Cross-Sex Hormone Treatment and Psychobiological Changes in Transsexual Persons: Two-Year Follow-Up Data

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Context: To date, there are few studies investigating the impact of body changes induced by cross-sex hormonal treatment (CHT) on psychobiological well-being in gender-dysphoric persons (GDs).

Objective: The objective of the study was to assess whether CHT-related body changes affect psychobiological well-being in GDs.

Methods: A consecutive series of 359 GDs was considered for a cross-sectional section of the study. In addition, 54 GDs were studied in a 2-year follow-up. A physical examination was performed, including body mass index, waist circumference, and hair distribution. We also evaluated breast development and testis volume in male to female subjects and clitoris length in female to male. Subjects were asked to complete several psychometric measures for the assessment of body uneasiness, GD, and psychopathology levels. The evaluation was repeated 2 years prospectively.

Results: The following results were found: 1) GDs undergoing CHT reported significantly lower subjective levels of GD, body uneasiness, and depressive symptoms as compared with those without; 2) CHT-induced body modifications were significantly associated with a better psychological adjustment; 3) during CHT, GDs reported a significant reduction of general psychopathology, depressive symptoms, and subjective GD, whereas social and legal indicators of GD showed a significant increase across time; and 4) among body changes induced by CHT, only breast development and increased body mass index had a significant impact on psychopathology reduction across time in male to female subjects and female to male subjects, respectively.

Conclusions: The aforementioned results support the efficacy of CHT intervention in improving subjective perception of one's own body, which was partially associated with objective changes. (***J Clin Endocrinol Metab*** **101: 4260–4269, 2016)**

Gender dysphoria (GD) is characterized by a marked incongruence between one's experienced/expressed gender and the assigned one, associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning (1). Because GD can occur with different levels of intensity, a flexible approach in treatment should be offered (2–5).

Regarding interventions aimed at reducing the discrepancy between body and gender identity, a medical approach should include cross-sex hormonal treatment

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Abbreviations: ANCOVA, analysis of covariance; BDI, Beck Depression Inventory; BMI, body mas index; BUT, Body Uneasiness Test; CHT, cross-sex hormonal treatment; FG, Ferriman and Gallwey; GIDYQ-AA, Gender Identity/Gender Dysphoria questionnaire; FtM, female to male; GD, gender dysphoria; GRS, genital reassignment surgery; GSI, global severity index; MtF, male to female; SCL-90-R, Symptom Checklist 90 revised;

(CHT) alone or together with genital reassignment surgery (GRS) (2).

To date, most studies have focused on the positive effects of GRS on mental and sexual health and satisfaction (6–13). Only recently have studies evaluated the potential benefits derived from CHT alone on psychological well-being (4, 14–17). A meta-analysis on sex reassignment shows that CHT alone reduces GD and improves quality of life and psychological and psychosocial well-being (18). More recently, other studies have shown similar results, reporting that CHT is associated with a better quality of life (19, 20), reduction of psychiatric comorbidity (15, 21), lower social distress (21), less body dissatisfaction (4), and an improved sex life (14).

However, among the aforementioned studies, only one (15) has prospectively analyzed psychiatric comorbidity in those with GD as a function of CHT, with a 12-month follow-up, with all the others being derived from cross-sectional evaluation. Furthermore, to date, there are no longitudinal studies that highlight a direct connection of CHT with body dissatisfaction and GD levels.

Considering that, for ethical issues, it is not possible to perform a randomized, placebo-controlled study (with a no-CHT control group), we performed a double-design study with a cross-sectional comparison between GD persons (GDs) vs no CHT at baseline and a prospective intervention study on the effect of CHT across time.

Materials and Methods

Aims

According to the aforementioned design, the main aims of the present study were to evaluate the following: 1) the differences in terms of psychological well-being between persons with vs no CHT (cross-sectional study); 2) whether gender-related body features may correlate with psychopathology (cross-sectional study); 3) the psychobiological effect of CHT over time (prospective study); and 4) the impact of different body changes in psychopathology modification over time (prospective study).

Design of the study

All subjects included were diagnosed with GD according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (1), as specified below. Two different studies were performed based on the reported previous CHT.

Cross-sectional study

Participants

Subjects referring for the first time to the center for GD assistance at the University of Florence were enrolled in the cross-sectional study, provided they met the following inclusion criteria: age older than 18 years and diagnosis of GD based on formal psychiatric classification criteria and performed through several sessions with two different mental health professionals specialized in GD.

The exclusion criteria were as follows: GRS performed; illiteracy; mental retardation; and disorder of sexual development

A total of 178 subjects were excluded from the initial sample because of the following reasons: changes in CHT prior to the study (n = 53), mental retardation (n = 1), dropout during assessment (n = 23), completed GRS (n = 78), disorder of sexual development (n = 3), or absence of GD diagnosis (three had internalized homophobia, seven transvestite fetishism, three personality disorder, and seven had gender nonconformity diagnosis). The selected sample included 359 participants, of which 140 (39.0%) were female to male (FtM) and 219 (61.0%) male to female (MtF). Supplemental Figure 1 reports the details of the participants in a flow chart.

