Journal of the Endocrine Society, 2021, Vol. 5, No. 9, 1–7
doi:10.1210/jendso/bvab068
Expert Endocrine Consult

Expert Endocrine Consult

An Approach to Nonsuppressed Testosterone in Transgender Women Receiving Gender-Affirming Feminizing Hormonal Therapy

Arvind Maheshwari,[1] Todd Nippoldt,[1] and Caroline Davidge-Pitts[1]

[1]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, MN 55905, USA

ORCiD numbers: 0000-0001-6956-3299 (A. Maheshwari); 0000-0002-9393-7745 (C. Davidge-Pitts).

Abbreviations: FGA, functional pituitary gonadotroph adenoma; FSH, follicle-stimulating hormone; GAFHT, gender affirming feminizing hormonal therapy; GnRH, gonadotropin-releasing hormone; LC-MS, liquid chromatography–mass spectrometry; LH, luteinizing hormone; SHBG, sex hormone–binding globulin; TGD, transgender and gender diverse.

Received: 4 February 2021; Editorial Decision: 7 April 2021; First Published Online: 16 April 2021; Corrected and Typeset: 14 July 2021.

Abstract

Nonsuppressed levels of testosterone are seen in up to a quarter of transgender women on gender-affirming feminizing hormonal treatment. Multiple factors contribute to this situation, including patient, medication, laboratory, and organ-specific concerns. We propose a stepwise approach to determine the etiology of nonsuppressed levels of testosterone in transgender women. This may lead to an appropriate feminizing hormonal therapy regimen and diagnosis of manageable medical conditions.

Key Words: transgender, hormones, testosterone, estrogen, anti-androgen

Transgender and gender diverse (TGD) people have gender identities that are not aligned with the sex recorded at birth. Gender-affirming care for TGD individuals can include medical and surgical interventions to better align physical characteristics with gender identity. Gender-affirming feminizing hormonal therapy (GAFHT) typically consists of estrogen and androgen- lowering or androgen-inhibiting therapy (Table 1). Estrogen exerts negative feedback at the hypothalamic-pituitary level, leading to decreased endogenous testosterone production from the gonads, along with feminizing effects by action at estrogen receptors. Current Endocrine Society guidelines recommend follow-up evaluation and sex hormone laboratory testing every 3 months during the first year on GAFHT [1]. Goal estradiol levels are 100 to 200 pg/mL and goal testosterone values are less than 50 ng/dL [1]. Expected changes on GAFHT include decreased libido and spontaneous erections, body composition changes including increased fat mass and decrease in muscle mass and strength, redistribution of body fat, breast development, skin softening, and hair changes including increasing softness and decreased terminal hair growth [2].

Testosterone levels on standard doses of estrogen therapy given to transgender women alone do not reliably reduce to values in the cisgender female reference range [3, 4]. The addition of anti-androgens and androgen-lowering therapies help further reduce testosterone levels or action and therefore also limits the dose of estrogen needed to induce feminizing physical changes [3, 4].

In a cohort of 98 transgender women on variable doses of spironolactone and estrogen, 25% did not suppress

ISSN 2472-1972

Table 1. Estradiols and adjunctive agents used in feminizing hormonal treatment

Estradiols	**Typical Doses**
Oral estradiol	2.0-6.0mg daily
Transdermal estradiol	0.025-0.2mg daily
Estradiol patch	
Parenteral estradiol	2-10 mg weekly
Cypionate or valerate	
Anti-androgens	**Typical doses**
Spironolactone	100-300 mg daily
Nonsteroidal anti-androgens	
Bicalutamide	25-50 mg daily
5-alpha reductase inhibitors	
Finasteride	1-5 mg daily
Androgen-lowering agents	**Typical doses**
GnRH analogs	3.75 mg SQ (SC) monthly or
Leuprolide	11.25 mg SQ (SC) 3-monthly
Cyproterone acetate	25-50 mg daily

Transformed from Hembree et al [1]

testosterone [5]. Baseline testosterone levels and spironolactone dosages do not predict successful suppression of testosterone levels. Another study of 229 transgender women in the European Network for the Investigation of Gender Incongruence (ENIGI) cohort showed that 7.9% of women on estrogen and variable anti-androgens (cyproterone acetate [CPA] or spironolactone) did not suppress testosterone [6]. Finally, 33% of transgender women in a cohort of 16 transgender women at University of California San Francisco who were on varying doses of estrogen and spironolactone did not achieve goal total testosterone levels, although only 6% of transgender women did not achieve goal levels of free testosterone [7].

