

ORIGINAL ARTICLE

A change in objective sleep duration is associated with a change in the serum adiponectin level of women with overweight or obesity undergoing weight loss intervention

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Summary

Background

Although the serum adiponectin level is inversely correlated to body mass index and closely associated with obesity and related diseases, neither the impact of weight loss on the adiponectin level nor other factors that might influence the adiponectin level during weight loss intervention are well documented.

Objective

The objective of the study is to assess the change in the serum adiponectin level during weight loss intervention and to determine if sleep parameters affect the serum adiponectin level.

Methods

Ninety women with overweight or obesity aged 25 to 65 years completed a 7-month cognitive behavioural therapy based weight loss intervention that included dieting, exercise and stress management. Serum adiponectin level, body fat percent, symptoms of depression and anxiety and objective sleep parameters, assessed by actigraphy, were measured at baseline and at the end of the intervention.

Results

The serum adiponectin level was significantly increased after the weight loss intervention ($P < 0.001$). In a multiple regression analysis, the change of the adiponectin level was positively associated with the magnitude of body fat loss ($\beta = -0.317$, $P < 0.001$) and an increase of sleep minutes ($\beta = 0.210$, $P = 0.043$).

Conclusion

An increase in objective sleep duration was related to a significantly increased serum adiponectin level independently of the change of body fat during the weight loss intervention.

Keywords: Actigraphy, adiponectin, obesity, sleep duration.

Introduction

Obesity is a risk factor for a number of diseases, including cardiovascular disease, diabetes mellitus, sleep disorders and several cancers, and is associated with an increased risk of morbidity and reduced life expectancy (1). Although the biological mechanisms that mediate the

association of obesity and chronic diseases are not fully understood, alternation in hormone signalling, especially insulin, sex steroids and adipokine pathways, may play an important role (2,3).

Adiponectin is an adipokine that is secreted by adipocyte cells. It is an insulin-sensitizing, anti-angiogenic, anti-inflammatory hormone that plays an important role

in energy homeostasis and lipid and glucose metabolism (4,5). A low serum adiponectin level has been reported to be associated with a variety of diseases, including type 2 diabetes (6,7), metabolic syndrome (8,9), cardiovascular disease (10), sleep apnoea syndrome (11,12), cancer (13) and depression (14,15). Furthermore, the circulating adiponectin level is inversely related to body weight, especially visceral fat accumulation.

However, neither the impact of weight loss on the adiponectin level (8,16) nor factors that influence the adiponectin level during weight loss intervention are known. Some studies have demonstrated an increase in the adiponectin level (17,18). In contrast, others found no such change (19) after weight loss intervention for obesity. In addition, the results are inconsistent about whether or not the magnitude of weight loss and the changes in the adiponectin level are associated (17–21).

Sleep restriction (22) and obstructive sleep apnoea (OSA) (11,23) have been reported to alter the adiponectin level. Both short sleep duration (24,25) and poor sleep quality (26) have been associated with obesity, and we recently reported that baseline objective sleep quality was predictive of the magnitude of weight loss in our cognitive behavioural therapy (CBT) weight loss programme (27). However, to our knowledge, no previous studies have assessed the impact of sleep on a change in the adiponectin level during weight loss intervention.

In the present study, we assessed the change in the serum adiponectin level during the 7-month weight loss phase of our CBT for obesity. We also evaluated clinical variables, including objective sleep parameters, that might influence the adiponectin level during weight loss intervention. We hypothesized that the greater the magnitude of fat loss, the larger would be the degree of increase in the serum adiponectin level. Furthermore, we also hypothesized that improvement of sleep would be associated with an increase in the serum adiponectin level.

Methods

Study design

This investigation was a part of a randomized controlled study consisting of a two-phase trial that examined two strategies for maintaining weight loss. The weight loss phase provided an intensive programme of CBT that lasted 7 months. Participants who lost at least 5% of their initial body weight during the weight loss phase were eligible for a 3-month programme of weight maintenance. In this phase, the participants were randomized to one of two weight loss maintenance interventions, with follow-up for 2 years after the end of treatment. All of the participants provided informed consent, and the Institutional

Review Board of Kyushu University Hospital approved the study protocol.

