0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(9):3470–3475

doi: 10.1210/jc.2007-0746

Long-Term Administration of Testosterone Undecanoate Every 3 Months for Testosterone Supplementation in Female-to-Male Transsexuals

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Context: The most common treatment regimen in female-to-male transsexuals is administration of short-acting testosterone esters im every 2 wk.

Objective: Our objective was to report the effects of administering long-acting testosterone undecanoate every 3 months on hormonal and clinical changes, mortality, morbidity, and safety during the first year of treatment in female-to-male transsexuals.

Design: This was a 1-yr observational study.

Setting: The setting was an outpatient department at a university hospital.

Patients: A total of 35 female-to-male transsexuals completed the first year of observation, whereas two patients discontinued the treatment regimen due to serious hypertension.

Intervention: The intervention was 1-yr im treatment with long-acting testosterone undecanoate every 3 months.

Main Outcome Measures: Gonadotropins, steroid hormones, liver enzymes, lipids, blood and coagulation parameter, body mass index, blood pressure, bone mineral density, and endometrium thickness were measured at the beginning of cross-sex hormone treatment and after 12 months. The mortality, morbidity, adverse effects, and desired clinical changes were recorded.

Results: There was a significant decrease in LH, prolactin, SHBG, high-density lipoprotein levels, and endometrium thickness, and a significant increase in body mass index, systolic and diastolic blood pressure, total testosterone and calculated androgens, triglycerides, hemoglobin, and hematocrit levels. No mortality was observed. Two cases of hypertension were noted. The patients reported a desirable increase in libido and clitoral growth. Acne was observed in five patients (14.3%).

Conclusions: The treatment of female-to-male transsexuals with long-acting testosterone undecanoate may be a feasible and safe option for testosterone augmentation in these subjects. However, monitoring of blood pressure should not be ignored during the treatment, to identify patients liable to develop hypertension. **(*J Clin Endocrinol Metab* 92: 3470–3475, 2007)**

IN TRANSSEXUAL PEOPLE, cross-sex hormone treatment is an important component of medical treatment, specifically to provide relief from the dichotomy between body habitus and gender identity (1). Endocrine treatment is guided by the development of the desired mental changes, and by the onset and maintenance of an acceptable physical state of the opposite sex. In female-to-male transsexuals, the aim is to achieve masculinizing effects until irreversible sex reassignment surgery (SRS) is considered. Subjects should have lived for at least 2 yr in the new sex; this is known as the "real-life test." Standards of care for the medical management of transsexual people have been proposed by the Harry Benjamin International Gender Dysphoria Association (2).

Optimal endocrine treatment is guided by the onset of an acceptable masculine physical state, combined with the lowest risks and side effects of hormone treatment. The goal of treatment in female-to-male transsexuals is to induce virilization, including a male pattern of sexual hair, a male voice and male physical contours, to stop menses, and induce clitoral growth (3, 4).

However, certain adverse effects of sex steroid therapy are real and apparent. Mortality and morbidity associated with the common treatment regimen have been reported in many patients. In particular, water and sodium retention, hypertension, increased erythropoiesis, decreased high-density lipoprotein (HDL), increased low-density lipoprotein (LDL), elevation of liver enzymes, obesity, acne, emotional and psychiatric problems such as increased aggressiveness, fluctuating moods and hypersexuality, sleep apnea, and a risk of osteoporosis and ovarian cancer have been reported (3, 5–11).

Testosterone is the key hormone in female-to-male transsexual endocrine treatment. For masculinizing endocrine treatment in female-to-male transsexual people, the most frequently used drugs are 100–250 mg testosterone esters im twice a week or every 10–14 d (3, 4, 10–15). Oral testosterone

