REVIEW

Review of Studies of Androgen Treatment of Female-to-Male Transsexuals: Effects and Risks of Administration of Androgens to Females

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ABSTRACT

Introduction. Testosterone supplementation in ovariectomized or elderly women may improve their sense of well-being and libido, muscle mass and strength, and bone mineral density. Naturally, androgens may have virilizing effects in women. It is often believed that androgens have deleterious effects on cardiovascular risks.
Aim. To obtain an inventory of the effects of administration of testosterone on female biological functions.
Methods. We reviewed here our publications on the effects of high-dose androgen administration to female-to-male transsexuals treated between 1975 and 2004 (N = 712). Annual accrual was at a steady rate of 22–30 persons. Dosages administered were far above those suited for women.
Main Outcome Measures. There was special focus on the potential negative effects on cardiovascular risk markers.
Results. The standard treatment was administration of testosterone esters, 250 mg/2–3 weeks, parenterally). With this dose, virilizing effects on the skin and clitoris were prominent. Spatial ability improved, while verbal fluency deteriorated. The ovaries developed polycystic characteristics. Adequate dosages of testosterone preserved bone mass in females. Androgens increased kallikreins, such as prostate-specific antigen, in female reproductive tissues. High-dose testosterone administration appeared to increase weight, visceral fat, and hematocrit, decrease high-density lipoprotein cholesterol, increase endothelin-1, increase C-reactive protein, and increase total homocysteine. But blood pressure, insulin sensitivity, fibrinolytic markers, arterial stiffness, and levels of von Willebrand factor, fibrinogen, and interleukin-6 remained largely unchanged.
Conclusions. Our studies demonstrated that, while some markers of cardiovascular risk factors showed a shift to a more negative risk profile, others were not affected. Androgen effects on cardiovascular risk markers are therefore not universally negative, and it is reasonable to assume that the latter effects will not be negative with the much lower doses suited for administration to women. **Gooren LJG, and Giltay EJ. Review of studies of androgen treatment of female-to-male transsexuals: Effects and risks of administration of androgens to females. J Sex Med 2008;5:765–776.**

The physiological role of androgens in women and the potential benefits of androgen replacement in ovariectomized women receive increasing attention [1–3]. Androgen treatment of women is, however, received with some reservation in view of the potential virilizing and deleterious effects androgen are thought to have on cardiovascular risks [1]. We review here our publications on the effects of high-dose androgen administration to female-to-male transsexuals treated between 1975 and 2004 (N = 712). Female-to-male transsexuals receive high-dose androgens (similar to doses for hypogonadal men) for their sex reassignment. Upon testosterone administration, some markers of cardiovascular risk factors show a shift toward a higher risk profile, but others do not show this pattern. Dosages of androgens suited for replacement in

women are much lower than those needed for sex reassignment in female-to-male transsexuals. It is reasonable to assume that the dosages given to women will be less detrimental to cardiovascular risks than those administered to transsexuals. This contribution is an update of an earlier evaluation of androgen administration to female-to-male transsexuals [4] and reviews the latest information from our own studies and the literature.

Transsexualism and Cross-Sex Hormones

Transsexualism is the condition in which a person with an apparently normal somatic sexual differentiation has the conviction that she/he is actually a member of the opposite sex. It is associated with an irresistible urge to be hormonally and surgically adapted to that sex. Traditionally conceptualized as a psychological phenomenon, research on the brains of male-to-female transsexuals has found that the sexual differentiation of one brain area (the bed nucleus of the stria terminalis) has followed a female pattern [5,6]. The latter finding may lead to a concept of transsexualism as a form of intersex, where the sexual differentiation of the brain is not consistent with the other variables of sex such as chromosomal pattern, nature of the gonad, and nature of internal/external genitalia. Basal serum levels of sex steroids and levels after endocrine stimulation/inhibition are not different between transsexuals and nontranssexuals [7]. The prevalence of transsexualism, assessed in the Netherlands, is 1:11,900 men and 1:30,400 women [8]. Similar prevalences have been encountered in Singapore [9] and Belgium [10], while from other countries, usually lower prevalences have been reported: Sweden [11], Germany [12], which may be explained by differences in social climates and accessibility to health care.

