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Research

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Changes of Fat Volume and Adipocytokines by the Randomized Intervention Program for Obesity Control Program (SCOP)

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ABSTRACT

Adipocytokines are bioactive substances synthesized and secreted by fat cell. Previous studies have reported an association between weight loss and adipocytokines. However, these studies are inconsistent and they have not clarified the relationship between weight regain and changes in circulating levels of adipocytokines. In this study, we analyzed the relationship between weight and fat volume changes and adipocytokines. The subjects were 235 obese people recruited in the Saku Control Obesity Program (SCOP). Participants were randomly assigned to either immediate (Group A) or delayed (Group B, control group). Group A participants were followed for another two years after completion of the one year intervention. As controls, Group B participants received the same intervention as Group A after a delay of one year. Then they were followed up for one year. The intervention consisted in a one-year lifestyle program to induce weight loss, based on a cognitive-behavioral approach. After the first year of the study, body weight, Body Mass Index (BMI), body fat and abdominal fat areas were significantly lower in group A participants, compared to controls. After the intervention, leptin levels were significantly lowered both in men and women. After one year follow-up, both men and women re-gained about 1.5 kg body weights on average. BMI, waist circumference, fat areas by Computed Tomography (CT) and Glycated hemoglobin (HBA_{1c}) significantly increased during the follow-up period. The change of adipocytokine levels by analysis of the quartile of body weight decrease and regain revealed that increased adiponectin and decreased leptin was noteworthy for weight reduction, while increase of leptin influenced the weight regain. In conclusion, our results suggest that leptin could have broad effects on the distribution of fat tissues and on lipid metabolism. Leptin inversely associated with adiponectin, which in turn was necessary to decrease body weight. In particular, leptin decreased remarkably in the process of weight reduction, and its increase seemed to be related in weight regain. The observed increase of adiponectin seemed to be induced by reduction in fat volume.

KEYWORDS: Adiponectin; Leptin; Biomarker; RCT; Obesity control; Human.

ABBREVIATIONS: SCOP: Saku Control Obesity Program; BMI: Body Mass Index; CT: Computed Tomography; HBA_{1c}: Glycated hemoglobin; CHD: Coronary Heart Disease; T2D: Type 2 Diabetes; TNF-α: Tumor Necrosis Factor-alpha; FFAs: Free Fat Acids; MetS: Metabolic syndrome; TFA: Total Fat Area; SFA: Subcutaneous Fat Area; VFA: Visceral Fat Area; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; TG: Triglyceride; SRL: Special Reference Laboratories; HMW: High Molecular Weight; ELISA: Enzyme-linked immunosorbent assay; ANOVA: Analysis of variance; SPSS: Statistical Pack-

age for the Social Science; CRP: C-reactive protein; RCT: Randomised Controlled Trial; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FFA: Free Fatty Acid; AMPK: AMP-activated protein kinase.

INTRODUCTION

Overweight and obese individuals are at a greater risk for developing Coronary Heart Disease (CHD), Type 2 Diabetes (T2D), and certain type of cancer compared with their normal-weight counterparts.[1,2] Weight loss can reduce these risks, but weight maintenance after weight loss is difficult to achieve.[3-5]

Adipose tissue has been considered to be the energy storage tissue, but recent studies have shown that fat cells synthesize and secrete various bioactive substances called adipocytokines, such as leptin, adiponectin, Tumor Necrosis Factor-alpha (TNF-α), Free Fat Acids (FFAs), resistin and angiotensinogen.[6] Most of the studies on adipocyte-derived cytokines have so far focused on the two adipocytokines, adiponectin and leptin, because of their role in the regulation of the metabolic homeostasis.[7-9]

Adiponectin is associated with insulin sensitivity and atherosclerosis. Despite the fact that adiponectin is secreted by the adipose tissue, plasma levels are lower in individuals with obesity, insulin resistance and T2D.[10-12]

Leptin inhibits food intake, stimulates energy expenditure, and regulating immune function.[13] In humans, serum leptin levels are positively correlated with obesity, T2D, hypertension and Metabolic syndrome (MetS).[14,15] Therefore, it is generally considered that obese people are associated with a state of resistance to the effects of leptin.[16,17]