First Published Online June 19, 2007

Abbreviations: Alb, Albumin; BMD, bone mineral density; BMI, body mass index; cBT, calculation of bioavailable testosterone; cFT, calculation of free testosterone; Chol, cholesterol; CV, coefficient of variation; DHEAS, dehydroepiandrosterone sulfate; E, estradiol; GGT, γ-glutamyl transferase; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; Hb, hemoglobin; Hct, hematocrit; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRL, prolactin; SRS, sex reassignment surgery; TG, triglyceride; TT, total testosterone.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

may not adequately suppress menstruation without the addition of a progestin (7, 16). The more recently developed transdermal patches provide better pharmacokinetics but frequently cause skin irritations (17). The appropriate dose of testosterone may vary from patient to patient. Dosing every 2 wk is recommended to maintain a blood level within the physiological range close to mid-male values near 17 nmol/liter (3). Injections for longer periods are not recommended, in view of the marked decline in testosterone levels noted after 2- to 3-wk injection intervals using short-acting testosterone preparations (18, 19).

We administered testosterone undecanoate, a long-acting depot preparation for testosterone treatment, in 35 female-to-male transsexuals for cross-sex hormone treatment. The advantage of this formulation is that injections are necessary only for longer periods of approximately 3 months, so that administration intervals are drastically prolonged in comparison with conventional im testosterone preparations. Testosterone undecanoate has recently become available in Europe, and initial clinical experience has been reported with the treatment of sexual or erectile dysfunction in hypogonadal patients with clinical symptoms of androgen deficiency (20–22).

The present study reports our experience with the administration of testosterone undecanoate every 3 months for endocrine treatment in 35 female-to-male transsexuals. The effects on hormonal and clinical changes, mortality, morbidity, and safety during the first year of treatment are reported.

Patients and Methods

Patients and sex hormone treatment

The study population consisted of 37 healthy, middle-aged, female-to-male transsexual people. After confirmation of the diagnosis of "transsexuality" by a psychologist, they wished to start cross-sex hormone treatment until reassignment surgery. The study was approved by the Ethics Committee of the Department of Medicine at Erlangen University Hospital, and informed consent was obtained from all patients. All participants were interviewed regarding their medical history, which had to be uneventful. None of them was suffering from thrombosis or other vascular diseases. They all underwent a screening panel, including complete blood count and serum chemistry profile, and any patients with significant abnormalities in any of these parameters were excluded. At the beginning of the study, all patients were eugonadal relative to clinical and biochemical criteria, and vaginal ultrasound revealed no pathology in the ovaries or endometrium. Systolic and diastolic blood pressure, current exercise, smoking, and alcohol consumption were recorded. All patients continued their normal diet throughout the study period.

In our department, endocrine treatment involves approximately 24 months of cross-sex hormone treatment, forming part of the "real-life test," until SRS (23–25). The study population was treated with injections of testosterone undecanoate 1000 mg (Nebido; Jenapharm, Jena, Germany) im every 12 wk. The patients were seen every 3 months in the outpatient department until SRS and were monitored over a 12-month period. Any other necessary medical intervention was recorded and documented. Vaginal ultrasound was performed to identify any ovarian pathology at the end of the study period. Clitoral growth was also measured at the end of the study period. Blood was sampled regularly in the morning before 1000 h to measure serum LH, FSH, total testosterone (TT), estradiol (E), prolactin (PRL), dehydroepiandrosterone sulfate (DHEAS), and SHBG levels at the beginning of cross-sex hormone treatment and after 12 months. In addition, after the initial 2 and 12 wk, LH, FSH, and TT were measured in 10 female-to-male transsexuals. All blood samples were assayed for hormone parameters immediately in a routine laboratory test. In addition, hemoglobin (Hb), hematocrit (Hct), coagulation parameters, albumin (Alb), fibrinogen, and liver enzymes [glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), γ-glutamyl transferase (GGT), LDL, HDL, cholesterol (Chol), and triglycerides (TGs)] were regularly measured using routine clinical chemistry methods.

Biochemical measurements

All assays were performed in our routine diagnostic endocrinology laboratory using established commercial assays routinely monitored by participation in external quality control programs.