As a consequence of treatment with parenteral androgens, resulting serum testosterone levels vary strongly over time following administration [13]. Serum testosterone levels, measured cross-sectionally, in the female-to-male transsexuals in our clinic treated with a mixture of parenteral testosterone esters (Sustanon, Organon,Oss, the Netherlands) for several months to several years, were 29 ± 14 nmol/L (mean ± standard deviation [SD]) [14]. Upon testosterone administration, serum 17β-estradiol values fall only modestly, a change which only in studies with large numbers of subjects becomes significant. For instance, in a study with 17 subjects, serum levels fell from 163 ± 53 to 131 ± 33 pmol/L ($P < 0.05$) upon testosterone administration [15]. These values remain biologically significant [14].

Studies into the biological effects of cross-sex hormones in transsexuals are sometimes regarded as only relevant to transsexuals themselves. They may yield, however, important scientific information, particularly when the effects of androgen administration to female-to-male transsexuals are compared to the effects of androgen deprivation in male-to-female transsexuals, thus providing a mirror image of the induction of androgen effects in female-to-male transsexuals. Effects of testosterone administration in female-to-male transsexuals and hypogonadal men are strikingly similar. Throughout our experiments, we have gained the impression that female-to-male transsexual subjects undergoing androgen administration can serve as a model of the hypogonadal male. There is, as yet, no information that in terms of androgen (receptor and post-receptor) physiology, human males differ from females. In fetal rats, there is an identical androgen receptor expression pattern in females and in males [16]. Further, female-to-male transsexuals starting androgen treatment are usually in an age range between 20 and 35 years. At that age, good health is the rule and a reasonable assumption is that measuring effects of testosterone administration in this group is not contaminated by age-related intervening variables.

The dosages of testosterone given to female-to-male transsexuals are similar to those administered to hypogonadal men. Testosterone treatment of women naturally uses much lower dosages. Cardiovascular morbidity/mortality in men is higher than in women of similar ages, and this sex difference is often attributed to the sex difference in circulating testosterone levels [17,18]. But critical examination shows that this view is no longer tenable, and testosterone is gradually exonerated from its alleged role in cardiovascular disease, both in men and in women [17,18].

The population of female-to-male transsexuals treated in our clinic between 1975 and 2004 (N = 712) is too small and the follow-up period too short to produce reliable clinical end-point data on cardiovascular disease, and this contribution will primarily focus on surrogate markers of cardiovascular disease in female-to-male transsexuals receiving high-dose testosterone. Other observations pertinent to androgen administration to women will be addressed as well.

Virilizing Effects

In almost all subjects, the pitch of the voice drops and a coarsening of the voice occurs within 6–12 weeks following androgen administration. We have monitored the development of sexual hair which follows essentially the pattern observed in pubertal boys: first on the upper lip, cheek, and pubic area, and after longer treatment, also on the chin, neck, legs and arms, and chest [19]. If there is a preexistent degree of hairiness on the legs or arms, androgen exposure increases hair growth first on these places [20]. We found that there is a strong genetic component to both the pace and degree of development of hairiness as is also the case with the development of alopecia androgenica, occurring in about 50% of female-to-male transsexuals after a period of 13 years of testosterone administration [21]. Although alopecia androgenica has been associated with an increased coronary heart disease morbidity and mortality [22], it could be shown that development of alopecia androgenica in female-to-male transsexuals was not associated with a less favorable cardiovascular risk profile [21].

Effects on Breast, Endometrium, Ovaries, and Clitoris

Two studies have reported findings of androgen effects on the breasts [23,24]. The effects varied strongly from one subject to the other: most subjects showed intralobular fibrous stroma and some extralobular fibrous stroma; approximately half showed lobular atrophy. Effects on both endometrium and breasts reflect probably the simultaneous action of androgens and estrogens generated by the high levels of androgens in these subjects. In women with the polycystic ovarian syndrome (PCOS), the risk of developing a postmenopausal breast carcinoma is not increased [25,26]. We have recently published a report on the effects of testosterone on the breast. Long-term administration of androgens in female-to-male transsexuals causes marked reduction of glandular tissue and prominence of fibrous connective tissue. These changes are similar to those observed at the end stage of menopausal mammary involution [27]. This subject has also recently been extensively reviewed [28]. Because part of the administered androgens is aromatized to estrogens, it seems advisable that candidates who have their own family history of breast cancer are carefully monitored when they receive androgens.

