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Erectile dysfunction in patients undergoing multiple attempts at hypospadias repair: Etiologies and concerns

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Summary

Introduction
One-third of adult patients presenting for the repair of persistent penile defects after failing multiple hypospadias repair attempts during childhood will complain of erectile dysfunction (ED). The goal of this paper is to identify possible etiological causes of its onset.

Materials and methods
Five selection criteria were used for entrance into the study: 1) Patients had to have failed $\geq$ three prior hypospadias repair attempts. 2) Present for evaluation between 18 and 40 years of age. 3) No known congenital or medical anomaly could be present that could have predisposed to erectile dysfunction. 4) Sexual history inventory for men (SHIM-5 score) completed. 5) All patients with moderate to severe ED (SHIM scores $\leq$ 16) underwent psychological screening; individuals with good quality spontaneous or self-stimulated erections, experiencing major life events, or had documented psychological problems were excluded from the study. One hundred consecutive patients meeting these criteria were assessed. We evaluated multiple factors to discern if they were associated with the onset of ED: the initial location of the urethral meatus, if a corporoplasty was performed, the type of corporoplasty used, if the urethral plate was divided or resected, the use of a ventral corporal graft, the total number of open reparative procedures performed before referral, the number of direct visual internal urethrotomies (DVIU) performed, the length of a urethral stricture at the time of the referral and whether lichen sclerosus was present. Statistical evaluations used chi-square analysis, two-tailed t-tests, or a logistic regression model where indicated, p-values < 0.05 were considered significant.

Results
37% (37/100) of our patients complained of moderate to severe ED (SHIM score $\leq$16). Statistical analysis comparing patients with ED to those without ED (63%:63/100), revealed patients with ED were older, median age 34 yrs (range 20—40) vs 26 yrs (range 18—40) $p = 0.0212$, had undergone division of the urethral plate 70.3% (26/37) vs 47.6% (30/63), $p = 0.0276$, had placement of a ventral corporal graft, 24% (8/33) vs 1.5% (1/67), $p = 0.0003$ or had undergone repetitive DVIU's to manage urethral stricture disease, median number 4 (range 0—15) vs 0 (range 0—6), $p < 0.0001$, see table.

Conclusions
The early onset of ED in patients that failed multiple attempts at hypospadias repair in childhood is associated with advancing age, division of the urethral plate, and prior ventral corporal grafting. Especially significant is the association of ED to the use of repetitive internal urethrotomy to manage urethral stricture disease.

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Introduction

Classically, patients presenting to a transitional urologist for repair of persistent penile defects following multiple failed attempts at hypospadias repair complain of either a ectopic meatus, urethrocutaneous fistula, urethral stricture, penile curvature, erectile dysfunction (ED), or a combination of the above components [1]. Recent publications have found that approximately one-third of the patients that failed multiple attempts at hypospadias repair will complain of moderate to severe ED when evaluated between 18 and 40 years of age [2]. This paper aims to elucidate what physical factors or surgical techniques, could be associated with the early onset of ED.

Materials and Methods

We performed an institutionally approved review (IRB #13−007328) of a prospectively maintained database that contains all patients referred for complications of hypospadias from 1986 to date. Subjects contained in this evaluation gave consent to be included in the database and analysis. To be entered in the study, individuals had to meet five criteria: 1) Failed $\geq$ three attempts to complete the hypospadias repair, and all prior operative records were reviewable. 2) Present between 18 and 40 years of age. 3) No known congenital or medical anomaly could be present that could have predisposed to ED, e.g., imperforate anus, partial or complete sacral agenesis, spina bifida, Diabetes mellitus, and hypertension. 3) A sexual history inventory for men (SHIM-5 score) had to have been completed on initial visit and again at 12 months following successful repair of any penile curvature noted at the time of referral [1,3,4]. 5) In patients with moderate to severe ED (SHIM scores $\leq$ 16), further patient history regarding erectile function was ascertained. Individuals with a history of sudden onset of ED, good quality spontaneous or self-stimulated erections, undergoing major life events (e.g., treatment for active drug or alcohol addiction, divorce), or had previously documented psychiatric problems were excluded from the study [5,6]. One hundred consecutive patients meeting the above five criteria were evaluated.

