ORIGINAL RESEARCH—TRANSGENDER AND GENDER NONCONFORMANCE

Cross-Sex Hormonal Treatment and Body Uneasiness in Individuals with Gender Dysphoria

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ABSTRACT

Introduction. Cross-sex hormonal treatment (CHT) used for gender dysphoria (GD) could by itself affect well-being without the use of genital surgery; however, to date, there is a paucity of studies investigating the effects of CHT alone.
Aims. This study aimed to assess differences in body uneasiness and psychiatric symptoms between GD clients taking CHT and those not taking hormones (no CHT). A second aim was to assess whether length of CHT treatment and daily dose provided an explanation for levels of body uneasiness and psychiatric symptoms.
Methods. A consecutive series of 125 subjects meeting the criteria for GD who not had genital reassignment surgery were considered.
Main Outcome Measures. Subjects were asked to complete the Body Uneasiness Test (BUT) to explore different areas of body-related psychopathology and the Symptom Checklist-90 Revised (SCL-90-R) to measure psychological state. In addition, data on daily hormone dose and length of hormonal treatment (androgens, estrogens, and/or antiandrogens) were collected through an analysis of medical records.
Results. Among the male-to-female (MtF) individuals, those using CHT reported less body uneasiness compared with individuals in the no-CHT group. No significant differences were observed between CHT and no-CHT groups in the female-to-male (FtM) sample. Also, no significant differences in SCL score were observed with regard to gender (MtF vs. FtM), hormone treatment (CHT vs. no-CHT), or the interaction of these two variables. Moreover, a two-step hierarchical regression showed that cumulative dose of estradiol (daily dose of estradiol times days of treatment) and cumulative dose of androgen blockers (daily dose of androgen blockers times days of treatment) predicted BUT score even after controlling for age, gender role, cosmetic surgery, and BMI.
Conclusions. The differences observed between MtF and FtM individuals suggest that body-related uneasiness associated with GD may be effectively diminished with the administration of CHT even without the use of genital surgery for MtF clients. A discussion is provided on the importance of controlling both length and daily dose of treatment for the most effective impact on body uneasiness. **Fisher AD, Castellini G, Bandini E, Casale H, Fanni E, Benni L, Ferruccio N, Meriggiola MC, Manieri C, Gualerzi A, Jannini E, Oppo A, Ricca V, Maggi M, and Rellini AH. Cross-sex hormonal treatment and body uneasiness in individuals with gender dysphoria. J Sex Med 2014;11:709–719.**

Key Words. Gender Identity Disorder; Cross-Sex Hormonal Treatment; Body Uneasiness

Introduction

The emerging conceptualization of gender nonconformity, as accepted by the World Professional Association for Transgender Health, is moving toward a definition of gender variance that incorporates people who challenge social norms of gender identity/role without necessarily experiencing distress [1]. Moreover, the new view proposes that passing for the opposite gender should not be assumed as the final goal for all nonconforming individuals [2,3]. Alternative options, such as accepting the variant gender role or identity, may also be a desired outcome. This new perspective in conceptualizing gender incongruence has two major implications for the way in which treatment is applied to individuals with gender dysphoria (GD). First, individuals with GD need to be conceptualized as a subgroup within a larger population of nonconforming individuals. Based on the DSM IV-TR criteria, the experience of distress becomes a key aspect of the diagnosis of GD [4]. The distress experienced by these individuals is the product of a discrepancy between gender identity and sex assigned at birth, gender role, and/or primary and secondary sex characteristics [5,6]. Second, the treatment needs to be designed to address the individual needs of the patient who may not wish to live fully as an individual of the opposite gender.

In line with this new conceptualization, individuals with GD could benefit from flexibility in treatment, depending on their final goals with regard to aligning identity with body. While some individuals may experience an amelioration of distress by changing gender expression, others may need different levels of body modifications [1,2]. Among interventions aimed at reducing the incongruence between body and gender identity, a medical approach includes cross-sex hormonal treatment (CHT) alone or together with surgical reassignment [1,2]. To date, studies have mostly focused on the positive effects of sex reassignment surgery on mental and sexual health and satisfaction, omitting the potential benefit derived from just CHT [7–22].

A meta-analysis of GD treatment published in 2011 [23] reported only five studies that described the effects of CHT on psychological outcomes. Findings from these individual studies showed higher quality of life [24] and better psychological [25] and psychosocial [26] adjustment for individuals following CHT, perhaps because CHT increased confidence in passing as a member of the new gender and maintaining the new role [26]. Recently, only two additional studies have been published on this topic, which essentially corroborated the concept that CHT is associated with higher quality of life [27], less social distress and anxiety, and fewer depressive symptoms [28].

The interpretation of the available literature is limited by several caveats that need to be considered. First, only a paucity of studies took into consideration the concurrent effects of both length and dosage of hormonal treatment [25,27,28]. Second, data are rarely presented for both male-to-female (MtF) and female-to-male (FtM) individuals, thus preventing any inferences on the differences between these two populations. Third, in some studies the isolated effect of CHT was confounded because individuals with and without surgical sex reassignment were included in the same group [28].