The effects of long-term androgen administration on the endometrium have been studied in 12 female-to-male transsexuals [29]. Six had mild hyperplasia of the endometrium, four a secretory endometrium, and two an inactive endometrium. Several authors have studied the effects of androgen administration on ovarian morphology [15,29,30]. The universal finding is that long-term high-dose androgen exposure (>18 months) induces the morphological features characteristic of the polycystic ovary as encountered in polycystic ovarian disease (PCOD). The ovaries are enlarged and show two- and threefold increases in cystic and atretic follicles, respectively. The ovarian cortex is three times thicker than normal and is collagenized. The ovaries show theca interna hyperplasia, luteinization, and stromal hyperplasia. These characteristics apparently can be brought about by exogenous androgens, without an intraovararian source of androgens as in PCOD. Also, the hormonal contents of the ovarian follicles (17β-estradiol, androstenedione, and inhibin) of androgen-treated female-to-male transsexuals are similar to those of women with PCOD [30]. The accompanying serum LH levels in the transsexuals are suppressed by high-dose testosterone administration, dissimilar to the elevated serum luteinizing hormone (LH) levels typical of PCOD [15].

Ovarian cancer is a common cause of cancer-related death in women and is the most common fatal gynecologic malignancy. Among the population of female-to-male transsexuals in the clinic of the authors, there have been two cases of ovarian cancer [31]; this is higher than expected. Another case has recently been reported [32].

The volume of the clitoris increases four to eight times upon testosterone administration. These findings are very similar to those reported by Meyer and coworkers [33]. Like penile growth, there is only a limited potential for growth. The younger the patient is at the start of androgen administration, the more growth is encountered. In some, the enlarged clitoris is sufficiently large to serve as a small phallus.

Effects on Bone

Sex steroids are important regulators of bone metabolism and bone mineral density (BMD). They play a substantial role in bone growth and in the pubertal acquisition of peak bone mass and maintenance of bone mass in adulthood in both sexes [34]. Transsexuals undergo gonadectomy,

and the question poses itself whether androgens can protect "female bones" from estrogen deprivation and vice versa. The latter can be positively answered [35] and has recently been extensively reviewed [36]. In a number of studies, we have addressed the effects of cross-sex hormone administration on bone. One year of administration of testosterone esters (250 mg/2 weeks) led to a significant increase in insulin-like growth factor-I (without a change in insulin-like growth factor-binding protein-3) and an increase in bone alkaline phosphatase. There was no significant increase in BMD after 1 year of testosterone administration [37]. It is of interest to note that part of the administered testosterone is aromatized to estradiol [14,37]. In another study, histomorphometry was performed in iliac crest biopsies of 15 female-to-male transsexuals (age 30.0 ± 6.1 years) who had been treated for a median period of 39 months with a similar androgen treatment regimen. The findings were compared to those of eugonadal men and postmenopausal women. Biochemical variables of bone formation were lower than in the two comparison groups. The *Z* score was as expected for age. Cortical thickness was higher in this group than in the comparison subjects (probably pointing to an androgenic-anabolic effect) and trabecular bone structure was similar as in the two comparison groups. The eroded surface was lower than in postmenopausal women, so there was probably a low bone turnover. The conclusion was that androgens protect the bone of female-to-male transsexuals from the usual effects of estrogen deprivation as observed in women deprived of estrogens [38]. It must be remembered that part of the positive effect might be due to androgen-derived estrogens. However, in a longer-term follow-up study of 28–63 months in 19 female-to-male transsexuals (age 16–39 years, median age 25, 13–35 months after ovariectomy), there was a significant decrease in BMD in the group over this period (from 1.14 ± 0.15 to 1.09 ± 0.12 g/cm^2). The best predictor of bone loss was the elevation of serum LH levels. We have interpreted this correlation as to indicate a probable undersubstitution with androgens in the longer term [39]. It is clinically of interest to note that our subjects take androgen dosages that compare to those in androgen-treated hypogonadal men (testosterone esters 250 mg/3 weeks or oral testosterone undecanoate 40 mg four capsules per day). So these androgen replacement regimens may be inadequate for men as well.

