Full Paper

Effect of weight reduction with dietary intervention on arterial distensibility and endothelial function in obese men

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Running title: Weight reduction and arterial function

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(20 pages [2 Table and 4 Figures])

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ABSTRACT

Obesity is an independent risk factor for cardiovascular morbidity and mortality.

Reduction in central arterial distensibility has recently been identified as a powerful

and independent risk factor for cardiovascular disease. However, the effect of weight

reduction on central arterial distensibility and endothelial function in obese subjects

has not yet been clarified. We investigated whether low-calorie diet-induced weight

reduction affects central arterial distensibility and endothelial function in middle-aged

obese men. Twelve obese men (age: 45 ± 2 yrs, body mass index: 30 ± 1 kg/m^2)

completed a 12-week dietary intervention. Caloric restriction significantly reduced

body weight and resulted in a significant decrease in body mass index. After the

weight reduction program, carotid arterial compliance (via simultaneous B-mode

ultrasound and arterial applanation tonometry on the common carotid artery)

significantly increased and β-stiffness index, an index of arterial compliance adjusted

for distending pressure, significantly decreased. Additionally, aortic pulse-wave

velocity, an index of arterial stiffness, significantly decreased after weight reduction.

Concentrations of plasma endothelin-1 (ET-1), a potent vasoconstrictor peptide

produced by vascular endothelial cells, significantly decreased and plasma nitric

oxide (NO) [measured as the stable end product (nitrite/nitrate)], a potent vasodilator

produced by vascular endothelial cells, significantly increased after the program.

Weight reduction by low-calorie diet in obese men increases central arterial

distensibility. This increase in central arterial distensibility may contribute to the

improvement in endothelial function, as noted by a decrease in ET-1 and an increase

in NO, after weight reduction.

Keywords: diet, arterial compliance, endothelial function

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INTRODUCTION

The vasculature was once considered to be a simple passive conduit. However, it is now recognized to be a complex organ capable of producing a number of local vasoactive factors, actively buffering cardiac pulsation.   Reduction in central arterial distensibility is believed to contribute to the pathophysiology of cardiovascular disease and has recently been identified as a powerful and independent risk factor for cardiovascular disease (1,2).

The prevalence of obesity has been increasing worldwide. Obesity has been identified as an independent risk factor for cardiovascular morbidity and mortality (3,4).   Several studies have investigated the relationship between obesity and large arterial function with contradictory results.   In some studies, obese subjects have been found to have lower degrees of arterial distensibility (5,6), while in other studies they had higher degrees of distensibility (7,8).   Thus, the relationship between obesity and arterial distensibility has not yet been clarified.   On the other hand, endothelial dysfunction is a common abnormality in obesity (9,10).   Vascular endothelial cells play an important role in the regulation of vascular activity by producing vasoactive substances, such as endothelin-1 (ET-1) and nitric oxide (NO). ET-1 is a potent vasoconstrictor peptide produced by vascular endothelial cells (11). NO produced by vascular endothelial cells has a potent vasodilator effect (12). Therefore, altered ET-1 and NO may reflect changes in endothelial function and could have important clinical significance.

The purpose of the present study was to examine whether low-calorie diet-induced weight reduction affects central arterial distensibility in middle-aged obese men, and if so, whether the endothelial function, as assessed by ET-1 and NO concentrations, participates in the mechanism underlying the adaptation of central arterial distensibility to weight loss.   We hypothesized that weight loss can increase

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central arterial distensibility in obese men, and ET-1 and NO participate in the

mechanism underlying this adaptation of central arterial distensibility to weight loss.

To test our hypothesis, we measured carotid arterial compliance; β-stiffness index, an

index of arterial compliance adjusted for distending pressure; aortic pulse-wave

velocity (PWV), a traditional index of arterial stiffness; and plasma ET-1 and NO

concentrations before and after a 12-week dietary intervention in obese men.

