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Understanding the Relationship between Chronic Systemic Disease and Lichen Sclerosus Urethral Strictures

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Abstract

Purpose—Lichen sclerosus is a chronic, inflammatory skin condition of the genitalia of unknown origin that accounts for nearly 10% of urethral stricture disease. In this study we determine systemic comorbidities associated with lichen sclerosus in men.

Materials and Methods—We analyzed data from 1,151 men who were enrolled in a multi-institutional prospective urethroplasty outcomes database. Individuals were grouped by stricture etiology, and baseline demographics, medical histories and patient reported outcome measures were retrospectively compared across groups.

Results—Of the 1,151 men in the database 81 (7.0%) were noted to have lichen sclerosus related urethral stricture disease. Average patient age was 46.06 ± 16.52 years, with those with lichen sclerosus being significantly older than those without lichen sclerosus (51.26 ± 13.84 vs 45.68 ± 16.64, p = 0.0011). Men with lichen sclerosus were more likely to have hypertension, hyperlipidemia and diabetes, and to use tobacco products. Controlling for age, men with lichen sclerosus related urethral stricture disease had a higher body mass index (aOR 1.089, 95% CI 1.050–1.130), and were more likely to have hypertension (aOR 2.028, 1.21–3.41) and be active tobacco users (aOR 2.0, 1.36–3.40). Mean preoperative patient reported outcome measures scores for urinary and sexual function were similar. Controlling for stricture length and location, the adjusted odds of surgical failure were higher for lichen sclerosus related urethral stricture disease (aOR 1.9, 95% CI 0.9–4.2).

Conclusions—Lichen sclerosus related urethral stricture disease is associated with chronic systemic diseases. This association may implicate a systemic inflammatory and/or autoimmune pathophysiology. A 2-hit mechanism implicating local and systemic factors for lichen sclerosus related urethral stricture disease development and progression is hypothesized.

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Keywords

lichen sclerosus et atrophicus; inflammation; autoimmune diseases; urethral stricture; reconstructive surgical procedures

Lichen sclerosus is a debilitating dermatologic condition, most commonly of the genitalia, that affects both genders of all ages.[1] Reported rates of genital LS are 70 out of 100,000, but given the sensitive location of the disease the true rate is estimated to be significantly higher.[2,3] In males the disease affects the prepuce and glans penis (also known in males as balanitis xerotica obliterans), leading to phimosis, lower urinary tract symptoms and sexual dysfunction. Importantly while many cases can be managed (although not often cured) with topical steroids or minor surgical procedures,[4] as many as 5% of cases will be associated with local malignancy (vulvar cancer in women, penile/urethral cancer in men).[5,6] More commonly, males with LS are affected by urethral stricture disease, present in nearly 30% of cases.[7,8] LSUSD can be recalcitrant to conventional treatments and often necessitates urinary diversion.[9]

The outcomes of urethral reconstruction for LSUSD are poor, with reported stricture recurrence rates ranging from 20% to 50%.[10] Potential reasons for these suboptimal success rates include a (generally) longer stricture and typical penile urethral location, both of which independently increase the risk of recurrence. In contrast, nonLS USD is usually shorter and in the bulbar urethra.[11] However, it is also possible that the factors (local/systemic) responsible for LS development are still active after urethral reconstruction. In other words, surgery for LSUSD does not cure the disease. This not only puts the surgical repair at risk, but also the areas of the nonstrictured, unoperated urethra. Ideally, surgeons would be able to repair the stricture and stop the disease process from returning. However, given our lack of understanding of the disease process, a means for this is not yet achievable.

A recent case-control study sheds light on the fact that LSUSD may simply be a local manifestation of a systemic disease process, revealing that men with LS had a higher BMI, were more likely to smoke and had higher rates of CAD.[12] They subsequently hypothesized that these associations may implicate end organ perfusion as a contributing etiology for the development of LS. Using data from the National Inpatient Sample, in a recent analysis of 514 patients with LSUSD vs nonLS USD, chronic hypertension, DM, rheumatoid arthritis/collagen vascular disease and obesity were associated with increased odds of having a LS diagnosis.[13] The purpose of the current study was to confirm these findings in a large, multi-institutional prospective database of patients with LSUSD and then to compare the systemic illnesses of the LSUSD population to men with traumatic/idiopathic USD. We hypothesized that because LSUSD is an inflammatory condition, systemic conditions associated with chronic inflammatory diseases will be present in higher rates in the cohort with LSUSD.

MATERIALS AND METHODS

We retrospectively reviewed patient demographics and stricture characteristics from a prospectively maintained urethral reconstructive, web based Filemaker® database developed for the TURNS (Trauma and Urologic Reconstructive Network of Surgeons). This group is

a multi-institutional surgical outcomes group that collects perioperative and longitudinal data on reconstructive urological disease.