Eligibility

All of the participants were women aged 20 to 65 years with a BMI of 25 kg m^{-2} or higher. They were able to understand and complete self-report questionnaires written in Japanese without assistance and had no physical impairment that would preclude simple exercise. Those who met the following criteria were excluded from the study: weight loss of more than 5 kg during the previous 6 months, current diagnosis of bulimia nervosa, past history of anorexia nervosa, current pregnancy or breastfeeding, planning to become pregnant within the next 24 months, taking any form of medication that would affect body weight, suffering from any health disorder affecting body weight, receiving nasal continuous positive airway pressure (nCPAP) therapy for sleep apnoea syndrome, receiving current treatment for a psychiatric disorder or planning to move within the next 10 months.

Recruitment and entry

We recruited participants through the local newspaper, the university website, posters in the university hospital or hospitals near the university, and a television programme. Those who were interested and potentially eligible were scheduled for an information session to learn more about the study. At the information session, the principal investigator provided the details of the study and answered questions from the participants. Those who met the eligibility criteria were enrolled in the study. After informed consent was obtained, we collected demographic, lifestyle and health history data.

Weight loss intervention

Cooper et al. originally developed the cognitive CBT programme for persons with obesity (28). The characteristics of their treatment programme are as follows: (i) because it was designed to encourage the acquisition and practice of weight maintenance skills, these differ from those required to lose weight; it consisted of a weight loss phase and a weight maintenance phase; (ii) in addition to the guidance on diet and physical activity, it adopted the training of stress management skills; (iii) it helped people accept and value more modest change in weight and acceptance in the latter part of the weight loss phase and prepared a programme to prevent regaining the weight that the patients lost in the weight maintenance phase. We modified it for use in a group therapy programme (29) that included the clinical guidelines on obesity of

the US National Institutes of Health (30), Look Action for Health in Diabetes (31) and the Diabetes Prevention Program (DPP) as a framework (32). A sleep education programme was also added. Our treatment programme was conducted in small groups of approximately 10 participants. It consisted of 38 group sessions, each lasting 90 min, and five individual sessions over a 44-week period. The sessions were conducted once a week for the first 34 consecutive sessions, with the remaining four sessions held once every two weeks.

Two doctors and two certified nutritionists were involved in the treatment as the healthcare providers. The participants were instructed to keep a daily food diary to track their consumption of all food and drinks and were advised to reduce their dietary intake by 500 calories per day from their caloric intake at the beginning of therapy. The nutritionists checked the nutritional balance of each participant's diet by examining the diary and advised the participants about the importance of eating vegetables and reducing the consumption of fat and sweets. On and after the seventh week, the participants were also instructed to wear a pedometer and to record their daily number of steps in an activity box on that day's recording sheet. They were advised to increase their level of physical exercise to a moderate intensity, such as walking 8,000–10,000 steps per day. In the sleep education session, we explained about the close relationship between sleep and obesity and introduced the CBT for insomnia (33). On and after seventh week, we asked them to keep their sleep duration in an activity box on the daily recording sheet. In the stress management sessions, we introduced problem-solving techniques, cognitive reframing and assertion training (28).

Anthropometric and body composition measurements

Height and weight were measured at baseline by our staff. The participants weighed themselves once a week, on the morning of their session. The percent of body fat was measured at baseline and at the end of the weight loss phase using a dual energy X-ray absorptiometry system (QDA4500A: HOLOGIC, Bedford MA).

Symptoms of depression and anxiety

Symptoms of depression and anxiety were assessed at baseline and at the end of the weight loss phase. Depressive symptoms were measured with the Japanese version of the Center for Epidemiologic Studies-Depression Scale (CES-D) (34). The CES-D is a 20-item, self-report questionnaire. The scores range from 0 to 60, with a higher score indicating the presence of depressive symptoms (35). Anxiety

symptoms were measured with the Japanese version of the State-Trait Anxiety Inventory (STAI). The STAI is a self-report questionnaire consisting of two scales, the state and trait forms (STAI-1 assesses state-anxiety and STAI-2 assesses trait-anxiety). Each scale consists of 20 items that indicate the presence or absence of anxiety symptoms (36).