Effects on Kallikreins and Prostate-Specific Antigen (PSA)

PSA is a serine protease with chymotrypsin-like enzymatic activity, produced in men by the prostate gland and stimulated by androgens. PSA has been detected in some female tissues (breast, ovarian, and endometrial tissues) and body fluids (amniotic fluid, milk, and breast cyst fluid). A recent study has shown that PSA levels in women are correlated with the degree of hirsutism and with levels of the androgen marker 3α-androstanediol glucuronide [40]. The finding that administration of androgens leads to an increase of PSA levels was confirmed in studies in female-to-male transsexuals [41,42]. An enzyme closely related to PSA is human glandular kallikrein [43]. It is also a trypsin-like protease and is also expressed in the prostate in men. We found that both urinary PSA and human glandular kallikrein increased upon testosterone administration in female-to-male transsexuals to a larger degree than could be explained by clearance from the circulation, leading to the assumption that periurethral and paraurethral glands (the equivalent of the female prostate?) secrete large amounts of PSA and other kallikreins into the urine [42]. Another likely source of PSA and human glandular kallikrein in women is breast tissue [44,45].

Effects on Psychological Functioning

In adulthood, men and women differ on number of psychological variables: men are more aggression prone, have a higher sexual arousability, and outperform women in visiospatial and mathematical abilities, while women perform better on tasks of verbal skill, perceptual speed, and fine manual dexterity [46]. We studied the effects of testosterone administration to female-to-male transsexuals [47,48]. While no significant differences were encountered with control women before testosterone administration, androgen administration was clearly associated with an increase in spatial ability performance, sexual arousability, and aggression proneness (the self-imagined preparedness to act). However, we have seen no adverse effects of testosterone administration on aggression or on sexual behavior in female-to-male transsexuals. Verbal fluency tasks were not consistently affected [47,48]. Our findings largely confirmed earlier reports on the effects of sex steroids on psychological functioning. An interesting aspect is that sex differences in these functions appear not to be determined by prenatal sex steroid exposure and

remain susceptible to sex steroids well into adulthood. The impact of sex steroids on these functions is more of a theoretical nature than of everyday life relevance. They are not spontaneously noted by the transsexuals.

Effects of Androgen Administration on Cardiovascular Risk Factors

In the group of androgen-treated female-to-male transsexuals, we have not found a higher degree of cardiovascular events in comparison with age-matched subjects (summarized in Table 1). We have observed two cases of myocardial infarction and three of angina pectoris among female-to-male transsexuals. This is not higher than expected on the basis of disease prevalence data [49].

The relationship between androgens and cardiovascular disease is complicated. There may be gender-specific effects of androgens on cardiovascular disease. Studies in men suggest that low rather than high endogenous androgen levels are related to coronary heart disease [50]. It has been shown that higher androgen levels found in the PCOS are associated with a higher cardiovascular risk [51]. The relationship between hyperandrogenism and atherosclerosis in these women is confounded by metabolic and hemodynamic disturbances clustered in the insulin resistance syndrome, such as hypertension, dyslipidemia, glucose intolerance, insulin resistance, visceral fat accumulation, and increased plasminogen activator inhibitor type 1 (PAI-1) levels [51–53]. Endogenous androgen levels are not consistently associated with cardiovascular disease in postmenopausal women in cross-sectional [54–56] or prospective studies [18,57]. In postmenopausal women, serum levels of androgens are positively [56] and inversely [55] associated with the degree of coronary artery disease (e.g., the maximum percentage reduction of the luminal diameter of coronary arteries or carotid artery intimal-medial thickness).

Table 1 Effects of testosterone administration on BMD and selected risk factors for cardiovascular disease in female-to-male transsexuals

Variable	Observed changes upon testosterone administration	Effect on the risk of morbidity
BMD	No effect / increase	—
Body composition		
Weight/BMI	Increase	▲
Body mass index	Increase	▲
Visceral fat	Slight increase	—▲
Lipid spectrum		
Total cholesterol	No effect	—
LDL cholesterol	No effect	—
HDL cholesterol	Decrease	▲
VLDL cholesterol	No effect	—
Triglycerides	Increase	▲
Insulin sensitivity		
Fasting glucose level	Decrease	▼
Fasting insulin levels	No change	—
Insulin sensitivity	Slight decrease	—▲
Cardiovascular risk factors		
Blood pressure	No effect	—
Fluid retention	Small increase	▲
Arterial stiffness	No effect	—
Hemostasis/fibrinolysis:	No overall effect	▼ / —
Total homocysteine	Increase	▲
Inflammation markers	Increase in some markers	▲

— indicates no change in risk; ▲ indicates an increased risk; ▼ indicates a decreased risk.
HDL = high-density lipoprotein; BMD = bone mineral density; LDL = low-density lipoprotein; VLDL = very low density lipoprotein; BMI = body mass index.

