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Anogenital distance in patients with Klinefelter syndrome

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Objective: Anogenital distance (AGD) is a sexually dimorphic marker of genital development and fetal androgen activity. Shortened AGD has been linked to impaired male fertility. The distinct phenotypic and reproductive characteristics associated with Klinefelter syndrome (KS) may influence AGD. This study aimed to investigate AGD measurements in men with KS and evaluate their clinical significance.
Methods: A case-control study was conducted involving 87 male participants categorized into three groups: normospermic (n=51), KS (n=18), and idiopathic non-obstructive azoospermia (iNOA; n=21). AGD was measured as the anoscrotal distance (AGD_{AS}) using a digital caliper. Physical and hormonal evaluations, semen analyses, and karyotyping were performed. Group differences were analyzed using analysis of variance with *post hoc* testing, and Pearson correlations were calculated between AGD and clinical variables.
Results: AGD measurements differed significantly between groups ($F(2,87)=15.2$, $p<0.0005$). AGD was longer in the normospermic group compared to the iNOA group ($p<0.0005$) and longer in the KS group than in the iNOA group ($p=0.015$). No significant difference was observed between normospermic and KS groups ($p=0.153$). Hormonal analyses showed lower testosterone and estradiol levels in KS patients compared to iNOA. Correlation analyses did not identify significant associations between AGD and clinical or hormonal parameters.
Conclusion: AGD in men with KS is comparable to normospermic individuals and longer than in iNOA patients. In clinical assessments, the presence of small testes in individuals with AGD measurements similar to normospermic men may raise suspicion for KS.

Keywords: Anogenital distance; Azoospermia; Infertility, male; Klinefelter syndrome

Introduction

Anogenital distance (AGD), defined as the distance between the anus and the genitals, is a sexually dimorphic trait established during fetal development, with males typically exhibiting a longer AGD than females [1-4]. AGD is considered a non-invasive biomarker of prenatal androgen exposure and has been correlated with male reproductive outcomes in both animal and human studies. Disrupted androgen signaling during critical periods of genital development has been shown to result in a shorter AGD and impaired testicular function, including abnormalities in sperm production and genital morphology [2,3,5,6].

Endocrine-disrupting chemicals (EDCs), such as phthalates, have been demonstrated to suppress fetal androgen signaling, leading to shorter AGD, reduced testicular volumes, and compromised Sertoli cell function in exposed male offspring, further supporting the association between AGD and reproductive toxicity [2,6-8]. AGD has been proposed as a component of testicular dysgenesis syndrome (TDS) and is reported to be shorter in individuals with TDS features. Specifically, AGD is reduced in patients with oligo-astheno-teratospermia [9-11], non-obstructive azoospermia [12], hypospadias and cryptorchidism [2,8,13-19], and testicular cancer [20,21].

Klinefelter syndrome (KS) is the most common chromosomal abnormality linked to non-obstructive azoospermia and is characterized by the presence of one or more additional X chromosomes [22]. Its prevalence is approximately 1 in 600 live male births (0.1% to 0.2%), and it accounts for 10% to 12% of cases among azoospermic individuals [22,23]. KS is characterized by tall stature, disproportion-

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ately long limbs, eunuchoid body habitus, and small, firm testes [22]. Furthermore, KS is associated with hypergonadotropic hypogonadism and may present with a low prevalence of hypospadias and cryptorchidism [24]. These clinical features suggest a possible association between KS and alterations in AGD.

Given AGD's established link to androgen exposure and testicular function, this study aimed to evaluate AGD in patients with KS, those with idiopathic non-obstructive azoospermia (iNOA), and normospermic controls. We also sought to determine whether AGD could serve as a distinguishing, non-invasive marker of impaired testicular development in KS.

Methods

1. Study population

This case-control, open-label study was conducted on patients presenting to our urology and andrology clinics for fertility evaluation. Eligible participants were assigned to three groups: normospermic men (defined by semen samples meeting World Health Organization 2010 criteria: sperm concentration >15 million/mL, total sperm count >39 million/mL, progressive motility >32%, and Kruger morphology >4%), non-obstructive azoospermic patients, and patients with KS (47,XXY) confirmed by chromosomal analysis. Exclusion criteria were the presence of Y chromosome microdeletions, prior orchiectomy, vasectomy, malignancy, testosterone therapy, chemotherapy or radiotherapy, orchitis, epididymitis, testicular torsion, or skeletal congenital anomalies/syndromes. Demographic and anthropometric data—including age, weight, and height—were recorded, and body mass index (BMI) was calculated. Azoospermic patients underwent chromosomal and Y chromosome genetic testing to differentiate KS from Y chromosome deletions. Only patients diagnosed with KS were included in the KS group.

