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Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria

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Abstract

Background: Sex hormones initiate profound physical and physiological changes during the pubertal process, but to what extent are they responsible for continuing the body composition changes of late adolescence and what happens to body composition on sudden sex hormone withdrawal?

Methods: Thirty-six healthy, phenotypically and chromosomally normal late and post-pubertal individuals aged 15–17 years with gender dysphoria (transgirls – birth-registered males identifying as female n = 11; and transboys – birth-registered females identifying as male n = 25) underwent Tanita body composition analysis at 0, 6 and 12 months during reproductive hormone suppression with Triptorelin as part of the standard therapeutic protocol.

Results and conclusions: In the transgirl cohort, paired t-test analysis demonstrated a significant decrease in height and lean mass standard deviation scores over the 12-month period, going against an expected trajectory over that time. In contrast, oestrogen suppression appeared not to affect the body composition of transboys; their measurements were not significantly different at baseline and after 12 months of treatment. The withdrawal of sex hormone secretion does not appear to have a significant impact on female post-pubertal body composition, in contrast to that seen at the menopause. This suggests that other factors may preserve normal body balance in adolescents in the absence of sex steroids.

Keywords: BMI; body composition; gender dysphoria; GnRHa treatment; sex hormones.

Introduction

Puberty and the hypothalamo-pituitary-gonadal (HPG) axis

Puberty is initiated through an interplay between environmental, genetic and physical factors with central accentuation of gonadotropin hormone-releasing hormone (GnRH) release [1]. Based on the knowledge of pubertal endocrine activity, GnRH analogues have been developed to suppress this stimulatory hormonal axis. Triptorelin, a GnRH agonist used in transgender adolescents, acts by overstimulation and thus interruption of the normal pulsatile activation of GnRH receptors. This results in receptor desensitization and downregulation, creating an overall suppression of the hormone axis.

Body composition changes during puberty

The described dramatic changes of puberty have been discovered to have a predictable pattern of occurrence. There is a striking sexual dimorphism in body composition as each gender pursues a contrasting pattern of growth and development. Prior to puberty however, gender differences are modest, with females having a slightly greater percentage in body fat and males a greater lean mass (fat-free mass) [2, 3]. Puberty acts as the key time for differentiation of body composition.

Veldhuis et al. report that during puberty males accrue a greater fat-free mass and skeletal mass while females gain significantly more fat mass. The net effect is the creation of a dimorphism where adult males have on average 13% body fat, while females, 25% [3–5].

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Body mass index (BMI) is a value generated to determine a 'healthy' weight for a person's height irrespective of age and sex and is generally used as a disease risk predictor [6]. BMI changes during puberty are useful to assess the nutritional status of individuals; with a multitude of body composition data collected demonstrating clear reproducible trends [7].

Gender dysphoria and its management

Gender dysphoria (GD) is increasingly recognized in children and young adolescent people. It is a condition where there is a 'marked difference in the individual's expressed/experienced gender' and their birth registered/assigned sex [8]. Psychological, social and biological factors are thought to influence GD and thus treatment is largely a multi-disciplinary approach [9].

Management of young people with GD will often depend on the age at which they present. Children are managed largely through the use of behavioural, family and psychological therapies. In adolescents over the age of 15, there is also the potential additional use of medical interventions such as GnRH analogues which act to suppress puberty, in particular the endogenous sex hormones [9–11].

GnRH analogues

After fulfilling the criteria for GD and following extensive psychological input, GnRH analogues can be offered to those young people in puberty with persistent dysphoria to prevent natural sex steroid production, thus halting puberty by lowering female oestrogen or male androgens. The physical effects are usually decreased breast tissue in girls and regressed testicular volume in boys, though the effect largely depends on the Tanner stage at the start of treatment [11]. The treatment is usually given for a minimum of 1 year from age 15, with regular review, before treatment with the opposite sex steroid can be considered (cross-sex hormone therapy) to gain the physical secondary sex characteristics of the desired gender. Although some side effects of stopping oestrogen in females can be predicted such as 'menopausal' symptoms, little is known about the effects on the rest of the body.