Prospective study

Participants

A subsample of patients enrolled in the cross-sectional study, referring to the center for GD assistance at the University of Florence from September 2012 to August 2015, were enrolled in the prospective study (Supplemental Figure 1), provided they met the following inclusion criteria: a request for GRS at the time of inclusion and a request to start CHT.

The use at any point in life of CHT and augmentation mammoplasty were considered the exclusion criteria for the prospective analysis.

A total of 54 participants were included before CHT start and evaluated at 3 (T1), 6 (T2), 12 (T3), and 24 months (T4) after CHT prescription. Of the included sample, 28 (51.9%) were MtFs and 26 (48.1%) FtMs. All MtFs received oral cyproterone acetate (50 mg) combined with oral estradiol valerate (66.7%) or transdermal estradiol (33.3%). All FtMs received testosterone undecanoate 1000 mg im, with the first injection repeated after 6 weeks, and then after 12 weeks. The injection interval was adjusted (normally between 10–14 wk) based on serum T levels with the aim of obtaining hormone levels in the normal reference range for males. All patients received standardized professional mental health support every 3 months.

Measures

Sociodemographic data

Subjects reported their sociodemographic information and previous cosmetic surgery interventions. Information was also collected regarding estrogen and/or antiandrogen treatment and patients' gender role.

Anthropometric measures

Anthropometric measurements were made by expert endocrinologists using standard calibrated instruments. In particular, patients underwent a complete physical examination, with measurement of height, weight, waist, and body mass index (BMI). Testis volume in MtFs was evaluated using a Prader orchidometer (22). Breast development during the CHT in MtFs was assessed according to Tanner staging (5). The degree of hair growth was assessed by the same endocrinologist (A.D.F.) according to the modified Ferriman and Gallwey (FG) scoring system (23). The score was then adjusted in MtFs by asking the patient to describe medium hair density during the last 2 weeks before

depilation or waxing. Total stretched clitoral length was measured as the distance from the tip of the glans to the point at the symphysis pubis at which the crura are thought to insert, thus including the clitoral body and glans (24).

Blood samples were drawn in the morning for the determination of glutamic-oxaloacetic transaminase and glutamic-pyruvate transaminase and were measured in a subsample of patients included in the cross-sectional study using routine clinical chemistry methods.

Psychometric evaluations

In addition, patients were asked to complete several psychometric tests, such as the Body Uneasiness Test (BUT) (25), the Symptom Checklist 90 revised (SCL-90-R) (26), the Gender Identity/Gender Dysphoria questionnaire (GIDYQ-AA) (27), and the Beck Depression Inventory (BDI) II (28).

A description of the aforementioned questionnaires has been reported in Supplemental Table 2.

Finally, physical (breast development, BMI, FG score, testis volume) and psychological (BUT-global severity index [GSI]) change ratios were calculated dividing the difference of score at T4 and T0 by the score at T0.

The study protocol was approved by the institution's ethics committee. All the patients have provided their written informed consent to participate to the study

Statistical analyses

Continuous variables were reported as mean ± SD, whereas categorical variables were reported as a percentage. For the assessment of between-group differences (CHT vs no-CHT groups), a χ^2 and an independent measures *t* test were applied for categorical and continuous variables, respectively. Differences between groups were evaluated in a multivariate model (adjusting for relevant clinical confounders) by means of an analysis of covariance (ANCOVA). Linear regression analyses were performed to assess the associations of continuous clinical variables. Linear mixed models (ANOVA mixed model with random intercept) were adopted for longitudinal data. In particular, these models were used to study the variation (time effect) of clinical variables within different time points. Paired-sample *t* tests were adopted to evaluate differences from one time point to another.

Results

Cross-sectional study

Sociodemographic and clinical characteristics of the cross-sectional sample according to CHT

Individuals from the CHT group (n = 167) were significantly older than in the no-CHT (n = 192; age ±SD 33.90 ± 9.19 and 29.11 ± 9.28 y, respectively; t = −4.76, $P \leq .0001$).

On average, MtFs (n = 125) and FtMs (n = 42) reported 1331 (31; 13 445) and 323 (33; 1095) days of hormone therapy, respectively.

Regarding the type of CHT, in the FtM group, 76.2% (n = 32) were using parenteral testosterone enanthate, 33.3% (n = 14) parenteral testosterone undecanoate, and 33.3% (n = 14) transdermal testosterone. For the MtF group, 44.0% (n = 55) was using oral estradiol valerate, 26.4% (n = 33) oral ethinyl estradiol, 28% (n = 35) transdermal estradiol hemihydrate, 19.2% (n = 24) estradiol gel, 3.2% (n = 4) oral finasteride, 4.0% (n = 5) oral dutasteride, 78.4% (n = 98) oral cyproterone acetate, and 1.6% (n = 2) oral spironolactone.

For eight MtFs and three FtMs in the CHT group, we did not have information on the type of treatment.

It should be noted that self-medication was often the reason for the mixed CHT profile of some subjects (eg, more than one type of estrogen formulation at the same time), as previously reported (4).

BMI was 23 ± 4.02 and 24.4 ± 3.61 kg/m^2, respectively, for MtFs and FtMs. Moreover, 54.8% of MtFs and 12.8% of FtMs reported any kind of cosmetic surgery.

