The Effect of Sibutramine on the Serum Adiponectin Level in Obese Women

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The Effect of Sibutramine on the Serum Adiponectin Level in Obese Women

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This certifies that the Master's Thesis
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ABSTRACT

The Effect of Sibutramine on the Serum Adiponectin Level in Obese Women

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The aim of this study was to evaluate the effects of sibutramine on serum adiponenctin levels, body mass index, body composition and insulin resistance in obesity women. Twenty-eight healthy, non-diabetic, obese (BMI >25 kg/m^2) women (mean age: 34.46±13.67 years, BMI: 31.00±4.10 kg/m^2) were enrolled in this study, and designed as sibutramine 10 mg, administered orally, once daily for 12 weeks period. We assessed body composition, and measured the level of serum adiponectin, TNF-α, insulin, C-peptide and various biochemical parameters. Twelve weeks of 10 mg/day sibutramine treatment achieved significant decrease in BMI from 31.00±4.10 to 28.72±4.16 kg/m^2 (p<0.01), total fat mass from 30.61±5.86 to 26.39±6.10 kg (p<0.01), percent body fat mass from 37.75±3.75 to 34.99±4.30% (p<0.01). Abdominal subcutaneous and visceral adipose tissue area were reduced from 315.74±125.35 to 263.71±117.87 cm^2 and from 114.77±41.14 to 91.88±33.05 cm^2 (p<0.01). Cross-sectional area of low density muscle (LDM) at the mid thigh decreased from 17.22±7.45 to 11.58±5.90 cm^2 (p<0.01). Insulin resistance (IR, as measured

using the homeostasis model assessment of insulin resistance) decreased from 2.76±1.37 to 2.20±1.12 (p<0.05). Serum adiponectin levels were increased from 5.34±1.27 to 6.37±1.67 μg/mL (p<0.01). Serum TNF-α levels were not statistically significant decreased (12.25±2.75 to 11.47±2.39 pg/mL). In this study, the change of HOMA-IR, adiponectin, free fatty acids, triglyceride and mid thigh low density muscle preceded weight loss. Therefore, the change of insulin resistance, fatty acids metabolism and energy homeostasis preceded weight loss. It is highly likely that this is in part caused by altered fatty acid metabolism, β_3-adrenoreceptors, or uncoupling protein. which is led by the increase in plasma adiponectin level.

Key Words: adiponectin, insulin resistance, HOMA, free fatty acids, low density muscle

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I. INTRODUCTION

Recently, fat cell had been thought to be the tissue in charge of simply storing energy into the state of triglyceride. However, after the discovery of leptin, expressed by *ob* gene in 1994, it came to be known that fat cell, by secreting hormone and cytokine, has various effects on dietary habit, energy metabolism, and carbohydrate and fat metabolism.[1]

Ob gene expressed by fat tissue is in charge of signal transduction of weight regulation, and leptin, by-product of this gene, made up of 167 amino acids, is known to play an important role in balancing energy homeostasis by regulating dietary amount and energy expenditure through circulation.[2]

Starting with leptin, research about hormone and cytokine secreted from fat tissue is actively under way, and it is revealed that these substances are essential in the regulation of weight and glucose homeostasis. For example, in the case of congenital and acquired lipodystrophy patients, severe insulin resistance is observed,[3] and when adipose tissue is transplanted, insulin resistance is improved in proportion to the transplanted amount.[4] In addition,

when leptin is given, insulin resistance is reduced but this doesn't return to normal.[5] When leptin is given to *ob/ob* mice lacking in leptin, leptin can bring down hyperglycemia, but blood insulin level cannot return to normal.[6] Considering all these things, leptins evidently related to insulin resistance, but other substances are also responsible. The adipose tissue secretes adipocytokines that influence insulin resistance including leptin, TNF-α, adiponectin, and resistin.

Among these, adiponectin which, tissue similar in structure to collagen and TNF-α, is glycoprotein expressed abundantly in adipose is lower in subjects with obesity and increased with body weight reduction.[7,8] In addition, adiponectin is presumed to play a role in the occurrence of obesity, atherosclerosis with metabolic syndrome, and cardiovascular disease.[9] Adiponectin regulates insulin and energy homeostasis, and low concentration of adiponectin is closely connected with obesity and insulin resistance.[10] Namely, in type 2 diabetic patients, serum insulin concentration and genetic expression of adiponectin in adipose tissue are in decreased state,[11,12] and in human, serum adiponectin is inversely correlated with insulin resistance and positively correlated with insulin-stimulated glucose disposal measured by hyperinsulinemic euglycemic clamp test.[13] Additionally adiponectin has an effect on insulin action regardless of body fat amount.[13] In recent animal study, recombinant adiponectin induced weight loss without dietary restriction, and significantly decreased plasma free fatty acids by an acute increase in fatty acid oxidation by muscle by inactivating acetyl CoA carboxylase (ACC) via activation of AMP-activated protein kinase (AMPK).[14,15] And insulin sensitivity was inversely related to skeletal muscle triglyceride content independently total adiposity.[16]

The administration of adiponectin makes glucose level decrease without stimulating insulin secretion from normal mice and diabetic mice and through direct action on liver.[17] Namely, adiponectin is an adipose tissue specific

antiatherogenic molecule and adipocytokine that could explain the mechanism of increased atherosclerosis in obese subjects.

