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Lifestyle modification increases serum testosterone level and decrease central blood pressure in overweight and obese men

Hiroshi Kumagai[1)], Asako Zempo-Miyaki[2)], Toru Yoshikawa[1)], Takehiko Tsujimoto[3)], Kiyoji Tanaka[3)] and Seiji Maeda[3)]

[1)] *Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan*
[2)] *Faculty of Sports and Health Sciences, University of Ryutsu keizai, Ryugasaki, Japan*
[3)] *Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Japan*

Abstract. Obesity has reached global epidemic proportions and is associated with multiple comorbidities, including cardiovascular disease. A novel predictor of cardiovascular disease is elevated central systolic blood pressure. In fact, lifestyle modifications have been shown to decrease the central systolic blood pressure in overweight and obese men. The mechanism underlying these changes has yet to be fully elucidated. Interestingly, testosterone has been found to have cardioprotective effects. Moreover, serum testosterone levels are lower in obese men than in normal weight men. However, it is still unclear whether testosterone participates in the decrease of central blood pressure in overweight and obese men following lifestyle modifications. So, the purpose of the present study was to investigate the effect of testosterone on central systolic blood pressure in overweight and obese men before and after the 12-week lifestyle modification program. Forty-four overweight and obese men completed a 12-week lifestyle modification program (aerobic exercise training and dietary modifications). For all participants, central systolic blood pressure and serum testosterone levels were measured before and after the program. After the program, central systolic blood pressure was significantly decreased while serum total testosterone levels were significantly increased in overweight and obese men. Moreover, we also found a significant negative relationship between the change in serum testosterone levels and that in central systolic blood pressure. The present study suggests that increased serum testosterone levels likely contribute to a decrease in central blood pressure in overweight and obese men.

Key words: Testosterone, Obesity, Central blood pressure, Lifestyle modification

OBESITY is strongly associated with hypertension and is a well known as an independent risk factor for cardiovascular disease [1-3]. Clinically, the brachial blood pressure is widely used to evaluate blood pressure. Recently, it has been reported that central blood pressure may be more relevant for predicting cardiovascular disease than the standard measure of brachial blood pressure [4]. Formerly, an issue with evaluating central blood pressure was the invasive methods (using a catheter), which could not be efficiently applied to daily medical practice. However, a non-invasive method has been recently developed and is capable of estimating the central blood pressure from radial arterial waveforms, has been developed [5, 6]. Previous studies have shown that central blood pressure is higher in obese individuals than in non-obese people [7]. Moreover, lifestyle modification decreases the central blood pressure in overweight and obese men [8]. However, the mechanisms underlying this effect have not yet been fully elucidated.

It has been reported that decreased serum testosterone levels are associated with future incidence of cardiovascular morbidity and mortality [9]. Recently, it has been implied that testosterone has cardioprotective effect [10-12]. Actually, acute intracoronary administration of testosterone, which causes coronary artery dilation and increases coronary blood flow, improved cardiac function in male patients with coronary artery disease [12]. Furthermore, supplementation of chronic and physio-

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Correspondence to: Seiji Maeda, Ph.D., Division of Sports Medicine, Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8574, Japan.
E-mail: maeda@taiiku.tsukuba.ac.jp

logical doses of testosterone have been found to alleviate angina symptoms and ischemic cardiac conditions in male patients [10, 11, 13]. Unfortunately, serum testosterone levels are lower in obese men than in normal weight individuals [14]. We previously found that lifestyle modification increases serum testosterone levels in overweight and obese men [15]. Taken together, low serum testosterone levels may be responsible for elevation of central blood pressure in obese men, which subsequently leads to cardiovascular diseases. However, the precise role of serum testosterone levels in lifestyle modification-induced decreases in central blood pressure is still unknown.

The purpose of the present study was to investigate the effect of testosterone on central blood pressure in overweight and obese men before and after the 12-week lifestyle modification program. We hypothesized that lifestyle modifications increases serum testosterone levels, which in turn participates in decreasing the central blood pressure in overweight and obese men. To examine our hypothesis, before and after the 12-week lifestyle modification program (*i.e.*, combining dietary modification and aerobic exercise training), we measured serum testosterone levels and central blood pressure in overweight and obese men.

Materials and Methods

Participants

Forty-four overweight and obese men (age, 51 ± 2 years; body mass index [BMI], 29 ± 1 kg/m^2) completed the lifestyle modification program. Eighteen participants were taking hypertensive, hypercholesterolemia or hypoglycemic medication and five participants were current smokers. The participants' medication use and smoking habits did not change during the study period. The sample size was estimated on the assumption that the 12-week lifestyle modification could decrease central blood pressure. On the basis of the power of 0.95 and alpha level of 0.01, a sample size of 32 was found to be necessary based on the data of an our previous study [8]. The present study was reviewed and approved by the institutional review board of the University of Tsukuba. All study procedures and potential risks were explained to the participants and they provided written informed consent to participate in the study.