Thus, adiponectin and leptin play an important role on obesity and metabolic disorders. Previous studies have reported an association between weight loss and adipocytokines.[18] However, these studies are inconsistent and they have not clarified the relationship between weight regain and changes of adipocytokines.[19-21] For example, Ambeba et al[19] conducted a 24-month weight loss trial and reported that adiponectin increased with weight reduction and decreased with weight regain. On the other hand, Bluher et al[20] reported continued increase in adiponectin levels with both weight loss and weight regain. They also reported that leptin levels decreased with weight reduction and increased with weight regain. In addition, Crujeiras et al[21] reported that leptin continued to decrease throughout weight reduction and regain. Using the effective intervention program for obesity control developed by our group, a nested randomized intervention trial in human dock examinees was designed to evaluate the multiple metabolic changes and factors involved in weight reduction. Plasma levels of adiponectin, leptin and other biomarkers could be analyzed in relationship with the body weight reduction and changes in fat volume.

SUBJECTS AND METHODS

Study Subjects

This study was performed as part of the Saku Control Obesity Program (SCOP). The outline of SCOP has been described previously.[22] The SCOP study protocol initially included 235 Japanese obese subjects (116 men and 119 women) recruited from the database of medical checkup record of Saku Central Hospital Human Dock Center, Nagano, Japan. The study participants had medical checkups since 2000 and were aged 40-64 years old, with a body mass index (Body Mass Index (BMI): kg/m^2)) greater than 28.3 (the upper 5 percentile of all examinees). They were asked to participate in an intervention program for weight control, i.e. SCOP. Exclusion criteria were: psychiatric disease; physical conditions (i.e., morbid hepatic or renal dysfunction; cardiovascular disease such as heart failure, stroke, and transient ischemic attacks); patients who were under treatment for obesity or any treatment known to affect eating or weight. Participants were randomly assigned to either immediate (Group A) or delayed intervention (Group B, control group). After guidance with written and oral information, including the purpose of the study, assurance of refusal, and confidentiality of personal information, written informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of the National Institute of Health and Nutrition.

Study Design

Participants were given a one-year lifestyle intervention program for weight loss, based on a cognitive-behavioral approach.[23-32] The program was conducted at the Saku Central Hospital Human Dock Center from July, 2006. The participants received individual counseling (30 minutes) from a registered dietician, and group sessions about effective physical activity (20 minutes) by exercise instructors. Body composition parameters were measured at baseline and at 1, 3, 6 and 9 months. The integrative interventions have been reported in detail previously.[23-32] Group A participants were followed for two years after one year intervention, without any period. Clinical and biological parameters were assessed at baseline (0 month), after the end of intervention (12 month) and during the follow-up (24 month) (Figure 1).

As controls, Group B participants received the same intervention as Group A after a delay of one year. Then they were followed up for one year. They received precise health check-up at 0 month, 12 month, 24 month and 36 month in the same way as Group A participants (Figure 1).

The height and weight of the subjects were measured with an automatic scale (Tanita, BF-220, Tokyo, Japan). Their BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured twice at the umbilicus level while the subject was in a standing position,

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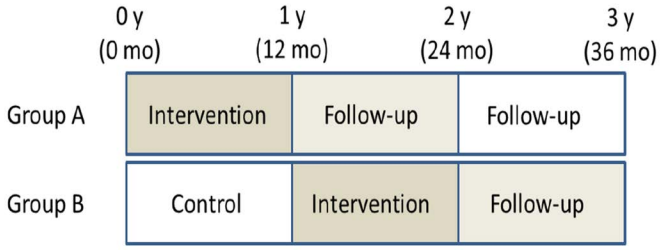

Figure 1: Study design.

using a fiberglass measuring tape. The average measurement was used for the analysis. Blood pressure was measured while the subject was in a sitting position using a validated automated blood pressure monitor (ES-H55; Terumo, Tokyo, Japan). Total fat areas were assessed by a computed tomography scan at the level of the umbilicus, with the subjects in the supine position. The Total Fat Area (TFA), Subcutaneous Fat Area (SFA) and Visceral Fat Area (VFA) were calculated using commercially available software (Fat Scan; N2 System Corp, Osaka, Japan). Following an overnight fast, blood samples were collected at the time of each health checkup at the Saku Human Dock Center. High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), Triglyceride (TG), HbA_{1c} and other blood and biochemical values were analyzed at the clinical laboratory of the Saku Central Hospital.

