Research Article

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Evaluation of Muscle Mass and Strength in Children and Adolescents with Disorders of Sex Development

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Abstract
Objective: The aim of this study was to evaluate muscle mass and strength in children and adolescents with disorders of sex development (DSD) whose sex assignment was determined by a multidisciplinary team, comparing these parameters both among the DSD cases and with healthy controls, and to assess the impact of hormone replacement therapy (HRT) on these outcomes.
Methods: 78 DSD cases and 118 healthy controls were included. Gender assignment followed multidisciplinary council decisions; some DSD cases underwent gender-appropriate surgical interventions, and HRT was initiated as puberty approached. Participants were divided into four age groups (<5, 5–10, 10–15, and ≥15 years), and anthropometric measures, pubertal status, muscle mass and strength, skinfold thickness, and sex hormone profiles were assessed.
Results: Among DSD cases, 30.8% had 46,XX DSD, 53.8% had 46,XY DSD, and 15.4% had mixed gonadal dysgenesis (MGD); ambiguous genitalia was the most common referral reason, and CYP21A2 was the most frequently identified mutation. In individuals aged ≥15 years, 46,XX DSD cases, regardless of gender of rearing, had lower height standard deviation scores (SDS) than healthy peers, whereas 46,XY DSD cases raised as females had higher height SDS than other DSD subgroups ($p<0.01$). In Individuals aged ≥15 years, muscle strength was highest in 46,XY DSD males and healthy males ($p<0.01$). Participation in sports was associated with higher muscle mass in both groups ($p=0.03$). Muscle strength correlated positively with serum testosterone ($p< 0.001$, $R = 0.563$).
Conclusion: Chromosomal sex predominantly influenced final height, whereas muscle strength aligned with gender of rearing and testosterone levels.
Keywords: Anthropometric measurements, body composition, childhood, disorders of sex development, hormone replacement therapy, muscle strength

What is already known on this topic?
- Disorders of sex development can affect growth, puberty, and body composition due to chromosomal, gonadal, and hormonal variations.
- Muscle mass and strength are influenced by sex hormones, particularly testosterone, and vary with gender of rearing and hormonal treatment.

What this study adds?
- Muscle strength in adolescents with DSD aligns more with gender of rearing than chromosomal sex, reflecting hormonal exposure.
- Serum testosterone correlates positively with muscle strength in participants aged ≥15 years.
- Final height is more closely associated with chromosomal sex.

Introduction

Disorders of sex development (DSD) arise from disruptions in one of the stages of sex differentiation, particularly during the first trimester of gestation, resulting in discordance among chromosomal composition, gonadal development, and anatomical structures (1). These conditions typically present with atypical genitalia, although they may also be diagnosed later in adolescence due to delayed puberty, hypogonadism, virilization, or infertility (2).
DSD can be associated with a variety of factors, including genetic determinants, developmental processes, and hormonal alterations (3,4). Currently, DSD are classified into three main categories based on the 2006 consensus: sex chromosome-related DSD, 46,XY DSD, and 46,XX DSD (1,5).
The incidence of DSD is approximately 1 in 4,500–5,500 live births (5). The most common cause of DSD is congenital adrenal hyperplasia (CAH), due to 21-hydroxylase deficiency. The global incidence of CAH-related 46,XX DSD is approximately 1 in 14,000–15,000, with variation according to ethnicity (6). This is followed by 46,XY androgen insensitivity syndrome (AIS) and mixed gonadal dysgenesis (MGD) (7).
Biochemical evaluation in DSD relies on the interpretation of hormone levels according to age and gestational week. In neonates, the primary assessments include 17-hydroxyprogesterone (17-OHP), serum electrolytes, androgen metabolites, anti-Müllerian hormone (AMH),

gonadotropins, and karyotype analysis. Electrolyte disturbances typically become evident after the fourth day of life. Diagnostic approaches also include basal hormone measurements, steroid profiling via LC-MS/MS, and stimulation tests with hCG and ACTH (5).
Gender assignment determined based on the collaboration between a multidisciplinary team and the family (4,8). Factors to be considered in gender assignment decisions include the anticipated gender identity, sexual function, genital appearance, surgical options and associated risks, lifelong need for hormone replacement therapy, fertility potential, prenatal androgen exposure of the brain, risk of gonadal malignancy, and psychosocial factors (family and cultural context).
In DSD cases, pubertal hormone replacement therapy aims to mimic the normal pubertal process, supporting growth, bone development, and the development of secondary sexual characteristics, as well as providing psychosocial benefits. Estrogen replacement is typically initiated in females at 11–12 years of age, while testosterone replacement is started in males at 12–13 years of age. The dosage and route of administration are adjusted according to individual patient needs (4,5).
Studies have shown that muscle mass and strength increase rapidly from childhood through adolescence, peak in early adulthood, and subsequently decline with age (9–11). Muscle development is influenced by growth hormone, IGF-1, sex steroids such as testosterone and estradiol, as well as prenatal factors (maternal nutrition, genetic determinants) and postnatal factors (physical activity, dietary intake, obesity) (12). During infancy and early childhood, hormonal effects are limited, with genetic and environmental factors playing a more prominent role. Hormonal changes peak during puberty; increased GH secretion enhances muscle mass and reduces fat percentage, while sex steroids shape fat and muscle distribution in a sex-specific manner and regulate secondary sexual characteristics (9).
In adolescent males, testosterone plays a key role in the increase of muscle mass and strength (9,12). Testosterone supports pubertal development, muscle and bone mass, metabolic balance, and psychosocial health (13). It promotes the myogenic differentiation of mesenchymal stem cells while inhibiting adipogenesis (14). Studies in adolescent and young males have demonstrated that testosterone exerts anabolic effects on muscle mass by stimulating protein synthesis and inhibiting proteolysis (13,15). Although the effects of estrogen on muscle mass and strength are less pronounced in males compared to testosterone, estrogen receptors are present in skeletal muscle, suggesting that estrogen may have anabolic effects on muscle (16). In males engaged in high-intensity endurance training, skeletal muscle expression of estrogen receptor alpha and beta was significantly higher than in moderately active males. This upregulation indicates enhanced estrogen signaling in muscle and suggests that estrogen may play an important role in muscle metabolism and adaptation (17).
This study aimed to compare muscle strength and muscle mass in these DSD subgroups with those of healthy individuals of the same assigned gender, as well as with DSD individuals raised according to their chromosomal sex. Furthermore, the effects of hormone replacement therapy (HRT) on muscle mass and strength were evaluated. Our study also sought to elucidate the impact of chromosomal sex, in addition to hormonal effects, on muscle development. Additionally, we aimed to address the recent debate regarding whether 46,XY DSD individuals raised as females exhibit significant differences in muscle mass and strength compared to 46,XX females.

