

Testosterone Treatment Improves Insulin Resistance in Japanese Male Metabolic Syndrome

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Abstract

The metabolic syndrome involves a cluster of clinical features including visceral obesity, insulin resistance, hypertension, glucose intolerance, and dyslipidemia. Recent studies have shown that low testosterone levels are significantly associated with metabolic syndrome and type 2 diabetes. We examined the change in insulin resistance after testosterone treatment in five Japanese men with metabolic syndrome and low free testosterone levels (age : 50.2 ± 8.7 yrs, BMI : 30.5 ± 5.0, waist : 97 ± 7 cm ; Mean ± SD). Testosterone supplements were administered by intramuscular injection (250 mg every 2 weeks) for 3 to 6 months. Fasting plasma glucose (FPG), fasting serum insulin (F-IRI), HbA1c, total cholesterol(TCHO), triglyceride(TG), HDL-C, LDL-C, free testosterone, LH, FSH, BMI and waist circumference were measured. We used homeostasis model assessment (HOMA-R) as an index of insulin resistance and investigated the change in insulin resistance after testosterone treatment. Average results before treatment were as follows: BMI 30.5 ± 5.0, waist 97 ± 7 cm, FPG 112 ± 6 mg/dl, F-IRI 25.1 ± 8.5 μIU/ml, HOMA-R 7.0 ± 2.7, HbA1c(NGSP) 5.8 ± 0.3%, TCHO 227 ± 31 mg/dl, TG 185 ± 64 mg/dl, HDL-C 43 ± 9 mg/dl, LDL-C 149 ± 37 mg/dl, free testosterone 5.9 ± 1.0 pg/ml, LH 1.7 ± 0.6 IU/ml, FSH 3.7 ± 0.7 IU/ml. After treatment, F-IRI, HOMA-R, TCHO and LDL-C were significantly decreased to 12.9 ± 3.6 μIU/ml, 3.3 ± 1.1 199 ± 29 mg/dl and 120 ± 31 mg/dl, respectively. Free testosterone was significantly increased to 8.5 ± 0.6 pg/ml. Other parameters were not changed significantly. In conclusion, these results suggest that testosterone treatment improves insulin resistance in Japanese men with metabolic syndrome and low free testosterone levels.

Keywords: Testosterone; Insulin resistance; Metabolic syndrome

Introduction

Levels of testosterone, an androgenic hormone, have long been known to decrease with aging, and a low testosterone level has been said to be related to diabetes mellitus, obesity, cardiovascular diseases, osteoporosis and decreased libido. Low testosterone levels can reportedly predict insulin resistance and the onset of type 2 diabetes mellitus [1-3]. It has also been reported that testosterone and insulin levels correlate negatively in healthy men [4-6] and also that testosterone replacement therapy improves insulin sensitivity [7]. Moreover, a recent report showed a relationship of low testosterone levels with metabolic syndrome.

Insulin resistance is considered to be a strong underlying contributor to metabolic syndrome, which has recently been receiving considerable research attention. The present study assessed changes in insulin resistance after administration of a testosterone preparation in male subjects with metabolic syndrome who had a low free testosterone level.

Methods

Subjects

Five men (mean age [mean ± SD], 50.2 ± 8.7 years; body mass index (BMI), 30.5 ± 5.0; waist circumference, 97 ± 7 cm) with metabolic syndrome who had a low free testosterone level were studied. Free testosterone levels below 8.5 pg/mL were defined as low, according to the Japanese guidelines for treatment of late-onset hypogonadism. Metabolic syndrome was diagnosed based on the diagnostic criteria used in Japan, i.e., having a waist circumference of 85 cm or more for men, and meeting at least 2 of the following 3 criteria: (1) systolic blood pressure of 130 mmHg or higher and/or diastolic blood pressure of 85 mmHg or higher; (2) fasting blood glucose of 110 mg/dL or higher; and (3) blood triglyceride of 150 mg/dL or higher and/or blood high

density lipoprotein (HDL)-cholesterol below 40 mg/dL. Of the 5 subjects, 3 were taking antihypertensive agents and 2 were taking antihyperlipidemic agents. Adequate informed consent to participate in this study was obtained from all 5 subjects.