As more transgender women seek care, a common question arises—why are testosterone levels nonsuppressed in up to a quarter of patients on GAFHT? Medical therapy plays a critical role in TGD persons to express their affirmed gender and reduce gender dysphoria. Proper workup of nonsuppressed testosterone levels in transgender women may have important long-term implications regarding appropriate feminizing hormonal therapy doses and early diagnosis of manageable medical conditions. In this paper, we propose an approach to determine causes of nonsuppressed testosterone in a patient on GAFHT (Fig. 1).

Case 1

A 28-year-old transgender woman was seen at the Mayo Clinic Transgender and Intersex Specialty Care Clinic to start GAFHT. She had a history of malnutrition due to avoidant/restrictive food intake disorder, with a body mass index of 17.23 kg/m^2 at baseline. Other medical history included microcephaly and childhood growth hormone deficiency. Physical exam, including genital examination, was unremarkable other than microcephaly and lean body habitus. Baseline hormonal levels included an estradiol level of 26 pg/mL measured by liquid chromatography–mass spectroscopy (LC-MS), follicle-stimulating hormone (FSH) level of 5.0 IU/L, luteinizing hormone (LH) level of 3.5 IU/L, and total testosterone level of 701 ng/dL (by LC-MS), all within reference range for an individual recorded male at birth.

After addressing her nutritional concerns, she was initiated on low-dose spironolactone 25 mg daily and 2 mg of oral estradiol, with a plan to return for follow-up in the clinic. Despite achieving goal levels of estradiol (171 pg/mL) on escalating doses of estradiol and spironolactone, her follow-up laboratory values revealed her total testosterone level remained out of feminine goal range at 514 ng/dL. She reported positive feminizing changes including facial skin softness and breast tenderness, decreasing libido, and loss of spontaneous erections.

Case 2

A 24-year-old transgender woman was seen at the Transgender and Intersex Specialty Care Clinic for follow-up. After a comprehensive evaluation revealed an unremarkable medical history and physical examination (including normal genital exam), she was initiated on GAFHT including oral estradiol and spironolactone. Baseline laboratory testing done at Mayo Clinic prior to GAFHT included total testosterone level of 505 ng/dL (LC-MS) and undetectable estradiol measured by immunoassay.

Follow-up visits revealed no clinical feminization achieved despite increasing doses of estradiol and changing to a different preparation—injectable estradiol valerate. Given her nonsuppressed testosterone levels, her spironolactone was switched to leuprolide—22.5 mg injected every 3 months. With these medication changes, both her LC-MS bioavailable testosterone and LC-MS total testosterone remained out of goal at 105 ng/dL and 476 ng/dL, respectively. Additionally, laboratory testing revealed an LC-MS estradiol level of 244 pg/mL, LH level of 0.3 IU/L (reference range, 1.3-9.6 IU/L), and FSH of 0.3 IU/L (reference range, 1.2-15.8 IU/L). At this visit, she described minimal breast enlargement and tenderness. Her testosterone levels were confirmed on a second blood draw.

Medication Errors

An initial first step would be to consider medication-specific concerns. Determining adherence and confirming the dose taken can often reveal a straightforward reason for having higher-than-expected testosterone levels on GAFHT. Having patients bring or show their prescription

