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Changes of Body Weight and Inflammatory Markers after 12-Week Intervention Trial: Results of a Double-Blind, Placebo-Control Pilot Study

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Purpose: Low grade inflammation is a well-known characteristic in obese subjects. We investigated body weight changes and inflammatory markers after 12-week intervention trial. **Materials and Methods:** Twenty-six obese subjects were enrolled and 19 (13 men and 6 women) completed the study. Sibutramine is an FDA-approved drug for body weight control; therefore, we chose this drug as the standard treatment medication in this study. Patients were randomly allocated to receive an anti-inflammatory agent (Diacerein treatment group; n = 12) or placebo (n = 7) for 12 weeks. Anthropometry, body proportion by dual-energy X-ray absorptiometry, and metabolic parameters at the beginning and end of study were measured and compared. **Results:** The treatment group had a tendency towards more reduction in anthropometry as compared to the placebo group, in body weight reduction (- 7.0 kg vs. - 4.6 kg), body mass index (- 2.51 kg/m^2 vs. - 1.59 kg/m^2), and waist circumference (- 7.3 cm vs. - 4.4 cm). These reductions were not statistically significant. Changes in levels of high-sensitivity C-reactive protein and adiponectin in the treatment group were more favorable than in the placebo group. **Conclusion:** This small pilot study showed no statistical difference for changes in anthropometry, and inflammatory markers between the two groups. Therefore, we could not find any additional effects of Diacerein on weight loss and inflammatory variables in this study.

Key Words: Inflammation, anti-inflammatory agent, adiponectin, TNF-α

INTRODUCTION

In Korea, the third National Health and Nutrition Survey in 2005 reported that the overall prevalence of adult obesity [defined as a body mass index (BMI) ≥ 25.0 kg/m^2] was 31.7% (35.2% in men and 28.3% in women),[1] which represents an increase from corresponding Figs. in 2001 (overall 29.6%, 31.2% in men and 27.9% in women). In Korea and elsewhere, obesity is a concern, as it heightens the risk of developing hypertension, diabetes, dyslipidemia, and cancers, and can cause pre-

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mature death.[2]

The increase in fat mass, particularly in the splanchnic region (visceral fat) of the body, is associated with chronic elevation of circulating levels of inflammatory mediators, including non-specific markers such as C-reactive protein (CRP), acute-phase inflammatory proteins, and proinflammatory cytokines.[3,4] The relationship between obesity, inflammatory markers such as adipocytokines, phase reactant proteins, and insulin resistance has been investigated in several populations.[5,6] Reviews on low grade inflammation have presented evidence indicating that the reversion of low grade inflammation and reduction of risk factors in obese individuals seems to coincide with reduced BMI and loss of adipose tissue.[7] Reduced body weight could result in normalized inflammation and reduction in increased inflammatory markers. Even a modest 5-10% loss of body weight in obese patients improves their cardiovascular risk profiles and reduces the future incidence of type 2 diabetes.[8-10] Therefore, weight reduction is a key factor in reducing inflammation and thus the risk of cardiovascular disease.

Diacerein is well-tolerated anti-inflammatory supplemental agent, which acts by inhibiting tumor necrosis factor-alphas (TNF-α) and interleukin-1 (IL-1) in rheumatoid and other forms of arthritis. This compound has also been used to reduce inflammation in addition to more conventional anti-inflammatory drugs.[11-14] Furthermore, only two studies have addressed whether pharmacological intervention[15-17] reduces inflammation.

Diacerein is an anti-inflammatory agent, which is often used in some clinical-based office of the obesity clinic in Korea. From a clinical view standpoint, obesity is equivalent to a status of low-grade inflammation; therefore, reduction of inflammation may lead to a change in body weight. However, there have been no reports of Diacerein effects on body weight control. Therefore, we wondered if this medication had any real effect on body weight control or inflammatory marker changes. The aim of this study was to evaluate the additional effect on body weight reduction, metabolic parameters, and inflammatory markers by addition of an anti-inflammatory agent to a standard 12-week obesity treatment regimen.

MATERIALS AND METHODS

Study subjects

We conducted a double-blind, placebo-controlled pilot study. Enrolled obese subjects were randomly allocated to take treatment medication (Diacerein) or placebo for 12 weeks. All subjects were enrolled following a private interview conducted at the Obesity Clinic of Ajou University Hospital, Suwon, South Korea, and all provided informed consent. We measured and compared the anthropometric changes of body weight and waist circumference), body proportion using Dual Energy X-ray Absorptiometry (DEXA), select metabolic parameters, and inflammatory markers before and after the 12-week body weight control program. The Institutional Review Board of Ajou University Hospital approved this study, and permission was received from the Korean Food and Drug Administration for the use of Diacerein.

