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EFFECT OF URETHROPLASTY ON ANXIETY AND DEPRESSION

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Introduction and Objective: Anxiety and depression (AD) in patients with urethral stricture disease (USD) and the impact of urethroplasty on mental health has never been explored. We hypothesized that patients with USD will have higher than normal AD levels and urethroplasty would improve mental health.

Methods: Patients undergoing anterior urethroplasty were retrospectively reviewed from a multi-institutional reconstructive urology database. Pre- and postoperative evaluation of AD and overall health was recorded using the validated EQ-5D-3L Questionnaire, while sexual function was evaluated with the International Index of Erectile Function (IIEF) and Men's Sexual Health Questionnaire (MSHQ). Stricture recurrence was defined as the need for subsequent procedure.

Results: Median follow-up of the 298 that met inclusion criteria was 4.2 months. Preoperative AD was reported by 86 (29%) patients. Patients with AD reported higher rates of marijuana use, worse preoperative IIEF score (17.5 vs 19.6, p=0.01), and lower image of overall health (66 vs. 79, p=<0.001). Improvement or resolution of AD was experienced by 56% patients undergoing urethroplasty. De novo postoperative AD was reported by 10%. These men reported decreased flow rates (16 ml/sec vs 25 ml/sec; p=0.01). Clinical failure (8 patients, 2.7%) had no effect on the development, improvement, or resolution of AD.

Conclusions: 56% of patients with preoperative AD reported improvement or resolution after urethroplasty. Although new onset AD was rare, these patients had a significantly lower postoperative max flow rate, possibly representing a group with a perceived suboptimal surgical outcome. A USD specific questionnaire is needed to further elucidate the interplay between USD and AD.

INTRODUCTION

Mental health illnesses are common and treatable disorders that have a significant impact on the United States population. Approximately 20% of the U.S. adult population is affected by a mental illness each year.[1] Anxiety and depression (AD) represent two of the most pervasive mental health disorders in the United States.

In the field of reconstructive urology, the relationship between surgery and mental illness remains underexplored. Recent studies have reported the prevalence of urinary urgency and incontinence in patients with Urethral Stricture Disease (USD) and the significant impact these symptoms have on quality of life and emotional well-being.[2,3] In addition, patients undergoing urethroplasty can develop erectile dysfunction[4], which has a previously well documented bi-directional association with depression.[5,6] The prevalence of mental health disorders and the effect of urethroplasty on their natural history has, to our knowledge, previously never been published. In this study, we investigated the prevalence of baseline AD and the effect of urethroplasty on AD. We hypothesized that 1) USD would have a higher prevalence of AD compared to the national average, 2) urethroplasty will lead to resolution or improvement of AD, and 3) patients who develop denovo AD will have a poor image of overall health and decreased sexual function.

METHODS

Study population

Institutional Review Board approval was obtained. From a prospectively maintained multi-institutional database, patients who underwent single-stage anterior urethroplasty between June 2013 and May 2016 were retrospectively identified from 6 surgeons who are members of the Trauma and Urologic Reconstruction Network of Surgeons (TURNS). Patients undergoing urethroplasty are followed according to a TURNS-specific protocol, which has been previously described.[7] Patient demographics, etiology of USD, and postoperative complications were recorded. The most recent evaluation was used for postoperative analysis.

Study Outcomes*:* 298 men completed both a preoperative and postoperative assessment of AD. Mental health and personal image of overall health were evaluated using the validated EQ-5D-3L Questionnaire.[8] Regarding "Anxiety/Depression" (Item 5 of EQ-5D-3L), patients reported symptoms as "absent", "moderate", or "extreme". Patients were asked to quantify their personal image of overall health using a scale of 1-100 with 1 representing "Worst imaginable health state" and 100 indicating "Best imaginable health state". Sexual function was evaluated using the International Index of Erectile Function (IIEF)[9] and ejaculatory function with the Men's Sexual Health Questionnaire (MSHQ)[10].

Stricture Recurrence: The TURNS study protocol asks for follow-up 3-6 months after surgery and at 12 months and yearly thereafter. At follow-up visits, questionnaires are completed in addition to uroflowmetry, post-void residual, and cystoscopy. For the purposes of this study, a functional definition of success was utilized; clinical failure was defined as the need for any additional stricture related procedure.