Action mechanism of adiponectin on glucose metabolism, although not fully revealed yet, decreases gluconeogenesis in liver, and lower serum fatty acids increasing the use of glucose by fatty acid oxidation in muscle.[8,14] In addition, action on central nervous system cannot be excluded.[18,19]

Currently in clinical use antiobesity agent, sibutramine is serotonin and noradrenaline reuptake inhibitor that induces weight loss by effects on satiety and metabolic rate in dose dependent manner. Sibutramine increases satiety by blocking the reuptake of serotonin and noradrenaline, and increase metabolic rate by enhancing peripheral noradrenaline function via β_3-adrenoreceptors leading to an increase in energy expenditure.[20]

Chronic administration of sibutramine can reduce weight gain, lower Non-esterified fatty acids (NEFA) concentrations, decrease hyperinsulinemia and ameliorate the insulin resistance of *ob/ob* mice.[21] According to recent study, vascular risk factors associated to insulin resistance were reduced after weight loss with sibutramine treatment in human.[22]

Clinical investigations on above findings are actively under way, but there have been few reports about the mechanism of decrease of insulin resistance. Thus, the aim of this study was to evaluate the effect before and after 12 weeks treatment with sibutramine 10 mg daily on body composition, insulin resistance, skeletal muscle triglyceride content and adiponectin.

II. MATERIALS AND METHODS

1. Subjects

Twenty-eight obese (BMI >25 kg/m^2) women with a mean age 34.5±13.7 years participated in the study. All subjects had no evidence of hypertension, diabetes, ischemic heart disease, severe hyperlipidemia (concentrations of plasma total cholesterol >7.76 mmol/L or triglyceride >3.38 mmol/L) or any other serious medical problems. None of subjects were treated by any kind of medication.

2. Design

This study designed as sibutramine 10 mg, administered orally, once daily for a 12 week period. All subjects received dietary counselling for a caloric restriction diet of 25 kcal/kg of ideal body weight. The suggested intake included 50% of calories from carbohydrates, 30% from lipids and 20% from proteins. They were provided with personalized diet prescriptions and dietary advice was provided at every 2 weeks. Blood samples and measurement of body composition were taken at 4 weeks intervals.

3. Measurement

A. Biochemical profiles

Serum glucose was measured immediately by an autoanalyzer using the hexokinase method (Roche, Hitachi 747). Serum insulin and C-peptide were determined by an enzyme chemiluminescence immunoassay (ECIA, DPC, Immulite 2000). HbA_{1c} was measured by the high performance liquid chromatography method (Bio-Rad, Variant Ⅱ). Serum total cholesterol, HDL-cholesterol and LDL-cholesterol were assessed by the enzymatic methods (Daiichi, Hitachi 747) and serum triglycerides were measured by the enzymatic colorimetric

methods (Roche, Hitachi 747). Serum free fatty acids were measured by the enzymatic colorimetric method (Daiichi, Olympus AU640). All subjects underwent a 75-g 2-hour oral glucose tolerance test (OGTT) with blood samples drawn at baseline, 30 min, 60 min, 90 min and 120 min for measurement of serum glucose levels.

B. Insulin sensitivity

The homeostasis model assessment was applied to estimate the degree of insulin sensitivity. Homeostasis Model Assessment of insulin resistance (HOMA-IR) was calculated as previously described[23];

HOMA-IR = [fasting insulin (U/mL)×fasting glucose (mmol/L)]/22.5

C. Body composition

Body mass index (BMI) was calculated as weight (kg)/height (m^2). Fat and lean mass were determined by dual-energy X-ray absorptionmetry (Delphi, Hologic QDR 1500) before and after 12 weeks sibutramine treatment. Computed tomography scan (Philips, Tomoscan 350, Mahway, NJ) of the abdomen and mid thigh was performed to quantify cross-sectional abdominal visceral and subcutaneous adipose tissue area, and mid thigh muscle and adipose tissue areas. With the subject supine position, a cross sectional scan at 10 mm thickness was acquired at the L4-L5 vertebral disc space and the mid portion between the anterior iliac crest and the patella, as described previously.[24] In image analysis, area of adipose tissue and muscle were measured by attenuation values.

