

## Association of Leptin and Adiponectin Levels with Three-year Weight Change among Japanese Male Workers

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The purpose of this study was to clarify, through a prospective study, the relationship between leptin and adiponectin levels, and subsequent weight change. The study subjects were 2,485 male office workers aged 35-64 employed by a company in Fukuoka Prefecture, Japan. Of these men, 1,936 (77.9%) received health check-ups both in 2005-2007 and 3 years later, in 2008-2010. Of the subjects who received both health check-ups, 352 were excluded due to cancer, cardiac infarction, stroke or diabetes mellitus, leaving a total of 1,584. We divided them into tertiles according to baseline leptin and adiponectin levels, and compared the subsequent change in body mass index (BMI) over 3 years. The subjects with the lowest leptin levels showed a significantly greater increase in BMI (difference in change in BMI = 0.178 kg/m<sup>2</sup>, 95% CI: 0.025-0.331 kg/m<sup>2</sup>) over 3 years when those with the highest leptin levels were regarded as the reference even after adjusting for age, baseline BMI, smoking status, drinking status and exercise. The subjects with the highest adiponectin levels showed a greater increase in BMI (difference in change in BMI = 0.099 kg/m<sup>2</sup>, 95% CI: -0.034-0.231 kg/m<sup>2</sup>) over 3 years when those with the lowest adiponectin levels were regarded as the reference, but this association was not statistically significant after adjusting for age, baseline BMI, smoking status, drinking status and exercise. Our findings suggest that higher leptin levels may suppress weight gain in Japanese male workers.

**Key words:** leptin, adiponectin, weight change, Japanese male workers, prospective study

Recently, the World Health Organization reported that more than 1.4 billion adults aged 20 or over were overweight. Of these over 200 million men and nearly 300 million women were obese. Worldwide obesity has more than doubled since 1980 [World Health Organization. Obesity and overweight. Available from <<http://www.who.int/mediacentre/factsheets/fs311/en/>>]. Japan has the lowest level of obesity, but the proportion of those overweight has shown a

continuously increasing trend in men (from 15.2% in 1976 to 30.3% in 2011) [1], [Ministry of Health, labour and welfare of Japan. The national health and nutrition survey in Japan, 2011. Available from <<http://www.mhlw.go.jp/bunya/kenkou/eiyou/dl/h23-houkoku-05.pdf>>]. Obese people are at risk for diabetes mellitus, ischemic heart disease, stroke, and certain cancers. Obesity is a worldwide health issue.

Adipose tissue was long considered passive tissue that specializes in energy storage, but recent research has demonstrated that it produces and secretes various bioactive substances, which are known as adipocytokines [2-8]. Leptin is an adipocyte-derived protein

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that acts on the hypothalamus to regulate appetite and energy expenditure [2, 3]. Adiponectin is another adipocyte-derived protein, and adiponectin levels are lower in the obese than in the non-obese [4]. Hypoadiponectinemia was found to be significantly and independently associated with diabetes mellitus type 2, metabolic syndrome, and cardiovascular diseases [5, 6, 8]. Kubota *et al.* reported that adiponectin stimulates food intake and decreases energy expenditure during fasting through its effects on the central nervous system, and suggested that the fundamental roles of leptin and adiponectin are to preserve an adequate fat reserve: leptin acts as a satiety signal, and adiponectin acts as a starvation signal [9]. Therefore, it is of interest to examine the relationship between leptin and adiponectin levels, and subsequent weight change.

Many prospective studies have been conducted to clarify the relationship between leptin and adiponectin levels, and subsequent weight change, but the results were inconsistent [10–18]. Some studies showed a positive association between leptin levels and subsequent weight change [10, 11], while others found no association or an inverse association [12–15]. One study found that high adiponectin levels were associated with significantly greater weight gain [16], but others showed no association between adiponectin levels and subsequent weight change [14, 17, 18].

Many of these previous prospective studies were conducted in the United States, where among adults aged 20 or over, 69.2% were overweight and 35.9% were obese [19]. To the best of our knowledge, there has been no previous prospective study on the relationship between leptin and adiponectin levels, and subsequent weight change in Japan, where the prevalence of obesity is much lower; the overweight and obese accounted for 30.3% and 4.6%, respectively, among men aged 20 or over in 2011 [Ministry of Health, labour and welfare of Japan. The national health and nutrition survey in Japan, 2011. Available from <<http://www.mhlw.go.jp/bunya/kenkou/eiyou/dl/h23-houkoku-05.pdf>>].

We conducted a prospective study to clarify the relationship between leptin and adiponectin levels, and subsequent weight change over 3 years in Japanese male workers aged 35 to 64.