Effects on Blood Pressure and Fluid Retention

All androgens cause some degree of sodium retention and expansion of extracellular fluid volume. This effect is usually small; weight increases by about 3% in healthy individuals [58]. In our studies, sodium and water retention was observed in 5 (of 293) cases, and could be corrected with a dose reduction of androgens (51). In 12 (of 293) subjects, an elevated blood pressure was found, which is in accordance with the expected number on the basis of prevalence studies in healthy subjects [59]. In a group of 74 female-to-male transsexuals, the mean systolic and diastolic blood pressures slightly but statistically significantly decreased after 3 or 4 months of testosterone administration (mean ± SD from 126.6 ± 13.1 to 122.0 ± 10.7 and from 79.8 ± 8.0 to 77.7 ± 6.8, $P < 0.05$, respectively) [21]. Further, in 17 female-to-male transsexuals in whom blood pressures were measured every 5 minutes for 2 hours using an automatic device, the mean systolic and diastolic blood pressures were not affected after 12 months of testosterone administration (mean ± SD from 121.4 ± 9.9 to 122.4 ± 8.2 and from 67.1 ± 7.5 to 66.9 ± 4.9, respectively) [60]. Thus, blood pressure did not seem to be affected by long-term androgen administration.

Effects on Endothelin-1, von Willebrand Factor (vWF), Fibrinolytic, and Thrombotic Parameters

Endothelin-1, vWF, and tissue-type plasminogen activator (tPA) may serve as markers of endothelial cell functioning. The endothelins are among the most significant vasoactive substances. Studies with endothelins and specific endothelin-receptor

antagonists have suggested that these peptides are important in vascular physiology and disease. It is likely that endothelin-1 plays a role in atherosclerosis and cardiac hypertrophy (for a review, see Gossl and Lerman [61]). In a study, we found that androgen deprivation with cyproterone acetate with simultaneous administration of ethinyl estradiol decreased endothelin-1 levels, while testosterone administration to female-to-male transsexuals increased plasma endothelin-1 levels (mean ± SD from 6.2 ± 1.1 to 7.8 ± 1.2 pg/mL, $P < 0.01$) [62]. It is unclear whether the increase in endothelin-1 levels in our study reflected an increase in its synthesis, a decrease in its degradation, or both.

vWF is endothelially synthesized and stored, and is partly complexed with factor VIII. It facilitates platelet aggregation and predicts future cardiovascular events. Our findings in female-to-male transsexuals are inconsistent. We observed a slight decrease in vWF levels after testosterone administration in one group of 10 female-to-male transsexuals [63], but a slight increase in another group of 17 female-to-male transsexuals (unpublished data). The level of vWF-propeptide (vWF : AgII) was not affected by testosterone [63]. The consequences of these findings for cardiovascular risk remain to be elucidated.

The process of fibrinolysis plays a pivotal role in the etiology of arterial and venous thrombosis. tPA activates plasmin, which acts as the circulating thrombolytic agent. PAI-1 is the major physiological inhibitor of tPA. Several cardiovascular risks appear to be associated with elevated levels of PAI-1, thus enhancing potential thrombosis formation. In 17 female-to-male transsexuals, testosterone treatment during 4 and 12 months was not associated with changes in plasma antigen levels of PAI-1 and tPA [64]. In another group of 17 female-to-male transsexuals, testosterone administration did not significantly affect plasma antigen levels of tPA (geometric means from [95% confidence interval (CI)] 8.5 ng/mL [5.5–13.2] to 9.8 [6.6–14.5], $P = 0.22$) and PAI-1 (from 26.7 ng/mL [18.9–37.8] to 24.7 [16.6–36.9], $P = 0.61$) [65]. Moreover, endothelial tPA synthesis—as assessed by venous occlusion tests eliminating the effects of hepatic clearance—was not affected by testosterone [65].

