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Correlation between change in body weight rather than current body weight and change in serum adiponectin levels in a Japanese population—the Funagata study

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Abstract

Serum adiponectin levels are decreased in obese subjects. We examined the association of current body weight (BW) and its change with a change in serum adiponectin levels. Serum adiponectin levels at the baseline (from 1995 to 1997) and the 5-year follow-up (from 2000 to 2002) examinations were evaluated in 1003 (M/F, 425/578; age at the baseline examinations, 58.3 ± 11.7/57.5 ± 11.0 years) Japanese subjects from a cohort population (N = 2013) of the Funagata study. Correlations and associations of BW at the baseline examinations and changes in BW between the baseline and the follow-up examinations (δBW) with changes in the serum adiponectin levels in the study period (δAdiponectin) were examined. Stepwise regression analyses revealed a significant correlation of the δBW ($r = -0.233$ and -0.204 for men and women, respectively; $r = -0.324$ for the upper tertile group divided based on their body mass index in women) with the δAdiponectin. However, the BW at the baseline examinations was not significantly correlated in both sexes. Multiple logistic regression analyses revealed that subjects who reduced their BW by 2 kg or more were 2.56 (95% confidence interval, 1.21-5.42; $P = .014$) and 8.24 times (95% confidence interval, 3.59-18.9; $P < .001$) more likely to be in the upper tertile of the δAdiponectin than those who increased their BW by 2 kg or more in men and women, respectively, independent of their BW at the baseline examinations. In conclusion, we showed here that the δBW was strongly associated with the δAdiponectin in both sexes, whereas the BW at the baseline examinations was not associated with the δAdiponectin, at least in women.

1. Introduction

Adiponectin is the most abundant serum adipokine that directly or indirectly affects obesity-linked diseases [1] and is secreted exclusively by the adipose tissue [1,2]. Serum adiponectin levels are decreased in patients with obesity-linked diseases such as type 2 diabetes mellitus (DM), metabolic syndrome, coronary artery disease, and hypertension [2,3]. Furthermore, the relation of decreased serum adiponectin levels with various traits related to obesity and insulin resistance has been reported in many human studies [4-10]. Adiponectin stimulates β-oxidation in muscle and decreases insulin resistance in the liver [11]. The administration of adiponectin improved insulin resistance in animal models of obesity and insulin resistance [12,13]. On the contrary, adiponectin-knockout mice showed diet-induced insulin resistance [14]. Therefore, it seems that decreased serum adiponectin levels cause insulin resistance and, as a consequence, are related to various traits seen with insulin resistance. On the other hand, insulin resistance increases serum insulin levels, which in turn act on the adipose tissue to decrease adiponectin synthesis and secretion [15-17]. Therefore, the mechanism that links serum adiponectin levels and insulin resistance seems to be complicated. However, because adiponectin is exclusively secreted from the adipose tissue and its serum levels are decreased in obese subjects, obesity seems to be, at least in part, a cause of decreased serum adiponectin levels, which, in turn, seems

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to lead to insulin resistance and eventually becomes one of the causes leading to various obesity-linked diseases.

Finding the clinical traits related to serum adiponectin levels may lead to the clarification of effective and/or efficient means to increase serum adiponectin levels and thus to prevent obesity-linked diseases. The association of clinical traits with serum adiponectin levels has been reported in many cross-sectional studies [4-10]. However, the traits related to change in the serum adiponectin levels or future serum adiponectin levels have not been examined well. In particular, although obese or overweight subjects are known to have decreased serum adiponectin levels [4-10], it is not clear whether these subjects are prone to have even more decreased serum adiponectin levels in the future compared with the others.