The following classification for ED based on the SHIM-5 score was used; 22−25 pts - none, 17−21 pts - mild (considered normal for this study) 11−16 pts - moderate, $\leq$10 pts severe ED [3,4]. SHIM scores used for evaluation were either the original score noted at referral in patients presenting without a penile curvature or the SHIM score obtained 12 months following successful release of the curvature [1]. Patients with a SHIM score $\leq$ 16 underwent an assessment with serum testosterone. If testosterone was abnormal (<280 ng/dL), a repeat serum testosterone, along with luteinizing hormone, follicular stimulating hormone, and prolactin measurements were obtained. If persistently abnormal testosterone levels were present with normal prolactin levels, individuals were treated with testosterone. Testosterone levels were then rechecked three months after initiating replacement therapy to verified testosterone had normalized, and the SHIM-5 score reassessed [7,8]. In individuals with normal serum testosterone levels and persistent ED, a PDE5 inhibitor was prescribed [7,8]. Patients failing two different PDE5 inhibitors underwent assessment for vascular penile impairment with penile Doppler penile ultrasound (DPU) with an injection of a pharmacological stimulant to assess cavernosal vascular impairment [9,10]. Cavernosal arterial insufficiency was defined as a peak systolic velocity of <25 cm/s, venous occlusive dysfunction (VOD), was characterized as end diastolic velocity (EDV) of >5 cm/s coexisting with resistant indices (RI) of <0.75 [9,10]. Patients with a positive response to injection therapy were offered this treatment. Nonresponsive patients were offered a trial of injection therapy, a penile compression ring, or a vacuum erection device. In patients with continued ED complaints, we proposed placement of an inflatable penile prosthesis (IPP).

Individuals who had failed multiple attempts at hypospadias repair with ED (SHIM score $\leq$16) were compared to those without ED (SHIM score $\geq$ 17). We evaluated multiple factors to discern if they were associated with the onset of ED: the initial location of the urethral meatus, if a corporoplasty was performed, the type of corporoplasty used, if the urethral plate was divided or resected, the use of a ventral corporal graft, the total number of open reparative procedures performed before referral, the number of direct internal urethrotomy (DVIU) completed, the length of a urethral stricture if present and whether lichen sclerosus was present. Statistical evaluations used chi-square analysis, two-tailed t-tests, or a logistic regression model where indicated, p-values $<$ 0.05 were considered significant.

Results

One hundred consecutive patients meeting our study criteria were evaluated. A total of 37% (37/100) had ED, SHIM scores ($\leq$16), 35% (13/37) had moderate (SHIM Score 11−16), and 65% (24/37 pts) had severe ED (SHIM score $\leq$10). The majority, 62% (23/37), responded to oral pharmacologic agents. The severity of the SHIM score was correlated to the individual's ability to respond to treatment, with 92% (12/13) of the patients with moderate ED responding to either Testosterone plus PDE-5 inhibitors, 1 pt, or PDE5 inhibitors alone 12 pts. In comparison, only 46% (11/24) with severe ED responded to either Testosterone plus PDE-5 inhibitors, 2 pts, or PDE-5 inhibitors alone 9 pts, p = 0.0064. A total of three patients with a history of ED were found to have low levels of testosterone, one with moderate and two with severe ED; none resolved their ED following normalization of their testosterone levels, all responded to the combination of testosterone replacement and a PDE-5 inhibitor [7,8,11].