Sleep parameters

Actigraphy (Micro-mini RC, Ambulatory Monitoring, Inc., Ardsley, NY, USA) was used to obtain objective sleep parameters. The participants were instructed to wear an actigraph, on the non-dominant wrist, continuously over a period of 5–7 consecutive days and nights, both at baseline and at the end of weight loss phase. It was set for 1-min epochs, in zero-crossing mode. The data retrieved from the actigraphy were downloaded to a personal computer using the automatic actigraphy interface unit and were analysed and scored using Action W-2 version 2.4.20 software (Ambulatory Monitoring, Inc., Ardsley, NY, USA) to calculate the sleep parameters. We used two parameters of the data obtained: sleep minutes (total minutes scored as sleep) and sleep efficiency ($100 \times \text{sleep minutes} / \text{duration from the first 20-min block of sleep to the last 20-min block}$). All actigraphy-based measurements were averaged over the total number of nights.

Sleep apnoea was evaluated with a subscale of the Japanese version of the Pittsburg Sleep Quality Index (PSQI) (37), a self-reported questionnaire that assesses sleep quality and disturbances over the preceding month (38). Question 10b from the apnoea subscale was used for statistical analysis.

Measurement of adiponectin

Blood samples were taken from the antecubital vein in the morning (10:00–12:00 am), at baseline and at the end of the weight loss phase. The separated serum samples were stored at -80°C until measurement. The serum adiponectin level was analysed by LA (BM-9030, JEOL, Ltd., Japan; intraassay coefficient of variation 1.09% and interassay coefficient of variation 1.60%).

Statistical analysis

Changes in clinical data between the baseline and the end of the weight loss phase were evaluated with the paired *t*-test. Simple regression was used to examine the association of the Δ adiponectin level with other clinical variables. A direct method multiple regression analysis was used to clarify which variables were predictive of a

change in the adiponectin level. Significant and near significant variables that were previously obtained by the univariate analysis (baseline body fat percent, baseline adiponectin level, Δ body fat percent, Δ sleep minutes and Δ CES-D score), age and baseline sleep minutes were entered in the multiple regression model as independent variables with the Δ adiponectin level as a dependent variable. The Δ is calculated using the following equation: Δ = values at the end of the weight loss phase minus the baseline values. All of the continuous variables are expressed as the mean \pm SD. All statistical analyses were

performed with the JMP pro 9.0 software package (SAS Institute Inc., Cary, North Carolina, USA). A value of $P < 0.05$ was considered to be significant.

Results

Recruitment and baseline characteristics

A total of 230 people were screened, and 119 were enrolled in the weight loss programme (Figure 1), with 90 (75.6%) completing the weight loss phase. Their baseline