The benefit of reducing body weight (BW) (or BW loss) on obesity-linked diseases can be explained, at least in part, as mediated by an increase in serum adiponectin levels. However, the previous studies that examined the association of reducing BW with an increase in serum adiponectin levels have not supported the above idea substantially [18-25]. In most studies in which the association was observed, the subjects were massively obese, and the amount of reduction in BW observed was also massive (>10 kg to as much as 57 kg) [18-23]. On the other hand, in studies in which relatively small amounts of reduction in BW (about 8 kg) were induced, no such an association was observed [24,25]. Therefore, reducing BW seemed to be associated with an increase in serum adiponectin levels only when a massive amount of BW was reduced. In other words, these results seemed to indicate that a small change in BW does not affect the serum adiponectin levels. However, these results seem to be contrary to the fact that serum adiponectin levels are decreased in obese subjects [4-10]. Therefore, the association between a change in BW and a change in serum adiponectin levels remains unclear.

In this report, we examined the association of clinical traits, especially BW, at the baseline and those changes in the 5-year study period with the change in the serum adiponectin levels in a long-term observation study of a large population-based Japanese sample, which was composed of both obese and nonobese subjects.

2. Subjects and methods

2.1. Subjects

The Funagata study is a population-based study held in Funagata, an agricultural area located about 400 km north of Tokyo, Japan [26]. All individuals older than 35 years residing in the town were considered registered for the study, and the number of residents registered for the study was 3706, as reported previously [26]. From 1995 to 1997, 2013 residents participated in health care examinations as the subjects for the Funagata study [4]. Among them, 1003 subjects participated in the follow-up examinations held 5 years later (from 2000 to 2002) after the baseline examinations and were enrolled in the present study. The follow-up rate was 58.7%. This study was approved by the Ethics Committee of Yamagata University School of Medicine, and informed consent to participate in this study was obtained from all participants.

2.2. Traits examined

The following clinical traits were obtained once at the baseline and once at the follow-up examinations, which were carried out from 7 to 9 AM, after a 10-hour over night fast: height, BW, body mass index (BMI), fasting and 2-hour plasma glucose in a 75-g oral glucose tolerance test, HbA_{1c}, waist circumference, hip circumference, waist-to-hip ratio, percent body fat, fasting serum insulin, an insulin resistance index assessed by homeostasis model assessment (HOMA-IR), systolic blood pressure, diastolic blood pressure, total serum cholesterol, serum triglycerides, and serum high-density lipoprotein cholesterol (HDL-C). Plasma glucose and HbA_{1c} were measured by using a hexokinase assay kit (Quickauto NEO GLU-HK; SHINO-TEST, Tokyo, Japan) and a latex agglutination immunoassay kit (Determiner HbA_{1c}; Kyowa Medics, Tokyo, Japan), respectively. Waist and hip circumferences were measured at the level of the umbilicus and the greater trochanters, respectively. Fasting serum insulin levels were measured by using an immuno-radiometric assay kit (INSULIN RIABEAD II; DAINABOT, Tokyo, Japan). Total serum cholesterol, serum triglyceride, and serum HDL-C were determined using enzymatic kits (L-type Wako CHO·H [Wako Pure Chemical Industries, Osaka, Japan], Pureauto S TG-N [Daiichi Pure Chemicals, Tokyo, Japan], and Cholestest N HDL [Daiichi Pure Chemicals, Tokyo, Japan], respectively). Percent body fat was assessed based on the principles of bioelectrical impedance [27]. As an exception, although fasting serum insulin levels were measured all the time at the baseline examinations, those were measured only at the follow-up examinations held in 2000 (n [M/F] = 189/270), and, thus, changes in fasting serum insulin levels and in HOMA-IR were evaluated only from these data. Correlation of the traits mentioned above and the change in the trait values between the baseline and the follow-up examinations (designated as the δtrait) with the change in the serum adiponectin levels between the baseline and the follow-up examinations (δAdiponectin) was examined. The sera obtained at the baseline and the follow-up examinations were kept at $-20^{\circ}C$ and were used to measure adiponectin levels in 2002 and 2004, respectively. Serum adiponectin levels were measured by an enzyme-linked immunosorbent assay as previously reported [10] in a commercial laboratory (Biomedical Laboratory, Tokyo, Japan).

