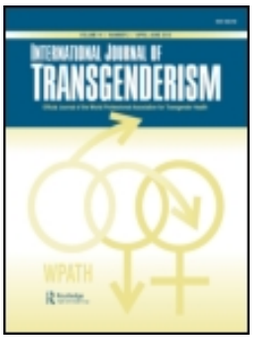

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Medical Treatment of Subjects with Gender Identity Disorder: The Experience in an Italian Public Health Center

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Medical Treatment of Subjects with Gender Identity Disorder: The Experience in an Italian Public Health Center

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ABSTRACT. Hormonal treatment is the main element during the transition program for transpeople. The aim of this paper is to describe the care and treatment of subjects, highlighting both the endocrine-metabolic effects of the hormonal therapy and the quality of life during the first year of cross-sex therapy in an Italian gender team. We studied 83 subjects (56 male-to-female [MtF], 27 female-to-male [FtM]) with hematological and hormonal evaluations every 3 months during the first year of hormonal therapy. MtF persons were treated with 17βestradiol and antiandrogens (cyproterone acetate, spironolactone, dutasteride); FtM persons were treated with transdermal or intramuscular testosterone. The WHO Quality of Life questionnaire was administered at the beginning and 1 year later. Hormonal changes paralleled phenotype modifications with wide variability. Most of both MtF and FtM subjects reported a statistically significant improvement in body image ($p < 0.05$). In particular, MtF subjects reported a statistically significant improvement in the quality of their sexual life and in the general quality of life ($p < 0.05$) 1 year after treatment initiation. Cross-sex therapy seems to be free of major risks in healthy subjects under clinical supervision during the first year. Selected subjects show an optimal adaptation to hormone-induced neuropsychological modifications and satisfaction regarding general and sexual life.

KEYWORDS. Gender identity disorder, cross-sex hormonal therapy, quality of life, androgens, estrogens, antiandrogens

Gender Identity Disorder (GID) is defined, as per the *DSM-IV-TR* manual, as a condition of severe unchangeable identification with the opposite sex, which determines uneasiness and

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inadequacy in one's own body to such an extent that the subject requires a physical transition. This disorder may affect both males (male-to-female [MtF]) and females (female-to-male [FtM]), and it is found in all social classes. In the Caucasian population, patient populations with GID are estimated to be in the range of 1:10,000 to 1:30,000 born male and 1:30,000 to 1:100,000 born female. Patients with GID are followed in their transition program by a team of a skilled professionals. The aim is to enable them to perform their transition in a healthy way, both biologically and psychologically (Bockting, 2008). Owning to their condition, patients with GID often seek medical help in order to transform their bodies to obtain the characteristics of their gender identity. Hormonal treatment is the main element in the transition program before surgery. The aim of this article is to describe the care and treatment of the subjects, highlighting the endocrine-metabolic effects of the hormonal therapy during the first year of the cross-sex therapy regimen at the C.I.D.I.Ge.M. Centre (Interdepartmental Centre for G.I.D. in Molinette Hospital in Turin). This is a multidisciplinary regional reference center dealing with complete transition programs including psychological, social, relational, and medical-surgical aspects from the beginning to the sex reassignment surgery (SRS) to the postoperative follow-up.

MATERIALS AND METHODS

Over the 6 years of C.I.D.I.Ge.M. activity, 298 subjects were assessed, 65 were excluded due to no GID diagnosis. The mean age was 33.7 ($\pm$ 5.4) years. Our observational study consisted of a sample of 83 subjects (56 MtF and 27 FtM), assessed periodically during the first year of hormonal therapy. All subjects showed a biological correct kariotype (46 XY in MtF and 46 XX in FtM subjects, respectively). C.I.D.I.Ge.M. follows the standards of care recommended by the National Observatory of Gender Identity (www.ONIG.it). GID diagnosis was made by a team of mental health professionals through clinical interviews, psychosexological assessment, and personality tests lasting about 6 months on average.

Differently from World Professional Association for Transgender Health Standards of Care (WPATH SOC), ONIG guidelines recommend a psychological evaluation for a period of at least 4–6 months, not only to assess gender dysphoria but also to verify the intake of responsibility about the choice to pursue transition. Real-life experience (RLE) must last at least 8 to 12 months to allow GID patients to develop adequate psychophysical characteristics. A constant psychotherapy is an absolute requirement in order to undergo surgical treatment. With the exception of mandatory psychotherapy, the general WPATH SOC criteria for the prescription of the hormonal therapy are also shared by ONIG (persistent and documented gender dysphoria, ability to make an informed choice, legal age; medical or psychological-psychiatric comorbidities need to be compensated).