Inclusion criteria for the initial 26 obese subjects were age ≥ 20-years-of-age, BMI ≥ 27.0 kg/m^2, or 27 kg/m^2 ≥ BMI ≥ 25.0 kg/m^2 with hypertension, type 2 diabetes, dyslipidemia, and family history of coronary heart diseases. Exclusion criteria were uncontrolled type 2 diabetes, hypertension, habitual alcohol consumption, history and/or current presence of any cancer, old stroke, and renal disease. Seven subjects dropped out due to personal problems that were unrelated to an adverse drug reaction. The remaining 19 subjects (13 men, 6 women) completed the study.

Weight reduction program and visit schedules

Subjects visited an out-patient clinic every 4 weeks for a meeting with the principal investigator and the coordinating nurse. At each visit, each subject was assessed and prompted to continue their prescribed routine. Items addressed at each visit included information on diet, daily activity, types and frequency of exercise, encouragement, and advice concerning target frequency of exercise (at least 30 min daily, more than 3 or 4 times a week). Each subject underwent an initial nutrition assessment by a registered dietician, who provided instructions on a low-calorie diet aimed at producing a 400-500 kcal daily energy deficit. Furthermore, a behavior modification program encouraged increased calorie expenditure while reducing intake, with an emphasis on long-term behavior change. In addition, Sibutramine was prescribed as a standard medical treatment for all subjects. Subjects were randomly assigned in a double-blind manner to the treatment group (n = 12) who additionally received the anti-inflammatory agent Diacerein, which is a TNF-α inhibitor, and to the placebo group (n = 7). Diacerein and placebo were made and provided by Myungmoon Pharmaceutical (Seoul, Korea). The capsules were identical in appearance; the placebo contained wheat flour instead of medication.

Measurements

A research nurse measured the height and body weight of the participants while they were wearing light clothing and no shoes. Their weight was measured to the nearest 0.1 kg, and height was measured to the nearest centimeter. BMI was calculated as the weight divided by height squared (kg/m^2). The nurse also measured the waist circumference between the lower rib and the iliac crest, electrically measured blood pressure using a model TM-2655P apparatus (PMS Instruments, Tokyo, Japan) after the participants had been at rest for at least 15 min, and checked each subject's nutritional status every 4 weeks by inspection of a food diary kept by each participant. The body composition of each participant was analyzed by DEXA using a IDXA series (LUNAR apparatus GE, Schenectady, NY, USA). Additionally, all of the subjects underwent blood tests [standard enzymatic measurements of total cholesterol, high-density lipoprotein cholesterol, triglycerides and fasting glucose, insulin, high-sensitivity C-reactive protein (hsCRP), homocysteine, fibrinogen, and other metabolic parameters in fresh serum samples] at the beginning and end of the 12-week program. All blood measurements were done using a model TBA-200FR apparatus (Toshiba, Tokyo, Japan). TNF-α was measured using a Quantikine Human TNF-α enzyme immune assay (EIA)(R&D Systems, Minneapolis, MN, USA). Adiponectin was measured using a human adiponectin radioimmunoassay (RIA) kit (R&D Systems). We also analyzed changes in intake of macronutrients using a three-day recall food diary by the CAN-Pro 3.0 nutrition analyzer (Korean Nutrition Society, Seoul, Korea).

Table 1. Baseline Characteristics of the Two Groups

	Treatment (n = 12)	Placebo (n = 7)	*p* value
Age (yrs)	39 ± 1	37 ± 1	0.299
Height (cm)	167 ± 2	171 ± 3	0.340
Weight (kg)	87 ± 4	89 ± 3	0.482
BMI (kg/m^2)	31 ± 1	30 ± 1	0.592
Waist (cm)	99 ± 2	99 ± 3	0.837
FFM (kg)	52 ± 2	53 ± 1	1.000
FM (kg)	31 ± 2	32 ± 3	0.650
F%M (kg)	37 ± 2	37 ± 2	0.902
s-BP (mmHg)	125 ± 3	121 ± 4	0.650
d-BP (mmHg)	78 ± 3	78 ± 4	0.902
Glucose (mg/dL)	108 ± 7	100 ± 2	0.902
HDLC (mg/dL)	46 ± 1	45 ± 4	0.650
LDLC (mg/dL)	120 ± 13	109 ± 12	0.837
TG (mg/dL)	186 ± 49	140 ± 25	0.902
TC (mg/dL)	203 ± 14	194 ± 9	0.837
TSH (μIU/mL)	1.8 ± 0.2	1.7 ± 0.2	0.902
Insulin (μU/μL)	16 ± 2	19 ± 4	0.650
HOMA-IR	4.5 ± 1.0	4.7 ± 1.1	0.773
WBC count (× 10^3/μL)	7.0 ± 0.5	7.1 ± 0.6	0.967
HsCRP (mg/dL)	1.21 ± 0.94	0.45 ± 0.09	0.261
Homocysteine (mg/dL)	11.1 ± 0.6	12.7 ± 0.5	0.340
Fibrinogen (mg/dL)	376.7 ± 14.0	367.5 ± 28.9	0.773
TNF-α (pg/mL)	15.7 ± 1.4	11.5 ± 2.7	0.227
Adiponectin (μg/mL)	6.2 ± 0.7	6.7 ± 1.1	0.773

