Original Article

Current Urology

OPEN

Scrotal base distance: A new key genital measurement in males with hypospadias and cryptorchidism

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Abstract

Background: Anogenital distance (AGD) in both humans and animals is a known reflection of fetal endocrine effect on genital virilization and the related abnormalities, including cryptorchidism and hypospadias. However, we introduce here and investigate scrotal base distance (SBD) as a sensitive genital anthropometric biomarker in human infants with cryptorchidism and hypospadias, which are considered early manifestations of testicular dysgenesis syndrome. We aim to assess SBD in patients with cryptorchidism or hypospadias against healthy subjects.

Material and methods: Patients with hypospadias (n=61, age 17.4±6.3 months) or cryptorchidism (n=51, age 11.4±4.8 months) were enrolled for assessment of SBD, AGD, and penile length; and compared with a cohort of 102 full-term healthy boys for standard ritual circumcision by measuring age-specific standard deviation scores.

Results: Patients having hypospadias had lower mean SBD, AGD, and penile length standard deviation scores than the control group ($p < 0.01$). These values in patients with cryptorchidism were longer than mean values in boys with hypospadias ($p < 0.01$) and shorter than mean values in the control group.

Conclusions: We showed that SBD, AGD, and penile length were lower in patients with cryptorchidism or hypospadias compared to normative data measured from a control group of healthy boys for ritual circumcision. These results enforce the use of SBD as an objective anthropometric measurement and a viable biomarker to assess the effects of fetal endocrine imbalance on male external genitalia development.

Keywords: Cryptorchidism; Hypospadias; Scrotal base distance; Testicular dysgenesis syndrome

1. Introduction

It is well established now that the incidence of hypospadias, cryptorchidism, and testicular malignancy is globally increasing with a significant geographic variation that might be influenced by their etiological background.[1,2] Although there is no distinct causative delineation of this group of diseases yet, they stand under the umbrella of an entity called "testicular dysgenesis syndrome" (TDS). A hypothesis that can explain abnormal testicular development in this group of patients is fetal endocrine disruption secondary to exposure to different environmental chemicals.[3] Several animal experiments had supported this explanation.[4,5]

Anogenital distance (AGD) is sexually dimorphic in several mammals, where it is longer in males in comparison to females. AGD is also considered an objective biomarker of fetal endocrine disruption in human beings[6] and is considered as a true reflection of fetal exposure to androgens and antiandrogens. Therefore, AGD is frequently utilized in preclinical reproductive toxicology experiments.[7] Furthermore, testicular dysfunction in postpubertal males secondary to fetal exposure to endocrine disruption can be reflected by the shortening of the AGD.[8,9] It was also shown that patients with hypospadias and cryptorchidism had shortened AGD.[10,11]

Several animal experiments showed that male fetus needed suitable amounts of androgen exposure within a masculinization programming window to ensure the healthy development of the male reproductive system.[12–14] Abnormal development of both internal and external genitalia can result from suboptimal exposure to endocrine stimuli within this critical timeframe with an associated risk of developing hypospadias, undescended testes (UDT) and abnormal sperm production.[13]

We proposed and investigated the reliability of a new parameter, "scrotal base distance" (SBD), as a reflection of external genitalia development in relationship to TDS, including hypospadias and cryptorchidism, which are the most common anomaly of the genitalia in children. This measurement has been chosen because it reflects directly one of the genital structures, which is the scrotal size primarily and its internal contents, that is, the testes secondarily, hence it has a robust hypothetical justification of being a significant reflection of in utero genital development. This has not been studied previously and might add a useful noninvasive tool for the assessment of hypo-development of the external genitalia. Establishment of an association between the novel SBD and hypospadias or UDT, which are considered

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Current Urology, (2021) 15, 214–218

Received February 6, 2020; Accepted April 6, 2020.