Adipocytokines (adiponectin, leptin, TNF-α, FFA) were measured using laboratory testing services provided by Special Reference Laboratories (SRL) Inc. (Tokyo, Japan). The High Molecular Weight (HMW) form of adiponectin (μg/mL) was measured by Enzyme-linked immunosorbent assay (ELISA) with a detection limit of 0.18 μg/mL. Leptin (ng/mL) was measured by a radioimmunoassay (Human Leptin RIA Kit, LINCO Research, St. Charles, MO, USA) with a sensitivity of 0.5 ng/mL.

Prevalence of metabolic abnormality, hypertension, dyslipidemia and diabetes mellitus, was determined according to Japanese diagnostic criteria for metabolic syndrome. The cut-off values defining metabolic abnormalities were established at 130/85 mmHg for high blood pressure; ≥150 mg/dL triglyceride and/or <40 mg/dL HDL cholesterol for dyslipidemia; and 110 mg/dL for high blood glucose; or patients being treated for hypertension, dyslipidemia, and/or diabetes .

Data Analysis

Statistical analysis was focused on the effect of intervention by Randomised Controlled Trial (RCT) design so that we compared Group A as intervention group and Group B as control group. Furthermore, we analyzed degree of rebound after intervention by combined group A and B data (Group A+B). Data are presented as mean±SD. Adipocytokines and C-reactive protein (CRP) were log-transformed to fit normality or linearity assumption for statistical analysis. The serum level of adipocytokines and CRP are presented the median and range (25 percentile and 75 percentile). Independent sample t-test was used to compare intervention group and control group in baseline and 1 year later. Spearman correlations were used to test the associations between body composition and blood data. In Group A+B, paired t-test was used to compare end point of intervention and follow-up. Weight reduction was calculated as the difference between before and after the intervention. Weight regain was calculated as the difference during follow-up period. Weight reduction and regain values are separated quartile groups, respectively. The significance of differences among that quartile were analyzed with one-way Analysis of variance (ANOVA) followed by Bonferroni and Games-Howell post hoc test. Statistical analysis was performed by Statistical Package for the Social Sciences (SPSS) version 20.0 software (SPSS Inc., Chicago, IL, USA).

Results

Effect of the Intervention by RCT

Baseline characteristics for men and women are displayed in Table 1. The mean age of the study population was 53.8 years for men and 54.7 years for women. BMI was 30.2±3.1 kg/m^2 for men and 31.0±3.0 kg/m^2 for women, the waist circumference was 100.0±6.5 cm and 103.2±8.1 cm, and the visceral fat area was 157±48 cm^2 and 129±47 cm^2 (mean±SD) (Table 1).

After one year of intervention we observed a 5% body weight reduction (6.1 kg in men and 4.0 kg in women in average) in 51% participants, 10% reduction in about one fourth participants. The changes of body weight, BMI, fat% in body composition, waist circumference, fat area by CT, and selected biochemical data by group are shown in Table 2. After the intervention, body weight, BMI, body fat and abdominal fat areas were significantly less than those of controls.

Adipocytokines, lipid, glucose and HbA_{1c} levels of intervention and control groups are shown in Table 3. Leptin was significantly lowered than control in both men and women after the intervention. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) improved after the intervention. Only in women, TNF-α was significantly increased by intervention (Table 3).