Finally, none of these studies focused on the effects of CHT on body-related distress, a dimension assumed to be at the core of GD development.

There is a paucity of studies empirically testing distress related to one's body in individuals with GD [29–31]. Initial evidence of the crucial role of this type of distress comes from the fact that medical GD treatment is not only effective in alleviating dysphoria [1] but can also improve general psychopathology and distress [32]. If treatment for GD is moving toward a more flexible approach in order to address subtle differences in the needs of these people, a better understanding of the potential benefits of CHT alone on body distress is warranted.

Aims of Our Study

One of the aims of the present study was to assess differences in body uneasiness and psychiatric symptoms between GD individuals taking CHT and those not taking hormones (no CHT). Secondary analyses were conducted to better understand if distress with specific parts of the body was less pronounced among individuals taking CHT. We also assessed whether length of CHT treatment and daily hormone doses provided an explanation for different levels of body uneasiness and psychiatric symptoms.

Methods

Participants

Subjects referred for the first time to the centers for GD assistance of the Universities of Florence,

Bologna, Turin, Cagliari, and L'Aquila between July 2008 and January 2013 were enrolled in the study, provided they met the following inclusion criteria:

- Age older than 18 years.
- Diagnosis of GD based on formal psychiatric classification criteria [1,4] and performed through several sessions with two different mental health professionals specializing in GD.

The exclusion criteria were as follows:

- Genital reassignment surgery.
- Use at any point in life of different CHT therapy from the one reported at the time of enrollment in the present study.
- Illiteracy.
- Mental retardation.

A total of 150 subjects were excluded from the initial sample because of the following reasons: changes in CHT treatment prior to the study (n = 53), disorders of sexual development (n = 3), internalized homophobia (n = 3), transvestite fetishism (n = 6), mental retardation (n = 1), incomplete assessment because of dropout during the clinical assessment (n = 13), and completed genital reassignment surgery (n = 69). The selected sample (MtF patients, n = 66; FtM patients, n = 59) included 53 participants from Florence, 55 from Bologna, 14 from Turin, 2 from L'Aquila, and 1 from Cagliari. Participants were divided into patients who had never taken CHT and patients taking estrogens and/or antiandrogens at the moment of the clinical interview.

Measures

The sociodemographic data were collected at the beginning of the first visit, through a face-to-face interview, by mental health professionals specialized in this field (EB, GC, HC, VR). Subjects reported their age, relationship status, morbidities, preferred sexual orientation, and previous cosmetic surgery interventions.

Anthropometric measurements were made by expert endocrinologists using standard calibrated instruments. Information was also collected regarding estrogen and/or antiandrogen treatment, including daily hormone dosage and the duration of treatment (in days). In order to convert ethinylestradiol dosage to a scale that allowed comparison with estradiol, daily ethinylestradiol doses (μg) were multiplied by 400 or 1000 based on the cumulative hormone dose reported [33]. Cumulative dose of estrogens (CD-E) was calculated as daily estradiol dose times days of treatment, while cumulative dose of antiandrogens (CD-CPA) was computed as daily androgen blocker (cyproterone acetate) dose times days of treatment.

Furthermore, levels of psychopathological distress were specifically investigated by means of the Italian version of the Symptom Checklist (SCL-90-R [34,35]), which was answered for the week preceding the clinical assessment. The 90 items of the questionnaire are rated on a five-point Likert-type scale (from 0 to 4) and are grouped together into nine domains (somatization, obsessive–compulsive thoughts, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid conceptions, and psychotic behavior). In this study we utilized the General Severity Index (SCL-GSI), indicating the overall psychological distress.

For the assessment of body uneasiness and dissatisfaction, the Body Uneasiness Test (BUT [36]) was administered. This self-reported measure comprises questions regarding 34 body experiences (BUT-A) and dissatisfaction with 37 body parts (BUT-B). BUT subscales include dissatisfaction regarding the body and its weight (BUT-WP; e.g., "I'm terrified of gaining weight," "My physical appearance is unsatisfying compared to my ideal body image"); avoiding and compulsive self-monitoring behavior (BUT-AV, BUT-CSM; e.g., "When I get undressed I avoid looking," "I spend a lot of time in front of the mirror," "I fear that my appearance may suddenly change"); experience of depersonalization, defined as separation and foreignness regarding the body (BUT-D, e.g., "When I look at myself in the mirror I feel a sense of anxiety and alienation"); and body image concerns (BUT-BIC). Answers are scored on a six-point Likert-type scale (from "never" to "always"). Higher scores indicate greater body uneasiness. In this study the BUT scores utilized were the total score of the test (Global Severity Index, BUT-GSI) and the subscales. In addition, the number of items from BUT-B with scores of 1 or higher was summed to indicate overall dislike of body parts (BUT-PST; e.g., skin, mouth, breasts, knees, moustache, hair, smell, noise, sweating, flushing). Finally, different body parts were considered individually for exploratory purposes.