http://dx.doi.org/10.1097/CU9.0000000000000031

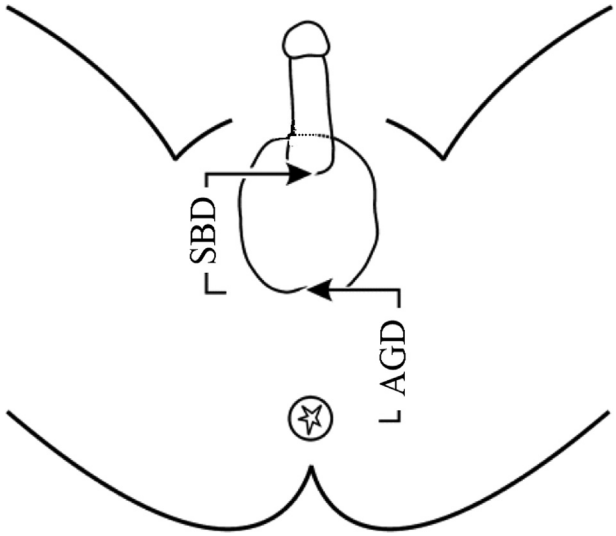

Figure 1. Illustration showing the landmark points for the measurements of anogenital distance (AGD) and scrotal base distance (SBD).

the most frequent genital abnormalities in male children, will help to support considering SBD as an objective reflection of fetal endocrine disruption and TDS. This pilot study will give us an idea about the normal range of SBD as well.

2. Methods

2.1. Study population

Males less than 2 years old with either isolated hypospadias or UDT were enrolled in this study following their assessment in the outpatient preoperative visits at the Hamad General Hospital, Doha, Qatar, between October 2016 and September 2018. Children with anogenital malformations that can preclude determination of the study landmarks, including severe penoscrotal transposition and penoscrotal webs, were excluded. Full-term boys with a birth weight of more than 2.5 kg and normal external genitalia who were admitted for standard ritual circumcision were enrolled as controls.

2.2. Measurements

The patients with either hypospadias or UDT had measurements of weight, body length, and body mass index measured during their outpatient visits and a set of SBD, AGD, and penile length measurements taken under general anesthesia just before the commencement of the surgical procedure. The standard deviation scores (SDS) of these various parameters were electronically correlated to the *z*-score values[15] as per the age of the patients. AGD was measured from the junction between the junction of the rugated hyperpigmented skin of the scrotum and the smooth perineal skin anteriorly to the center-point of the anal verge posteriorly[16] using digital calipers (Trossen Robotics, IL) (Fig. 1). SBD was measured from the anterior extent of the scrota rugae to junction between the rugated skin of the scrotum and smooth perineal skin posteriorly (Fig. 2). Stretched penile length was measured from the tip of the stretched penis to the upper surface of the pubic bone using these digital calipers.

2.3. Statistics

All SDS calculations were adjusted for gestational age at birth. AGD is associated with weight[9]; hence, weight SDS was used as a covariate in multivariable linear models (version 18.0; SPSS for Windows, IBM, Chicago, IL). The data are expressed as mean ± SD unless otherwise specified.

3. Results

Fifty-one patients with UDT (11.4 ± 4.8 months old) and 61 having hypospadias (17.4 ± 6.3 months old) were enrolled in the study (Table 1).