During psychosexological assessment, professionals examined self-perception, body image, sexual orientation, interpersonal relationships, and the presence of any significant psychopathology. The World Health Organization Quality of Life–100 (WHOQOL-100) questionnaire has been administered to assess both the general quality of life and the quality of sexual life. In our assessment, we have considered the general quality of life, quality of sexual life scores, and two subscale values related to body image and social relationships. WHOQOL-100 was administered at the beginning of the transition program and 1 year after the beginning of cross-sex therapy. We underline that the cutoff score related to a good quality of life is $\geq$ 50. After the diagnosis of GID is confirmed, subjects are eligible to start cross-sex therapy under an endocrinologist's supervision and may live according to their gender identity role (RLE). The latter is considered to be a diagnostic aid, which confirms the subject's real identity. RLE includes weekly sessions of individual psychotherapy, aimed to assess both psychological and relational functioning. This period of life is also useful to support the subject decision about SRS. The aim of cross-sex therapy is to convert secondary sex characteristics and reduce the gender dysphoria related to them. This goal

is achieved by pharmacological castration and by cross-sex steroid administration. RLE must last at least 1 year to significantly modify the phenotype in prevision of SRS. The duration can be extended according to individual and therapeutic needs. At the end of the program, the subjects who wish to undergo SRS require a court order, which is obtained by presenting a specific medical and psychological report. This step is also necessary to change details on personal documents according to Italian law 164/82. Following surgical gonadectomy, primary hypogonadism occurs, which must be treated with chronic replacement therapy, requiring life-long endocrinological follow-up.

Inclusion Criteria

Our study included all patients with a GID diagnosis confirmed by mental health professionals according to *DSM-IV* criteria. Diagnosis required an average time of 8.25 months. Patients with severe psychopathologies (i.e., schizophrenic spectrum disorder, substance abuse, mild or severe mental retardation and dementia) were excluded. Patients who met both eligibility criteria for hormonal treatment and the feasibility requirements of the Italian Consensus SIAMS-ONIG (Godano et al., 2009) were considered suitable to enter the transition program. Hematological and hormonal evaluations were performed prior to the initiation of cross-sex therapy, as provided by consensus and shown in Table 1. The presence of congenital thrombophilia risk was also evaluated in MtF patients prior to the initiation of estrogen treatment (Table 2).

Statistical Analysis

Results are expressed as $M \pm SD$. The student two-tailed test for paired data was used to compare average measurements within the same group before and during hormone therapy. A p value of ≤ 0.05 was considered statistically significant.

General Aspects of Treatment

Starting at the beginning of cross-sex therapy, all patients performed weekly psychodynamic psychotherapy. Cross-sex therapy was prescribed "off-label," according to guidelines ("Endocrine Society New Guideline," Hembree et al., 2009) and required specific written informed consent. The endocrine staff had the opportunity to provide cross-sex hormonal drugs directly from the Piedmont Regional Health Service through the Molinette Hospital pharmacy (only for persons who were residents of the Piedmont region and followed the transition program in C.I.D.I.Ge.M.).

TABLE 1. Hematological and Hormonal Evaluations

Hematological parameters
Glucose (and HbA1c in diabetes or strong family history)
Creatinine
Lipid profile (total cholesterol, HDL, LDL, triglycerides)
Liver enzymes
Na^+ and K^+ in case of hypertension
PSA (only in MtFs over age 40)
HBsAg, anti-HBc IgM, anti-HCV IgM, HIV, TPHA
Complete urinalysis
FSH, LH, SHBG, total testosterone, 17βestradiol, PRL, TSH
17αOHP (only in FtMs)

MtF Sample

Major baseline characteristics are shown in Table 3. Physical examination in all patients showed normal testes with a volume of 17.0 ± 3.0 cc. In 10.7% of the patients the testes were voluntarily positioned in the inguinal channel. One subject was affected by a microprolactinoma and was already under dopaminergic treatment. Data from WHOQOL showed the following baseline scores: Body Image scale, 43.25; Quality of Life scale, 62.50; Quality of Sexual Life scale, 56.25; Interpersonal Relationship scale, 50.25.

TABLE 2. Additional Evaluations in MtF Subjects

Coagulation factors
Factor V and Prothrombin Mutations
C and S coagulative proteins
Anti-Thrombin III

TABLE 3. Baseline Characteristics of the MtF Group

Characteristics	*M* ± *SD*	*n*/*N* (%)	Range/Mean value
Age	32.7 ± 8.8 yr		
Body weight	66.4 ± 17.2 kg		
Height	172 ± 7.38 cm		
BMI ≥ 30 kg/m^2		5/56 (8.9)	
Hypercolesterolemia		6/56 (10.7)	Total cholesterol 215–291 mg/dl
Familial hypercolesterolemia		1/56 (1.8)	Total cholesterol 338 mg/dl
Familial hypertriglyceridemia		1/56 (1.8)	Triglycerides 489 mg/dl
Glucose intolerance		No	
DM 1		1/56 (1.8)	HbA1c = 8%
DM 2		1/56 (1.8)	HbA1c = 6.9%
Metabolic syndrome (according to ATP III criteria)[a]		4/56 (7.1)	
Subjects with 2/5 criteria		2/56 (3.6)	
HIV+		3/56 (5.3)	
Smoking habit		22/56 (39)	15.2 cigarettes/day
Sexual orientation			
Heterosexual		54/56 (96.4)	
Homosexual		1/56 (1.8)	
Bisexual		1/56 (1.8)	
Presence of stable relationship		35/56 (62.5)	

Note. MtF = male to female; BMI = body mass index; ATP = Adult Treatment Panel III.
[a] *Source*: "Third Report of the National Cholesterol Education Program" (2002).