Demographics (age, race), body morphology (weight, BMI, circumcision status), preoperative comorbidities, stricture characteristics (length, location) and surgical management techniques were compared between men undergoing urethral reconstruction with vs without a documented history of LSUSD. A diagnosis of LS was made by visualization of classic dermatologic characteristics, including whitish skin, tissue fusion, scarring, chronic irritation etc. Confirmatory biopsies were not performed routinely, although in 64% of cases a preoperative tissue diagnosis was obtained, most commonly to rule out malignancy. In an additional 12 cases (15%) tissue was obtained at the time of surgery showing LSUSD.

Demographics were first compared using univariate techniques. We then performed bivariate analyses controlling for age, looking for patient characteristics that were independently associated with LSUSD. We did not adjust this model for comorbidities because comorbidities were associated with LS and would mask the effect of our variable of interest (LS vs nonLS). In LS vs nonLS USD we also compared the mean preoperative and post-operative scores from patient reported outcomes measures including I-PSS, MSHQ and SHIM. Finally we compared urethroplasty outcomes by etiology, defining recurrence as the need for any unplanned secondary operation, endoscopic or open. Patients undergoing planned 2-stage repairs were evaluated only after the second stage had been performed. All analyses were performed using SAS® with statistical significance at $p < 0.05$.

RESULTS

Of the 1,151 men in the database 81 (7.0%) were noted to have LSUSD. Patients with LS were significantly older than those without LS (51.3 ± 13.8 vs 45.7 ± 16.6, $p = 0.0011$). Patient comorbidities are shown in table 1. Hypertension, hyperlipidemia,DM and tobacco use were more common in men with LSUSD than in those with nonLS USD. Controlling for age, men with LSUSD had a higher BMI (aOR 1.1, 95% CI 1.050–1.130), were more likely to have hypertension (aOR 2.028, 1.21–3.41) and to be active tobacco users (aOR 2.0, 1.36–3.40). Subset analysis of the nonLS stricture group confirmed no difference in comorbidities between patients with a history of urethral trauma vs idiopathic etiology of USD (results not shown).

Results from preoperative PROMs are shown in table 2. Mean preoperative PROM scores for urinary and sexual function were similar between the 2 groups. However, the I-PSS and I-PSS QOL remained higher postoperatively in the LS group even after eliminating those with known recurrences.

Stricture characteristics and treatments are shown in table 3. Strictures associated with LS were longer and more likely to be in the penile urethra. None of the LS strictures were managed with excisional repair. Instead nearly 40% were managed with perineal urethrostomy. Information on circumcision status was available for 49% of men and of these, 100% of LS and 84% of nonLS cases were circumcised ($p < 0.0001$). The timing of

circumcision relative to the urethral stricture operation was not recorded. At a median followup of 15.6 ± 13.2 months overall success rates were 82% for LS strictures and 92% for nonLS strictures (p=0.0066). Controlling for stricture length and location, the adjusted odds of failure were higher for LS strictures (aOR 1.9, 95% CI 0.9–4.2).

DISCUSSION

Compared to men with USD due to conditions other than LS, men with LSUSD are more likely to be obese, use tobacco and be diagnosed with diseases associated with chronic systemic inflammation such as DM and hypertension. Furthermore, the strictures associated with LS are considerably different than those caused by other etiologies. LS strictures are typically longer, are significantly more likely to occur in the penile urethra, and are far less likely to be managed with simple excision and primary anastomosis urethroplasty. Finally, success rates of urethroplasty are lower in patients with LS. Taken together, these findings might suggest that traditional local surgical approaches to LS strictures may not be adequate treatment for a disease that appears to have a systemic pathophysiology.

Etiology of Lichen Sclerosus

Pure dermatologic LS has been well studied but remains poorly understood. Similar to other dermatologic conditions, it is associated with inflammation of the skin, leading to irritation and bothersome itching and bleeding. What sets LS apart from the less aggressive lichen planus arethe disease chronicity and the resulting scar tissue that forms in the skin’s deeper dermal layer. Lichen sclerosus can permanently disfigure the affected tissue, leading to vulvar contraction in females (and the resulting dyspareunia and sexual dysfunction) and scarring of the prepuce in males, which is associated with USD in up to 30% of cases.[14]

A familial association of LS suggests a genetic predisposition to the disease.[15] An autoimmune association has also been indicated, with studies in women showing higher rates of associated autoimmune disorders (eg autoimmune thyroid disease) and higher rates of circulating autoantibodies to the basement membrane antigens, specifically extracellular matrix protein 1, which is found in the urethra.[16] It is unknown whether these antibodies are the cause or the result of the disease process. In other words, while the antibodies are clearly leading to the local inflammatory reaction, it is unknown whether this inflammation resulted de novo or as the result of repeated exposure of the extracellular matrix protein 1 antigen after urethral insults (eg urethritis, traumatic catheterization).