Fat tissue area was computed as the area with an attenuation range of 150 ~ -50 Hounsfield units, and for muscle, an attenuation range of 0~100 Hounsfield units was used. Skeletal muscle area of mid thigh was further characterized as normal density muscle area (attenuation values within 2 SD

of the mean attenuation value of normal muscle, 31～100 Hounsfield units) and low density muscle area (muscle with lower than normal attenuation values, 0～30 Hounsfield units) as described by Goodpaster et al.[25]

D. Adipocytokines

Fasting blood samples were collected in prechilled tubes and immediately separated by centrifugation. Samples were frozen at -70℃ for subsequent analysis. Serum adiponectin levels were determined by a newly developed specific human adioponectin radioimmunoassay (Linco, USA, RIA). Serum TNF-α concentrations were measured by a solid-phase enzyme amplified sensitivity immunoassay (Biosource, Belgium, ELISA).

4. Statistical analyses

All values are expressed as means±SD. Associations between anthropometric and biochemical parameters, body compositions or regional fat distributions and the HOMA scores were identified using Pearson correlations. Differences were considered to be significant if p-value <0.05.

III. RESULTS

Baseline anthropometric and biochemical chrarcteristics of 28 obese subjects were described at table 1 and 2.

At the end of 12 weeks sibutramine treatment, there was statistically significant change in BMI, percent of total body fat, abdominal visceral and subcutaneous fat, and thigh low density muscle, HOMA IR, free fatty acids, serum triglyceride, adiponectin, and TNF-α. However there were no significant change in serum cholesterol, HDL-cholesterol, LDL-cholesterol, HbA1c, and serum C-peptide level. Mean weight loss after 12 weeks sibutramine treatment was 5.9±2.86 kg (7.4% of baseline level). Reduction in BMI, fat mass, and percent of total body fat were 2.28±1.14 kg/m^2, 4.22±1.85 kg, 2.76±1.91%. There was substantial reduction in abdominal adipose tissue (Table 3, Fig. 1). Total abdominal adipose tissue decreased by 74.9±38.0 cm^2 (18% of baseline level), subcutaneous abdominal adipose tissue decreased by 52.3±33.8 cm^2 (17% of baseline level), and visceral abdominal adipose tissue decreased by 22.9±16.8 cm^2 (19% of baseline level). And mid thigh adipose tissue decreased by 3.64±2.68 cm^2 (20% of baseline level). Serum adiponectin levels were increased by 1.03±0.86 μg/mL (20% of the mean baseline level) with a 7% reduction in BMI. And serum TNF-α levels were decreased by 0.78±1.37 pg/mL (5.2% of the mean baseline level).

Fig. 3 and 4 show the sequential changes of anthropometric and biochemical parameters during 12 weeks sibutramine treatment.

Table 5 and Fig. 2 shows the sequential changes of insulin resistance and adipocytokines during 12 weeks sibutramine treatment.

Significant reductions ($p<0.05$) in the serum concentrations of insulin, free fatty acids, triglyceride, adiponectin, HOMA, mid thigh low density muscle area were observed after four weeks sibutramine treatment, where as, those of BMI, total body fat percent, abdominal subcutaneous and visceral fat area

were after 8 weeks sibutramine treatment. Serum TNF-α concentration did not statistically significant decrease after sibutramine treatment and did not correlate HOMA and adiponectin level.

Table 6 shows the sequential changes of correlation between serum adiponectin concentrations and metabolic variables before and 4 and 12 weeks during sibutramiene treatment. After 4 weeks sibutramine treatment, the serum adiponectin concentration was significantly correlated with thigh low density muscle area (γ= -0.47, p=0.05), free fatty acids (γ= -0.41, p=0.05), and HOMA-IR (γ= -0.64, p= 0.01). After 12 weeks sibutramine treatment, where as, the serum adiponectin concentration was significantly correlated with BMI (γ= -0.47, p=0.05), total abdominal fat area (γ= -0.40, p=0.05), abdominal visceral fat area (γ= -0.62, p=0.01), thigh low density muscle area (γ= -0.51, p=0.01), free fatty acids (γ= -0.44, p=0.05), and HOMA-IR (γ= -0.63, p=0.01).

The change of serum adiponectin levels before and after sibutramine treatment was significantly correlated with those of BMI (γ= -0.485, p=0.01), abdominal visceral fat area (γ= -0.441, p=0.05), mid thigh low density muscle area (γ= -0.671, p=0.01), HOMA-IR (γ= -0.379, p=0.05), and serum free fatty acids (γ = -0.415, p=0.05) (Fig 3).