For those patients with available information on liver function (n = 103), no significant differences were found in transaminase levels between CHT and no-CHT persons, in both MtFs and FtMs (see Supplemental Table 3).

Differences in terms of psychological well-being between persons with vs without CHT

Table 1 reports psychological characteristics of both groups and their differences in an age-, gender role-, and cosmetic surgery-adjusted ANCOVA models.

Considering depressive symptoms in FtMs, BDI-II levels were significantly lower in the CHT vs no-CHT group. For MtFs, this figure does not reach statistical difference (9.41 ± 7.91 and 7.31 ± 8.55 in no-CHT and CHT FtMs, respectively; $P = .027$). In addition, significantly lower levels of body uneasiness were observed in the CHT group in both genders, as compared with no-CHT. Regarding the GIDYQ-AA total score, CHT individuals showed significantly higher levels of global GD. However, when GIDYQ-AA subscales were considered in MtFs, the subjective GD was significantly higher in the CHT sample vs no-CHT. An opposite figure was found in the CHT group vs no-CHT for legal and social GDs, which were significantly lower, respectively, in FtMs and MtFs.

Psychopathological correlates of gender-related body features

Considering MtFs, after adjustment for the aforementioned confounders (age, cosmetic surgery, and gender role) and for BMI, the FG score was significantly associated with higher levels of subjective GD (GIDYQ-AA, $\beta = -0.334$, $P = .049$, Figure 1A), body uneasiness (BUT-GSI, $\beta = .445$, $P = .002$, Figure 1B), and with a tendency of increased psychopathology (SCL-GSI, $\beta = .292$, $P = .058$, Figure 1C). In addition, considering the BUT subscales, hair growth (FG score) was significantly associated with

Table 1. Summary of Estimated Means and SEs for MtF and FtM Participants by CHT Group, Including Results for Differences Tested With ANCOVA, Adjusted for All Outcome Variables

	FtMs				MtFs			
	No CHT	CHT	Adjusted D Value	Adjusted *P* Value	No CHT	CHT	Adjusted D Value	Adjusted *P* Value
SCL-90-R GSI	0.52 ± 0.44	0.48 ± 0.47	0.07 ± 0.09	.43	0.53 ± 0.05	0.45 ± 0.08	0.07 ± 0.09	.50
BUT-GSI	2.34 ± 0.09	1.80 ± 0.14	0.53 ± 0.17	**.02**	2.42 ± 0.91	1.69 ± 1.01	0.53 ± 0.17	<**.001**
BDI-II	7.17 ± 6.97	3.08 ± 3.32	4.03 ± 2.06	**.05**	9.41 ± 7.91	7.31 ± 8.55	1.86 ± 1.67	.27
GIDYQ-AA global score	2.19 ± 0.36	2.10 ± 0.27	0.11 ± 0.13	**.01**	2.28 ± 0.34	2.26 ± 0.49	0.01 ± 0.093	<**.001**
GIDYQ-subjective indicator	1.99 ± 0.35	2.20 ± 0.31	0.20 ± 0.13	.12	1.99 ± 0.41	2.29 ± 0.49	0.29 ± 0.10	**.01**
GIDYQ-social indicator	2.70 ± 0.55	2.37 ± 0.32	0.34 ± 0.19	.08	2.87 ± 0.64	2.41 ± 0.50	0.37 ± 0.13	**.01**
GIDYQ-sociolegal indicator	2.5 ± 0.90	1.56 ± 0.88	0.03 ± 0.33	**.01**	2.61 ± 1.01	2.38 ± 1.24	0.13 ± 0.25	.57
GIDYQ-somatic indicator	1.36 ± 0.7	1.14 ± 0.20	0.22 ± 0.21	.31	1.47 ± 0.71	1.57 ± 1.03	0.10 ± 0.20	.60

D, Difference.

body image avoidance (BUT-Avoidance, $\beta = .475$, $P = .001$), body image concerns (BUT-Body image concerns, $\beta = .404$, $P = .006$), and estrangement feelings toward the body (BUT-Depersonalization, $\beta = .327$, $P = .027$). When different body parts were analyzed, hair representation in lip, chin, upper abdomen, arms, and leg were positively associated with BUT-GSI ($\beta = .38$, $P = .01$; $\beta = .396$, $P = .006$; $\beta = .385$, $P = .04$; $\beta = .358$, $P = .007$; $\beta = .358$, $P = .007$, respectively). Furthermore, FG scores for chest, leg, and upper abdomen were negatively associated with subjective GIDYQ-AA ($\beta = -.375$, $P = .032$; $\beta = -.434$, $P = .007$; $\beta = -.370$, $P = .032$, respectively). When patients who had undergone augmentation mammoplasty were excluded, breast development was negatively associated