Failure to respond to oral pharmacologic agents occurred in 38% (14/37) of the ED patients. In these individuals, a DPU with injection was performed. The assessment revealed VOD (EDV ranging from 8 to 13 cc/sec, RI ranging from 0.53 to 0.74) in 42% (6/14) pts, and was normal in 58% (8/14). The ability to respond to injections is directly related to DPU findings with 85% (7/8) patients with normal DPU responding to cavernosal injections compared to only 16% (1/6)of the patients with venous leak, p = 0.008 [4]. In the six that failed to respond to injection therapy, three elected to proceed to the placement of an

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inflatable penile prosthesis, two elected not to proceed with treatment, and one pursued long term treatment with a vacuum erection device.

Fifty-six percent (56/100) of our patients underwent division of and or resection of the urethral plate. The urethral plate was divided for correction of ventral curvature at the time of initial hypospadias repair in 44 patients. In twenty of whom no further resections of the corpus spongiosum or reconstructed urethra occurred, 40% (8/20) had moderate to severe ED. Twenty-four patients had division of the urethral plate at the time of hypospadias repair, and then later also underwent resection of an atretic strictured urethra, 42% (10/24) complained of moderate to severe ED. Twelve patients underwent resection of an anterior urethral plate only as a step in managing severe urethral stricture disease, 66% (8/12) complained of moderate to severe ED. There is no statistical difference in the onset of ED between these three patient groups, $p = 0.2826$. It is noteworthy; however, that division of and/or resection of the anterior urethral plate was associated with the onset of ED, $p = 0.0276$.

Ten patients had ventral graft placement in childhood, no patient underwent a ventral graft placement following referral to our practice [1]. The type of grafts placed consisted of three tunica vaginalis, three small intestinal submucosal (SIS −ply not specified), and four dermal grafts. The one patient with normal erections had a tunica vaginalis graft; SHIM score 18. Ninety percent (9/10) of patients with a history of a ventral graft had ED, one with a SHIM score of 13, eight with a SHIM score $\leq$10. One third (3/9) responded to oral agents, one third (3/9) responded to injectable agents (DPU; normal in all), and one third (3/9 pts) failed injections (DPU with VOD in all), two of whom underwent placement of a penile prosthesis. In our 14 patients who failed to respond to oral pharmacologic agents, 43% (6/14) had a ventral corporal graft placement.

Statistical analysis of the two contrasting patient populations that had failed multiple attempts at hypospadias repair, those with and without ED are outlined in table one. Patients with ED were significantly older, median 34 years of age (range 20−40 years) vs. those without ED, median 26 years of age (range 18−40 years) $p = 0.0212$. Patients with ED were more likely to have undergone division or resection of the urethral plate 70% (26/37) vs 48% (30/63), $p = 0.0276$, placement of a ventral graft 24% (9/37) vs 2% (1/63), $p = 0.0003$ or had undergone repetitive DVIU, median number 4 (range 0−15) vs median 0 (range 0−6), $p < 0.0001$. See Tables 13.

Table 1 Patients failing multiple attempts at hypospadias repair in childhood: Initial findings, prior surgery performed and their associations with the onset of erectile dysfunction.

	No Erectile Dysfunction N = 63 patients	Erectile Dysfunction N = 37 patients	Total N = 100 patients	p value
Age in years				
Mean (SD)	28.7 (8.6)	32.6 (7.3)	30.1 (8.3)	**0.0212**
Median	26.0	34	30	
Q1,Q3	20.0, 39	26,40	23,40	
Range	18−40	20−40	18−40	
Initial Meatus location				
Distal 1/3	28.6% (18/63)	16.2% (6/37)	24% (24/100)	**0.1868**
Mid-shaft	12.7% (8/63)	8.1% (3/37)	11% (11/100)	
Proximal 1/3	19% (12/63)	13.5% (5/37)	17% (17/100)	
$\geq$ Penoscrotal	39.7% (25/63)	62.2% (23/37)	48% (48/100)	
Dorsal corporoplasty				
None	31.7% (20/63)	18.9% (7/37)	27% (27/100)	**0.1793**
Dorsal plication	14.3% (9/63)	5.4% (2/37)	11% (11/100)	
Nesbit	39.7% (25/63)	54.1% (20/37)	45% (45/100)	
Nesbit variant	14.3 (9/63)	21.6% (8/37)	17% (17/100)	
Division of Urethral Plate				
No	52.4% (33/63)	29.7% (11/37)	44% (44/100)	**0.0276**
Yes	47.6% (30/63)	70.3% (26/37)	56% (56/100)	
Ventral Graft				
No	98.4% (62/63)	75.7% (28/37)	90% (90/100)	**0.0003**
Yes	1.6% (1/63)	24.3% (9/37)	10% (10/100)	
Number of Open Surgeries Prior to Referral	63 pts	37 pts	100 pts	
Mean (SD)	6.2 (2.9)	6.7 (2.9)	6.4 (2.9)	**0.2314**
Median	5	6	5.0	
Number of DVIU's Performed Prior to Referral				
Mean (SD)	0.5 (1.2)	4.4 (3.6)	2.0 (3.0)	**<0.0001**
Median	0	4	0	
Q1,Q3	0,1	2, 5	0, 3	
Range	0−6	0−15	0−15	