BMI, body mass index; Waist, waist circumference; FFM, fat free mass; FM, fat mass; F%M, fat mass Percentage in body; s-BP, systolic blood pressure; d-BP, diastolic blood pressure; Glucose, fasting glucose; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; TSH, thyroid stimulating hormone; HOMA-IR, homestasis Model Assessment of Insulin Resistance; WBC, white blood cells; hsCRP, highly-sensitive C-reactive protein; TNF-α, tumor necrosis factor-α.
p values from Mann-Whitney U test.
All data are expressed as mean±standard error; *p* values from Mann-Whitney U test comparing changes between the two groups.

Table 2. Comparisons of Anthropometry, Calorie Intake and Metabolic Changes between the Two Groups for 12 Weeks

Variable	Treatment (n = 12)	Placebo (n = 7)	*p* value
Δ Bwt (kg)	- 7.0 ± 0.9*	- 4.6 ± 1.2*	0.167
Δ BMI (kg/m^2)	- 2.5 ± 0.3*	- 1.5 ± 0.4*	0.120
Δ Wc (cm)	- 7.3 ± 1.9*	- 4.4 ± 1.0*	0.340
Δ FM (kg)	- 4.1 ± 0.7*	- 3.1 ± 0.7*	0.335
Δ F%M (%)	- 2.4 ± 0.4*	- 2.0 ± 0.5*	0.616
Δ FFM (kg)	- 1.9 ± 0.6*	- 1.4 ± 0.6*	0.682
Δ s-BP (mmHg)	- 8.7 ± 4.6	- 1.7 ± 3.7	0.340
Δ d-BP (mmHg)	- 5.1 ± 4.7	- 0.7 ± 5.2	0.482
Δ Glucose (mg/dL)	10.2 ± 3.3	4.2 ± 4.6	0.650
Δ TC (mg/dL)	- 22.6 ± 18.6	- 8.4 ± 6.2	0.773
Δ HDLC (mg/dL)	7.4 ± 6.2	5.2 ± 1.7	0.837
Δ LDLC (mg/dL)	- 12.8 ± 7.2*	3.1 ± 9.3	0.261
Δ TG (mg/dL)	164.5 ± 191.3	- 29.4 ± 16.9	0.711
Δ Insulin (μU/μL)	- 1.5 ± 2.0	-7.9 ± 3.8	0.261
Δ HOMA-IR	- 0.16 ± 0.82	- 1.73 ± 0.82	0.261
Δ Calories$_{total}$ (kcal)	- 178.3 ± 93.3	- 113.5 ± 89.7	0.964
Δ Carbohydrate (g)	- 1.0 ± 1.8	4.3 ± 1.9	0.083
Δ Fat (g)	- 1.9 ± 2.0	- 2.1 ± 1.1	0.750
Δ Protein (g)	2.1 ± 1.1	- 0.3 ± 2.1	0.213

Δ, amount of change; BMI, body mass index; FM, fat mass; F%M, fat mass Percentage in body; FFM, fat free mass; s-BP, systolic blood pressure; d-BP, diastolic blood pressure; Glucose, fasting glucose; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TG, triglyceride; TSH, thyroid stimulating hormone; ΔCalories$_{total}$, change in total calorie intake; ΔCarbohydrate, change in carbohydrate intake; ΔFat, change in fat intake; ΔProtein, amount of protein intake changes.
All data are expressed as mean ± standard error; *p* values from Mann-Whitney U test comparing changes between the two groups.
*$p < 0.05$ by paired t test before and after the changes of each parameter in the same groups.