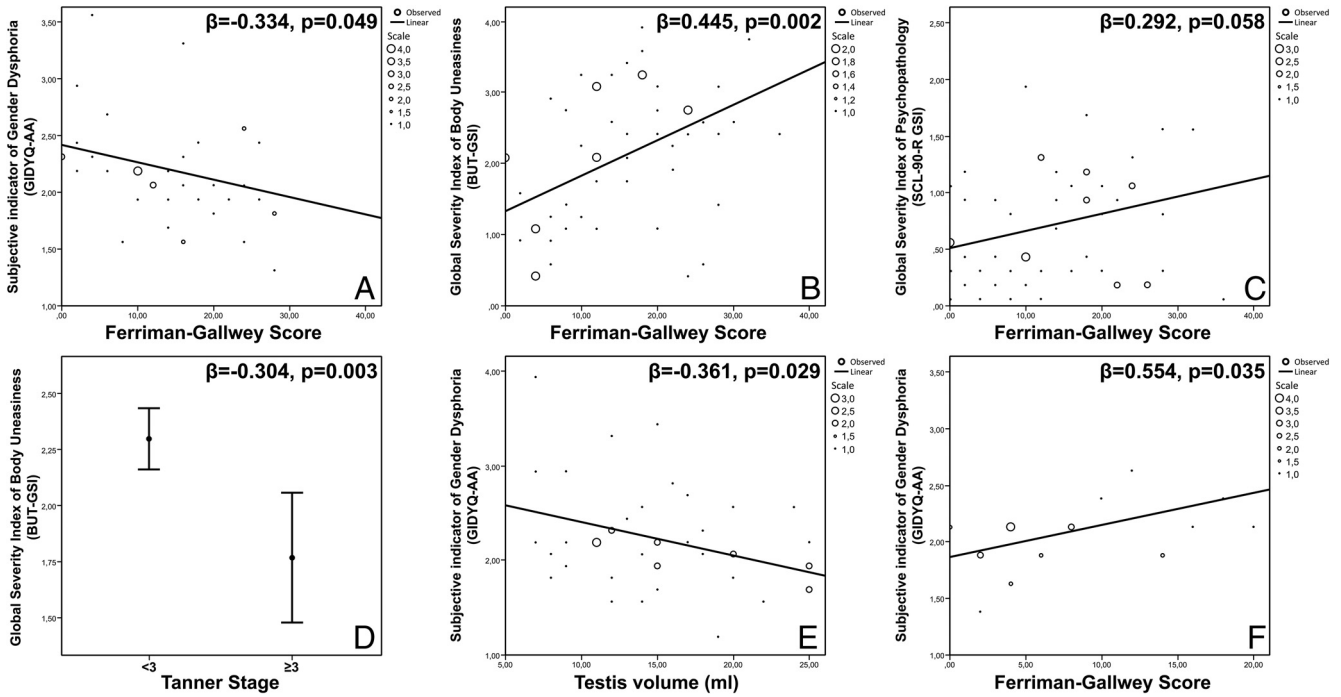

Figure 1. Associations between psychological (GIDYQ-AA, BUT-GSI, and SCL-90 R) and physical (FG score, Tanner stage, and medium testis volume) features in MtFs (panels A–E) and FtMs (panel F).

with global body uneasiness (BUT-GSI, $\beta = -.304$, $P = .003$, Figure 1D), weight phobia ($\beta = -.297$, $P = .044$), body image concerns (BUT-Body image concerns, $\beta = -.340$, $P = .017$), body avoidance (BUT-Avoidance, $\beta = -.275$, $P = .05$), and depersonalization ($\beta = -.240$, $P = .04$). Moreover, mean testis volume (Prader orchidometer) was negatively associated with a subjective GD ($\beta = -.361$, $P = .029$, Figure 1), suggesting that smaller testes are associated with lower levels of GD, as subjectively perceived. Finally, we found no correlation between T levels and testis volume ($\beta = .220$ $P = .129$),as well as between T levels and subjective GD ($\beta = -.004$, $P = .990$).

Considering FtMs, after adjustment for confounders (age, BMI, cosmetic surgery, and gender role), the FG score was associated with lower levels of subjective GD (GIDYQ-AA, $\beta = .554$, $P = .035$, Figure 1F).

Follow-up data

Psychobiological effect of CHT over time

In the sample enrolled in the longitudinal survey, average age at baseline for MtFs and FtMs resulted statistically different (t = −2.26, $P = .03$), being 32.52 ± 11.06 and 26.32 ± 7.29 years, respectively.

General psychopathology

Over time, both groups showed a significant reduction in SCL-GSI (time effect FtMs: $\beta = -.06$, $P = .01$; MtFs: $\beta = -.08$, $P = .001$), with a higher effect in MtFs (group by time interaction: F = 9.50; $P < .001$). Whereas MtFs showed a significant reduction in SCL-GSI at all time points (all $P < .01$), FtMs had a significant reduction only at T3 (t = 2.45, $P = .022$) and T4 (t = 3.40, $P = .002$) (Figure 2A).

Depressive symptoms

In addition, depressive symptoms according to BDI-II showed a significant reduction in both groups (time effect FtMs: $\beta = -1.31$, $P < .001$; MtFs: $\beta = -1.41$, $P < .001$), with a higher effect in MtFs (group by time interaction: F = 26.67; $P < .001$, Figure 2B).

Body uneasiness levels

A significant reduction of general body uneasiness was also found (time effect FtMs: b = −.24, $P = .001$; MtFs: b = −.24, $P < .001$), with a higher effect in MtFs (F = 19.70; $P < .001$, Figure 2C).