2. Ethical approval

The study was approved by the local Institutional Ethical Board of Recep Tayyip Erdogan University School of Medicine (protocol number: 2019/54). Written informed consent was obtained from all participants prior to inclusion in the study.

3. Study design

All participants underwent comprehensive diagnostic evaluation, including detailed medical history, physical examination with scrotal assessment, semen analysis, sex steroid hormone profiling, scrotal Doppler ultrasound, AGD measurement, and, for azoospermic patients, karyotype analysis. Based on diagnostic findings, participants were classified as normospermic, KS, or iNOA.

4. Physical examination and AGD measurement

Physical and genital examinations were performed at the Andrology Clinic. Testes, epididymides, and bilateral ductus deferens were palpated, and assessment for varicocele was performed. The methodology for AGD measurement has been previously described [2,6]. Anoscrotal distance (AGD_{AS}) was measured in millimeters from the posterior aspect of the scrotum to the center of the anus using a stainless-steel digital caliper. The posterior scrotum was defined as the point where rugated scrotal skin meets the perineum. Measurements were obtained with participants in the lithotomy position, thighs at a 45° angle to the table. Two physicians independently performed AGD measurements, each repeating the measurement twice. Although some studies measure both AGD_{AS} and anopenile distance (anus to tip of the penis), this study measured only AGD_{AS}, which was considered a reliable and reproducible metric.

5. Hormonal analyses

Blood samples were collected from all participants between 8:00 AM and 12:00 PM following an overnight fast. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were measured using the chemiluminescent microparticle immunoassay method on an Abbott Architect i2000 analyzer (Abbott Laboratories).

6. Semen analysis

Semen samples were collected via masturbation into sterile containers after 3 to 5 days of sexual abstinence. Analysis was performed in the Andrology Unit laboratory by two experienced biologists. Samples were incubated at 37 °C for liquefaction. Semen volume was determined by gravimetric method (assuming sperm density of 1 g/mL). Sperm concentration (10^6/mL) was determined using a Neubauer Improved hemocytometer (Shanghai Qijing Biochemical Instrument Co. Ltd.), and total sperm count was calculated. Progressive motility (WHO grades A+B) and sperm morphology were assessed according to Kruger's strict criteria.

7. Statistical analysis

Descriptive statistics were calculated for anthropometric variables, stratified by normospermic, KS, and iNOA groups. Group differences in continuous variables were analyzed using analysis of variance (ANOVA) for parametric data. Hormonal values were compared between KS and iNOA groups using the independent sample *t*-test. Pearson correlation coefficients were calculated to evaluate the relationship between AGD_{AS} and other variables within each group. All statistical analyses were performed using IBM SPSS ver. 23.0 (IBM Corporation). A $p<0.05$ was considered statistically significant.

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Results

This study included 87 male participants aged 22 to 57 years, divided into three groups: normospermia (n=51), KS (n=18), and iNOA (n=21). All patients in the KS group exhibited azoospermia, except for one individual who demonstrated six to seven sperm following pellet incubation (cryptozoospermia). The demographic and clinical characteristics of the entire cohort are summarized in Table 1.

1. Statistical results

One-way ANOVA was conducted to examine differences among the three groups (normospermia, KS, and iNOA) in age, height, weight, BMI, and AGD_{AS}. The results demonstrated statistically significant differences in age ($F(2,87)=5.53$, $p=0.006$), height ($F(2,87)=5.19$, $p=0.007$), and AGD_{AS} ($F(2,87)=15.2$, $p<0.0005$) (Tables 2-4). No significant differences were observed in weight ($p=0.252$) or BMI ($p=0.214$). The distribution of AGD_{AS} measurements across groups is shown in Figure 1.

