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## INVITED OPINION

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# Should cross-sex hormone treatment of transsexual subjects vary with ethnic group?

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**G**uidelines for cross-sex hormone treatment of transsexual people have been developed, but no attention has been paid to the specifics of ethnic groups. South East (SE) Asian male-to-female (MtoF) transsexual people may be able to transition to the female sex with lower doses of estrogens/progestins than Caucasians thus reducing health risks. Female-to-male (FtoM) may virilize less profoundly with standard doses of androgens, but this is probably sufficient to pass acceptably as men in view of the less pronounced sex differences in physique in Asians compared with Caucasians. It is timely that studies in Asians are conducted to get a better insight into their specific needs and risks of cross-sex hormone treatment.

In the biomedical sciences, it is widely assumed that (patho) physiological mechanisms reliably established in a certain ethnic group (practically almost always Caucasians), carry a general validity for other groups, regardless of their ethnic background. In its generality this is a workable principle.

Guidelines for cross-sex hormone treatment of transsexual people are now in place.<sup>1</sup> These guidelines have essentially been developed with the Caucasian transsexual person in mind. Ethnic differences in physique and endocrine functioning may, however, warrant tailoring these guidelines specifically to the ethnicity of transsexual persons. This contribution focuses on transsexual people in North/SE Asia.

## HORMONE THERAPY IN MALE-TO-FEMALE TRANSSEXUALS

In general, goals are induction of breast formation, elimination of sexual hair growth, and a more female fat distribution. Sexual hairiness is much less of a problem in people in SE Asia compared with Caucasians. Furthermore, Asian males have more subcutaneous fat in adulthood than Caucasians.<sup>2</sup> The induction of breast formation amounts to pharmacologically mimic the pathophysiology of gynecomastia: an increase of the estrogen stimulus and reduction of the inhibitory effect of androgens on breast tissue.<sup>3</sup> While administration of estrogens alone will decrease androgen production, a combination with a gonadotropin-releasing hormone analogue or a compound that suppresses androgen production or activity, appears more effective. Male contraceptive studies show some baseline differences in the male reproductive system between different ethnic groups, including differences in testicular structure and testosterone metabolism predisposing East Asian men to a higher sensitivity to steroidal contraceptives.<sup>4</sup> Studies of serum hormone levels and production rates of testosterone showed that young Chinese men residing in China have lower testosterone production rates, total testosterone and sex hormone-binding globulin (SHBG) levels compared with Chinese or Caucasian men living in the United States, probably explained by environmental/dietary factors.<sup>4</sup> The  $5\alpha$ -reduced steroids dihydrotestosterone,  $3\alpha$ - $17\beta$  androstane diol glucuronide and androsterone glucuronide levels and their ratios to testosterone are lower in East Asian men, suggestive of lower  $5\alpha$ -reductase enzyme activity in East Asians.<sup>4</sup> There is no evidence that MtoF transsexual people differ biologically from men. For optimal feminization with

estrogens, androgen levels should be as much as possible suppressed, and MtoF of SE Asian extraction might achieve androgen suppression with lower doses of progestational compounds. Progestational compounds have no role in the feminization of the body and should be discontinued after orchiectomy. In postmenopausal women, estrogens combined with progestins increased the risks of coronary disease, venous thrombo-embolism, stroke and breast cancer.<sup>5</sup>

Sebaceous gland activity in SE Asians is less than in other ethnic groups. Reduction of androgen action reduces the sebaceous gland activity and may lead to dry skin in MtoF.

Many MtoF in SE Asia self-medicate, usually with oral contraceptives containing ethinyl estradiol, taken in high doses. Ethinyl estradiol, in comparison with other estrogens, increases the risk of venous thrombosis and cardiovascular death.

A side-effect of estrogen administration may be the induction of hormone sensitive tumors such as breast carcinomas. Asian people may be less prone to develop breast cancer, but they do so at a younger age. It is not clear whether breast carcinomas in MtoF must be regarded as male or female breast cancer.<sup>6</sup> It is of note that male breast cancer has a worse prognosis than female breast cancer.