Methods

A testosterone enanthate (Enarmon Depot Intramuscular Injection 250 mg, every 2 weeks) was administered to the subjects. Before and 3 to 6 months after administration of the testosterone enanthate, BMI, waist circumference, fasting plasma glucose (FPG), fasting plasma immunoreactive insulin (F-IRI), HbA1c, homeostasis model assessment ratio (HOMA-R), total cholesterol (TCHO), triglyceride (TG), HDL-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), free testosterone (Free-Testo), luteinizing hormone(LH), and follicle-stimulating hormone(FSH) were measured and the changes in these parameters were compared. HOMA-R was calculated from FPG and F-IRI values: $HOMA-R = FPG \text{ (mg/dL)} \times F-IRI \text{ (}\mu\text{U/mL)} / 405$. The results are displayed as mean ± SD. Student's *t*-test was employed, and a difference was considered to be statistically significant when the hazard ratio was less than 5%.

Results

The changes in the parameters after versus before administration

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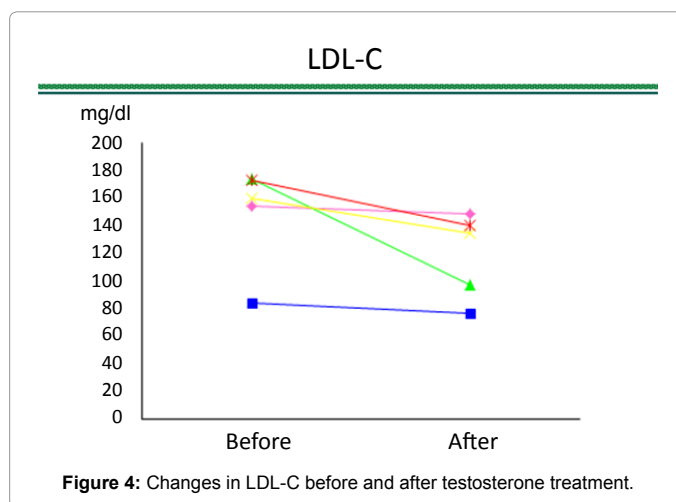
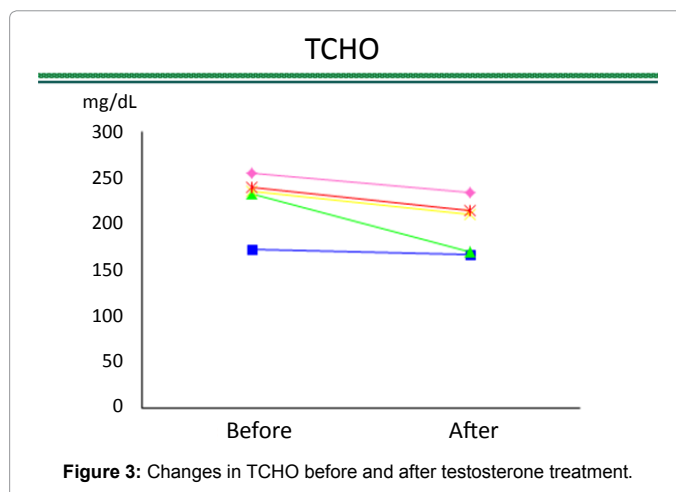
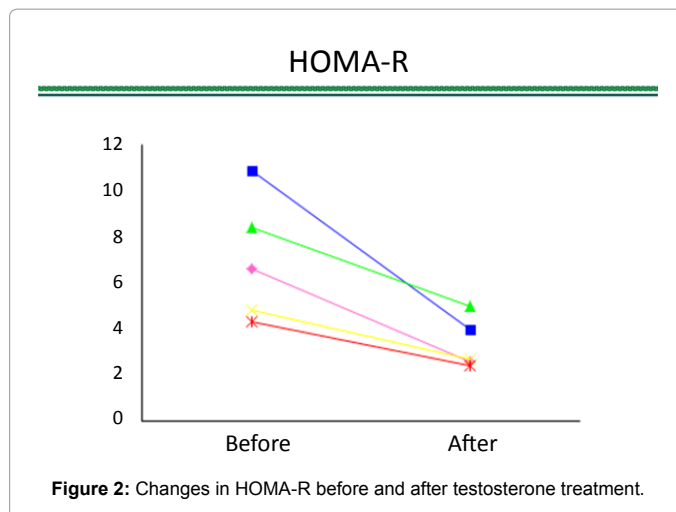
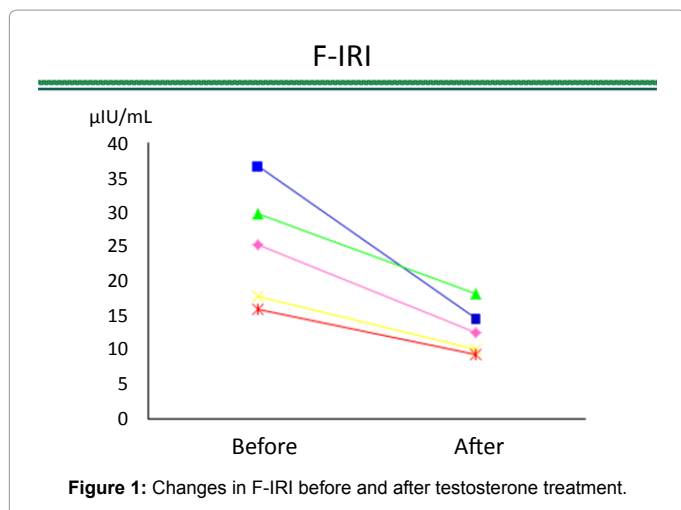
of the testosterone preparation are presented in Table 1. F-IRI decreased significantly from $25.1 \pm 8.5 \mu\text{IU/mL}$ before administration to $12.9 \pm 3.6 \mu\text{IU/mL}$ after administration. HOMA-R also decreased significantly from 7.0 ± 2.7 to 3.3 ± 1.1 . As to the lipid profile, TCHO decreased from $227 \pm 31 \text{ mg/dL}$ before administration to $199 \pm 29 \text{ mg/dL}$ after administration, and LDL-C from $149 \pm 37 \text{ mg/dL}$ to $120 \pm 31 \text{ mg/dL}$, with both decreases being significant. Administration of the testosterone enanthate significantly increased blood free testosterone from $5.9 \pm 1.0 \text{ pg/mL}$ to $8.5 \pm 0.6 \text{ pg/mL}$, and the changes in this parameter were considered to be attributable to the effects of testosterone. Changes in F-IRI, HOMA-R, TCHO, LDL-C, and Free-Testo in individual subjects are presented in Figures 1-5. The parameters related to insulin resistance (F-IRI and HOMA-R) were reduced in all 5 subjects, while those related to the lipid profile (TCHO and LDL-C) decreased markedly in some subjects but only slightly in the others. Thus, inter-patient differences in these parameters were suspected. No significant changes after versus before administration of the testosterone enanthate were observed in the other parameters (BMI, waist circumference, FPG, HbA1c, TG, HDL-C, LH, and FSH).