METHODS

Subjects.　Twelve obese men participated in the study (45 ± 2 yrs, body

mass index [BMI]: 30 ± 1 kg/m^2).　Candidates who were current smokers or who

were taking any medications were excluded.　All subjects had no apparent

cardiovascular disease as assessed by medical history and physical examination.

This study was reviewed and approved by the Institutional Review Board at the

University of Tsukuba.　All potential risks and procedures of the study were

explained to the subjects, and they gave written informed consent to participate in the

study.

Experimental Design.　All obese men were studied before and after 12

weeks of a diet-induced weight reduction program (i.e., an energy-restricted diet

program).　All measurements were performed after abstinence from caffeine and an

overnight fast.　Subjects were studied under supine resting conditions in a quiet,

temperature-controlled room (24–26°C).　All measurements were performed after a

resting period of at least 20 min.

Dietary Intervention.　The protocol used has been reported as a low-calorie

diet intervention with effects on body composition, body fat distribution, and coronary

heart disease risk factors (13).　Based on the diet protocol in this study, all subjects

were instructed to take meals consisting on average of 420 kcal of protein, 840 kcal of

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carbohydrate, and 420 kcal of fat per day (total: 1,680 kcal/day).   Subjects kept daily

food diaries during the 12-week intervention period and learned about proper daily

nutrition (well-balanced protein, carbohydrate, fat, amino acids, vitamins, and

minerals) through weekly lectures and counseling by skilled dieticians.

Abdominal Adipose Tissue Area by CT*.*   Visceral fat area and

subcutaneous fat area (cm^2) were measured at the level of the umbilicus (L4–L5)

using CT (computed tomography) scans (Somatom AR.C, Siemens, Erlangen,

Germany) performed on subjects in the supine position.   Visceral fat area and

subcutaneous fat area were calculated using a computer software program (FatScan,

N2system, Osaka, Japan). The intra-class correlation for repeated determinations in

the laboratory which performed this measurement was 0.99.

Blood Pressure Measurement*.*   The supine systolic blood pressure,

diastolic blood pressure, mean arterial pressure, and heart rate were recorded from

the left arm using a semi-automated device (Dinamap, Johnson & Johnson, New

Jersey, USA).

Carotid Artery Compliance.

 The combination of ultrasound imaging of a common carotid artery with

simultaneous applanation of tonometrically obtained arterial pressure from the

contralateral carotid artery permits noninvasive determination of dynamic arterial

compliance.   Subjects were studied under quiet resting conditions while they were in

the supine position.   Common carotid artery diameter was measured from the

images derived from an ultrasound machine (EnVisor, Koninklijke Philips Electronics,

Eindhoven, Netherlands) equipped with a high-resolution (7.5 MHz) linear-array

transducer.   Longitudinal images of the cephalic portion of the common carotid

artery were acquired 1 to 2 cm proximal to the carotid bulb with the transducer placed

at a 90 degree angle to the vessel so that near and far wall interfaces were clearly

discernible.   These images were recorded on a computer recorder for later offline analysis.   The computer images were analyzed with the use of image analysis software.   All image analyses were performed by the same investigator.   Time points that corresponded with maximal systolic expansion of the carotid artery and basal (minimum) diastolic relaxation were selected.   The distances (or the diameter) between the vessel far-wall boundary, corresponding to the interface of the adventitia and media, were then measured.

To characterize central arterial compliance as comprehensively as possible, two different measures, arterial compliance (14) and beta-stiffness index (15), were calculated.   Cross-sectional compliance (CC) was calculated from the change in cross-sectional area (dA) and local pulse pressure (dP) using the formula CC = dA/dP. dA was calculated as dA = $\pi \cdot [(D + dD) / 2]^2 - \pi \cdot (D/2)^2$.   Pressure wave forms of the left common carotid artery were recorded with an applanation tonometry device (formPWV/ABI, Colin Medical Technology, Komaki, Japan) and calibrated by equating the carotid mean arterial and diastolic blood pressure to that of the brachial artery (16).