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n	unit	116	119
Age	years	53.8±6.5	54.7±6.4
Height	cm	168.4±6	155.1±5.7
Weight	kg	85.7±10.4	74.8±9.4
BMI	kg/m^2	30.2±3.1	31.0±3.0
Waist circumference	cm	100.0±6.5	103.2±8.1
Body fat	%	28.8±4.1	40.7±5.4
Total fat area	cm^2	404±111	468±111
Sq fat area	cm^2	247±91	339±90
Vis fat area	cm^2	157±48	129±47
Total cholesterole	mg/dl	204±29	217±39
HDL-cholesterole	mg/dl	50±10	56±12
LDL-cholesterole	mg/dl	121±28	131±33
Triglyceride	mg/dl	171±120	151±81
FFA	mEq/L	0.5±0.2	0.6±0.2
TNF-α	pg/ml	1.1(0.9-1.4)	1.2(0.9-1.4)
Leptin	ng/mL	6.7(4.9-9.2)	18.0(13.6-25.3)
Adiponectin	μg/mL	2.2(1.6-3.6)	4.8(3.5-7.4)
CRP	mg/dl	0.12(0.07-0.18)	0.11(0.07-0.24)
SBP	mmHg	133±15	136±18
DBP	mmHg	82±13	83±12
Fasting glucose	mg/dl	111±26	114±27
HBA_{1C}	%	5.8±1.1	5.9±1.2

Mean±SD. Adipocytokines and CRP showed median and range (25 percentile and 75 percentile).

Table 1: Baseline data of the participants.

At baseline health examination revealed the prevalence of dyslipidemia was 64.3% and 40.4% in men and women, high blood pressure was 69.6% and 67.3%, and high blood glucose was 35.7% and 38.5%. The prevalence were improved 19% in both sex in dyslipidemia, 21% and 11% in men and women in high blood pressure, 5% and 30% in high blood glucose, respectively.

Effect of Intervention with Group A+B

Effect of intervention in fat tissues and adipocytokines: BMI and fat area usually showed good correlations in both males and females (Table 4). TG correlated with visceral fat and Free Fatty Acid (FFA). After the intervention TG showed strong positively correlation with leptin and negatively correlation with adiponectin than before the intervention, except for adiponectin in women. Adiponectin and leptin inversely correlated only in men. Leptin was widely interrelated among BMI and various fat areas, but not with TG, FFA and HbA_{1c} in women before the intervention and FFA and HbA_{1c} after the intervention. In men leptin and TG was significantly correlated. TNF-α correlated with visceral fat, TG, FFA, leptin, and HbA_{1c} in women before the intervention, but after the intervention only TG and HbA_{1c} remained. In men TNF-α did not show any association with the above variables.

The change of weight, adiponectin and leptin between before and after the intervention is shown by the quartile of body weight reduction (Figure 2). Leptin decrease and increase of adiponectin was noticed in upper quartile of body weight reduction by intervention both men and women.

Weight regain during follow-up period: Weight, BMI, waist circumference, HBA_{1c}, TFA and VFA were significantly increased at the end of follow-up in Group A+B analysis. Both men and women gained about 1.5 kg body weight gain on average. However, these the end of follow-up values remained significantly

	A: Intervention group		B: Control group			
	M(n=56)	F(n=52)	M(n=49)		F(n=52)	
Age	53.7±6.7	55.0±6.6	53.9±6.3		54.5±6.2	
Height	167.9±5.9	155.1±5.7	168.9±6.0		155.2±5.7	
Body wt 0y	84.2±8.5	74.5±8.4	87.3±12.1		75.2±10.3	
Body wt 1y	79.3±8.7	70.7±9.3	87.5±13	**	75±11	*
Body wt difference 0_1y	5.0±5.1	3.8±3.7	-0.2±2.8	**	0.2±2.5	**
BMI 0y	29.8±2.3	31.0±2.9	30.6±3.8		31.1±3.0	
BMI 1y	28.1±2.5	29.4±3.4	30.5±4.2	**	31.0±3.2	*
BMI difference 0_1y	1.7±1.8	1.6±1.5	0±1.0	**	0.1±1.0	**
Body fat 0y	28.5±3.6	39.7±5.2	29.2±4.6		41.8±5.4	*
Body fat 1y	26.8±4.4	37.8±5.9	29.6±5.1	**	41.8±5.8	**
total fat 0y	393±82	467±98	417±137		468±123	
sq fat 0y	243±66	343±80	253±114		335±100	
abd fat 0y	150±48	125±47	164±48		133±47	
total fat 1y	333±81	402±93	397±104	**	455±108	**
sq fat 1y	207±62	302±76	238±96	*	326±88	
abd fat 1y	126±46	100±38	159±48	**	130±45	**
total fat difference 0_1y	60±64	65±57	19.7±57.9	**	13.2±44.0	**
sq fat difference 0_1y	36±38	41±44	14.3±32.6	**	9.7±30.7	**
abd fat difference 0_1y	24±33	24±26	5.4±33.3	**	3.5±22.4	**

Significantly different between intervention and control groups.