Treatment and Follow-Up in MtF Patients

MtF patients were treated with 17βestradiol mainly by oral administration: 2 mg/day during the first 3 months and 4 to 6 mg/day orally or transdermally from the fourth month onward, depending on the clinical condition. Subjects age 40 years or older, recent severe smokers, and subjects with any trombophilic traits were preferentially treated with transdermal estrogen preparations.

The same applied for subjects with coagulation factor V heterozygous mutations (7%). Antiandrogens with central and peripheral action were co-administered along with estrogen treatment:

- cyproterone acetate (CPA) starting with 50 mg/day, then 100 mg/day, with a maintained average dose of 75 mg/day;
- spironolactone 100–200 mg/day when anti-hypertensive and diuretic effects were required; and
- dutasteride 0.5 mg/day in subjects with an androgenic defluvium

Two patients (3.6%) with contraindications to the use of CPA (severe obesity and hypertension) were treated with daily transdermal estradiol and a monthly administration of a GnRH analog. Among the 54 subjects treated with CPA, 34 (63%) were treated also with other antiandrogens.

During the RLE year, fasting LH, total testosterone, and estradiol were assessed every 3 months; fasting cholesterol with its fractions, triglycerides, and glucose were evaluated every 6 months. In subjects treated with spironolactone (21%), sodium and potassium were evaluated every 6 months.

Eight to 12 months after the initial estrogen therapy, all subjects underwent a mammography screening to check the development and characteristics of the mammary gland. According to the policy established by the radiologists in our hospital, the presence of a significant

TABLE 4. Baseline Characteristics of the FtM Group

Characteristics	*M* ± *SD*	*n/N* (%)	Mean value
Age	30.2 ± 8.1 yr		
Body weight	65.0 ± 15.4 kg		
Height	160 ± 6.69 cm		
BMI ≥ 30 kg/m^2		6/27 (22)	
Hypercolesterolemia		No	
Familial hypercolesterolemia		No	
Familial hypertriglyceridemia		No	
Glucose intolerance		No	
DM 1		No	
DM 2		No	
Metabolic syndrome (according to ATP III criteria)[a]		1/27 (3.7)	
Subjects with 2/5 criteria		2/27 (7.4)	
Smoking habit		11/27 (40.7)	13 cigarettes/day
HBV, HCV, or HIV+		No	
Sexual orientation			
Heterosexual		27/27 (100)	
Homosexual		No	
Bisexual		No	

Note. FtM = female to male; BMI = body mass index; ATP III = Adult Treatment Panel III.
[a] *Source*: "Third Report of the National Cholesterol Education Program" (2002).

gynecomastia is defined by a breast thickness (calculated during mammography from muscle to nipple level) greater than 6 cm.

FtM Sample

Major baseline characteristics are shown in Table 4. Pelvic sonography showed microcystic ovaries in 2 subjects (7.4%) whose hormonal profile indicated polycystic ovary syndrome. Nobody was affected by adrenal androgenism. Data from WHOQOL showed the following baseline scores: Body Image scale, 21.85; Quality of Life scale, 63.25; Quality of Sexual Life scale, 50.25; Interpersonal Relationship scale, 50.02.

Treatment and Follow-Up in FtM Patients

FtM patients were treated with testosterone, starting with a daily low dose transdermal gel (half a bag of T = 25 mg) or an intramuscular preparation every 10 to 15 days (T enanthate 100 mg).

Intramuscular testosterone undecanoate 1000 mg every 3 or 4 months was then used. Blood test was initially performed 2 months after the injection.

During the RLE year, fasting hematocrit, total testosterone, and estradiol were assessed every 3 months; fasting cholesterol with its fractions, triglycerides, and fasting glucose were evaluated every 6 months.

