Assessment of Gender-Affirming Hormone Therapy Requirements

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Abstract

Purpose: There are currently no recommendations regarding the starting doses of hormone therapy for individuals with gender dysphoria. The purpose of this study was to assess the hormone dose needed to achieve target hormone levels in transgender men and transgender women, and whether body mass index (BMI) affects these doses.

Methods: A retrospective chart review of subjects seeking gender-affirming hormone therapy was performed. Height, weight, hormone doses, and serum hormone levels were collected from charts. Data were analyzed for a correlation between BMI and effective hormone dosing (dose that achieved hormone levels in the target range).

Results: Charts from 319 subjects were reviewed; however, only 84 transgender women and 71 transgender men had serum hormone levels available and only 40 transgender women and 54 transgender men had plasma hormone levels in the target range (normal range for affirmed gender). For transgender women, there was a significant negative correlation between BMI and effective estradiol dose ($r = -0.337$, $p = 0.04$). For transgender men, there was a positive correlation between BMI and effective testosterone dose ($r = 0.409$, $p = 0.002$).

Conclusion: Increased BMI was associated with lower estrogen dose requirements in transgender women. In transgender men, an increase in BMI was associated with increased testosterone dose requirements. These results suggest that BMI may influence effective gender-affirming hormone dosing; however, further studies are needed to examine its utility in determining the initial hormone dose.

Keywords: clinical care, hormone, obesity, transgender

Introduction

TRANSGENDER IS AN UMBRELLA TERM for people whose gender identity and/or gender expression differs from the sex they were assigned at birth. Individuals identifying as transgender often seek gender-affirming hormone therapy; the University of Kentucky's Endocrinology Clinic provides such therapy following guidelines published by the Endocrine Society.¹ However, hormone doses for transgender men and transgender women are not standardized; instead, they are subjectively personalized.

The Endocrine Society has published guidelines that address the endocrine treatment of gender-dysphoric/gender-incongruent persons.¹ The guideline committee concluded that individuals with gender dysphoria require a safe and effective hormone regimen that will (1) suppress endogenous

sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. They also suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications.¹ However, the guidelines do not currently have recommendations regarding specific doses of hormones needed to achieve target levels in transgender men and transgender women. Rather, the guidelines have suggested hormone regimens, which include routes of administration of estrogen and testosterone, and dose ranges.¹ This leaves the provider with essentially an "educated guess" of what dose of hormone to initiate for a particular individual, taking into account the prior experience of the provider.

Body mass index (BMI) has an effect on many endocrine and metabolic processes, and it may affect serum hormone

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levels of this population. For example, classes I and II obesity (BMI 30–39.9 kg/m²) are associated with lower levels of sex hormone-binding globulin (SHBG) and total testosterone; class III obesity (BMI ≥40 kg/m²) is associated with decreases in free testosterone, likely due to suppression of luteinizing hormone pulses.² Conversely, obesity is associated with increased levels of estrogen.³ To date, there is no literature supporting the recommended doses of testosterone or estradiol needed to achieve target serum hormone levels.

The purpose of this study was to assess the hormone dose needed to achieve target hormone levels in transgender men and transgender women, and whether BMI affects the hormone dose needed to achieve target hormone levels in transgender men and transgender women. The study was initiated with the hypothesis that BMI affected estradiol dose requirements for transgender women, following observations in the clinic that obese transgender women were often on much lower estradiol doses than were lean transgender women, despite having similar estradiol levels when they were in the target range.

Methods

Study description

This study was approved by and work was completed in compliance with the Institutional Review Board (IRB) of the University of Kentucky. As this was a retrospective chart review, the consent requirement was waived by the IRB; all data collected in the study were approved by the IRB. A retrospective chart review of subjects attending endocrinology clinics between September 1, 2008 and August 22, 2016 was performed. Subjects were identified based on ICD-9 codes 302.85 (Gender identity disorder in adolescents or adults) and 302.6 (Gender identity disorder in children)⁴ and ICD-10 codes F64.1 (Gender identity disorder in adolescence and adulthood), F64.2 (Gender identity disorder of childhood), F64.8 (Other gender identity disorders), and F64.9 (Gender identity disorder, unspecified).⁵ As this study was a retrospective chart review, the provision of medical care, monitoring, hormone prescriptions, laboratory screening, and patient management were not part of this study.