*:$P<0.05$,**:$P<0.01$

Sq: subcutaneous, abd: abdominal.

Table 2: Baseline and post intervention data of the participants by the arm.

lower than those before the intervention (Table 5).

Leptin value at the end of follow-up showed significantly lower than the end of intervention for men and women. Adiponectin and TNF-α was significantly decreased at the end of follow-up than at the end of intervention both men and women (Table 5).

The change of weight and adipocytokine levels for weight regain groups between follow-up periods is shown by the quartile of body weight regain (Figure 3). Leptin was significantly higher in upper quartile of weight regain.

DISCUSSION

In this study, we achieved a 5 percent body weight loss through a one-year lifestyle intervention program using a behavioral approach. In parallel with the weight reduction, many metabolic syndrome-related factors significantly improved. During the intervention, energy source, crops and diary decreased, while the intake of green yellow vegetables increased.[27] Eating speed improved and physical activity also increased compared to the control group.[32] Especially in Group A, women increased their daily physical activity and improved their irregular eating habits during the follow-up period. Eating motivation could be changed through the cognitive-behavior approach.

Following encouragements from trainers, physical activity seemed to be more frequent during the intervention period. This did not last during the follow-up period, while dietary habits seemed to be maintained even after intervention. Altered dietary habit could contribute to the later life. As body weight significantly increased at the end of follow-up examination compared to the weight at the end of the intervention program, fixation of

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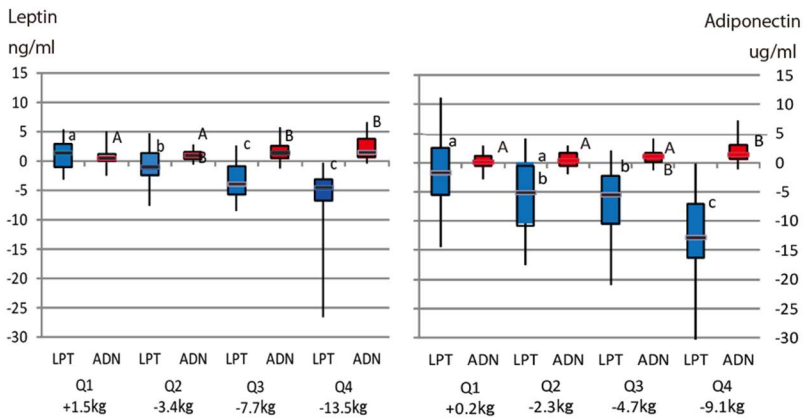
	A: Intervention group		B: Control group			
	M(n=56)	F(n=52)	M(n=49)		F(n=52)	
Triacylglycerol 0y	170±98	131±61	173±141		172±94	**
Triacylglycerol 1y	143±74	118±58	159±72		164±87	**
LDL cholesterol 0y	123±29	128±32	119±28		134±35	
LDL cholesterol 1y	124±31	129±26	123±29		130±30	
HDL cholesterol 0y	48±11	56±12	52±9		56±12	
HDL cholesterol 1y	50.3±12.7	57.2±13	48.7±8.8		53.5±12	
FFA 0y	0.53±0.17	0.60±0.20	0.48±0.20		0.55±0.22	
FFA 1y	0.43±0.17	0.50±0.18	0.40±0.17		0.50±0.17	
TNFα0y	1.1(0.9-1.5)	1.2(0.9-1.4)	1.2(1.0-1.4)		1.2(0.8-1.4)	
TNFα1y	1.3(1.1-1.5)	1.4(1.1-1.7)	1.3(1.1-1.5)		1.1(1.0-1.4)	**
Leptin 0y	6.7(4.2-9.1)	17.7(13.2-23.5)	6.9(5.2-9.4)		18.9(13.9-25.7)	
Leptin 1y	5.7(3.8-8.8)	15.7(10.7-20.7)	8.3(5.7-11.4)	**	22.3(16.2-29.3)	**
Adiponectin 0y	2.2(1.5-3.6)	5.1(4.1-8.4)	2.3(1.7-3.7)		4.3(2.5-5.6)	**
Adiponectin 1y	3.2(2.1-5.9)	6.8(5.1-10.2)	2.7(2.0-4.5)		5.5(3.8-8.6)	*
CRP 0y	0.11(0.08-0.18)	0.10(0.06-0.21)	0.10(0.06-0.21)		0.13(0.08-0.26)	
CRP 1y	0.07(0.05-0.14)	0.08(0.04-0.13)	0.08(0.04-0.13)		0.14(0.07-0.24)	
SBP 0y	132±15	133±16	134±15		139±19	
SBP 1y	126±14	127±17	134±18	*	135±18	*
DBP 0y	81±14	81±11	83±12		84±12	
DBP 1y	79±11	78±12	85±13	*	85±12	*
Fasting blood glucose 0y	111±28	112±30	112±23		115±25	
Fasting blood glucose 1y	109±24	110±36	116±20		112±19	
HbA_{1c} 0y	5.7±1.1	5.9±1.2	6.0±1.1		6.0±1.2	
HbA_{1c} 1y	5.5±0.8	5.6±1.0	5.8±0.8	*	5.7±0.8	