Discussion

In the present study, administration of a testosterone enanthate to male subjects with metabolic syndrome, who at baseline had a low free testosterone level, resulted in improvement of HOMA-R, an index of

	Before	After	
BMI(kg/m ²)	30.5 ± 5.0	30.8 ± 4.6	
waist (cm)	97 ± 7	95 ± 6	
FPG(mg/dl)	112 ± 6	109 ± 9	
F-IRI(μIU/ml)	25.1 ± 8.5	12.9 ± 3.6	P<0.01
HbA1c(%) (NGSP)	5.8 ± 0.3	5.7 ± 0.4	
HOMA-R	7.0 ± 2.7	3.3 ± 1.1	P<0.01
TCHO(mg/dl)	227 ± 31	199 ± 29	P<0.05
TG(mg/dl)	185 ± 64	188 ± 47	
HDL-C(mg/dl)	43 ± 9	47 ± 12	
LDL-C(mg/dl)	149 ± 37	120 ± 31	P<0.05
Free-Testosterone(pg/ml)	5.9 ± 1.0	8.5 ± 0.6	P<0.05
LH (IU/ml)	1.7 ± 0.6	1.8 ± 0.6	
FSH (IU/ml)	3.7 ± 0.7	3.7 ± 0.6	

Table 1: Changes of clinical parameters before and after testosterone treatment.



insulin resistance, as well as improvements in TCHO and LDL-C levels in some subjects. These results are considered to be important as they raise the possibility that testosterone improves lifestyle-related disease conditions.