Methods

Patients

This prospective, single-center study included 78 DSD cases who were raised as either females or males according to multidisciplinary council decisions, underwent corresponding surgical interventions, and received HRT. Cases with other chronic diseases, malnutrition, or irregular clinical follow-up, as well as those using medications or substances that could affect muscle strength or mass, were excluded.

Case Classification and Data Collection

DSD cases were categorized into four age groups: <5 years, 5–10 years, 10–15 years, and 15–18 years. The patient cohort was divided into two groups based on gender assignment determined by the multidisciplinary council. DSD cases were also stratified according to karyotype into three subgroups: 46,XX DSD, 46,XY DSD, and mixed gonadal dysgenesis.
A total of 118 healthy children and adolescents served as the control group. Demographic data, presenting symptoms, anthropometric measurements, physical examination findings including Tanner staging (18), genetic analysis results, and serum total testosterone and estradiol levels were recorded and compared with the control group. Anthropometric data of the cases were evaluated according to assigned sex, and standard deviation scores (SDS) were calculated (19). Bone age was determined from left-hand and wrist radiographs using the Greulich and Pyle method (20). Decisions of the multidisciplinary council and corresponding surgical reports were included in the study records.

Bioelectrical Impedance Analysis (BIA)

For DSD cases taller than 100 cm and older than 5 years, as well as for all control subjects, muscle mass was assessed using bioelectrical impedance analysis (BIA) method using a segmental body composition analyzer (Tanita MA 780MC, Tokyo, Japan). Total body water was not included as a parameter in the body composition analysis. Body composition was calculated based on muscle mass, fat mass, and mineral content.

Handgrip Strength and Skinfold Caliper Measurements

In cases older than 5 years and in healthy controls, muscle strength was measured using a hand dynamometer tool that measures isometric contraction force (GRIP-D dynamometer). Measurements were performed on two separate days without conditions that could influence muscle strength, and the average of the obtained values was used for analysis. Triceps skinfold thickness, an indicator of subcutaneous fat, was measured in all participants. Triceps skinfold thickness was measured at the midpoint between the olecranon and acromion using a skinfold caliper, with the arm relaxed at the side in a vertical orientation.

Ethics

The study protocol was approved by the Ethics Committee of Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (protocol no: TBAEK-649, date: 03.10.2024) and informed consent was obtained from the families of the participants.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as mean ± standard deviation (SD) for normally distributed data and as median (minimum–maximum) for non-normally distributed data. The normality of continuous variables was assessed using histograms and the Kolmogorov–Smirnov test. The chi-square test was used for categorical variables. For comparisons between two independent groups, the *t*-test was applied for normally distributed data, and the Mann–Whitney U test for non-normally distributed data. The Kruskal–Wallis H test was used for variance analysis (with Dunnett's T3 test for post-hoc comparisons). Pearson's correlation was used for normally distributed data, and Spearman's correlation for non-normally distributed data. A p value <0.05 was considered statistically significant.

Results

Classification by Age and Karyotype

The mean age of the DSD cases was 12.0 ± 5.4 years, ranging from 1.1 to 17.9 years. The healthy control group had a mean age of 11.1 ± 3.7 years (range: 5–17.9 years). DSD cases were classified into age groups as <5 years (n = 5, 6.4%), 5–10 years (n = 26, 33.3%), 10–15 years (n = 11, 14.1%), and 15–18 years (n = 36, 46.2%) (Table 1).
Based on multidisciplinary council decisions, 43 cases (55.1%) were assigned female gender, while 35 cases (44.9%) were assigned male gender. Among those assigned female, 18 (23.1%) had 46,XX DSD, 17 (21.8%) had 46,XY DSD, and 8 (10.2%) had MGD. Among those assigned male, 6 (7.7%) had 46,XX DSD, 25 (32.1%) had 46,XY DSD, and 4 (5.1%) had MGD. In the healthy control group, the sex distribution was equal, with a female-to-male ratio of 1:1 (Table 1).

Presentation Findings

Analysis of the reasons for referral to our clinic revealed that the most common presenting complaint was atypical genitalia (n = 54; 69.2%), followed by primary amenorrhea (n = 10; 12.8%). Less frequent reasons for referral included short stature (n = 5; 6.4%), gynecomastia (n = 3; 3.9%), hirsutism (n = 3; 3.9%), adrenal crisis (n = 2; 2.6%), and menstrual bleeding (n = 1; 1.2%) (Table 1).

