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ORIGINAL RESEARCH—ENDOCRINOLOGY

Safety of Physiological Testosterone Therapy in Women: Lessons from Female-to-Male Transsexuals (FMT) Treated with Pharmacological Testosterone Therapy

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ABSTRACT

Introduction. The safety of long-term physiological doses of testosterone (T) therapy in women with sexual dysfunction is a contentious issue, in part, because of fear of adverse effects, such as breast cancer, vascular disease, and excessive virilization. This unsubstantiated fear has hampered progress in treating women with sexual dysfunction using T therapy in physiological doses to achieve circulating levels in the normal range.

Aim. To examine evidence derived from studies in female-to-male transsexuals (FMT) treated with supraphysiological (pharmacological) doses of T for long periods of time with no apparent major adverse effects.

Methods. A comprehensive literature search of relevant articles published between 1980 and 2010 pertaining to the topic of T in FMTs was performed using PubMed. The following key words were used: female-to-male transsexuals; testosterone; virilization; gender re-assignment; and androgen therapy in women. Relevant articles were retrieved, reviewed, and the information was analyzed and evaluated for study methodology and major findings.

Main Outcome Measures. Data from peer-reviewed publications were critically analyzed and the information was summarized.

Results. The data from the studies reported in the literature to date strongly suggest that treatment of FMTs with supra-physiological doses of T had minimal adverse effects. No increase in mortality, breast cancer, vascular disease, or other major health problems were reported.

Conclusions. No significant serious adverse effects were reported in FMTs treated with pharmacological doses of T. In light of the findings with supraphysiological doses of T, we suggest that treatment with T at doses producing physiological levels in women with sexual dysfunction are expected to produce limited and minimal adverse effects.

Traish AM, and Gooren LJ. Safety of physiological testosterone therapy in women: Lessons from female-to-male transsexuals (FMT) treated with pharmacological testosterone therapy. J Sex Med 2010;7:3758–3764.

Key Words. Testosterone; Female to Male Transsexual; Adverse Effects; Breast Cancer; Sexual Dysfunction; Safety of Testosterone

Introduction

The long-term safety of testosterone (T) therapy in women with sexual dysfunction remains a contentious issue in the field of women's sexual health [1–4]. More recently the International Consensus on Sexual Medicine Committees (#23) (ICSM Committees #23) [5,6] on "Endocrine Aspects of Women's Sexual Dysfunction," which convened as part of the 3rd International Consultation on Sexual Medicine, held in Paris, July 10–13, 2009 and sponsored by the World Health Organization, also made recommendations on T therapy in women, discouraged diagnosis and treatment of women with sexual dysfunction with T therapy, citing lack of long-term safety [5,6]. A serious concern regarding the utility of such recommendations is that neither the Endocrine Society Guidelines Panel [7] nor the ICSM Committees (#23) [5,6] comprehensively assessed the

evidence available in literature on use and safety of T in women. The safety of long-term use of T in female-to-male transsexuals (FMT) [8–12] was not discussed in the aforementioned reports [5–7]. Given that no serious adverse events were reported with pharmacological doses of T administered for prolonged time periods [8–12], such findings strongly suggest that physiological T treatment in women with sexual dysfunction is expected to be safe and, at best, produces minimal adverse events. Here we provide a summary of discussions from various clinical and research settings on use of supraphysiological T doses in FMT with no serious adverse effects.

Safety Concerns Regarding Physiological T Therapy in Women

Clinical studies on the efficacy and safety of physiological T therapy in women with androgen insufficiency and sexual dysfunction have demonstrated significant improvement in the various domains of sexual function with minimal side effects [13–18]. Van Staa and Sprafka [19] discussed the safety outcomes in women using T therapy in the clinical setting in which 2,103 women were treated with T with 6,309 control subjects. There were no major differences in the rate of Ischemic Heart Disease or Breast Cancer in women using T compared with controls. Further, no differences were noted in outcomes with or without hormone replacement therapy. There were no significant cases of clitorimegaly. However, there was an increase in acne and hirsutism, which were noted in many prior studies discussed herein.