Data collection

Inclusion criteria were use of oral estradiol (with or without spironolactone) for transgender women or injected testosterone therapy for transgender men, continuous use of hormone therapy for at least 6 months, and at least one on-therapy plasma hormone level available (only testosterone levels drawn mid-way between injections ±1 day were included; estradiol levels could be drawn at any time). Subjects who reported variable doses or formulations of hormone therapy, including use of hormones off prescription, use of sublingual estrogen, or BMI <16 or >50 kg/m², were excluded. Data collected included age at initiation of hormone therapy, race/ethnicity, height and weight, and medication dose (mg/day for oral estradiol; daily testosterone dose was calculated as injected dose divided by days between administration).

Data were analyzed by gender transition for all subjects, and for subjects who achieved plasma hormone levels in the target range. For transgender women, the Endocrine

Society guidelines define the target range of estradiol as 100–200 pg/mL (367–734 pmol/L)¹; as many providers in our practice do not titrate therapy when estradiol levels are above 90 pg/mL (330 pmol/L), the range of 90–200 pg/mL (330–734 pmol/L) was used to define effective estrogen dosing. For transgender men, the Endocrine Society guidelines definition of 320–1000 ng/dL (11.1–34.7 nmol/L) was used to define effective testosterone dosing.¹

Statistical analyses

Baseline and demographic data are presented as mean ± standard deviation. Where multiple data points per subject were available, the data were averaged⁶; thus, only one value per subject is shown. The number of unique subjects is specified under results. Correlation analyses were performed by using linear regression (GraphPad Prism; GraphPad Software, La Jolla, CA). When data were not normally distributed (plasma estradiol level in Fig. 1A, C, and estradiol dose in Fig. 1B, D) the data were log-transformed and regression was performed on transformed data. However, data are shown in raw (non-transformed) form. *p* values <0.05 were considered statistically significant.

Results

A total of 319 subjects were seen for gender-affirming hormone therapy between September 1, 2008 and August 22, 2016. However, only 84 transgender women and 71 transgender men met the inclusion criteria. Two subjects (both transgender women) were excluded due to having a BMI >50 kg/m²; 24 transgender women were excluded due to the use of estrogen via transdermal preparations (*n*=6) and injected estrogen (*n*=17). The remaining 138 subjects were excluded due to not having hormone laboratory results available or duration of therapy <6 months at the limit of the IRB-approved study review dates.

Transgender women

Eighty-four subjects met inclusion criteria, but only 40 subjects achieved estradiol levels in the target range (90–200 pg/mL [330–734 pmol/L]; 5 of these 40 subjects had estradiol levels in the 90–99 pg/mL [330–363 pmol/L] range). There were no differences in average age at initiation of hormone therapy, BMI, spironolactone use, or race/ethnicity between the total group and the group that had estradiol levels in the target range (Table 1). Of the 40 subjects with estradiol levels in the target range, 33 used spironolactone with an average dose of 142 mg/day (range 100–400 mg/day). Within the total group, the daily dose of estradiol used ranged from 1 to 10 mg/day, and estradiol levels on therapy ranged from 20 to 363 pg/mL (73–1295 pmol/L; Fig. 1A). There was a significant correlation between estradiol dose and plasma estradiol level for the overall cohort (*r*=0.385; *p*=0.0005; Fig. 1A). For the 40 subjects who achieved estradiol levels in the target range, the correlation between estradiol dose and plasma level was not significant (NS) (Fig. 1B). There was no correlation between BMI and plasma estradiol levels for the overall group (Fig. 1C); however, for the group that achieved target plasma estradiol levels, there was a significant negative correlation between BMI and effective estradiol dose (*r*=−0.337; *p*=0.04; Fig. 1D).

FIG. 1. Hormone doses, levels, and BMI in transgender women. (A) Plasma estradiol levels correlate with daily estradiol dose. $n = 84$ subjects. (B) Lack of correlation between daily estradiol dose and plasma estradiol level in subjects who achieved target estradiol levels. $n = 40$ subjects. (C) Lack of correlation between BMI and plasma estradiol levels in the total cohort. $n = 84$ subjects. (D) Negative correlation between BMI and estradiol dose for subjects who achieved target estradiol levels. $n = 40$ subjects. Daily dose is mg/day. Target estradiol levels 90–200 pg/mL (330–734 pmol/L). Data are shown as untransformed values. BMI, body mass index; NS, not significant.