2.3. Statistical analysis

Data are given as means ± SD. The statistical significance of the differences in the trait values between the baseline and the follow-up examinations was assessed by the

Table 1
Clinical characteristics of the study groups

Trait	Men (n = 425)				Women (n = 578)			
	Baseline	Follow-up	Change	*P*	Baseline	Follow-up	Change	*P*
Adiponectin (10× log μg/mL)	7.89 ± 2.29	9.01 ± 2.28	1.12 ± 1.63	<.001**	9.75 ± 2.16	10.61 ± 2.09	0.86 ± 1.43	<.001**
Age (y)	58.3 ± 11.7	63.1 ± 11.8	4.84 ± 0.89	<.001**	57.5 ± 11.0	62.3 ± 11.1	4.82 ± 0.85	<.001**
Height (cm)	161.5 ± 7.1	160.7 ± 7.3	−0.82 ± 1.06	<.001**	150.6 ± 6.2	149.7 ± 6.4	−0.94 ± 1.30	<.001**
BW (kg)	62.3 ± 10.0	61.5 ± 10.4	−0.68 ± 3.16	<.001**	54.2 ± 8.0	53.0 ± 8.4	−1.17 ± 3.01	<.001**
Waist circumference (cm)	81.9 ± 7.9	82.4 ± 7.8	0.63 ± 5.40	.020*	76.0 ± 8.6	76.0 ± 8.5	0.09 ± 5.91	.714
Hip circumference (cm)	91.1 ± 4.7	91.8 ± 4.6	1.08 ± 3.79	<.001**	91.2 ± 4.7	90.5 ± 4.9	−0.64 ± 4.32	.001**
Waist-to-hip ratio (%)	88.7 ± 5.3	89.3 ± 5.8	−0.6 ± 5.2	.023*	82.0 ± 6.5	82.6 ± 6.0	0.7 ± 6.1	.010*
BMI (kg/m^2)	23.8 ± 3.0	24.8 ± 3.6	0.05 ± 2.07	.632	23.9 ± 3.2	23.7 ± 3.6	−0.23 ± 1.34	<.001**
Percent body fat (%)	22.8 ± 5.8	21.4 ± 5.7	−1.30 ± 3.92	<.001**	29.5 ± 6.2	27.5 ± 6.8	−1.93 ± 5.08	<.001**
Fasting plasma glucose (mg/dL)	95.9 ± 11.5	97.3 ± 13.8	1.7 ± 11.8	.004**	93.0 ± 11.0	92.8 ± 10.3	0.1 ± 8.8	.827
2-h plasma glucose (mg/dL)	108.6 ± 39.4	127.2 ± 54.6	20.1 ± 41.2	<.001**	114.5 ± 33.9	119.7 ± 38.6	6.2 ± 30.6	<.001**
HbA_{1c} (%)	5.5 ± 0.5	5.1 ± 0.5	−0.4 ± 0.4	<.001**	5.4 ± 0.4	5.0 ± 0.4	−0.34 ± 0.26	<.001**
Fasting serum insulin (μU/mL)	4.1 ± 3.3	4.4 ± 2.7[a]	−0.19 ± 3.36[a]	.427	7.0 ± 11.1	5.4 ± 2.9[a]	−4.47 ± 14.74[a]	<.001**
HOMA-IR	1.00 ± 0.90	1.07 ± 0.69[a]	−0.06 ± 0.88[a]	.383	1.69 ± 2.90	1.24 ± 0.74[a]	−1.13 ± 3.79[a]	<.001**
Total cholesterol (mg/dL)	201.0 ± 34.8	195.3 ± 32.2	−5.7 ± 27.7	<.001**	211.0 ± 37.6	207.5 ± 32.4	−3.4 ± 28.2	.005*
HDL-C (mg/dL)	54.6 ± 13.3	55.3 ± 13.9	0.7 ± 10.0	.199	59.2 ± 14.5	61.0 ± 14.3	1.8 ± 9.7	<.001**
Triglyceride (mg/dL)	127.0 ± 99.9	136.6 ± 193.9	10.5 ± 189.9	.257	101.0 ± 54.4	101.3 ± 54.6	0.8 ± 52.1	.729
Systolic blood pressure (mm Hg)	128.4 ± 16.9	130.4 ± 15.8	2.0 ± 15.6	.009*	124.1 ± 17.4	126.9 ± 17.1	2.8 ± 16.9	<.001**
Diastolic blood pressure (mm Hg)	76.6 ± 9.5	78.3 ± 9.5	1.7 ± 10.2	<.001**	72.3 ± 10.0	75.3 ± 9.6	3.0 ± 10.3	<.001**