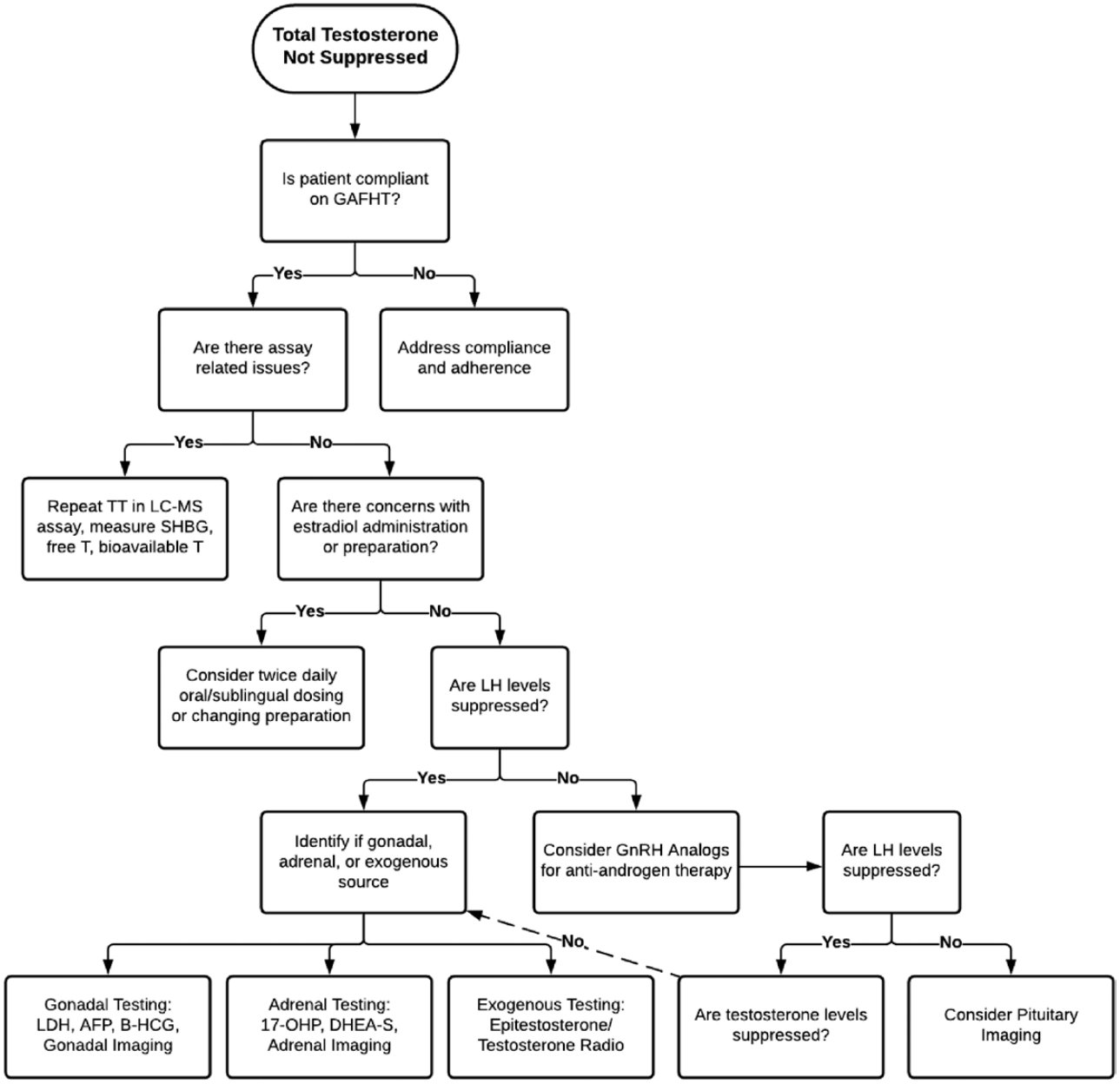

Figure 1. Approach to nonsuppressed testosterone levels on GAFHT. Abbreviations: GAFHT, gender-affirming feminizing hormonal treatment; TT, total testosterone; T, testosterone; SHBG, sex hormone–binding globulin; LH, leutinizing hormone; GnRH, gonadotropin-releasing hormone; LDH, lactate dehydrogenase; AFP, alpha-fetoprotein; B-HCG, beta-human chorionic gonadotropin; 17-OHP, 17-hydroxyprogesterone; DHEA-S, dehydroepiandrosterone sulfate.

along with associated supplies can help eliminate any confusion. Parenterally administered medications may often have challenges when considering self-administration, different available dose concentrations, and syringe sizes. A dispensed concentration of parenteral estradiol may also be different than the prescribed estradiol concentration due to insurance coverage.

Laboratory Testing Issues

Various assays (total, bioavailable, and free testosterone) can be used to measure circulating testosterone. Circulating testosterone can be unbound, albumin-bound, or sex hormone–binding globulin (SHBG)-bound [8]. Total testosterone measures all circulating testosterone, free testosterone measures unbound testosterone, while bioavailable testosterone measures unbound and albumin-bound testosterone. Through the free hormone hypothesis, unbound or free testosterone is thought to exert the biologic actions of testosterone [9]. In cisgender men, both total and free testosterone measurements can be indicators of androgen activity [10, 11]. Albumin does not have as high binding affinity to testosterone as SHBG and therefore dissociates freely, and this portion of circulating testosterone

is thought to also be biologically active [12]. Thus, measurement of free and/or bioavailable testosterone assays can be valuable markers of testosterone activity if there is discordance in feminization and total testosterone levels.

