·*Clinical Experience*·

Testosterone decreases adiponectin levels in female to male transsexuals

Marta Berra[1], Francesca Armillotta[1], Laura D'Emidio[1], Antonietta Costantino[1], Giuseppe Martorana[2], Giuseppe Pelusi[1], Maria Cristina Meriggiola[1]

[1] *Department of Obstetrics and Gynecology,* [2] *Department of Urology, S. Orsola-Malpighi Hospital, University of Bologna, Bologna 40138, Italy*

Abstract

Aim: To evaluate the effect of testosterone (T) on adiponectin serum levels in transsexual female patients. **Methods:** We measured adiponectin, leptin, luteinizing hormone and follicle stimulating hormone, T, estradiol, lipid profile, biochemical parameters and body composition in 16 transsexual female patients at baseline and after 6 months of T treatment (100 mg Testoviron Depot /10 days, i.m.). **Results:** Adiponectin levels were 16.9 ± 7.3 mg/mL at baseline and 13.5 ± 7.4 mg/mL at month 6 of T treatment ($P < 0.05$). Leptin and high-density lipoprotein cholesterol decreased significantly, whereas body mass index, waist circumference and lean body mass increased significantly after 6 months of T treatment. No changes in insulin or Homeostasis Model Assessment were detected. **Conclusion:** T can significantly reduce adiponectin serum levels in transsexual female patients. *(Asian J Androl 2006 Nov; 8: 725–729)*

Keywords: adiponectin; testosterone; transsexualism

1 Introduction

Transsexual patients suffer from gender identity disorder (GID) and seek cross-sex hormone treatment to reduce the characteristics of their own sex and to develop characteristics of the opposite sex to which they feel they belong [1]. Therefore, female patients affected by GID (female to male: FTM) are treated with testosterone (T) to develop male secondary sexual characteristics, such as beard, body hair, increased muscle mass and deeper voice.

Testosterone administration leads to metabolic effects, such as decreased high-density lipoprotein (HDL)-cholesterol, increased central adiposity and changes in the cytokine secretion pattern from the adipose [2–7]. These acquired characteristics are thought to be related to cardiovascular disease and might, therefore, predispose these patients to an increased cardiovascular risk [5].

Adiponectin/ACPR30, a 30-kDa protein member of the TNF-α family, is present only in adipocytes that secrete it into the circulation. Adiponectin is the only known adipocyte-secreted factor that increases tissue sensitivity to insulin [5]. Its level negatively correlates with body mass index (BMI), abdominal fat and insulin resistance and it is thought to be involved in the pathogenesis of metabolic and cardio-

vascular disease [6]. Adiponectin levels are 2–3 times higher in women than in men and the extent of the role played by T in this gender difference has not been defined.

In the present study, we measured serum adiponectin levels in 16 FTM transsexual patients undergoing T treatment. We evaluated changes in adiponectin levels after 6 months of T treatment, in relation to changes in insulin resistance, lipids, body composition and leptin serum levels.

2 Patients and methods

2.1 Patients

Sixteen healthy FTM transsexual patients, with a BMI of 19–30 kg/m^2 but without history of familial hypercholesterolemia or dyslipidemia, were enrolled in the present study. None of the participants have had oophorectomy.

The Ethics Committee of S. Orsola Hospital and the University of Bologna approved the present study.

2.2 Protocol

At baseline and month 6 of T treatment, the 16 healthy FTM transsexual patients underwent overnight fasting blood sampling for measurement of serum adiponectin, leptin, lutenizing hormone (LH), follicle stimulating hormone (FSH), T, estradiol, sex hormone binding globuline (SHBG), total cholesterol, HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, glucose and insulin. Clinical examination was performed, and body weight, body measurement recordings and bioelectrical impedance for body composition measurements were recorded at baseline and after 6 months of hormone administration.

2.3 Drugs

FTM: transsexual patients received 100 mg Testoviron depot (Shering Spa, Milano, Italy) (100 mg testosterone enanthate + 25 mg testosterone propionate) i.m. every 10 days for 6 months.