Values are expressed as means ± SD. *P* values compared the values at the baseline examinations with those at the 5-year follow-up examinations. The Student paired *t* test was used for the analyses.

[a] These values were obtained only from the subjects who attended the follow-up examinations held in 2000 (n [M/F] = 189/270).

* $P < .05$.

** $P < .01$.

Student paired *t* test and that among more than 3 groups was assessed by analysis of variance (ANOVA). The Scheffé post hoc test was used after ANOVA. When ANOVA did not show a significant difference, but the presence of outliers seemed to affect the results, the Kruskal-Wallis test was also used as a supplement. Simple and stepwise multiple linear regression analyses were performed to examine the correlation of the traits with the δAdiponectin. For the regression analysis, the serum adiponectin levels were log transformed (log_{10}) to approximate a normal distribution. The subjects were divided into tertiles based on their BMI at the baseline examinations (upper [U]–, middle [M]–, and lower [L]–BMI groups). The number of subjects and the range (kg/m^2) of BMI of each group were 137 and ≥24.82, 141 and 24.81 to 22.57, and 141 and ≤22.51 for the U-, M-, and L-BMI groups, respectively, in men. Those in women were 190 and ≥25.31, 190 and 25.29 to 22.29, and 193 and ≤22.27 for the U-, M-, and L-BMI groups, respectively. We considered the U-BMI group as the obese group in this study because 25 is the BMI cutoff point for obesity proposed by the Japanese Society for the Study of Obesity [28]. The subjects were also divided into 3 subgroups based on their δBW (change in BW between the baseline and the follow-up examinations) (gained ≥2 kg [G], changed BW by <2 kg [stable, or S], and reduced BW by ≥2 kg [R] BW subgroups). The cutoff points to define the subjects considered as weight-stable (S-BW subgroup) were made as changes in their BW by less than 2 kg because these changes could be explained as a change in water weight. Furthermore, other cutoff points larger than these seem to lower the statistical power for the analysis substantially because about half of the subjects were in the S-BW subgroup even with these cutoff points, and, thus, these cutoff points seemed to be acceptable for this study. The relationship between the δBW and the δAdiponectin was analyzed in each of the BMI groups as well. Multiple logistic regression analysis was performed to determine the independent association of age, the BW at the baseline examination, and the δBW with being in the upper tertile of the δAdiponectin. $P < .05$ was considered statistically significant.

3. Results

3.1. Changes in the trait values from the baseline to the follow-up examinations

This study was conducted in consideration of sex differences because serum adiponectin levels are known to be higher in women than in men [6]. The baseline characteristics and those at the follow-up examinations in each sex are shown in Table 1. In both sexes, the percent body fat, BW, and serum total cholesterol levels were decreased in the study period, whereas plasma glucose levels were increased. These findings may indicate that most subjects reduced their body fat composition and that the frequency of subjects with abnormal glucose tolerance increased during the study period or with aging. Fasting serum insulin levels and HOMA-IR decreased in the study period, which may be explained as a decrease in insulin

secretion in the study period, because glucose tolerance worsened as mentioned above.