Table 1. Baseline anthropometric characteristics of 28 subjects

Parameters	
Body weight (kg)	81.04±12.94
BMI (kg/m^2)	31.00±4.10
Fat mass (kg)	30.61±5.86
Lean mass (kg)	47.35±8.14
Percent body fat (%)	37.75±3.75
Visceral fat (cm^2)	114.77±41.14
Subcutaneous abdominal fat (cm^2)	315.74±125.35
VSR	0.42±0.23
Total abdominal fat (cm^2)	430.52±127.73
Thigh low density muscle (cm^2)	17.22±7.45
Thigh normal density muscle (cm^2)	111.63±31.36

Data are means±SD. BMI, body mass index; VSR, visceral fat/subcutanepus fat ratio

Table 2. Baseline biochemical characteristics of 28 subjects

Parameters	
Fasting glucose (mmol/L)	5.40±0.44
OGTT 2-hr glucose (mmol/L)	7.30±1.28
HbA1c (%)	5.57±0.36
Fasting serum insulin (pmol/L)	67.46±29.99
Fasting serum C-peptide (nmol/L)	1.17±0.54
Free fatty acid (mmol/L)	632.18±228.19
HOMA-IR	2.76±1.37
Total cholesterol (mmol/L)	5.39±0.96
Triglyceride (mmol/L)	1.52±0.74
HDL cholesterol (mmol/L)	1.35±0.36
LDL cholesterol (mmol/L)	3.69±0.87

Data are means±SD. HOMA-IR, homeostasis model assessment of insulin resistance; OGTT 2-hr glucose, oral glucose tolerance test 2-hour glucose

Table 3. Anthropometric sequential changes before and after weight loss of 28 women treated with sibutramine

	Baseline	4 weeks	8 weeks	12 weeks
Weight (kg)	81.0±12.9	79.2±12.9	77.3±13.1*	75.1±13.1**
BMI (kg/m^2)	31.00±4.10	30.36±4.21	29.62±4.13*	28.72±4.16**
Fat mass (kg)	30.6±5.9	29.3±5.7	28.4±6.0*	26.4±6.1**
Lean mass (kg)	47.4±8.1	46.8±8.4	46.3±8.4*	45.9±8.3**
Body fat (%)	37.8±3.8	37.0±4.0	36.7±3.9*	35.0±4.3**
AVF (cm^2)	114.8±41.14	108.2±39.5	100.9±36.2*	91.9±33.1**
ASF (cm^2)	315.7±125.4	306.2±122.8	288.3±118.4*	263.7±117.9**
TAF (cm^2)	430.5±127.7	414.6±126.5	389.3±126.9*	355.6±124.6**
TLDM (cm^2)	17.2±7.5	15.7±6.1*	14.4±5.7**	13.6±5.9**
TNDM (cm^2)	111.6±31.4	109.2±33.6	107.3±35.9	105.1±38.6

Data are means±SD. *p<0.05; **p<0.01. BMI, body mass index; AVF, abdominal visceral fat; ASF, abdominal subcutaneous fat; TAF, total abdominal fat; TLDM, thigh low density muscle; TNDM, thigh normal density muscle

Table 4. Biochemical parameter and adipocytokine sequential changes before and after weight loss of 28 women sibutramine treatment

	Baseline	4 weeks	8 weeks	12 weeks
Fasting glucose (mmol/L)	5.40±0.44	5.38±0.39	5.38±0.40	5.35±0.32
2-hr glucose (mmol/L)	7.30±1.28	7.27±1.31	7.31±1.29	7.29±1.16
HbA1c (%)	5.57±0.36	5.58±0.36	5.55±0.29	5.54±0.30
Fasting insulin (pmol/L)	67.46±29.99	60.45±27.28*	57.16±25.46*	55.56±24.83*
Fasting C-peptide (nmol/L)	1.17±0.54	1.16±0.53	1.14±0.48	1.11±0.46
Free fatty acid (mmol/L)	632.2±228.2	586.2±201.6*	573.8±161.5*	544.0±137.8*
HOMA-IR	2.76±1.37	2.41±1.21*	2.28±1.18*	2.20±1.12*
Total cholesterol (mmol/L)	5.39±0.96	5.38±0.88	5.35±0.79	5.33±0.72
Triglyceride (mmol/L)	1.52±0.74	1.39±0.59*	1.34±0.58*	1.35±0.47*
HDL-cholesterol (mmol/L)	1.35±0.36	1.36±0.37	1.38±0.40	1.39±0.38
LDL-cholesterol (mmol/L)	3.69±0.87	3.65±0.72	3.61±0.76	3.62±0.66
Adiponectin (μg/mL)	5.34±1.27	5.87±1.49*	6.21±1.55**	6.37±1.67**
TNF-α (pg/mL)	12.25±2.75	12.16±2.73	11.78±2.50	11.47±2.39

Data are means±SD. *p<0.05; **p<0.01. 2-hr glucose, oral glucose tolerance test 2-hour glucose; HOMA-IR, homeostasis model assessment of insulin resistance

Table 5. Insulin resistance and adipocytokine sequential change before and after weight loss of 28 women sibutramine treatment

