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Endocrine treatment of transsexuals: assessment of cardiovascular risk factors

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"Supraphysiological doses or blood levels of estrogen lead to increased risk for thromboembolic disease, liver dysfunction and development of hypertension."

Gender identity disorder (GID) is characterized by strong and persistent cross-gender identification and by persistent discomfort with one's anatomical sex. Transsexualism is considered to be the extreme end of the spectrum of GID, which is characterized by a pursuit of sex reassignment surgery. The recent information on the prevalence of the transsexual end of the GID spectrum from The Netherlands is one in 11,900 males and one in 30,400 females [101], although biological mechanisms of GID are still under investigation [1,101].

Transsexuals who require transition to their desired gender must undergo hormonal therapy that masculinize or feminize the body, such as administering testosterone to biologic females or estrogen to biologic males. In many countries, people with GID are treated according to the Standards of Care (SOC) 6th version of the World Professional Association for Transgender Health (WPATH), formerly known as the Harry Benjamin International Gender Dysphoria Association (HBIGDA) a professional organization devoted to the understanding and treatment of gender identity disorders [101]. The Endocrine Society is also formulating practice guidelines for endocrine treatment of transsexual persons [2,3].

Hormone regimens in transsexuals

Transsexual adolescents (Tanner stage 2, age 11 years [9–13 years]) are treated by endocrinologists to suppress puberty with gonadotropin-releasing hormone (GnRH) agonists until 16 years of age, after which cross-sex hormones may be given. GID can be reliably assessed only after the first signs of puberty [2]. Progestins such as medroxyprogesterone are relatively effective but the efficacy is far less than that of the GnRH agonists.

Estrogen is given to male-to-female (MTF) transsexuals orally as conjugated estrogens, or 17β-estradiol as transdermal estrogen, or parenteral estrogen esters (Table 1). The estrogen with/without compounds with antiandrogenic properties or GnRH agonists causes physical changes including breast growth, feminine shape, restraint of penile erection, and decreased libido. Although facial and body hair and oiliness of skin are decreased, complete removal of male sexual hair usually requires electrolysis, or laser treatment. Furthermore, endocrine treatment cannot fully change the voice. There is no evidence that progestagen has beneficial effects on treatment with estrogen. Although higher doses of estrogens may not lead to more rapid or dramatic clinical changes, transsexual persons tend to self-administer high hormonal doses to achieve rapid physical changes. Supraphysiological doses or blood levels of estrogen lead to increased risk for thromboembolic disease, liver dysfunction and development of hypertension. Endocrine treatment to suppress endogenous sex hormones should maintain physiologic levels of gender-appropriate sex hormones and hormone doses should be further lowered in patients with cardiac or other comorbidities.

Measurement of serum testosterone level is clinically useful to monitor the effectiveness of endocrine treatment in MTF transsexuals and it should be maintained in the female range of under 55–100 ng/dl. Measurement of serum 17β-estradiol levels can be used to monitor oral, parenteral or

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Table 1. Hormone regimens in male-to-female transsexuals.

Hormone type	Route of administration	Hormone form	Dosage
Estrogen	Oral	17β-estradiol	2.0–6.0 mg/day
		Conjugated estrogens	1.25–5.0 mg/day
		Ethinyl estradiol	50–100 µg/day
	Transdermal	17β-estradiol patch	100–400 µg twice weekly
		17β-estradiol gel 0.1%	1.0 g/day
	Intramuscular injection	Estradiol valerate, cypionate or dipropionate	5–20 mg every 2 weeks or 2–10 mg every week
Antiandrogens	Oral	Spironolactone	100–200 mg/day
		Cyproterone acetate	50–100 mg/day
		Finasteride	5 mg/day
GnRH agonist	Subcutaneous injection	Leuprolide acetate	1.88–3.75 mg monthly
		Buserelin acetate	3.6 mg monthly or 10.8 mg every
		Goserelin acetate	12–13 weeks
	Nasal spray	Buserelin acetate	900 µg/day
		Nafarelin acetate	400 µg/day

Transdermal or parenteral administration of estrogen is recommended for older male-to-female transsexuals. 17β-estradiol or conjugated estrogens is recommended if oral administration is required. Antiandrogens or a GnRH agonist is effective in reducing endogenous testosterone levels and in reducing administration dose of estrogen.

transdermal 17β-estradiol or its esters and it should be maintained in the peak physiological range for young healthy females, with ideal levels 200 pg/ml. However, conjugated estrogens or synthetic estrogens cannot be monitored by serum 17β-estradiol levels.