When comparing total testosterone assays, the more common immunoassays generally have higher variability than mass spectrometry assays (gold standard for total testosterone) especially at low and high testosterone concentrations [12]. Given this variability, the Centers for Disease Control and Prevention offers certification of total testosterone assays through a hormone standardization program with a goal performance criterion limiting bias to ±6.4% [13].

SHBG abnormalities can lead to incongruence between total and free or bioavailable testosterone levels. Patients with elevated SHBG levels may have elevated total testosterone levels, while their bioavailable or free testosterone levels remain low or within the goal range. Thus, a potential cause of nonsuppressed total testosterone values may be elevated SHBG levels. SHBG elevation can be caused by aging, various medications (estrogen, anticonvulsants, and metformin), medical conditions (liver disease, hyperthyroidism, and HIV disease) [11]. Rarely SHBG polymorphisms are also responsible for a rise in SHBG levels [11]. Though an elevated SHBG by itself is not a medical contraindication to GAFHT, the etiology of the SHBG elevation should be considered. In this scenario, it is more appropriate to follow free or bioavailable testosterone levels, unaffected by SHBG.

Likewise, SHBG levels affect estradiol measurements [14]. If SHBG levels are elevated, total estradiol may be in range but may not reflect circulating levels of biologically active free estradiol. In circumstances in which patients have testosterone above goal range and feminization is not occurring as expected, targeting a higher total estradiol target or measuring free estradiol may be appropriate. If a patient is taking conjugated equine estrogens, it might be difficult to determine if they are receiving an adequate dose, as estradiol levels cannot be measured in these patients.

In summary, when considering nonsuppressed testosterone levels, laboratory testing issues are important to consider. If expected feminization is occurring while total testosterone remains high, measuring total testosterone on different assays is reasonable. Additionally, measuring free or bioavailable testosterone and SHBG levels may point to total testosterone not being the most reliable indicator of active androgens.

Gender-Affirming Hormone Therapy Preparations

Estrogen

Bioidentical 17-beta–estradiol is the preferred estrogen for GAFHT, thereby avoiding synthetic estrogens which could have higher thromboembolic and cardiovascular risks [15]. 17-beta-estradiol can be provided in oral, transdermal, or parenteral formulations (Table 1). Some patients place the oral tablet under the tongue to mimic sublingual route.

Oral administration is subject to significant first-pass metabolism (converted to estrone and estrone sulfate—significantly less potent estrogens than estradiol). Peak estradiol values occur several hours after ingestion and can remain raised for up to 12 hours before decreasing [16]. Sublingual administration of estradiol avoids first-pass metabolism, is rapidly absorbed, results in peak estradiol levels in 1 hour, and then decreases within 3 hours. In a small cohort of 10 transgender women, when comparing similar doses of oral to sublingual estradiol, sublingual estradiol had higher mean concentrations of serum estradiol levels than oral estradiol in the initial 8 hours after therapy [17]. Given these pharmacokinetics, once-daily oral and sublingual estradiol may not have optimal 24-hour coverage and may lead to testosterone escape through loss of inhibition of the hypothalamic-pituitary-gonadal axis.

Parenteral and transdermal preparations are thought not have a first-pass metabolism and do not affect liver protein synthesis as oral preparations do. Transdermal preparations typically peak within several hours of administration and typically last 7 days and are recommended to be applied once to twice per week depending on the manufacturer [16]. Patch and gel administration is associated with a high variation in circulating estradiol values—even within the same patient in cisgender women [18]. Areas of application may affect absorption with significant differences in bioavailability (scrotum, abdomen, buttocks regions have the highest absorptions). Other factors modifying absorption include variations in dermal blood flow (circadian differences), skin thickness, and dehydration or humidity. In this scenario of poor absorption, estradiol levels would be low along with the higher-than-expected testosterone levels.

Parenteral estradiol shows a peak of estradiol values in 2 to 4 days with an average duration of 7 to 11 days (depending on the specific preparation—valerate vs cypionate and its lipophilicity) [16]. Subcutaneous and intramuscular estradiol administration appear to have similar pharmacokinetics [16]. Measuring peak, mid-cycle, and trough estradiol levels may reveal intra-individual variation in absorption.