Japanese patients with diabetes mellitus reportedly have lower

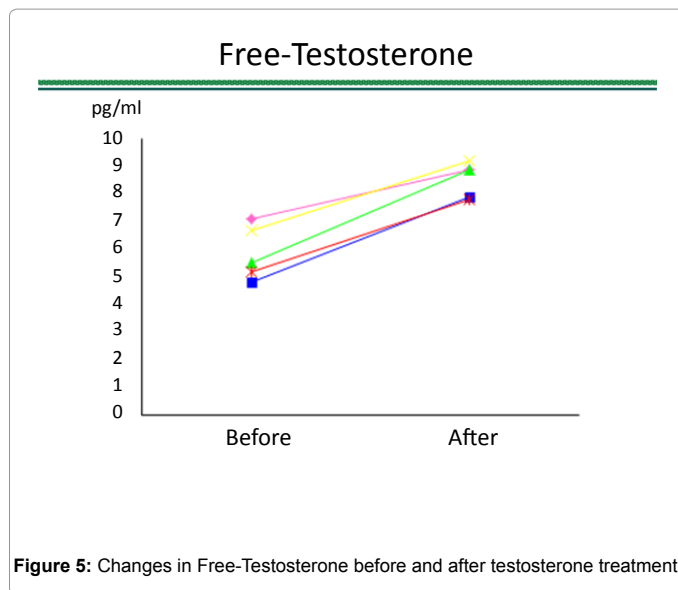


Figure 5: Changes in Free-Testosterone before and after testosterone treatment.

testosterone levels than healthy people of the same age [8]. Diabetes mellitus is associated not only with obesity and increased insulin resistance but also with depression, sleep disorders, cognitive impairment, and sexual dysfunction. Diabetic patients are also a high-risk group for cardiovascular diseases. These symptoms are considered to be attributable, at least partly, to decreased testosterone levels. Diabetic animals were reported to have reduced numbers of Leydig cells in the testes and decreased testosterone secretion [9]. This is hypothesized to be a consequence of microcirculatory dysfunction of the testes due to hyperglycemia. As to humans, it has also been reported that blood testosterone and blood glucose levels were inversely correlated in non-diabetic men [10]. The Endocrine Society of the United States recommends measurement of blood testosterone because decreased testosterone occurs at a high rate in patients with type 2 diabetes mellitus. There is a report describing an investigation of factors determining serum testosterone in male patients with type 2 diabetes mellitus [11]. Testosterone was reported to show a strong inverse correlation with age and a significant positive correlation with total cholesterol. Since sex hormones are produced from cholesterol, caution is required regarding an excessive decrease in cholesterol as this may lead to a decrease in testosterone. Hyperinsulinemia related to obesity is also said to have an effect on Leydig cells, thereby reducing the secretion of testosterone.

Decreases in androgenic hormone levels lead to insulin resistance and promote the onset of lifestyle-related diseases such as diabetes mellitus, dyslipidemia, and hypertension. Hyperglycemia and insulin resistance in turn decrease the secretion of testosterone. To stop this vicious cycle, lifestyle improvements to reduce obesity and hyperinsulinemia/hyperglycemia are important as an initial step. Hormone replacement therapy implemented as necessary is also considered to be useful.

Reduction of visceral fat is speculated to be a possible mechanism by which a testosterone treatment improves insulin resistance in men with metabolic syndrome. However, no significant changes in BMI or waist circumference were observed in this study. The testosterone treatment was administered for 6 months at the most in this study, and administration over a longer period may be required to achieve significant decreases in BMI and waist circumference. This issue is anticipated to be clarified in future studies. In hypogonadal men with type 2 diabetes, there is a report that testosterone replacement therapy improves insulin resistance, glycemic control, visceral adiposity and hypercholesterolemia. In this report, although patients were treated with intramuscular testosterone 200 mg every 2 weeks for 3 months, testosterone treatment resulted in a reduction in visceral adiposity as assessed by waist circumference and waist/hip ratio. For long-term treatment of testosterone, transcutaneous administration of an ointment formulation may prove to yield more favorable compliance than intramuscular injection.

Conclusion

It is suggested that testosterone treatment improves insulin resistance in Japanese men with metabolic syndrome and low free testosterone levels.

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