Experimental design

All overweight and obese men were studied before and after the 12-week lifestyle modification program (dietary modification and aerobic exercise training). All of the measurements were taken after abstinence from caffeine and an overnight fast, and none of the participants exercised the day before measurements were taken. Participants were studied under supine resting conditions in a quiet, temperature-controlled room (24–26°C). All measurements were performed after a rest period of at least 20 minutes.

Lifestyle modification

In the present study, the patients underwent a lifestyle modification similar to that used the protocol used in our previous study [15]. Briefly, the dietary modification protocol is a low-calorie diet intervention that affects body composition, body fat distribution, and coronary heart disease risk factors [16, 17]. Based on the diet protocol used in this study, all of the participants were instructed to take meals consisting of an average of 420 kcal of protein, 840 kcal of carbohydrate, and 420 kcal of fat per day (1680 kcal/day). In addition, the participants kept daily food diaries during the 12-week program period of lifestyle modification and learned about proper daily nutrition (well-balanced protein, carbohydrate, fat, amino acids, vitamins, and minerals) through weekly lectures and counseling by skilled dietitians. The participants performed exercise training in the form of walking and jogging for sessions of 40–60 minutes each (3 days/week) as previously described with minor modifications [18]. Briefly, the participants were supervised by 2 or 3 exercise instructors. In the first 2 months, the exercise consisted only of walking, with the target Borg's scale ranging from 11 (light) to 13 (fairly hard). The distances walked were 3.5 and 4.5 km in the first and second months, respectively. In the last month, the participants performed a combination of a 3.0-km brisk walk and a 1.0-km medium-intensity jog with the target Borg's scale ranging from 13 (fairly hard) to 15 (hard). The participants measured their heart rate using portable heart rate monitors (s610i; Polar Electro OY, Oulu, Finland) while walking and jogging and recorded the duration (in minutes) and intensity (heart rate or Borg's scale) during each exercise session. Again, the subjects recorded their actual exercise and additional physical activity in a diary. Finally, the daily steps during the 12-week lifestyle modification program were recorded using a uniaxial electrical accelerometer (Lifecorder; LC, KENZ, Nagoya, Japan).

Anthropometric measurements

Anthropometric measurements were performed before and after the 12-week lifestyle modification program. During each measurement, the Body weight was measured once to the nearest 0.1 kg using a digital scale (WB-150; TANITA, Tokyo, Japan) and the height was measured once to the nearest 0.1 cm using a wall-mounted stadiometer (YG-200; Yagami, Nagoya, Japan) with the subjects in their underwear and barefoot prior to eating in the morning. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was measured directly on the skin at the levels of the umbilicus in the standing position. The waist circumference measurements were taken in duplicate to the nearest 0.1 cm.

Serum testosterone levels and blood biochemistry

We collected blood from each subject before and after the program. Each blood sample was placed in a serum separator tube, clotted for 2 hours and then centrifuged at 3,000 rpm for 15 minutes at 4°C. The serum obtained was stored at –80°C until assay. Total testosterone serum concentration was determined using standard radioimmunoassay procedures [19]. The intra-assay coefficient of variation ranged 4.5–5.7 %. Serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and insulin were determined using standard enzymatic techniques.

Peak oxygen uptake ($\dot{V}O_{2peak}$)

Before and after the 12-week lifestyle modification program, peak oxygen uptake ($\dot{V}O_{2peak}$) was determined during a graded exercise test using a cycling ergometer (828E; Monark, Stockholm, Sweden). After a 2-minute warm-up at 30 Watt (W), the subjects started with a workload of 15 W each minute until they felt exhausted or reached 85% of the age-predicted maximal heart rate. Their individual $\dot{V}O_{2peak}$ was calculated using regression analysis of the slopes of CO_2 production, O_2 uptake, and minute ventilation plots. Pulmonary ventilation and gas exchange were also measured, breath-by-breath, using an online data acquisition system (Oxycon Alpha System; Mijnhardt, Breda, The Netherlands).