A Tukey *post hoc* test revealed the following. (1) Age: The normospermia group was significantly younger than the KS group ($p=0.002$) and the iNOA group ($p=0.026$). (2) Height: The KS group

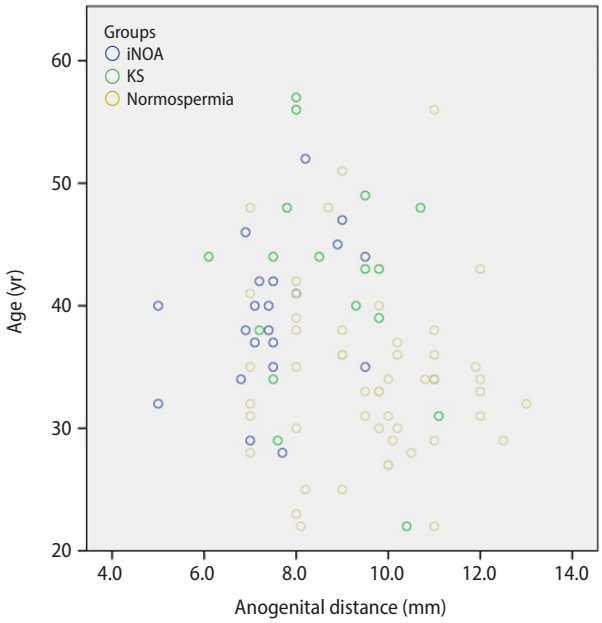

Figure 1. Distribution of anoscrotal distance (AGDAS) across Klinefelter syndrome (KS), idiopathic non-obstructive azoospermia (iNOA), and normospermia groups.

Table 1. Demographic and clinical characteristics of normospermia, KS, and iNOA groups

Characteristic	Normospermia	KS	iNOA
Age (yr)	34.1 ± 7.0 (22–56)	41.2 ± 9.05 (22–57)	39.1 ± 5.9 (28–52)
Height (cm)	173.7 ± 4.6 (160–186)	177.6 ± 8.2 (160–194)	172.3 ± 3.7 (165–180)
Weight (kg)	87.6 ± 18.3 (60–150)	83.3 ± 11.1(60–96)	85.4 ± 10.4 (60–113)
BMI (kg/m^2)	28.9 ± 5.5 (20.4–47.3)	26.6 ± 4.4 (18.8–35.2)	28.7 ± 3.3 (19.8–34.9)
AGDAS (cm)	9.6 ± 1.6 (7–13)	8.8 ± 1.4 (7.0–11.1)	7.4 ± 1.1 (5.0–9.5)
Seminal volume (mL)	3.5 (1.5–8.5)	2.1 (0.4–4.3)	3.1 (1.6–5.8)
Sperm concentration ($\times 10^6$/mL)	63.7 (16–210)	0	0
Total sperm count ($\times 10^6$)	214.2 (32 –652)	0	0
Sperm motility (%)	50.7 (39–78)	0	0
Sperm morphology (%)	6 (4–9)	0	0
Varicocele (n)	12	0	3
Undescended testis (n)	0	0	3

Values are presented as mean±standard deviation (range).
KS, Klinefelter syndrome; iNOA, idiopathic non-obstructive azoospermia; BMI, body mass index; AGDAS, anoscrotal distance.

Table 2. One-way ANOVA for age

Source	SS	df	MS	F	*p*-value
Between	827.028	2	413.514	7.901	0.001
Within	4,553.594	87	52.340		
Total	5,380.622	89			

ANOVA, analysis of variation; SS, sum of squares; df, degrees of freedom; MS, mean square.

Table 3. One-way ANOVA for height

Source	SS	df	MS	F	*p*-value
Between	299.146	2	149.573	5.189	0.007
Within	2,507.843	87	28.826		
Total	2,806.989	89			

ANOVA, analysis of variation; SS, sum of squares; df, degrees of freedom; MS, mean square.

was significantly taller than both the normospermia (p=0.026) and iNOA groups (p=0.007). (3) AGD_{AS}: AGD_{AS} was significantly longer in the normospermia group than in the iNOA group (p<0.0005) and in the KS group compared to the iNAO group (p=0.015). No significant difference in AGD_{AS} was observed between the normospermia and KS groups (p=0.153).