Androgen induces masculinization in female-to-male (FTM) transsexuals (Table 2) including cessation of menses, increased facial and body hair, the oiliness of the skin, and increased muscle. Physical changes also include deepening of the voice, clitoromegaly and increased libido. Serum testosterone level in FTM transsexuals treated with either parenteral or transdermal preparations should be maintained in the normal male range of 250–1000 ng/dl.

> "Measurement of serum testosterone level is clinically useful to monitor the effectiveness of endocrine treatment in male-to-female transsexuals..."

Adverse medical conditions & monitoring plan

To evaluate development of physical changes and adverse outcomes in transsexual persons, regular laboratory monitoring and measurement of blood pressure and body weight are performed after the first 3 months of treatment and then twice yearly.

Adverse outcome of estrogen in MTF transsexuals includes thromboembolic disease, severe liver dysfunction, breast cancer, coronary artery disease, cerebrovascular disease, migraine headaches, macroprolactinoma, decrease in muscle mass and strength, and depression. Progestagens may have side-effects such as salt/water retention and dyslipidemia, which are associated with cardiovascular diseases. Blood tests should be performed to evaluate anemia, liver dysfunction, increased triglyceride, insulin resistance and hyperprolactinemia. For individuals treated with spironolactone, serum potassium should initially be monitored every 2–3 months during the first year.

Adverse outcomes of androgen in FTM transsexuals include breast cancer, uterine cancer, severe liver dysfunction, erythrocytosis, acne, male-pattern hair loss, and increased visceral fat mass.

In FTM transsexuals treated with androgen, blood tests can evaluate erythrocytosis (>50%), liver dysfunction, salt retention, and dyslipidemia. Periodic monitoring of liver function is recommended because up to 15% of FTM transsexuals treated with parenteral or transdermal testosterone have transient elevations in liver enzymes.

To evaluate risk factors for venous thromboembolic events, physical examination should be performed to assess excessive weight gain, increased waist:hip ratio, and hypertension, although usefulness of monitoring D-dimer levels during treatment is controversial [4]. Routine screening for cancer of the breasts, colon, prostate, and uterus is recommended in transsexual persons. Bone mineral density testing should be performed if risk factors for osteoporotic fracture, such as prolonged hypogonadism caused by gonadectomy or treatment with GnRH agonists, are present.

A mental health professional must participate in ongoing care throughout the endocrine transition, which is sometimes associated with confusion caused by the consequences of the social role change [5]. The number of deaths in MTF transsexuals was five-times the number expected, owing to increased numbers of suicide and death of unknown cause [6]. Combined treatment with estrogen and cyproterone acetate in MTF transsexuals is known to be associated with depressive mood changes (15-fold) [6]. Our observation demonstrated that mental instability increased in 15% of MTF transsexuals after initiation of endocrine treatment.

Before endocrine treatment, all transsexual individuals should be informed and counseled regarding options for fertility. For MTF transsexuals in a later phase of puberty or in adulthood, cryopreservation of sperm can be an option to store fertility. Androgen causes polycystic ovaries in FTM transsexuals, which are observed under ultrasonography. In the large majority of FTM transsexuals, we observe polycystic ovaries during androgen treatment and the resumption of menstruation after discontinuance

of androgen treatment. Pregnancy has been reported in FTM transsexual persons who have had prolonged androgen treatment [7].

Venous thromboembolism

A 20-fold increase in venous thromboembolism occurs in MTF transsexuals treated with oral ethinyl 17β-estradiol, which means the morbidity rate is 2–6% [6]. This thrombogenic effect is considered to be typical of oral ethinyl 17β-estradiol but not of oral 17β-estradiol or parenteral or transdermal oestrogens [6]. A decrease in cardiovascular events has been reported by standardizing the regimen that transdermal 17β-estradiol is given once patients reach 40 years of age [6].