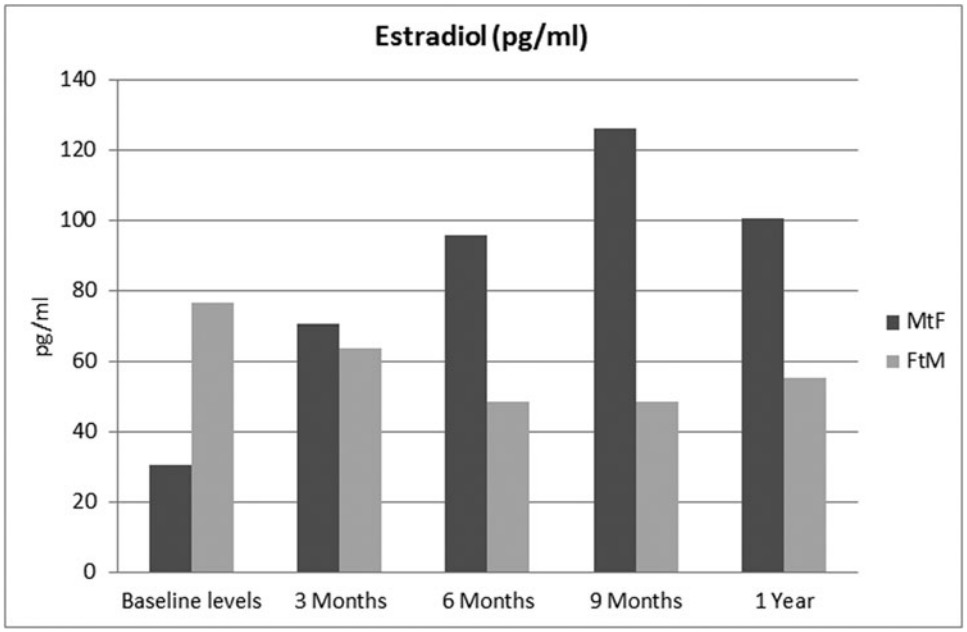
RESULTS

MtF Patients

Phenotype and Hormonal Status

Hormonal changes paralleled phenotype modifications, although with a large interindividual variability, mainly related to subject's age at the beginning of treatment. Mean body weight after 12 months was 69.04 ± 15.01 kg ($p = ns$). Five subjects were obese (8.9%). As a clinical impression we observed that progressive feminization started to occur in the first 6 months of treatment, with a body fat redistribution according to a gynoid pattern, a reduction in muscle mass, and a reported physical strength decrease. Mammary gland development began during the first semester and gradually progressed in the following months, reaching a good trophism at the end of the first year of estrogen treatment. Glandular thickness was > 6 cm in 34/56 (60.7%) subjects; maximal thickness was 10.7 cm bilaterally. In 22/56 (39.3%) subjects glandular thickness was < 6 cm, ranging from 4.5 to 5.5 cm. At the end of the first year of treatment, testis volume was reduced by 25% and reached a 50% reduction with the continuation of hormonal treatment (mean testicular volume 8.0 ± 2.0 cc). At the end of the first month of treatment skin thickness was reduced. Antiandrogen therapy led to a clinical impression of regression of

FIGURE 1. Male-to-female (MtF) and female-to-male (FtM) values of estradiol (median, $n = 83$)



cutaneous androgenization (slowed body-hair growth and less frequent shaving), as well as a progressive reduction of balding along with hair regrowth in such areas. Estradiol levels increased as expected and after 3 months reached a normal female range (Figure 1). The inhibition of testosterone production was immediate, with concentrations below the normal range in all subjects within the first 3 months and below 0.5 ng/ml in 32% (18/56 subjects; Figure 2).

FIGURE 2. Male-to-female (MtF) and female-to-male (FtM) values of testosterone (median, $n = 83$)

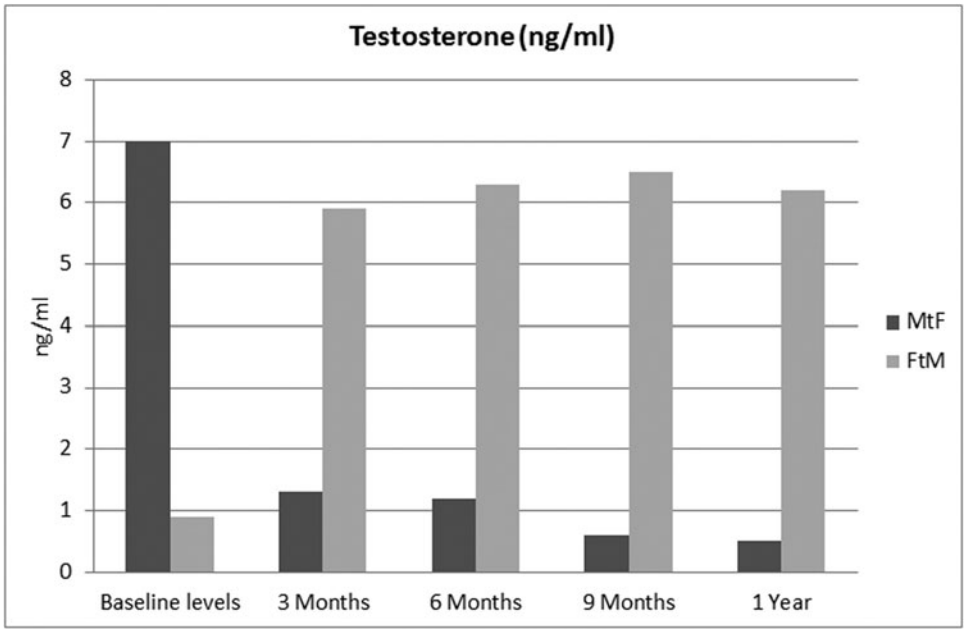
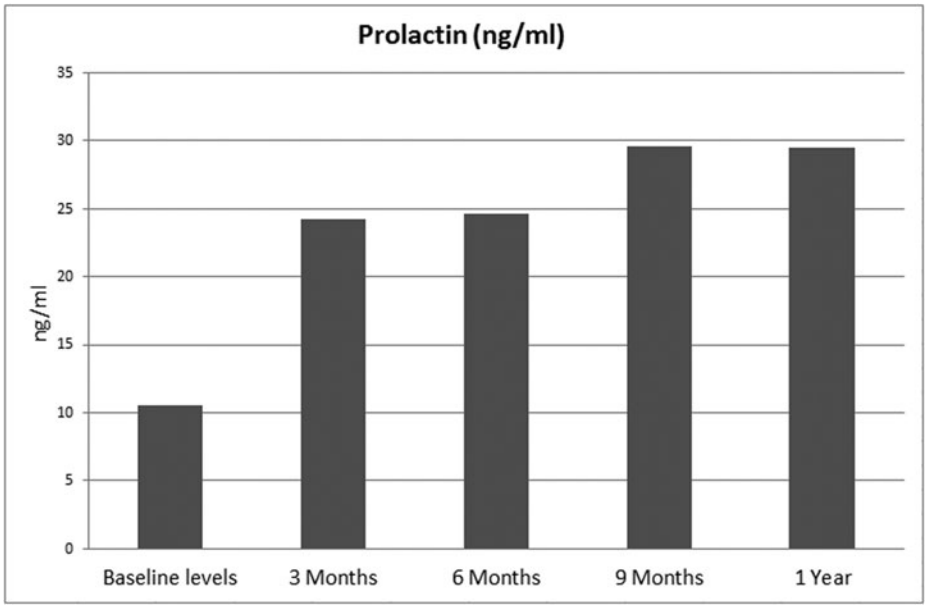