To measure gender role, a standard dichotomous item was used: "Do you have a full-time male gender role in daily life?" For the FtM group, a rating of 0 corresponded to no full-time male gender role and 1 to full-time male gender role, and

for the MtF group, a rating of 0 corresponded to no full-time female gender role and 1 to a full-time female gender role. Answers were adjusted considering clinical observations during the assessment. For example, if a MtF subject answered that she had a full-time female gender role, but the clinician's opinion during the interview was different, the answer was coded as 0.

Procedure

The study was designed as a naturalistic cross-sectional survey, and it was planned and conducted at the Interdepartmental Center for Gender Identity Disorder Assistance (CIADIG), Sexual Medicine and Andrology Unit, University of Florence, and in other dedicated centers in Bologna, Turin, L'Aquila, and Cagliari. Participants were recruited from consecutive referrals by family doctors and other clinicians. All the diagnostic procedures and the psychometric tests were part of the routine clinical assessment for GD at our clinics. Patients were asked to provide their written informed consent to participation in the study. The study was carried out in accordance with the ethical standards of the responsible institutional committees.

Data Analysis

A 2×2 ANCOVA (gender × CHT) was utilized to assess differences in BUT-GSI. Control variables used in this model were age, body mass index (BMI), gender role, and cosmetic surgery. Also, follow-up analyses for the BUT subscales and for the BUT-B (individual body parts) were used to provide a more comprehensive explanation of the significant effects observed in the primary analyses. A similar 2×2 ANCOVA model was used to test differences in overall psychiatric symptoms (SCL-90-R). Follow-up univariate analyses were computed for the MtF and FtM samples separately to understand the interaction effects observed in the main analyses.

When the CHT and no-CHT groups showed significant differences (specifically, in BUT-GSI between MtF groups), we conducted an analysis to clarify the effects of cumulative hormone dose (defined as daily dose of hormone times duration of treatment) on BUT-GSI. Thus, for these secondary analyses we included only MtF individuals taking hormones, as only this group showed significant differences for primary analyses comparing CHT with no CHT. In this analysis, we utilized a two-step hierarchical linear regression where BMI, age, gender role, and cosmetic surgery were entered in step 1. In step 2, cumulative hormone dose was entered. We selected this approach to assess whether cumulative hormone dose provided a unique contribution to the explanation of BUT-GSI above and beyond the effects of the covariates included in step 1. Significant changes in step 2 are an indication that cumulative hormone dose added significantly to the prediction of BUT-GSI, above and beyond the effects of the variables entered in step 1.

Results

Differences Between the MtF and FtM Groups

In the MtF group (n = 66), 24 patients had never taken CHT, and 42 were taking estrogens and antiandrogens. Specifically, the breakdown of the medications taken by these patients was as follows: 28.6% (n = 12), estradiol valerate; 28.6% (n = 12), transdermal estradiol hemihydrate; 14.3% (n = 6), estradiol gel; 92.9% (n = 39), oral cyproterone acetate. It should be noted that self-medication was often the reason for the mixed CHT profile of some subjects (e.g., more than one type of estrogen formulation at the same time).

For the FtM group (n = 59), 33 had never had CHT and 26 were on CHT. Of those individuals taking hormones, 54.5% (n = 12) were using testosterone enanthate injections, 4.5% (n = 1) were using parenteral testosterone undecanoate, and 40.9% (n = 9) used transdermal testosterone. For four FtM patients in the CHT group, we did not have information on the type of androgen taken.

On average, MtF and FtM subjects reported 467 days (SD = 323, median = 430, range 45 to 10,845) and 1,940 days (SD = 2,595, median 799, range 33 to 1,021) of hormone therapy, respectively.

A description of the demographics of the MtF and FtM patients is given in Table 1. MtF individuals were on average 33.1 (SD = 10.25) years old, and their BMI was 22.1 (SD = 3.9) kg/m^2. It was found that 53.8% (n = 35) of the individuals in the MtF group reported an onset of GD during adolescence. Similarly, FtM individuals were on average 28.7 (SD = ± 6.5) years old, with BMI of 24.7 (SD = 4.5) kg/m^2; 70.7% (n = 41) reported GD onset during adolescence.

