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Physiologic Response to Gender-Affirming Hormones Among Transgender Youth

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Abstract

Purpose: The purpose of this study was to examine the physiologic impact of hormones on youth with gender dysphoria. These data represent follow-up data in youth ages 12–23 years over a two-year time period of hormone administration.

Methods: This prospective, longitudinal study initially enrolled 101 youth with gender dysphoria at baseline from those presenting consecutively for care between February 2011 and June 2013. Physiologic data at baseline and follow-up were abstracted from medical charts. Data were analyzed by descriptive statistics.

Results: Of the initial 101 participants, 59 youth had follow-up physiologic data collected between 21 and 31 months after initiation of hormones available for analysis. Metabolic parameters changes were not clinically significant, with the exception of sex steroid levels, intended to be the target of intervention.

Conclusions: Although the impact of hormones on some historically concerning physiologic parameters, including lipids, potassium, hemoglobin, and prolactin, were statistically significant, clinical significance was not observed. Hormone levels physiologically concordant with gender of identity were achieved with feminizing and masculinizing medication regimens. Extensive and frequent laboratory examination in transgender adolescents may be unnecessary. The use of hormones in transgender youth appears to be safe over a treatment course of approximately two years.

Keywords

Transgender; Transgender youth; Gender transition; Cross-sex hormones; Gender dysphoria

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IMPLICATIONS AND CONTRIBUTIONS

This prospective, observational data suggest the safety of cross-sex hormone use among youth with gender dysphoria over a treatment course of at least two years. The findings reported here may help improve provider and caregiver comfort moving forward with hormonal therapy for minors and young adults with gender dysphoria.

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Over the past seven years, there has been a significant increase in the number of youth presenting for care related to gender dysphoria in gender-specific clinics, and in primary care settings [1-3]. Gender dysphoria is widely understood as the persistent distress that arises as the result of an incongruence between one's assigned sex at birth (male or female) and one's experienced gender (male, female, both, or neither). Many youth with gender dysphoria seek medical intervention (pharmacological and/or surgical) to bring their phenotypic presentation into closer alignment with their gender of identity. Because there is a paucity of data related to the impact of gender-affirming hormones in youth, providers, caretakers, and community members experience trepidation about the safety and efficacy of their use in transgender adolescents. This article describes the physiologic impact of gender-affirming hormones among adolescents seeking phenotypic gender transition after approximately two years of gender-affirming hormone treatment.

Background

Although the presence of primary sex characteristics is often described as a source of distress for transgender youth, the development of "incorrect" secondary sex characteristics during endogenous puberty is the cause of great suffering for many. Some youth describe feeling confused by sexually incongruent development, some feel betrayed by their bodies, and many experience heightened levels of anxiety, depression, and sometimes suicidal thoughts and attempts [3]. The past decade has improved access to care for many youth, but the scarcity of skilled and knowledgeable medical providers has continued to make access to care challenging for transgender youth throughout the country. The dearth of available data regarding medical protocols and outcomes contributes to a lack of continuity about hormone administration, timing, doses, and expected response. Dutch investigation indicates that hormone treatment in adolescence followed by gender confirmation surgery is effective in mitigating gender dysphoria [4]. Despite these findings, there remains an ongoing concern among providers and parents about the safety of hormone use among youth with gender dysphoria.

In 2006, the use of gonadotropin-releasing hormone (GnRH) analogs for suppression of endogenous puberty was introduced by a team of professionals in the Netherlands, and significantly altered the landscape of transgender youth care [5]. For those youth who present early enough for care, having endogenous puberty placed on hold allows them an opportunity to explore gender, learn more about exogenous hormones, and get a deeper understanding of the challenges of navigating the world as an individual of transgender experience [6]. However, most youth are presenting for care well into, or even beyond their endogenous pubertal development. Most youth presenting well into endogenous puberty desire hormones to bring their bodies into closer alignment with their gender.