2.4 Effect variables

The primary effect variable reported in the present study was the change in serum adiponectin levels.

The secondary effect variables were the changes in the adiponectin levels in relation to changes in body composition, leptin, insulin resistance and lipids.

2.5 Measurements

Blood samples for hormone measurements were stored at –20ºC and assayed at the end of the study. Serum samples collected at baseline and month 6 were run in the same assay. Serum levels of LH, FSH and SHBG were measured by highly specific time-resolved fluoroimmunoassays (DELFIA, Wallac, Turku, Finland). T was measured by radioimmunoassay (TKTT5 Diagnostic Products Corp., Los Angeles, CA, USA). The lower limits of quantitation were 0.019 IU/L, 0.016 IU/L, 0.35 nmol/L and 1.56 nmol/L for LH, FSH, T and SHBG, respectively. The mean intra–assay coefficients of variation (CV) were: 10.5% and 5.0% for LH, 8.3% and 2.3% for FSH, 10.0% and 6.6% for T, 3.8% and 2.2% for SHBG in the low and the high parts of the standard curves, respectively. The mean inter–assay CV were 17.5% and 8.7% for LH, 18.5% and 4.6% for FSH, 11.2% and 9.8% for T, 2.7% and 7.8% for SHBG in the low and the high parts of the standard curve, respectively. Estradiol was measured by radioimmunoassay (DSL-39100, Diagnostic System Laboratories, Webster, TX, USA). The lower limit of quantitation was 5.5 pmol/L. The mean intra-assay CV in the low and the high parts of the standard curve were 5.6% and 5.3%, and the mean inter–assay CV were 7.8% and 9.0%, respectively.

Clinical chemistry, such as total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, glucose and insulin, were performed according to previously described methodologies [6].

Leptin levels were measured by radioimmunoassay (Linco Research, Saint Charles, MO, USA). The assay sensitivity was 0.5 ng/mL. Inter–assay CV were 11.4% and 10.0% in the low and the mid-part of the standard curve, respectively.

Adiponectin was measured by radioimmunoassay (Linco Research, Saint Charles, MO, USA). The assay sensitivity was 1.56 µg/mL. Inter-assay CV were 4.3% and 5.2% in the low- and the mid-part of the standard curve, respectively.

Plasma glucose levels were determined by the glucose-oxidase method and insulin was analyzed as previously described. The Homeostasis Model Assessment (HOMA) insulin resistance index was calculated as proposed by Matthews *et al.* [8].

Body weight without shoes was measured to the nearest 0.1 kg, and body height was assessed to the nearest 0.5 cm. The waist and hip circumferences were also measured according to the recommendations of the World

Health Organization [9].

The percentage of fat and fat-free mass were assessed by bioelectrical impedance using a multiple frequency bioimpedance analyzer (Body Fat Analyzer, Model BT-905; Skylark Device & System, Taipei, Taiwan, China). This method of determining body composition has been used in previous studies and is considered reliable when the BMI is higher than 15 [10].

2.6 Statistical analysis

Continuous data were reported as mean ± SD. The non-parametric Wilcoxon Test using the Monte Carlo method for small sample sizes was used to compare the baseline values to the 6-month values in FTM. Pearson correlation was used to study relationships between two continuous data. When there was no normal distribution we performed the Spearman rank correlation test.

3 Results

Baseline and 6-month characteristics of the patients group involved in the present study are reported in Tables 1 and 2. Mean ± SD age was 30.4 ± 5.4 years.

3.1 Hormones

As indicated in Table 1, adiponectin serum levels and leptin serum levels were significantly lower after 6 months of T administration compared to those at baseline ($P < 0.05$ and $P < 0.01$, respectively). There was a significant direct correlation between leptin and adiponectin at both baseline and after 6 months of T therapy (baseline: $R = 0.721$, $P < 0.0005$; month 6: $R = 0.407$, $P < 0.05$). Testosterone serum levels were

increased significantly after 6 months of T administration as compared to those at baseline. There was no significant correlation between adiponectin and T. Sex hormone binding globuline serum levels were significantly decreased after 6 months of T administration as compared to those at baseline ($P < 0.001$). There was no significant correlation between adiponectin and SHBG. Estradiol serum did not differ at baseline and after 6 months of T treatment. LH and FSH serum levels did not show any significant changes after 6 months of T administration as compared to those at baseline.