GD levels

GD levels (GIDYQ-AA) showed a significant change over time in both groups (time effect FtMs: $\beta = -.05$, $P = .001$; MtFs: $\beta = -.06$, $P < .001$, Figure 3A), without differences between them (F = 1.39; $P = .23$). In particular, GIDYQ-AA total score significantly increased at T1 and subsequently decreased at T2, T3, and T4. When GIDYQ-AA subscales were considered, a different pattern was found for subjective GD with respect to social and sociolegal ones (Figure 3, B–D). In particular, a significant decrease of subjective GD and a concurrent increase of GD related to social and sociolegal presentation were found according to months of treatment (all $P < .05$).

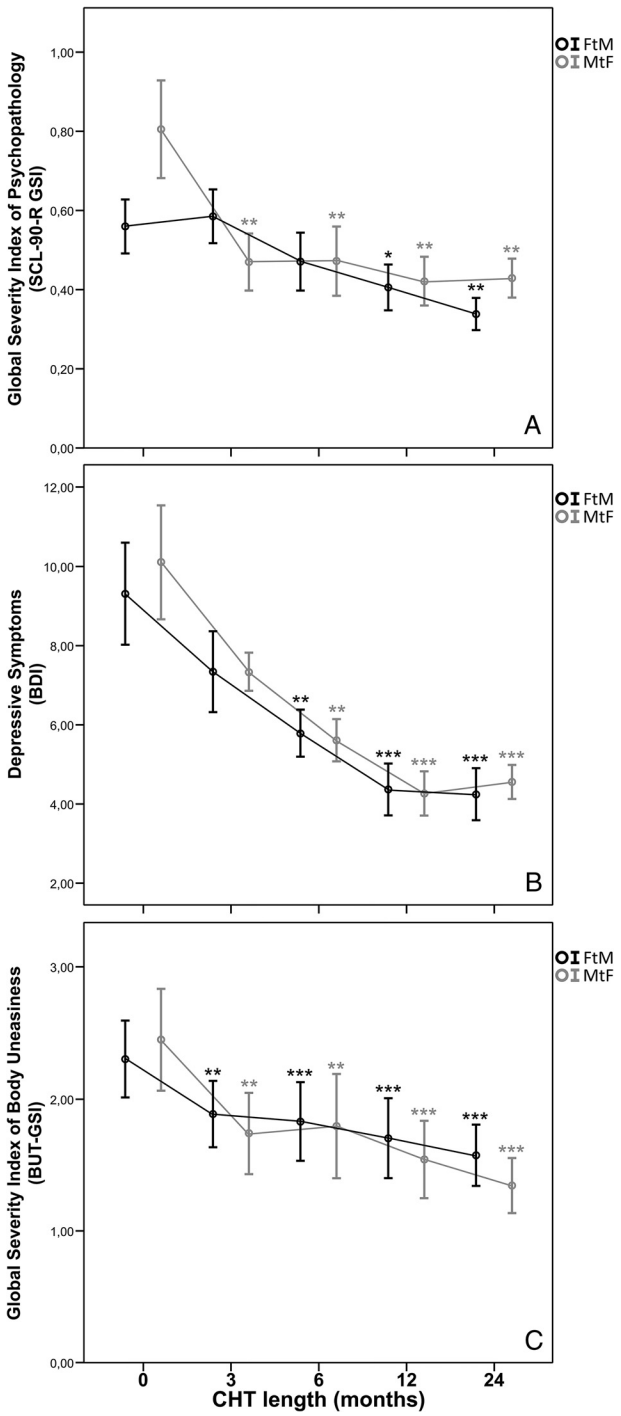

Figure 2. SCL-90 R-GSI (A), BDI (B), and BUT-GSI (C) scores at 0, 3, 6, 12, and 24 months of CHT in FtMs and MtFs (dark and gray lines, respectively). *, $P < .05$, **, $P < .01$, ***, $P < .001$ across time vs time 0 in FtM and MtF groups, respectively.