Molecular Genetic Analysis

Genetic analysis identified a pathogenic variant in 27 cases (34.6%). Chromosome analysis revealed MGD in 12 cases (15.4%), while in the remaining 39 cases (50.0%), either evaluation was still ongoing or no variant was detected in the performed analyses. The most frequently identified genetic variant was a CYP21A2 mutation, observed in 17.8% of cases (Table 1).

Anthropometric Measurements

Final height SDS were significantly different in the ≥15-year age group. The mean height SDS of 46,XX DSD cases raised as females was -2.02 ± 0.37 (mean height = 151.0 ± 2.6 cm), which was significantly lower than that of healthy female controls (-0.29 ± 1.2; mean height = 160.1 ± 7.0 cm). Similarly, 46,XX DSD cases raised as males had a mean height SDS of -2.61 ± 0.7 (mean height = 160.0 ± 5.1 cm), significantly lower than that of healthy male controls (-0.24 ± 0.93; mean height = 170.0 ± 7.2 cm) ($p < 0.01$) (Table 2).

In the ≥15-year age group, 46,XY DSD cases raised as females had a higher mean final height SDS (1.55 ± 0.60; mean height = 171.7 ± 3.2 cm) than all other DSD cases, including those raised as males, and compared with healthy female controls (-0.29 ± 1.2; mean height = 160.1 ± 7.0) ($p < 0.01$) (Table 2). Additionally, the mean weight SDS of 46,XY DSD cases assigned female gender in this age group (1.23 ± 0.80) was significantly higher than that of all other DSD cases raised as females and 46,XX DSD cases raised as males (-1.45 ± 0.60) ($p < 0.01$) (Table 2). However, there was no significant difference in mean body mass index (BMI) SDS among these groups ($p = 0.761$).

In the other age groups (<5 years, 5–10 years, and 10–15 years), no statistically significant differences were observed in height, weight, or BMI SDS between DSD cases and healthy controls or among DSD subgroups ($p > 0.05$).

Treatment

Estrogen replacement therapy (oral tablets or transdermal patches) was initiated at a mean age of 13.4 ± 1.3 years in DSD cases assigned female gender, and treatment was continued with gradual dose escalation. In DSD cases assigned male gender, intramuscular testosterone therapy was started at a mean age of 15.1 ± 1.1 years with an initial dose of 50 mg/month, gradually increased up to 250 mg/month. In selected cases, topical testosterone gel or, more commonly, topical dihydrotestosterone gel was used to promote penile growth. In addition, cases diagnosed with CAH received supportive therapy with hydrocortisone and fludrocortisone. All DSD cases were evaluated for osteoporosis, and calcium and vitamin D supplementation was initiated when indicated. Psychosocially, all DSD cases were followed under regular psychiatric supervision, with intermittent consultations to monitor their progress.

Bioelectrical Impedance Analysis (BIA)

In the ≥15-year age group, DSD cases raised as females had a mean body muscle mass of 71.0 ± 4.9% and a fat mass of 27.0 ± 4.9%. In DSD cases raised as males, the corresponding values were 74.2 ± 4.1% and 23.9 ± 3.9%, respectively. Among healthy controls of the same age group, males had a mean muscle mass of 72.8 ± 6.5% and fat mass of 22.2 ± 6.5%, while females had a mean muscle mass of 69.4 ± 5.8% and fat mass of 25.6 ± 5.8% (Table 2). No statistically significant differences in body muscle-to-fat composition were observed between DSD subgroups or when compared with healthy controls ($p = 0.158$ for muscle mass; $p = 0.118$ for fat mass). Similarly, no significant differences were found in bioelectrical impedance analysis results between DSD cases aged 5–15 years and age-matched healthy controls ($p > 0.05$).

Skinfold Caliper Measurements

A moderate positive correlation was observed between skinfold measurements and fat percentage (Table 2) determined by bioelectrical impedance analysis ($R = 0.452$, $p < 0.001$). Skinfold thickness values were further analyzed across all age groups according to BMI categories (underweight, < −2 SDS; normal weight, −1 to +1 SDS; overweight, > +1 SDS; obese, > +2 SDS), and no statistically significant differences were observed between DSD subgroups or when compared with healthy controls.

Handgrip Strength Measurements

Handgrip strength measured by dynamometry increased significantly with age in cases over 5 years and in healthy controls, with the highest mean values observed in the ≥15-year age group. Across all groups, the highest mean muscle strength was observed in 46,XY DSD cases raised as males aged ≥15 years (26.5 ± 1.7 N), followed by healthy males in the same age group (24.3 ± 4.3 N).

Significant differences in handgrip strength were observed particularly in DSD cases aged ≥15 years. Mean muscle strength was higher in 46,XY DSD cases raised as males (26.5 ± 1.7 N) and in healthy male controls (24.3 ± 4.3 N) compared with DSD cases raised as females (overall mean for all subgroups: 17.3 ± 2.4 N) and healthy female controls (19.1 ± 4.2 N) in the same age group ($p < 0.001$) (Table 3).

In the 5–10 year age group, handgrip strength was significantly lower in 46,XX DSD cases raised as females (7.3 ± 2.1 N) compared to age-matched healthy girls (12.7 ± 2.9 N; $p < 0.001$). Similarly, 46,XY DSD cases raised as males in the same age group had lower muscle strength (10.1 ± 3.0 N) than healthy boys (14.0 ± 2.7 N; $p < 0.001$), with boys exhibiting higher mean grip strength than girls. Although no statistically significant differences were observed between all patient and control groups aged 10–15 years ($p = 0.268$), males continued to show higher mean handgrip strength than females (Table 3).