Differences in Body Uneasiness Based on Gender (MtF vs. FtM) and CHT Use

Results from the 2×2 (gender × CHT) ANCOVA (age, BMI, gender role, and cosmetic surgery as covariates) showed a significant main effect for CHT

Table 1 Main clinical and sociodemographic features of our sample as derived from patient history and medical records

	MtF ($n = 66$)	FtM ($n = 59$)	t (df)	P	d	χ^2 (df)
Age (years), mean ± SD	33.1 ± 10.3	28.7 ± 6.5	–2.93 (111.32)	0.004	0.53	
BMI (kg/m^2), mean ± SD	22.2 ± 3.9	24.7 ± 4.52	1.99 (43)	0.053	–0.6	
Gender dysphoria onset during adolescence, % (n)	53.8 (35)*	70.7 (41)*		0.055		3.68 (1)
Non-Italian natives, % (n)	16.7 (11)	15.3 (9)		0.830		0.46 (1)
Marital status, % (n)						
Stable relationship	6.2 (4)	1.8 (1)				
Unmarried	89.2 (58)	91.1 (51)				
Divorced	4.6 (3)	5.4 (3)				
Cohabitation status, % (n)				0.278		3.85 (3)
With parents	30.3 (20)	35.6 (21)				
With partner	19.7 (13)	30.5 (18)				
With friends	18.2 (12)	10.2 (6)				
Alone	31.8 (21)	23.7 (14)				
Education, % (n)				0.129		5.66 (3)
Primary school	37.9 (25)	28.8 (17)				
Secondary school	25.8 (17)	44.1 (26)				
Professional diploma	16.7 (11)	16.9 (10)				
University	19.7 (13)	10.2 (6)				
Employment, % (n)				0.848		0.037 (1)
Student	10.6 (7)	11.9 (7)				
Retired	3 (2)	0.0 (0)				
Employed	57.6 (38)	67.8 (40)				
Unemployed	28.8 (19)	20.3 (12)				
Cosmetic surgery, % (n)						
Facial cosmetic surgery	13.6 (9)	5.2 (3)		0.112		2.530 (1)
Breast cosmetic surgery	18.2 (12)	5.1 (3)		0.024		5.060 (1)
Any other cosmetic surgery	22.7 (15)	10.2 (6)		0.61		3.515 (1)

For the assessment of between-group differences (MtF and FtM), χ^2 and Student's t-test were applied for categorical and continuous variables, respectively.
*Data missing for 1 person.

Table 2 Summary of BUT-GSI and SCL differences explained by 2 × 2 (gender × CHT) ANCOVA, controlling for age, gender role, and surgery

Variable	SS	df	F	P	η^2
BUT-GSI					
Age	0.03	1	0.04	0.841	<0.01
Gender role	0.72	1	0.90	0.345	0.01
Surgery	2.97	1	3.70	0.057	0.03
Gender	0.13	1	0.16	0.690	<0.01
CHT/no CHT	4.65	1	5.80	0.018	0.05
Gender × CHT	4.20	1	5.24	0.024	0.04
SCL					
Age	1.46	1	1.65	0.202	0.01
Gender role	0.88	1	0.99	0.323	0.01
Surgery	0.24	1	0.27	0.601	<0.01
Gender	0.71	1	0.80	0.373	0.01
CHT/no CHT	0.81	1	0.91	0.341	0.01
Gender × CHT	1.28	1	1.44	0.233	0.01

BUT-GSI = Global Severity Index of Body Uneasiness Test; CHT = cross-sex hormonal treatment, SCL = Symptom Checklist; SS = sum of squares

($F(1,116) = 5.80$, $P < 0.05$, $\eta^2 = 0.05$) (Table 2). When data were controlled for covariates, individuals taking CHT (mean = 1.86, SEM = 0.12) had a lower BUT-GSI than individuals in the no-CHT group (mean = 2.28, SEM = 0.13). As illustrated in Figure 1, there was also a significant interaction effect for gender × CHT ($F(1,116) = 5.24$, $P < 0.05$, $\eta^2 = 0.04$).

To better understand the interaction, we stratified the file by gender and computed one-way ANCOVAS for CHT using the same covariates as in the principal analysis (Table 3). For the MtF group, individuals using CHT (mean = 1.67, SEM = 0.17) reported lower BUT-GSI ($F(1,60) = 7.14$, $P < 0.01$, $\eta^2 = 0.11$) compared

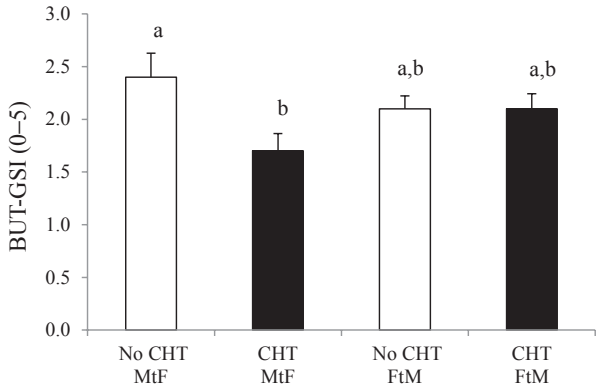

Figure 1 Differences in BUT-GSI according to gender (MtF vs. FtM) and therapy (CHT vs. no CHT). Columns labeled with different letters are significantly different from each other ($P < 0.05$). BUT = Body Uneasiness Test; GSI = Global Severity Index; MtF = male to female; FtM = female to male; CHT = cross-sex hormonal treatment.