Central blood pressure and brachial blood pressure measurement

Arterial pulse waveforms of the left radial artery were measured non-invasively by an automated tonometric system (HEM-9000AI, form PWV/ABI; Omron Healthcare, Kyoto, Japan) with a seated position, as similar to our previous report [8]. The first and second systolic peaks were automatically identified using the fourth derivative wave as the second and third zero crossing points, respectively. Late systolic blood pressure (SBP) in the radial artery was used as an estimate of the central SBP; measurements of the central SBP estimated by the HEM-9000AI are very close to that determined following invasively recorded aortic central SBP [6]. Brachial blood pressure and heart rate were measured simultaneously in the right brachium with an oscillometric device incorporated in HEM-9000AI. Brachial pulse pressure (PP) and mean brachial blood pressure (MBP) was calculated from brachial SBP and diastolic blood pressure (DBP) {PP = SBP – DBP, MBP = [DBP + (SBP – DBP) / 3]}, while central PP was calculated from central SBP and brachial DBP (central PP = central SBP – brachial DBP) as well as previous studies [20]. The day-to-day coefficient of variations for central blood pressure measurement was 4.3 ± 2.9 %.

Statistical analysis

All data are expressed as mean ± SE. To evaluate the differences in the levels before and after the lifestyle modification program, the student's *t*-test for paired values was used. Analysis of covariance was used to determine the effects of smoking and medication. The correlation between the changes in central SBP or those in serum testosterone levels and other factors were analyzed using Pearson's correlation, partial correlation and stepwise multivariable linear regression analysis. The partial correlation coefficients were adjusted for age, smoking, medication and changes in body mass. For stepwise multivariable linear analysis, central SBP were used as dependent variables, whereas changes in body mass and that in serum testosterone levels were used as independent variables. Values of $P < 0.05$ were accepted as significant.

Results

Table 1 shows the characteristics of the overweight and obese men before and after the 12-week lifestyle modification program. We found that the body mass, BMI and waist circumstance markedly decreased and that the concentration of total cholesterol, LDL cho-

Table 1 Characteristics of overweight and obese men before and after the lifestyle modification

	Before	After
Age (years)	51 ± 2	-
Height (cm)	170.6 ± 1.3	-
Body mass (kg)	85.1 ± 2.3	73.6 ± 2.0**
Body mass index (kg/m^2)	29 ± 1	25 ± 1**
Waist circumference (cm)	100 ± 2	88 ± 2**
Total cholesterol (mmol/L)	5.3 ± 0.3	4.6 ± 0.2**
HDL cholesterol (mmol/L)	1.3 ± 0.1	1.4 ± 0.1*
LDL cholesterol (mmol/L	3.2 ± 0.2	2.7 ± 0.2**
Triglycerides (mmol/L)	1.8 ± 0.3	0.9 ± 0.2**
Insulin (μU/mL)	9.1 ± 1.5	4.8 ± 0.9**
$\dot{V}O_{2peak}$ (mL/min/kg)	28.6 ± 1.5	35.1 ± 1.6**
Steps (steps/day)	7615 ± 702	11262 ± 716**
Total energy intake (kcal/day)	2063 ± 118	1456 ± 57**

HDL, high-density lipoprotein; LDL, low-density lipoprotein. Date are expressed as mean ± SE. Significant difference *VS.* before lifestyle modification, ** $P < 0.01$, * $P < 0.05$.

Table 2 Hemodynamics of overweight and obese men before and after lifestyle modification

	Before	After
Brachial systolic blood pressure (mmHg)	134 ± 4	119 ± 3**
Brachial diastolic blood pressure (mmHg)	85 ± 2	75 ± 1**
Brachial mean blood pressure (mmHg)	103 ± 3	91 ± 2**
Brachial pulse pressure (mmHg)	49 ± 2	43 ± 2**
Heart rate (beat/min)	66 ± 2	55 ± 2**

Date are expressed as mean ± SE. Significant difference *VS.* before lifestyle modification, ** $P < 0.01$.