Relationship Between Serum Sex Hormones and Other Parameters

In DSD cases aged ≥15 years, the mean serum total testosterone level was 4.0 ± 2.0 µg/L in 10 DSD cases raised as males receiving testosterone replacement therapy, while the mean serum estradiol level was 29.0 ± 17.4 ng/L in 26 DSD cases raised as females receiving estrogen replacement therapy (Table 1). No statistically significant differences were observed between these hormone levels and those of age-matched healthy male and female controls ($p = 0.236$).

In the ≥15-year age group, handgrip strength was positively correlated with serum total testosterone levels ($p < 0.001$, $R = 0.563$). However, no significant correlations were observed between serum estradiol or testosterone levels and height SDS or body muscle mass percentage.

Exercise and Muscle Strength

Among the study participants, 16.7% of DSD cases (n = 13) and 16.3% of controls (n = 19) reported regular engagement in sports or other physical activities. Within all DSD subgroups, no significant differences in handgrip strength were observed between physically active and inactive individuals ($p = 0.330$), whereas body muscle percentage was significantly higher in those who were active ($p < 0.01$). In the control group, both muscle mass percentage and handgrip strength were significantly higher in active participants compared with inactive ones ($p < 0.01$ and $p = 0.03$, respectively). These findings may vary depending on factors such as the type of sport, duration and regularity of training, and genetic influences.

Discussion

In this study, we evaluated the relationship between body composition, muscle strength, and anthropometric parameters by comparing individuals with DSD cases both among themselves and with healthy controls. Our findings indicate that hormonal influence plays a key role in determining muscle strength, whereas chromosomal origin appears to have a significant impact on final height.

When classified according to chromosomal patterns, 42 cases (53.8%) in our cohort had 46,XY DSD, 24 cases (30.8%) had 46,XX DSD, and 12 cases (15.4%) were diagnosed with MGD. While 46,XX CAH is reported as the most common cause of DSD in the literature (6), the largest patient group in our study comprised 46,XY DSD cases. As our center is the only tertiary care facility in the region managing DSD cases in a multidisciplinary manner, the distribution of cases may differ from that reported in the literature. Moreover, Comprehensive parental counseling, widespread prenatal follow-up, and neonatal heel-prick screening programs allow early diagnosis of girls with CAH, thereby may have reducing the number of virilized CAH girls requiring surgical board assessment.

In a study by Aydın BK et al. (21) investigating the frequency of ambiguous genitalia, among 18 cases with atypical genitalia, 15 were 46,XY, one was 46,XX, one had MGD, and one case's karyotype was not analyzed. Similar to our study, the largest patient group consisted of 46,XY DSD cases.

Half of the DSD cases in our cohort (n=39), a specific genetic variant had not yet been identified. Literature data also indicate that the rate of achieving a definitive molecular diagnosis in DSD cases remains low, ranging between 20–50%. In 46,XX individuals presenting with virilization, the majority have CAH, making genetic diagnosis more straightforward in this subgroup (1). In 46,XY DSD cases, the diagnostic yield of molecular analyses is variable, averaging around 50% (22,23). While the diagnostic rate is higher in CAIS (complete androgen insensitivity syndrome) and disorders of androgen biosynthesis, ranging from 60–90%, it is notably lower in cases with gonadal dysgenesis and PAIS (partial androgen insensitivity syndrome) (22). In the near future, whole-genome sequencing is likely to become a first-line diagnostic tool; however, current limitations include long turnaround times, high costs, inadequate coverage by national healthcare systems, and challenges in result interpretation.

Individuals with a 46,XX karyotype and a diagnosis of CAH are typically raised as females in the majority of cases (>90%) (1). This practice aligns with the high likelihood of female gender identity development and the preservation of fertility potential. In our cohort, 14 (87.5%) out of 16 virilized 46,XX CAH cases were raised as females. However, two cases, due to severe virilization, delayed presentation, parental preference, and the individuals' adoption of a male gender identity, were raised as males.

In our cohort, all 16 cases with a 46,XY karyotype who had CAIS or gonadal dysgenesis were assigned female gender. Similarly, in the literature, 46,XY individuals with CAIS or complete gonadal agenesis are predominantly raised as females due to the combination of female gender identity tendency, female genital phenotype, and infertility (24). In contrast, for individuals with 5α-reductase type 2 (5α-RD-2) deficiency, masculinizing changes during puberty, a high likelihood of developing male gender identity, and preserved fertility potential support male gender assignment and gonadal preservation (8). In our study, one 46,XY DSD case with an SRD5A2 variant was raised as female, based on both the child psychiatrist's recommendation and the case's adopted female identity, while the gonads were preserved and closely monitored. Another 46,XY DSD patient with an SRD5A2 variant was reared as male and managed with masculinizing surgery combined with topical dihydrotestosterone gel therapy. Among the 12 cases with MGD, gender assignment was individualized: eight were raised as females and four as males.