FIGURE 3. Male-to-female (MtF) values of prolactin (median, $n = 56$)



Over 20% of subjects showed a hyatrogenic hyperprolactinemia due to the direct estrogen and CPA effects on pituitary lactotroph cells (Figure 3). Table 5 shows the percentage of subjects with hyatrogenic hyperprolactinemia accordingly to the female range (< 20 ng/ml).

Hematological Assessment

All subjects under spironolactone treatment (12/12 = 100%) showed constantly normal sodium and potassium levels. In spite of a few changes in Hb and HCT values, no subjects developed true anemia (Hb between 12 and 16 g/dl in 56/56 subjects).

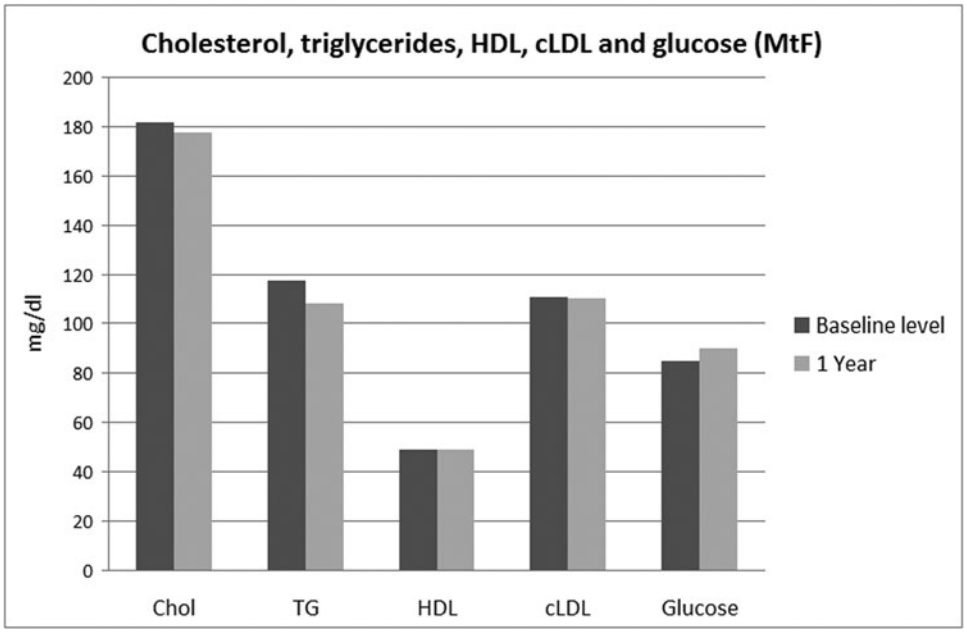
Lipid and Glucose Metabolism

The average levels of cholesterol, triglycerides, HDL, cLDL, and glucose (at baseline and after 1 year of hormonal treatment) are shown in Figure 4. Regular metabolic checks showed clear improvement in all 6 hypercholesterolemic subjects. In these cases, cholesterol levels were on average compensated by diet and pharmacological treatment (mean total cholesterol level at the end of the first year: 183.65 mg/dl ($p = ns$). In the 2 subjects with severe familial dyslipidemia, who continued their previous pharmacological therapy, a good lipid profile was observed, with triglyceride and total cholesterol levels of 256 mg/dl and 194 mg/dl, respectively, 1 year after hormonal treatment initiation. Overall, in all other subjects starting with a normal lipid profile (48/56 = 85.7%), sporadic cases of mild hypercholesterolemia were recorded (total cholesterol 250–285 mg/dl in 6/48 = 12.5% subjects). All these cases returned to normal with a stricter diet regimen. LDL cholesterol level at the end of the first year was 100.75 ± 18.01 mg/dl ($p = ns$). No new cases of impaired glucose tolerance or diabetes mellitus were recorded. HbA1c in the subject with DM1 was 6.9% after 1 year, due to diet restrictions required to enter the transition program. Fasting blood glucose in the subject with DM2 showed a good metabolic control. Two subjects developed a metabolic syndrome according to Adult Treatment Panel III (ATP III) criteria ("Third Report

TABLE 5. Percentage of Male-to-Female Subjects with Hyperprolactinemia During Real Life Experience (Median, $n = 56$)

I trimester	II trimester	III trimester	IV trimester
23.8%	31.6%	43.7%	43.7%

FIGURE 4. Male-to-female (MtF) values of cholesterol, triglycerides, HDL, cLDL, and glucose (at baseline and after 1 year of hormonal treatment; median, $n = 56$)



of the National Cholesterol Education Program," 2002) after 1 year of hormonal treatment. On the other hand, one of the 4 subjects with the metabolic syndrome diagnosed before entering the study did not meet the diagnostic criteria 1 year later, due to dietary measures.