Statistical Analysis

Patients were stratified into groups according to baseline AD: absent, moderate, or extreme. New onset AD was defined as patients who reported moderate or extreme AD postoperatively who initially reported absent AD preoperatively. Improved or resolved AD was defined as patients who initially reported moderate or extreme AD and experienced improvement to moderate AD or resolution of symptoms (absent AD). Univariate analysis was performed to evaluate potential differences in baseline characteristics for patients with the presence or absence of preoperative AD. Statistical analysis included a combination of chi-square test, Fisher's exact test, Student's t-test, or ANOVA, as appropriate. All statistical analyses and data management were performed in R using R Studio (*R Core Team 2013).* Significance was defined at the α=0.05 level; p-values were two-sided.

RESULTS

298 patients met inclusion criteria with complete information regarding AD in both pre- and postoperative questionnaires. Median follow-up time was 4.2 months. Of the 298 patients, 86 (29%) reported preoperative AD. At baseline, the group reporting preoperative AD were similar to those without AD in age and prevalent comorbidities. There were no differences between groups in underlying etiology of USD, previous treatment obtained, or preoperative urinary function parameters (PVR, average flow rate). The group reporting preoperative AD had a worse mean preoperative SHIM score (17.5 vs 19.6, p=0.01) and lower image of overall health (66 vs. 79, p=<0.001) (Table 1) compared to those without preoperative AD. Patients with preoperative AD had a higher rate of marijuana use (6 vs. 3, p=0.03). The limited number of patients reporting usage limits the power of this finding, despite statistical significance.

Out of the cohort of 298 patients, 77 and 9 patients reported preoperative moderate and extreme AD, respectively. Postoperatively, there were 52 and 9 patients reporting moderate and extreme AD, respectively. On subgroup analysis of the 86 men who reported preoperative AD, 48 (56%) improved or resolved, 35 (41%) stayed the same, and 3 (3%) experienced worsening of AD. (Figure 1) Due to the small cohort of patients reporting worsened AD, no further statistical analysis was performed on this group. Patients with improved/resolved AD reported a significantly more optimistic image of overall health on their preoperative questionnaires (72 vs. 58, p=0.001) compared to those without improvement or resolution of AD (Table 2). Both groups experienced an improvement in health image after urethroplasty. However, there was no statistically significant difference in the mean change of patient perceived overall health between any of the groups analyzed (p=0.2).

On subgroup analysis of the 212 patients who reported absent AD preoperatively, 21 patients (10%) developed de novo AD after urethroplasty (Table 3). These patients were older (54 vs. 47 years, p=0.03) and had a lower preoperative health image (64 vs. 81, p=0.002) compared to patients who remained free of AD postoperatively. Surgical intervention further increased the health image divide between groups (64 vs. 86, p<0.001). Men who developed de novo AD had a lower pre-operative MSHQ score (9.9 vs. 13.4, p=0.03), and experienced minimal improvement after surgery in comparison to their counterparts (10.3 vs. 15.7, p=0.002). A higher proportion, 28.6% vs. 16.8%, experienced a worsening of SHIM $\geq$ 3, however this

difference failed to reach statistical significance (p=0.25). New-onset AD patients were found to have a decreased postoperative max flow rate (16 ml/sec vs 25 ml/sec; p=0.01), although there was no difference in clinical failure between the depression onset groups (2 vs 5, p=0.14). There were no differences in complication rates between any of the groups.

DISCUSSION

To our knowledge, this study is the first report on the mental health of the population of patients with USD and the effect of urethroplasty on anxiety and depression. We hypothesized that 1) USD would have a higher prevalence of AD compared to the national average, 2) urethroplasty would lead to resolution or improvement of AD, and 3) patients who developed de novo AD would have a poor image of overall health and decreased sexual function. Our results confirmed our hypotheses. The prevalence of AD in our population was 28.9%, significantly higher than the combined national average of anxiety and depression, 24.8%.[11] Despite this increased prevalence, a remarkable 56% of men experienced improvement or resolution of AD after urethroplasty. Finally, our study revealed two major predictors of postoperative de novo AD: decreased sexual function and a poor patient-reported image of overall health.