Recently, Braunstein [20] and Shufelt and Braunstein [21,22] suggested that the major adverse reactions of physiological T administration in women were hirsutism and acne. Within the physiological doses of T, there do not appear to be increased cardiovascular risk factors and most of the data available to date support a neutral or beneficial effect of T. No increased risks in breast cancer, hepatotoxicity, neurobehavioral abnormalities or sleep apnea have been reported with use of physiological doses of T. Clitoris growth increases with T administration, but this growth is limited in adult mature women. In young women, however, the potential growth of the clitoris is more marked. Physiological levels of T have been shown to have minimal effects on clitoral enlargement in some women [19,23]. In a study by Davis et al. [13] more than 520 women were treated with T with only four women (<1%) experiencing clitoral enlargement, albeit mild, and none withdrew from the study because of clitoral growth.

The therapeutic administration of T in physiologic doses was deemed safe for up to several years [20–22]. Several recent reports have addressed the safety of T therapy women and concluded that T therapy improved sexual function with minimal adverse effects on women's health [19,24,25].

Studies of Pharmacological T therapy in FMTs

To shed more light on the safety of physiological T use in women with androgen insufficiency, we reviewed data from studies investigating the effects of pharmacological T administration in FMT for periods ranging from 18 to 36 months. The effects of T on laboratory variables (Table 1) and clinical endpoints, such as cardiovascular morbidity and mortality, over a longer period were assessed. The findings from such studies are summarized in Tables 1–3. In FMT, T therapy produced small changes in lipid profiles and did not produce significant changes in liver enzymes. Further, hemoglobin and hematocrit rose upon T administration but remained within the physiological range. The most prominent effects of administration of high-doses of T in FMT were on skin and clitoris [8,9]. The ovaries exhibited some signs of polycystic characteristics (Table 2). T treatment also caused preservation of bone mass, increased weight, visceral fat, and hematocrit, and decreased high-density lipoprotein cholesterol, albeit nonsignificantly (Tables 1 and 3). No significant changes were noted in blood pressure, insulin sensitivity, fibrinolytic markers, arterial stiffness, and levels of von Willebrand factor, fibrinogen, and interleukin-6 [8,9,39]. These data suggest that although some markers of cardiovascular risk factors showed a shift to a negative risk profile, others were not affected, indicating that androgen effects on cardiovascular risk markers in women are not universally negative [8,9]. It should be emphasized that as the T doses used in treatment of FMT are supra-physiological, it is reasonable to speculate that relative to the supra-physiological doses reported in various studies, the adverse effects of physiological doses of T on cardiovascular function in women will be markedly reduced [8–11,26].

Jacobeit et al. [12,26] examined the effects of long-acting T in FMT over a period of 36 months. No serious side effects were observed over the study period. T caused a small yet significant decrease in plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) but

Table 1 Effects of pharmacological testosterone on total T levels, lipids, hemoglobin, and hematocrit in female-to-male transsexuals