TT was measured quantitatively using a solid-phase competitive chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA). The calibration range of the assay was 0.69–55.47 nmol/liter, with an analytical sensitivity of 0.52 nmol/liter. The intraassay coefficients of variation (CVs) were 11.7, 10, and 8.3% at the levels of 2.98, 5.27, and 9.71 nmol/liter, respectively. The corresponding interassay CVs were 13, 10.3, and 9.1%. The cross-reaction with 5-α-dihydrotestosterone was 2%.

E was measured using a solid-phase competitive chemiluminescent enzyme immunoassay (Immulite 2000). The calibration range of the assay was 73–7342 pmol/liter, with an analytical sensitivity of 55 pmol/liter. The intraassay CVs were 9.9, 7.8, and 4.3% at the levels of 327, 660, and 1692 pmol/liter, respectively. The corresponding interassay CVs were 16, 11, and 6.7%. The cross-reactivity with 17-β E valerate was 1.14%.

PRL was measured using an immunometric assay (Immulite 2000). The calibration range of the assay was up to 3180 mIU/liter, with an analytical sensitivity of 3.4 mIU/liter. The intraassay CVs were 2.8, 3.6, and 2.3% at the levels of 186.6, 402.6, and 466.6 mIU/liter, respectively. The corresponding interassay CVs were 8.2, 7.4, and 5.9%. No cross-reactivity with other compounds is known.

DHEAS was measured using a solid-phase competitive chemiluminescent enzyme immunoassay (Immulite 2000). The calibration range of the assay was 0.41–27 μmol/liter, with an analytical sensitivity of 0.08 μmol/liter. The intraassay CVs were 8, 6.5, and 6.3% at the levels of 4.42, 5.81, and 14.14 μmol/liter, respectively. The corresponding interassay CVs were 9.8, 9.3, and 8.8%. No cross-reactivity with other compounds is known.

LH was measured with an immunometric assay (Immulite 2000). The calibration range of the assay was up to 200 mIU/ml, with an analytical sensitivity of 0.05 mIU/ml. The intraassay CVs were 3.04, 3.71, and 3.6% at the levels of 1.04, 1.89, and 8.7 mIU/ml, respectively. The corresponding interassay CVs were 6.6, 6.2, and 6.7%. The cross-reactivity with human chorionic gonadotropin was 0.20%.

FSH was measured with an immunometric assay (Immulite 2000). The calibration range of the assay was up to 170 mIU/ml, with an analytical sensitivity of 0.1 mIU/ml. The intraassay CVs were 2.5, 2.9, and 2.1% at the levels of 4, 9.1, and 40 mIU/ml, respectively. The corresponding interassay CVs were 6.3, 5.5, and 4.3%. The cross-reactivity with thyroid-stimulating hormone was 0.01%.

SHBG was quantitated with an immunometric assay (Immulite 2000). The calibration range of the assay was up to 180 nmol/liter, with an analytical sensitivity of 0.02 nmol/liter. The intraassay CVs were 2.5, 2.5, and 5.3% at the levels of 1.2, 21, and 80 nmol/liter, respectively. The corresponding interassay CVs were 4.2, 5.2, and 6.6%. No cross-reactivity with other compounds was known.

Hb, Hct, GOT, GPT, GGT, TG, Chol, LDL, HDL, Alb, coagulation parameters, and fibrinogen were regularly measured using routine clinical chemistry methods and documented.

Calculation of free testosterone (cFT) and bioavailable testosterone (cBT)

cFT and cBT were performed using the formula available on the web site of the International Society for the Study of the Aging Male (http://www.issam.ch/freetesto.htm) from TT, SHBG, and Alb values measured in the same sample from each individual. This method is described in detail by Vermeulen *et al.* (26).

Bone mass measurements

Bone mineral densities (BMDs) in the lumbar spine and at the femoral neck were measured using dual-energy x-ray absorptiometry with a

Prodigy densitometer and an Encore software platform (General Electric Medical Systems, Solingen, Germany). The scan areas of the lumbar spine (L2–L4) and femoral neck were used in the calculations.