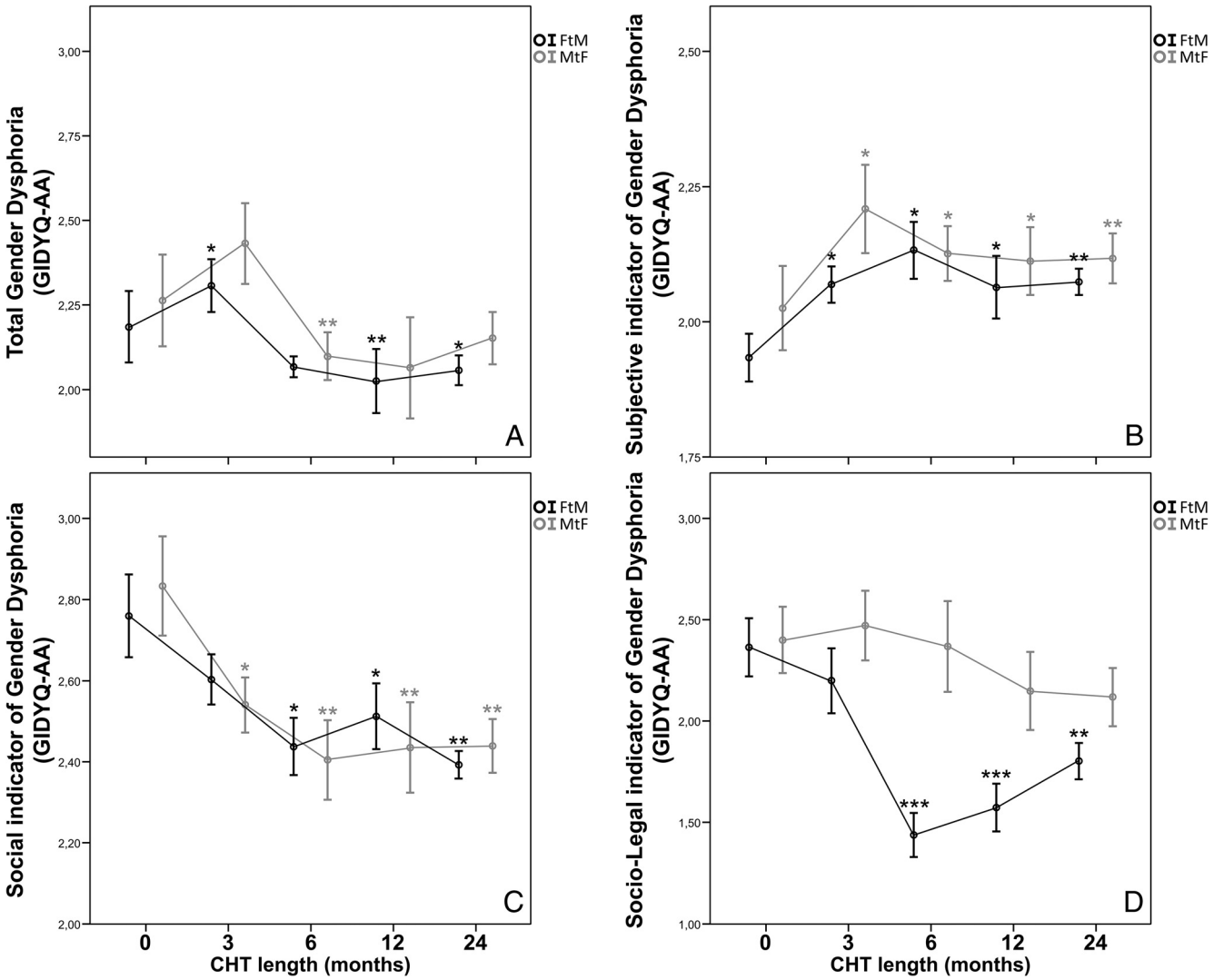

Figure 3. GIDYQ-AA total score (A), and GIDYQ-AA subjective, social, and sociolegal subscales (B–D, respectively) at 0, 3, 6, 12, and 24 months of CHT in FtMs and MtFs (dark and gray lines, respectively). *, $P < .05$, **, $P < .01$, ***, $P < .001$ across time vs time 0 in FtM and MtF groups, respectively.

Body modifications

Regarding body changes in FtMs, BMI showed a significant increase from baseline at T1 (t = −3.99, P = .001), with a further increase as a function of CHT length (all $P < .05$, Table 2), whereas waist circumference significantly increased only at T4 vs T0 (t = −3.20, P = .004). Considering genitals, clitoris length showed a marked increase from baseline at T1 (t = −9.73, $P <$ .0001), with a further, smooth increase according to CHT duration (between T0 vs T2, T0 vs T3, and T0 vs T4, all $P < .001$). Finally, the FG score showed a significant increase at T1 (t = −2.91, $P < .0001$), with further significant modification during follow-up (between T0 vs T2, T0 vs T3, and T0 vs T4, all $P < .0001$).

Considering MtFs, BMI and waist showed a significant increase as a function of CHT length (all $P < .05$, Table 2). As expected, the FG score showed a significant reduction from baseline at T1 (t = 2.55, P = .02), with a further significant modification during the following months of treatment (all $P < .0001$). In particular, a medium score lower than 8 was observed only after 24 months of CHT (t = 9.42, $P < .0001$ vs T0, see Table 2).

Regarding testis volume, we observed a significant reduction from baseline at T1 (t = 7.78, $P < .0001$), with a further significant reduction during follow-up (all $P <$ .001, Table 2). In addition, breast development showed a significant increase at T1 (F = 273.6, $P < .0001$) and a stepwise further modification according to CHT length (all $P < .0001$ at ANCOVA, Figure 4).

Impact of body changes on psychopathology over time

Males to females

In MtFs, when variations in all body parameters potentially affecting BUT (breast development, BMI, FG

Table 2. Body Changes at Baseline and 3, 6, 12, and 24 Months of CHT, Respectively, in FtMs and MtFs