3.2. No correlation of the traits at the baseline examinations with changes in the serum adiponectin levels

As shown in Table 2, a simple regression analysis revealed that many traits, including BW at the baseline examinations, were positively correlated with the δAdiponectin in both sexes. In women, a significant negative correlation of serum HDL-C with the δAdiponectin was also observed. However, a stepwise multiple regression analysis revealed that HOMA-IR in men and fasting serum insulin in women were the only traits correlated with the δAdiponectin, independent of other traits. Furthermore, even for those traits that showed a significant correlation, the correlation coefficients were very small, and the r^2 values of the stepwise multiple regression analysis were also very small (0.030 and 0.017 for men and women, respectively). These facts indicate that no trait at the baseline examinations, including age or those related to body fat composition, can predict future changes in serum adiponectin levels.

3.3. Changes in trait values correlated with changes in the serum adiponectin levels

Table 3 shows the results of the simple and the stepwise multiple regression analyses. As in the analyses for the traits at the baseline examinations, a significant correlation of change in many trait values, including BW, percent body fat, HOMA-IR, and serum HDL-C, with the δAdiponectin was observed in both sexes. However, a stepwise multiple regression analysis to determine independent correlations revealed a negative correlation of δBW and δ2-hour plasma glucose and a positive correlation of serum δHDL-C with the δAdiponectin in both sexes. A negative correlation of HOMA-IR in women with the δAdiponectin was also observed. Although the correlation coefficients of these traits were not very high, the r^2 values of the stepwise multiple regression analysis were substantially high, especially for women (0.267). Therefore, the observed correlations of several δtraits with the δAdiponectin seem to have clinical relevance, at least in women. Furthermore, the correlation coefficient of the δBW with the δAdiponectin was as high as −0.324 ($P < .001$) when it was examined in the U-BMI group in women.

Table 2
Baseline clinical characteristics correlated with the change in serum adiponectin levels determined by regression analysis

Trait	Men		Women	
	Simple	Stepwise	Simple	Stepwise
r^2 of the test	–	0.030	–	0.017
BW (kg)	0.099*	NA	0.031	–
BMI (kg/m^2)	0.090	–	0.033	–
Waist-to-hip ratio (%)	0.048	–	0.087*	NA
Percent body fat (%)	0.115*	NA	0.013	–
Fasting plasma glucose (mg/dL)	0.053	–	0.040	–
2-h plasma glucose (mg/dL)	0.122*	NA	0.039	–
HbA_{1c} (%)	0.015	–	0.033	–
Fasting serum insulin (μU/mL)	0.109*	–	0.132**	−0.132
HOMA-IR	0.129**	0.123	0.128**	–
Total cholesterol (mg/dL)	0.079	–	−0.071	–
Triglyceride (mg/dL)	0.102*	NA	0.020	–
HDL-C (mg/dL)	−0.023	–	−0.088*	NA

Correlation coefficients (r) are shown. – indicates not included; NA, not accepted; r value, accepted as significant for the stepwise multiple regression analysis.

* $P < .05$.

** $P < .01$.

Table 3
Changes in clinical characteristics (δtraits) correlated with the change in serum adiponectin levels determined by regression analysis

Trait	Men		Women	
	Simple	Stepwise	Simple	Stepwise
r^2 of the test	–	0.169	–	0.267
δBW (kg)	−0.125*	−0.223	−0.267**	−0.204
δBMI (kg/m^2)	−0.050	–	−0.248**	–
δWaist-to-hip ratio (%)	0.057	–	−0.142**	NA
δPercent body fat (%)	−0.138**	NA	−0.181**	NA
δFasting plasma glucose (mg/dL)	−0.078	–	−0.054	–
δHbA_{1c} (%)	0.064	–	−0.133**	–
δ2-h plasma glucose (mg/dL)	−0.174**	−0.159	−0.180**	−0.169
δFasting serum insulin (μU/mL)[a]	−0.194**	–	−0.297**	–
δHOMA-IR[a]	−0.212**	NA	−0.297**	−0.216
δTotal cholesterol (mg/dL)	0.051	–	0.077	–
δTriglyceride (mg/dL)	−0.043	–	−0.038	–
δHDL-C (mg/dL)	0.118*	0.153	0.265**	0.267

Correlation coefficients (r) are shown.