Study (reference cited)	No. of subjects	Duration of treatment	Nature of T administered	Changes in total T, lipids and hemoglobin levels.	Values at baseline	Values at the end of treatment
[12] Jacobeit et al.	17	>36 months	Testosterone undecanoate (TU) (intramuscular)	TT (ng/mL)	0.50 ± –0.25	6.2 ± 1.3*
				Cholesterol (mg/dL)	218 ± 47	188 ± 42*
				LDL (mg/dL)	139 ± 48	139 ± 48*
				HDL (mg/dL)	50 ± 11	51 ± 10
				TGs (mg/dL)	88 ± 14	87 ± 15
				Hemoglobin (g/dL)	13.6 ± 1.2	16.0 ± 1.5
				Hematocrit (%)	41 ± 4	46 ± 4
[26] Jacobeit et al.	12	1 year	Testosterone undecanoate (TU) (intramuscular)	TT (ng/mL)	0.50 ± 0.27	5.5 ± 1.8
				TC (mg/dL)	215.8 ± 58.5	118.3 ± 30.7*
				LDL (mg/dL)	140.5 ± 47.0	196.7 ± 39.6*
				HDL (mg/dL)	51.7 ± 10.8	52.2 ± 11.6
				Hemoglobin (g/dL)	13.8 ± 1.22	15.1 ± –0.68*
				Hematocrit (%)	41 ± 3.6	44.3 ± 1.4*
[27] Mueller et al.	35	1 year	Testosterone undecanoate (TU) (intramuscular)	TT (nmol/l)	1.65 ± 0.83	27.54 ± –15.32.8
				TC (mg/dL)	187.26 ± 45.65	191.00 ± 42.9
				LDL (mg/dL)	126.6 ± 35.27	133.49 ± 36.87
				HDL (mg/dL)	59.00 ± 10.88	48.29 ± 9.77*
				TGs (mg/dL)	122.14 ± 54.67	152.43 ± 51.24*
				Hemoglobin (g/dL)	13.17 ± 1.35	14.83 ± –1.15*
				Hematocrit (%)	41.50 ± 3.33	46.25 ± 3.35*
[28] Meriggiola et al.	5	1 year	TU	TT (nmol/l)	7.19 + 6.04	25.2 ± –10.3
				TC (mmol//l)	4.86 + 0.92	4.64 ± 0.83
				LDL (mmol/L)	2.67 + 0.78	2.54 ± 0.59
				HDL (mmol/L)	1.55 + 0.46	1.48 ± 0.18
				Hemoglobin (g/dL)	14.8 + 1.42	15.90 ± –1.06
				Hematocrit (%)	42.70 + 2.84	45.7 ± 3.07
[29] Elbers et al.	17	12 months	Intramuscular 250 mg T every 2 weeks	TT (nmol/L)	1.6 ± 0.6	31 ± 11
				TC (mmol/L)	4.2 ± 0.9	4.0 ± 0.8
				LDL (mmol/L)	2.57 ± 0.87	2.69 ± 0.85
				HDL (mmol/L)	1.22 ± 0.32	0.98 ± 0.17*
				TGs (mmol/L)	0.69	0.87*
[30] Berra et al.	16	Six months	100 mg testosterone enanthate + 25 mg testosterone propionate im every 10 days	TT (nmol/L)	1.3 ± 1.1	22.5 ± 14.4
				TC (mmol/L)	4.86 ± 0.92	4.64 ± 0.83
				LDL (mmol/L)	2.67 ± 0.78	2.54 ± 0.59
				HDL (mmol/L)	1.55 ± 0.46	1.48 ± 0.18*
				Insulin (mU/mL)	6.1 + 0.7	5.48 + 0.6
				HOMA index	1.3 ± 0.5	1.1 ± 0.04

*Denotes significant change from base line.

Table 2 Effects of T administration on ovaries, endometrium, and breast tissue in female-to-male transsexuals

Study (Reference cited)	Number of Subjects	Duration	Testosterone formulation administered	Comments
[10] Mueller et al.	61	Long-term	Not reported	PCOS was not significantly increased in FMTs in comparison with controls.
[31] Perrone et al.	27	At least 1 year	Intramuscular 100 mg Testovirone depot every 10 days	Exogenous T administration does not stimulate endometrial proliferation in FMT and may have an atrophic effect.
[32] Futterweit & Deligdisch	19	Varying time points	Not reported	Enlarged or borderline enlarged ovaries were noted in several subjects and multiple cystic follicles noted in 17 patients. Diffuse ovarian stromal hyperplasia seen in 16 patients.
[33] Burgess & Shousha	29	Not available	Not available	Long-term androgen administration does not appear to have any significant lasting effect on the normal human female breast.
[34] Slagter et al.	23	18–24 months	Sustanon-250; Organon, Oss, the Netherlands	Long-term administration of androgens in young women causes marked reduction of glandular tissue and promotion of fibrous connective tissue, changes similar to those seen in women in menopause.