Statistics

Changes in the serum levels of TT, cFT, cBT, E, PRL, LH, FSH, and SHBG, Alb, liver enzymes, Hb, Hct, LDL, HDL, Chol, and TG, body mass index (BMI), endometrium thickness, blood pressure, coagulation parameters, fibrinogen, and the BMD in the femoral neck and lumbar spine after 12 months of intervention were compared with baseline levels using a paired *t* test. LH, FSH, TT, cFT, and cBT levels after 2 and 12 wk were compared with baseline levels using repeated-measures ANOVA. The population (n = 35) was strictly treated, and the parameters were analyzed according to the protocol. Values are reported as means plus or minus SD. All calculations were performed using the Statistical Program for the Social Sciences (SPSS, version 13.0 for Windows; SPSS, Inc., Chicago, IL). *P* values < 0.05 were considered statistically significant.

Results

Adverse and desired clinical effects

In general, there was a significant increase in systolic and diastolic blood pressure during the study period. However, this change was clinically relevant only in two female-to-male transsexuals, who discontinued the testosterone administration because they developed hypertension after their first injection, although they had shown no hypertension at baseline. They were not included in the further analysis of other parameters. Both had TT levels higher than 40 nmol/liter in the first weeks after im administration of testosterone undecanoate. The hypertension disappeared after discontinuation of testosterone treatment in both patients. No other side effects were reported during the study period. There were 13 patients who were smokers, whereas two discontinued smoking during the observation period. After starting the testosterone administration, all patients reported one last vaginal bleed, and menstruation ceased completely thereafter. The female-to-male transsexuals reported a considerable increase in their libido during the study period, and the patients were satisfied partly with their clitoral growth, which was considerable and reached a mean length of 4.0 ± 0.7 cm at the end of the study period. No ovarian pathology was noted using vaginal ultrasound at the end of the study. No noticeable endometrial pathology was observed during vaginal ultrasound examinations, and the endometrial thickness was reduced significantly after testosterone undecanoate treatment. Troublesome acne was observed in five patients (14.3%). The treatment regimen resulted in various levels of deepened voice and an increase in body hair growth, and induced beard hair growth, so that shaving became necessary in 27 of the patients (77.1%). Most patients reported a decline in breast size. However, all of them wished to undergo mastectomy as part of SRS after the real-life test. No evidence of aggression or hostility or sleep apnea was noted in the population studied.

Hormone parameters

All values for the 35 patients are reported in Table 1. After the start of cross-sex hormone treatment, the hormonal status

TABLE 1. Values for the study population at baseline and after 12 months of intervention (n = 35)

	Baseline	12 months	*P* value
Age (yr)	29.63 ± 8.95	30.57 ± 8.83	<0.0001
BMI (kg/m^2)	23.94 ± 4.86	24.29 ± 4.64	0.03
FSH (IU/liter)	6.78 ± 5.75	4.64 ± 6.38	0.14
LH (IU/liter)	9.89 ± 14.43	3.90 ± 4.72	0.02
TT (nmol/liter)	1.65 ± 0.83	27.54 ± 15.32	<0.0001
cFT (nmol/liter)	0.03 ± 0.04	0.80 ± 0.52	<0.0001
cBT (nmol/liter)	0.47 ± 0.09	18.65 ± 12.14	<0.0001
E (pmol/liter)	195.93 ± 171.67	133.10 ± 67.90	0.06
PRL (mIU/liter)	273.36 ± 131.49	213.45 ± 118.23	0.02
DHEAS (μmol/liter)	6.44 ± 2.91	5.83 ± 2.60	0.17
SHBG (nmol/liter)	46.70 ± 22.32	22.88 ± 9.08	<0.0001
Alb (g/liter)	46.15 ± 2.44	46.35 ± 2.98	0.75
TG (mg/dl)	122.14 ± 54.67	152.43 ± 51.24	0.02
Chol (mg/dl)	187.26 ± 45.65	191.00 ± 42.09	0.53
HDL (mg/dl)	59.00 ± 10.88	48.29 ± 9.77	<0.0001
LDL (mg/dl)	126.60 ± 35.27	133.49 ± 36.87	0.22
Hb (g/dl)	13.17 ± 1.35	14.83 ± 1.15	<0.0001
Hct (%)	41.50 ± 3.33	46.25 ± 3.35	<0.0001
GOT (U/liter)	18.89 ± 6.30	21.71 ± 6.77	0.05
GPT (U/liter)	20.34 ± 9.92	24.49 ± 9.37	0.05
GGT (U/liter)	15.83 ± 11.05	20.71 ± 12.22	0.05
Endometrium thickness (mm)	9.9 ± 4.2	5.7 ± 1.4	<0.0001
Systolic blood pressure (mm Hg)	129.43 ± 13.38	133.71 ± 11.33	0.04
Diastolic blood pressure (mm Hg)	81.14 ± 8.14	84.00 ± 5.25	0.02
Femoral neck BMD (g/cm^2)	1.05 ± 0.10	1.08 ± 0.17	0.31
T score	0.43 ± 0.86	0.46 ± 0.72	0.05
Lumbar spine BMD (g/cm^2)	1.25 ± 0.13	1.25 ± 0.12	0.55
T score	0.41 ± 1.13	0.14 ± 1.05	0.86