Feminizing hormones

The use of gender-affirming hormones in transgender adults for the purpose of phenotypic gender transition is well documented, and demonstrates both efficacy and safety [7,8]. Weinand and Safer reviewed published longitudinal data examining the impact of hormones in transgender adults. Among transfeminine adults (those assigned male at birth who

identify somewhere along the feminine spectrum) who were administered feminizing hormones for phenotypic changes, a small risk of venous thrombotic events ranging between 1% [8] and 8% [9] was reported depending on the type of estrogen used in the treatment protocol and other existing risk factors (smoking, proximity to surgery, hypercoagulable states). Other cardiovascular events reported were also rare. Among these studies, findings consistently describe no increased cancer risk for transfeminine individuals undergoing hormone therapy. Changes in physiologic measures for transfeminine individuals include mixed results about changes in lipid profile [10]. Liver function tests and hematocrit did not change with feminizing hormone use [10,11]. An increase in prolactin levels, enlarged pituitary glands, and prolactinomas (six cases) has been reported with feminizing hormone therapy [7,12]. Increased mortality among the transfeminine population is a result of AIDS-related complications, suicide, substance abuse, and cardiovascular disease [13].

Masculinizing hormones

Among adult transmasculine individuals (those assigned female at birth who identify somewhere along the masculine spectrum of gender) who underwent hormone therapy with testosterone, there was no reported increase in cardiovascular disease, cancer, or reproductive tract sequelae. Hemoglobin and hematocrit increased in those taking testosterone, but remained within normal male range. Increased insulin resistance and fasting glucose were both noted as sequelae for transmasculine individuals taking hormones. A higher rate of polycystic ovary syndrome diagnoses among pre-hormone transmasculine individuals may contribute to some of these findings in that cohort [14]. Finally, there has been no increase in mortality noted for transmasculine individuals taking testosterone. Overall, the authors concluded that gender-affirming hormone therapy is safe, with careful monitoring for potential complicating factors [7].

Present study

Little has been reported about transgender adolescents and their response to hormone therapy. A recent retrospective article by Jarin et al. reported the minimal impact of hormone treatment on 116 adolescents aged 14–25 years with gender dysphoria who were treated over time. Jarin et al. demonstrated that among adolescents treated for a period of 1–6+ months, the only findings were an increase in hemoglobin, hematocrit, and body mass index, and a lowering of high-density lipoprotein levels in those using testosterone for masculinization. Among those using estrogen for feminization, lower testosterone and alanine aminotransferase (ALT) were reported [15]. These findings are consistent with data from adults undergoing phenotypic gender transition with exogenous hormones, and indicate short-term safety of hormone use. The results from this retrospective study are useful for helping to allay some of the concerns that providers and parents have about safety. This study is limited by its retrospective design, and the challenges faced by many trying to collect data from adolescents—sporadic follow-up, frequent relocation, and inconsistent medication adherence.

The Center for Transyouth Health and Development at Children's Hospital in Los Angeles is the largest clinic dedicated to the care of transgender and gender non-conforming children, adolescents, and young adults in the United States. The center currently provides services for approximately 925 youth between the ages of 3 and 25 years, and provides multidisciplinary care that includes mental health, medical intervention, advocacy, and referral resources for transgender and gender non-conforming youth and their families. The center has been providing gender-affirming hormones for adolescents and young adults since 1993. Growth of the clinic numbers has been unprecedented, and demand has far outpaced capacity.

This article offers preliminary results from a prospective study examining the physiologic impact of gender-affirming hormones in a cohort of adolescents aged 12–24 years with gender dysphoria over approximately two years of hormone use.

Methods

Self-identified transgender youth between the ages of 12 and 24 years presenting consecutively for care at the center between February 2011 and June 2013 were screened for participation in this prospective study. Eligibility criteria for the study included age between 12 and 24 years old, self-identification of an internal gender identity different from the sex assigned at birth, presence of gender dysphoria, a desire to undergo phenotypic gender transition, naivety to cross-sex hormones or less than three months of previous hormone use, and ability to read and comprehend English. Participants under the age of 18 required consent from their legal guardians to participate in the study.