Significantly different between intervention and control groups.

*:P<0.05,**:P<0.01

FFA: Free Fatty Acid, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

Table 3: Changes of adipocytokine, serum lipids and some biochemial data by arm.



The distinct of character shows statistically significant difference (p<0.05; A-B and a-b;, p<0.01 a-c).

Figure 2: Leptin (blue) and adiponectin (red) concentration after intervention by quartile of body weight loss.

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1y end / baseline	BMI 1y	total fat 1y	sq fat 1y	vis fat 1y	TG 1y	FFA 1y	HBA_{1C} 1y	L_leptin 1y	L_adipo 1y	L_TNF 1y	**after the intervention**
BMI 0y		.873**	.807**	.461**	.278**	.195	.281**	.622**	-.336**	-.026	BMI 1y
total fat 0y	.846**		.852**	.635**	.293**	.164	.279**	.738**	-.219*	-.095	total fat 1y
sq fat 0y	.817**	.859**		.136	.091	.145	.101	.632**	-.106	-.064	sq fat 1y
vis fat 0y	.266**	.495**	-.021		.421**	.097	.378**	.464**	-.257**	-.085	vis fat 1y
TG 0y	.125	.088	-.043	.246*		.233*	.122	.429**	-.436**	-.039	TG 1y
FFA 0y	-.006	.032	.015	.037	.311**		.062	.129	-.192	-.141	FFA 1y
HBA_{1C} 0y	.185	.128	.008	.236*	.124	.127		.241*	-.147	.038	HBA_{1C} 1y
L_leptin 0y	.608**	.668**	.618**	.255**	.227*	-.036	.166		-.356**	-.028	L_leptin 1y
L_adipo 0y	-.128	-.067	.018	-.162	-.275**	-.244*	-.105	-.080		-.081	L_adipo 1y
L_TNF 0y	.059	.013	.076	-.103	-.094	-.014	.026	.079	-.108		L_TNF 1y
baseline	BMI 0y	total fat 0y	sq fat 0y	vis fat 0y	TG 0y	FFA 0y	HBA_{1C} 0y	L_leptin 0y	L_adipo 0y	L_TNF 0y	

Men(n=102)