Aim

The aim of this study was to observe the effect of suddenly withdrawing sex hormones on the body composition in late-pubertal adolescents with GD using GnRH analogues. Our study aims to provide further evidence in this field, and to observe whether suppressing gonadal steroids would recreate the changes seen in later life.

Materials and methods

Study population

The present study was conducted in 36 healthy individuals aged 15–17 diagnosed with GD attending the University College London Hospital (UCLH) Gender Identity Development Service between 2013 and 2015. Triptorelin (Gonapeptyl Depot 3.75 mg or Decapeptyl SR 11.25 mg) was administered subcutaneously for at least 1 year as part of the standard therapeutic protocol [9]. Sex hormone suppression was confirmed biochemically. Tanita body composition analysis was performed at 0, 6 and 12 months of treatment, with height, weight and body mass index additionally recorded. Data was taken from this routine clinic monitoring of patients and subsequently anonymized.

Thirty-six adolescents, 11 transgirls (birth-registered males identifying as female) and 25 transboys (birth-registered females identifying as male) receiving GnRH treatment, whose data were complete, were included in this study. They were verified to be phenotypically and chromosomally normal through physical examination and karyotype analysis. Others were only excluded if they had an incomplete set of body composition data or if any other confounding factor was identified from routine clinic questioning about lifestyle that could affect the results (n = 4). Examples included patients that had excessive weight gain due to body-building activities and excessive weight loss when diagnosed with anorexia.

Body composition analysis

Whole-body impedance at 50 kHz (Z, in Ω) was measured using a Tanita Body Composition Analyzer, Model type/Number BC-418MA III. The conventional whole-body impedance index (height^2/Z) was calculated and used as an indicator of lean mass. Standard deviation scores (SDSs) for lean mass were calculated using recent UK body composition reference data [12]. Height, weight and BMI SDS were derived from UK90 data [13].

Statistical analysis

All data were analysed using the Statistical Package for Social Sciences (SPSS, IBM Ltd, Portsmouth, UK) version 21. Changes in anthropometric and body composition variables between 0 and 12 months were tested using paired t-tests. Measurements were also compared to the reference populations using a one-sample t-test. Statistical significance was considered to be p-value <0.05.

Ethical considerations

Specific ethical consideration was not required as this was a retrospective evaluation of routine clinical data. All data were analysed and are presented anonymously.

Results

Thirty-six adolescents at the University College London Hospital (UCLH) gender identity clinic, at the point in time when analysis was conducted had a complete set of body composition measurements over the initial 12-month period of GnRH analogue treatment.

The mean age for transboys was 16.6 years (1 SD = ±0.69 years) and for transgirls was 16.4 years (1 SD = ±0.66 years). The mean age of menarche in the transboys was 11.9 years (1 SD = ±1.10 years). All transgirls were in late puberty (Tanner stages G4 and 5).

Average baseline age, height, weight and BMI data are shown in Table 1 as combined data and also stratified by birth sex. There was no significant difference in age, weight and BMI between the two sexes. Transgirls, however, were significantly taller than transboys as expected for a late pubertal cohort.

The effect of GnRH analogues on BMI SDS was not significantly different between transboys and transgirls. Over the whole 12-month treatment period, the average BMI SDS in transgirls decreased by 0.07. In the transboys there was a fall in BMI SDS between 0 and 6 months but overall by 12 months there was an increase of 0.1 indicating a small but insignificant upward trend. Figure 1 demonstrates the BMI SDS trends for each individual over the 12-month treatment period for transboys (upper panel) and transgirls (lower panel), respectively.

The results for birth male and female SDSs of lean mass, height, weight and BMI are shown in Table 2. Paired t-tests demonstrated that despite the small sample size, the fall in height SDS and lean mass SDS from baseline to 12 months is significant in transgirls whilst weight and BMI SDS did not change significantly.