exerted no changes in high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), or liver enzymes. Modest increases in hemoglobin and hematocrit were noted, but the values remained within the physiological range (Table 1). Breasts and gonads/internal genitalia did not show pathological changes over the observation period (Table 2). These data suggest that T use in FMT produced no significant side effects over a long time period. In contrast to the aforementioned studies, Goh et al. [40] showed significantly higher levels of TGs, TC, LDL-C, and apolipoprotein-B (Apo B) and a significantly lower level of HDL-C in T-treated women. These observations indicate that T at supra-physiological doses may promote atherogenicity in women. Also, a potential cardiovascular risk of high dose of T was reported by Emi et al. [41] who noted that long-term and high-dose administration of T may cause increased arterial stiffness in FMT transsexuals and suggested a periodic checkup and pharmacological therapies for hypertension to be tailored on an individual basis to prevent atherosclerosis and cardiovascular events. In successive clinical studies of side effects of cross-sex hormone administration of the same population, no evidence was found in support of longer term T administration causing increased cardiovascular morbidity and mortality [39,42,43]. A recent review pertaining to the potential adverse effects of T on breast tissue suggested that there is no substantiated association between T levels and increased risk of breast cancer [44].

Several other studies have suggested that T increased cortical bone thickness and bone mineral density in FMT and that T treatment did not result in significant adverse effects [28,37,38,45]. Some of the effects of long-term T administration in young, non-obese, female subjects include increased visceral fat [35]. T treatment also significantly reduced adiponectin serum levels in FMT [30] but this treatment did not significantly alter lipid profiles or adrenal steroidogenesis [46]. Furthermore, Perrone et al. [31] showed that exogenous T administration did not stimulate endometrial proliferation in FMT and may even exert atrophic effects on the endometrium. T treatment in FMT also caused marked reduction of glandular mammary gland tissue and prominence of fibrous connective tissue. Recently, several studies have focused on the potential adverse effects of T on breast tissue [10,27,33,34,47–49]. Most of these studies reported no serious adverse events with long-acting T with the exception of a single case of breast carcinoma [48] and several cases of ovarian cancer. These changes are similar to those observed at the end-stage of menopausal mammary involution [34,39,42,47].

The information derived from observational and uncontrolled studies in FMTs carry inherent limitation because of varying study designs, sample sizes, durations of therapy, formulations of T, and route of administration, as well as the clinical end points measured [50]. Further, lack of randomized, placebo control clinical trials in FMTs, for obvious reasons, contributes to the limitations of such studies. These methodological shortcomings contribute to the perceived low quality of evidence in such studies. Nevertheless, information gathered from these studies over the past three decades have contributed immensely to the advancement

Table 3 Effects of T administration on body composition and bone density in female-to-male transsexuals

Study (reference cited)	Number of subjects	Duration	Testosterone formulation administered	Comments
[35] Elbers et al.	10	3 years	(Sustanon) 250 mg T esters im every 2 weeks	Long-term T administration in FMT increased body weight, visceral fat and muscle mass.
[29] Elbers et al.	17	1 year	(Sustanon) 250 mg T esters (im) every 2 weeks	Long-term T administration in FMT increased body weight, BMI, visceral fat and muscle mass.
[36] Goh HHV & Ratnam SS	97	Ranges from 2 to 12 years	(Sustanon) 250 mg T esters (im) every 2 weeks	Significant increase in bone mass in overiectomized women treated with androgen therapy.
[37] Turner et al. Clinical Endocrinology	15	2 years	Testosterone Esters 70 mg/week	Significant increase in bone mineral density at the femoral neck and modest increase in at the spine.
[38] Lips P et al.	15	~39 months	Intramuscular 250 mg of T esters every 2 weeks or oral T undecanoate 160 mg/day	Testosterone treatment increased cortical thickness and appeared to protect bone in FMT due to estrogen deficiency

of management of gender reassignment with considerable success and with limited serious side effects [8,9,39]. Further the limited adverse effects observed with the pharmacological doses of T in FMT suggest that adverse effects of physiological T doses would be much less serious and limited in scope and scale.