The prevalence of AD, 28.9%, was higher in our population than the national average. The underlying etiology for the increased prevalence observed is currently unknown. Voiding dysfunction may play a role in these men, and could explain in part why the majority of patients undergoing urethroplasty report improvement or resolution following surgery. Alternatively, preoperative AD could be related to surgical intervention itself with improvement experienced after resolution of the psychological stressor. In men who do not experience an improvement in their mental health following urethroplasty, we hypothesize a more severe organic form of AD, unrelated to their symptoms of USD, may be present.

In our population, decreased sexual function and lower health image were associated with preoperative AD. As previously stated, there is a well-documented bidirectional relationship with mental health and erectile function. Thus, the association of preoperative depression and erectile dysfunction is not surprising. Additionally, a poor health image was a strong predictor of preoperative depression. Given the similar medical comorbidities between groups, this patient reported outcome measure could represent a poor body image that predisposes to symptoms of AD, rather than a true reflection of overall health. Regardless of etiology, patients' image of health had a pervasive effect on all outcomes, including the prediction of preoperative AD, the improvement/resolution of AD, and development of de novo AD. Alternatively, a more optimistic health image appeared to have a protective effect against de novo AD and was strongly associated with the resolution of AD after urethroplasty. With regard to clinical application, this patient reported preoperative parameter represents an important tool for identification of men at risk of baseline AD or development of postoperative AD, and an opportunity to identify patients who might benefit from treatment of AD. Our study design limited the ability to determine causative relationship between AD and health image, and determine associations with other questions of the EQ5D. Future studies with a study design dedicated to further characterization of the interplay between AD and health image, and possible associations with other facets of EQ5D (pain, mobility, self-care) are needed to improve understanding of this patient population.

Men who developed new onset AD reported decreased ejaculatory function (MSHQ) before and after surgery. Urethroplasty has previously been shown to have minimal effect on ejaculatory function[12], thus surgical intervention is not expected to improve this preoperative indicator. Sexual function appears to have less of an effect on the resolution of AD, as the men who experienced resolution of AD after surgery had similar sexual health at baseline and improvement noted after surgery when compared to men without resolution of AD. Palminteri et al. previously reported significant preoperative anxiety regarding the effect of surgery on sexual life in a population of men undergoing bulbar urethroplasty.[13] Thus, the psychological relief of maintained sexual function after surgery could represent one of the causal factors leading to resolution of AD.

Men with preoperative AD had a short-term surgical success rate of >95%. Within this cohort, 56% reported improvement/resolution of AD after surgical intervention. This remarkable rate of improvement suggests USD was a significant psychological stressor contributing to preoperative mental health, and that urethroplasty may alleviate this cause of AD. Therefore, men reporting preoperative AD may be counseled that the majority of patients experience an improvement in mental health symptoms after urethroplasty. Conversely, men who developed de novo AD experienced a higher rate of clinical failure than their counterparts (14% vs. 3%, p=0.07). In a larger population of patients, clinical failure may have achieved conventional statistical significance. The decreased postoperative max flow rate observed in this group could be representative of a suboptimal surgical outcome. Further studies with a more in-depth analysis of this patient population will help determine whether postoperative AD is due in part to a poor surgical outcome. Nonetheless, the knowledge that 10% of postoperative patients may experience new feelings of anxiety or depression, potentially as a result of a suboptimal surgical outcome, emphasizes the importance of postoperative screening by surgeons and referral for further evaluation if necessary.

The strengths of this study include a relatively large, multi-institutional population of patients and the prospective nature of data collection using validated patient-reported outcome questionnaires. The lack of pre- and postoperative data regarding selective serotonin reuptake inhibitors is a weakness and potential confounder for postoperative resolution of AD. However, we believe this weakness is likely mitigated by our decision to evaluate patients at early follow-up after urethroplasty in order to best evaluate the immediate impact of surgery on AD. The incorporation of both anxiety and depression into a single questionnaire item could be interpreted as a weakness. However, mental health disorders often overlap in their presentation and manifestation. Depression and anxiety share a number of diagnostic criteria and have a significant level of comorbidity.[14] With this knowledge in the context of a previously validated questionnaire, we determined our methods appropriate for a streamlined analysis of mental health in USD patients undergoing urethroplasty. The absence of a control group in our study design limits the ability to definitively conclude the improvement in AD observed was unique to the USD population and due exclusively to urethroplasty alone. Future studies, with inclusion of a control group (ie. observation or non-urethroplasty intervention), would further clarify whether the findings reported herein are unique to the USD population and due to urethroplasty alone.

