ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2023.2023-1-13

J Clin Res Pediatr Endocrinol 2023;15(3):276-284

Endocrinological Approach to Adolescents with Gender Dysphoria: Experience of a Pediatric Endocrinology Department in a Tertiary Center in Turkey

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What is already known on this topic?

In Turkey, the number of transgender adolescents seeking hormonal treatment has tended to increase in recent years. However, there are generally very few centers, which are providing gender-affirming care for transgender adolescents.

What this study adds?

This study conducted in a tertiary pediatric endocrinology department in Turkey contributes to the literature regarding medical interventions for adolescents with gender dysphoria. A multidisciplinary approach in the follow-up of these individuals may improve their general health care and also support choosing their gender identity.

Abstract

Objective: A significant rise in the number of trans adolescents seeking medical interventions has been reported in recent years. The aim of this study was to report the clinical features, treatment, and follow-up of adolescents with gender dysphoria (GD) with our increased experience.

Methods: Twenty-six male-to-female (MTF) and twenty-seven female-to-male (FTM) adolescents who were referred to the GD-outpatient clinic between 2016 and 2022 were reviewed. The clinical and laboratory findings of thirty transgender adolescents (15 FTM /15 MTF) who received medical intervention were evaluated retrospectively.

Results: Most individuals (60.4%) were admitted between 2020 and 2022, and the remaining (39.6%) were admitted between 2016 and 2019. At the time of referral, median age was 16.3 years [interquartile range (IQR) 1.53; range 13.2-19.4] in 26 MTF, and 16.4 years (IQR 1.74; range 11.7-21.6) in 27 FTM adolescents. The median age at pubertal blockage with gonadotropin-releasing hormone analog and androgen receptor blocker was 16.4 years (IQR 1.4; range 11.7-17.8) in 22 adolescents (9 MTF, 13 FTM), and 17.4 years (IQR 1.4; range 15.5-19.4) in 6 MTF individuals, respectively. Cross-sex hormone therapy was commenced in 21 adolescents (12 MTF, 9 FTM) at the median age of 17.7 years (IQR 0.61; range 16-19.5). Fifteen individuals (8 MTF, 7 FTM) have been transferred to the adult endocrinology department in transition clinics.

Conclusion: All treatments were generally well tolerated and effective, including bicalutamide, and no significant side effects were observed. Transition clinics played an important role in the better management of gender reassignment processes.

Keywords: Transgender, gender reassignment, gonadotropin-releasing hormone treatment, bicalutamide, cross-sex hormone, transition, multidisciplinary follow-up

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Conflict of interest: None declared
Received: 17.01.2023
Accepted: 27.03.2023

Introduction

Gender dysphoria (GD) is characterized by incongruence between the experienced gender and the natal sex, which also affects various aspects of daily life. Previously defined as "gender identity disorder" by "Diagnostic and Statistical Manual of Mental Disorders: DSM-5", the term has been updated in DSM-5 with distinct diagnostic criteria for children and also adolescents with GD (1).

Following psychiatric evaluation, medical treatment consists of three phases in adolescents with severe and persistent GD (2). The first phase is the suppression of puberty with gonadotropin-releasing hormone agonist analogs (GnRHa) in those who have reached at least pubertal stage 2. In the second phase, cross-sex steroid hormones (CSH) are added to GnRHa treatment to induce sex characteristics consistent with the appropriate gender (3,4). Most adolescents have sufficient mental capacity by 16 years of age to give informed consent to gender-affirming hormone treatment (3). The final phase is genital/gonadal surgery procedures after the age of 18 years, when the individuals reach legal adulthood, and also maintaining the use of CSH (2,3). Legal procedures are in line with the recent guidelines, and surgical interventions are made in adulthood with the approval of the related committees in Turkey.

The start of the gender reassignment process for transgender adolescents in adulthood leads to problems in the social roles of these individuals due to their undesirable secondary sex characteristics. It has been observed that when puberty is suppressed at an early age before the full development of secondary sex characteristics, there is greater patient satisfaction in the postoperative period (3).

However, the knowledge and experience regarding hormonal therapies for adolescents with GD are not widespread in many pediatric endocrinology departments (4,5,6,7). During this challenging process, a multidisciplinary team is effective while accessing the necessary reports, and providing the correct guidance while making the process more suitable for these individuals (2).

This is the first study to be carried out in adolescents with GD in a tertiary pediatric endocrinology clinic in Turkey. The aim was to raise awareness about these individuals by presenting the clinical features and follow-up during hormonal therapy and by emphasizing the benefits of support from a multidisciplinary team.

Methods

Subjects

The medical records of all adolescents diagnosed with GD following at least six months of psychiatric follow-up and who were referred to our GD outpatient clinic between the years 2016 and 2022 were reviewed retrospectively.