2. Hormonal profiles

The independent samples t-test was used to compare sex steroid hormone levels between the KS and iNOA groups. Data are presented as mean±standard deviation unless otherwise stated. There were no outliers, as assessed by a boxplot inspection. Distribution at each level of each parameter was normal according to the Shapiro-Wilk test (p>0.05), with homogeneity of variances for all variables except LH, as indicated by the Levene test (p<0.029). Testosterone and estradiol levels were significantly lower in patients with KS, while LH and FSH levels were significantly higher (Table 5).

Table 4. One-way ANOVA for anoscrotal anogenital distance

Source	SS	df	MS	F	p-value
Between	68.342	2	34.171	15.199	0.000
Within	195.598	87	2.248		
Total	263.940	89			

ANOVA, analysis of variation; SS, sum of squares; df, degrees of freedom; MS, mean square.

3. Correlation analysis

Pearson correlation analysis was conducted to assess the relationship between AGD_{AS} and multiple variables, including age, height, semen parameters, and sex steroid hormone levels, separately for each group. No significant correlations were found between AGD_{AS} and any of the tested variables in any group (Tables 6-8).

Discussion

In this study, we found that men with KS have AGD_{AS} measurements comparable to those of normospermic men and significantly longer than those of patients with iNOA. Despite markedly lower testosterone and higher FSH and LH levels in the KS group, AGD_{AS} did not correlate with serum sex steroid concentrations in any group. Furthermore, anthropometric measurements such as height, weight, and BMI were not associated with AGD_{AS}. These findings suggest that AGD_{AS} is established during fetal development and remains unaffected by postnatal hormonal status or body size, reflecting distinct etiological mechanisms between KS and iNOA.

Previous studies have consistently reported shorter AGD_{AS} in men

Table 5. Comparison of hormonal profiles between Klinefelter syndrome and azoospermic groups

	KS	iNOA	Mean difference	95% CI	t (df) [37]	p-value
Testosterone	265.1 ± 129.5 (71–534)	444.2 ± 205.8 (205–890)	–179.07	–292.9 to –65.2	–3.18	0.003
Estrone	26.7 ± 10.2 (14–54)	34.4 ± 13.0 (19–71)	–7.75	–15.45 to –0.05	–2.04	0.049
LH	17.9 ± 6.7 (9–31)	9.3 ± 3.7 (5–16)	8.55	4.88 to 12.23	5.0	< 0.0005
FSH	34.1 ± 11.9 (19–61)	20.6 ± 9.3 (8–35)	13.5	6.6 to 20.4	3.9	< 0.0005

Values are presented as mean±standard deviation (range).
KS, Klinefelter syndrome; iNOA, idiopathic non-obstructive azoospermia; CI, confidence interval; df, degrees of freedom; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Table 6. Pearson correlation coefficients between AGD_{AS} and multiple variables in the normospermia group

	AGD_{AS}	
	r	p-value
Age	–0.073	0.609
Height	0.189	0.183
Seminal volume	–0.015	0.918
Sperm concentration (10^6/mL)	0.056	0.698
Total sperm count (10^6)	0.073	0.611
Sperm motility (%)	0.119	0.404
Sperm morphology (%)	0.018	0.899

AGD_{AS}, anoscrotal distance.

Table 7. Pearson correlation coefficients between AGD_{AS} and multiple variables in the KS group

	AGD_{AS}	
	r	p-value
Age	–0.291	0.241
Height	0.235	0.348
Seminal volume	0.184	0.465
Testosterone	–0.401	0.099
Estradiol	–0.239	0.340
LH	0.198	0.431
FSH	–0.227	0.365

AGD_{AS}, anoscrotal distance; KS, Klinefelter syndrome; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

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Table 8. Pearson correlation coefficients between AGD_{AS} and multiple variables in the iNOA group

	AGD_{AS}	
	r	*p*-value
Age	0.358	0.111
Height	0.250	0.274
Seminal volume	0.217	0.345
Testosterone	–0.157	0.496
Estradiol	–0.237	0.301
LH	–0.001	0.997
FSH	–0.049	0.804

AGD_{AS}, anoscrotal distance; iNOA, idiopathic non-obstructive azoospermia; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

with poor semen quality and azoospermia, supporting its role as a marker of impaired testicular development and fertility potential [9-12]. However, comparative data across different etiologies of azoospermia are limited. In one study, iNOA patients had significantly shorter AGD_{AS} than those with obstructive azoospermia, suggesting that AGD_{AS} may help distinguish iNOA from obstructive azoospermia [12]. Unlike anopenile distance, AGD_{AS} does not correlate with circulating sex steroid hormone levels during puberty or minipuberty [25], further supporting its stability and prenatal origin [25,26]. As AGD_{AS} is determined during prenatal development, it may serve as a more reliable non-invasive marker for iNOA than for milder forms of impaired semen quality [26].