Summary and Discussion

T is an endogenous sex steroid hormone produced by the ovaries and the adrenal in women and plays an important physiological role in women's health [51]. T insufficiency in women impacts women's sexual health [52]. It is logical to speculate that in women with androgen insufficiency, physiological T replacement therapy restores or improves some domains of sexual function, especially in surgically or naturally postmenopausal women. Clinical studies have documented positive effects of T therapy on women sexual function [13–18,24,53–57]. Nevertheless, fear of adverse effects of T in women has been used as an argument to halt or prevent diagnosis of androgen deficiency in women and to halt use of T in treatment of women's sexual dysfunction [1,5–7]. Unfortunately, the purported fear of T replacement therapy in women remains unsubstantiated, at best. Considerable knowledge was gained from treatment of FMT with supra-physiological doses of T with no serious adverse events reported [6,8,9,39,43]. These findings strongly suggest that physiological doses of T needed to treat women with androgen insufficiency and sexual dysfunction are significantly far lower than those pharmacological doses of T needed to treat sex reassignment and would produce minimal adverse effects. This conclusion is corroborated by a host of studies that examined use of physiological T in women treated for sexual dysfunction for periods ranging from 6 months to 4 years [13–18,24,53–57].

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Category 3

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References

1 Schover LR. Androgen therapy for loss of desire in women: Is the benefit worth the breast cancer risk? Fertil Steril 2008;90:129–40.
2 Basson R. Pharmacotherapy for women's sexual dysfunction. Expert Opin Pharmacother 2009;10:1631–48.
3 Basson R. Testosterone for low libido. N Engl J Med 2009;360:728.
4 Basson R. Testosterone supplementation to improve women's sexual satisfaction: Complexities and unknowns. Ann Intern Med 2008;148:620–1.
5 Basson R, Wierman ME, van Lankveld J, Brotto L. Summary of the recommendations on sexual dysfunctions in women. J Sex Med 2010;7:314–26.
6 Wierman ME, Nappi RE, Avis N, Davis SR, Labrie F, Rosner W, Shifren JL. Endocrine aspects of women's sexual function. J Sex Med 2010;7:561–85.
7 Wierman ME, Basson R, Davis SR, Khosla S, Miller KK, Rosner W, Santoro N. Androgen therapy in women: An Endocrine Society Clinical Practice guideline. J Clin Endocrinol Metab 2006;91:3697–710.
8 Gooren LJ, 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;5:765–76.
9 Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: Extensive personal experience. J Clin Endocrinol Metab 2008;93:19–25.
10 Mueller A, Gooren L. Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2008;159:197–202.
11 Pache TD, Chadha S, Gooren LJ, Hop WC, Jaarsma KW, Dommerholt HB, Fauser BC. Ovarian morphology in long-term androgen-treated female to male transsexuals. A human model for the study of polycystic ovarian syndrome? Histopathology 1991;19:445–52.
12 Jacobeit JW, Gooren LJ, Schulte HM. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. Eur J Endocrinol 2009;161:795–8.
13 Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S, Koch H, Moufarege A, Studd J, APHRODITE Study Team. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 2008;359:2005–17.