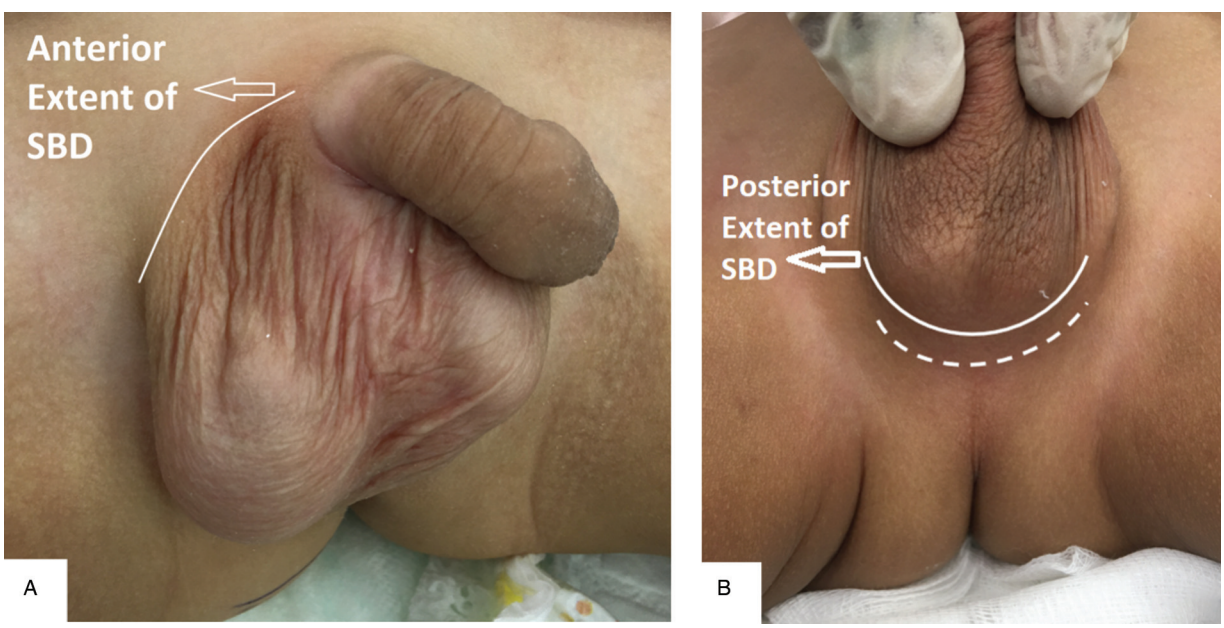

Figure 2. Photographs are showing (A) how to measure the anterior extent of the SBD in a patient with moderate penoscrotal transposition and (B) the measurement of the posterior limit of the SBD where the end of the scrotal rugae ends "continuous line" but not the skin indentation and slight hyperpigmentation "dotted line." SBD = scrotal base distance.

Table 1

Various characteristics and measurements among the studied patient population.

	UDT	Hypospadias	Controls
Number of patients, n	51	61	102
Age, mo	12.9 (11.4±4.8)	15.3 (17.4±6.3)	13.1 (15±2.6)
Birth weight, kg	2.3 (2.1±0.4)	1.9 (2.0±0.5)	2.3 (2.2±0.6)
Weight at measurement, kg	10.9 (11.3±0.8)	9.1 (8.2±1.1)	11.2 (12.1±2.1)
Height, cm	72.2 (68±3.9)	68.1 (63±8.1)	74 (70±7)
Gestational age, wk	38.9 (39±1.2)	38.1 (38±0.7)	39.8 (40±1.3)
AGD, mm	55 (52±4.2)	50.2 (49.5±2.9)	61.3 (60.2±2.5)
SBD, mm	33.4 (33.5±0.3)	30.3 (31.5±1.3)	40.2 (3.3±1.4)

AGD = anogenital distance; SBD = scrotal base distance; UDT = undescended testes.