Table 3 Summary of estimated means and standard errors for MtF and FtM participants by CHT group, including results for differences tested with one-way ANOVA for all outcome variables

	MtF					FtM				
	No CHT (n = 22)		CHT (n = 42)			No CHT (n = 32)		CHT (n = 24)		
	Mean	SEM	Mean	SEM	*F*(dfs)	Mean	SEM	Mean	SEM	*F*(dfs)
BUT-GSI	2.51	1.04	1.63	1.07	9.12 (1,63)**	2.13	0.69	2.04	0.69	0.09 (1,56)
SCL-90-R	0.74	0.15	0.70	0.11	0.04 (1,63)	0.50	0.21	0.84	0.23	1.11 (1,56)
BUT-BIC	3.07	1.30	1.96	1.32	10.47 (1,63)**	3.11	1.02	2.84	1.06	0.59 (1,56)
BUT-AV	2.16	1.25	0.95	1.11	14.22 (1,63)***	1.55	0.92	1.60	1.15	0.11 (1,56)
BUT-D	2.40	1.05	1.34	1.35	9.66 (1,63)**	3.14	5.61	2.00	1.03	0.59 (1,56)
BUT-PST	21.75	8.71	16.14	9.53	4.21 (1,63)*	12.46	8.71	13.65	7.22	0.63 (1,56)
BUT-CSM	1.93	1.33	1.53	1.06	0.51 (1.63)	1.14	0.83	1.24	0.66	0.39 (1,56)
BUT-WP	2.56	1.01	2.04	1.11	3.02 (1,63)	2.04	0.89	2.21	0.78	0.18 (1,56)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
MtF = male to female; FtM = female to male; CHT = cross-sex hormonal treatment, BUT = Body Uneasiness Test; GSI = Global Severity Index; SCL-90-R = Symptom Checklist-90 Revised; BIC = body image concerns; AV = avoidance; D = depersonalization; PST = positive symptoms total (dislike for body parts); CSM = compulsive self-monitoring; WP = weight phobia

with individuals in the no-CHT group (Mean = 2.44, SEM = 0.23).[1] As illustrated in Table 3, no significant differences were observed between CHT and no-CHT groups among the FtM individuals ($F(1,54) = 0.12$, $P = 0.736$). As BUT-GSI was significantly different for the MtF group, we followed up with analyses of differences in BUT subscales between CHT and no-CHT patients within this group to better understand the aspects of BUT implicated by the primary analyses. Cosmetic surgery, age, BMI, and gender role were included as covariates in these models. BUT-GSI was not associated with CHT for the FtM group. We report follow-up analyses of differences in BUT subscales between CHT and no-CHT groups for the FtM group (Table 3) only for reasons of completeness. In agreement with primary analyses, BUT subscales did not significantly differ between the CHT and the no-CHT group among FtM patients (Table 3). The subscales that showed significant differences between MtF patients who did and did not use CHT were BUT-BIC ($F(1,63) = 10.47$, $P < 0.01$, $\eta^2 = 0.14$), BUT-AV ($F(1,63) = 14.22$, $P < 0.001$, $\eta^2 = 0.18$), BUT-D ($F(1,63) = 9.66$, $P < 0.01$, $\eta^2 = 0.13$), and BUT-PST ($F(1,63) = 4.21$, $P < 0.05$, $\eta^2 = 0.06$). The *F*-statistics, means, and standard errors are illustrated in Table 3. Differences in the other two subscales, BUT-WP and BUT-CSM, were not significant.

The same models were utilized to assess differences for each individual BUT-B item (body part) to highlight potential patterns in aspects of body image that were more strongly associated with CHT for the MtF group, controlling for age, BMI, gender role, and cosmetic surgery when appropriate (i.e., an ANCOVA testing satisfaction with the face controlled for facial cosmetic surgery, but an ANCOVA testing satisfaction with the hands did not). These analyses should be considered secondary analyses conducted to further explore the significant differences observed in BUT-PST. Bonferroni corrections were not utilized, as the results of the primary analyses were significant. Given the descriptive purpose of these analyses, a stronger emphasis was placed on effect sizes (Cohen's *d*) than on statistical significance. Based on Cohen's power guidelines, an η^2 between 0.01 and 0.04 was considered small, one between 0.05 and 0.12 was moderate, and one above 0.13 was large [37]. As highlighted in Table 4, MtF patients who did and did not use CHT showed significant differences ($P < 0.05$) in their dislike of their body hair ($\eta^2 = 0.072$), arms ($\eta^2 = 0.103$), chest ($\eta^2 = 0.115$—but not breasts, $\eta^2 = 0.007$), smell ($\eta^2 = 0.008$), and buttocks ($\eta^2 = 0.082$). Surprisingly, differences in dislike of eyes ($\eta^2 = 0.086$) also reached significance.