Medical intervention was commenced in individuals who were diagnosed with GD based on DSM-5 diagnostic criteria (1) by a mental health professional (MHP). Medical treatment was administered in adolescents, in whom informed consent was taken from both themselves and their legal guardians, and follow-up of these individuals was performed at an interval of 3-6 months. In addition, all transgender adolescents and their parents were informed about fertility preservation.

Pubertal suppression therapy consisted of intramuscular (IM) injections of the GnRHa (triptorelin acetate, 3.75 mg every 4 weeks, or leuprolide acetate 3.75 mg every 4 weeks-11.25 mg every 12 weeks). The selection of GnRHa preparation was dependent on availability in the market. Oral vitamin D (1000-2000 U/day) and calcium (Ca) (500-1000 mg/day) were commenced during pubertal suppression.

In older male-to-female (MTF) adolescents, in whom insurance coverage of GnRHa therapy could not be provided, the potent androgen receptor blocker bicalutamide was started at a dose of 25 mg/day and gradually increased up to 50 mg/day. Bicalutamide was combined with transdermal estradiol (E2) in the initial phase of this treatment. Cyproterone acetate was also commenced in adolescents, who chose not to receive bicalutamide.

During GnRHa therapy, CSH was added in incremental doses to induce novel puberty in both female-to-male (FTM) and MTF adolescents who were evaluated by a MHP (with expertise in gender identity) for emotional readiness to cope with the treatment. Female and male puberty was induced by administering transdermal/oral E2 and IM injections of testosterone (T) -esters (a mixture of T -propionate, -phenylpropionate, -isocaproate, and decanoate) respectively. The management of hormonal therapy was planned according to recent guidelines (2).

Adolescents who reached the legal age (18 years) were transferred to the adult endocrinology department through transition clinics. Legal procedures for surgical operations were also managed in those who received at least one year of CSH therapy by a multi-disciplinary team. This multi-disciplinary team consisted of at least one specialist from the departments of adult and pediatric psychiatry, adult and pediatric endocrinology, gynecology, urology, plastic surgery, and forensic medicine.

Physical Examination

All physical examinations were done by the same examiner at each visit (EKÖ). Heights and weights of all individuals

and their parents were measured using a wall-mounted calibrated Harpenden Stadiometer (Holtain Ltd, Crymych, United Kingdom) sensitive to 0.1 cm and an electronic scale sensitive to 0.1 kg. Body mass index (BMI) was calculated as weight (kg)/height (m^2). All measurements were expressed as standard deviation scores according to age and birth-registered sex in accordance with the national standards (8). Pubertal development was assessed using the Tanner-Marshall scale (9). Since most of these adolescents are generally very sensitive about genital examination, it was only performed in those who gave consent.

Laboratory Investigations

Complete blood count, glucose and lipid profile, and serum concentrations of Ca, phosphorus (P), alkaline phosphatase, 25-OH vitamin D, aspartate aminotransferase, and alanine aminotransferase were performed at the third and sixth months of treatment and every six months thereafter.

Luteinizing hormone (LH), and follicle-stimulating hormone were analyzed by electro-chemiluminescence immunoassay (Cobas, Roche Diagnostics, Mannheim, Germany). Prolactin (PRL), T, and E2, were measured by immune-chemiluminescence assay (Immulite 2000 system, Siemens AG, Berlin and Munich, Germany).

Imaging

Bone mineral density (BMD) of the spine (L1-L4) was measured using dual-energy X-ray absorptiometry (Hologic QDR 4500A Fan Beam X-ray Bone Densitometer, Hologic, Bedford, MA, USA). BMD results are presented in z-scores, which were calculated according to age and birth-registered sex appropriate for this device.

Ethical Approval

Medical ethical approval was granted by the Local Medical Ethics Committee of İstanbul University with the file number 2021/559, date: 12.04.2021. Informed consent revealing the risks and benefits of medical treatments has been obtained from individuals and their legal guardians.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistic Base, version 22.0 (Chicago, IL., USA). The prevalence analysis stating frequency is indicated both as number (n) and percentage (%). Values are stated as median [interquartile range (IQR); range]. The distribution of variables was evaluated using the Kolmogorov-Smirnov test. In addition, the Mann-Whitney U test was used for the analysis of quantitative data. The significance of a p value is considered to be ≤0.05.

Results

Twenty-one individuals (39.6%) were admitted between 2016 and 2019, and the remaining thirty-two (60.4%) were admitted between 2020 and 2022. The distribution of transgender adolescents according to presentation year is illustrated in Figure 1.

At the time of referral, the median age was 16.3 years (IQR 1.53; range 13.2-19.43) in 26 MTF and, 16.4 years (IQR 1.74; range 11.74-21.64) in 27 FTM adolescents.