	FtMs					MtFs				
	Baseline	3 Months	6 Months	12 Months	24 Months	Baseline	3 Months	6 Months	12 Months	24 Months
Waist, cm	90.97 ± 13.44[a]	90.93 ± 10.39	89.81 ± 11.40	89.97 ± 11.57	98.50 ± 10.56[b]	83.07 ± 7.84	84.00 ± 7.83	86.80 ± 7.23[b]	83.07 ± 7.85[c]	88.03 ± 5.07[b]
BMI, kg/m^2	24.88 ± 0.47[d]	25.61 ± 4.66[e]	25.84 ± 4.72[e]	25.63 ± 3.88[c]	27.72 ± 3.97[b]	21.91 ± 2.82	22.08 ± 2.48	22.45 ± 2.66[b]	22.89 ± 2.09[e]	23.02 ± 2.23[e]
Weight, kg	64.86 ± 13.86	66.68 ± 13.92[b]	66.85 ± 13.88[b]	66.85 ± 13.03[c]	75.66 ± 10.78[e]	65.26 ± 10.11	65.50 ± 9.05	67.29 ± 8.74	69.15 ± 6.69[b]	67.07 ± 4.26
FG score	4.46 ± 3.94[f]	6.92 ± 2.98[b]	13.62 ± 6.19[e]	17.65±.4.90[e]	25.46 ± 4.99[e]	16.75 ± 7.00	13.25 ± 4.66[c]	10.04 ± 3.86[e]	9.93 ± 2.76[e]	4.74 ± 2.90[e]
Medium testis volume, mL						18.06 ± 3.62	12.15 ± 0.66[e]	11.67 ± 1.63[e]	11.08 ± 1.47[e]	10.91 ± 1.05[e]
Clitoris length, cm	1.95 ± 0.62[e]	3.19 ± 0.54[e]	3.26 ± 0.60[e]	3.58 ± 0.55[e]	3.83 ± 0.42[e]					

[a] $P < .05$.

[b] $P < .01$.

[c] $P < .05$.

[d] $P < .01$.

[e] $P < .001$ across time vs time 0 in FtM and FtM groups, respectively.

[f] $P < .001$ between FtMs and MtFs.

score, testis volume) were entered as covariates in the same regression analysis model, along with the BUT score decrease, only breast development was significantly associated with a BUT reduction ($\beta = -0.405$, $P = .04$).

Females to males

When a similar model was applied to FtMs (entering as covariates clitoris length, BMI, and FG score), only the BMI increase was found to be significantly associated with a BUT decrease ($\beta = -.488$, $P = .03$).

Discussion

This is the first study simultaneously evaluating GD levels and psychopathology in transsexuals under CHT and the impact of CHT-related body changes on psychological well-being. The strength of the present study is in its multidisciplinary prospective design, evaluating both psychological and physical aspects of gender transitioning, and in the size of the population studied. Results from a cross-sectional study were also evaluated.

The main results are the following: 1) GDs under CHT reported significantly lower levels of subjective GD, body uneasiness, and depressive symptoms as compared with those without (cross-sectional study); 2) CHT-induced body modifications were significantly associated with a better psychological adjustment (cross-sectional study); 3) during CHT, patients reported a significant reduction of general psychopathology, depressive symptoms, and sub-

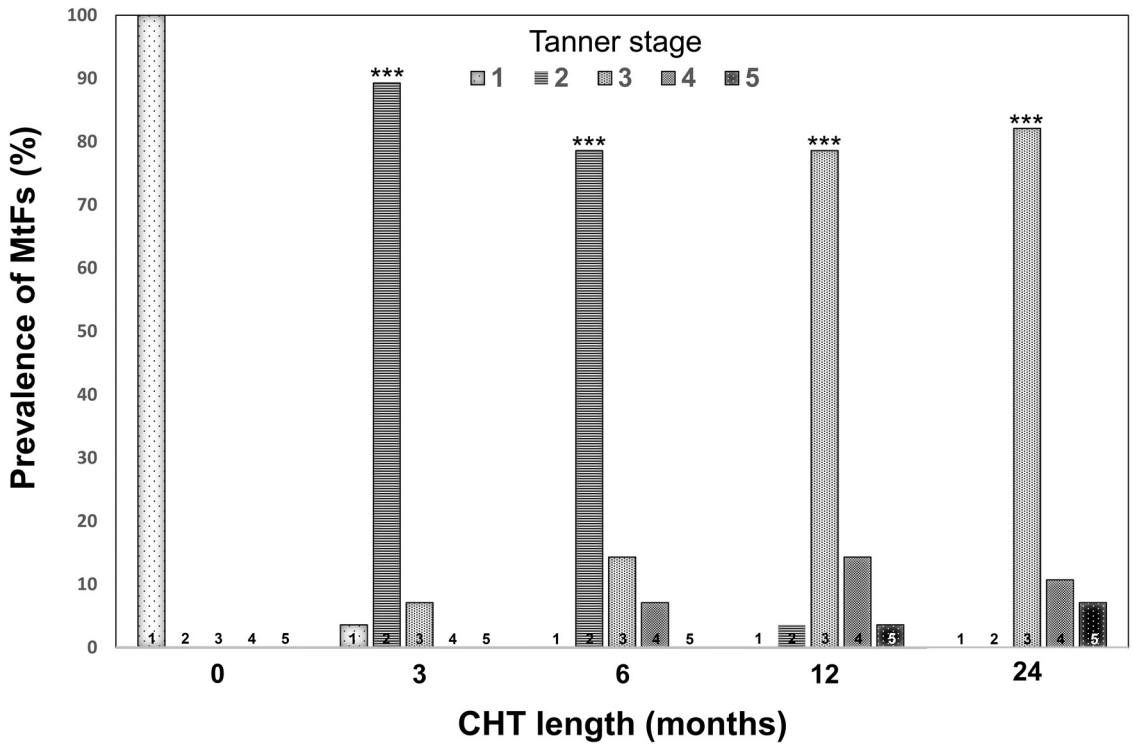

Figure 4. Percentages of MtFs with a specific Tanner stage (1–5) at 0, 3, 6, 12, and 24 months of CHT. ***, $P < .001$ across time vs time 0.

jective GD, whereas social and sociolegal GD showed a significant increase over time (prospective study); and 4) among body changes induced by CHT, only breast development and increased BMI showed a significant impact on psychopathology reduction over time in MtFs and FtMs, respectively (prospective study).