14 Shifren JL, Davis SR, Moreau M, Waldbaum A, Bouchard C, DeRogatis L, Derzko C, Bearnson P, Kakos N, O'Neill S, Levine S, Wekselman K, Buch A, Rodenberg C, Kroll R. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: Results from the INTIMATE NM1 Study. Menopause 2006;13:770–9.
15 Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, Moufarege A, Rodenberg C, Buch A, Purdie DW. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: A randomized, placebo-controlled trial. Menopause 2006;13:387–96.
16 Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, Bachman G, Aguirre OA, Lucas JD, Rodenberg C, Buch A, Watts NB. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: A randomized, placebo-controlled trial. Arch Intern Med 2005;165:1582–9.
17 Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, Miller S, Waldbaum A, Bouchard C, Derzko C, Buch A, Rodenberg C, Lucas J, Davis S. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. J Clin Endocrinol Metab 2005;90:5226–33.
18 Buster JE, Kingsberg SA, Aguirre O, Brown C, Breaux JG, Buch A, Rodenberg CA, Wekselman K, Casson P. Testosterone patch for low sexual desire in surgically menopausal women: A randomized trial. Obstet Gynecol 2005;105:944–52.
19 van Staa TP, Sprafka JM. Study of adverse outcomes in women using testosterone therapy. Maturitas 2009;62:76–80.
20 Braunstein GD. Safety of testosterone treatment in postmenopausal women. Fertil Steril 2007;88:1–17.
21 Shufelt CL, Braunstein GD. Testosterone and the breast. Menopause Int 2008;14:117–22.
22 Shufelt CL, Braunstein GD. Safety of testosterone use in women. Maturitas 2009;63:63–6.
23 Basaria S, Dobs AS. Safety and adverse effects of androgens: How to counsel patients. Mayo Clin Proc 2004;79(4 suppl): S25–32.
24 Nachtigall L, Casson P, Lucas J, Schofield V, Melson C, Simon J. Safety and tolerability of the transdermal testosterone patch for up to 4 years in surgically menopausal women on estrogen/progestin therapy. St Petersburg, FL: Program of the International Society for the Study of Women's Sexual Health (ISSWSH); 2010:(Abstract # 24).
25 Somboonporn W, Davis S, Seif MW, Bell R. Testosterone for peri- and postmenopausal women. Cochrane Database Syst Rev 2005;19:CD004509.
26 Jacobeit JW, Gooren LJ, Schulte HM. Long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. J Sex Med 2007;4:1479–84.
27 Mueller A, Kiesewetter F, Binder H, Beckmann MW, Dittrich R. Long-term administration of testosterone undecanoate every 3 months for testosterone supplementation in female-to-male transsexuals. J Clin Endocrinol Metab 2007;92:3470–345.
28 Meriggiola MC, Armillotta F, Costantino A, Altieri P, Saad F, Kalhorn T, Perrone AM, Ghi T, Pelusi C, Pelusi G. Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. J Sex Med 2008;5:2442–53.
29 Elbers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, Gooren LJ. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf) 2003;58:562–71.
30 Berra M, Armillotta F, D'Emidio L, Costantino A, Martorana G, Pelusi G, Meriggiola MC. Testosterone decreases adiponectin levels in female to male transsexuals. Asian J Androl 2006;8:725–9.
31 Perrone AM, Cerpolini S, Maria Salfi NC, Ceccarelli C, De Giorgi LB, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C,