Differences in General Psychopathology Based on Gender (MtF vs. FtM) and Use of CHT

The 2×2 (gender × CHT) ANCOVA model used above was utilized to assess differences in psychological health between groups (Table 2). No significant differences in SCL score were observed according to gender (MtF vs. FtM; $F(1,113) = 0.80$, $P = 0.373$), hormones (CHT vs. no-CHT; $F(1, 113) = 0.91$, $P = 0.341$), or the interaction of these two variables ($F(1, 113) = 1.44$, $P = 0.233$).

[1]Note that means and SEM are provided for BUT-GSI scores calculated after controlling for covariates.

Table 4 Summary of means, standard deviations and statistical differences in dislike of body parts (BUT-B) between MtF participants in no-CHT and CHT groups, with adjustment for age, body mass index, gender role, and cosmetic surgery when appropriate

	No CHT		CHT				
	Mean	SD	Mean	SD	F(dfs)	*P*	η^2
Height	1.23	0.31	0.70	0.24	1.69 (1,55)	0.200	0.030
Head shape	0.70	0.33	0.92	0.25	0.26 (1,55)	0.612	0.005
Face shape	1.50	0.38	1.26	0.29	0.25 (1,54)	0.619	0.005
Skin	0.91	0.23	0.54	1.80	1.44 (1,55)	0.235	0.025
Hair	2.14	0.43	1.05	0.33	3.7 (1,55)	0.057	0.064
Forehead	1.78	0.35	0.92	0.27	3.45 (1,55)	0.069	0.059
Brows	1.11	0.30	0.53	0.23	2.25 (1,55)	0.139	0.039
Eyes	0.84	0.21	0.21	0.17	5.10 (1,54)	0.028*	0.086
Nose	2.03	0.38	1.44	0.29	1.40 (1,54)	0.241	0.025
Lips	1.35	0.31	0.57	0.24	3.70 (1,54)	0.060	0.064
Mouth	0.79	0.22	0.33	0.17	2.60 (1,53)	0.113	0.047
Teeth	1.35	0.33	0.87	0.25	1.28 (1,54)	0.263	0.023
Ears	0.92	0.26	0.62	0.20	0.73 (1,55)	0.397	0.013
Neck	1.49	0.33	0.86	0.26	2.05 (1,45)	0.158	0.037
Chin	1.39	0.37	1.00	0.29	0.63 (1,54)	0.431	0.012
Moustache	4.22	0.46	3.36	0.36	2.01 (1,54)	0.158	0.037
Beard	4.58	0.42	3.64	0.33	2.91 (1,55)	0.094	0.05
Body hair	4.77	0.36	3.81	0.27	4.16 (1,54)	0.046*	0.072
Shoulder	2.03	0.41	1.42	0.32	1.28 (1.55)	0.262	0.023
Arms	1.67	0.31	0.66	0.24	6.35 (1,55)	0.015*	0.103
Hands	1.68	0.33	0.98	0.25	2.67 (1,55)	0.108	0.046
Chest	2.80	0.42	1.34	0.32	7.05 (1,54)	0.010*	0.115
Breast	1.28	0.43	1.62	0.33	0.36 (1,53)	0.552	0.007
Belly	1.55	0.38	0.71	0.30	2.81 (1,55)	0.099	0.049
Womb	1.24	0.36	0.85	0.28	0.71 (1,55)	0.404	0.013
Genitals	4.45	0.34	3.01	0.26	0.65 (1,55)	0.423	0.012
Buttocks	1.76	0.35	0.74	0.27	4.94 (1,55)	0.030*	0.082
Hips	1.12	0.34	1.01	0.27	0.67 (1,55)	0.800	0.001
Thighs	0.93	0.25	0.45	0.20	2.14 (1,53)	0.150	0.039
Knees	0.84	0.25	0.43	1.99	1.48 (1,54)	0.229	0.027
Legs	1.18	0.28	0.49	0.22	3.55 (1,55)	0.065	0.061
Ankles	1.02	0.27	0.64	0.211	1.11 (1,55)	0.297	0.020
Feet	2.27	0.42	1.75	0.32	0.89 (1,55)	0.348	0.016
Body scent	1.12	0.23	0.28	0.18	7.68 (1,55)	0.008*	0.123
Body sounds	1.41	0.32	0.68	0.24	3.18 (1,52)	0.080	0.058
Sweating	2.53	0.43	1.80	0.33	1.68 (1,55)	0.200	0.030
Blushing	1.04	0.31	1.08	0.24	0.01 (1,55)	0.914	0.000

*$P < 0.05$.
MtF = male to female; CHT = cross-sex hormonal treatment; SD = standard deviation; CHT = cross-sex hormonal treatment

Daily Hormone Dose and CHT Length and the Body Uneasiness of MtF Subjects

The findings of a two-step hierarchical regression showed that CD-E (daily estradiol dose times days of treatment) and CD-CPA (daily androgen blocker dose times days of treatment) added significantly to the explanation of BUT-GSI above and beyond the effects of age, gender role, cosmetic surgery, and BMI (predictors in step 1; $\Delta F(2,7) = 6.46$, $P < 0.05$, $\Delta R^2 = 0.48$). An analysis of beta coefficients revealed that only CD-E had a significant and unique effect ($\beta = -1.37$, $P < 0.05$, sr = –0.62). CD-CPA was not significant ($\beta = 1.66$, $P = 0.14$, sr = 0.32). This relationship is illustrated in Figure 2.