The β-stiffness index provides an index of arterial compliance adjusted for distending pressure.   The β-stiffness index was calculated using the equation β = ln (Ps / Pd) / [(Ds - Dd) / Dd)], where Ds and Dd are the maximum and minimum arterial diameters and Ps and Pd are the highest and lowest blood pressures, respectively (15).

Aortic PWV.   Aortic PWV was measured using applanation tonometry as previously described (17) with minor modifications.   Briefly, carotid and femoral arterial pulse waves were obtained in triplicate using arterial applanation tonometry incorporating an array of 15 transducers (formPWV/ABI, Colin Medical Technology,

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Komaki, Japan).   The distance traveled by the pulse waves was assessed in

triplicate with a random zero-length measurement over the surface of the body with a

nonelastic tape measure.   Pulse-wave transit time was determined from the time

delay between the proximal and distal "foot" waveforms.   The foot of the wave was

identified as the commencement of the sharp systolic upstroke, which was

automatically detected.   Aortic PWV was calculated as the distance divided by the

transit time.

Blood Biochemistry.   Each blood sample was placed in a chilled tube

containing aprotinin (300 kalikrein-inactivating U/ml) and EDTA (2 mg/ml) and was

then centrifuged at 2000 *g* for 15 min at the 4°C.   The plasma was stored at - 80°C

until assayed.   Plasma concentrations of ET-1 were determined using a

sandwich-EIA Kit (Immuno-Biological Laboratories, Fujioka, Japan).   The ET-1

assay was carried out as previously described (18).   Plasma NO (measured as its

stable end product, nitrite/nitrate [NOx]) concentration was determined as previously

described (19).   Serum concentrations of cholesterol and triglycerides and plasma

concentrations of glucose were determined using standard enzymatic techniques.

Statistical Analysis.   Data are expressed as means±SE.   To evaluate

differences in the levels before and after the weight reduction program in obese men,

the Student's *t*-test for paired values was used.   *P* < 0.05 was accepted as

significant.

RESULTS

Table 1 shows the characteristics of obese men before and after 12 weeks of

the weight reduction program.   Body weight, BMI, and body fat areas markedly

decreased after the weight reduction program (Table 1).   Serum concentrations of

cholesterol and triglycerides and plasma concentrations of glucose also significantly

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decreased after the program (Table 1). After the weight reduction program, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, and heart rate significantly decreased (Table 2).

The arterial compliance significantly increased and β-stiffness index significantly decreased after the weight reduction program (Fig. 1). Additionally, aortic PWV significantly decreased after weight reduction (Fig. 2). Thus, weight reduction by a low-calorie diet in obese men increased central arterial distensibility.

The plasma ET-1 concentration significantly decreased after the weight reduction program (Fig. 3). On the other hand, the plasma concentration of NOx significantly increased with weight loss (Fig. 4).

DISCUSSION

In the present study, we determined central arterial distensibility and endothelial function in obese men before and after a 12-week diet-induced weight reduction program. After the program due to which body weight and BMI markedly decreased, carotid arterial compliance significantly increased and beta-stiffness index significantly decreased. Additionally, aortic PWV significantly decreased after weight loss. Thus, weight reduction by low-calorie diet in obese men induced an increase in central arterial distensibility. We also demonstrated that the low-calorie diet in obese men significantly decreased plasma ET-1 and significantly increased plasma NOx, a stable end product of NO, suggesting an improvement in endothelial function. Therefore, we suggest that increased central arterial distensibility with weight loss may contribute to the improvement in endothelial function after weight reduction.