In summary, consideration of estradiol pharmacokinetics and application of therapy can reveal a reason for nonsuppressed testosterone levels. Providers can choose to adjust their prescription to avoid the phenomenon of testosterone escape. Oral or sublingual estradiol can be given twice daily in divided doses. A trial of transdermal estradiol applied at different body parts may reveal significant differences in absorption. Changing preparations or the route of

estradiol may be another strategy to suppress testosterone if adequate estradiol absorption is not achieved.

Anti-Androgens and Androgen-Lowering Therapies

Anti-androgens and androgen-lowering therapies vary in their mechanisms to achieve desired feminization. Several classes of therapies are available—spironolactone, gonadotropin-releasing hormone analogs (GnRH), nonsteroidal anti-androgens, CPA, and 5-alpha reductase inhibitors (Table 1). Choice of adjunctive therapy may reflect region-specific regulatory approval, price, availability, adverse effect profile, and prescriber preference [19].

Spironolactone, the most common anti-androgen prescribed in the United States, limits androgens in multiple methods. It acts as an antagonist at the androgen receptor, may block testosterone synthesis at the 17-alpha hydroxylase, 17, 20-lyase enzymatic steps at the adrenal level, and additionally has a weak progestin action exerting negative feedback at the hypothalamic and pituitary levels, thereby lowering testosterone secretion from the gonads. Nonsteroidal anti-androgens also act as antagonists at the androgen receptor, though more potently.

GnRH analogs act at the hypothalamus, decreasing GnRH secretion and thereby decreasing gonadotropin (LH and FSH) secretion, which in turn leads to decreased testosterone synthesis. Cyproterone acetate (CPA), which is not approved in the United States by the Food and Drug Administration, is a potent progesterone receptor agonist that leads to suppression of the hypothalamic-pituitary-gonadal axis along with antagonistic effects at the androgen receptor level. Lastly, 5-alpha reductase inhibitors decrease the conversion of testosterone to the more potent dihydrotestosterone in androgen-sensitive target tissues and are often used to reduce androgen action in scalp hair follicles to limit alopecia.

When comparing GnRH analogs with CPA, similar levels of LH and testosterone suppression were achieved at 12 months on standard dosing in 40 transgender women in 1 study, although a more rapid suppression of LH and testosterone was found at 3 months in the GnRH agonist group [20]. Another study compared estradiol with spironolactone to estradiol with CPA to estradiol alone in a cross-sectional analysis. The lowest testosterone levels were found to be achieved in the CPA group, with the spironolactone group next, and finally the estradiol alone group [21]. Spironolactone use in transgender women has mostly led to lower levels in testosterone in most studies, although some studies show levels of testosterone that do not significantly lower when comparing estradiol to estradiol plus spironolactone therapy [4, 21]. The addition of 5-alpha reductase inhibitors seems to increase testosterone levels when combined with estradiol [4].

Therefore, choice of anti-androgen and androgen-lowering therapy may influence testosterone levels. However, due to the variation in anti-androgen mechanisms, individual responses to various preparations may vary considerably in serum testosterone levels and potential clinical feminization response.

Gonadal Pathology

Pathologic gonadal sources of testosterone production may also be discovered during GAFHT. In these cases, gonadotropin levels are typically low or suppressed, with testosterone levels that remain above goal range along with potentially inadequate feminization on GAFHT. Multiple case reports with testicular cancer have been reported in the literature diagnosed after initiation of GAFHT [22-24]. These cases were diagnosed due to elevated testosterone levels despite adequate estradiol levels and multiple high-dose anti-androgen medications, with stalled feminization. Low LH levels, testicular mass on exam, and nonrevealing adrenal workup leading to testicular imaging and relevant elevated tumor markers (lactate dehydrogenase, alpha-fetoprotein, and beta-human chorionic gonadotropin [β-HCG]) ultimately revealed the diagnosis [22-24].

Adrenal Pathology

Excess adrenal androgen production needs to be considered in patients with nonsuppressed testosterone levels despite adequate GAFHT. Similar to gonadal pathologies, LH levels would be low or suppressed along with inadequate feminization on GAFHT. Adrenal androgens such as dehydroepiandrosterone and dehydroepiandrosterone sulfate are precursors to testosterone synthesis and may be elevated. Adrenal pathologies can include congenital adrenal hyperplasia and androgen-producing adrenal tumors.