## Materials and Methods

The study subjects were 2,485 male office workers aged 35–64 employed by a company in Fukuoka Prefecture, Japan. Of these, 2,360 received health check-ups in 2005–2007 (baseline). Of these 2,360, 322 men retired or resigned in the 3 years between 2005–2007 (baseline) and 2008–2010 (endpoint), and 102 did not have endpoint health check-ups. Thus, of the initial 2,485 men, 1,936 (77.9%) received both baseline and endpoint health check-ups, and had their leptin and adiponectin levels measured at baseline. The endpoint health check-ups were carried out in the morning of the same calendar month as the baseline health check-ups 3 years earlier. We excluded 352 men from the analysis because they had a history of cancer, cardiac infarction or stroke, or had received treatment for diabetes mellitus, or had a hemoglobin A1c (HbA1c) level of 6.5% or more at the endpoint; thus, we analyzed a total of 1,584 men. We collected information on their smoking status, drinking status and exercise by self-administered questionnaire at the endpoint and measured height without footwear and weight in light clothing at the baseline and the endpoint. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Leptin and adiponectin levels were determined immediately after drawing blood. All subjects agreed to have their serum leptin and adiponectin levels measured. The level of serum leptin was evaluated by enzyme immunoassay (Human Leptin RIA Kit; Linco Research, St. Charles, MO, USA) and that of serum adiponectin was determined by enzyme-linked immunosorbent assay (Otsuka Pharmaceutical Co., Ltd, Tokushima, Japan). HbA1c was measured by latex agglutination using a commercially available kit (Fuji Rebio, Tokyo, Japan). In order to obtain measurements equivalent in value to those used by the US National Glycohemoglobin Standardization Program (NGSP), we added 0.4 to the value of HbA1c, because HbA1c values measured in Japan are 0.4 lower than NGSP measurements [20].

For the purpose of the present study, serum leptin and serum adiponectin levels were divided into tertiles. The tertile points were 2.1 ng/mL and 3.4 ng/mL for leptin, and 5.1  $\mu$ g/mL and 7.4  $\mu$ g/mL for adiponectin. We divided smoking status into 3 categories (current smokers, ex-smokers and never-smokers),

alcohol status into 3 categories (regular drinkers, occasional drinkers and non-drinkers), and exercise into 2 categories (exercise positive: exercise for more than 30 min at a time and more than twice a week; exercise negative: less than exercise positive).

Associations between the tertiles of leptin and adiponectin levels, and the various factors under consideration were analyzed by one-way analysis of variance (ANOVA) or the Kruskal-Wallis rank sum test for continuous variables and by chi-square test for categorical variables. Analysis of covariance (ANCOVA) was conducted using the difference in change in BMI over 3 years as a dependent variable, and the tertiles of leptin levels and of adiponectin levels as main predictive variables, with age (continuous variable), smoking status, drinking status, exercise and BMI at baseline as covariates. All analyses were performed using the Statistical Analysis System, Version 9.1 (SAS Institute, Cary, NC, USA).

The study protocol was approved by the Ethics Committee of Fukuoka University and written

informed consent was obtained from each participant.

## Results

***Lifestyle factors and age distribution according to leptin and adiponectin levels.*** Lifestyle factors and age distribution are shown in Tables 1 and 2 according to leptin and adiponectin levels, respectively. Both leptin and adiponectin levels were significantly associated with age, and were not significantly associated with drinking status or exercise. Smoking status was significantly related to leptin levels, but not adiponectin levels.

***Average of BMI and change in BMI over three years according to leptin and adiponectin levels.*** Average of height, BMI at baseline and at endpoint and change in BMI over 3 years, and range of BMI at baseline are shown in Table 3 and Table 4 according to leptin and adiponectin levels, respectively.

Leptin levels showed a significant positive associa-

**Table 1** Lifestyle factors and age distribution according to leptin levels

Variables	Tertile 1	Tertile 2	Tertile 3	P value
	(n = 538)	(n = 519)	(n = 527)	
Mean leptin value (ng/mL)	1.45	2.67	5.24	
Mean age (years)	47.1	47.2	46.2	0.015 <sup>§</sup>
Age (years)				0.048
35-44	216 (40.2)	200 (38.5)	238 (45.2)	
45-54	237 (44.1)	253 (48.8)	231 (43.8)	
55-64	85 (15.8)	66 (12.7)	58 (11.0)	
Smoking status				<0.001
Current smokers	346 (64.3)	302 (58.2)	257 (48.8)	
Ex-smokers	72 (13.4)	95 (18.3)	106 (20.1)	
Never-smokers	120 (22.3)	122 (23.5)	164 (31.1)	
Drinking status				0.839
Regular drinkers	298 (55.4)	283 (54.5)	274 (52.0)	
Occasional drinkers	139 (25.8)	140 (27.0)	148 (28.1)	
Non-drinkers	101 (18.8)	96 (18.5)	105 (19.9)	
Exercise				0.254
Positive	121 (22.5)	108 (20.8)	97 (18.4)	
Negative	417 (77.5)	411 (79.2)	430 (81.6)	