In the transboys, there were no significant differences in any of the variables between baseline and 12 months ($p > 0.05$).

When compared to population reference data using a one-sample t-test, the mean height and lean mass SDS for the transgirls was lower than expected at all time points ($p < 0.05$), with no difference for weight or BMI SDS.

In contrast, for the transboys, weight and BMI SDS were significantly higher than expected at all time points, with no difference in height and lean mass SDS.

Discussion

This study adds to the body of evidence on the effects of sex hormone suppression by GnRH analogues on body composition in adolescents with GD. The decision to use

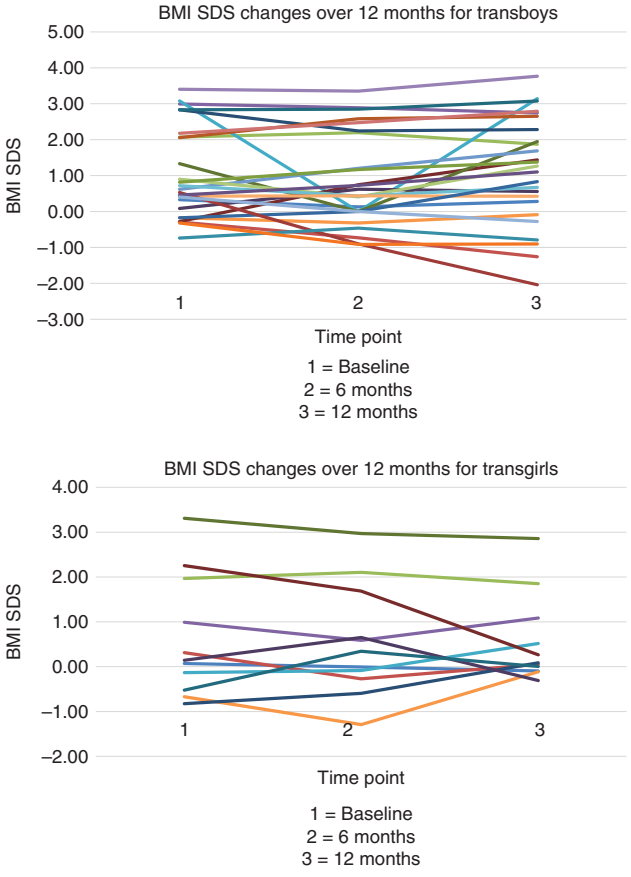

Figure 1: Standard deviation scores (SDS) for BMI at baseline, 6 months and 12 months of GnRH treatment in transboys (birth-assigned natal females) (upper panel) and transgirls (birth-assigned natal males) (lower panel).
BMI SDS zero represents the population mean. Each coloured line shows data for a single subject.

Table 1: Descriptive characteristics of all participants.

	All	Transgirls	Transboys	p-Value
Number	36	11	25	
Mean age (SD), years	16.5 (15.8–17.2)	16.4 (15.7–17.1)	16.6 (15.9–17.3)	0.50
Mean height (SD), cm	164.3 (157.9–170.7)	167.7[a] (161.8–173.6)	162.8[a] (156.4–169.2)	0.03[a]
Mean weight (SD), kg	65.8 (50.4–81.2)	64.4 (48.5–80.3)	66.4 (51.0–81.8)	0.72
Mean BMI (SD), kg/m^2	24.4 (18.7–30.1)	23.0 (17.2–28.9)	25.0 (19.3–30.7)	0.32

[a]Denotes significant values <0.05 between transgirls and transboys.

Table 2: One-sample test comparing standard deviation scores (SDS) for height, weight, BMI and lean mass to a reference population.