Psychological modifications induced by CHT

Individuals under CHT alone (ie, without GRS) reported a significant reduction of subjective GD (GIDYQ-AA subjective indicator). In addition, we prospectively observed that CHT has a positive effect in alleviating body-related uneasiness (BUT). The CHT-induced concurrent improvement in both GD and body uneasiness levels highlights the centrality of body image concerns in GD development (29, 30). This is further suggested by our results from the cross-sectional sample regarding psychobiological correlates of gender-related body features.

Our results confirm that CHT is associated with a relevant improvement of general psychopathology (SCL-90-R [15, 21, 31]) and demonstrate, for the first time, a significant reduction of depressive symptoms (BDI-II) as a function of months of treatment.

The opposite trend observed during follow-up for social and sociolegal GD (GIDYQ-AA) with respect to subjective subscale can appear, at first glance, surprising. However, this conflicting result can be explained considering the sociolegal and cultural difficulties that GDs have to deal with in the Italian context.

Body modifications induced by CHT

With regard to hormonal impact on body modifications, we here evaluated the dermatological effect of CHT in a larger sample and with a longer follow-up than in previous surveys (32, 33). Our results show that 6-month T treatment was able to induce in the majority (92.7%) of FtMs an average FG score that, in women, is indicative for hirsutism (>8, 23). CHT was less effective in MtFs in obtaining the desired hair pattern (Table 2). However, the lower reliability of the FG score system should be considered in this particular population. In fact, in MtFs, hair density is often the final result of effect(s) of other hair removal systems (laser or electrolysis) in addition to CHT.

Regarding effects of CHT on body distribution, we observed in both MtFs and FtMs a significant increase of BMI and waist circumference, an indirect expression of abdominal fat distribution. These results suggest a gender-specific effect of T on fat distribution. In FtMs, T increase is associated with visceral adiposity accumulation, as observed in polycystic ovary syndrome women and in previous studies on GD (33–36) In contrast, in native males, T deficiency is associated with an increased waist circumference (37) as here observed in MtFs.

Estrogens and antiandrogens resulted in breast growth, with a significant progression over 2 years of treatment. In addition, CHT induced a marked testis volume decrease, which resulted in a 40% and 50% reduction after 1 or 2 years, respectively. This figure is higher than that previously reported by Meyer et al (38) after 1.5 years (25%) but, however, in a smaller sample and with older estrogen preparations.

Finally, in FtMs the clitoris starts to increase by 60% after only 3 months from starting T treatment and continues to grow, almost doubling after 2 years, at variance with the aforementioned study (38), demonstrating a plateau after 1 year.

Impact of body changes on psychopathology over time

Considering the psychological impact of body modifications in MtFs, only CHT-induced breast development showed a significant effect on body uneasiness decrease, whereas, surprisingly, hair distribution did not. However, it should be considered that the BUT scale is more related to the private relationship with one's own body, rather than to the distress caused by how one may appear to others (4).

Considering FtMs, CHT-induced BMI increase was the only covariate significantly associated with body uneasiness reduction. It could be speculated that in FtMs a higher BMI and waist circumference make the self-perceived body image more masculine (30) and a surrogate way to hide female shapes.

Limitations

The results of the longitudinal study should be considered as preliminary, given the small sample size, and interpreted in light of some limitations. First of all, we did not include a control, untreated group for obvious ethical reasons. However, comparisons between CHT and non-CHT subjects in the cross-sectional study support the longitudinal observations.

Another limitation is that some clinical measures were self-reported, and this could bias the results. Regarding the measures of objective body change, the subjective nature of the FG score system and breast development may lead to interobserver variability. For this reason, minimizing the number of examiners, as performed in the present study, decrease the risk of ascertainment bias, as previously suggested (23).

We did not collect ovarian morphology and polycystic ovary prevalence, due to different reasons, including uncomfortable feelings associated with transvaginal ultra-

sound and the previously reported increased incidence of polycystic ovary in FtMs (39).

Finally, hair growth in MtFs is often influenced by other cosmetic treatments (such as laser removal and electrolysis) with wide interindividual variability. However, for ethical reasons, it was not possible to ask MtFs not to use any kind of hair removal before each assessment. In addition, data regarding the extent and variety of types of hair treatment were not collected.

In conclusion, the combination of the cross-sectional and longitudinal results of the present study supports the efficacy of CHT intervention in improving the subjective perception of one's own body, which was partially associated with objective changes. Consequently, when the perceived resembles the desired body, subjective GD progressively decreases as well as the general psychopathology.

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