The majority of individuals (n = 38, 71.7%) were uncomfortable with their natal sex from early ages (< 10 years) and their discomfort had increased especially during puberty. In the remaining individuals (n = 15, 28.3%), this disturbance had started at pubertal ages (> 10 years). While forty-three (81.3%) of the individuals were referred by a MHP, the remaining ten individuals (18.7%) were brought by legal guardians regarding suspicions of hormonal disorders. Five FTM adolescents have been taking hormonal medications without a prescription. Before presenting to a MHP, five (4 FTM, 1 MTF, 9.4%) had attempted suicide.

At the time of referral, the pubertal stage of four adolescents (3 MTF, 1 FTM) had not reached Tanner 4. Except for an 11.7-year-old FTM who was in stage 4 puberty, all FTM were postmenarchal and in stage 5 puberty. No signs of a difference/disorder of sex development were detected, and all subjects had appropriate sex characteristics of the sex assigned at birth. Seven FTM adolescents were diagnosed with polycystic ovary syndrome (PCOS), and PCOS treatment was refused by these adolescents. A MTF individual had metabolic syndrome and metformin was started due to impaired glucose tolerance.

Out of 53 adolescents, 23 were not suitable for hormonal therapy, and 2 adolescents began their treatments in adult endocrinology. Twenty-eight individuals (13 FTM, 15 MTF)

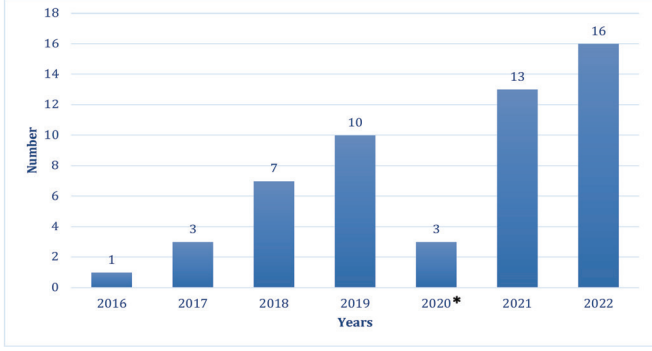

Figure 1. The distribution of transgender youth according to presentation year to outpatient clinics

**During the COVID-19 pandemic*

started hormonal therapy. Out of these, 21 (9 FTM, 12 MTF) continued with cross-sex hormone therapy and transition to adult units was conducted for 15 individuals (8 MTF, 7 FTM). A flowchart of adolescents' inclusion in the study is illustrated in Figure 2 and the details of the hormonal therapy of individuals are shown in Supplemental Table 1.

The median L1-L4 spine BMD z-score was lower in those with low BMI (Figure 3) ($p = 0.0006$, $R^2 = 0.4$). This correlation was stronger in MTF subjects ($p = 0.0135$, $R^2 = 0.5$). The basal median L1-L4 spine BMD z-score of MTF and FTM adolescents was -1.1 (IQR 3.4) and 0.4 (IQR 1.9), respectively, no statistical difference was detected ($p = 0.254$).

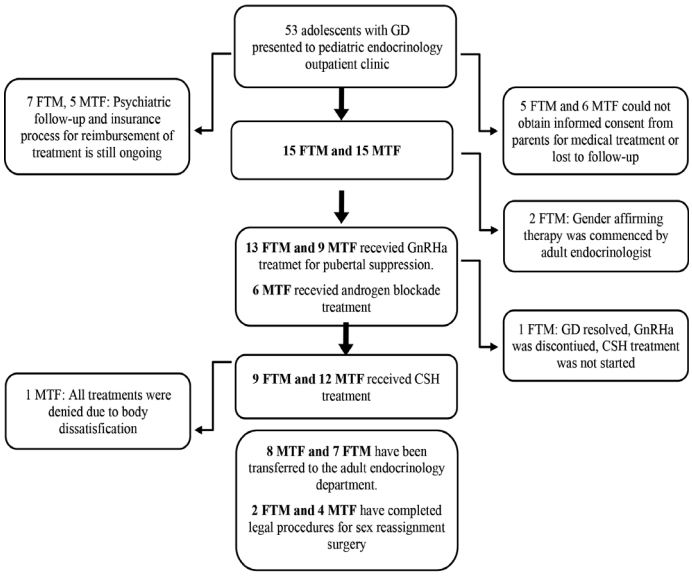

Figure 2. A flowchart of adolescents with gender dysphoria receiving medical treatment

GD: gender dysphoria, FTM: female-to-male, MTF: male-to-female, GnRHa: gonadotropin-releasing hormone analog, CSH: cross-sex hormone, GnRHa: gonadotropin-releasing hormone analog