Table 3. Comparisons of Changes in Inflammatory Markers between the Two Groups for 12 Weeks

Variable	Treatment (n = 12)	Placebo (n = 7)	*p* value
Δ WBC (×10^3/μL)	0.03 ± 0.45	0.02 ± 0.35	0.482
Δ hsCRP (mg/dL)	- 0.86 ± 0.86*	- 0.21 ± 0.10	0.227
Δ Homocysteine (mg/dL)	3.84 ± 2.25	1.98 ± 1.29	0.902
Δ Fibrinogen (mg/dL)	25.16 ± 11.46	12.57 ± 25.01	0.773
Δ TNF-α (pg/mL)	- 5.37 ± 2.56	- 6.20 ± 3.23	0.837
Δ Adiponectin (μg/mL)	0.72 ± 0.63*	- 0.45 ± 0.53	0.227

Δ, amount of change; WBC, white blood cell; hsCRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor-α.
All data are expressed mean ± standard error.
p values from Mann-Whitney U test.
*$p < 0.05$ by paired t test before and after the changes of each parameter in the same groups.

Statistical analyses

This study sample size was small, so we used non-parametric comparison (Mann-Whitney U test) to see the difference between the two groups. We used an χ^2 test to evaluate the rates of over 5% and 10% weight reduction between the two groups. All significant values were defined by $p < 0.05$ as determined by SPSS version 11.5 (SPSS, Chicago, IL, USA).

RESULTS

After random allocation according to age, BMI, 19 of 26 subjects (73%) completed the study. Twelve subjects (7 men and 5 women) were in the treatment group and seven subjects (6 men and 1 woman) were in the placebo group. The mean age was 39.58 ± 1.42 years in the treatment group and

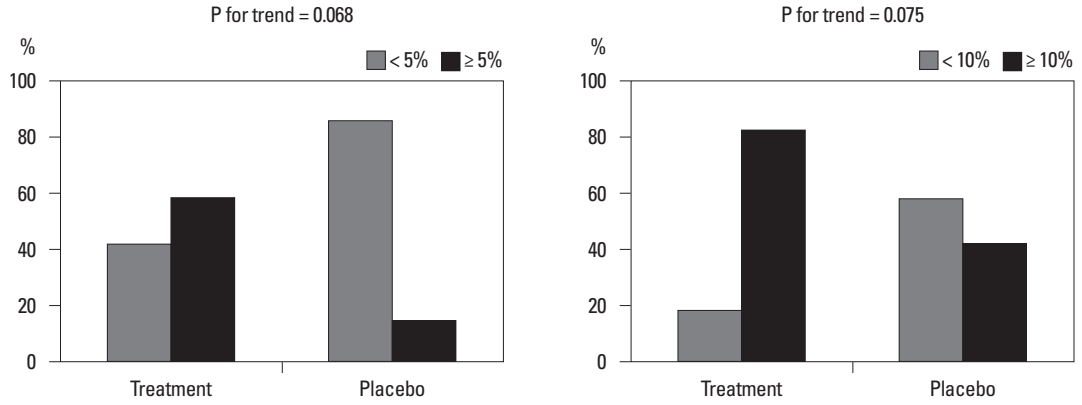

Fig. 1. Response rate: weight reduction of ≥ 5% and ≥10% in the two groups. The top panel shows the response rate of ≥ 5% or < 5% weight reduction subjects after the 12-week intervention. The lower panel shows the response rate of ≥ 10% or < 10% weight reduction.

37.57 ± 1.11 in the placebo group, and the mean BMI was 31.02 ± 1.08 kg/m^2 in the treatment group and 30.51 ± 1.94 kg/m^2 in the placebo group. Besides the anthropometric measurements, other metabolic parameters [blood pressure, fasting blood sugar, lipid profiles, thyroid stimulating hormone, insulin, and homeostasis model assessment-Insulin Resistance (IR)], and several inflammatory markers including white blood cell count, hsCRP, homocysteine, fibrinogen, TNF-α, and adiponectin level were also measured; no differences between the two groups were evident (Table 1). We had difficulty mentioning the two-way ANOVA test because we did not divide the time-dependent grouping. We only measured body composition and inflammatory markers at baseline and 12 weeks. Following the 12-week weight reduction program the mean changes in body weight, BMI, and waist circumference were - 7.00 kg, - 2.51 kg/m^2, and - 7.37 cm, respectively, in the treatment group, and - 4.64 kg, - 1.59 kg/m^2, and - 4.42 cm, respectively, in the placebo group. The anthropometric comparison before and after intervention showed significant changes in both groups. A tendency towards more reduction in anthropometric parameters in the treatment group was observed, but there was no statistical difference between the two groups. In addition, there were no statistical differences in the changes of metabolic parameters and calorie intake between the treatment and control groups (Table 2). We also evaluated the changes in inflammatory markers between the two groups. Again, no statistical differences were apparent. Although there were no differences between the two groups, hsCRP, and adiponectin showed more favorable change in the treatment group than in the placebo group. Other inflammatory markers were not shown as expected, but TNF-α was decreased in both groups after intervention (Table 3). Finally, we observed the response rate of ≥ 5% and ≥ 10% weight reduction between the two groups, in spite of the small sample size. Both response rates were higher in the treatment group than in the placebo group. Even though there were no statistical differences between the two groups, P for trend showed weak correlation in more weight reduction tendency in the treatment group than in the placebo group (Fig. 1). In spite of these results, we could not find any additional effects of Diacerein on weight loss and inflammatory variables in this study.