Meriggiola MC. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. J Sex Med 2009;6:3193–200.
32 Futterweit W, Deligdisch L. Effects of androgens on the ovary. Fertil Steril 1986;46:343–45.
33 Burgess HE, Shousha S. An immunohistochemical study of the long-term effects of androgen administration on female-to-male transsexual breast: A comparison with normal female breast and male breast showing gynaecomastia. J Pathol 1993;170:37–43.
34 Slagter MH, Gooren LJ, Scorilas A, Petraki CD, Diamandis EP. Effects of long-term androgen administration on breast tissue of female-to-male transsexuals. J Histochem Cytochem 2006;54:905–10.
35 Elbers JM, Asscheman H, Seidell JC, Megens JA, Gooren LJ. Long-term testosterone administration increases visceral fat in female to male transsexuals. J Clin Endocrinol Metab 1997; 82:2044–7.
36 Goh HH, Ratnam SS. Effects of hormone deficiency, androgen therapy and calcium supplementation on bone mineral density in female transsexuals. Maturitas 1997;26:45–52.
37 Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V. Testosterone increases bone mineral density in female-to-male transsexuals: A case series of 15 subjects. Clin Endocrinol (Oxf) 2004;61:560–6.
38 Lips P, van Kesteren PJ, Asscheman H, Gooren LJ. The effect of androgen treatment on bone metabolism in female-to-male transsexuals. J Bone Miner Res 1996;11:1769–73.
39 van Kesteren PJM, Asscheman H, Megens JAJ, Gooren LJG. Mortality and morbidity in transsexuals subjects treated with cross-sex hormones. Clin Endocrinol (Oxf) 1997;47:337–42.
40 Goh HH, Loke DF, Ratnam SS. The impact of long-term testosterone replacement therapy on lipid and lipoprotein profiles in women. Maturitas 1995;21:65–70.
41 Emi Y, Adachi M, Sasaki A, Nakamura Y, Nakatsuka M. Increased arterial stiffness in female-to-male transsexuals treated with androgen. J Obstet Gynaecol Res 2008;34:890–7.
42 Asscheman H, Gooren LJG, Eklund PLE. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. Metabolism 1989;38:869–73.
43 Asscheman H, Giltay EJ, Megens JAJ, Gooren LJG. Long term mortality in hormone-treated transsexuals. Endocrine Society Abstract 2009.
44 Traish A, Fetten K, Miner M, Hansen M, Guay A. Testosterone and risk of breast cancer: Appraisal of existing evidence. Horm Mol Biol Clin Invest 2010;2:177–90.
45 Sapino A, Pietribiasi F, Godano A, Bussolati G. Effect of long-term administration of androgens on breast tissues of female-to-male transsexuals. Ann N Y Acad Sci 1990;586: 143–5.
46 Futterweit W, Green G, Tarlin N, Dunaif A. Chronic high-dosage androgen administration to ovulatory women does not alter adrenocortical steroidogenesis. Fertil Steril 1992;58: 124–8.
47 Fanchin R, Dubost G, Colau JC, Brémont-Weil C, Frydman R, Ayoubi JM, Grynberg M. Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population. Reprod Biomed Online 2010;20:553–8.
48 Burcombe RJ, Makris A, Pittam M, Finer N. Breast cancer after bilateral subcutaneous mastectomy in a female-to-male trans-sexual. Breast 2003;12:290–3.
49 Mueller A, Gooren LJ, Naton-Schötz S, Cupisti S, Beckmann MW, Dittrich R. Prevalence of polycystic ovary syndrome and hyperandrogenemia in female-to-male transsexuals. J Clin Endocrinol Metab 2008;93:1408–11.
50 Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: A systematic review and meta-analyses. Clin Endocrinol (Oxf) 2010;72:1–10.
51 Traish AM, Feeley RJ, Guay AT. Testosterone therapy in women with gynecological and sexual disorders: a triumph of clinical endocrinology from 1938 to 2008. J Sex Med 2009;6:334–51.
52 Kingsberg S. Testosterone treatment for hypoactive sexual desire disorder in postmenopausal women. J Sex Med 2007;4(suppl 3):227–34.
53 Davis SR, Hirschberg AL, Wagner LK, Lodhi I, von Schoultz B. The effect of transdermal testosterone on mammographic density in postmenopausal women not receiving systemic estrogen therapy. J Clin Endocrinol Metab 2009;94:4907–13.
54 Davis SR. Should women receive androgen replacement therapy, and if so, how? Clin Endocrinol (Oxf) 2010;72:149–54.
55 Davis SR. Testosterone for low libido in postmenopausal women not using systemic oestrogen therapy. Med J Aust 2009;191:134–5.
56 Davis SR, Wolfe R, Farrugia H, Ferdinand A, Bell RJ. The incidence of invasive breast cancer among women prescribed testosterone for low libido. J Sex Med 2009;6:1850–6.
57 Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas 2008;61:17–26.