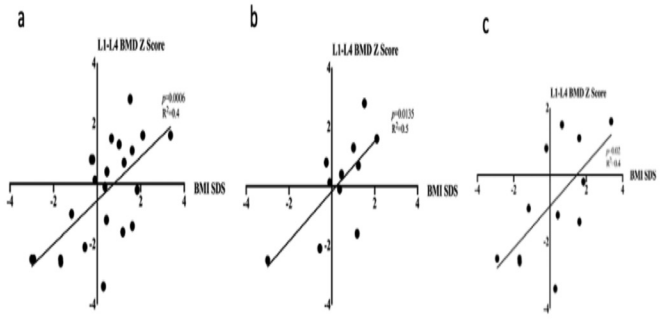

Figure 3. The relationship between basal BMI SDS and L1-L4 BMD z scores in individuals receiving medical interventions. The median L1-L4 spine BMD z-score was lower in those with low BMI SDS in all groups (a). While this correlation was strong in MTF individuals (b), it was weak in FTM individuals (c)

BMI: body mass index, SDS: standard deviation score, BMD: bone mineral density, MTF: male-to-female, FTM: female-to-male

During medical interventions, complete blood counts and biochemical parameters (liver and renal function) were within normal ranges in all subjects. The other details of clinical and laboratory findings and comparison of parameters are shown in Table 1.

Pubertal Blockage with GnRHa

Twenty-two individuals (9 MTF, 13 FTM) commenced GnRHa treatment [3.75 mg/4 weeks (n = 7), 11.25 mg/12 weeks (n = 15)]. The median age at the start of treatment was 16.4 years (IQR 1.4; range 11.7-17.8) and the median duration from presentation to pediatric endocrinology clinic to treatment (provided that at least 6 months followed by psychiatry) was 0.2 years (IQR, 0.2; range, 0-2.5).

The median duration of GnRHa monotherapy in nine MTF and six FTM individuals was 0.9 years (IQR 0.4; range 0.04-1.12) and 0.6 years (IQR 0.5; range 0-1.9) respectively. In an FTM adolescent (S4), GnRHa treatment was continued as this had been started two years earlier in another center.

The data of clinical characteristics of adolescents receiving medical intervention (including age at the first presentation, age at the start of hormone treatment, type of hormone treatment, anthropometry at presentation and last examination, and history of surgery) are shown in Table 1.

Three months after starting GnRHa treatment, menstrual suppression was achieved and persisted throughout the treatment process in twelve FTM. The median LH concentration was 2.0 mIU/mL (IQR 3.1). Vaginal bleeding occurred in two FTM adolescents (S4, S9), in one at the start of the GnRHa treatment, and in the other two years after starting GnRHa treatment, at the time of CSH treatment. Menstrual cessation was obtained with oral norethisterone (10 mg/day).

In a FTM adolescent (S5) whose GD started in the pubertal period, GD resolved after one year of GnRHa monotherapy and she did not continue with CSH treatment.

Pubertal suppression was sustained in 3 MTF (S1, S2, S9) receiving 3.75 mg of GnRHa every 4 weeks (mean LH 0.83 mIU/mL), however, spontaneous erections persisted in 3 MTF (S3, S4, S6). The mean level of LH was 12.2 mIU/mL in one of them receiving 3.75 mg of GnRHa every 4 weeks, and in the remaining individuals receiving 11.25 mg of GnRHa every 12 weeks, it was 5.2 mIU/mL and 7.25 mIU/mL respectively. The dose of GnRHa was increased to 7.5

Table 1. The comparison of clinical and laboratory findings of adolescents receiving medical interventions at the onset of treatments