DVIU = Direct Visual Internal Urethrotomy, SD = Standard Deviation.

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Table 2 Patients failing multiple attempts at hypospadias repair in childhood: Relationship in the performance of a DVIU for management of a urethral stricture related to the onset of erectile dysfunction and initial hypospadias meatus location.

Hypospadias Meatal Location	No ED No DVIU	No ED $\geq$ 1 DVIU	ED No DVIU	ED $\geq$ 1 DVIU
Distal 1/3rd Penile shaft	83% (15/18 pts)	17% (3/18 pts)	0% (0/6 pts)	100% (6/6 pts)
Mid-shaft	50% (4/8 pts)	50% (4/8 pts)	33% (1/3 pts)	67% (2/3 pts)
Proximal 1/3rd shaft	75% (9/12 pts)	25% (3/12 pts)	20% (1/5 pts)	80% (4/5 pts)
$\geq$ Penoscrotal	80% (20/25 pts)	20% (5/25 pts)	13% (3/23 pts)	87% (20/23 pts)
Total	76% (48/63 pts)	24% (15/63 pt)	14% (5/37)	86% (32/37 pts)

DVIU associated with onset of ED.
$p < 0.0001$.

Discussion

Erectile dysfunction following hypospadias repair: psychogenic impact

The impact and prevalence of psychogenic ED within both the general hypospadias patient population and patients who have failed multiple attempts at hypospadias repair are challenging to discern [12—14]. There is no doubt that there is an increased incidence of sexual inhibition and anxiety regarding penile appearance that is directly related to the number of operations performed, the length of time taken to complete the repair, and the patient's age at which the hypospadias repair has been completed [15,16]. It is critical to note when evaluating our data, that we used well-established screening criteria to rule out psychogenic ED, with omission of the high risk group from the study [5,6,14]. That fact being stated, we cannot rule out an element of psychogenic ED may still have existed within the community under analysis.

Relationship of the initial meatus location to ED

Multiple publications have documented that the overall incidence of ED in adults who have undergone repair of congenital hypospadias is low with almost no patients complaining of severe ED, mild to moderate ED, in general ranging from 10 to 25%, with the age range at the time of assessment of 14—35 years, mean age of 27 years [12,13,15,16]. It is also noteworthy that several prior publications have found a two to fourfold increased risk for the onset of mild to moderate ED in patients with proximal hypospadias compared to patients with distal hypospadias [12,13,15,16].

In contrast, to these published reviews, we found a significant increase in the severity of ED, with moderate to severe ED noted in up to 1/3rd of the patients who had undergone multiple failed attempts at hypospadias repair. Moreover in contrast to published reports we could not document a relationship in the initial meatus location to the onset of ED, see Table 1 ($p = 0.1868$). We postulate our contrasting findings are related to the multiple failed attempts at hypospadias repair, combined with an older patient population, median age of the patients with ED, 34 years, range 20—40. We believe that these two factors alone could have critically impacted the prevalence and severity of ED.