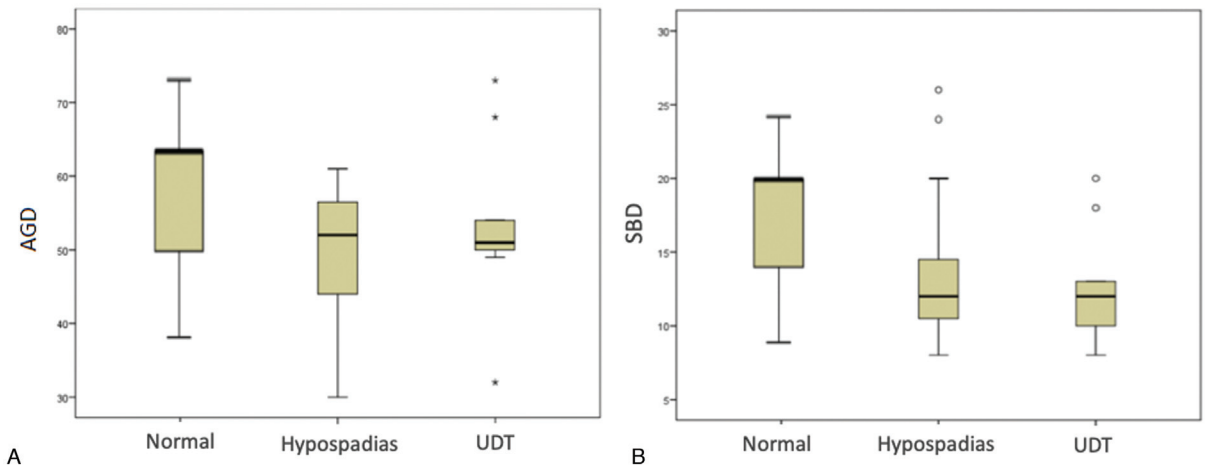

Figure 3. Different (A) AGD and (B) SBD measurements in the 3 groups. AGD = anogenital distance; SBD = scrotal base distance; UDT = undescended testes.

3.1. Undescended testis

Children with UDT had a narrower age range than those with hypospadias, with a peak at 1 year of age. Mean values for birth weight, weight at measurement, and body length SDS were similar between the UDT patients and controls. Both mean AGD SDS ($p < 0.01$) and SBD SDS ($p = 0.12$) were lower in cryptorchid boys than in controls (Fig. 3).

3.2. Hypospadias

Hypospadias was distal, mid-penile, proximal in 41, 14, and 6 boys, respectively. Boys with hypospadias had lower mean birth weight SDS ($p = 0.01$). SBD and AGD of boys with hypospadias were shorter compared with healthy boys (both $p < 0.01$) (Fig. 3 and Table 2).

3.3. Undescended testis compared to hypospadias

Patients with hypospadias had lower mean birth weight SDS than that of the patients with UDT ($p = 0.05$). Mean AGD SDS ($p = 0.05$) and SBD SDS ($p < 0.01$) values were also lower for boys with hypospadias than for UDT patients.

An overall significant correlation between AGD and SBD was observed over the study group (Fig. 4). This figure illustrates a

Table 2

Various characteristics and measurements among the different types of hypospadias cases.

	Type of hypospadias		
	Distal	Mid-penile	Proximal
Number of patients, n	41	14	6
Age, mo	14.3 (14±2)	15.3 (17.4±6.3)	13.1 (15±2.6)
Birth weight, kg	2.1 (2.0±0.5)	1.9 (2.0±0.5)	1.2 (1.2±0.6)
Weight at measurement, kg	11.9 (11.3±0.8)	9.1 (8.2±1.1)	9.2 (12.1±2.1)
Height, cm	73.2 (68±3.9)	68.1 (63±8.1)	63 (60±7)
Gestational age, wk	38.3 (38.4±1.2)	37.1 (36±0.7)	37.8 (40±1.3)
AGD, mm	53 (52±4.2)	52.2 (49.5±2.9)	40.3 (40.2±2.5)
SBD, mm	33.3 (33.5±0.3)	32.3 (31.5±1.3)	30.2 (4.3±1.4)

AGD = anogenital distance; SBD = scrotal base distance.

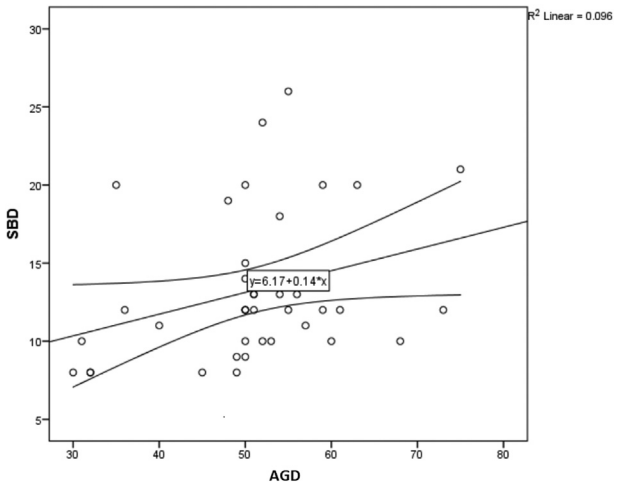

Figure 4. Correlation between SBD and AGD over the study group. AGD = anogenital distance; SBD = scrotal base distance.

reasonable correlation between AGD and SBD; higher values of SBD are matched with larger numbers of AGD and vice versa.