	GnRHa			CSH				
	MTF median (IQR)	FTM median (IQR)	p	MTF median (IQR)			FTM median (IQR)	p**
				After GnRHa	p*	Combined androgen receptor blocker		
n	9	13		6		6	9	
Age (yrs)	16.7 (1.2)	16.7 (1.0)	**0.797**	17.3 (1.1)	**0.931**	17.5 (1.3)	17.8 (0.4)	**0.159**
Height (cm)	176.1 (3.0)	160.8 (5.0)	**< 0.001**	177.9 (2.0)	**0.329**	169.4 (3.3)	164.9 (7.4)	**0.019**
Height SDS*	0.6 (0.9)	-0.2 (1.5)	**0.331**	0.3 (0.5)	**0.329**	0.4 (1.3)	-0.4 (1.4)	**0.587**
BMI (kg/m^2)	24.8 (5.8)	23.1 (4.5)	**0.290**	20.1 (0.7)	**1.000**	19.8 (5.9)	24.5 (6.9)	**0.243**
BMI SDS*	0.7 (1.5)	0.7 (1.5)	**0.845**	-1.2 (0.7)	**1.000**	-0.9 (2.1)	1.1 (2.9)	**0.247**
Systolic BP (mmHg)	110 (20)	107.5 (11)	**0.081**	105 (10)	**0.913**	105 (15)	110 (14)	**0.199**
Diastolic BP (mmHg)	80 (10)	69 (8.8)	**0.023**	67.5 (6.3)	**0.737**	62.5 (8.8)	70 (7.5)	**0.300**
LH (mIU/mL)	4.5 (1.7)	6.7 (4.1)	**0.420**	5.0 (4.7)	**0.937**	4.5 (2.8)	2.3 (3.0)	**0.214**
FSH (mIU/mL)	4.1 (2.9)	4.7 (3.3)	**0.357**	NA	**NA**	4.3 (3.5)	NA	**NA**
E2 (pg/mL)	25.9 (18.0)	68.9 (58.6)	**0.008**	18.5 (10.5)	**0.167**	27.3 (28)	9.3 (1.0)	**0.881**
T (ng/mL)	5.3 (1.8)	0.3 (0.3)	**< 0.001**	0.3 (0.7)	**0.082**	6.3 (3.2)	0.4 (0.1)	**1.000**
PRL (ng/mL)	8.4 (10.8)	15.2 (4.1)	**0.078**	16.1 (3.8)	**0.381**	12.3 (4.0)	12.7 (5.1)	**1.000**
Glucose (mg/dL)	86.5 (5.1)	86 (10.5)	**0.955**	90 (5.0)	**0.714**	93.5 (7.8)	89 (4.0)	**0.369**
Insulin (µg/mL)	13.3 (16.6)	9.0 (4.4)	**0.137**	9.7(3.2)	**0.786**	7.1 (2.3)	12.6 (3.2)	**0.151**
HbA1c (%)	5.4 (0.4)	5.0 (0.2)	**0.052**	5.6 (0)	**0.203**	5.1 (.0.5)	5.2 (0.1)	**0.230**
Total cholesterol (mg/dL)	183 (54.9)	157.7 (47.5)	**0.484**	167.8 (45.3)	**0.610**	166.3 (14.1)	158 (46)	**0.576**
Triglycerides (mg/dL)	115 (26.8)	63 (13.9)	**0.005**	87.5 (59.4)	**1.000**	74.6 (31.4)	57 (14.1)	**0.396**
HDL (mg/dL)	40 (1.9)	55 (4.7)	**< 0.001**	59.1 (19.3)	**0.831**	55.5 (16.1)	52.3 (16.1)	**0.364**
LDL (mg/dL)	130 (48.5)	91.5 (50.3)	**0.381**	95.3 (20.8)	**0.476**	90 (17.3)	94.5 (42.5)	**0.868**
25-hydroxyvitamine (ng/mL)	26.8 (10.6)	15.7 (6.9)	**0.009**	16.7 (3.4)	**0.329**	15.9 (2.3)	21.9 (17.9)	**0.787**
L1-L4 BMD z-score	-1.0 (3.3)	0.4 (1.9)	**0.412**	-0.91 (3.1)	**1.000**	-1.2 (2.3)	-0.9 (1.0)	**0.940**

#SDS was calculated according to birth-registered sex.
*Comparison of parameters between group GnRH analog and group androgen receptor blocker.
**Comparison of parameters between MTF and FTM Groups receiving CSH.
GnRHa: gonadotropin-releasing hormone analog, CSH: cross-sex hormone, IQR: interquartile range, FTM: female-to-male, MTF: male-to-female, BMI: body mass index, SDS: standard deviation score, BP: blood pressure, LH: luteinizing hormone, FSH: follicle-stimulating hormone, E2: estradiol, T: testosterone, PRL: prolactin, HDL: high-density lipoprotein, LDL: low density lipoprotein, BMD: bone mineral density, NA: not available, yrs: years

mg/month in three individuals. After increasing the dose to 7.5 mg/month, the mean levels of LH were 1.3 mIU/mL, 3.2 mIU/mL, and 0.6 mIU/mL respectively.

Cross-sex Hormone Therapy (Combined with GnRHa or Androgen Receptor Blockers)

Sixteen adolescents (7 MTF, 9 FTM) received CSH treatment in addition to GnRHa treatment. The median age at the start of the induction of CSH was 17.7 years (IQR 0.6; range 16-19.5). In 5 MTF adolescents (S10-14) the median age at the start of combined treatment (bicalutamide and E2) was 17.4 years (IQR 1.4; range 16.2-19.5). At presentation, a 17.3 years old MTF adolescent (S15) was receiving cyproterone acetate (12.5 mg/day) and sublingual E2 (2 mg divided into 3 doses) for 3 weeks; this treatment was continued.