	Baseline	4 weeks	8 weeks	12 weeks
HOMA-IR	2.76±1.37	2.41±1.21*	2.28±1.18*	2.20±1.12*
Adiponectin (μg/mL)	5.34±1.27	5.87±1.49*	6.21±1.55**	6.37±1.67**
TNF-α (pg/mL)	12.25±2.75	12.16±2.73	11.78±2.50	11.47±2.39

Data are means±±SD. *p<0.05; **p<0.01. HOMA-IR, homeostasis model assessment of insulin resistance

Table 6. The correlation between serum adiponectin concentrations and metabolic variables before and 4 and 12 weeks during sibutramine treatment

	Baseline	4 weeks	12 weeks
Age	-0.11	-0.13	-0.13
BMI	-0.47*	-0.32	-0.47*
Fat mass	-0.25	-0.27	-0.26
Percent body fat	0.18	0.14	0.11
Visceral fat	-0.55**	-0.35	-0.62**
Subcutaneous abdominal fat	-0.27	-0.26	-0.24
VSR	-0.27	-0.30	-0.33
Total abdominal fat	-0.44*	-0.38	-0.40*
Thigh low density muscle	-0.50**	-0.47**	-0.51**
Fasting serum insulin	-0.68**	-0.56**	-0.61**
Free fatty acid	-0.40*	-0.41*	-0.44*
HOMA-IR	-0.69**	-0.64**	-0.63**
TNF-α (pg/mL)	-0.35	-0.37	-0.34

*p<0.05; **p<0.01. BMI, body mass index; VSR, visceral fat/subcutanepus fat ratio; HOMA-IR, homeostasis model assessment of insulin resistance.

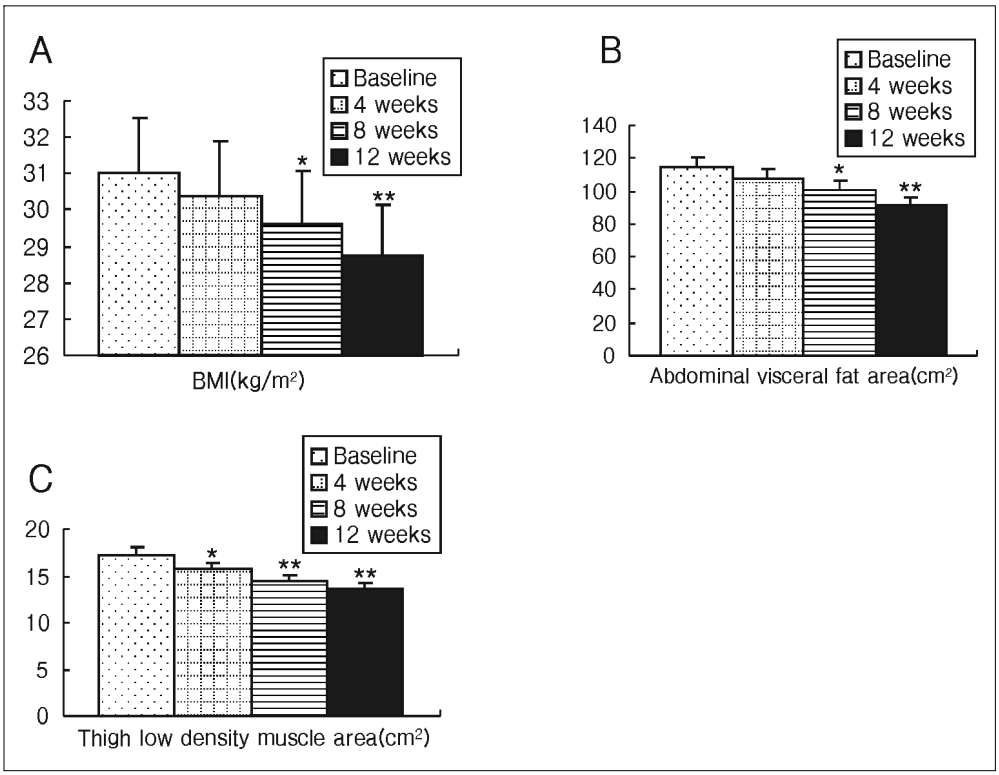

Fig. 1. Sequential changes of body composition before and after sibutramine treatment. **A**: BMI. **B**: abdominal visceral fat area. **C**: mid thigh low density muscle area. *p <0.05; **p<0.001.