Significant differences in final height SDS were observed among the groups aged ≥15 years in our study. Cases with 46,XX DSD raised as females were notably shorter compared to other DSD cases and healthy controls. The majority of this group (18 cases) consisted of individuals with CAH (14 cases, 77.8%). Consistently, Aycan et al. (25) reported that among 24 cases with classic CAH, 79.1% had a final height below the target height, and 20.8% had a final height below the 3rd percentile. Similarly, in a meta-analysis by Eugster EA et al. (26), cases with 21-hydroxylase deficiency (both males and females) were found to have a mean final height approximately 1.2 SDS below the target height and 1.37 SDS below the general population reference. In these cases, short final stature is likely due to exposure to testosterone and its precursors and the degree of virilization.

Conversely, cases with 46,XY DSD raised as females aged ≥15 years had higher final height compared to all other DSD cases, including those raised as males, as well as healthy female controls. This finding highlights the significance of sex chromosome origin on final height. Han et al. study (27) comparing height in CAIS and 46,XY gonadal dysgenesis (GD) cases found that 46,XY GD individuals were taller than CAIS cases, and both groups were significantly taller than 46,XX GD females. Delayed gonadectomy and the late onset of estrogen replacement therapy may be associated with increased adult height in CAIS women. Overall, the height differences observed between CAIS and 46,XY GD females reflect hormonal effects on long bones, whereas the height differences between 46,XY GD and 46,XX GD females are likely attributable to Y chromosome-linked genetic influences.

In the literature, the recommended age for initiating HRT is 11–12 years for 46,XX DSD cases raised as females and 12–13 years for those raised as males (4). In contrast, the mean age at HRT initiation in our cohort was approximately two years later. This delay was attributed to postponement of therapy to avoid adverse effects on final height based on bone age assessments, as well as late diagnosis in some cases.

In male children during puberty, testosterone plays a pivotal role in the increase of muscle mass and strength. While estrogen causes fat deposition, testosterone supports lipolysis. Gonadal sex steroids, in conjunction with the GH/IGF-I axis, are primary determinants of changes in body composition (9,12). A study in mice (28) evaluated muscle fiber type, fiber diameter, and capillary density. Total muscle mass, capillary density, and muscle fiber diameter were significantly higher in male mice compared to females. Similarly, Welle S et al. (29) analyzed vastus lateralis muscle biopsies from adult male and female participants using microarray profiling. Higher expression of mitochondrial and ribosomal proteins and certain translation initiation factors in males, whereas genes inhibiting IGF-1 signaling and limiting muscle growth were more highly expressed in females. These findings provide a molecular basis for greater muscle mass in males and limited muscle development in females. Furthermore, in a study of 366 children and adolescents aged 6–23 years, the cross-sectional area of the forearm muscles measured by quantitative computed tomography was significantly greater in males, particularly after Tanner stage 3 of puberty (30). In our study, both healthy male controls and males raised as DSD cases exhibited higher lean body mass compared to females, although the difference did not have statistical significance.

Handgrip dynamometry provides a rapid and practical assessment of muscle strength (31). A study conducted in Dutch children, adolescents, and young adults demonstrated a strong correlation between handgrip strength and total body muscle mass (r = 0.736–0.890) (32). Similarly, in a cohort of 641 Chinese male adolescents aged 11–18 years, positive correlations were observed between testosterone levels, lean body mass, and handgrip strength (33). In our study, handgrip measurements also showed an age-related increase in mean muscle strength, with significantly higher values in participants raised as male. Although no significant differences were observed in lean body mass percentage, the higher muscle strength in males indicates that factors beyond muscle mass distribution (such as total muscle mass (kg), capillary density, hormone levels, neuromuscular adaptation, and resistance training) also contribute to strength development (34). Notably, the group with the highest muscle strength in our study was the 15 years and older 46,XY DSD cohort, highlighting the important role of sex chromosome complement and testosterone replacement therapy on muscle strength.

In a meta-analysis by Nuzzo JL et al., including 34 studies (35), a total of 6,634 participants (3,497 males, 3,137 females) were evaluated across three age groups (5–10, 11–13, and 14–17 years). The findings demonstrated that males exhibited higher muscle strength than females throughout childhood and adolescence, with the difference becoming more pronounced during puberty.

In a study by Mauras N et al. (15), gonadal steroid production in six healthy young males was suppressed using a GnRH analogue (leuprolide) for 10 weeks, resulting in dramatic reductions in testosterone levels, increased protein breakdown, reduced lean mass, increased fat mass, and decreased muscle strength and energy expenditure. These results underscore the direct effect of testosterone deficiency on body protein and fat metabolism. In line with this, in our study, a positive correlation between total testosterone levels and muscle strength was observed in the cohort aged ≥15 years ($p<0.001$, $R=0.563$).

Study Limitations

The inability to identify genetic variants in all cases represents a limitation of our study, consistent with previous reports. Although the overall sample size of the pediatric DSD cohort was adequate, the relatively small sample sizes in the subgroup analyses constitute a limitation of the study. Another limitation is that deviations from target height SDS based on parental heights were not evaluated when calculating final height SDS. Variability in the timing of hormone replacement therapy, treatment adherence, and physical activity could not be standardized, potentially influencing body composition and muscle strength outcomes.

Conclusion

Disorders of sex development constitute a complex group of conditions that require a multidisciplinary approach in close collaboration with the patient and family. Consistent with the literature, our study demonstrated a positive correlation between muscle strength and serum testosterone levels. Muscle strength appeared to align with the assigned gender rather than chromosomal sex, a finding particularly attributable to testosterone replacement therapy in individuals reared as males. Additionally, the observation that 46,XY DSD individuals reared as females had higher mean height SDS compared to all other DSD cases reared as females highlights the significance of sex chromosome origin on final height. This study also aims to address the recently debated question of whether athletes with 46,XY DSD reared as females exhibit significant differences in muscle strength and muscle mass compared to 46,XX female athletes.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine (Protocol No: TBAEK-649, Date: 03.10.2024).