Data are shown as means ± SD. *P* values < 0.05 were considered statistically significant. Normal ranges for adult women (for hormones early follicular phase of the menstrual cycle) were: Alb, 35–55 g/liter; Chol, <200 mg/dl; E, <73 pmol/liter; FSH, 3–15 IU/liter; GGT, <38 U/liter; GOT, <31 U/liter; GPT, <34 U/liter; Hb, 12–16 g/dl; Hct, 38–48%; LH, 1–11 IU/liter; PRL, 40–530 mIU/liter; SHBG, 18–110 nmol/liter; TG, <200 mg/dl; TT, 0.7–2.25 nmol/liter; and DHEAS, 0.94–7.59 μmol/liter. Normal ranges for adult men were: Alb, 35–55 g/liter; Chol, <200 mg/dl; E, <145 pmol/liter; FSH, 1–11 IU/liter; GGT, <38 U/liter; GOT, <31 U/liter; GPT, <34 U/liter; Hb, 12–16g/dl; Hct, 40–53%; LH, 0.8–8 IU/liter; PRL, 55–350 mIU/liter; SHBG, 13–71 nmol/liter; TG, <200 mg/dl; TT, 9–55 nmol/liter; and DHEAS, 2.17–14.82 μmol/liter.

was checked for the first time after 2 wk and then after 12 wk in 10 patients (Table 2). There was a significant decrease in the levels of serum LH and FSH after 2 wk, whereas LH was also significantly reduced after 12 wk. The augmentation of TT, cFT, and cBT was significant at all times. In the whole study population, there was no increase in gonadotropin levels after 12 months. SHBG decreased significantly, whereas the decrease in E levels was not significant. PRL levels were significantly decreased, whereas DHEAS levels were not influenced by cross-sex hormone treatment.

Liver enzymes, lipids, Hb, Hct, and coagulation parameters

No clinically significant changes in liver enzymes, Alb, or Chol were noted during the cross-sex hormone treatment. However, there was a trend toward an increase of all three liver enzymes. No changes were observed in Alb levels. TGs increased significantly. HDL was significantly decreased, whereas LDL was not influenced. Hb and Hct also increased significantly. No changes were observed in coagulation parameters or fibrinogen in the 28 patients for whom these results were available (Table 3).

BMI and BMD

The BMI increased slightly but significantly during the intervention period; the initial BMI was 23.94 kg/m^2 (SD 4.86), in comparison with 24.29 kg/m^2 (SD 4.64) after 12 months. As shown in Table 1, there was an increase in femoral neck BMD, but the change was not significant. BMD in the lumbar spine was unchanged after 12 months of cross-sex hormone treatment.

Discussion

To our knowledge, this is the first study that reports experience with the endocrine treatment of 35 female-to-male transsexuals receiving injections of testosterone undecanoate every 3 months. Use of this treatment regimen in transsexual people has never previously been reported, although this testosterone preparation has been used successfully for long-term treatment of men with hypogonadism (27–29).