4. Discussion

Both hypospadias and UDT are among the most frequently occurring congenital malformations of the external genitalia in males with an incidence of about 0.5% and 3%, respectively.[17] Although their pathogenesis is yet poorly delineated, they both exist under the umbrella of the TDS[3] that has an association with exposure to endocrine disruption.[18] Moreover, reduced insulin-like factor 3[19] and increased gonadotropin levels[20] compared to healthy controls support the presence of testicular dysfunction as an underlying reason.

In our study, we defined the SBD as limited between the penoscrotal junction anteriorly and perineo-scrotal junction posteriorly. It can easily be defined and does reflect the caudal portion of the genital swelling that later develops into a scrotum.[21] The mean SBD, AGD, and penile length measurements were shorter in patients with hypospadias or UDT than in the control group. This suggests a correlation between this physical biomarker and the severity of the endocrine disruption that has been proposed to explain these pathologies.[22] Our study has several advantages: being conducted under general anesthesia that increases the reliability of the measurements as well as using digital calipers with higher accuracy. However, the translatability of this tool into clinic and measurement without general anesthesia is our aim and is potentially a viable option. Furthermore, all the measurements were taken by a single investigator to limit inter-observer discrepancy. However, we plan to quantify inter-rater variability in a future study.

We believe that current anthropometric tools used in infants (like AGD) have lower consistency in comparison to our novel SBD. AGD measurements rely upon ill-defined anatomical landmarks of soft tissues. Structures, for example, "the mid-point of the anus" or "the back of scrotum," are not unmistakably identified. Moreover, any slight extra pressure applied to the perineum or encompassing structures during measurements could change these measures (Fig. 5). However, SBD can readily be measured on easily exposed anatomical landmarks, making it potentially highly reproducible. Although penile length is an important marker of virilization, we did not look into this correlation as we believe that there will be major caveat in the methodology of measuring the stretched penile length in cases of hypospadias.

In conclusion, a new biometric parameter, "scrotal base distance" can be a sensitive and reliable reflection of external genitalia development with relationship to TDS, including hypospadias and cryptorchidism, which are the most common anomalies of the genitalia. This, however, can also be used as a noninvasive method to reflect on the severity of these diseases' measurements before puberty in forecasting later reproductive function.

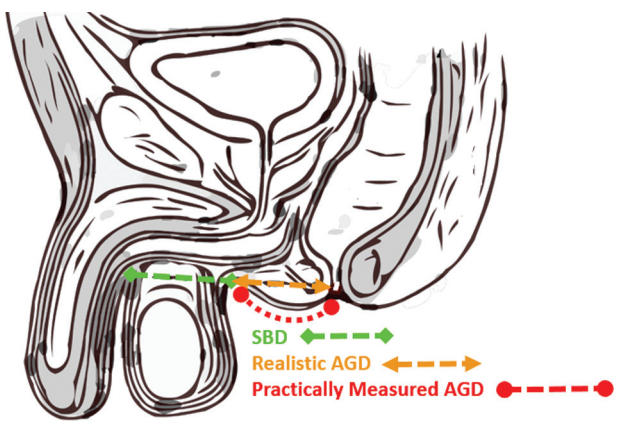

Figure 5. Limitation of AGD measurement. The practically measured AGD is longer than the realistic AGD according to the thickness of the perineal fat of every patient. The SBD has the potential to be less discrepant in patients and easier to measure than AGD. AGD = anogenital distance; SBD = scrotal base distance.

Acknowledgments

The authors are very grateful to the Qatar National Library for the financial support to report this study.

Statement of ethics

This project has been approved by the Medical Research Centre (16090/16), IRB, Hamad Medical Corporation, Doha, Qatar. All patients gave written informed consent. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Funding source

None.

Author contributions

None.

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How to cite this article: Abbas TO, Ali M. Scrotal base distance: A new key genital measurement in males with hypospadias and cryptorchidism. *Curr Urol* 2021;15(4):214–218. doi: 10.1097/CU9.0000000000000031