lesterol, triglycerides and insulin also significantly decreased after the 12-week lifestyle modification program compared to values before the program. Furthermore, levels of HDL cholesterol, the $\dot{V}O_{2peak}$ and the number of steps all significantly increased while the total energy intake significantly decreased. Table 2 shows the hemodynamics of the overweight and obese men before and after the lifestyle modification program. Brachial SBP, brachial DBP, brachial MBP, brachial PP and heart rate all significantly decreased after the lifestyle modification program compared to those values before program. Of note, the central SBP was also significantly lower after the 12-week program (from 114 ± 3 to 101 ± 4 mmHg, $P < 0.01$) (Fig. 1). Meanwhile, serum testosterone levels were significantly increased (from 12.3 ± 0.9 to 13.2 ± 1.1 nmol/L, $P < 0.05$) (Fig. 2). The changes in central SBP and serum testosterone levels were similar to our previous studies [8, 15]. In addition, analysis of covariance revealed that smoking and medication did not affect the changes in central SBP and those in serum testosterone levels. Furthermore, we found a significant positive correlation between changes in central SBP and those in body mass ($r = –0.301$, $P < 0.05$), and a significant negative correlation between the changes in serum testosterone levels and those in central SBP ($r = –0.33$, $P < 0.05$) (Fig. 3). There was also significant correlation between the changes in the serum testosterone levels and serum insulin levels ($r = –0.32$, $P < 0.05$). Following normalization by age, smoking, medication and changes in body mass usage partial correlation analysis, the relationships between the changes in serum testosterone levels and central SBP remained significant ($\beta = –0.396$, $P < 0.05$). However, the significant relationship between serum testosterone levels and serum insulin levels disappeared. On stepwise multivariable liner regression analysis, change in central SBP was significantly associated with those in serum testosterone levels ($\beta = –0.332$, $P < 0.05$), but not body mass. After the 12-week lifestyle modification, the central PP was significantly decreased (from 30 ± 2 to 27 ± 2 mmHg, $P < 0.05$). There was significant correlation between the changes in central PP and serum testosterone levels ($r = –0.32$, $P < 0.05$).

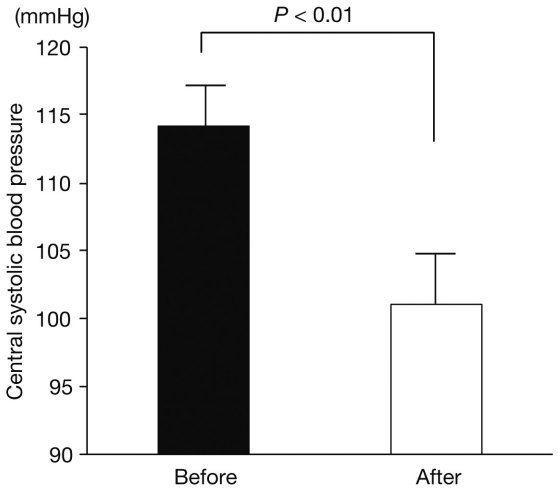

Fig. 1 Central systolic blood pressure before and after the 12-week lifestyle modification. Date are expressed as mean ± SE.

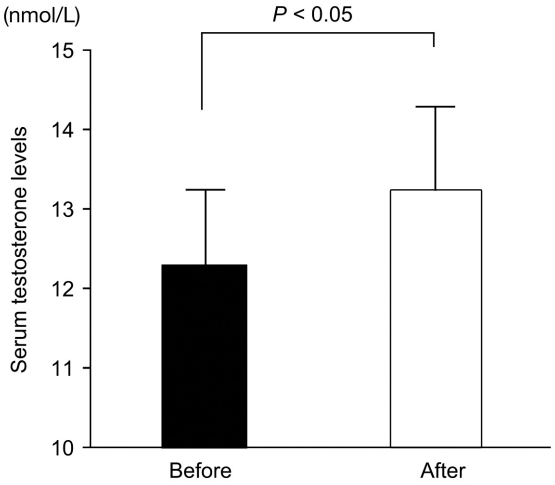

Fig. 2 Serum testosterone levels before and after the 12-week lifestyle modification. Date are expressed as mean ± SE.

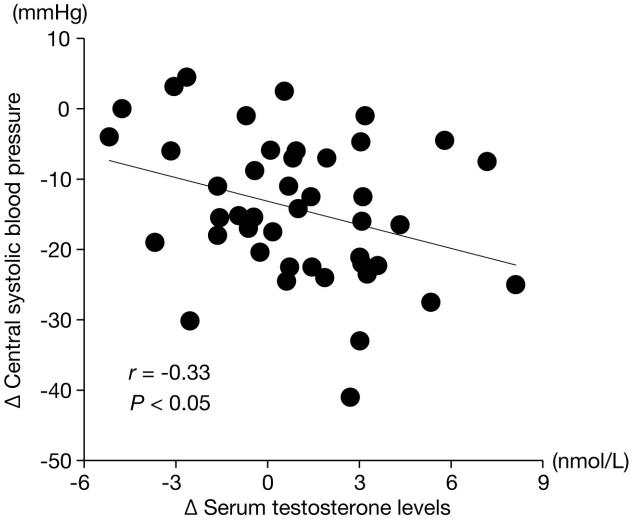

Fig. 3 Relationship between the changes in the central systolic blood pressure and serum testosterone levels.