3.2 Anthropometric parameters

As shown in Table 2, body weight, BMI and waist circumference increased significantly after 6 months of T treatment ($P < 0.001$, $P < 0.001$ and $P < 0.05$, respectively). The change in waist to hip ratio (WHR) was not significant at month 6 of T treatment, but there was a significant inverse correlation between WHR and adiponectin ($R = -0.37$, $P < 0.05$). The decrease in fat mass at 6 months of T treatment was significant only when considered in percentage ($P < 0.05$), but the increase in lean mass was significant both in kilograms and in percentage ($P < 0.001$ and $P < 0.05$, respectively).

3.3 Clinical chemistry

After 6 months of T treatment, total cholesterol, LDL-cholesterol and triglycerides did not change significantly (baseline *vs.* month 6: total cholesterol 4.5 ± 0.8 mmol/L *vs.* 4.7 ± 0.7 mmol/L, $P > 0.05$; LDL-cholesterol 2.5 ± 0.8 mmol/L *vs.* 2.8 ± 0.8 mmol/L, $P > 0.05$; triglycerides 0.6 ± 0.1 mmol/L *vs.* 0.7 ± 0.1 mmol/L, $P > 0.05$). HDL-cholesterol decreased significantly after 6 months

Table 1. Serum hormone levels (mean ± SD) at baseline and month 6 of testosterone treatment. SHBG, sex hormone binding globuline; LH, lutenizing hormone; FSH, follicle stimulating hormone. [b]$P < 0.05$, [c]$P < 0.01$ and [d]$P < 0.001$, respectively, compared with corresponding values at baseline.

	Baseline	Month 6
Adiponectin (pg/mL)	16.9 ± 7.3	13.5 ± 7.6[b]
Leptin (IU/L)	7.8 ± 2.9	5.1 ± 2.7[c]
Total testosterone (nmol/L)	1.3 ± 1.1	22.5 ± 14.4[c]
SHBG (nmol/L)	69.5 ± 28.3	30.8 ± 7.4[d]
LH (IU/L)	10.3 ± 7.8	12.6 ± 9.6
FSH (IU/L)	5.2 ± 4.7	6.0 ± 2.6
Estradiol (pmol/L)	345 ± 132	320 ± 114

Table 2. Serum anthropometric parameters (mean ± SD) at baseline and month 6 of testosterone treatment. BMI, body mass index; WHR, waist to hip ratio. [b]$P < 0.05$, [c]$P < 0.01$ and [d]$P < 0.001$, respectively, compared with corresponding values at baseline.

	Baseline	Month 6
Body weight (kg)	58.2 ± 8.7	60.4 ± 7.2[d]
BMI (IU/L)	21.8 ± 2.9	22.8 ± 2.6[d]
Waist (cm)	77.1 ± 9.4	78.1 ± 17.6[b]
WHR	0.80 ± 0.08	0.81 ± 0.06
Fat mass (kg)	16.5 ± 9.0	14.2 ± 7.2
(%)	27.1 ± 10.7	22.4 ± 9.4[b]
Lean mass (kg)	40.9 ± 5.2	46.9 ± 4.7[c]
(%)	72.3 ± 11.6	77.6 ± 9.4[b]

of T treatment as compared to that at baseline (1.7 ± 0.4 mmol/L *vs.* 1.5 ± 0.4 mmol/L, *P* <0.005). Insulin and HOMA index did not show any significant changes after 6 months of T administration (baseline *vs.* month 6: insulin 6.1 ± 0.7 mU/mL *vs.* 5.48 ± 0.61 mU/mL, *P* > 0.05; HOMA index 1.3 ± 0.5 *vs.* 1.1 ± 0.4, *P* > 0.05).