Obesity is strongly associated with cardiovascular disease (3,4,9,10). On the other hand, reduced arterial distensibility has been implicated in the

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pathophysiology of cardiovascular disease and has been identified as an

independent risk factor for cardiovascular disease (1,2).   The relationship between

obesity and large arterial function has been investigated in several studies.   The

results of these studies vary considerably.   In some studies, obese individuals have

been found to have a lower degree of arterial distensibility (5,6), while in other studies

they have had a higher degree of arterial distensibility (7,8).   The arterial

distensibility in middle-aged obese humans in the present study was clearly lower

than in middle-aged normal weight humans (15,20).   These discordant results may

be due to the method used to describe arterial distensibility.   Few interventional

studies have investigated the effects of weight loss on arterial distensibility.

Toto-Moukouo et al. (21) have shown that aortic PWV decreased with weight

reduction in obese hypertensive subjects.   Weight reduction has also been

associated with increased arterial compliance in obese men and women (22,23).   In

the present study, we demonstrated increased arterial compliance, decreased

β-stiffness index, and reduced aortic PWV with weight loss in obese men.   These

findings strongly suggest that weight reduction in obese men induces increased

central arterial distensibility, which may have beneficial effects on the prevention of

cardiovascular disease.

Obesity is strongly associated with endothelial dysfunction [9,10] that may

play a role in the development of decreased arterial distensibility.   Vascular

endothelial cells produce ET-1 and NO (11,12).   ET-1 produced by vascular

endothelial cells has potent vasoconstrictor activity and potent proliferative effects on

vascular smooth muscle cells (11,24).   Furthermore, arterial distensibility was

decreased by intra-arterial infusion of ET-1 and increased by the administration of an

ET-1 receptor antagonist (25,26).   NO produced by vascular endothelial cells has a

potent vasodilator effect and plays an important role in the regulation of

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platelet-vessel wall interactions and vascular resistance and growth (12).   Arterial

distensibility decreased following intra-arterial infusion of an NO synthase inhibitor

(27).   These findings suggest that endogenous ET-1 and NO participate in the

regulation of arterial distensibility.   In the present study, we showed decreased

plasma ET-1 concentrations and increased plasma NOx concentrations with weight

reduction in obese men.   On the basis of results from past studies along with the

present results, we propose that the increase in central arterial distensibility with

weight loss may contribute to improved endothelial function, as assessed by

decreased ET-1 and increased NO, after weight reduction.

         In conclusion, the present study demonstrated that low-calorie diet-induced

weight reduction increased central arterial distensibility in middle-aged obese men.

The improvements in arterial compliance were associated with a reduction in plasma

ET-1 and an increase in plasma NOx, a stable end product of NO, and consequently,

improved endothelial function.   These results indicate that ET-1 and NO participate

in the mechanism underlying the increase in central arterial distensibility with weight

loss.

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ACKNOWLEDGEMENTS

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FIGURE LEGENDS

Figure 1.   Arterial compliance (A) and β-stiffness index (B) before and after 12 weeks dietary intervention.   Data are expressed as means ± SE.

Figure 2.   Aortic PWV before and after a 12-week dietary intervention.   Data are expressed as means ± SE.

Figure 3.   Plasma endothelin-1 concentrations before and after a 12-week dietary intervention.   Data are expressed as means ± SE.

Figure 4.   Plasma nitrite/nitrate (NOx; the stable end product of nitric oxide) concentrations before and after a 12-week dietary intervention.   Data are expressed as means ± SE.

Figure 1

A

P < 0.01

8.9 ± 1.0

12.1 ± 1.5

Arterial compliance （10^{-2}mm^2/mmHg）

Before   After

B

P < 0.05

12.5 ± 1.4

9.8 ± 0.8

Beta stiffness index

Before   After

Figure 2

Figure 3

P < 0.01

Plasma endothelin-1 level (pg/ml)