Discussion

In the present study, we investigated the effect of testosterone on the lifestyle modification-induced decrease in central blood pressure in overweight and obese men following a 12-week lifestyle modification program. Our results revealed that the serum testosterone levels were significantly increased while the central SBP was significantly decreased after the lifestyle modification program concluded. Furthermore, we observed a negative correlation between the change in serum testosterone levels and that in central SBP before and after the 12-week lifestyle modification program in overweight and obese men. These results suggest that the 12-week lifestyle modification program increases serum testosterone levels in overweight and obese men, and the increase in serum testosterone levels leads to decrease central SBP.

It has been reported that several sex hormones (*i.e.*, testosterone, estradiol, and dehydroepiandrosterone; DHEA) have cardio protective effects and some of them have been found a significant association with vascular function [11, 12, 21, 22, 23]. In the previous study, androgen suppressive therapy was found to increases the central SBP pressure in male patients with prostate cancer [24]. Thus, it is possible that the central SBP is affected by serum testosterone levels in men. In the present study, the 12-week lifestyle modification increased the serum levels of testosterone that has vasodilator effect and decreased central SBP. Furthermore, we observed significant negative relationship between the change in serum testosterone levels and that in central SBP. Therefore, it is possible that increased serum testosterone levels induce decrease in central SBP in overweight and obese men. However, we did not measure other sex steroid hormones. Therefore, the relation between central SBP and other sex steroid hormones were remains unclear.

Low levels of serum testosterone are also associated with cardiovascular morbidity and mortality in men [9]. Circulating testosterone levels in obese men is low compared to age-matched normal weight men [14]. We previously reported that lifestyle modifications (dietary

modification and regular exercise) increase serum testosterone levels in overweight and obese men [15]. In addition, previous studies have reported that decreasing levels of serum insulin increase serum testosterone levels [15, 25] and that serum insulin levels decrease after aerobic exercise training and dietary modification in obese people [26, 27]. In the present study, we also demonstrated that the serum insulin levels significantly decreased in overweight and obese men after the lifestyle modification (combination of dietary modification and aerobic exercise training). Moreover, there is a significant correlation between the changes in serum testosterone and serum insulin. On the other hand, in animal studies, it has been suggested that aerobic exercise training significantly increased plasma and muscular sex steroid hormones via increase in steroidogenesis-related enzymes [28, 29]. Therefore, decreases in serum insulin levels and aerobic exercise training may indirectly and/or directly result in an increase in the serum testosterone levels in overweight and obese men.

In this study, we suggested that an increase in testosterone by lifestyle modification contributes to a decrease in central SBP. On the other hand, aerobic exercise training-induced increase in blood flow decreases arterial stiffness (Nichols *et al*. J Cardiovasc Pharmacol Ther. 2001). Furthermore, we previously demonstrated that aerobic exercise training-induced reduction of arterial stiffness decreases cSBP (Higashino *et al*. Blood Press Monit. 2013). Therefore, lowering of cSBP after lifestyle modification in obese men in the present study might have been shown, not only by increased testosterone, but also by increased blood flow after aerobic exercise training.

Recently, Roman *et al*. has reported that central SBP may be more relevant than brachial blood pressure for predicting cardiovascular disease [4]. Moreover, it is clear that the central SBP is higher in obese individuals than in non-obese people [7]. However, weight loss and lifestyle modifications abrogate this increase. In the present study, the 12-week combination of dietary modification and aerobic exercise training also was able to lower the central SBP in overweight and obese men. Alternatively, other studies have reported that lifestyle modifications do not affect the central SBP in obese individuals [30, 31], but the amounts of weight loss in these studies were less (–8.0 kg and –4.4 kg) than that of the present study (–12.7 kg). Furthermore, in these studies, the subjects were categorized as obese even after the intervention, because their average BMI was still over 30 kg/m^2 [30, 31]. In the present study, the body mass markedly decreased and the average value of BMI was approximately 25 kg/m^2 after the 12-week lifestyle modification. Taken together, it is possible that the degree of weight reduction by lifestyle modification affects the changes in central SBP in obese individuals.

In conclusion, the present study demonstrated that the 12-week lifestyle modification program (i.e., combining dietary modification and aerobic exercise training) increased the serum testosterone levels and decreased central SBP in overweight and obese men. Furthermore, we observed that the changes in serum testosterone levels before and after lifestyle modification have a negative relationship with that of central SBP in overweight and obese men. These results suggest that increases in testosterone may participate, at least in partly, in the mechanisms underlying lifestyle modification-induced decreases in central SBP in overweight and obese men.

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Conflict of Interest

The authors report no conflicts of interest with respect to this manuscript.

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