One-sample test					Paired-sample test
Body composition measure	**Birth assigned sex**	**0 month**	**6 months**	**12 months**	**Paired sample t-test (between 0 and 12 months) p-value**
Height (mean SDS)	Male	−0.88[a]	−0.98[a]	−1.05[a]	0.012[b]
	Female	−0.09	0.01	−0.05	0.087
Weight (mean SDS)	Male	0.05	−0.09	−0.14	0.303
	Female	0.88[a]	0.74[a]	1.02[a]	0.367
BMI (mean SDS)	Male	0.63	0.55	0.56	0.802
	Female	1.04[a]	0.85[a]	1.14[a]	0.555
Lean mass (mean SDS)	Male	−0.68[a]	−0.79[a]	−1.11[a]	0.002[b]
	Female	0.15	0.01	−0.08	0.087

[a]Denotes significance difference ($p < 0.05$). Paired sample t-test comparing changes for height, weight, BMI and lean mass from baseline to 12 months in the GD cohort. [b]Denotes significant values ($p < 0.05$). Birth-assigned male = transgirl; birth-assigned female = transboy.

this treatment demands that the full side effect profile of the drug is known. Information on this has accumulated, with the major side effects reported to be hypogonadism, hot flushes, decreased libido, headaches, changes in skin texture and bone mineral density depletion [9, 14, 15]. An area, however, requiring further investigation, particularly in transgender adolescents, is the effect of GnRH treatment on body composition with a current small body of research at present [11]. Studies using dual X-ray absorption (DXA) techniques in a slightly younger cohort but with comparable Tanner stages have demonstrated similar changes to ours in transgirls [16, 17]. We report, however, some differences in body composition in our cohort to these previous studies.

Analysis of body composition additionally provides a unique opportunity to observe the effects of sudden sex hormone withdrawal at a late pubertal stage. The situation essentially produces a 'pseudo-menopause' and it would be interesting to compare if similar changes would occur.

What our results showed

Effects of the treatment on anthropometry and body composition were gender-specific with no apparent effect on body composition from the parameters measured for transboys.

In the transgirls, there was a significant decrease in height and lean mass SDSs over the 12-month period indicating that these birth-assigned males were not maintaining the expected height and lean mass increase over that 1-year period. This significant decrease is likely explained by the fact that these patients are suspended at the same point of puberty as when they started treatment whereas reference data tend to demonstrate an increase in these parameters as age advances.

On average the cohort was 16.5 years old; when most birth-registered male adolescents expect to be at the latter stages of pubertal maturation [18]. The slowing in height and lean mass accretion may reflect a desirable outcome for transgirls who wish to proceed to a full female sex change and these results have also been reported by other studies [16, 17]. We found no significant change in BMI SDSs, which agrees with combined analysis of studies conducted on patients with precocious puberty treated with GnRH suppression [19]. However, the body of evidence on this is conflicting, with Schagen et al. reporting in a cohort with mean age 13.6 a small increase in BMI SD [17]. This inconsistency suggests that more data are required to allow more reliable advice to be given to patients on expected BMI changes. A relevant finding, however, is that studies have reported using dual-energy X-ray absorptiometry (DXA) scanning show an increase in total body fat percentage in transgirls undergoing treatment [16, 17]. This is an important consideration in patient counselling.

Treatment was commenced in the transboys at an age when most would have completed their sexual development (median age of 16.6 years). Recent studies have shown that breast development to Tanner stage B5 occurs around 15.0 years of age and genital development to stage G5 at 15.4 years [18]. Hence this study demonstrates the impact of GnRH analogue post-pubertally which possibly explains why we observed no significant changes in our transboys. Interestingly, studies using DXA scanning in younger cohorts have demonstrated body composition changes, although the findings are conflicting. Schagen et al., with a younger transboy cohort aged 14.2 years, reported a fall in height SDSs over a year of

GnRH treatment [17]. They also reported that lean body mass decreased in the transboys, and Klaver et al. showed a small decrease in lean body mass in both genders by late puberty [16].

When comparing those on GnRH analogues to an age- and sex-matched reference cohort of adolescents, the transgirls were shorter and had less lean mass whilst the transboys had a higher BMI and weighed more than the average population. However, as this was significantly different at all time points, including the baseline measurement, it is unlikely to be due to the GnRH analogue treatment.