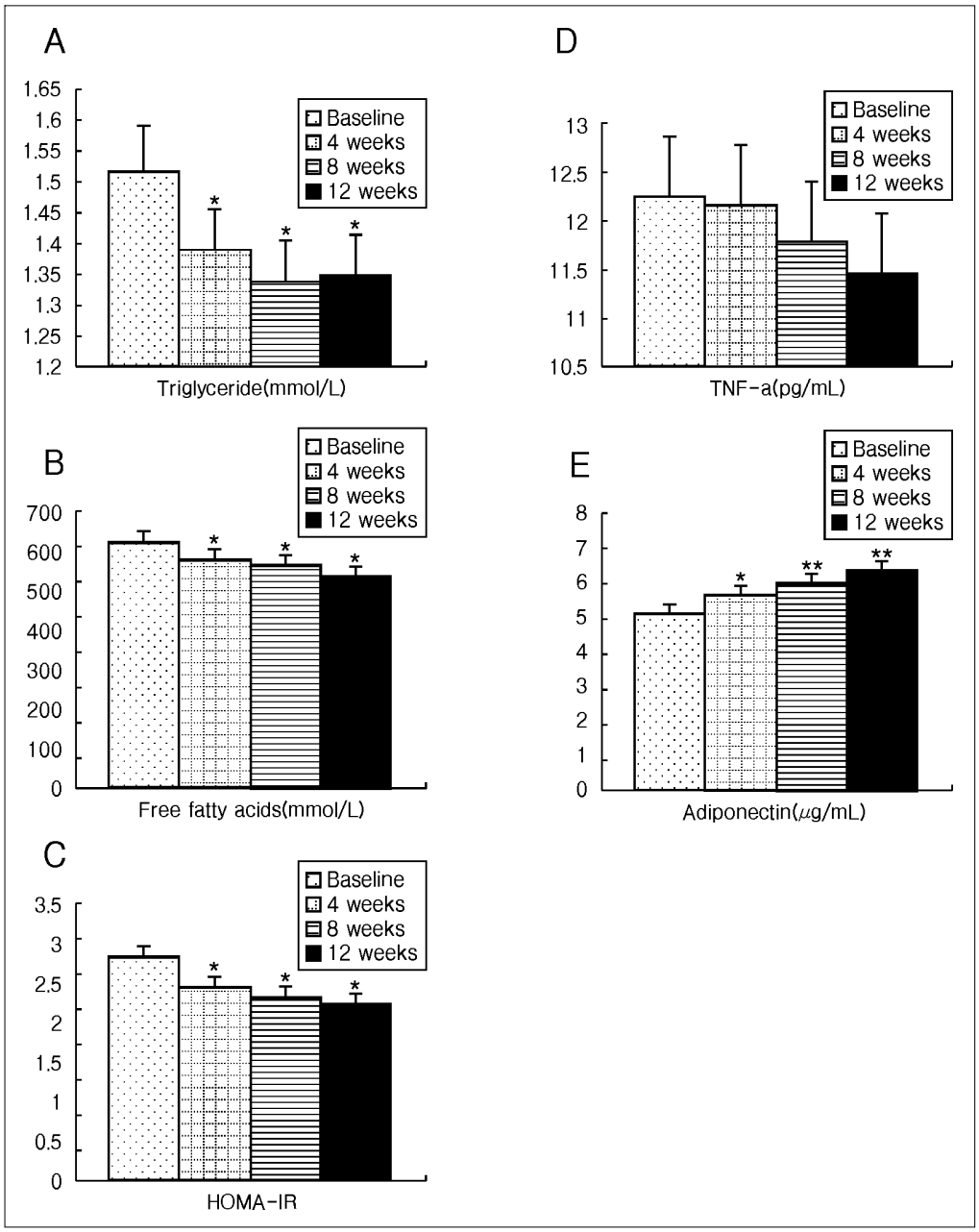

Fig. 2. Sequential changes of insulin resistance before and after sibutramine treatment. **A**: Serum triglyceride. **B**: Serum free fatty acids. **C**: HOMA-IR. **D**: Serum TNF-α. **E**: Serum adiponectin *p<0.05; **p<0.001.