Demographic data were collected via computer-assisted survey at baseline after participants were screened and consented. Baseline and follow-up physiologic data were abstracted from the medical charts of the participants. One hundred one participants were evaluated for physiologic parameters at baseline. Follow-up physiologic data were available for 59 youth (34 transmasculine and 25 transfeminine participants). The Committee on Clinical Investigations at Children's Hospital Los Angeles approved this study. This study was supported by the Saban Research Institute at Children's Hospital Los Angeles, The National Center for Research Resources, and the National Center for Advancing Translational Sciences, National Institutes of Health, and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Hormone regimens

Transfeminine youth were started on hormone protocols that usually included a testosterone blocking agent and feminizing medications. Spironolactone (100–200 mg orally per day) or a GnRH analog was used for testosterone blocking and induction of feminizing features with 17 β estradiol, and in some cases, the addition of progesterone. At the time of this study, spironolactone and GnRH analogs were not covered by most insurance plans; therefore, seven (28%) of these youth did not have their endogenous testosterone blocked specifically in the first two years of treatment. One transfeminine young person was on GnRH analogs since early puberty. Eighteen participants used an escalating dose of oral estradiol ranging from 1 to 6 mg each day; four switched to injectable estradiol over the course of treatment,

and one was off of hormones at the follow-up visit. Six participants initially started, and continued using injectable estradiol at doses ranging from 20 to 30 mg delivered intramuscularly every 14 days.

Transmasculine youth were all treated with testosterone cypionate via subcutaneous delivery at escalating doses ranging from 12.5 mg to 75 mg weekly. At follow-up, most youth were at a dose of 50–75 mg weekly. Two transmasculine youth were on simultaneous GnRH analogs that were started earlier in adolescence. Doses for both cohorts were adjusted based on clinical response and circulating levels of sex steroids.

Statistical analysis

Descriptive statistics were used to report baseline characteristics. Categorical variables were summarized using frequencies and percentages. Paired samples *t* tests were used to determine whether there were statistically significant differences in physiologic parameters measured before initiation of hormone therapy and at two-year follow-up

Results

Demographic information

Physiologic data for 59 youth (25 transfeminine participants and 34 transmasculine participants) were available for follow-up comparison at 21–31 months following the initiation of exogenous hormones for phenotypic transition. Twenty-five (42%) of the participants were assigned male at birth and identified somewhere along the female gender spectrum (transfeminine), and 34 (58%) were assigned female at birth and identified somewhere along the masculine gender spectrum (transmasculine). Youth ranged in age from 12 to 23 years at initiation of therapy, with a mean age of 18 years. Thirteen (22%) youth started hormones younger than age 16 years. More than half (55%) of the participants identified as Caucasian, 29% Latino/a, 10% African-American, 2% Asian Pacific Islander, and 3% identified as other ethnicity. Almost all (91%) of the transmasculine participants identified their gender as male, 6% as gender queer, 3% bi-gender, and none as female. Of the transfeminine youth, almost all identified their gender as female (91%), one youth identified as a gender bender, and one as “other” (Table 1).

Physiologic parameters (transfeminine youth)

Transfeminine youth showed statistically significant changes in high-density lipoprotein (HDL), aspartate aminotransferase, potassium, prolactin, and hemoglobin at follow-up. Although these metabolic parameters were statistically significant, they were not clinically significant, and did not present a safety concern. A decrease in hemoglobin is an expected physiologic response to the lowering of testosterone, which stimulates the production of erythropoietin and subsequently hemoglobin. Only one participant dropped into borderline anemia, all others were within the normal range for cisgender females. An increase in the mean HDL, although statistically significant, lacks clinical significance because it is within the normal range for cisgender females. An overall increase in prolactin levels is an expected change related to increased estrogen levels [16]. Physiologic parameters including blood pressure and glucose were within normal clinical range for most of the participants.

Additionally, prolactin levels statistically, but not clinically, increased with hormone use. Blood pressure and lean body mass index at follow-up did not change. Induction of desired feminine physical features as well as achieving a female range of sex steroids is the goal of hormone use in transfeminine patients; therefore, the decrease in mean testosterone and increase in mean estradiol levels is expected, and contributes to desired clinical changes. The mean estradiol level at 24 months is higher than expected with standard dosing (286.04 pg/mL) with a very large range (5–1,993 pg/mL). For those youth taking estradiol via oral route, the levels at follow-up have a smaller range than those getting intramuscular injections (19–331 pg/mL and 5–1,933 pg/mL respectively), and lower mean at follow-up (135.3 vs. 577.6 pg/mL). These differences are likely because of the fluctuating levels of medication delivered via injections versus oral delivery. Mean total testosterone level decreased from 425.9 ng/dL to 169 ng/dL (Table 2).