Transgender men

Seventy-one subjects met inclusion criteria, but only 54 subjects achieved testosterone levels in the target range. There were no differences in average age at initiation of hormone therapy, BMI, or race/ethnicity between the total group and the group that had testosterone levels in the target range (Table 1). The dose of testosterone used ranged from 3.5 to 21.4 mg/day (reflecting doses from 25 to 150 mg weekly,

or from 50 to 300 mg every 2 weeks), and testosterone levels on therapy ranged from 33 to 1600 ng/dL (1.14–55.5 nmol/L; Fig. 2A). There was no significant correlation between testosterone dose and plasma testosterone level for the overall cohort ($r = 0.164$; $p = \text{NS}$; Fig. 2A). For the 54 subjects who achieved testosterone levels in the target range (320–1000 ng/dL; 11.1–34.7 nmol/L), there was no significant correlation between testosterone dose and plasma level (Fig. 2B). There was a significant negative correlation

TABLE 1. DEMOGRAPHIC DATA

	Transgender women (all)	Transgender women achieving estradiol 90–200 pg/mL (330–734 pmol/L)	Transgender men (all)	Transgender men achieving testosterone 320–1000 ng/dL (11.1–34.7 nmol/L)
Number	84	40	71	54
Age (years), mean $\pm$ SD	29.9 $\pm$ 12.3	30.7 $\pm$ 11.2	25.8 $\pm$ 6.7	26.2 $\pm$ 6.7
BMI (kg/m ²), mean $\pm$ SD	28.7 $\pm$ 9.1	31.1 $\pm$ 10.8	29.3 $\pm$ 7.3	29.5 $\pm$ 7.3
Spironolactone use, n (%)	73 (87)	33 (82)	n/a	n/a
White, non-Hispanic, %	85	85	91	85
Black, %	11	12	7	9
Other, %	4	3	2	6

BMI, body mass index; n/a, not applicable; SD, standard deviation.

FIG. 2. Hormone doses, levels, and BMI in transgender men. (A) Plasma testosterone levels do not correlate with daily testosterone dose. $n=71$ subjects. (B) Lack of correlation between daily testosterone dose and plasma testosterone levels for subjects who achieved target testosterone levels. $n=54$ subjects. (C) A significant negative correlation between BMI and plasma testosterone levels in the total cohort. $n=71$ subjects. (D) Positive correlation between BMI and testosterone dose in subjects who achieved target testosterone levels. $n=54$ subjects. Daily dose was calculated as injected dose divided by days between injections. Target testosterone levels 320–1000 ng/dL (11.1–34.7 nmol/L).

between BMI and plasma testosterone levels for the overall group ($r = -0.243$; $p = 0.04$; Fig. 2C). For the group that achieved target plasma testosterone levels, there was a significant positive correlation between BMI and daily testosterone dose ($r = 0.409$; $p = 0.002$; Fig. 2D).

Discussion

This retrospective chart review of transgender subjects undergoing gender-affirming hormone therapy demonstrated that increased BMI is associated with lower estrogen dose requirements in transgender women, but higher testosterone requirements in transgender men. Strikingly, there was a very wide range of achieved hormone levels on gender-affirming hormone therapy, including both very low and very high levels. For transgender women, there was a significant correlation between daily estradiol dose and hormone level. When we restricted our analyses to only those subjects achieving hormone levels in the target range, there was no correlation between hormone dose (termed “effective” hormone dose) and achieved hormone level for either transgender women or transgender men. However, there was a significant corre-

lation between BMI and effective hormone dose for both transgender men and transgender women (positive correlation for transgender men and negative correlation for transgender women).

Thus, our data suggest that BMI may influence gender-affirming hormone dosing. At present, providers have very little data to guide their selection of hormone doses, and many start at low doses and titrate up based on hormone levels. However, our data suggest that for transgender women, starting at low doses for lean subjects may delay desired physical changes, whereas even low doses in obese subjects may achieve supraphysiological estrogen levels, with potential risks for adverse effects.

The negative correlation between dose required and BMI in transgender women is likely a result of the aromatization of endogenous androgens to estrogens that occurs in adipose tissue. Several studies document the reduction in plasma concentrations of SHBG and testosterone with a concomitant rise in plasma concentration of estrogen in obesity.^{3,7,8} The rise in estrogen has a negative effect on the hypothalamus by altering the gonadotropin-releasing hormone pulses, resulting in suppression of gonadotropin follicle-stimulating

hormone and luteinizing hormone secretions, thus leading to hypogonadotropic hypogonadism.^{3,7,8} This is believed to be due to the increased peripheral aromatization of androgens in adipose tissue.⁸ Enhanced conversion of androstenedione to estrogen has been found in obese men compared with normal weight men, independent of the production rate of androstenedione,⁹ providing further evidence that enhanced aromatization of androstenedione due to an increased adipose tissue mass may account for the high plasma estrogen levels observed in obese men. We do not have estradiol levels on subjects before initiation of hormone therapy, but the literature leads us to expect that those with obesity would have higher pre-treatment estradiol levels compared with those at a normal body weight.