*:P<0.05,**:P<0.01

1y end / baseline	BMI 1y	total fat 1y	sq fat 1y	vis fat 1y	TG 1y	FFA 1y	HBA_{1C} 1y	L_leptin 1y	L_adipo 1y	L_TNF 1y	**after the intervention**
BMI 0y		.846**	.777**	.535**	.253*	.175	.185	.620**	-.057	.040	BMI 1y
total fat 0y	.802**		.924**	.622**	.253*	.103	.189	.622**	-.127	.019	total fat 1y
sq fat 0y	.722**	.904**		.274**	.128	.031	.049	.546**	-.039	-.046	sq fat 1y
vis fat 0y	.477**	.588**	.186		.372**	.196	.375**	.445**	-.238*	.141	vis fat 1y
TG 0y	.077	.092	-.054	.314**		.137	.212*	.260**	-.150	.245*	TG 1y
FFA 0y	.227*	.118	.033	.208*	.153		.275**	.000	.072	.157	FFA 1y
HBA_{1C} 0y	.022	.055	-.107	.328**	.217*	.382**		.139	-.260**	.254*	HBA_{1C} 1y
L_leptin 0y	.550**	.549**	.462**	.387**	.126	-.062	-.061		-.150	.118	L_leptin 1y
L_adipo 0y	.054	.072	.125	-.072	-.192	.008	-.171	-.050		-.112	L_adipo 1y
L_TNF 0y	.145	.210*	.032	.421**	.248*	.250*	.268**	.218*	-.202*		L_TNF 1y
baseline	BMI 0y	total fat 0y	sq fat 0y	vis fat 0y	TG 0y	FFA 0y	HBA_{1C} 0y	L_leptin 0y	L_adipo 0y	L_TNF 0y	

Women(n=98)

*P<0.05,**:P<0.01

Table 4: Correlation analysis between fat and adipocytokines.

good health habit would be very difficult without decision of individuals.

Decrease and increase of fatty tissue should be a basis of body weight change. Adipose tissue is a major source of energy for the human body. It is also a source of major adipocytokines, adiponectin and leptin.[6] In this study, leptin changed markedly in the process of weight reduction and regain. Adiponectin decreased according to the weight reduction, but not changed between weights regain quartile. Leptin seemed to be highly sensitive to weight changes than adiponectin.

A few studies have explored the relationship between weight change and changes of adipocytokines, but results are inconsistent.

Leptin inhibits food intake, stimulates energy expenditure, and regulating immune function.[13] In humans, serum leptin levels are positively correlated with obesity, T2D, hypertension and Metabolic syndrome (MetS).[14,15] Leptin levels increase in obesity and subcutaneous fat has been a major determinant of circulating leptin levels. The net action of leptin is to inhibit appetite, stimulate thermogenesis, enhance fatty acid oxidation,

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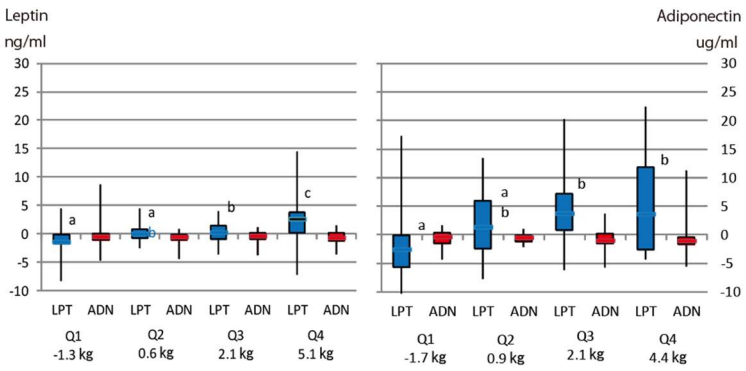
		Men(n=102)			Women(n=98)		
		End intervention	End follow-up		End intervention	End follow-up	
		mean±SD	mean±SD	t	mean±SD	mean±SD	t
Weight	kg	79.9±10.1	81.5±10.3	**	70.7±10.1	72.0±10.2	**
BMI	kg/m^2	28.2±3.0	28.8±3.1	**	29.3±3.4	29.9±3.4	**
Waist circumference	cm	95.8±8.6	97.5±8.4	**	99.1±9.4	100.7±9.2	**
Total fat area	cm^2	333±95	366±103	**	403±100	425±99	**
Sq fat area	cm^2	204±74	213±75	**	302±82	307±84	
Vis fat area	cm^2	129±50	153±61	**	102±40	118±44	**
Total cholesterol	mg/dl	194±34	196±31		210±27	213±33	
HDL-cholest	mg/dl	52±11	52±12		57±12	57±12	
LDL-cholest	mg/dl	118±30	121±29		129±26	133±30	
Triglyceride	mg/dl	132±76	143±79		117±58	120±54	
Leptin	ng/mL	4.9(3.3-7.4)	5.5(3.8-7.7)	*	14.0±(8.4-19.0)	15.0±(10.2-21.7)	**
Adiponectin	µg/mL	3.4(2.2-5.6)	2.9(1.8-5.0)	**	6.3±(4.8-9.6)	5.6±(4.1-8.4)	**
TNF-α	pg/ml	1.3(1.1-1.5)	1.2(1.0-1.5)	*	1.3±(1.0-1.6)	1.2±(1.0-1.3)	*
FFA	mEq/L	0.5±0.2	0.4±0.2		0.5±0.2	0.5±0.2	
CRP	mg/dl	0.07(0.04-0.15)	0.08(0.04-0.18)		0.08(0.04-0.13)	0.09±(0.04-0.16)	
SBP	mmHg	128±15	128±14		128±18	126±16	
DBP	mmHg	80±11	80±11		80±11	77±10	**
Fast glucose	mg/dl	108±22	108±20		109±29	108±23	
HBA_{1C}	%	5.6±0.9	5.7±0.8	*	5.7±0.9	5.8±0.9	*