Concerning the thrombotic risk, treatment with testosterone decreased the normalized activated protein C (APC) sensitivity ratios significantly (from 2.0 ± 0.8 to 1.3 ± 0.7, $P < 0.001$). APC resistance is a major risk factor of venous thrombosis. All female-to-male transsexuals, except one carrier of factor V Leiden, showed a reduction of the normalized APC sensitivity ratio. Furthermore, protein S levels increased during testosterone treatment (total protein S from 105 ± 22 to 118 ± 19%, $P = 0.037$; free protein S, 83 ± 20 to 97 ± 15%, $P = 0.012$), whereas levels of protein C and prothrombin levels remained unchanged. Thus, treatment with testosterone has mild antithrombotic effects in female-to-male transsexuals [66].

Effects on Total Homocysteine (tHcy) and Acute-Phase Proteins

An elevated plasma level of tHcy level is an independent risk factor for atherosclerotic and thrombotic disease [67]. Higher total plasma tHcy in healthy men vs. premenopausal women may be explained by their differences in sex steroids [68]. We studied the effects of administration of androgens in 17 female-to-male transsexuals. Plasma tHcy levels increased from geometric mean 7.7 mmol/L (range 2.9–19.0) to 9.0 mmol/L (range 3.6–27.1, mean change +17%, $P = 0.005$) upon androgen administration [69]. In another group of 17 female-to-male transsexuals, a similar increase was found ($P = 0.002$, unpublished data). Besides direct effects of testosterone on tHcy levels, the increase could be secondary to anabolic effects on muscle mass and creatine–creatinine metabolism. Changes in serum creatinine levels correlated positively with changes in tHcy levels in both male-to-female and female-to-male transsexuals [69,70].

Interleukin-6, C-reactive protein, and fibrinogen levels are nonspecific markers of low-grade systemic inflammation. Elevated levels of circulating C-reactive protein, interleukin-6, and fibrinogen [71] are associated with an increased future cardiovascular risk, indicating that chronic low-grade inflammation may play a role. Cytokines such as interleukin-6 augment the hepatic synthesis of acute-phase reactants such as C-reactive protein and fibrinogen. Besides being an acute-phase protein, fibrinogen is a determinant of thrombus formation, platelet aggregation, and plasma viscosity. We found that testosterone administration strongly increased C-reactive protein levels in female-to-male transsexuals (by +141%, $P = 0.001$) [72]. Fibrinogen and interleukin-6, however, were not affected following 4 and 12 months of testosterone administration in 15 female-to-male transsexuals (unpublished data).

Effects on High-Density Lipoprotein (HDL) Cholesterol

Serum HDL cholesterol levels are found to be lower in eugonadal men than in premenopausal women. This sex difference is not manifest before puberty. Many studies in both men and women have shown that the administration of androgens reduces HDL cholesterol levels [18]. In experiments wherein androgen levels were severely lowered, HDL cholesterol levels increased, and serum levels of HDL cholesterol decreased to normal male levels when serum androgens levels subsequently were returned to normal [73]. There were, however, many differences in study designs and whether endogenous or exogenous androgen effects were investigated. The picture is also complicated by the fact that both endogenous and exogenous testosterone can be metabolized to estrogens.

In our own study, the (aromatizable) oral androgen testosterone undecanoate was administered to both hypogonadal men and to previously nontreated female-to-male transsexuals. While serum estradiol levels in the females were three to four times higher during testosterone administration, in both sexes, levels of HDL cholesterol and HDL2 cholesterol declined and were eventually of the same magnitude. This has led us to conclude that testosterone is indeed the major determinant of the sex difference in HDL cholesterol levels [74]. In line with this finding is that women with hyperandrogenism show "male-like" plasma lipoprotein profiles [75]. In other studies of female-to-male transsexuals, parenteral testosterone administration likewise decreased HDL cholesterol (as well as HDL2 and HDL3 cholesterols) and slightly decreased total cholesterol [60,76]. Also, other studies using the new long-acting parenteral testosterone undecanaote in female-to-male transsexuals found a decrease of plasma HDL cholesterol [77,78] Although HDL cholesterol exerts several potentially antiatherogenic actions, it is still unclear whether the HDL-lowering effect of testosterone leads to an increased cardiovascular risk [18]. The metabolism rather than circulating levels appears to determine atherogenicity [18,79]. The relationships between hyperandrogenism, HDL cholesterol levels, and cardiovascular events may be confounded by other elements clustered in the insulin resistance syndrome [18].