Comorbidities

All 3 HIV-positive patients were able to undergo the cross-sex treatment maintaining their retroviral therapy and follow-ups. Mild side effects of hormonal therapy such as fatigue, temporary nausea, hypotension, mood swings, and mastodinia due to progressive gynecomastia were reported by 60% of subjects. Two patients (2/56 = 3.6%) showed induced galactorrhea. No prolactinomas were diagnosed. The subject with the previous microprolactinoma continued dopaminergic treatment during the cross-sex therapy with no complications. Two new cases of cholelithiasis were recorded (2/56 = 3.6%) and managed solely with medical treatment. Mammograms and mammary sonographies showed glandular lesions in 2 subjects. One subject (1/56 = 1.8%) was diagnosed with a suspect lesion, which was removed with a histological finding of fibroadenoma. In another subject, a sonography showed the presence of anechoic cystic lesions < 1 cm.

Smoking Habit

All smokers greatly reduced cigarette smoking at the beginning of treatment reaching an average of 10.1 cigarettes/day, while 4 subjects (4/22 = 18.2% of all smokers at the beginning of treatment) quit smoking.

Psychosexological Aspects

Most of the MtF patients maintained their heterosexual orientation according to their gender identity role (52/56 = 92.8% attracted to men). Two subjects changed their sexual orientation from heterosexual to homosexual (3/56 = 5.4% attracted to women), while 1 subject continued to be bisexual. At the end of the first RLE year 36/56 (= 64.3%) subjects had a stable relationship or cohabitation. Most MtF subjects (80%) reported a general trend toward a higher emotional lability and sensitivity in interpersonal relationships. They reported a higher emotional intensity (for both positive and

negative emotions) in dealing with life events, with a subjective perception of psychological well-being. One year after starting cross-sex therapy, the Body Image subscale average score was 68.75 ($p < 0.05$), the average Quality of Life score was 72.2 ($p < 0.05$), while the average Quality of Sexual Life scale score was 62.05 ($p < 0.05$). The Interpersonal Relationship scale reported an average score of 75 ($p < 0.05$).

FtM Patients

Phenotype and Hormonal Status

Hormonal changes paralleled phenotype modifications, although with a large interindividual variability, mainly related to the subject's age at the beginning of treatment. Mean body weight after 12 months was 67.5 ± 13.9 kg ($p = ns$); 5 subjects were obese (5/27 = 18.5%). As a clinical impression we observed the following changes: progressive virilization started to occur in the first trimester of treatment, with a muscle-mass increase and body-fat redistribution according to a male pattern; seborrhoea and acne started to develop in the first months of treatment and hair growth and fat redistribution were observed from the second trimester; beard growth occurred later, starting from the sixth month of testosterone treatment; beard growth was accelerated by frequent shaving in almost all transsexual men; in genetically predisposed subjects, balding was observed; voice deepening was induced by testosterone after the first 3–6 months and continued in the following months. Menstrual cycles were blocked in 87.5% of subjects in the first trimester, although sporadic spotting was reported (7 uterine bleedings in 27 evaluated transition programs). Testosterone levels progressively increased as expected and after the first trimester reached a normal male range, with a mean concentration in the first year of treatment of 6.13 ng/ml (Figure 2). Moreover, a reduction in circulating estradiol concentrations was observed (Figure 1). Interestingly, estradiol levels were not completely suppressed but remained higher than the normal male range.

Hematological Assessment

In spite of a general increase in Hb and HCT values, no subjects developed true polycythemia (Hb between 12 and 16 g/dl in 27/27). The hematocrit average level during the first year of testosterone treatment is shown in Figure 5.

Lipid and Glucose Metabolism

The average levels of cholesterol, triglycerides, HDL, cLDL, and glucose (at baseline and after 1 year of hormonal treatment) are shown in Figure 6. Regular metabolic checks showed neither hypercholesterolemia nor hypertriglyceridemia during testosterone treatment. Moreover, three cases with impaired fasting glucose underwent OGTT and HbA1c evaluations: No impaired glucose tolerance nor diabetes mellitus were recorded. LDL cholesterol level at the end of the first year was 110.50 ± 35.08 mg/dl ($p = ns$). Two subjects showed a metabolic syndrome according to ATP III criteria ("Third Report of the National Cholesterol Education Program," 2002) after 1 year of hormonal treatment. One of them showed 2/5 criteria at the beginning of cross-sex therapy, while the second one was already affected.

Comorbidities

No evidence of atherogenic alterations of the lipid profile was recorded. Excessive cutaneous virilization occurred in 2 genetically predisposed subjects (seborrhoic acne on face and chest in 2 subjects, mild defluvium in 3 subjects, and mild male baldness in the remaining subjects).