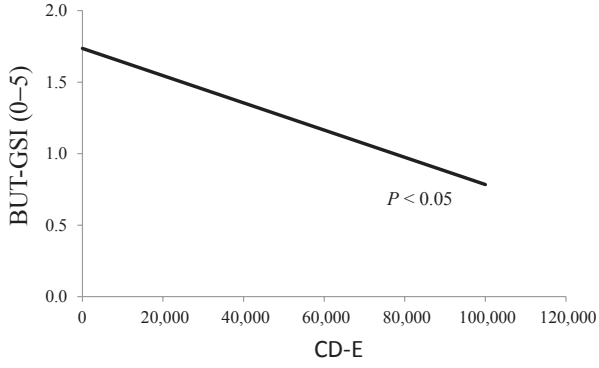

Figure 2 Representation of the regression predicting the effects of cumulative dose of estradiol on BUT-GSI. BUT-GSI = Global Severity Index of Body Uneasiness Test; CD-E = cumulative dose of estradiol (daily dose times days of treatment).

Discussion

To our knowledge, this is the first published study testing differences in body uneasiness according to use of CHT in individuals with GD. In particular, we have demonstrated that, among MtF subjects, body uneasiness was lower in those in the CHT group than in the no-CHT group. Also, interestingly, we observed a negative relationship between CHT and body uneasiness for the MtF group but not for the FtM group. Even if some authors have reported a more satisfied perception of the body after sex reassignment surgery [38], to date no empirical studies have focused on the effects of CHT on body image. These findings are in line with our clinical observations that modifying sexually dimorphic body characteristics through hormones can lead to a relief in body-related distress. Also, this new empirical result implies that a more flexible approach for treating individuals with GD (i.e., not automatically including surgery) may be better suited to address clients' variety of needs. Specifically, our results provide initial empirical evidence that supports the last version of the World Professional Association for Transgender Health Standards of Care [1] advocating individualized treatment goals.

Patterns in the body uneasiness subscales emerged when we further investigated the differences between the CHT and the no-CHT groups of MtF subjects. In particular, less severe body uneasiness and less avoidance of thoughts about the body were observed in those MtF individuals taking hormones as compared with those not taking hormones. A significant difference was present even after controlling for age, gender role, BMI, and cosmetic surgery. This finding could be explained by CHT-induced improvement in the acceptance and appreciation of a body shape more in line with patients' ideal. Previous studies have shown that depersonalization, a psychopathological phenomenon defined as the feeling of being outside of one's body, was reduced after sex reassignment surgery [31,39,40]; however, here we provide evidence that MtF individuals taking hormones also suffer less body dysphoria, adding novel information for the field.

No significant differences were observed between CHT and no-CHT patients in the MtF group with regard to compulsive self-monitoring and weight phobia. The lack of significant difference in compulsive self-monitoring is not surprising given that this scale captures cognitive distortions usually produced by a pathological view of the self, as observed in body dimorphic disorder [36]. The pathology of compulsive self-monitoring is based on a view of the self that is distorted from reality (i.e., individuals perceive themselves differently from how they really appear). For individuals with GD, the discrepancy between mind and body results from a misalignment between how they look and how they would like to appear. However, their view of their body remains aligned with reality (i.e., they really look the way they perceive themselves). Weight concerns were not significantly different between MtF individuals taking hormones and those not taking them. The relationship among hormones, weight gain, and weight concerns may be more complex than our design is able to explain. One potential explanation can be derived from previous studies showing that CHT increases weight in MtF clients [41]. As in Western culture thinness is associated with femininity and attractiveness [42], being thin could represent a way to conform to femininity [30,43,44]. Based on this logic, one could infer that worries of MtF individuals about treatment-induced weight gain may counteract any satisfaction that CHT may have introduced for the newly gained womanly shape (i.e., accumulation of fat around the hips). Thus, rather than no change, CHT may lead both to positive changes and to negative changes that may attenuate the actual overall satisfaction. However, the present results should be interpreted with caution in the light of such complexity and the controversial physical effects of CHT.

The absence of significant differences in body uneasiness between CHT and no-CHT patients among FtM subjects is unexpected and could be explained in several different ways. One would expect androgens to lead to more socially visible alterations in the body. For example, the growth of a beard may provoke a significant change in the way the person is perceived by others and thus may help the individual to pass as male. However, the BUT scale is more concerned with the private relationship between an individual and his/her body [36], meaning that it asks how a person feels about his/her own body and not the distress caused by how one may appear to others. The scale focuses on aspects that the individual faces when undressed in front of the mirror, within the private walls of the bathroom or bedroom [36]. Within this context, the types of changes that CHT causes in an FtM individual may not be enough to bring about an amelioration in body uneasiness. For example, CHT may ameliorate breast-related dis-

tress in MtF individuals by increasing breast size. On the other hand, CHT-induced breast atrophy is limited for FtM individuals, and thus CHT alone may not be sufficient to ameliorate distress caused by breasts in FtM subjects.