Effects on Arterial Stiffness

Arterial compliance and distension reflect the ability of an artery to expand and recoil with cardiac pulsations and relaxations. These are a major determinant of cardiac workload and systolic blood pressure. Large artery stiffening (i.e., a decreased arterial compliance and distensibility) may contribute to the development of cardiovascular disease [80,81]. Data on a possible sex difference in arterial stiffness are contradictory. Measurement of pulse wave velocity, an estimate of regional arterial stiffness, indicates that arteries in men are stiffer than those in premenopausal women [80].

In 18 female-to-male transsexuals, the effects of testosterone administration on arterial stiffness were studied. The distension coefficient, reflecting the intrinsic vascular wall elasticity, and the compliance coefficient, reflecting the buffering capacity of the vessel wall, were calculated from the arterial diameter, the change in arterial diameter during the heart cycle (i.e., distension), and pulse pressure. We found that testosterone on average did not affect any of these arterial stiffness indices of the common carotid, the femoral, and the brachial arteries [82]. Thus, the stiffness of large arteries—a noninvasive predictor of cardiovascular risk—was not affected by testosterone administration. This finding is not consistent with reports of testosterone administration to female-to-male transsexuals [83] and to hypogonadal men [84]. We have no explanation to offer for the discrepancy with these two studies except that the subjects in our study were on average somewhat younger.

Effects on Insulin Sensitivity

There is substantial evidence that insulin resistance induces an unfavorable lipid profile (i.e., a decrease in plasma HDL cholesterol and an increase in plasma triglycerides) and hypertension [85]. Coexistence of insulin resistance and hyperandrogenism has been described frequently, mainly in women with the polycystic ovary syndrome. An improvement of insulin resistance could be observed when the hyperandrogenism was corrected in these women [51].

In our own experiments, using the hyperinsulinemic-euglycemic clamp method, we studied the effects of 3 months' administration of 250-mg testosterone esters/2 weeks on insulin resistance in a group of 13 female-to-male transsexuals [86]. In hyperinsulinemic-euglycemic clamp studies, insulin is infused at preset standardized infusion rates, and the amount of glucose required to keep blood glucose levels constant provides a reliable indication of insulin sensitivity or, alternatively, of insulin resistance. In our study,

glucose utilization slightly but significantly decreased after 4 months, showing that less glucose entered the cells; in other words, insulin became biologically less effective in its effect to deliver glucose to the cell, i.e., the development of peripheral insulin resistance [86]. By contrast, 12 months of testosterone administration in 17 female-to-male transsexuals did not induce significant changes in fasting insulin levels or insulin sensitivity in the physiological range [60]. Only a statistically significant reduction in insulin sensitivity was observed during infusion of supraphysiological levels of insulin, which is consistent with a study in healthy women, showing upon methyltestosterone administration that whole-body glucose uptake was not significantly affected during low-dose insulin infusion and decreased during high-dose insulin infusion [87]. It is of interest to note that different testosterone preparations with different pharmacological properties and different thresholds for androgen action must be taken into account when comparing and interpreting these studies.

Effects on Body Fat Distribution

From puberty on, males and females differ in their body distribution of fat over the subcutaneous and intra-abdominal (or visceral) fat depots. Subcutaneous fat disappears largely in normal-weight boys, and visceral fat stores are also small but start to become manifest with increasing age. From age 20 to 30 years on, men have approximately twice as large visceral fat storage as women with a comparable body mass index. If men store fat, they accumulate it preferentially intra-abdominally, while in premenopausal women, this occurs preferentially subcutaneously on hips and thighs. That androgens are involved in this sex-specific fat distribution pattern has become increasingly clear, although the precise mechanism remains unknown. Women with elevated levels of serum androgens have more visceral fat than control women [18]. In our own experiments, we studied the effects of androgen administration on fat distribution in female-to-male transsexuals undergoing sex reassignment. It could be shown that androgens lead to a quick depletion of subcutaneous fat, while it takes between 1 and 3 years for visceral fat accumulation to become manifest [76]. We also showed that hormone-sensitive lipase (HSL) activity was increased in 16 female-to-male transsexuals treated with testosterone for 2 and 12 months (mean ± SD from 16.8 ± 5.3 to 28.7 ± 9.0 to 27.4 ± 8.3 mol fatty acid (FA)/hour/mL, $P < 0.001$) [60]. Testosterone decreased total body fat mass through the activation of HSL in adipocytes, in accordance with the literature [18].