2.4

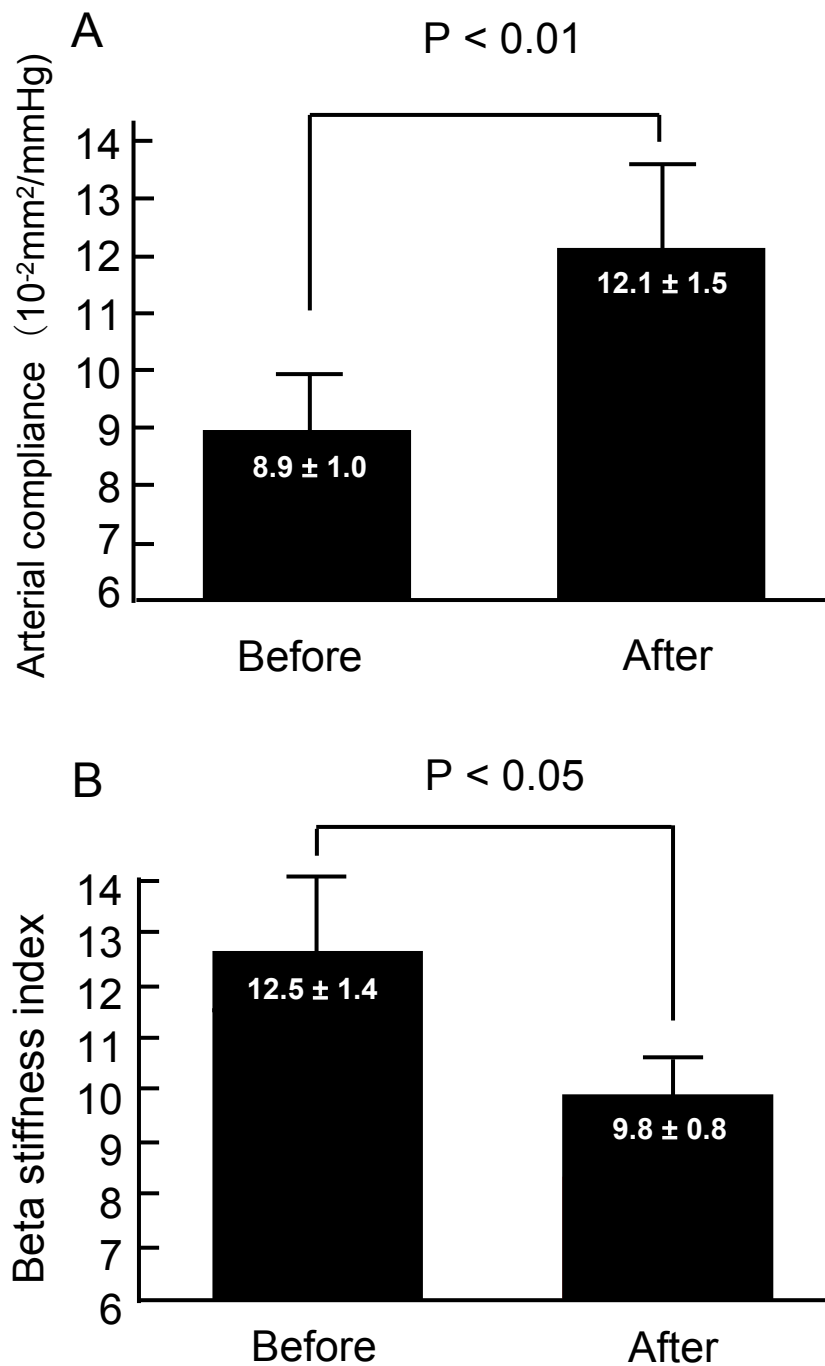2.0 — 1.9 ± 0.1

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1.3 ± 0.1

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0.8 —

Before   After