Informed Consent: Written informed consent was obtained from the parents of all participating children, and age-appropriate verbal assent was obtained from the children themselves.

References

1. Lee PA, Houk CP, Ahmed SF, Hughes IA, Achermann J, Ahmed F, et al. Consensus statement on management of intersex disorders. Pediatrics. 2006;118(2):e488–500.
2. Witchel SF. Disorders of sex development. Best Pract Res Clin Obstet Gynaecol. 2018;48:90-102.
3. Koopman P, Gubbay J, Vivian N, Goodfellow P, et al. Male development of chromosomally female mice transgenic for Sry. Nature. 1991;351(6322):117–21. doi:10.1038/351117a0
4. Wilson J, Rivarola M, Mendonca B, et al. Advice on the management of ambiguous genitalia to a young endocrinologist from experienced clinicians. Semin Reprod Med. 2012;30(5):339-350.
5. Lee PA, Nordenström A, Houk CP, et al. Global disorders of sex development update since 2006: perceptions, approach and care. Horm Res Paediatr. 2016;85(3):158–180. doi:10.1159/000442975
6. Pang SY, Wallace MA, Hofman L, Thuline HC, Dorche C, Lyon IC, et al. Worldwide experience in newborn screening for classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics. 1988;81:866-874.
7. Das S, Saikia UK, Saikia KK, Sarma D, Choudhury BK, Bhuyan AK, et al. Spectrum of 46 XY disorders of sex development: a hospital-based cross-sectional study. Indian J Endocr Metab. 2020;24(4):360-365. doi:10.4103/ijem.IJEM_98_20
8. Bakula DM, Mullins AJ, Sharkey CM, Wolfe-Christensen C, Mullins LL, Wisniewski AB. Gender identity outcomes in children with disorders/differences of sex development: predictive factors. Semin Perinatol. 2017;41(4):214–217.
9. Veldhuis JD, Roemmich JN, Richmond EJ, et al. Endocrine control of body composition in infancy, childhood, and puberty. Endocr Rev. 2005;26(1):114–146. doi:10.1210/er.2003-0038
10. Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, et al. Grip strength across the life course: normative data from twelve British studies. PLoS One. 2014;9(12):e113637.
11. Curtis E, Litwic A, Cooper C, Dennison E. Determinants of muscle and bone aging. J Cell Physiol. 2015;230(11):2618–2625.
12. Orsso CE, Tibaes JRB, Oliveira CLP, et al. Low muscle mass and strength in pediatric patients: why should we care? Clin Nutr. 2019;38(5):2002–2015. doi:10.1016/j.clnu.2019.04.012
13. Stancampiano MR, Lucas-Herald AK, Russo G, Rogol AD, Ahmed SF. Testosterone therapy in adolescent boys: the need for a structured approach. Horm Res Paediatr. 2019;92(4):215–228.
14. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. Curr Opin Clin Nutr Metab Care. 2004;7(3):271–277.
15. Mauras N, Hayes V, Welch S, et al. Testosterone deficiency in young men: marked alterations in whole body protein kinetics, strength, and adiposity. J Clin Endocrinol Metab. 1998;83(6):1886–1892. doi:10.1210/jcem.83.6.4892
16. Cooke PS, Nanjappa MK, Ko C, Prins GS, Hess RA. Estrogens in male physiology. Physiol Rev. 2017;97(3):995–1043. doi:10.1152/physrev.00018.2016
17. Wiik A, Gustafsson T, Esbjörnsson M, Johansson O, Ekman M, Sundberg CJ, Jansson E. Expression of oestrogen receptor alpha and beta is higher in skeletal muscle of highly endurance-trained than of moderately active men. Acta Physiol Scand. 2005;184(2):105–112. doi:10.1111/j.1365-201X.2005.01433.x
18. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291–303.
19. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, et al. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol. 2015;7(4):280–93.
20. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford (CA): Stanford University Press; 1959. p. 50–250.
21. Aydin BK, Saka N, Bas F, et al. Frequency of ambiguous genitalia in 14,177 newborns in Turkey. J Endocr Soc. 2019;3(6):1185–1195. doi:10.1210/js.2018-00408
22. Hughes IA. Disorders of sex development: a new definition and classification. Best Pract Res Clin Endocrinol Metab. 2008;22(1):119-134.
23. Ahmed SF, Cheng A, Dovey L, et al. Phenotypic features, androgen receptor binding, and mutational analysis in 278 clinical cases reported as androgen insensitivity syndrome. J Clin Endocrinol Metab. 2000;85:658–665.
24. McCarty BM, Migeon CJ, Meyer-Bahlburg HFL, Zacur H, Wisniewski AB. Medical and psychosexual outcome in women affected by complete gonadal dysgenesis. J Pediatr Endocrinol Metab. 2006;19(7):873–878. doi:10.1515/JPEM.2006.19.7.873
25. Aycan Z, Akbuğa S, Cetinkaya E, et al. Final height of patients with classical congenital adrenal hyperplasia. Turk J Pediatr. 2009;51(6):539–544.
26. Eugster EA, Dimeglio LA, Wright JC, Freidenberg GR, Seshadri R, Pescovitz OH. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. J Pediatr. 2001;138(1):26–32. doi:10.1067/mpd.2001.110527
27. Han TS, Goswami D, Trikudanathan S, Creighton SM, Conway GS. Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. Eur J Endocrinol. 2008;159(2):179–185. doi:10.1530/EJE-08-0166
28. O'Reilly J, Ono-Moore KD, Chintapalli SV, Rutkowsky JM, Tolentino T, Lloyd KCK, Olfert IM, Adams SH. Sex differences in skeletal muscle revealed through fiber type, capillarity, and transcriptomics profiling in mice. Physiol Rep. 2021;9(18):e15031. doi:10.14814/phy2.15031
29. Welle S, Tawil R, Thornton CA. Sex-related differences in gene expression in human skeletal muscle. PLoS One. 2008;3(1):e1385. doi:10.1371/journal.pone.0001385
30. Neu CM, Rauch F, Rittweger J, Manz F, Schoenau E. Influence of puberty on muscle development at the forearm. Am J Physiol Endocrinol Metab. 2002;283(1):E103–E107. doi:10.1152/ajpendo.00445.2001
31. Jansson D, Domellöf M, Andersson H, Theos A, Lundberg E. Factors associated with muscle strength in 10-16-year-old trained male children and adolescents. BMC Sports Sci Med Rehabil. 2025;17(1):238. doi:10.1186/s13102-025-01272-6