DISCUSSION

In this pilot study, we did not find any additional effects of Diacerein on weight loss and inflammatory variables. As mentioned above, two-way ANOVA may not be useful in this study. Therefore, we had only simple comparison by non-parametric test. The treatment group as compared to the placebo group showed a reduction in body weight (- 7.0 kg vs. 4.6 kg), BMI (- 2.51 kg/m^2 vs. - 1.59 kg/m^2), and waist circumference (- 7.3 cm vs. - 4.4 cm); however, there was no statistical significance between the two groups. Changes in levels of low-density lipoprotein, hsCRP, and adiponectin in the treatment group showed improvement, which were also not significant when compared to those in the placebo group. Other inflammatory markers such as white blood cells, homocysteine, fibrinogen, and TNF-α were not significantly different either.

There have been many studies of changes of the inflammation and body weight in several different body weight control programs. For instance, studies on the changes in inflammatory markers after weight reduction reported different results, which may have reflected the different study methods. One study showed that during the eucaloric phase, a low-fat, high-carbohydrate diet unfavorably influ-

enced inflammatory markers. In contrast, ad libitum low-fat, high-carbohydrate intake caused weight loss and affected inflammatory markers favorably. Thus, the energy content of a low-fat, high-carbohydrate diet determined changes in inflammatory markers.[18] Another study reported an overall favorable effect of a low-carbohydrate diet on lipoprotein subfractions and inflammation in high-risk subjects.[19] In another study, no significant changes were evident in either median adiponectin or IL-10 levels after body weight reduction.[20] In this study, the authors opined that the anti-inflammatory status of obesity might require prolonged periods of energy-restricted diets to revert to normal. A study in which metformin was provided for 17 weeks reported significant reduction in body weight, but not in levels of TNF-α and CRP.[21] Metformin improved the plasma levels of some markers of endothelial activation and coagulation in subjects with impaired glucose tolerance, whereas it had no effect on markers of inflammation. In a study of 316 community-dwelling, older overweight or obese sedentary men and women with osteoarthritis, diet-induced weight-loss intervention resulted in significantly greater reductions in CRP, IL-6, and TNF-α than treatment not intended to reduce weight.[22] In this study, CRP and IL-6 were not associated with changes in body weight. The addition of cis-9, trans-11 conjugated linoleic acid also did not produce any differences between groups in body composition in a double-blind, placebo-controlled 3-month study of 25 abdominally obese men.[23] While a decrease in many inflammatory markers such as TNF-α, CRP-reactive protein and IL-6 were reported in another study, adiponectin levels were significantly higher after intervention.[24]

Many studies evaluating changes of inflammatory marker after different periods or regimens of weight reduction have not yielded consistent results. However, the decrease in inflammatory markers such as TNF-α, CRP, and IL-6 and increase of adiponectin level has been apparent after weight reduction.[25-28]

Changes in other metabolic parameters including lipid profiles, glucose level, and TNF-α were insignificant in both groups, which may be due to the small sample size. In addition, there was no adverse drug reaction in the treatment group for the 3-month intervention period.

There are some limitations to this pilot study. The main limitation concerns the small number of subjects. This may be a crucial limitation that weakens the significance of the results, but not their reality. We tried to equally allocate to each group, but there was some follow-up loss in this study for personal reasons. Furthermore, the relatively short duration of this intervention would contribute to the lack of change in inflammatory markers, as in previous studies. Another limitation is that the intervention medication we used (Diacerein, an anti-inflammatory agent that is a TNF-α and IL-1 inhibitor) is not an officially recognized agent in the regulation of inflammation in the obese. Additionally, we could not evaluate total exercise time and frequency, which are important confounding factors. Nonetheless, to our knowledge, this is the first randomized, placebo-controlled study that investigated the effect of inclusion of an anti-inflammatory agent to a traditional obesity control regimen involving medication with Sibutramine, to evaluate whether there was additional reduction of weight and of inflammatory markers. In conclusion, we did not find any additional effects of Diacerein on weight loss and inflammatory variables in this study.

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