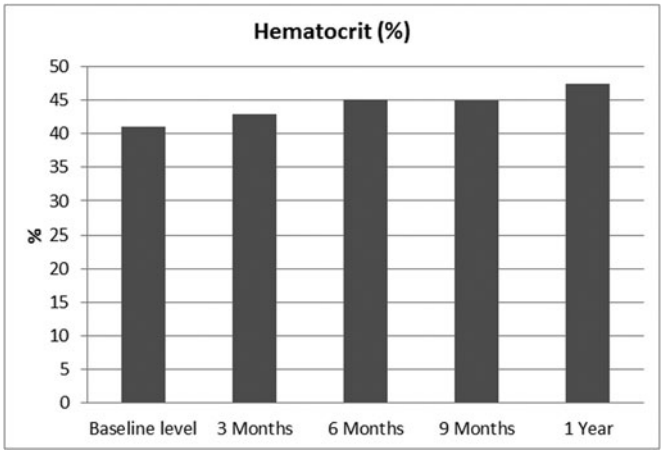
Smoking Habit

All smokers greatly reduced cigarette smoking reaching an average of 7.3 cigarettes/day, but no subjects quit smoking completely.

Psychosexological Aspects

At the end of the first RLE year all subjects maintained their heterosexual orientation according to their gender identity role. At the end of the first RLE year, 22/27 (= 81.5%) subjects had a stable relationship or cohabitation. All subjects reported a general increase in sexual desire and a general improvement in sexual performance. Most subjects (23/27 = 85%) reported an increase in impulsiveness and

FIGURE 5. Female-to-male (FtM) values of hematocrit (median, $n = 27$)

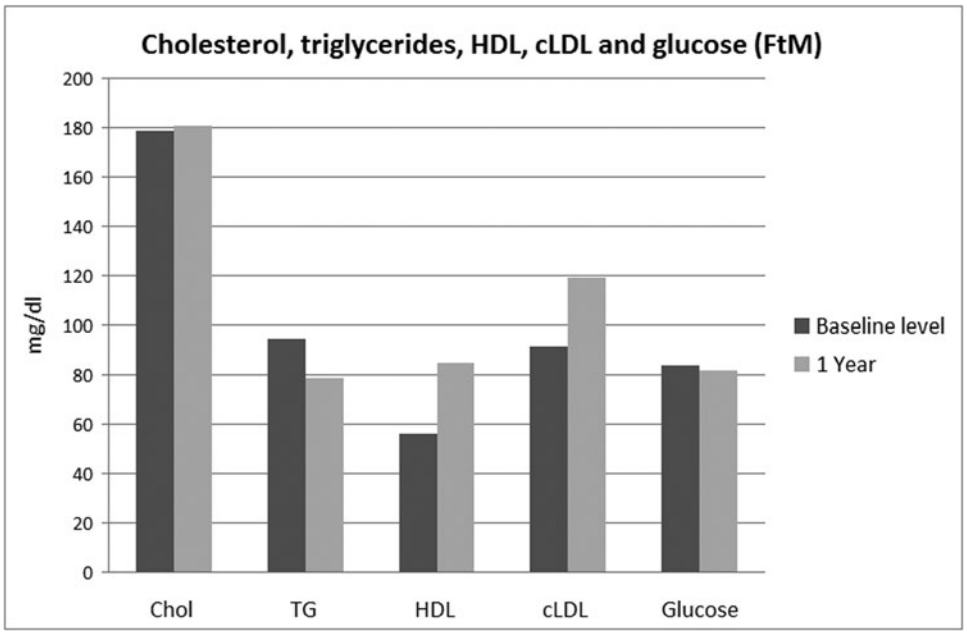


aggressiveness and a higher trend to express anger. No episodes of uncontrolled impulses were recorded. One year after starting cross-sex therapy, the average Body Image subscale score was 63.25 ($p < 0.05$), the average Quality of Life score was 68.75 ($p = ns$), the average Quality of Sexual Life scale score was 56.25 ($p = ns$), and the Interpersonal Relationship scale average score was 81.25 ($p < 0.05$).

DISCUSSION

Although the social, cultural, and relational background of patients with GID determines

FIGURE 6. Female-to-male (FtM) values of cholesterol, triglycerides, HDL, cLDL, and glucose (at baseline and after 1 year of hormonal treatment; median, $n = 27$)



some significant differences in the outcome of their transition program, our sample expresses a clear positive experience already in the first year of their real life experience. In the MtF sample, the feminization process was experienced in a positive way and allowed a real life experience in a complete female role. This situation was confirmed by the WHOQOL-100 showing a significant improvement on Body Image scale scores 1 year after cross-sex therapy versus baseline (68.75 vs. 43.25) and Quality of Sexual Life scores (62.05 vs. 56.25) with both a subjective and an objective improvement and a significant difference in social relationships (Social Relationship scale scores, 75.00 vs. 50.25). The effects of antiandrogen preparations on hair growth and scalp were visible and clinically registered, sometimes also with photographs, after the first 6 months and improved the female phenotype contributing to the subjectively perceived quality-of-life improvement. This outcome was also confirmed by the Quality of Life scores (72.2 vs. 62.5), which were significant improved over baseline evaluations.