Leptin level of tertile 1, <2.1 ng/mL; Leptin level of tertile 2, 2.1-3.3 ng/mL; Leptin level of tertile 3, ≥3.4 ng/mL; Numbers in parentheses are percentages. Exercise: exercise for more than 30 min at a time and more than twice a week (exercise positive) and less than that (exercise negative).

<sup>§</sup>: the Kruskal-Wallis rank sum test was used.

**Table 2** Lifestyle factors and age distribution according to adiponectin levels

Variables	Tertile 1	Tertile 2	Tertile 3	P value
	(n = 535)	(n = 522)	(n = 527)	
Mean adiponectin value ( $\mu\text{g}/\text{mL}$ )	3.92	6.15	10.39	
Mean age (years)	46.1	46.8	47.6	<0.01 <sup>s</sup>
Age (years)				
35-44	250 (46.7)	212 (40.6)	192 (36.4)	<0.001
45-54	237 (44.3)	239 (45.8)	245 (46.5)	
55-64	48 ( 9.0)	71 (13.6)	90 (17.1)	
Smoking status				
Current smokers	317 (59.3)	303 (58.1)	285 (54.1)	0.077
Ex-smokers	77 (14.4)	101 (19.4)	95 (18.0)	
Never-smokers	141 (26.4)	118 (22.6)	147 (27.9)	
Drinking status				
Regular drinkers	295 (55.1)	278 (53.3)	282 (53.5)	0.942
Occasional drinkers	137 (25.6)	145 (27.8)	145 (27.5)	
Non-drinkers	103 (19.3)	99 (19.0)	100 (19.0)	
Exercise				
Positive	105 (19.6)	120 (23.0)	101 (19.2)	0.247
Negative	430 (80.4)	402 (77.0)	426 (80.8)	

Adiponectin level of tertile 1, < 5.1  $\mu\text{g}/\text{mL}$ ; Adiponectin level of tertile 2, 5.1-7.3  $\mu\text{g}/\text{mL}$ ; Adiponectin level of tertile 3,  $\geq 7.4 \mu\text{g}/\text{mL}$ ; Numbers in parentheses are percentages. Exercise: exercise for more than 30min at a time and more than twice a week (exercise positive) and less than that (exercise negative).

<sup>s</sup>: the Kruskal-Wallis rank sum test was used.

**Table 3** Average BMI and change in BMI over three years according to leptin levels

Variables	Tertile 1 (n = 538)	Tertile 2 (n = 519)	Tertile 3 (n = 527)	P value
Height at baseline, mean $\pm$ SD (cm)	169.1 $\pm$ 6.1	169.4 $\pm$ 6.0	169.8 $\pm$ 5.7	0.158
BMI at baseline, mean $\pm$ SD ( $\text{kg}/\text{m}^2$ )	21.59 $\pm$ 2.41	23.52 $\pm$ 2.33	26.16 $\pm$ 3.00	<0.001
Range of BMI at baseline ( $\text{kg}/\text{m}^2$ )	15.0-28.4	14.9-31.3	17.5-38.4	
BMI at endpoint, mean $\pm$ SD ( $\text{kg}/\text{m}^2$ )	21.88 $\pm$ 2.53	23.74 $\pm$ 2.41	26.15 $\pm$ 3.19	<0.001
Change of BMI over three years, mean $\pm$ SD ( $\text{kg}/\text{m}^2$ )	0.29 $\pm$ 0.94	0.22 $\pm$ 0.97	-0.01 $\pm$ 1.16	<0.001

Leptin level of tertile 1, < 2.1ng/mL; Leptin level of tertile 2, 2.1-3.3ng/mL; Leptin level of tertile 3,  $\geq 3.4\text{ng}/\text{mL}$ ; BMI, body mass index; SD, standard deviation; P values were calculated by one-way analysis of variance.