Physiologic parameters (transmasculine youth)

Transmasculine youth experienced statistically, and mildly clinically, significant changes in blood pressure and HDL. Statistical, but not clinically significant increases in triglycerides, aspartate aminotransferase, ALT (ALT), potassium, and hemoglobin were noted. The change in mean hemoglobin reflects and expected shift that occurs related to testosterone induced amenorrhea and increased production of erythropoietin. Induction of desired masculine physical features and achieving a male range of circulating sex steroids is the goal of testosterone therapy, and is reflected in the changes in total testosterone serum levels of this cohort. Mean total testosterone level increased from 41.2 ng/dL to 533.3 ng/dL. Mean estradiol serum level at follow-up was 50.8 pg/mL, higher than most cisgender men, but lower than many cisgender women. Among this sample, mean body mass index, total cholesterol, and random glucose levels did not change over the course of treatment (Table 3).

Discussion

To our knowledge, this is the first prospective study examining the physiologic changes that occur among minors and young adults undergoing treatment with gender-affirming hormones for the purpose of phenotypic gender transition. As the demand for care continues to exponentially increase across the United States, much more data are needed about the impact of hormonal therapy on both physical and mental health in transgender adolescents. This study was limited by the variability in the adherence rates to medication, a problem common to both adolescents and those undergoing care for gender dysphoria. Barriers to access to medication, medical provider follow-up visits, and the natural tendency for youth to geographically relocate pose challenges to collecting data among this cohort. Additionally, the youth in this study were predominantly Caucasian and Latino/a and therefore these results may not be generalizable to youth of other ethnicities.

Current guidelines recommend monitoring physiologic parameters during induction of puberty at baseline and as often as every three months during the first year of hormone use [17,18]. Given the findings of this study, Weinand [7], and Jarin et al. [15], extensive and frequent laboratory examination in transgender adolescents may be unnecessary simply in response to the induction of puberty with gender-affirming hormones. Specifically,

monitoring complete blood counts and chemistries including LFTs are unnecessary except perhaps in transwomen who plan to go on spironolactone in which case baseline potassium and creatinine levels would be reasonable. In transwomen, monitoring prolactin is unnecessary unless galactorrhea, or other clinically concerning symptoms occur. Increases in blood pressure seen in transmasculine individuals warrant ongoing monitoring and standard treatment for those who develop hypertension. In other cases where further medical investigation is warranted, it should be undertaken according to clinical necessity.

Frequent concerns about the safety of hormone use in individuals younger than 18 years can create barriers for youth to access medically necessary interventions that have been demonstrated to improve the lives of transgender adolescents. Concerns about the impact of cross-sex hormones on metabolic parameters are starting to be assuaged with clinical experience, retrospective analysis, and more recently, the undertaking of prospective, longitudinal investigations. Among this cohort of youth reported here, there were several statistically significant changes in mean values of physiologic parameters over time, but these did not translate to clinical safety concerns. Hormone levels were impacted as anticipated, and reflect the therapeutic goals of the care. These data indicate that gender-affirming hormone therapy is safe over a time period of approximately two years. Future studies and follow-up information that includes longitudinal results are necessary.

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Table 1

Descriptive characteristics (n = 58 participants' survey results available for analyses)

	Transfeminine youth (n = 23) n (%)	Transmasculine youth (n = 35) n (%)	Total (n = 58) n (%)
Race/Ethnicity			
African-American/black	2 (9)	4 (11.4)	6 (10)
Asian/Pacific Islander	0 (0)	1 (3)	1 (2)
Caucasian	10 (43)	22 (63)	32 (55)
Latino(a)	10 (43)	7 (20)	17 (29)
Other	1 (4)	1 (3)	2 (3)
Gender identity			
Male	0 (0)	32 (91)	32 (55)
Female	21 (91)	0 (0)	21 (36)
Gender queer	0 (0)	2 (6)	2 (3)
Gender bender	1 (4)	0 (0)	1 (2)
Bi-gendered	0 (0)	1 (3)	1 (2)
Other	1 (4)	0 (0)	1 (2)