Various treatment regimens are available for endocrine intervention in female-to-male transsexuals, using short-acting testosterone esters with application intervals between twice a week and every 2 wk. In men with hypogonadism, as well as in female-to-male transsexuals, these treatment regimens often result in supraphysiological serum testosterone levels (28, 30).

The use of testosterone undecanoate injection intervals of more than 6 wk has been described (27). These long intervals make this formulation attractive for im testosterone supplementation, particularly in healthy female-to-male transsexuals, because im testosterone is the most frequently used application (3, 4). In general, the treatment was well tolerated, with only a low rate of reversible adverse effects.

The only adverse effects noted were hypertension in two individuals after their first injections; the hypertension was reversible after discontinuation of treatment. It is known that injectable testosterone produces supraphysiological serum levels of TT during the initial days after injection, and hypertension is reported as a typical side effect of testosterone supplementation in female-to-male transsexuals (3, 4, 29). Therefore, screening for hypertension in female-to-male transsexuals should be recommended before treatment with testosterone preparations is started, particularly when long-acting testosterone preparations are chosen. Alternatively, one might consider starting testosterone treatment using a short-acting preparation. In contrast to the findings reported by Futterweit and Deligdisch (31), no noticeable endometrial pathology (*e.g.* endometrial hyperplasia) was observed in the present study with the treatment regimen described.

There are a number of serious problems involved in the measurement of testosterone in plasma or serum. A platform-based direct immunoassay for measuring testosterone levels has limitations, especially in women with lower testosterone ranges, although it is almost adequate for diagnosing hypogonadism in men, who normally have higher testosterone ranges (32). Despite these limitations, the use of a platform-based direct immunoassay for measuring testosterone may be acceptable in this study to compare testosterone values before and during the intervention. In addition, it makes it possible to calculate free testosterone from TT and SHBG in the same sample, which is an advantage when time-consuming and complex manual reference measurement procedures are not practicable (26, 32–34).

In this study we observed supraphysiological levels of TT only after the first 2 wk, whereas the TT levels after 12 wk and after 12 months were lower and closer to the physiological ranges in eugonadal men. This contrasts to some extent with the values reported by von Eckardstein and Nieschlag (28) and Schubert *et al.* (29), which were lower after 1-wk testosterone undecanoate administration in hypogonadal men. However, the patients in the present study were younger and had a lower mean BMI, at 24 kg/m^2, in comparison with 28 kg/m^2 reported by other authors. In addition, the patients in the present study were biological women and might have had differences in testosterone clearance in comparison with biological men. Elbers *et al.* (30) also described a significant increase in BMI in female-to-male transsexuals treated with short-acting testosterone esters (7). These findings are in similar ranges to the results described here.

As a result of the high TT levels, there was sufficient

TABLE 2. Values at baseline, and 2 and 12 wk after the initial administration of testosterone undecanoate (n = 10)

	Baseline	2 wk	12 wk	*P* value
FSH (IU/liter)	6.55 ± 3.04	2.82 ± 0.90	4.35 ± 1.23	<0.001
LH (IU/liter)	7.46 ± 3.85	3.77 ± 1.76	4.59 ± 1.55	0.009
TT (nmol/liter)	1.83 ± 1.12	36.34 ± 6.95	21.86 ± 6.34	<0.0001
cFT (nmol/liter)	0.03 ± 0.02	1.13 ± 0.25	0.65 ± 0.25	<0.0001
cBT(nmol/liter)	0.76 ± 0.52	26.41 ± 5.91	15.30 ± 5.86	<0.0001

Data are shown as means ± SD. *P* values < 0.05 were considered statistically significant.