Although the median serum E2 concentration was higher [54.4 (IQR 26.5) pg/mL] in bicalutamide with CSH group when compared to the GnRHa with CSH group [32.5 (IQR 18.8) pg/mL], there was no statistical difference between the groups (p = 0.429). The details of clinical and laboratory findings of MTF individuals receiving E2 combined with androgen receptor blockers or GnRHa are given in Table 2.

In the first six months of transdermal E2 treatment, in one MTF (S5), a transient elevation in PRL concentration (up to 63.3 ng/mL) was detected. In the first year of treatment, the serum PRL concentrations returned to normal ranges without any intervention. In a FTM (S10) who received combined bicalutamide and E2 treatment, a mild elevation in PRL concentrations (up to 31.8 ng/mL) was detected.

Table 2. The clinical and laboratory findings of transwomen during the treatment of cross-sex hormone following GnRH analog or combined androgen receptor blockers

Subjects	The age of treatment onset (yrs)	Duration of CSH treatment (yrs)	At initial time				Last evaluation			
			Breast development (Tanner stage)	Serum E2 level (pg/mL)	Serum T level (ng/mL)	Serum PRL level (ng/mL)	Breast development (Tanner stage)	Serum E2 level (pg/mL)	Serum T level (ng/mL)	Serum PRL level (ng/mL)
GnRHa + CSH										
1	17.8	0.9	1	39.1	7.4	-	2	17.6	0.4	-
2	17.7	0.7	1	25.9	5	16.1	2	-	-	-
3	17.8	0.3	1	16	5.2	-	-	39.7	0.22	-
4	16.6	1.7	1	34.8	9.6	11.2	3	110	0.24	19.8
5	16	1.9	1	12	-	5.7	#	33	0.4	27
6	18.2	0.8	1	-	5.5	-	2	36.7	0.26	11.3
Androgen receptor blocker + CSH										
10	19.5	0.5	1		8.8	10.8	3	54	12.9	24
11	16.3	1.0	1	26	7.5	9.6	3	34	6.4	9
12	17.9	0.7	1	28.6	7.2	13.9	2	69.1	9.5	16.1
13	16.2	0.4	1	20.5	3.9	13.9	2	54.7	4.7	20
14	17.7	0.7	1	13.1	5.3	8.8	3	18.6	5.7	7.9
15*	17.3	0.4	1	74.9	0.2	30.9	4	139	0.03	27

#Breast augmentation.
*The individual using cyproterone acetate 12.5 mg/day and sublingual E2 divided into 3 doses.
GnRHa: gonadotropin-releasing hormone analog, CSH: cross-sex hormone, E2: estradiol, T: testosterone, PRL: prolactin

At the start of T therapy, hemoglobin (HGB) levels were normal in all FTM, but when the dose of T was increased to the full dose, HGB levels increased to 15.5 g/dL in two FTM adolescents (S1, S2). On further follow-up, no subsequent increase in HGB levels was detected, thus no additional treatment was needed. These adolescents were also cigarette smokers.

Surgery

Two individuals (S1, S2) underwent mastectomy surgery at another center on their own and their families' initiative without our direction. Five MTF individuals (S1-S5) had voice and facial feminization surgery and one of them received breast augmentation without our initiative at another centre. Due to body dissatisfaction related to cosmetic appearance after the surgery, a MTF adolescent (S5) developed depression and refused to go outside. Therefore all treatments were discontinued in this adolescent and psychiatric follow-up was recommended. Fifteen individuals (8 MTF, 7 FTM) have been transferred to the adult endocrinology department.

Discussion

This is the first comprehensive study conducted in a tertiary pediatric endocrinology clinic in Turkey that evaluated clinical follow-up of transgender adolescents during medical interventions. It was possible to facilitate the transgender adolescents' treatment management and transitions to the adult clinic after 18 years of age within the multidisciplinary team. Legal requirements for the gender reassignment process were also provided by this team.

Although presentation numbers of transgender adolescents decreased during the lockdown because of the COVID-19 pandemic, it is remarkable that half of the presentations occurred in the last year (Figure 1). In parallel with the increasing experience of our multidisciplinary team, the number of transgender individuals who presented to our center has increased gradually over the years. Similarly, a significant rise in the number of trans people seeking treatment for GD has also been reported in the literature (10).

In the present study, 53 % of all adolescents (n = 28) were able to start medical intervention in our department. The legal guardians of 11 adolescents with GD (21 % of the total) did not give consent, so they were not able to start any treatment and they were lost to follow-up. However, there is a genuine concern that improper drug use may spread among individuals whose access to standard treatment is somehow blocked. In our cohort, hormonal medication use

without a prescription was observed in five MTF adolescents. Inappropriate hormone use among trans adolescents may be problematic, which could deteriorate their general health and lead to physical and mental problems (10).