The extent to which 'gender dysphoria' explains the observed differences between our cohort and the reference population is debatable. Studies have shown that patients with GD have body image problems beyond the sexual and physical appearances [20]. It is reasonable to suggest therefore that transgirls may consciously control their diet to make themselves thinner and smaller whilst transboys may try to increase muscle bulk (reflecting in the higher BMI). This could possibly explain why before commencing treatment the transgirls had a lower lean mass compared to the birth-assigned male reference population.

Another explanation for the disparity could be that the reference data chosen is not representative of the 'normal' adolescents in present times. The UK90 data was taken from a cohort measured between 1978 and 1990 [13] and it is possible that our transboys are simply representative of heavier contemporary birth-registered females.

The use of GnRH analogues has allowed us to observe the impact of sex hormone suppression on body composition in phenotypically and chromosomally normal young healthy adolescents. Sudden withdrawal of oestrogen during the post-pubertal period does not appear to have a significant impact on female body composition (with regard to the parameters measured). However, we did interestingly see an insignificant trend towards a decrease in lean mass over the 12-month period of GnRH analogue treatment. This reflects a well-documented phenomenon at menopause where body composition does change when oestrogen falls. Women are found to develop a more 'android' body shape, characterised by an increase in fat mass, decrease in lean mass and greater central adiposity [21]. Our results therefore support the role of oestrogen in body composition changes, although at the time of puberty it is likely that there are other factors which are preserving the normal body balance, the adrenal and growth hormone axes playing a seminal role [3]. A similar comparator for men cannot be made as there is no set time point that defines a male 'menopause'. Nevertheless, from our study we observed that height SDS and lean mass SDS are significantly reduced if testosterone is artificially suppressed. Although this was observed in only a small sample size, it warrants further investigation into the role of testosterone in body composition. Research in older men (mean age 64.5 years) demonstrated that testosterone therapy increased lean mass and reduced total body fat with no change in the overall body weight [22].

Strengths and limitations of the study

The main limitation of our study was the relatively small sample size, especially for the transgirls. Tanita bioelectrical impedance analysis (BIA) was chosen as the method to measure body composition in our cohort of patients. This was based on the safety, ease and convenience it provided in measuring body composition during routine clinic appointments. We chose to use the impedance index ($height^2/Z$) to generate lean mass SDS rather than converting impedance data to total body water and then to lean mass and fat mass using published equations. This avoided introducing further error by making assumptions which may not hold for our subjects. In a recent evaluation, we reported that $height^2/Z$ explained 95% of the variance in 4-C lean mass [23].

Lean mass, along with height, weight and BMI SDS, provided a useful and wide-ranging analysis of body composition, although we were not able to measure bone mass which would also be of relevance in these patients.

Future work

This initial study has given useful information into the side effect profile of GnRH analogues and provided further insight into the role of sex hormones in the post-pubertal period. The natural course of this investigation will be to next analyse the effects of cross hormone treatment on body composition in this cohort. This is part of the current regimen treatment protocol, should patients wish to continue to a full sex change. The decision to receive cross sex hormone treatment is often more difficult for individuals due to its lack of reversibility [10]. This further investigation would therefore importantly give the required information on the safety and expected outcomes of this treatment, allowing individuals to make a more informed choice. It will additionally provide a unique opportunity to improve understanding of the effects of sex steroids and their reinstatement.

Conclusions

GnRH analogues do not appear to have significant harmful effects on body composition when used in healthy post-pubertal adolescents. There is a significant slowing of height and lean mass in transgirls. This could, however, be potentially detrimental if the patient decides not to go ahead with transition. Interestingly, the body composition changes are much less profound than the natural equivalent in middle age. It is possible, therefore, that other factors may preserve normal body balance even in the absence of sex hormone secretion, and this will require further study.

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