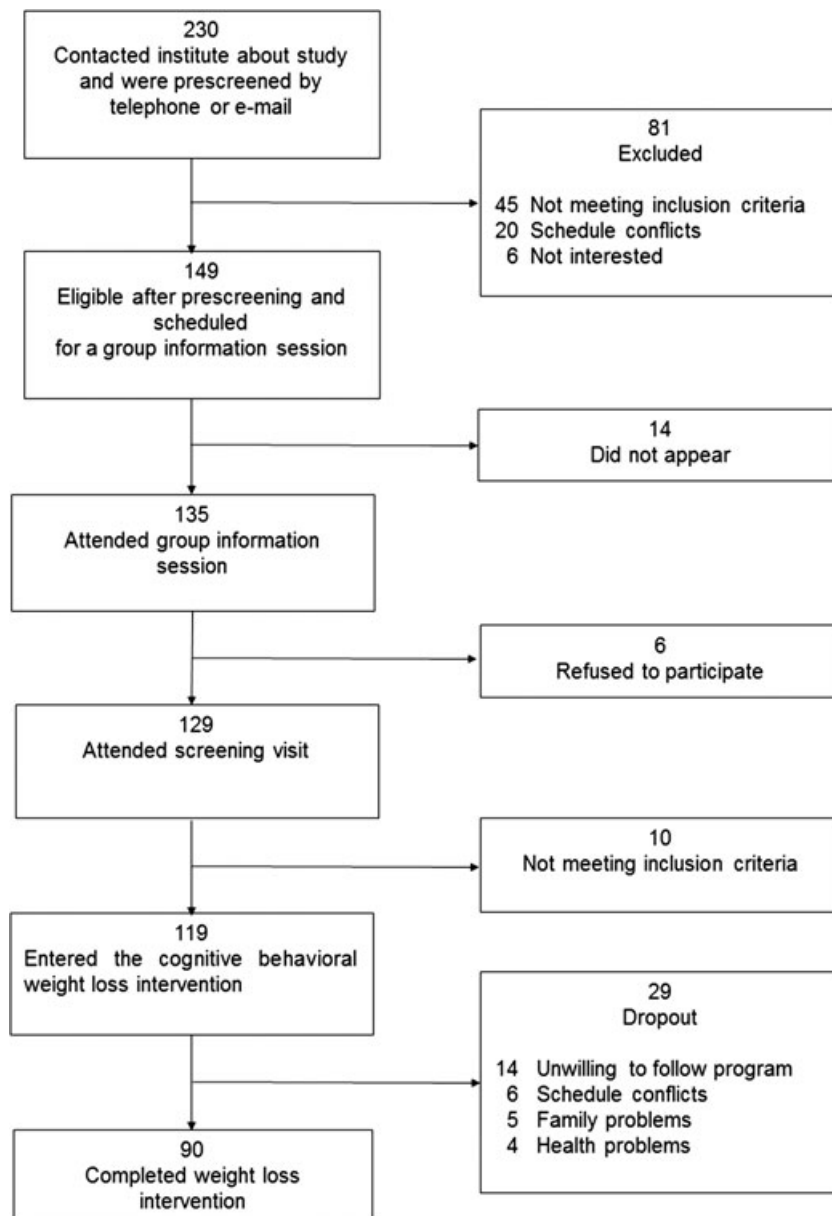


Figure 1 Flow diagram of the study regimen.

characteristics are presented in Table 1. The mean age and BMI were 47.9 (25 to 65) years and 31.1 (25.1 to 46.0) kg m⁻² respectively.

Kinetics of body weight

Changes in the clinical data between baseline and the end of the weight loss phase are presented in Table 1. The mean values for weight loss and reduction of body fat were 10.3 ± 4.8 kg and 4.8 ± 3.2% respectively. All participants who completed the weight loss phase lost more than 5% of their initial body weight, with 65 (72%) losing 10% or more.

Relation between change in the adiponectin level and other clinical variables

As shown in Table 1, the adiponectin level and sleep efficiency were significantly increased and the PSQI apnoea subscale significantly decreased at the end of the weight loss phase. The sleep minutes did not significantly change, although there was a tendency towards an increase after the weight loss intervention. Simple regression analysis (Table 2) demonstrated that the Δ adiponectin level was significantly associated with both the adiponectin level and percent body fat at baseline, the Δ body fat (%) and Δ CES-D and that there was a weak association with Δ sleep minutes. In the multiple regression analysis, Δ adiponectin was significantly associated with

Δ sleep minutes ($\beta = 0.210$, $P = 0.043$) and Δ body fat (%) ($\beta = -0.317$, $P < 0.001$) after adjustment for age, baseline body fat (%), baseline adiponectin level, baseline sleep minutes and Δ CES-D

Discussion

In the current study, the serum level of adiponectin was significantly increased after 7 months of weight loss intervention. As we hypothesized, the increase in the adiponectin level was associated with the magnitude of body fat loss and an increase of sleep minutes.

The effects of long-term weight loss intervention on the adiponectin level have not yet to be clearly established. Summer et al. reported that the adiponectin level increased with a low-carbohydrate, but not a low-fat, diet with no correlation between weight loss and the increase in adiponectin concentration (18). Abbenhardt et al. evaluated the change in adiponectin level in a randomized controlled study that compared the effect of a 12-month weight loss intervention with diet, exercise or diet plus exercise (17). The results showed that the adiponectin concentration increased in both the diet and diet plus exercise groups, but not in the exercise only group. They also showed that the degree of weight loss was inversely associated with the concentration of adiponectin. The results of our study were similar to those of the DPP (39), which included a lifestyle group that prescribed a reduced calorie weight-loss programme and increased physical