We believe that an increase in the number of gender health care clinics and multidisciplinary committees for transgender adolescents in our country may provide improved access to available and monitored treatment, as well as preventing negative outcomes and drop-out.

We observed anecdotal improvements in the quality of life of individuals following appropriate hormone therapy, although we did not conduct a survey specifically into this subject. Furthermore, we did not observe drop-out in adolescents receiving hormonal treatment except for one MTF individual. Despite close follow-up, this individual attempted suicide during CSH treatment, due to persistent body dissatisfaction, which led to severe depression. She refused all medical interventions because of the assumption that medical interventions did not work in her body. Beginning GD medical interventions in an older adolescent period may result in persistent physical disturbance and depression, based on relatively slow physical changes. It is also reported that major depression and suicide attempts are more frequent among trans individuals when compared to the general population (11).

Pubertal suppression with GnRHa at standard dose was relatively inadequate in MTF adolescents. Therefore, we had to increase the dose. It was observed that in older adolescents, 3-monthly injections of 11.25 mg may not be adequate. To cope with body dissatisfaction and rapid physical changes, a relatively rapid dose increase of CSH may be more suitable in older individuals (older than 16 of age). Neyman et al. (12) reported that in their cohort, 84.6% of the adolescents aged between 12 and 18.4 years on bicalutamide treatment had breast development ranging from Tanner stage 2-5. In our cohort, 5 MTF individuals aged between 16.2 and 19.5 years received bicalutamide. The breast development stage was 2 at the third month of treatment in two individuals and it was 3 in the remainder, whereas breast development reached Tanner stage 3 at most, in those who received GnRHa and CSH treatment. Indeed, the median serum E2 concentration was higher in the bicalutamide group, although there was no statistical difference between the groups. This result may be due to the limited number of individuals. Another noteworthy finding regarding treatment was that in an MTF adolescent receiving cyproterone acetate combined with sublingual E2 (divided into 3 doses), serum E2 level was quickly increased and breast development was quite fast as it progressed from Tanner stage 1 to stage 3 in one month. Thus, potent androgen receptor blockers, such as bicalutamide, may be effective and promote rapid feminization in older MTF adolescents who want to experience rapid physical changes. Additionally, although it is limited to the observation of only one case in our cohort, divided doses and a sublingual route of E2 seems more effective for obtaining a feminizing effect.

It has been reported that prepubertal-onset GD may be transient in the majority of adolescents by late pubertal periods (13). However, we observed that prepubertal-onset GD was persistent and it was exacerbated in the pubertal period. This difference may be related to the fact that most of the children with prepubertal-onset GD are not referred to pediatric endocrinology departments. Indeed, the majority of our cohort consisted of adolescents, who were in the late pubertal period. Besides, we observed that in our cohort GD was resolved only in one FTM individual, who notably had pubertal-onset GD, and decided not to continue with CSH after GnRHa. Therefore, pubertal suppression with GnRHa in the first step is suitable, even in adolescents who present late to the endocrinology department, and whom the recent guideline is also applicable for (2). Briefly, the varying range of attitudes, ranging from impatience to indecisiveness, were observed among these individuals in our cohort. Therefore, we highlighted the importance of close psychiatric follow-up, which is crucial at each step taken toward the transition to cope with the effects of these challenging processes.

During CSH induction, increased serum E2 levels may result in a transient elevation in PRL concentrations. It has been reported that this elevation may be observed often in the first few months of E2 treatment (14). We observed significant PRL elevation in only one MTF adolescent, but this was not persistent and returned to normal ranges. Additionally, in two FTM individuals, a transient T-induced increase in hematocrit concentration was remarkable in the first months, but again this decreased on follow-up. Indeed, during all medical interventions, we did not observe a situation requiring interruption of the treatment.

The negative effect on peak bone mass of pubertal suppression among MTF adolescents has been previously reported (15,16). The lower physical activity among transgender girls might be responsible for a decrease in muscle mass, which is mandatory to reach the peak bone mass in young adulthood (16). At presentation, the median BMD z-scores of the spine of MTF adolescents were below the population mean, albeit with sufficient vitamin D levels. Moreover, following CSH administration, no significant improvement in the median BMD z-scores was observed, again with sufficient vitamin D and Ca replacement. This result was consistent with previous reports in MTF populations (15,16). In MTF, the median L1-L4 BMD z-score was normal at the

start of treatment despite insufficient vitamin D levels. Yet, it decreased during pubertal suppression. This decrease in the z-score was especially evident in those with a lower BMI. A relatively high-dose CSH therapy may be appropriate in this period, which is important to achieve peak bone mass and density. However, due to the relatively small number of transgender adolescents evaluated, the changes in bone health could not be reliably evaluated.