The effect of aging on erectile dysfunction in hypospadias cripples

Aging has a known effect on penile physiology characterized by decreased arterial blood flow, loss of penile elasticity, and progressive VOD [17—19]. Loss of penile elasticity is associated with an accumulation of extracellular matrix, a decrease in the number of corporal smooth muscle cells, and an increase in collagen fibers, in essence, corporal fibrosis. Progression of these pathologic findings eventually resulting in the onset of VOD [17—19].

The physiologic abnormalities that develop during penile aging need to be linked with the congenital physiologic corporal abnormalities found in children with hypospadias [17,18,20]. Specifically, compared to normal controls, the

Table 3 Patients failing multiple attempts at hypospadias repair in childhood: Findings at time of referral and their associations with erectile dysfunction.

	No Erectile Dysfunction N = 63 patients	Erectile Dysfunction N = 37 patients	Total N = 100 patients	p values
Length of Urethral Stricture at Presentation				
Mean (SD)	6.6 cm (4.0)	7.4 cm (3.5)	6.9 (3.8) cm	0.2058
Median	5 cm	6 cm	6.0 cm	
Q1, Q3	3.0, 10.0	5.0, 10.0	4.0.10.0	
Range	0—16 cm	2—15 cm	0.0—16 cm	
Lichen Sclerosis Present				
No	77.8% (49/63)	78.4% (29/37)	78% (78/100)	0.9442
Yes	22.2% (14/63)	21.6% (8/37)	22% (22/100)	

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corporal tissues in children with hypospadias have an inherent decrease in penile elasticity; this abnormality exists at birth and can be further altered by surgical intervention [17,20]. Notably progressive loss of corporal elasticity, e.g., corporal fibrosis, can be stimulated to occur by androgen deficiency, corporal ischemia, repetitive penile trauma, and cavernosal nerve injury [18,19].

These findings lead us to hypothesize that there is an inherently abnormal quality of hypospadias corporal spongy tissue caused by an aberration in androgen function during penile development. The pre-existing decreased elasticity of the corporal cavernosal spongy tissue can be exacerbated by repetitive surgical interventions and is intensified by the normal aging process. We hypothesize that the combination of congenital, surgical induced, and aging defects will result in the early onset of ED within patients who have failed multiple attempts at hypospadias repair [17,20]. It is noteworthy that our findings regarding the association between the patient's age and the prevalence of erectile dysfunction in patients who have failed multiple hypospadias repairs ($p = 0.0212$) is not novel and has been previously reported on by Stein and colleagues [2].

Does erectile dysfunction in hypospadias cripples with a low testosterone level resolve with androgen replacement therapy?

The relationship between hypospadias, erectile dysfunction, and low testosterone levels is murky at best; it is, however, well documented that physiologic androgen defects are associated with hypospadias and that low testosterone levels can alter corporal integrity resulting in ED [18]. We hypothesized that low testosterone values would be a common aberration found in our patients with ED. This hypothesis cannot be substantiated with low testosterone levels found in only 8% (3/37 pts) of our patients with ED. It is also noteworthy that documented correction of the low testosterone levels failed to resolve the ED within any of these individuals. These findings suggest that low levels of testosterone alone are rarely the sole cause of ED within this patient population [8,11].

Doppler penile ultrasound (DPU) evaluation for ED

Classically when DPU studies are performed in men ≤ 40 years of age with ED who are resistant to oral pharmacologic agents, one third will be found to have arteriogenic ED, VOD in approximately 15%, and normal studies in the remainder of patients [10,11]. It is believed that the majority of pharmacologically resistant patients with a normal DPU have their ED as a result of physiologic dysfunction of the corpora smooth muscle that is poorly characterized by Doppler penile ultrasonography [5,14,21,22].