Among 60 MTF transsexuals treated with a GnRH agonist and oral 17β-estradiol, deep vein thrombosis occurred in one MTF transsexual who has thrombophilia, a homozygous *MTHFR* mutation [8]. It has been reported that incidence of deep vein thrombosis does not increase in treated MTF and FTM transsexuals despite an 8.0 and 5.6% incidence of thrombophilia, respectively [9]. However, a personal or family history of venous thromboembolism should be questioned before initiating hormone treatment and surgical interventions. Estrogen or androgen administration should be discontinued 4 weeks prior to elective surgical intervention.

Risk factors in cardiovascular events

Previous epidemiologic studies have revealed that a gender difference exists in the incidence of cardiovascular disease, with males being at higher risk than females. Previously, we reported that women with polycystic ovary syndrome have high testosterone levels and dyslipidemia [10]. The increasing abuse of androgenic anabolic steroids and reports of cases of sudden death and myocardial infarction among bodybuilders have raised concerns about an increase in cardiovascular risk when taking androgens. Concentric cardiac hypertrophy and atherosclerosis in the coronary arteries was observed in a FTM transsexual, of whom resulted in a sudden and unexpected death [11].

In FTM transsexuals treated with androgen, the two atherogenic indices, low-density lipoprotein-/high-density lipoprotein-cholesterol and Apo-AI/APO-B, were reported to be significantly raised and lowered, respectively. Androgen treatment in FTM transsexuals significantly reduces serum adiponectin [12] and increases serum big-endothelin-1 [6], which is a marker protein for endothelial cell functions.

We have reported significant increases in blood pressure, total cholesterol and triglyceride and a significant decrease in high-density lipoprotein-cholesterol in FTM transsexuals taking androgen [13]. We also demonstrated that arterial stiffness is increased in FTM transsexuals treated with androgen, although this is controversial. We observed a significant increase in brachial–ankle pulse wave velocity (baPWV) [13], which is known to be a marker for both the severity of vascular damage and the prognosis of atherosclerotic vascular diseases [13].

Table 2. Androgen regimens in female-to-male transsexuals.

Route of administration	Form	Dosage
Intramuscular injection	Testosterone enanthate, cypionate, or propionate Testosterone undecanoate	100–250 mg every 2 weeks or 50–125 mg weekly 1000 mg initially, followed by an injection at 6 weeks, then every 12 weeks
Transdermal	Testosterone gel 1% Testosterone patch	2.5–10 g/day 2.5–7.5 mg/day
Oral	Testosterone undecanoate Methyl testosterone Fluoxymesterone	160–240 mg/day 25–50 mg/day 2–10 mg/day

Transdermal or parenteral administration of androgen is recommended because oral administration of androgens may cause liver dysfunction.

Estrogens with and without antiandrogens decrease the plasma level of the endogenous nitric oxide synthase inhibitor, asymmetric dimethylarginine [14]. Oral ethinyl 17β-estradiol and transdermal 17β-estradiol both reduce plasma homocysteine, which is known to be a risk factor for atherotrombotic diseases [6]. Oral estrogen also causes significant changes in various inflammatory markers such as IL-6, IL-1, and IL-8, which may be involved in the pathogenesis of vascular disease [15]. We have also observed that baPWV in MTF transsexuals treated with estrogen is significantly lower than that in untreated MTF transsexuals [Nakatsuka M *et al.*, Unpublished Data].

> "The increasing abuse of androgenic anabolic steroids and reports of cases of sudden death and myocardial infarction among bodybuilders have raised concerns about an increase in cardiovascular risk when taking androgens."

Conclusion

Although effects of cross-sex hormonal treatments on the cardiovascular system have not been fully determined [16], cardiovascular risk factors such as smoking, obesity, advanced age, hypertension, dyslipidemia, diabetes mellitus, insulin resistance and some endocrine abnormalities should be evaluated in individual transsexuals.

Evaluation of arterial stiffness such as measurement of baPWV may be a strong motivation to start and continue lifestyle interventions such as smoking cessation, weight reduction, appropriate diet and exercise for transsexuals. Furthermore, long-term studies on quality of life and ideal lifestyle in the transgender community undergoing endocrine treatment are necessary.

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