32. Wind AE, Takken T, Helders PJ, Engelbert RH. Is grip strength a predictor for total muscle strength in healthy children, adolescents, and young adults? Eur J Pediatr. 2010;169(3):281–287. doi:10.1007/s00431-009-1010-4
33. Xu Y, Wen Z, Deng K, Li R, Yu Q, Xiao SM. Relationships of sex hormones with muscle mass and muscle strength in male adolescents at different stages of puberty. PLoS One. 2021;16(12):e0260521. doi:10.1371/journal.pone.0260521
34. Round JM, Jones DA, Honour JW, Nevill AM. Hormonal factors in the development of differences in strength between boys and girls during adolescence: a longitudinal study. Ann Hum Biol. 1999;26(1):49–62. doi:10.1080/030144699282976
Nuzzo JL, Pinto MD. Sex differences in upper- and lower-limb muscle strength in children and adolescents: a meta-analysis. Eur J Sport Sci. 2025;25(5):e12282. doi:10.1002/ejsc.12282

Table 1. Demographics, Clinical Characteristics, Hormonal Profiles, and Genetic Analysis of Study Population	
Variable	**n (%)**
Patient group (DSD) Control group Total	78 (39.8) 118 (60.2) 196 (100)
	mean ± SD
Age (DSD), mean ± SD (min–max)	12.0 ± 5.4 (1.1-17.9)
Age (control), mean ± SD (min–max)	11.1 ± 3.7 (5-17.9)
Age groups (DSD)	**n (%)**
<5 years	5 (6.4)
5-10 years	26 (33.3)
10-15 years	11 (14.1)
≥ 15 years	36 (46.2)
Total	78 (100)
Sex assignment	78 (100)
Female (DSD)	43 (55.1)
Female (XX)	18 (23.1)
Female (XY)	17 (21.8)
Female (MGD)	8 (10.2)
Male (DSD)	35 (44.9)
Male (XX)	6 (7.7)
Male (XY)	25 (32.1)
Male (MGD)	4 (5.1)
Control group	118 (100)
Female (control)	59 (50)
Male (control)	59 (50)
Presenting complaints	
Inadequate oral intake /lethargy/coma	2 (2.6)
Ambiguous genitalia	54 (69.2)
Hirsutism	3 (3.9)
Short stature	5 (6.4)
Amenorrhea	10 (12.8)
Menarche	1 (1.2)
Gynecomastia	3 (3.9)
Sex hormones (≥ 15 years)	**mean ± SD**
Male (DSD)	
Total Testosterone (µg/L)	4.0 ± 2.0
Estradiol (ng/L)	20.6 ± 12.5
Female (DSD)	
Total Testosterone (µg/L)	0.5 ± 0.6
Estradiol (ng/L)	29.0 ± 17.4
Male (Control)	
Total Testosterone (µg/L)	4.3 ± 0.7
Estradiol (ng/L)	10.4 ± 3.6
Female (Control)	
Total Testosterone (µg/L)	0.1 ± 0.1
Estradiol (ng/L)	39.6 ± 8.0
Genetic analysis	**n (%)**
CYP21A2 mutation	14 (17.8)
CYP11B1 mutation	2 (2.6)
CYP17A1 mutation	2 (2.6)
CYP19A1 mutation	2 (2.6)
Androgen receptor mutation	1 (1.3)
SRD5A2 mutation	2 (2.6)
StAR gene mutation	2 (2.6)
AMHR2 gene mutation	1 (1.3)
DHCR7 gene mutation	1 (1.3)
Mixed gonadal dysgenesis	12 (15.3)
Undefined	39 (50.0)

The results were expressed as the number of cases n (%) and as mean ± standard deviation (SD).
min: minimum; max:maximum; µg/L: micrograms per liter; ng/L: nanograms per liter.