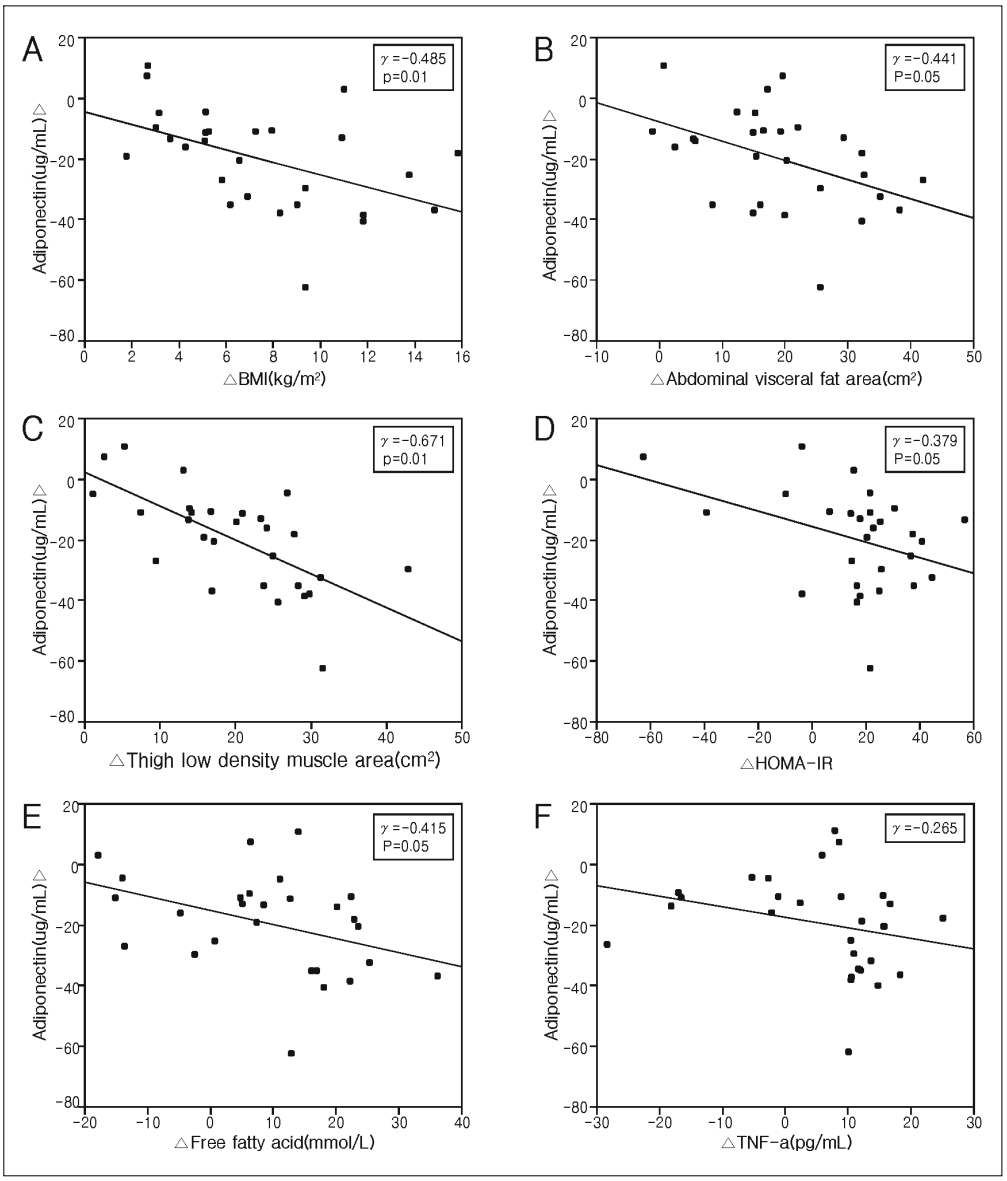

Fig. 3. The change (Δ) of serum adiponectin levels before and after sibutramine treatment plotted against the changes (Δ) in BMI (**A**), abdominal visceral fat area (**B**), mid thigh low density muscle area (**C**), HOMA-IR (**D**), serum free fatty acids (**E**), and serum TNF-α level (**F**) in 28 subjects.

IV. DISCUSSION

This study showed simultaneous improvement insulin sensitivity and reduction of adipose tissue during 12 weeks treatment with sibutramine. And we showed that elevation of serum adiponectin levels was correlated with the change of BMI, abdominal visceral and subcutaneous fat area, thigh low density muscle area, free fatty acids, triglyceride and HOMA-IR.

Recently, it was demonstrated that recombinant adiponectin reduced plasma fatty acid levels in mice.[14] This indicates that adiponectin may related to fatty acid and energy homeostasis. We observed a significant decrease in triglyceride and free fatty acids levels after weight reduction. Thigh low density muscle area was inversely correlated with the circulating free fatty acids and triglyceride in this study. Plasma concentrations of free fatty play an important role in determining the rate of free fatty acids uptake by skeletal muscle.[16] Additional evidence pertinent to mitochondrial metabolism in skeletal muscle is the finding of increased content of uncoupling protein 2 (UCP2) in obese patients.[26] Because we did not assay change of uncoupling protein 2 in this study, whether this is secondary to the change of uncoupling protein 2 remains unknown. Therefore, further studies are warranted.