Table 1 Demographic and clinical data

Characteristic	At baseline	At the end of weight loss phase	P value*
Sociodemographics			
Age	47.9 ± 12		
Smoking status – smoker, n (%)	13 (14.4%)		
Clinical			
BMI (kg m ⁻²)	31.1 ± 4.7	26.9 ± 4.6	<0.001
Body weight (kg)	77.6 ± 12	66.1 ± 12	<0.001
Waist (cm)	98.6 ± 11	86.9 ± 12	<0.001
Hip (cm)	107.2 ± 9.9	97.1 ± 9.7	<0.001
Body fat (%)	37.6 ± 3.8	32.9 ± 5.1	<0.001
Sleep-related parameters			
Sleep minutes (min)*	331.7 ± 66.9	345.2 ± 68.7	0.07
Sleep efficiency (%)*	92.9 ± 5.1	94.3 ± 4.9	0.009
PSQI apnoea subscale	0.3 ± 0.9	0.2 ± 0.6	0.005
Psychological			
Depression (CES-D)	11.4 ± 6.8	13.2 ± 10.1	0.057
Anxiety (STAI-state)	41.1 ± 9.3	42.2 ± 10.7	0.33
Anxiety (STAI-trait)	44.1 ± 11.9	45 ± 11.3	0.42
Adiponectin (µg mL ⁻¹)	9.8 ± 6.0	11.2 ± 6.1	<0.0001

*Evaluated with the paired *t*-test.

Values are expressed as the means ± SD or n (%) of 90 participants. BMI: body mass index. PSQI: Pittsburg Sleep Quality Index. CES-D: Center for Epidemiologic Studies-Depression Scale. STAI: State-Trait Anxiety Inventory.

Table 2 Simple and multiple regression analysis of the Δ adiponectin level and clinical variables

Independent variables	Simple regression		Multiple regression*	
	β	<i>P</i>	β	<i>P</i>
Age	0.13	ns	0.190	0.045
Smoking status	0.027	ns	ni	ni
Baseline body fat (%)	-0.392	<0.001	-0.308	0.0014
Baseline adiponectin level	-0.250	0.019	-0.203	0.033
Sleep minutes	0.069	ns	0.881	ns
Δ Body fat (%)	-0.310	0.004	-0.317	<0.001
Δ Sleep minutes	0.180	0.086	0.210	0.043
Δ Sleep efficiency	0.169	ns	ni	ni
Δ PSQI apnoea subscale	-0.043	ns	ni	ni
Δ CES-D	-0.284	0.007	-0.125	ns
Δ STAI-state	-0.066	ns	ni	ni
Δ STAI- trait	-0.106	ns	ni	ni

β : standard regression coefficients. ns: not significant. ni: not inserted.

Δ = values at the end of weight loss phase minus values at baseline.

*Age, baseline body fat (%), baseline sleep minutes, baseline adiponectin level, Δ body fat(%), Δ sleep minutes and Δ CES-D were entered as independent variables in a direct multiple regression model with the Δ adiponectin level as the dependent variable. Adjusted $R^2 = 0.308$, $F = 7.15$, $P < 0.0001$

BMI: body mass index. PSQI: Pittsburg Sleep Quality Index. CES-D: Center for Epidemiologic Studies- Depression Scale. STAI: State- Trait Anxiety Inventory.

activity, that showed an increase in adiponectin after one year in their lifestyle (diet plus exercise) group. Our diet intervention was partly based on the DPP lifestyle intervention. Overall, our data and the data from other studies suggest that weight loss and/or reduction in body fat might be triggers for an increase in adiponectin concentration. The mechanisms involved in this paradoxical increase of the serum adiponectin level in spite of a decrease of the body fat volume during a weight loss programme remain unclear. However, William et al. recently demonstrated that bone marrow adipose tissue, not white adipose tissue, increases during caloric restriction (40). They identified marrow adipose tissue as an endocrine organ that contributes significantly to increased serum adiponectin during caloric restriction.

Furthermore, one of the most important findings of the present study was that an increase in sleep minutes was significantly associated with an increase in the adiponectin level, even after adjustment for changes in the percentage of body fat. There are some points to be considered in interpreting these results because the objective sleep duration of our participants at baseline was 330 min, which was quite short, and increased by only 14 min at study end. Recent studies reported that both the objective and subjective sleep durations of Japanese women are the shortest among the Organization for Economic Co-operation and Development countries (41,42). Also, previous studies that revealed a close relation between obesity and short sleep duration (24,43). Therefore, it is understandable that the

objective sleep duration of our participants with obesity before and after treatment was much shorter than the Japanese norm. Moreover, even though the increase in sleep minutes after weight loss is small, it might be responsible for the increase in the adiponectin level of patients with obesity who have short sleep duration.

