bodyweight loss) during a mean period of 3.2 years accounted for 55% reduction in the risk of diabetes, and that subjects who lost more than 5–7% of bodyweight reduced the risk of type 2 diabetes mellitus by $> 90\%$. However, the mean baseline bodyweight and BMI of the participants in the aforementioned Diabetes Prevention Program trial were more than 90 kg and 31 kg/m², respectively, which are significantly different from those in the Japanese population. Therefore, it is important to investigate the effect of weight reduction on diabetes in Japanese subjects.

The results of the present study showed that in Japanese men with visceral fat accumulation and HbA1c ranging from 5.6 to 6.4%, a weight loss of $\geq 4.3\%$ reduced the risk of diabetes by approximately 80%, compared with the bodyweight gain group (mean weight gain, 2.8%) during the 3-year study period, whereas weight loss of $< 4.3\%$ did not have a significant impact on the risk of diabetes mellitus. Furthermore, the results also showed that in participants with higher levels of HbA1c

(6.0–6.4%), there was no incidence of diabetes after weight loss of $\geq 4.3\%$, whereas no change in the risk was noted when weight loss was $< 4.3\%$, compared with the weight gain group. These results show that to produce a meaningful reduction in the risk of diabetes, at least 4–5% weight reduction should be achieved by those Japanese men with visceral fat accumulation and HbA1c of 5.6–6.4%, or with HbA1c of 6.0–6.4%. Using the same method of evaluation, the results also showed that the risk of diabetes can be minimized by reducing WC and eVFA by 5.5 and 20.0%, respectively. The quantitative data on these parameters can potentially serve as important indexes to help in the prevention of diabetes in Japanese obese men. In this regard, the present study showed that approximately 14% of the participants with HbA1c of 5.6–6.4% achieved more than 4.3% weight reduction, and approximately 12% of those with higher HbA1c (6.0–6.4%) lost more than 4.3% bodyweight. These data confirm that the present study provided proof that the tentative goals set in the study (i.e. prevention of development of diabetes) are not theoretical, but rather, clinically practical and can be achieved by the patients.

The present study also analyzed the population attributable risk (PAR). Several confounding factors for diabetes (e.g., age, BMI, eVFA, WC and family history of diabetes) were not different between the weight gain group and the $\geq 4.3\%$ weight loss group. Accordingly, the PAR by $\geq 4.3\%$ weight reduction of the weight gain group was 5.6% (attributable risk = $0.162 - 0.031 = 0.131$, and thus $PAR = [0.131 \times \{205/482\} \times 100 = 5.6\%$). The cumulative incidence of diabetes was also significantly different between the $\geq 4.3\%$ weight loss group and 0 to $< 1.2\%$ weight loss group. Accordingly, the calculated PAR by $\geq 4.3\%$ weight reduction of 0 to $< 1.2\%$ weight loss group was 2.2% (attributable risk = $0.183 - 0.031 = 0.152$, with $PAR = [0.152 \times \{70 / 482\} \times 100 = 2.2\%$). As there was no significant difference in the cumulative incidence of diabetes between the $\geq 4.3\%$ weight loss group and other weight loss groups, the total PAR by $\geq 4.3\%$ weight reduction was 7.8% (5.6 + 2.2%). In other words, the incidence of diabetes was reduced by 7.8% had all participants achieved $\geq 4.3\%$ weight loss.

Muramoto *et al.*¹⁴ recently reported the results of their study involving 3,480 Japanese patients with obesity disease or metabolic syndrome who participated in a 6-month lifestyle modification program followed by 6-month follow-up period. The results showed that 11 obesity-related parameters measured in the study, including FPG and HbA1c, improved significantly in participants who achieved 3 to < 5 and $\geq 5\%$ weight reduction, compared with the participants of the control group (who achieved only $\pm 1\%$ weight change). Although the follow-up period was relatively short, it seems that $\geq 4.3\%$ weight reduction is also acceptable for minimization of obesity-related risk factors other than diabetes.

The present study had certain limitations. The study included participants with HbA1c of 5.6–6.4% and FPG of < 126 mg/dL or casual plasma glucose of < 200 mg/dL, thus, not all participants could be regarded as prediabetics. In addition, the

primary end-point was the development of diabetes, defined as HbA1c of $\geq 6.5\%$ or FPG ≥ 126 mg/dL, or casual plasma glucose ≥ 200 mg/dL, rather than being confirmed by an oral glucose tolerance test, because of the lack of sufficient data. In clinical practice in Japan, however, patients with obesity and HbA1c of 5.6–6.4%, and FPG < 126 mg/dL receive government-provided health guidance. Thus, it is important to educate such individuals about the extent of weight reduction necessary to prevent deterioration of glycemic control.

In conclusion, the present study showed a significantly lower 3-year cumulative incidence of diabetes after a weight reduction program in Japanese men who presented with excess visceral fat and HbA1c of 5.6–6.4%, and later lost $\geq 4.3\%$ in bodyweight, whereas no such protection was noted in those who achieved $< 4.3\%$ weight loss. Based on these results, we propose that any weight reduction program set for Japanese men with excess visceral fat and HbA1c of 5.6–6.4% should aim at reducing bodyweight by more than 4–5% for optimal diabetes risk minimization.

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DISCLOSURE

The authors declare no conflict of interest.

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