In animal study, there was a report about the effects of sibutramine on insulin resistance. Chronic administration of sibutramine reduced weight gain, lowered free fatty acids concentrations, decreased hyperinsulinemia and ameliorated the insulin resistance of *ob/ob* mice.[21] And in that animal study, it appears that sibutramine can also act independently to influence metabolic parameters, for example, when sibutramine was stopped in *ob/ob* mice, the plasma free fatty acids and insulin concentrations quickly returned to placebo values, but only a small amount of weight was regained and very slowly.[21]

In this study, serum TNF-α concentration did not statistically significant correlate insulin resistance and adiponectin level. Adiponectin was shown to

supressess TNF-α production and phagocytic acitivity in macrophages.[8] Therefore, it is highly possible that adiponectin may enhance insulin sensitivity by interfering with TNF-α production and signaling. TNF-α has the highly labile nature. And TNF-α receptor are easily detectable in serum and appear to act as a buffer system.[27] We did not assay change of TNF-α receptor in this study. This awaits further investigation about the interaction of adiponectin and TNF-α.

In this sibutramine study, the change of HOMA-IR, adiponectin, free fatty acids, triglyceride and mid thigh low density muscle preceded weight loss. Therefore, the change of insulin resistance, fatty acids metabolism and energy homeostasis preceded weight loss. The mechanism of regulating plasma adiponectin levels by body weight change are still unknown. In this study, the change of insulin resistance precede the body weight change, which may indicate that sibutramine directly can have an effect on insulin resistance. It is highly likely that this is in part caused by altered fatty acid metabolism secondary to the increase in plasma adiponectin level. Nevertheless, even if sibutramine has no direct effect on insulin sensitivity, it improves insulin sensitivity parameters before reduction of adipose tissue.

V. CONCLUSION

In conclusion, this study demonstrates that sibutramine treatment in obese women promote clinically significant weight loss. Weight loss with sibutramine treatment are associated with improvement in insulin resistance and increased serum adiponectin level. In this study, the improvement of insulin resistance precedes the weight change, which may reply the direct effect of sibutramine on insulin resistance independently of body weight change probably via free fatty acids, β_3-adrenoreceptors, or uncoupling protein. Further studies for the mechanism are warranted.

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국문요약

비만 여성에서 Sibutramine이 혈중 Adipocytokine에 미치는 영향

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본 연구에서는 비만 여성에서 sibutramine이 체성분 변화와 혈중 adiponectin 농도 및 인슐린 저항성에 미치는 영향을 알아보고자 하였다. 다른 질환을 동반하지 않은 28명의 비만 여성 (BMI >25 kg/m^2)을 대상으로 하였고, 평균 연령은 34.5±13.7세, 평균 체질량지수는 31.0±4.1 kg/m^2였다. 12주간 매일 10 mg의 sibutramine을 복용하도록 하였고, 공복 후 혈청 총 콜레스테롤, 중성지방, 고밀도지단백 콜레스테롤, 인슐린, C-peptide, 유리지방산, TNF-α 및 adiponectin 농도를 측정하였다. 또한 모든 환자에서 체성분석 검사를 시행하였고, 요추 4～5와 대퇴 중간수준에서 컴퓨터단층촬영을 시행하여 복부 피하지방 및 내장지방, 대퇴부 저밀도 근육 면적을 측정하였다. 체질량지수는 31.0±4.1에서 28.7±4.2 kg/m^2, 체지방량은 30.6±5.9에서 26.4±6.1 kg, 체지방률은 37.8±3.8에서 35.0～4.3%으로 투여 8주 후 통계적으로 의미 있는 감소를 보였다 (p<0.01). 복부 피하지방 및 내장지방 면적도 315.7±125.6에서 263.7±117.9 cm^2와 114.8±41.1에서 91.9±33.1 cm^2로 투여 8주 후 통계적으로 의미 있게 감소하였다 (p<0.01). 반면 대퇴부 저밀도 근육 면적은 투여 4주 째부터 17.2±7.5에서 11.6±5.9 cm^2 으로 통계적으로 의미 있는 감소를 보였다 (p<0.01). 인슐린 저항성 지표인 HOMA score는 2.76±1.37에서 2.20±1.12로 투여 4주째부터 의미 있게 감소하였다 (p<0.01). 혈중 adiponectin 농도도 5.34±1.27에서 6.37±1.67 μg/mL로 투여 4주째 통계적으로 의미 있게 증가하였다 (p<0.01). 혈중 TNF-

α 농도는 통계적으로 의미 있는 변화를 보이지 않았다(12.25±2.75 to 11.47±2.39 pg/mL). 본 연구에서 혈중 adiponectin, 유리 지방산, 중성지방과 HOMA score 및 대퇴부 저밀도 근육의 변화는 체중 감량을 선행하였다. 즉, 인슐린 저항성과 유리 지방산 대사의 변화가 체중의 감량보다 선행되었다. 이는 sibutramine 투여 시 혈중 adiponectin 농도가 증가되고, 여기에 유리 지방산 대사, β_3-adrenoreceptors, 또는 uncoupling protein의 변화가 관여할 것으로 사료된다.

핵심 되는 말: adiponectin, 인슐린 저항성, HOMA, 유리 지방산, thigh low density muscle