Gender reassignment surgery procedures were discussed in multi disciplinary councils after the transition to adults' department after 18 years of age according to international guidelines. Some individuals in our cohort who were under the age of 18, underwent minor plastic surgical interventions (without our direction) and they generally reported satisfaction afterwards. Nevertheless, the importance of psychiatric follow-up was stressed in these cases as well.

Study Limitations

Conducting surveys is necessary to measure the quality of life. In this retrospective study, difficulties were encountered in accessing data for certain cases.

Additionally, during the COVID-19 period, face-to-face meetings with individuals could not be conducted. Furthermore, evaluating responses to all treatments requires larger population studies.

Conclusion

The follow-up and hormonal therapy of transgender adolescents is clinically challenging. Until recently, there were very few centers in our country providing gender-affirming care for transgender adolescents. However, with the increase in the number of healthcare centers for transgender adolescents, we believe that parental awareness about GD, and accordingly trans adolescents' access to treatment will increase. Potent drugs or rapid dose increases of CSH may be a solution for older adolescents who expect rapid physical change. GnRHa treatment is also reasonable as the first step and provides support during the diagnostic process in young adolescents. Psychiatric evaluation is mandatory during treatment at each step. Thus, we are guiding these individuals medically and also supporting them on the journey to increase their quality of life and thus overall satisfaction with their lives. Moreover, we believe that multidisciplinary teams and multidisciplinary transition clinics, in which endocrinologists (pediatric/adult) and psychiatrists (pediatric/adult) play important roles, will contribute to better management of gender reassignment processes according to the physical and mental conditions of transgender adolescents.

Ethics

Ethics Committee Approval: Medical ethical approval was granted by the Local Medical Ethics Committee of İstanbul University with the file number 2021/559, date: 12.04.2021.

Informed Consent: Informed consent revealing the risks and benefits of medical treatments has been obtained from individuals and their legal guardians.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Financial Disclosure: The authors declared that this study received no financial support.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: APA, 2013.
2. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GG. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017;102:3869-3903.
3. Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and pediatric endocrinology aspects. Eur J Endocrinol 2006;155:131-137.
4. Cohen-Kettenis PT, Klink D. Adolescents with Gender Dysphoria. Best Pract Res Clin Endocrinol Metab 2015;29:485-495. Epub 2015 Jan 24
5. Gridley SJ, Crouch JM, Evans Y, Eng W, Antoon E, Lyapustina M, Schimmel-Bristow A, Woodward J, Dundon K, Schaff R, McCarty C, Ahrens K, Breland DJ. Youth and Caregiver Perspectives on Barriers to Gender-Affirming Health Care for Transgender Youth. J Adolesc Health 2016;59:254-261. Epub 2016 May 24
6. Vance SR Jr, Halpern-Felsher BL, Rosenthal SM. Health care providers' comfort with and barriers to care of transgender youth. J Adolesc Health 2015;56:251-253.
7. Safer JD, Coleman E, Feldman J, Garofalo R, Hembree W, Radix A, Sevelius J. Barriers to healthcare for transgender individuals. Curr Opin Endocrinol Diabetes Obes 2016;23:168-171.

8. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol 2015;7:280-293.
9. Goksen D, Darcan S, Coker M, Kose T. Bone mineral density of healthy Turkish children and adolescents. J Clin Densitom 2006;9:84-90. Epub 2006 Mar 27
10. Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One 2018;13:e0202330.
11. Eisenberg ME, Gower AL, McMorris BJ, Rider GN, Shea G, Coleman E. Risk and Protective Factors in the Lives of Transgender/Gender Nonconforming Adolescents. J Adolesc Health 2017;61:521-526. Epub 2017 Jul 21
12. Neyman A, Fuqua JS, Eugster EA. Bicalutamide as an Androgen Blocker With Secondary Effect of Promoting Feminization in Male-to-Female Transgender Adolescents. J Adolesc Health 2019;64:544-546. Epub 2019 Jan 4
13. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. Clin Child Psychol Psychiatry 2011;16:499-516. Epub 2011 Jan 7
14. Nota NM, Dekker MJHJ, Klaver M, Wiepjes CM, van Trotsenburg MA, Heijboer AC, den Heijer M. Prolactin levels during short- and long-term cross-sex hormone treatment: an observational study in transgender persons. Andrologia 2017:49. Epub 2016 Aug 25
15. Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman JM, Schreiner T, Haraldsen I, T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. Bone 2013;54:92-97. Epub 2013 Jan 28
16. Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab 2015;100:270-275. Epub 2014 Nov 26

Click for Supplementary Table 1. The data of clinical characteristics of adolescents receiving medical intervention

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