Female (XX): Individuals with a 46,XX karyotype who were reared as female **Female (XY):** Individuals with a 46,XY karyotype who were reared as female

Female (MGD): Individuals with mixed gonadal dysgenesis who were reared as female
Female (control): Healthy females with a 46,XX karyotype
Female (DSD): Cases with disorders of sex development (DSD) who were reared as female
Male (XX): Individuals with a 46,XX karyotype who were reared as male
Male (XY): Individuals with a 46,XY karyotype who were reared as male
Male (MGD): Individuals with mixed gonadal dysgenesis who were reared as male
Male (control): Healthy males with a 46,XY karyotype
Male (DSD): Cases with disorders of sex development (DSD) who were reared as male

	Table 2. Final Anthropometric Measurements, Body Composition, and Skinfold Thickness Assessments in Cases Aged ≥15 Years According to Sex													
			Height SDS		Weight SDS		BMI SDS		Muscle Mass (%)		Fat Mass (%)		Skinfold Thickness (mm)	
		n	mean ± SDS	p	mean ± SDS	p	mean ± SDS	p	mean ± SDS	p	mean ± SDS	p	mean ± SDS	p
Sex	Female (XX)	7[e,i,j]	-2.02 ± 0.37	**<0.01**	-0.98 ± 1.07	**<0.01**	0.22 ± 1.17	0.761	71.3 ± 5.8	0.158	26.7 ± 5.8	0.118	14.0 ± 2.2	0.015
	Female (XY)	11[a,d,e,f,h,k]	1.55 ± 0.60		1.23 ± 0.80		0.50 ± 0.97		69.2 ± 4.8		28.8 ± 4.8		16.1 ± 1.2	
	Female (MGD)	8[f]	-1.42 ± 0.87		-0.85 ± 0.83		0.08 ± 1.00		72.6 ± 4.0		25.4 ± 4.0		14.6 ± 2.1	
	Female (control)	25[b,h,i]	-0.29 ± 1.2		-0.17 ± 1.37		-0.17 ± 1.21		69.4 ± 5.8		25.6 ± 5.8		13.2 ± 2.2	
	Male (XX)	6[b,c,d,k]	-2.61 ± 0.70		-1.45 ± 0.60		-0.15 ± 0.97		75.5 ± 4.3		22.7 ± 4.0		12.7 ± 2.5	
	Male (XY)	4[a,b]	-0.78 ± 0.37		-0.45 ± 0.57		0.36 ± 0.76		72.2 ± 3.3		25.7 ± 3.3		15.2 ± 2.4	
	Male (MGD)	0	-		-		-		-		-		-	
	Male (control)	16[c,g,j]	-0.24 ± 0.93		-0.10 ± 1.00		0.03 ± 1.00		72.8 ± 6.5		22.2 ± 6.5		14.4 ± 2.3	
	Total	77	-0.55 ± 1.41		-0.23 ± 1.25		0.05 ± 1.05		71.2 ± 5.6		25.1 ± 5.7		14.1 ± 2.3	

Data are presented as *mean ± standard deviation score (SDS)* or *n (%)* as appropriate.
Group comparisons were performed using the **Kruskal–Wallis test**. When significant differences were detected, pairwise comparisons were conducted using the **post-hoc Dunnett's T3 test** (a,b,c,d,e,f,g,h,i,j,k). A p value of <0.01 was considered statistically significant.
SDS: standard deviation score; BMI: body mass index; mm: millimeter.
Group Definitions:
Female (XX): 46,XX individuals reared as female;
Female (XY): 46,XY individuals reared as female;
Female (MGD): individuals with mixed gonadal dysgenesis reared as female;
Female (control): 46,XX healthy control females;
Male (XX): 46,XX individuals reared as male;
Male (XY): 46,XY individuals reared as male;
Male (MGD): individuals with mixed gonadal dysgenesis reared as male;
Male (control): 46,XY healthy control males

Table 3. Comparison of muscle strength measurements according to sex assignment and age groups										
Muscle strength										
	Age	5-10 years			10-15 years			≥15 years		
		n	mean ± SDS (newton)	p	n	mean ± SDS (newton)	p	n	mean ± SDS (newton)	p
Sex	Female (XX)	7[b,c]	7.3 ± 2.1	**<0.001**	2	12.0 ± 2.9	0.268	7[e,i]	15.5 ± 1.6	**<0.001**
	Female (XY)	0	-		4	13.8 ± 5.0		11[d,j]	19.2 ± 3.2	
	Female (MGD)	0	-		0	-		8[f]	16.1 ± 2.1	
	Female (control)	28[c]	12.7 ± 2.9		6	16.0 ± 3.5		25[g,h]	19.1 ± 4.2	
	Male (XX)	0	-		0	-		6[h]	20.0 ± 1.6	
	Male (XY)	14[a]	10.1 ± 3.0		5	15.4 ± 1.5		4[d,e,f,g]	26.5 ± 1.7	
	Male (MGD)	2	9.6 ± 2.0		0	-		0	-	
	Male (control)	22[a,b]	14.0 ± 2.7		21	17.1 ± 3.9		16[i,j]	24.3 ± 4.3	
	Total (n=188)	73			38			77		

Data are presented as *mean ± standard deviation score (SDS)* or *n (%)* as appropriate.
Group comparisons were performed using the **Kruskal–Wallis test**. When significant differences were detected, pairwise comparisons were conducted using the **post-hoc Dunnett's T3 test** (a,b,c,d,e,f,g,h,i,j,k). A p value of <0.01 was considered statistically significant.
SDS, standard deviation score; BMI, body mass index.
Group Definitions:
Female (XX): 46,XX individuals reared as female;
Female (XY): 46,XY individuals reared as female;
Female (MGD): individuals with mixed gonadal dysgenesis reared as female;
Female (control): 46,XX healthy control females;
Male (XX): 46,XX individuals reared as male;
Male (XY): 46,XY individuals reared as male;
Male (MGD): individuals with mixed gonadal dysgenesis reared as male;
Male (control): 46,XY healthy control males