TABLE 3. Coagulation analysis and fibrinogen measurements available in 28 patients

	Baseline	12 months	*P* value
PT (INR)	1.01 ± 0.03	1.02 ± 0.03	0.11
apTT (sec)	31.56 ± 3.10	31.46 ± 3.43	0.85
Thrombin time (sec)	10.91 ± 0.72	11.08 ± 0.55	0.25
Fibrinogen (g/liter)	2.71 ± 0.27	2.74 ± 0.36	0.83

Data are shown as means ± SD. *P* values < 0.05 were considered statistically significant. Normal ranges were: apTT, 26–38 sec; thrombin time, 8–13 sec; and fibrinogen, 1.7–4.1 g/liter. apTT, Activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

suppression of both gonadotropins, whereas LH in particular was significantly reduced over the entire study period. LH has been an adequate marker of hormone substitution and osteoporosis risk in transsexual patients (35).

In contrast to Turner *et al*. (36), who described an increase in BMD during testosterone treatment in transsexual patients over a 2-yr period, it was found in the present study that there was no significant increase but rather maintenance of the BMD in the femoral neck and lumbar spine (L2–L4) over a period of 12 months. van Kesteren *et al*. (37) also reported no increase in BMD occurring in female-to-male transsexuals treated with testosterone. Generally, transsexual patients do not have a higher risk of osteoporosis when there is adequate cross-sex hormone supplementation (10, 23, 35, 38).

Transient elevations of liver enzymes have been reported not only in male-to-female transsexuals, but also in female-to-male transsexuals (3, 8, 10). No clinically important changes were observed in the group of patients studied here, although a trend toward an increase in liver enzyme levels was noted. A significant decline in SHBG and HDL levels and a steady state for TGs and total Chol levels during testosterone supplementation were reported by Elbers *et al*. (30) in conventionally treated female-to-male transsexuals. Together with the increase in Hb and Hct as a result of testosterone-stimulated erythropoiesis, reported previously by other authors, these changes in lipid status may be associated with increased risk factors for cardiovascular events in testosterone-augmented transsexuals. However, no changes in the morbidity and mortality rates have been observed to date (3, 7, 8, 39). These changes in lipids and SHBG were also seen in the present study population.

The clinical changes, with increased libido, induction of clitoral growth, development of acne, deepening of the voice, increased body hair, and beard hair growth, were similar to those reported by other authors describing treatment regimens with conventional short-acting testosterone esters (3, 4, 7, 8, 10, 40). No further menstrual bleeding was recorded during the study period.

The observable increase in BMI might be due to fluid retention, or an increase in lean body mass or fat mass. This should be evaluated by body composition measurements in further studies. However, Berra *et al*. (12) reported that there was a trend toward a decrease in fat mass, whereas the lean body mass increased significantly in female-to-male transsexuals conventionally treated with short-acting testosterone esters.

No cases of ovarian pathology were detected; however, a few cases of ovarian carcinoma have been reported among transsexuals receiving long-term testosterone treatment (4, 11). It might be considered that bilateral ovariectomy could prevent the development of ovarian malignancies. However, in a study by van Kesteren *et al*. (35), a significant decrease in BMD associated with an increase in LH levels was reported in biological females who underwent bilateral ovariectomy and were continuously treated with testosterone. It was postulated that the testosterone dose was not sufficient to preserve bone mass and that the measurement of LH is better than testosterone itself for monitoring adequate testosterone replacement. Further examinations and long-term studies are required to determine the safety of the treatment regimen described here, and to evaluate the risks for developing thrombosis, embolism, and stroke, cardiovascular disturbances, and disturbances of liver function and glucose use during treatment with long-acting testosterone preparations. The advantage of the long-acting testosterone preparation is that injections are only necessary every 3 months. However, the long-acting nature of the preparations might be a disadvantage if patients develop possible side effects.

In summary, we would propose that treatment of female-to-male transsexuals with long-acting testosterone undecanoate may be a feasible and safe option for testosterone augmentation in these subjects. The treatment regimen described caused desired clinical changes comparable with those in treatment regimens using short-acting testosterone ester, with no further increase in adverse effects. However, monitoring of blood pressure should not be ignored during the treatment, to identify patients with a tendency to develop hypertension.

Acknowledgments

Received April 2, 2007. Accepted June 12, 2007.

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Disclosure Statement: The authors have nothing to disclose.

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