CONCLUSION

The majority of patients with baseline AD experienced an improvement or resolution of AD after urethroplasty. Preoperative sexual dysfunction and a poor image of overall health are associated with the

presence of baseline AD as well as new onset postoperative AD. Although the development of new onset AD was rare, patients exhibited a decreased max flow, suggesting a perceived suboptimal surgical result. Identifying patients at-risk for AD who may benefit from referral for further evaluation is important. A more comprehensive USD specific patient questionnaire is needed to elucidate the interplay between USD and AD.

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Table 1. Background Characteristics of Patients with and without Preoperative Anxiety or Depression

	Total	Anxiety/Depression Present	Anxiety/Depression Absent	P value
Total Patients	298	86 (28.9%)	212 (71.1%)	
Procedure				1
EPA (n)	87	25	62	
Onlay (n)	211	61	150	
Baseline Characteristics				
Age (mean)	47	46.8	47.2	0.86
BMI (mean)	30.4	30.2	30.3	0.9
Diabetes (n)	26	10 (11.6%)	16 (7.5%)	0.37
Hypertension (n)	89	32 (37.2%)	57 (26.9%)	0.1
Hyperlipidemia (n)	67	20 (23.3%)	47 (22.2%)	0.96
Coronary Artery Disease (n)	22	7 (8.1%)	15 (7.1%)	0.94
Preop Image of Overall Health (mean)	75.8	66.2	78.9	<0.001
Urological Factors				
Prior Urethroplasty (n)	64	24 (27.9%)	40 (18.9%)	0.12
Previous Dilations (n)	134	40 (46.5%)	94 (44.3%)	0.35
Previous DVIU (n)	71	19 (22.1%)	52 (24.5%)	0.21
Preop Avg Flow Rate (mean)	5.1	5.25	5.05	0.72
Preop PVR (mean)	93.5	92.43	93.98	0.95
Preop MSHQ (mean)	12.7	11.8	13.1	0.059
Preoperative SHIM Score* (mean)	19.02	17.53	19.63	0.01
*268 patients reported preoperative SHIM score				

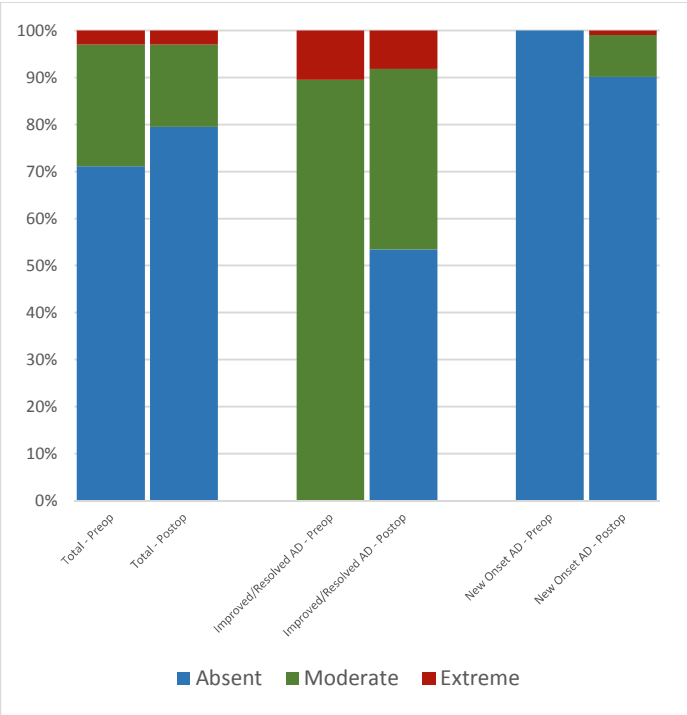
Table 2. Univariate Analysis of Factors Predicting Improvement or Resolution of Anxiety or Depression