Conflicting results have been published about the relation between sleep duration and the adiponectin level. The Wisconsin Sleep Cohort Study, a population-based study of sleep disorders, demonstrated no association between the serum adiponectin level and sleep minutes assessed by nighttime polysomnography and a sleep diary (44). In contrast, Simpson et al. showed that sleep restriction (five nights of sleep restricted to 4 h per night) resulted in a decrease in the plasma adiponectin level of Caucasian women (22). Our findings support their results that an increase in sleep minutes through weight loss intervention is associated with an increase in the adiponectin level. In contrast, Robertson et al. reported that 3 weeks of mild sleep restriction (habitual bedtime minus 1.5 h) had no effect on the plasma adiponectin level of young normal-weight men (45). No consistent conclusions have been reported about the relation between sleep minutes and the adiponectin level. Further study will be necessary to clarify the relation and mechanisms related to the association.

Both sleep quantity and sleep quality are often poor among patients with obesity. OSA is a sleep related breathing disorder that aggravates sleep quality. It is

characterized by recurrent episodes of obstruction of the upper airway, which leads to sleep fragmentation and symptoms of excessive daytime sleepiness. Although we did not evaluate OSA objectively and the Δ PSQI apnoea subscale was not associated with the Δ adiponectin level in the present study, OSA has been associated with the adiponectin level in previous studies. Mutairi et al. demonstrated that adiponectin decreased significantly with increasing severity of OSA among 147 patients with suspected OSA and concluded that adiponectin is an independent marker of disease severity (23). Yoshikawa et al. reported that the plasma adiponectin level was inversely correlated with the apnoea hypopnea index and %time in SpO₂ < 90%, but not with the BMI of 22 patients with OSA (11). They also revealed that the plasma adiponectin level was increased after long-term nCPAP treatment (3 months) of 10 patients. Furthermore, recent studies have demonstrated that mRNA degradation of adiponectin is accelerated under hypoxia compared with normoxia (12,46). The studies mentioned previously suggest that hypoxic stress caused by sleep apnoea leads to adipocyte dysfunction and a decrease in the secretion of adiponectin among patients with OSA. The improvement of OSA because of weight loss might mediate the association with a change of sleep minutes and adiponectin. However, in the present study we did not find an association between change in the PSQI apnoea score and change of the adiponectin level. In addition, we did not find any association between change in adiponectin and change in sleep efficiency, which has been reported to be worsened in patients with OSA. This may be partly explained by the fact that sleep efficiency was relatively high from the beginning of the present study; therefore, the magnitude of the increase in sleep efficiency was small, although the change was significant. This might have affected the result that the change in sleep efficiency was not associated with the change in adiponectin level.

Our CBT-based weight loss programme included a session about sleep education, with the participants receiving information about the relation between sleep and obesity. Our results showed that improving sleep duration may be rather important for increasing the adiponectin level. Considering the fact that the sleep minutes of our participants were much shorter than the national norm, even after the intervention, more intensive intervention for increasing sleep duration may be needed. In addition, it may be helpful to evaluate the possibility of OSA before weight loss intervention and, if necessary, to do nCPAP therapy to reduce the risk of obesity-related diseases.

A strength of our study is that the magnitude of weight loss and body fat reduction was relatively large, which

provided a strong test of the relation between the changes in adiponectin and sleep minutes. However, it should be noted that the present study has several limitations. First, our sample size is relatively small and we cannot apply our results to men with obesity or people of other races/ethnicities because all of the participants were Japanese women. Second, we cannot exclude the possibility that variables other than those we examined, such as OSA, may have affected our results. Finally, the dropout rate was relatively high, which may have contributed to selection bias.

In summary, an increase in sleep minutes was associated with an increase in the serum adiponectin level, even after adjustment for confounding factors. It will be important to develop strategies to improve the sleep duration of people participating in weight loss intervention, which reduces the risk of obesity-related diseases.

Conflict of Interest Statement

The authors declare no conflict of interest.

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