A second explanation of the CHT-related difference in body uneasiness between MtF and FtM individuals may be the objective difference in the amount of change induced by the treatment. Specifically, it is possible that changes induced by androgens in body parts, such as breasts, may be less drastic than the changes that estrogens produce in the same area. Ideally, we would want to compare body changes using objective measures that allow use of the same scale for MtF and FtM individuals. However, differences in hormones and in the biological makeup of the two populations does not allow such comparison.

In the secondary analyses that investigated individual body parts listed in the BUT, we also found evidence for a significant difference between CHT and no-CHT groups for chest, arms, and buttocks in the MtF sample. Specifically, the CHT group reported less dislike for these body parts. These findings could be the results of hormone-induced body mass redistribution [41]. Also, we found more satisfaction with body scent in the CHT group, a finding in line with the literature showing that androgen-related changes in physiological mechanisms result in a less masculine scent, which MtF individuals appear to appreciate [45–47].

As far as mental health is concerned, we did not observe differences between CHT and no-CHT individuals for either group (FtM or MtF), and overall, subjects showed a low level of psychopathology. It is possible that CHT may have a positive effect on psychological well-being, but the restricted range of psychopathology scores may have prevented us from finding differences between the two groups. This finding is in disagreement with a previous study [28] reporting less social distress and anxiety and fewer depression symptoms among subjects receiving CHT. However, these results cannot be directly compared with ours, as in this previous study researchers combined individuals taking CHT only with individuals who received genital reassignment surgery. The low level of psychopathology symptoms in our subjects is in line with previous studies reporting lower scores in psychopathology among GD clients as compared with patients with eating disorders [31] and similar scores to healthy controls [31,48]. Moreover, we add to the extant literature by showing a positive effect of CHT on quality of life [27] and providing the first evidence that body uneasiness is lower in MtF individuals using hormonal treatment compared with those not using hormones.

The analyses on cumulative hormone dose showed that the cumulative dose of estrogens, but not that of antiandrogens, provided a unique and significant contribution to the prediction of lower body uneasiness. The fact that antiandrogens did not show a unique and independent effect should not be interpreted as a lack of significant effect on the part of these hormones but rather as indicating that changes in levels of estrogens may be more closely related to psychological state with regard to the body, or that the effects of androgens are produced through the interaction of androgens with estrogens.

It should be noted that in our study we combined length of therapy (days) with daily dose level, and therefore the significant relationship between body uneasiness and CHT needs to be considered as the interaction between these two variables. Administering higher daily doses of hormones may not lead to the same positive effects observed for cumulative hormone dose. Indeed, high doses of estrogens have been reported to be deleterious to body health [41]. Individuals self-medicating and taking hormones not medically prescribed may be more likely to use higher daily doses but may perhaps adopt a more discontinuous pattern. Our data suggest that the combination of number of days and daily dose matters, and thus a lower-daily-dose but more stable and continuous treatment may be more effective than a high-daily-dose and sporadic pattern of treatment.

Several limitations of the present study should be recognized. The cross-sectional design of the study does not allow for causal inferences with regard to the relationship between the target variables and CHT. Second, there are some potential limitations in the way we collected data on CHT treatment: while for some people we were able to check self-reports against medical records, for the majority of participants we had to rely on self-report information collected during a medical history interview. Third, it should be taken into account that the relatively small sample size in this study could lead to a reduced power in detecting significant differences; however, the fact that significant effects were found for the MtF group but not for the FtM group speaks to meaningful differences between these two populations. Fourth, our findings refer to patients seeking CHT and cannot be generalized to the whole gender-variant

population. However, given that the study was conducted to provide clinically relevant information to clinicians treating individuals with GD seeking CHT, we feel that the findings in this study provide novel information on CHT's role in alleviating distress. Fifth, the dichotomous measure we used for gender role does not reflect the real variability of GD phenomena. In fact, it should be considered that a linear measure would better honor the diversity of clients' transitions. However, it should be noted that in the present study, gender role was utilized as a covariate, not a main variable, and therefore does not affect the outcome. Finally, given the cross-sectional design of the study, it is not possible to ascertain a causal interpretation for our results. However, this study is the first to test a possible correlation between CHT and body uneasiness in GD subjects and therefore provides a meaningful insight into a topic that warrants further exploration.

In conclusion, our findings are in line with the hypothesis that cross-sex hormonal therapy can alleviate body uneasiness, a core element of GD, even without surgery. Such effects were observed only for MtF subjects and were associated with greater cumulative hormone dose, suggesting that a continuous treatment with a set daily dose and number of days may be an effective approach to treat gender dysphoria in MtF clients, with or without surgical intervention.

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