**Table 4** Average BMI and change in BMI over three years according to adiponectin levels

Variables	Tertile 1 (n = 535)	Tertile 2 (n = 522)	Tertile 3 (n = 527)	P value
Height at baseline, mean $\pm$ SD (cm)	169.6 $\pm$ 5.8	169.5 $\pm$ 6.1	169.3 $\pm$ 6.0	0.588
BMI at baseline, mean $\pm$ SD ( $\text{kg}/\text{m}^2$ )	24.98 $\pm$ 3.02	23.97 $\pm$ 3.02	22.26 $\pm$ 2.98	<0.001
Range of BMI at baseline ( $\text{kg}/\text{m}^2$ )	16.9-38.4	15.0-35.5	14.9-37.2	
BMI at endpoint, mean $\pm$ SD ( $\text{kg}/\text{m}^2$ )	25.07 $\pm$ 3.15	24.11 $\pm$ 3.08	22.53 $\pm$ 2.99	<0.001
Change of BMI over three years, mean $\pm$ SD ( $\text{kg}/\text{m}^2$ )	0.09 $\pm$ 1.06	0.14 $\pm$ 1.06	0.27 $\pm$ 0.97	<0.014

Adiponectin level of tertile 1, < 5.1  $\mu\text{g}/\text{mL}$ ; Adiponectin level of tertile 2, 5.1-7.3  $\mu\text{g}/\text{mL}$ ; Adiponectin level of tertile 3,  $\geq 7.4 \mu\text{g}/\text{mL}$ ; BMI, body mass index; SD, standard deviation; P values were calculated by one-way analysis of variance.

tion with BMI at both the baseline and the endpoint. Adiponectin levels, on the other hand, showed a significant negative association with BMI at both the baseline and the endpoint. Correlation coefficients were 0.648 ( $p < 0.001$ ) between leptin and baseline BMI, and  $-0.381$  ( $p < 0.001$ ) between adiponectin and baseline BMI.

Leptin levels showed a significant negative relationship with change in BMI over 3 years in a dose-response manner, while adiponectin levels showed a significant positive relationship.

**Results of analysis of covariance for difference in change in BMI over three years.** ANCOVA was carried out to examine the association of leptin and adiponectin levels with change in BMI over 3 years, adjusting for age (continuous variable), BMI at baseline, smoking status, drinking status, and exercise. The results are shown in Table 5.

With leptin, tertile 1 showed a significantly greater increase in BMI (adjusted difference in change in BMI =  $0.178 \text{ kg/m}^2$ , 95% CI:  $0.025\text{--}0.331 \text{ kg/m}^2$ ) over three years when tertile 3 was regarded as the reference.

With adiponectin, when tertile 1 was regarded as the reference, no significant adjusted difference in change of BMI over 3 years was observed between tertile 3 and tertile 1 (adjusted difference in change in BMI =  $0.099 \text{ kg/m}^2$ , 95% CI:  $-0.034\text{--}0.231 \text{ kg/m}^2$ ), or between tertile 2 and tertile 1.

## Discussion

Leptin acts on the hypothalamus to regulate appetite and energy expenditure [3]. In animal models,

leptin deficiency results in severe obesity that is reversed by exogenous leptin administration [3]. However, previous epidemiological studies showed that leptin levels were significantly positively associated with BMI, suggesting that obese individuals had leptin resistance [3, 10–12]. Previous prospective studies on leptin levels and subsequent weight change produced inconsistent results [10–15]. Chessler *et al.* found that relatively increased leptin levels are significantly associated with greater subsequent gains in weight and adiposity [10]. Chu *et al.* also reported that higher leptin levels were significantly associated with 4-year weight gain among overweight men, but not among normal-weight men [11]. In some studies, no significant association between leptin levels and subsequent weight change was observed [12–14]. One study found that relatively low leptin levels may play a role in the development of obesity in Pima Indians, who have an extremely high prevalence of obesity and diabetes mellitus type 2 [15].

The present results for leptin were inconsistent with previous studies that showed that leptin levels were either significantly associated with subsequent weight gain or were not associated with subsequent weight change. Heterogeneity between our results and these previous studies may be attributed in part to differences in average BMI and in leptin resistance in the subjects studied. Most of these previous studies were conducted in the US, where the proportions of overweight and obese individuals were reported to be 69.2% and 35.9%, respectively, among adults aged 20 or over [19]. The present subjects, whose proportions of overweight and obese individuals were

**Table 5** Results of analysis of covariance for differences in change in BMI over three years

Variables	Adjusted difference in change in BMI ( $\text{kg/m}^2$ )		P value
	Difference in change in BMI (95% CI)		
Leptin levels			
Tertile 1 (< 2.1 ng/mL)	0.178	( 0.025–0.331)	0.023
Tertile 2 (2.1–3.3 ng/mL)	0.023	(–0.106–0.153)	0.773
Tertile 3 ( $\geq 3.4$ ng/mL)	0	(Reference)	
Adiponectin levels			
Tertile 1 (< 5.1 $\mu\text{g/mL}$ )	0	(Reference)	
Tertile 2 (5.1–7.3 $\mu\text{g/mL}$ )	0.082	(–0.045–0.210)	0.206
Tertile 3 ( $\geq 7.4$ $\mu\text{g/mL}$ )	0.099	(–0.034–0.231)	0.145

adjusted for age (continuous variable), smoking status, drinking status, exercise, and BMI at baseline. BMI, body mass index; CI, confidence interval.