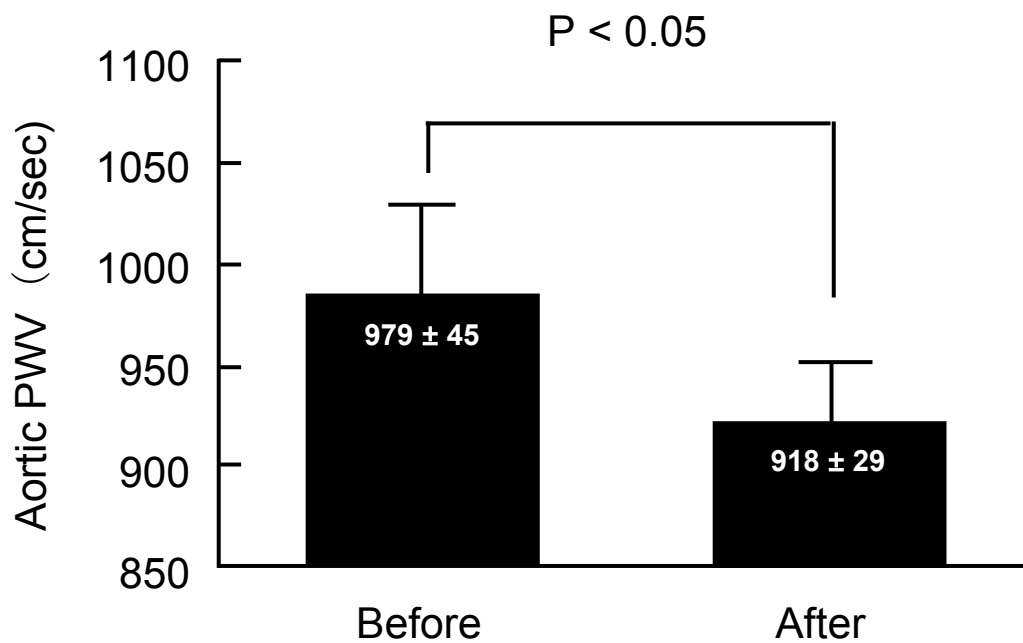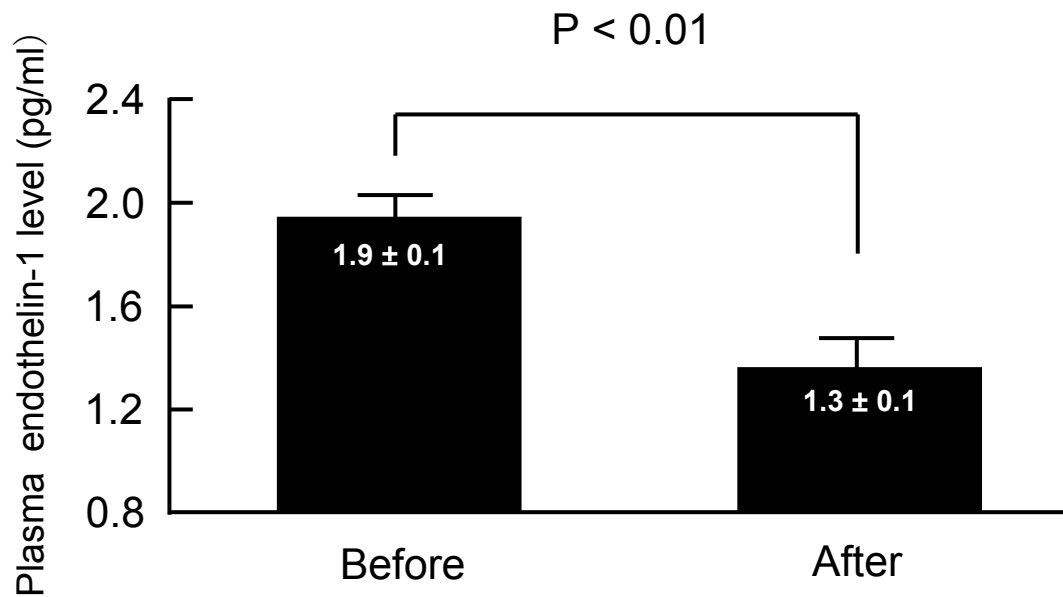
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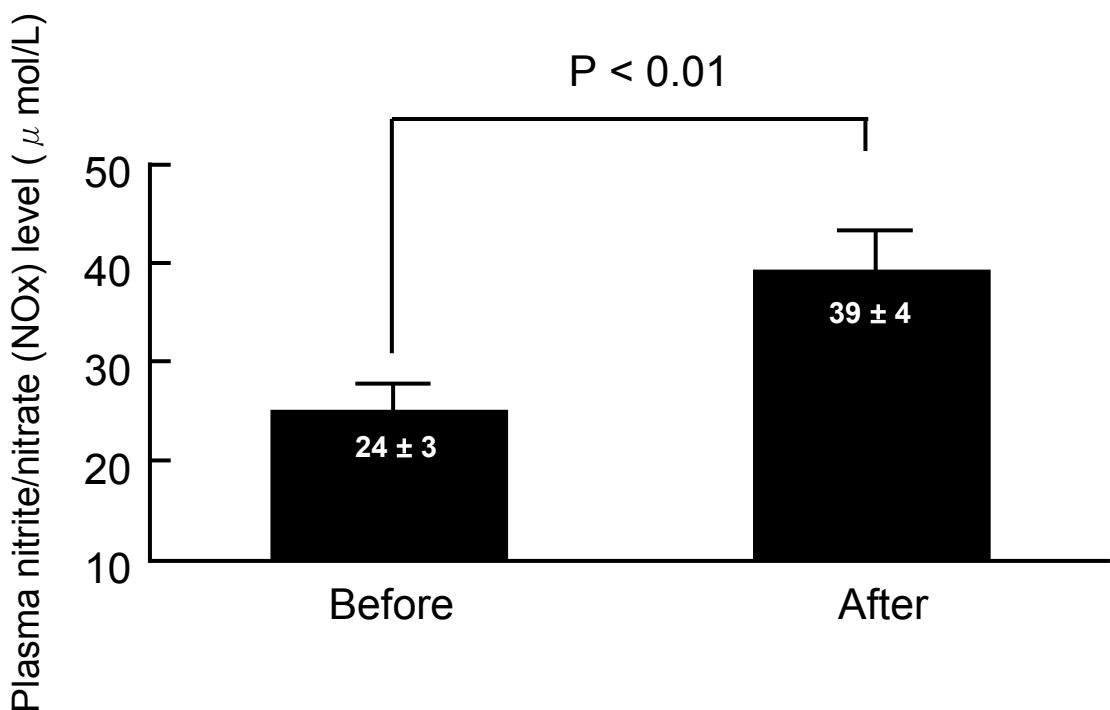52
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Figure 4