Nonclassic congenital adrenal hyperplasia 21-hydroxylase deficiency may be asymptomatic in transgender women, but many may have acne [25]. Diagnostic testing includes measuring 17-hydroxyprogesterone levels, baseline and with co-syntropin stimulation [25]. Pure androgen secreting adrenal tumors are infrequently reported, with co-secretion of cortisol being more common [26]. Presence of elevated androgen production and signs of rapid hypervirilization should prompt suspicion for adrenocortical carcinoma[26]. Imaging of adrenal glands may reveal adrenal enlargement and diagnostic testing should evaluate for adrenal hyperfunction.

Pituitary Pathology

A rare potential cause of nonsuppressed testosterone values may also be a functional pituitary gonadotroph adenoma (FGA) with hypersecretion of testosterone. A central cause can be suspected with elevated LH levels along with elevated testosterone levels despite adequate estradiol therapy. At the present time, no FGAs have been described in the literature in TGD individuals.

A review of FGAs reveals that most gonadotroph-secreting adenomas are not functional and adenomas secreting functional gonadotropins are exceedingly infrequent [27]. Most reports of functional gonadotroph adenomas are in cisgender women and are a clinical rarity in cisgender men. In those functional FGA cases, there is a universal elevation of FSH levels with variable LH and testosterone levels along with clinical manifestations of testicular enlargement due to the trophic effect of FSH and visual field deficits such as bi-temporal hemianopsia due to the pituitary adenoma [27]. These FGAs often have suprasellar or parasellar extension as compared to other pituitary adenomas [27].

Case 1 Resolution

We performed further testing on our patient with testosterone levels out of goal range despite adequate estradiol levels including bioavailable testosterone levels and SHBG. On a combination of spironolactone and estradiol therapy, her bioavailable testosterone was suppressed below the cisgender male range (reference range, 83-257 ng/dL). Her SHBG level was elevated to 99 nmol/L (reference range, 10-57 nmol/L). Simultaneously, she was admitted to the hospital for further management of her avoidant food intake disorder. After a 4-week inpatient admission and additional weight gain, she was subsequently discharged. Follow-up laboratory testing showed a total testosterone of 28 pg/dL and bioavailable testosterone of 3.6 pg/dL.

Her SHBG elevation was thought to be due to a combination of oral estradiol therapy and malnutrition. Therefore, not only was her total testosterone misleading, but her estradiol dose might have also been subtherapeutic with her elevated SHBG levels. Given her adequate feminization, a plan was made to adjust her GAFHT dosages to the target bioavailable testosterone and free estradiol values.

Case 2 Resolution

Given the combination of suppressed gonadotropin and elevated testosterone levels, we ordered testicular imaging, and tumor marker levels including alpha-fetoprotein and β-HCG. Scrotal ultrasound revealed a left-sided 2.7-cm hypoechoic mass suspicious for a primary testicular neoplasm. β-HCG levels were elevated on multiple draws—4.9 and 4.4 IU/L (reference range, <1.4 IU/L). Due to these findings, she was referred to Urology for further management for concern of a germ cell tumor.

After negative whole-body imaging looking for metastatic involvement, she underwent a bilateral orchiectomy. Her contralateral testis was removed in the same procedure as a gender-affirming surgical procedure. Final surgical pathology revealed a left-sided mixed germ cell tumor including teratoma, embryonal carcinoma, and yolk sac tumor. Postoperatively, her leuprolide was discontinued, and her estradiol was continued.

Conclusion

Nonsuppressed testosterone levels on GAFHT requires a straightforward approach to determine the etiology and therapeutic approach. An initial step is to review the degree of feminization achieved, medication-specific concerns, and assay-related reasons. Medication administration education, dosing adjustments, changes in estradiol preparations and routes of administration, and choice of testosterone assays may address the nonsuppressed testosterone levels. If these common reasons are nonrevealing, the next step would be to consider pituitary, adrenal, and gonadal sources of elevated testosterone. Gonadotropin levels and organ-specific testing and imaging can ultimately lead to the diagnosis.

Additional Information

Correspondence: Caroline Davidge-Pitts MBBCh, Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA. Email: Davidge-Pitts.Caroline@mayo.edu.