Table 2

Physiologic parameters of trans feminine youth

	n	Baseline			24-Month follow-up			p value
		Mean (SD)	Range		Mean (SD)	Range		
Systolic BP (mm Hg)	25	122.68 (14.4)	98–151		124.84 (12.10)	96–148		.465
Diastolic BP (mm Hg)	25	71.08 (10.66)	45–86		70.80 (7.68)	57–84		.898
BMI (kg/m ²)	24	24.60 (4.73)	17.7–34.0		24.86 (5.34)	17.1–37.8		.554
Cholesterol (mg/dL)	23	168.96 (41.68)	93–256		166.13 (23.97)	125–218		.718
HDL (mg/dL)	23	43.83 (10.42)	24–62		50.91 (14.34)	27–75		<.001 ^b
Triglycerides (mg/dL)	23	135.52 (83.85)	44–383		115.96 (66.22)	45–317		.259
AST (U/L)	23	72.52 (42.19)	18–139		30.83 (17.39)	15–87		<.001 ^b
ALT (u/L)	23	30.09 (12.74)	15–57		25.37 (11.59)	5–55		.236
Potassium (mEq/L)	23	4.25 (.31)	3.5–4.9		4.47 (.36)	3.8–5.1		.040 ^a
Glucose (mg/dL)	23	90.26 (11.14)	66–110		91.96 (14.00)	74–129		.625
Hemoglobin (g/dL)	22	15.31 (1.13)	12.9–18.1		14.05 (1.24)	11.8–16.0		<.001 ^b
Testosterone free (pg/mL)	24	80.90 (49.83)	7–200.2		28.54 (43.17)	3–167.4		<.001 ^b
Testosterone total (ng/dl)	24	425.88 (233.82)	4–927		169.00 (217.61)	6–782		<.001 ^b
Estradiol (pg/mL)	23	26.16 (14.55)	2–61		286.04 (492.04)	5–1,993		.018 ^a
Prolactin (ng/mL)	13	8.27 (5.98)	1.0–22.0		11.99 (5.44)	3.2–19.7		.047 ^a

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; SD = standard deviation.

p values were calculated using paired-samples t tests.

^aSignificant at $p < .05$.^bSignificant at $p < .001$.

Table 3

Physiologic parameters of transmasculine youth

	n	Baseline		24-month follow up		p value
		Mean (SD)	Range	Mean (SD)	Range	
Systolic BP (mm Hg)	34	115.62 (15.15)	76–153	128.03 (11.40)	102–157	<.001 ^b
Diastolic BP (mm Hg)	34	67.15 (12.57)	40–95	72.32 (12.15)	48–96	.024 ^a
BMI (kg/m ²)	35	27.27 (6.17)	16.9–44.2	27.99 (5.53)	19.8–38.2	.188
Cholesterol (mg/dL)	35	163.57 (33.42)	122–256	164.49 (41.40)	94–339	.840
HDL (mg/dL)	35	51.74 (11.37)	30–72	44.49 (12.73)	26–78	.001 ^a
Triglycerides (mg/dL)	35	109.86 (92.43)	36–486	144.40 (87.91)	47–403	.044 ^a
AST (U/L)	34	55.85 (33.55)	20–129	40.00 (27.42)	16–155	.034 ^a
ALT (u/L)	35	22.23 (10.64)	7–53	32.86 (16.67)	14–80	<.001 ^b
Potassium (mEq/L)	35	4.23 (.36)	3.5–5.2	4.55 (.41)	3.4–5.5	.002 ^a
Glucose (mg/dL)	35	89.20 (17.48)	47–148	84.66 (11.39)	61–119	.172
Hemoglobin (g/dL)	34	13.02 (.97)	10.8–14.8	15.50 (1.12)	11.4–16.9	<.001 ^b
Testosterone free (pg/mL)	35	5.79 (7.71)	.3–47.0	117.43 (80.51)	5.7–310.5	<.001 ^b
Testosterone total (ng/dl)	35	41.17 (45.31)	7–288	533.26 (331.31)	63–1,272	<.001 ^b
Estradiol (pg/mL)	34	81.93 (81.95)	7–372	50.79 (43.21)	9–185	.061

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; SD = standard deviation.

p values were calculated using paired-samples *t* tests.^a Significant at $p < .05$.^b Significant at $p < .001$.