Table 1.   Physiological characteristics of obese men before and after the weight reduction program

	Before			After		
Age, years	45	±	2		-	
Height, cm	172	±	2		-	
Weight, kg	88	±	3	80	±	4**
Body mass index, kg/cm^2	30	±	1	27	±	1**
Visceral fat area, cm^2	169	±	9	119	±	10**
Subcutaneous fat area, cm^2	256	±	21	196	±	25**
Total fat area, cm^2	424	±	25	315	±	32**
Total cholesterol, mg/dl	217	±	12	196	±	13*
HDL-cholesterol, mg/dl	56	±	3	57	±	4
LDL-cholesterol, mg/dl	130	±	11	121	±	12
Triglyceride, mg/dl	157	±	24	92	±	11**
Blood glucose, mg/dl	100	±	14	93	±	7*

Data are expressed as means ± SE.   Significant difference vs. before dietary intervention, *P < 0.05; **P < 0.01.

Table 2.   Hemodynamics of obese men before and after weight reduction program

	Before		After	
Systolic blood pressure, mmHg	137 ± 4		123 ± 6**	
Diastolic blood pressure, mmHg	80 ± 3		72 ± 3**	
Mean blood pressure, mmHg	99 ± 3		89 ± 4**	
Pulse pressure, mmHg	57 ± 4		50 ± 4**	
Heart rate, bpm	79 ± 5		63 ± 3**	

Data are expressed as means ± SE.   Significant difference vs. before dietary intervention, **$P < 0.01$.