4 Discussion

In the present study, we found that T administration tended to decrease adiponectin levels in 16 FTM transsexual patients. The increase in body weight, BMI, lean mass and waist circumference accopamied with decrease of fat mass and adiponectin. No change of insulin resistance (as measured by the HOMA index) was recorded. These effects occurred despite the fact that there were no changes in gonadotropins or estradiol levels, suggesting that the changes in adiponectin levels were a direct result of T (or its metabolite, dihydrotestosterone).

The exact relationship between T and adiponectin in humans has yet to be completely defined. Spontaneous or induced hypogonadal men have higher adiponectin levels as compared to normal men and T administration decreases serum adiponectin levels in these patients [6, 11]. In prepubertal boys and girls, adiponectin levels are similar, whereas during the progression of puberty, adiponectin levels decrease in boys as compared to those in girls, parallel to increasing testosterone levels [12]. However, conflicting results regarding the relationship between adiponectin and T have been reported in polycystic ovarian syndrome (PCOS) women as compared to normal controls [13–15]. The lack of accuracy in the measurements of low T levels might be the reason for these inconsistent results [16]. Indeed, the decrease of T levels in women treated with oral contraceptives plus flutamide and metformin was accompanied by a significant increase of adiponectin levels [17]. Our results, although collected in a small number of FTM transsexual patients, confirmed that an inverse relationship between T and adiponectin exists in women, demonstrating that supraphysiological T administration in normal-weight women decreases adiponectin levels. It is possible that high T levels are necessary to decrease adiponectin, whereas only modest T increases, such as those found in some PCOS women, are not sufficient to modify serum adiponectin levels. In the present study, we could not detect any significant correlation between adiponectin and T serum concentration, probably because of the fact

that the blood samples were not drawn at the same time after T injections in the FTM patients.

The mechanism by which T reduces adiponectin is still unclear. In the present study, T administration did not induce significant change in total body fat. The decrease of adiponectin levels in the presence of unchanged fat mass seems to contradict previous cross-sectional studies in which a decrease in adiponectin levels is accompanied by an increase in fat mass [18]. We found a redistribution of body fat from a female phenotype to a male phenotype, as indicated by the increase of waist circumference. In our transsexual female patients the changes in fat distribution might have played a determining role in lowering adiponectin in spite of the fact that the total amount of body fat remained unchanged.

However, other data support the hypothesis that T has a direct suppressive effect on adiponectin secretion and that sex could be more important than body size in determining serum concentrations of this cytokine. A recent study shows that, in rats, T administration selectively reduces the high molecular weight form of adiponectin by preferentially inhibiting its secretion from the fat tissue [19]. This could be a potential mechanism for the sexual dimorphism of adiponectin and explain our findings that adiponectin serum levels dropped significantly after only 6 months of T administration in spite of no significant change in fat mass.

Previous studies suggest that adiponectin plays a major role in the regulation of glucose metabolism [20]. In the present study, in FTM transsexual patients treated with T, we did not find any significant change in insulin resistance as assessed by the HOMA index, despite the decrease in adiponectin. Although the number of patients in the present study was small, these observations resemble those reported in previous studies where an increase in insulin resistance in FTM patients treated with T for 12 months could not be detected [4]. Low adiponectin levels have been reported to be associated with increased insulin resistance in children and adults, regardless of body fat content [20]. Homozygous adiponectin-deficient (*adipo-/-*) mice showed moderate insulin resistance. As previously discussed, the matter of adiponectin levels in normal weight PCOS women with variable degrees of insulin resistance is still controversial [21]. We could hypothesize that the decrease of adiponectin might precede a future decrease in insulin sensitivity. At this point, the role of adiponectin in the regulation on glucose homeostasis in humans has yet to

be clearly defined.

In conclusion, our data suggest that T administration in FTM transsexual patients decreases serum adiponectin levels with a mechanism related neither to changes in body fat nor to insulin sensitivity. These results extend and confirm previous data in men [19], further suggesting a direct suppressive effect of T, which is not related to gender. The mechanism by which T affects adiponectin secretion and the long-term consequences of this effect remain to be defined.

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