[a] The data used for this analysis were obtained only from the subjects who attended the follow-up examinations held in 2000 (n [M/F] = 189/270).

* $P < .05$.

** $P < .01$.

3.4. Correlation of the change in the BW with changes in the serum adiponectin levels

Among the traits observed as independently correlated with the δAdiponectin, the negative correlation of the δBW with the δAdiponectin is of interest because obesity, or particularly, higher BMI and/or BW, is considered to be, at least in part, a cause of decreased serum adiponectin levels. Thus, we further evaluated this correlation using other analyses. The subjects were divided into tertiles based on their BMI at the baseline examinations and into 3 subgroups based on their δBW, as described in Subjects and Methods. The δAdiponectin was shown in consideration of the δBW subgroups in each of the BMI groups (Fig. 1). In both sexes, the δAdiponectin of the S-BW subgroup was not significantly different among the BMI groups, indicating that current BMI does not affect future serum adiponectin levels.

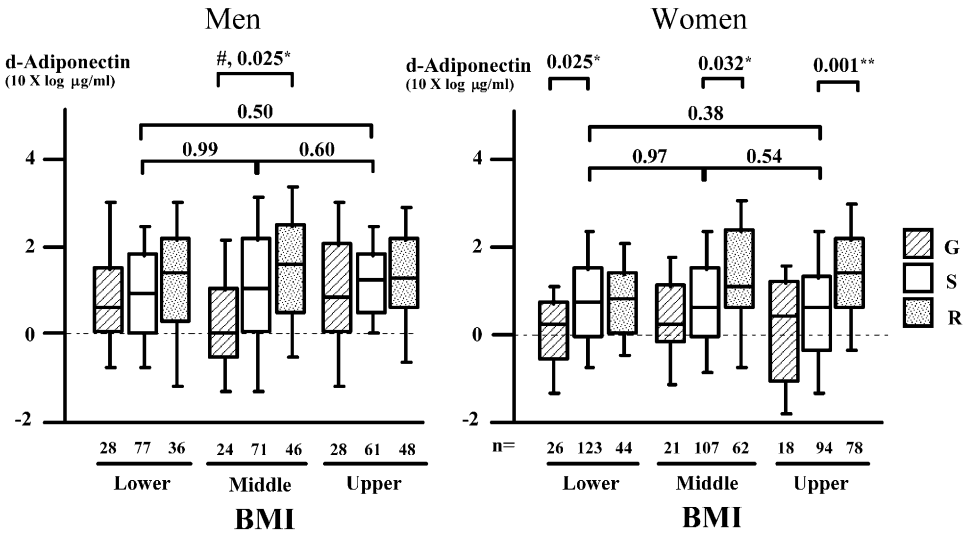

Fig. 1. Correlation of the δBW with the δAdiponectin. The box-and-whisker plots of the δAdiponectin are shown in consideration of the δBW subgroups (R-, S-, and G-BW subgroups) in each of the BMI groups (criteria for these groups were described in detail in Subjects and Methods). The number for each δBW subgroup in each BMI group is shown below the panel. The 5 horizontal lines in the box plots (from the bottom to the top) indicate 10th, 25th, 50th (median), 75th, and 90th percentile. The statistical significance was determined by ANOVA with Scheffé post hoc test. The difference among the δBW subgroups in the M-BMI group in men was examined by Kruskal-Wallis test as well. The *P* values for the analyses to examine the difference in the δAdiponectin of the S-BW subgroup among the BMI groups are shown above the panels. For other analyses, only the *P* values that are less than .05 are shown. #*P* value obtained by the Kruskal-Wallis test; **P* < .05. ▨, indicates reduced (R)-BW subgroup; □, stable (S)-BW subgroup; ■, gained (G)-BW subgroup.