Visceral fat accumulation has been found to be a risk factor for cardiovascular disease and for noninsulin-dependent diabetes mellitus [88]. In one of our studies, it could be shown that a factor affecting fibrinolysis, PAI-1 is positively correlated with the amount of visceral fat in healthy young transsexual men and women [64].

Conclusions

This is a report of our observations of testosterone administration to female-to-male transsexuals. The initial assessment of transsexualism is based on psychodiagnostic instruments and is generally done by a mental health professional. It is important to diagnose accurately the subject's gender identity disorder and to see whether there is any comorbid psychiatric diagnosis that may require treatment. The indication for hormonal treatment is based on the expectation that it will resolve the subject's gender dysphoria. Psychological and medical counseling is also recommended during cross-sex hormone administration. In their zest to become members of the desired sex, transsexuals may overdose themselves with cross-sex hormones.

Close monitoring of the effects of androgen administration to female-to-male transsexuals can provide important scientific information for the understanding of androgen (patho)physiology both in men and in women. It is obviously unethical to administer high-dose androgens to nontranssexual women over a prolonged period. Monitoring this process in female-to-male transsexuals provides clues to the pathology of long-standing hyperandrogenism in women. And, as stated previously, a cohort of uniformly hypogonadal men in a similar age range is difficult to recruit by a single research center. They may thus serve as a model for the effects of androgens in hypogonadal men. Most transsexuals are young and healthy when they start sex reassignment, so there are fewer variables to consider, and they are interested themselves in the effects of long-term testosterone on their health, thus providing motivated research subjects.

The Relative Safety of Androgen Administration

High-dose androgen administration to female-to-male transsexuals showed many effects in vivo, and appeared to increase weight, increase visceral fat,

increase hematocrit, decrease HDL cholesterol, increase endothelin-1, increase C-reactive protein, and increase tHcy. These assessments of cardiovascular risk factors showed convincingly a shift to a more negative risk profile which could be demonstrated to be androgen related, which raises concern for atherosclerotic and thrombotic events. Yet blood pressure, insulin sensitivity, fibrinolytic markers, arterial stiffness, and levels of vWF, fibrinogen, and interleukin-6 remained largely unchanged. Also, administration of androgens to 293 female-to-male transsexuals with a total exposure of 2,481 patient years (individual exposure varied from 1 to 20 years) was a safe procedure in a retrospective study [89]. There were no major complications. The actually observed cardiovascular mortality and morbidity was not higher than expected on the basis of Dutch health statistics. This includes an increasing number of female-to-male transsexuals in our population over the age of 50. The observation that cardiovascular risk factors shift to a male-like risk profile has prompted us to encourage female-to-male transsexuals to adopt a healthy lifestyle: avoidance of overweight, a healthy diet, enough exercise, and no smoking. Indeed, in some aging female-to-male transsexuals, we observe the development of the metabolic syndrome. It is our policy to follow up hormone-treated transsexuals throughout their lives to treat and make an inventory of long-term complications. Transsexuals, in their understandable desire to embark on life in the desired sex, tend to sever ties with the clinic that provided sex reassignment.

Dosages of androgens suited for replacement in women are much lower than those needed for sex reassignment in female-to-male transsexuals. Traditionally, in transsexuals, the classical parenteral testosterone esters have been used, resulting in supraphysiological plasma testosterone levels in the first days after the injection. Recent studies with the long-acting parenteral testosterone undecanoate show a much more favorable pharmacokinetic profile [77,78]. Also, transdermal administration of testosterone gel is a major improvement in testosterone treatment. The suitability of testosterone preparations for treatment of female-to-male transsexuals is not different from those used for hypogonadal men [90,91]. The implications of the aforementioned review for androgen administration to women are that it is reasonable to assume that the dosages given to women will be less detrimental to cardiovascular risks than those administered to transsexuals.

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