It is noteworthy that in our evaluation, we found no cases of arteriogenic ED, the most common pathologic abnormality being VOD, in 42% (6/14) pts, with normal physiologic parameters found in 58% (8/14). The absence of arteriogenic ED within our patient population may be related to the methodology employed within our study. Expressly, all patients with predisposing medical illnesses that could have caused arteriogenic ED, such as diabetes or hypertension, were not admitted into the study.

Division-resection of the anterior penile urethral plate

Division and/or resection of the anterior urethral plate occurred in a total of 56% (56/100) of our patients [23,24]. Whether mobilization, division, and/or resection of the anterior urethral corpus spongiosum can lead to erectile dysfunction is controversial, with some authors stating that there is little to no anatomical basis for ED to occur following this procedure [16,25]. In contrast, others say that ED can arise secondary to surgical induced damage to either: the penile sensory nerves, corporal cavernosal tissues, or the integrity of the corpora cavernosa tunica albuginea [16,23,25,26,27]. Our data support the concept that transection/resection of the corpora spongiosum can be associated with ED, $p = 0.0276$.

Impact of DVIU on ED

ED is reported to occur in up to 10% of men undergoing a DVIU [21,22]. The incidence of ED directly related to the stricture location, risk greatest with pendulous penile urethral strictures, urethral strictures of >3 cm in length or following the performance of multiple DVIUs, all three risk factors almost invariably present in our patient population that had failed multiple hypospadias repairs and complained of ED [21,22]. Classically, when evaluating patients with new-onset of ED following a DVIU, one-third will be found to have venous leak phenomena. In the remaining two-thirds, Doppler studies are normal for vasculogenic abnormalities [21,22]. These reported findings are similar to ours, where we found 42% (6/14) pts with VOD, and normal physiologic parameters in 58% (8/14).

Regarding the repetitive use of DVIU's to manage urethral stricture disease following hypospadias repair, we would fervently recommend it be abandoned. It is our opinion that the medical literature has proven that the repetitive use of this procedure is of little benefit, may lengthen the urethral stricture, is not cost beneficial, associated with the onset of ED, and could increase the complications of a definitive stricture repair [21,28,29].

Ventral corporal grafting

We did find a significant correlation regarding ED to the use of a ventral corporal graft, $p = 0.0006$. We hypothesize that ED associated with ventral grafting arises due to a loss of smooth muscle dysfunction incited by surgical trauma, foreign body response to the graft material, or a weakening of the corpus cavernosum tunic causing venous leak phenomena. The graft's impact on ED becoming increasingly manifest with time due to the additive effects of penile aging [4,9,30]. We would like to stress that although we have documented an association of ventral corporal grafting to the onset of ED, our data cannot be used to comment on the incidence of long-term erectile dysfunction following ventral penile grafting for the correction of congenital ventral penile curvature.

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Disclaimers

The practice of any transitional or reconstructive urologist is significantly flavored by the inheritance of our patients from our pediatric urologic colleagues. We would therefore caution that a poorly delineated referral bias may have impacted any associations we found related to ED. We also acknowledge that our methodology deliberately removed patients with psychogenic induced ED or ED associated with underlying congenital anomalies or concurrent medical illnesses.

Conclusions

This paper elucidates the possible etiologies for erectile dysfunction in patients who have failed multiple attempts at hypospadias repairs. Although we cannot comment on the psychological impact of ED within this population, we believe our data can support recommendations for the surgeon to reduce the possible surgical causes for ED. Specifically, we would caution against the repetitive usage of DVIU in patients whose hypospadias repairs are complicated by urethral stricture development. We raise concerns regarding resection or division of the anterior urethral plate and the use of ventral penile grafts in the restoration of severe ventral penile curvature.

We strongly endorse the pursuit of basic science research, looking into the physiologic response of corporal smooth muscle tissue and tunic function (dysfunction) following the surgical maneuvers used in the correction of congenital ventral penile curvature. Finally, we would foster the concept that we pursue a cosmetically and functionally acceptable hypospadias repair associated with the least possible surgical induced trauma.

Conflict of interest/Funding

None.

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