In contrast, the δAdiponectin of the R-BW subgroup was significantly higher than those of the S-BW subgroup in both the U-BMI group and the M-BMI group in women. Furthermore, the δAdiponectin of the G-BW subgroup was significantly lower than those of the S-BW subgroup in the L-BMI group in women. In men, similar relationships with the δAdiponectin seemed to exist among the δBW subgroups in each of the BMI groups, but the relationships were not shown to be significant by ANOVA. However, the Kruskal-Wallis test showed a significant difference in the δAdiponectin among the δBW subgroups in the M-BMI group.

We further examined the independence of the correlation of the δBW with the δAdiponectin from the correlation of the BW at the baseline examinations with the δAdiponectin using multiple logistic regression analysis (Table 4). In women, gaining BW decreased the possibility of being in the upper tertile of the δAdiponectin, independent of the BW at the baseline examinations, which did not influence the possibility. Furthermore, subjects who reduced their BW by 2 kg or more (and were in the R-BW subgroup) were 8.24 times (95% confidence interval [CI], 3.59-18.9; *P* < .001) more likely to be in the upper tertile of the δAdiponectin than those who gained 2 kg or more, independent of their BW at the baseline examinations. In men, the δBW was similarly associated with being in the upper tertile of the δAdiponectin. However, the BW at the baseline examination was also shown as significantly associated with being in the upper tertile of the δAdiponectin, although the effect seemed to be slight (odds ratio [OR] per 1 kg, 1.04). Together, these facts indicate that change in BW, but not current BMI and BW, affects future serum adiponectin levels, at least in women.

Table 4
Association of the δBW with being in the upper tertile of the change in serum adiponectin levels between the baseline and the 5-year follow-up examinations

Traits	Men			Women		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (per 1 y)	1.03	1.00-1.05	.040*	0.99	0.97-1.01	.367
BW at baseline (per 1 kg)	1.04	1.00-1.07	.026*	1.00	0.98-1.03	.821
δBW (per 1 kg)	0.86	0.79-0.94	<.001**	0.79	0.72-0.85	<.001**
δBW (kg)						
≤−2	2.56	1.21-5.42	.014*	8.24	3.59-18.9	<.001**
>−2 and <2	1.79	0.89-3.61	.102	2.61	1.21-5.59	.014*
≥2	1	–	–	1	–	–

The results of the multiple regression analyses are shown.
* *P* < .05.
** *P* < .01.

4. Discussion

Several studies have examined the association of a change (or decrease) in BW with an increase in serum adiponectin levels [18-25]. The major difference between our study and previous studies is that our study is a population-based cohort study, whereas previous studies were case-control studies of massively obese subjects (mean BMI, 35-52; in one such study, in which the mean BMI was not indicated, the BMI ranged from 29 to 36 [25]).

Therefore, quite differently from other studies, we examined the association of a change in BW with a change in serum adiponectin levels in a 5-year study period in groups divided based on their BMI, namely, not only in obese subjects, but also in normal (middle) or lower-BMI (ie, nonobese) subjects. Furthermore, we were able to examine the association of the BW at the baseline examinations with the change in serum adiponectin levels in the study period and found no association of the BW at the baseline examinations with the δAdiponectin in women. We showed here that a decrease in BW in the 5-year study period resulted in an increase in serum adiponectin levels in both obese and nonobese subjects, at least in women.

The correlations of various traits with serum adiponectin levels have been examined thoroughly in many cross-sectional studies [4-10]. In brief, negative correlation of serum adiponectin levels with serum triglyceride levels, fasting and postprandial plasma glucose levels, and traits related to obesity and insulin resistance, as well as a positive correlation of serum adiponectin levels with serum HDL-C levels, has been reported [5-9]. However, the correlations of changes in various traits with a change in serum adiponectin levels have not been examined well. Therefore, in addition to the negative correlation of the δBW with the δAdiponectin, the correlations of the other δtraits observed may also be interesting. Several studies that showed decreased serum adiponectin levels were able to predict a future progression to DM [4,29,30], the close relations between decreased serum adiponectin levels and insulin resistance [8,12-14], and the decrease in serum adiponectin levels in parallel with the progression of insulin resistance during the progression to DM in rhesus monkeys [31] may support the observed negative correlations of the δ2-hour plasma glucose and the δHOMA-IR with the δAdiponectin, although these correlations should be examined in more depth in the future.