Disclosures: The authors have no financial disclosures. Hormone therapy for gender dysphoria/incongruence is off-label.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;**102**(11):3869-3903.
2. Hamidi O, Davidge-Pitts CJ. Transfeminine hormone therapy. *Endocrinol Metab Clin North Am*. 2019;**48**(2):341-355.
3. Prior JC, Vigna YM, Watson D. Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. *Arch Sex Behav*. 1989;**18**(1):49-57.
4. Leinung MC, Feustel PJ, Joseph J. Hormonal treatment of transgender women with oral estradiol. *Transgend Health*. 2018;**3**(1):74-81.

5. Liang JJ, Jolly D, Chan KJ, Safer JD. Testosterone levels achieved by medically treated transgender women in a United States endocrinology clinic cohort. *Endocr Pract*. 2018;**24**(2):135-142.
6. de Blok CJM, Klaver M, Wiepjes CM, et al. Breast development in transwomen after 1 year of cross-sex hormone therapy: results of a prospective multicenter study. *J Clin Endocrinol Metab*. 2018;**103**(2):532-538.
7. Deutsch MB, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gynecol*. 2015;**125**(3):605-610.
8. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone's binding in circulation: physiological and clinical implications. *Endocr Rev*. 2017;**38**(4):302-324.
9. Mendel CM. The free hormone hypothesis. Distinction from the free hormone transport hypothesis. *J Androl*. 1992;**13**(2):107-116.
10. Antonio L, Wu FC, O'Neill TW, et al.; European Male Ageing Study Study Group. Low free testosterone is associated with hypogonadal signs and symptoms in men with normal total testosterone. *J Clin Endocrinol Metab*. 2016;**101**(7):2647-2657.
11. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;**103**(5):1715-1744.
12. Trost LW, Mulhall JP. Challenges in testosterone measurement, data interpretation, and methodological appraisal of interventional trials. *J Sex Med*. 2016;**13**(7):1029-1046.
13. Centers for Disease Control and Prevention. HoSt/VDSCP: hormone and vitamin D standardization programs. http://www.cdc.gov/labstandards/hs.html
14. Rosner W. Free estradiol and sex hormone-binding globulin. *Steroids*. 2015;**99**(Pt A):113-116.
15. Asscheman H, T'Sjoen G, Lemaire A, et al. Venous thromboembolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014;**46**(7):791-795.
16. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric*. 2005;**8**(Suppl 1):3-63.
17. Doll EE, Ian Gunsolus B, Lamberton N, Tangpricha V, Lynne Sarvaideo J. SUN-LB9 pharmacokinetics of sublingual versus oral estradiol in transgender women. *J Endo Soc*. 2020;**4**.(Suppl 1):SUN-LB9. Published online May 8, 2020. doi:10.1210/jendso/bvaa046.2237
18. Lycette JL, Bland LB, Garzotto M, Beer TM. Parenteral estrogens for prostate cancer: can a new route of administration overcome old toxicities? *Clin Genitourin Cancer*. 2006;**5**(3):198-205.
19. Mamoojee Y, Seal LJ, Quinton R. Transgender hormone therapy: understanding international variation in practice. *Lancet Diabetes Endocrinol*. 2017;**5**(4):243-246.
20. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol (Oxf)*. 2016;**85**(2):239-246.
21. Angus L, Leemaqz S, Ooi O, et al. Cyproterone acetate or spironolactone in lowering testosterone concentrations for transgender individuals receiving oestradiol therapy. *Endocr Connect*. 2019;**8**(7):935-940.
22. Elshimy G, Tran K, Harman SM, Correa R. Unmasked testicular seminoma during use of hormonal transgender woman therapy: a hidden hCG-secreting tumor. *J Endocr Soc*. 2020;**4**(7):bvaa074.
23. Kvach EJ, Hyer JS, Carey JC, Bowers M. Testicular seminoma in a transgender woman: a case report. *LGBT Health*. 2019;**6**(1):40-42.
24. Wolf-Gould CS, Wolf-Gould CH. A Transgender woman with testicular cancer: a new twist on an old problem. *LGBT Health*. 2016;**3**(1):90-95.
25. Merke DP, Auchus RJ. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *N Engl J Med*. 2020;**383**(13):1248-1261.
26. Sherlock M, Scarsbrook A, Abbas A, et al. Adrenal incidentaloma. *Endocr Rev*. 2020;**41**(6):775-820.
27. Ntali G, Capatina C, Grossman A, Karavitaki N. Clinical review: functioning gonadotroph adenomas. *J Clin Endocrinol Metab*. 2014;**99**(12):4423-4433.