Unfortunately, many of our subjects do not have health insurance coverage and pay out of pocket for their health care costs. Further, there are no data to guide therapy in transgender women who achieve target estradiol levels but who do not achieve target testosterone levels (or *vice versa*). To minimize costs to our subjects, our practice does not routinely measure testosterone or SHBG in transgender women. Thus, we do not have data to address whether the estrogen ± spironolactone doses administered provided sufficient suppression of testosterone levels. A recent study investigating hormone levels in transgender women found no correlation between average oral estradiol dose and corresponding serum estradiol, and it found variable suppression of testosterone levels.¹⁰ Notably, only 25% of their subjects achieved testosterone levels <50 ng/dL,¹⁰ which is defined as the target by the Endocrine Society guidelines.¹ Further, although this study did find that obesity led to lower testosterone levels, the researchers did not examine the relationship between obesity and effective hormone dosing.¹⁰ Further research is needed to determine whether both estradiol and testosterone levels should be targeted, or which is the more important to achieve the desired physical changes in transgender women.

For transgender men, we found a positive correlation between BMI and effective testosterone doses. There are very few data regarding dose adjustments of testosterone therapy, perhaps, in part, due to the fairly wide normal range of testosterone levels. Our practice usually only measures estradiol levels in transgender men if they have persistence of menses despite testosterone levels in the therapeutic range, in part to minimize costs. Thus, we do not have sufficient data to address whether the testosterone doses administered provided sufficient suppression of estradiol levels. There had been at least a theoretical concern that aromatization of testosterone could lead to supraphysiologic estradiol levels. However, several studies have found decreased estradiol levels in transgender men using testosterone therapy.^{11–13}

Limitations

This was a retrospective chart review; thus, our data were limited by what was available in the chart at the time of the review. It was striking that many of our subjects did not have laboratory test results available, despite the fact that our standard protocol is to order hormone levels after 6–12 months of initiation of therapy and after each dose titration. As discussed in the previous sections, to minimize costs our practice does not routinely measure testosterone in transgender

women or estradiol in transgender men; thus, the effectiveness of doses at suppressing these hormones is not available. Despite our efforts to minimize costs to subjects by minimizing laboratory orders, the low rate of hormone results may be due, in part, to cost concerns. In addition, many of our subjects had only a few visits at our clinic, or large gaps (years) between visits. The reasons for this are unclear, but they may reflect cost constraints or other socioeconomic factors limiting access to care.

This was a single-center study with a primarily self-identified White population, with a high prevalence of overweight or obesity. Due to provider preference and cost issues, the majority of subjects in this practice are treated with oral estradiol (transgender women) or injectable testosterone (transgender men), and only data on these subjects were included. Thus, the results may not be translatable to other populations using injected or transdermal formulations of estrogen, or transdermal forms of testosterone.

There is a paucity of data on the effect of spironolactone on estrogen levels; however, the use of spironolactone was variable and thus not included in our study. Further, cyproterone acetate or gonadotropin-releasing hormone agonists were not used in this practice; these agents may have different effects on target hormone levels. The timing of dose titration(s) was not available and, therefore, we cannot comment on the rate of titration to achieve target range. Another limitation was that various laboratories were used by subjects and thus the hormone assays were not consistent; however, this reflects the “real world” practices of many providers who base clinical decision making on available resources. Finally, in this retrospective chart review, we were unable to collect information regarding physical changes or subject satisfaction with their hormone therapy; thus, we cannot draw any conclusions regarding the impact of achieving target hormone levels on subject outcomes.

Conclusion

Our study revealed a correlation between BMI and effective hormone therapy dosage, which suggests that BMI may influence effective gender-affirming dosing. A prospective trial is needed to determine whether BMI can guide hormone therapy dose, and to provide definitive data on hormone dosing, measurements, efficacy, and safety. However, based on these data, we suggest consideration of lower initial estradiol doses for obese transgender women, and higher initial doses for lean transgender women, then titrating doses based on achieved plasma levels. For transgender men, we recommend considering higher testosterone doses for obese subjects. An important consideration is the education of transgender women to explain the doses chosen that may seem counter-intuitive.

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Disclaimer

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Author Disclosure Statement

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