Because adiponectin is secreted exclusively by the adipose tissue, a change in fat mass can be expected as being more significantly correlated with a change in serum adiponectin levels than that in BW. In the present study, we measured percent body fat as a marker for fat mass. As shown in Table 3, the correlation of the δPercent body fat with the δAdiponectin was significantly observed in a simple regression analysis. However, this correlation became insignificant when the δBW was included as a covariable for multiple regression analysis. Further examination of the correlation of the δPercent body fat with the δAdiponectin using multiple logistic regression analysis as examined for the δBW revealed that the increase in the percent body fat significantly decreased the possibility of being in the upper tertile of the δAdiponectin when the δPercent body fat was the only variable for the analysis (OR per 1% increase, 0.92; 95% CI, 0.85-0.99; $P = .018$ and OR, 0.89; 95% CI, 0.85-0.94; $P < .001$ for men and women, respectively). However, this correlation again became insignificant when the δBW was included as a covariable for the analysis (OR, 0.97; 95% CI, 0.89-1.05; $P = .404$ and OR, 0.95; 95% CI, 0.91-1.00; $P = .073$ for men and women, respectively), whereas the δBW remained significantly correlated (OR, 0.88; 95% CI, 0.80-0.98; $P = .016$ and OR, 0.82; 95% CI, 0.75-0.89; $P < .001$ for men and women, respectively). Therefore, δBW seems to be a stronger variable correlated with δAdiponectin than δPercent body fat, at least in the present study population.

Serum adiponectin levels have been reported to have increased with aging even after adjusted for BMI, percent body fat, or intra-abdominal fat mass [4,32,33], although such an increase has not been consistently observed [34]. Similarly, the serum adiponectin levels increased significantly in the 5-year period in our study period as expected (Table 1). These findings indicate the importance of taking the increase in serum adiponectin levels with aging into account, at least in this study. Therefore, the associations of age and aging with the serum adiponectin levels were taken into account in all analyses in this study.

The follow-up rate in the study does not seem to be so high. Therefore, selection bias may have some influences in the results. Therefore, we examined the differences in the trait values at the baseline examinations between the subjects who attended the 5-year follow-up examinations and those who did not and found that the subjects who attended the 5-year follow-up examinations were younger than those who did not (57.8 ± 11.3 vs 59.4 ± 13.7 years, $P = .009$) and, thus, had better values in the traits related to glucose metabolism such as fasting plasma glucose (94.2 ± 11.3 vs 95.5 ± 15.4 mg/dL, $P = .038$), 2-hour plasma glucose (112.1 ± 36.4 vs 119.6 ± 54.2 mg/dL, $P < .001$), and HbA_{1c} (5.43% ± 0.46% vs 5.50% ± 0.63%, $P = .004$). However, all other trait values including serum adiponectin levels (8.97 ± 2.37 vs 8.91 ± 2.50 10× log μg/mL, $P = .578$) were not significantly different between them. Therefore, with respect to examining the correlation between the changes in the serum adiponectin levels and those in the other clinical trait values, selection bias seemed to be, if any, very little to affect the conclusion obtained here.

In conclusion, we showed here that the δBW was strongly associated with the δAdiponectin in both sexes, whereas the BMI and the BW at the baseline examinations were not associated with the δAdiponectin, at least in women. These findings indicate that current BW has no influence or, at least, no substantial influence on future change in serum adiponectin levels, but a change in BW has considerable influence. In particular, although obese subjects seem to have decreased serum adiponectin levels, their serum adiponectin levels change as those of nonobese subjects if their BW remains constant. On the contrary, when the BW increases, serum adiponectin levels decrease even in subjects who are not currently obese. Based on these findings, the advice to reduce or to avoid increasing the BW seems to be applicable not only to obese but also to nonobese subjects.

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