## HORMONE THERAPY IN FEMALE-TO-MALE TRANSSEXUAL PERSONS

The goal of treatment in FtoM transsexual persons is to induce virilization. This includes a male pattern of sexual hair growth and the development of male physical contours, as well as stopping uterine bleeding which may require a progestational agent. The principal hormonal treatment is exogenous testosterone. While serum testosterone indicates the strength of the androgen

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stimulus, eventual androgen action is modified by differential enzyme and androgen receptor activity.  $5\alpha$ -reductase convert testosterone into  $5\alpha$ -dihydrotestosterone (DHT), with a many times greater affinity to the androgen receptor than testosterone. Its activity seems to vary among ethnic groups. It appeared highest in African-Americans, intermediate in Caucasians, and lowest in Asian-Americans.<sup>4</sup> This provides circumstantial evidence for the increased body hair observed in the Caucasian men. Increased levels of precursor androgens may also play a role.<sup>7</sup> Sexual hairiness may be less pronounced in Asian PtoM, while acne is quite common, explained by the fact that in the same pilosebaceous unit, two different genetic mechanisms with differences in the metabolic fate of DHT may operate.<sup>8</sup>

The genetic differences in the gene encoding the androgen receptor itself contribute to the ability to respond to testosterone. One of the most important genetic differences found is called the CAG repeat polymorphism. The number of CAG repeats an individual has determines how effective his or her androgen receptor is at binding testosterone; those with less repeats are more sensitive to testosterone and those with a greater amount of repeats are

less sensitive.<sup>9</sup> Small but significant differences in the average CAG repeat length were found between different ethnic groups. Men of African descent were found to have the lowest number of repeats at 18-20, Caucasians at 21-22, and East Asians at 22-23, but effect size is small.

Another factor may be the effect of phytoestrogens on testosterone metabolism. Vegetarians and Asian men seem to have higher plasma levels of SHBG and lower levels of free and total testosterone than do men on a Western diet. Weak estrogens may stimulate the synthesis of SHBG in the liver.<sup>10</sup>

### COMPETING INTERESTS

The authors declare that they have no competing interests.

### REFERENCES

- 1 Gooren LJ. Clinical practice. Care of transsexual persons. *N Engl J Med* 2011; 364: 1251-7.
- 2 Hull HR, Thornton J, Wang J, Pierson RN Jr, Kaleem Z, et al. Fat-free mass index: changes and race/ethnic differences in adulthood. *Int J Obes (Lond)* 2011; 35: 121-7.
- 3 Johnson RE, Murad MH. Gynecomastia: pathophysiology, evaluation, and management. *Mayo Clin Proc* 2009; 84: 1010-5.
- 4 Ilani N, Liu PY, Swerdloff RS, Wang C. Does ethnicity matter in male hormonal contraceptive efficacy? *Asian J Androl* 2011; 13: 579-84.
- 5 Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 2012; 7: CD004143.
- 6 Gooren LJ, van Trotsenburg MA, Giltay EJ, van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. *J Sex Med* 2013; 10: 3129-34.
- 7 Lookingbill DP, Demers LM, Wang C, Leung A, Rittmaster RS, et al. Clinical and biochemical parameters of androgen action in normal healthy Caucasian versus Chinese subjects. *J Clin Endocrinol Metab* 1991; 72: 1242-8.
- 8 Toscano V, Balducci R, Bianchi P, Guglielmi R, Mangiantini A, et al. Two different pathogenetic mechanisms may play a role in acne and in hirsutism. *Clin Endocrinol (Oxf)* 1993; 39: 551-6.
- 9 Simanainen U, Brogley M, Gao YR, Jimenez M, Harwood DT, et al. Length of the human androgen receptor glutamine tract determines androgen sensitivity *in vivo*. *Mol Cell Endocrinol* 2011; 342: 81-6.
- 10 Dorgan JF, Judd JT, Longcope C, Brown C, Schatzkin A, et al. Effects of dietary fat and fiber on plasma and urine androgens and estrogens in men: a controlled feeding study. *Am J Clin Nutr* 1996; 64: 850-5.

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