31.1% and 3.6%, have a much lower average BMI than those of the previous studies. Chu *et al.* [21] and Murakami *et al.* [22] found that leptin levels were significantly associated with physical activity and dietary factors, which, they suggested, might increase leptin sensitivity, leading in turn to a subsequent decline in leptin production through unknown feedback mechanisms. Chu *et al.* reported that increased physical activity is associated with lower leptin levels and that fat intake was found to be positively related to leptin levels with marginal significance among normal-weight men [21]. Murakami *et al.* indicated that the intake of dietary fiber, vegetables and pulses was significantly inversely associated with leptin levels among young Japanese women [22]. Winnicki *et al.* showed that a fish-rich diet is associated with lower leptin levels in the population of Tanzania, Africa [23]. Japanese consume much more fish and pulses, and less fat than Americans [24]. Therefore, one possible explanation is that, in our subjects with the highest leptin levels, leptin can suppress weight gain because although they are overweight or obese, and therefore have some leptin resistance, they nevertheless retain more sensitivity to leptin than Americans.

Adiponectin is exclusively secreted by adipocytes and is the most abundant adipose tissue-derived protein [4]. Adiponectin levels in humans are lower in obese subjects than in the non-obese, and in patients with coronary artery disease, metabolic syndrome or diabetes mellitus type 2 than in healthy subjects [4, 6, 8, 25]. A recent study shows that adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake [9]. The fundamental role of adiponectin is presumed to be to preserve an adequate fat reserve [9]. Adiponectin may have weight-regulating functions.

Three previous studies showed no significant association between adiponectin levels and subsequent weight change [14, 17, 18]. Vozarova *et al.* studied Pima Indians, who have an extremely high prevalence of obesity and diabetes mellitus type 2 [17], and Bennett *et al.* studied Afro-Jamaicans [18]; these 2 studies had relatively small numbers of subjects. Langenberg *et al.* studied white men and women aged 60 to 91, most of whom had spontaneous weight loss [14]. Hivert *et al.* found that higher adiponectin levels were associated with significantly greater weight gain among healthy women [16]. The present results

indicated that higher adiponectin levels were associated with greater weight gain, but this association was attenuated and did not show statistical significance after adjusting for age, baseline BMI, smoking status, drinking status and exercise. The difference between our results and Hivert's may be attributed to gender and ethnicity. Adiponectin levels in women are generally higher than in men [26], and women with higher adiponectin levels may therefore have a greater capacity to accumulate fat than men with higher adiponectin levels. The impact of adiponectin on subsequent weight change may, for genetic reasons, be greater in Caucasians than in Japanese.

Our study had a prospective design and a large number of subjects, but has certain limitations. One limitation of the present study was the lack of information on whether the subjects had tried to make voluntary changes in food intake to reduce their weight, though attempts to lose weight are common among obese men but rarely successful. Another limitation was that our study did not investigate genetic factors. We conducted a reanalysis, excluding men with a BMI of more than 30 who may have some genetic factors for obesity, but the results showed, as before, that subjects with the lowest leptin levels had a significantly greater increase in BMI over three years than those with the highest leptin levels. More definite conclusions might be reached in future research by using a robust analytical approach, for example, fixed-effect analysis.

In conclusions, the subjects with the lowest leptin levels showed a significantly greater increase in BMI over 3 years than those with the highest leptin levels even after adjusting for age, baseline BMI, smoking status, drinking status and exercise. This finding suggests that higher leptin levels could suppress weight gain in Japanese male workers, who have a low prevalence of obesity, and supports the theory that leptin is one of the biological systems that maintain homeostatic control of body weight [3].

The subjects with the highest adiponectin levels showed a greater increase in BMI over 3 years than those with the lowest adiponectin levels, but this association was not statistically significant after adjusting for confounding factors. The present study thus cannot prove the hypothesis that Japanese men with higher adiponectin levels have a greater capacity to accumulate fat than those with lower adiponectin

levels.

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