Significantly different between end of intervention and follow-up.

*:P<0.05,**:P<0.01

Table 5: Changes of body weight and biomarkers during follow-up.



The distinct of character shows statistically significant difference (p<0.05; A-B and a-b;, p<0.01 a-c).

Figure 3: Difference of leptin (blue) and adiponectin (red) concentration during follow-up period by quartile of body weight gain.

decrease glucose, and reduce body weight and fat. Our results suggest that leptin change associated with weight reduction and regain, and other effects on metabolic markers.

Weight loss significantly elevates plasma adiponectin levels. We measured HMW-adiponectin in this study. Adiponectin is present in serum as a trimer, hexamer, or high molecular weight form. HMW adiponectin is closely related to coronary artery disease and weight reduction, it affects insulin-sensitizing.[33,34] Moreover, HMW-adiponectin contributes to the activation of AMP-activated protein kinase (AMPK), to the suppression of endothelial cell apoptosis, and to cytostatic activity.[35,36] We propose that early reports describing variable effects of adiponectin should be interpreted with caution, as HMW adiponectin is a more reliable assay reflecting the active form of adiponectin. A reduction in adiponectin has previously been associated with insulin resistance, dyslipidemia, and atherosclerosis in humans.

TNF-α significantly increased by intervention in women even though body weight and fat area decreased. At the end of follow-up, TNF-α significantly decreased than at the end of intervention both in men and women even though body weight and fat area increased. TNF-α is secreted from not only fat cells but also macrophages. Thus, the changes of TNF-α may be influenced by other factors independently from body weight, obesity or fat cell. It may need further study in the future.

Ambeba et al[19] conducted the 24 month weight loss trial. They reported that adiponectin increased with weight reduction and decreased with weight regain. These results are similar to our observations. On the other hand, Bluher et al[20] reported an increase in adiponectin with weight loss. However, there was a continued increase in adiponectin levels with weight regain. There are several differences between Bluher's and our study. First, we conducted separate statistical analysis between sexes, while they analyzed aggregate data. Furthermore, most of the participants were men (86%). Bluher et al[20] conducted a 2-year intervention for weight loss, using calorie or carbohydrate diet restrictions.

Our study has several limitations. We could set control group in intervention phase by cross-over design, as Group B participants waited their intervention for one year as a control group of A. However, follow-up period of Group A could not be combined to control group of intervention, because they trailed the effect of intervention. It was impossible to set monthly or yearly wash out period, so this problem should be elaborated in the future epidemiological design of human study. So, there was no control group in follow-up phase. Secondly, the relationship between dietary and physical activity was not sufficiently connected to the adipocytokine changes. Individual health conditions, different absorption capacities, and different intestinal microbiota could affect the metabolism of individuals and their predisposition to obesity or leanness.[37] Further studies are necessary to better integrate individual holistic variables.

In conclusion, our results suggest that leptin should have broad effects among fat tissues and lipid metabolism. Leptin inversely associated with adiponectin, which in turn was necessary to decrease body weight. In particular, leptin decreased remarkably in the process of weight reduction, and its increase seemed to be related in weight regain. Increase of adiponectin seemed to be induced by the reduction of fat volume.

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CONFLICTS OF INTEREST

The authors declare that they has no conflicts of interest.

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