As for treatment side effects, no significant body-weight changes occurred in MtF patients. The mild weight increase is justified by estradiol-induced fat tissue modifications (Nott et al., 2008; Zitzmann & Nieschlag, 2007). No new cases of dyslipidemia were recorded, while pre-existing lipid metabolism alterations were well compensated due to lifestyle changes and specific pharmacological treatments. Reducing or quitting smoking was always difficult. This aspect also emerged from psychological evaluations, which showed how such habit is correlated to the emotional impact that the transition program exerts in everyday life. In the FtM sample, the virilization process was experienced in a very positive way by all subjects. Phenotype changes contributed to a subjective improvement of body image—confirmed by the psychosexological tests—which show a significant improvement (specific scores 63.25 vs. 21.85 at baseline). Interpersonal relationships significantly improved as well. Test evaluations reported above-average scores (81.25 vs. 50.02 at baseline), suggesting that a self-image improvement corresponds to a better adaptation to social and relational life. General Quality of Life and Sexual Life scores showed the highest increments (68.75 vs. 63.25 and 56.25 vs. 50.25, respectively) in comparison to baseline values. This increase is not statistically different because of the low size of the FtM sample. Interestingly, estradiol levels in FtMs were not reduced to the normal male range due to the maintenance of aromatase activity in biological female subjects when androgen precursors are present, especially when an increase in adipose tissue occurs. This condition is responsible for the spotting episodes, which do not represent a real problem, but require an adequate re-elaboration of psychological imaging in these patients. The slight body-weight increase in the majority of FtM subjects expresses androgen anabolic and orexigenic effects as well as the difficulty in dietary restriction compliance during the transition period. In particular, the preferential abdominal fat deposition may represent a dysmetabolic symptom (Gooren & Giltay, 2008; Mueller, Kiesewetter, Binder, Beckmann, & Dittrich, 2007), which requires evaluation and treatment. This study shows how the metabolic impact of hormonal treatment in patients with GID may be disregarded in a well-controlled setting, in contrast to previous reports in the 1990s (Moore, Wisniewski, & Dobs, 2003; Van Kesteren, Asscheman, Megens, & Gooren, 1997). In fact, in these studies, hormonal treatments different from current therapies were prescribed. More recent reports (Asscheman et al., 2011; Jacobeit, Gooren, & Schulte, 2009; Ott, Kaufmann, Bentz, Huber, & Tempfer, 2010; Traish & Gooren, 2010) confirm the possibility of performing an effective and safe hormonal treatment, thanks to more physiological preparations, that guarantees optimal hormone circulating levels and shows no major side effects. These reports are particularly important for reducing earlier concerns regarding atherogenic modifications in FtM subjects as long as they maintain a normal body weight (Elamin, Garcia, Murad, Erwin, & Montori, 2010). We may thus state that hormonal cross-sex treatment induces biochemical and metabolic modifications that lead to a hematological profile overlapping the male one. Such effects are affected by the treatment type, by its duration, and by the genetic milieu (Meriggiola et al., 2008). From a psychosexual

and relational point of view, hormonal treatment effects must be interpreted in relation to the affective and interpersonal conditions the subject lives in. The presence or absence of a stable relationship and of family and social support greatly influences the subject's quality of life and psychological well-being (Motmans, Meier, Ponnet, & T'Sjoen, 2012).

Based on our results collected during the first year, we can conclude that cross-sex hormone therapy seems to be free of major risks in healthy subjects, even if it is not performed at a young age. A constant and regular clinical supervision is mandatory (Asscheman et al., 2011; Gooren, Giltay, & Bunck, 2008) in order to maintain normal metabolic and cardiovascular conditions. The most serious side effects previously reported in the literature did not occur in our study because we applied the new endocrine guidelines (Hembree et al., 2009; Godano et al., 2009), although our observations are limited to the first year of RLE. Moreover, maintaining physiological estradiol and testosterone concentrations led to a safer metabolic condition (Meriggiola & Berra, 2012). This aspect will need to be confirmed from analysis of endocrine and metabolic status after gonadectomy. Altogether, our data confirm that subjects correctly selected and recruited for the transition therapy show an optimal adaptation to hormone-induced neuropsychological modifications. The most relevant aspect is represented by the overall satisfaction in general and sexual life. Our clinical experience confirms literature data (Gómez-Gil et al., 2011; Gorin-Lazard et al., 2012) indicating that opposite-sex hormone administration leads not only to the desired physical transition but also to important effects on cognitive functioning particularly on some sex-specific characteristics with an improvement in interpersonal and sexual relationships. Moreover, Gorin-Lazard et al. (2012) underline the role of confounding factors, and they concluded that hormonal therapy is independently linked to better quality of life. Deep satisfaction for the achievement of a clear integration between gender role and identity does not seem to be altered by the presence of difficulties in general health status nor by a non-complete satisfaction for the obtained phenotypic aspect. These data suggest that in these patients hormonal treatment is the first therapeutic choice, as matching physical appearance with the perceived gender identity is ultimately gratifying per se.

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