To our knowledge, this is the first study to evaluate AGD_{AS} in patients with KS. Previous research has shown that patients with cryptorchidism [2,8,13,15,19], hypospadias [16-18], azoospermia [12], or male infertility—clinical features of TDS—typically exhibit shorter AGD measurements. While KS is associated with small testes, clinical manifestations of TDS, and a more pronounced degree of hypogonadism than iNOA, AGD_{AS} in these individuals was not reduced [27,28]. This unexpected finding may have clinical implications: in males presenting with small testes but a normal-range AGD_{AS}, KS may be suspected, and further genetic evaluation (such as karyotyping) may be warranted. The longer AGD_{AS} in KS compared to iNOA suggests that fetal androgen activity during the masculinization programming window (MPW) may be preserved in KS.

Masculinization during fetal development, particularly during gestational weeks 8 to 14 (MPW), is critically dependent on androgen exposure [8,29]. AGD_{AS} is thought to reflect androgen activity during this period and remains stable despite postnatal changes in sex steroid levels, consistent with our findings [8,11,14,29-30]. Experimental studies have shown that suppression of androgen signaling after the MPW does not alter AGD, underscoring its determination during early fetal life [14].

In rodents, masculinization depends entirely on fetal testicular testosterone regulated locally. In humans, the process is more complex, involving placental human chorionic gonadotropin-driven testicular testosterone production and additional androgen synthesis via the 'backdoor pathway' from fetal organs such as the placenta, liver, and adrenal glands [14,29]. Exposure to anti-androgenic EDCs reduces AGD in male rodents and is similarly associated with shorter perineal length in human male offspring [4,6]. These findings highlight the importance of intact androgenic pathways during development, as placental dysfunction is linked to conditions such as hypospadias and cryptorchidism. Notably, infants with KS exhibit normal testosterone, FSH, and LH levels until puberty, and testicular histology appears normal during fetal and pre-pubertal stages [31-33]. These data suggest that androgenic activity during the MPW is preserved in KS, potentially explaining the normal AGD development and low incidence of hypospadias and undescended testes in these patients.

We also observed no association between AGD_{AS} and height, weight, or BMI, in line with previous studies suggesting that AGD_{AS} is independent of body size and reflects specific developmental processes established *in utero* [11,26,34]. Thus, the increased height characteristic of men with KS does not influence AGD_{AS} measurements.

This study has several limitations. The single-center, referral-based setting may have introduced selection bias. AGD_{AS} measurements were obtained at a single time point, and although standardized, some interobserver variability is possible. Additionally, the KS sample size was relatively modest, precluding subgroup analyses between mosaic and non-mosaic KS. Future research should explore whether AGD_{AS} can predict outcomes of testicular sperm extraction in non-obstructive azoospermic men. An extended AGD_{AS} may represent a favorable marker for successful sperm retrieval.

In conclusion, KS patients demonstrate AGD_{AS} measurements comparable to normospermic men and higher than those observed in iNOA patients. Thus, during clinical evaluation, the presence of small testes in individuals with an AGD_{AS} similar to normospermic men may raise clinical suspicion for KS.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: HU, MHY. Methodology: HU, MHY, GA. Formal analysis: HU, MHY, GA, EO. Data curation: MHY, EO, YK, BS. Project administration: HU, MHY. Visualization: HU, MHY, GA. Validation: HU, MHY, GA, EO. Investigation: HU, MHY, GA, EO, YK, BS. Writing-original draft: HU. Writing-review & editing: HU, MHY, GA, EO, YK, BS. Approval of final manuscript: HU, MHY, GA, EO, YK, BS.

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