	Patients with Resolution or Improvement of Anxiety or Depression	Patients without Improvement or Resolution of Anxiety or Depression	P value
Total Patients (N=86)	48 (55.8%)	38 (44.2%)	
Procedure			1
EPA (n)	14	11	
Onlay (n)	34	27	
Baseline Demographics			
Age (mean)	46.2	47.6	0.68
BMI (mean)	30.4	30	0.84
Preop Image of Overall Health (mean)	72.1	58.5	0.001
Postop Image of Overall Health (mean)	80.4	68.8	0.002
Urological Factors			
Prior Urethroplasty (n)	12 (25.0%)	12 (31.6%)	0.66
Previous Dilations (n)	26 (54.2%)	14 (36.8%)	0.5
Previous DVIU (n)	8 (16.7%)	11 (28.9%)	0.36
Preop Avg Flow Rate (mean)	4.95	5.74	0.49
Postop Max Flow Rate (mean)	25.5	27.5	0.6
Preop PVR (mean)	87.2	101.4	0.75
Postop PVR (mean)	54	63.8	0.74
Preop MSHQ (mean)	12.3	11.1	0.33
Postop MSHQ (mean)	13.9	12.6	0.4
Worsened SHIM (decrease $\geqq$3) (n)	7 (14.6%)	8 (21.1%)	0.66
Post-op Complications			
Urine Leak (n)	1 (2.1%)	2 (5.3%)	0.82
Total Complications (excluding leak) (n)	7 (14.6%)	1 (2.6%)	1
Clinical Failure			1
Post-op Procedure Required (n)	1 (4.2%)	0	
No Post-op Procedure Required (n)	47 (95.8%)	38 (100.0%)	

Table 3. Univariate Analysis of Factors Predicting New Onset Anxiety or Depression

	Patients with New Onset Anxiety or Depression	Patients with Anxiety or Depression Absent	P value
Total Patients (N=212)	21 (9.9%)	191 (90.1%)	
Procedure			0.86
EPA (n)	7	55	
Onlay (n)	14	136	
Baseline Demographics			
Age (mean)	53.8	46.5	0.03
BMI (mean)	29.9	30.4	0.73
Preop Image of Overall Health (mean)	64	80.5	0.003
Postop Image of Overall Health (mean)	63.5	85.5	<0.001
Urological Factors			
Prior Urethroplasty (n)	6 (28.6%)	34 (17.8%)	0.37
Previous Dilations (n)	4 (19.0%)	90 (47.1%)	0.003
Previous DVIU (n)	3 (14.3%)	49 (25.7%)	0.17
Preop Avg Flow Rate (mean)	5.7	5	0.74
Postop Max Flow Rate (mean)	16.3	24.7	0.01
Preop PVR (mean)	38.3	97.9	0.051
Postop PVR (mean)	124.2	63.8	0.3
Preop MSHQ (mean)	9.9	13.4	0.03
Postop MSHQ (mean)	10.3	15.7	0.002
Worsened SHIM (decrease $\geqq 3$) (n)	6 (28.6%)	32 (16.8%)	0.25
Post-op Complications			
Urine Leak (n)	1 (4.8%)	8 (4.2%)	1
Total Complications (excluding leak) (n)	2 (9.5%)	29 (9.9%)	1
Clinical Failure			0.14
Post-op Procedure Required (n)	2 (9.5%)	5 (2.6%)	
No Post-op Procedure Required (n)	19 (90.5%)	186 (97.4%)	

Figure 1. Distribution of patients according to EQoL 5D-3L classification of extreme, moderate, or absent anxiety or depression during the preoperative and postoperative periods. N = 298 total patients, 86 patients in improved/resolved AD subgroup analysis, and 212 patients in new onset AD subgroup analysis.



Key of Definitions for Abbreviations

AD = Anxiety and Depression
USD = Urethral Stricture Disease
TURNS = Trauma and Urologic Reconstruction Network of Surgeons
IIEF = International Index of Erectile Function
MSHQ = Men's Sexual Health Questionnaire
SHIM = Sexual Health Inventory for Men