Association of LS with Systemic Disease Processes

This study prospectively recorded demographic and comorbidity information in a large cohort of men undergoing urethral reconstruction, and demonstrated that tobacco use, diabetes, obesity and hypertension were more common in men with LSUSD than in those without it. Similar associations have been described before in this population using a different study methodology,[12] as well as in other dermatologic disease processes such as lichen planus and psoriasis. While DM, HTN and obesity are intimately linked clinically through metabolic syndrome pathways, how these relate to LS is largely unknown. However, these conditions, as well as smoking, have strong associations with acquired

autoimmune antibodies[17-19] and chronic inflammation.[20,21] Therefore, the associations of chronic systemic disease and LS development (and presumably progression) may be causative through a systemic, proinflammatory pathway. Recent studies have also suggested that the association of DM, HTN and obesity with LS may implicate a common vascular and/or perfusion pathway of systemic disease in LSUSD.[12,13]

A 2-hit hypothesis for disease development and progression is presented in the figure, and is based on the current study findings and the best basic and clinical research conducted to date. The hypothesis suggests that a predisposition to inflammation/autoimmunity (genetic or acquired) and a physical local insult and/or local infection are required for the development of LSUSD. Admittedly we present no direct evidence that the LS cohort experienced a physical local insult as a cause of their USD. Still, given the high prevalence of DM, HTN, smoking and obesity in the United States population and the relatively low prevalence of LSUSD, we suspect that some physical local insult is necessary.

The clinical implications of such a 2-hit hypothesis might be that lifestyle modification and/or medical treatment of these associated conditions, likely combined with nonsurgical urethral treatments that target the inflammatory pathway, could reverse and/or stop the progression of LS. We suggest that the 2-hit hypothesis may serve as a guide for future interventional trials. However, an alternative hypothesis for the development of LSUSD might simply be that LS alone is the cause of non-traumatic strictures and no second hit (trauma) is required for the development of LS in the setting of systemic disease.

The physical insult necessary for LS development/progression might be explained by the Koebner phenomenon, which is a well described dermatologic process that explains the migration of skin lesions (classically psoriasis) along the lines of trauma.[22] Serum levels of inflammatory growth factors, including nerve growth factor and basic fibroblast growth factor, have been found in much higher levels in patients susceptible to the Koebner phenomenon, suggesting that this process, while local, is dependent on systemic factors to occur. The Koebner phenomenon has been hypothesized as a way that LS lesions may migrate down the urethra, as described by Barbagli et al.[23]

Obesity and LS

Obesity likely contributes to the presence of LS by synergistic means. Obesity is a pro-inflammatory state and as previously mentioned it is associated with an increase in the presence of autoantibodies.[12,18] In addition, obesity, especially truncal obesity, can lead to an acquired buried penis, which increases the risk of trauma and infection of the glans penis and meatus.[24] It was conventional wisdom that childhood circumcision was protective of LS (and penile cancer), but this does not appear to be true in the modern male.[25] Our study revealed that 100% of men undergoing definitive surgery for LSUSD were circumcised at presentation to our reconstruction clinic. While it is possible that many of these men had adult circumcision specifically for LS (unfortunately the data do not include timing of circumcision), anecdotally we know that LS developed in many previously circumcised men only after the development of an acquired buried penis. This implies that the buried penis creates a situation that results in some type of local physical insult. One theory is that although the inner layer of the prepuce is akin to mucosa and functions well in a moist

environment, the penile shaft skin that forms the neo-prepuce in the buried penis is stratified squamous epithelium that is susceptible to urinary dermatitis, resulting in the “second hit.” The obesity epidemic in the United States will likely lead to an increase in these types of strictures in the coming decades and, thus, our ability to treat and prevent these devastating conditions will become increasingly important.

Implications for LSUSD Treatment

The mainstays of treatment for LS are high dose topical steroids (eg clobetasol), which have been shown to stop the progression of LS in men and women and even cure the disease in some cases.[2,4,26] In male LSUSD it appears that earlier intervention (surgical and medical) may stop the proximal progression of the urethral disease.[4] However, steroids largely affect only local inflammation, and while this may be effective for external and local disease such as LS of the glans penis or urethral meatus, it is difficult to achieve a steroidal effect in the more proximal urethra. Thus, urologists must resort to surgical means. While often successful in maintaining a functional urethra, these procedures are exceedingly complex and generally require tissue transfer of buccal mucosa.[7,9] The long-term results of surgically treated LSUSD are poor relative to nonLS USD,[9,27] perhaps implicating a disease process that continues to affect the urethra after urethroplasty.

If local and systemic insults are indeed necessary for LS migration, this may suggest the need for systemic therapies in patients with LSUSD that treat the stricture, or more likely, prevent recurrences after definitive endoscopic or open surgical options. Only a few studies have evaluated the use of systemic medication for the treatment of lichen sclerosus,[28-30] but none have specifically addressed its use in LSUSD. If our 2-hit hypothesis is correct, this might imply that established local treatments, combined with systemic therapies that target inflammation and the immune system (ie targeting both “hits”), may be necessary to achieve optimal outcomes in LSUSD.

Limitations

This study is limited by the lack of serological and pathological data on men with LSUSD, preventing us from testing our immunologic and inflammatory hypotheses as previously stated. This study also lacks a control group, ie a group of men without USD, by which to compare the prevalence of these comorbid conditions in the general population. Finally, the second hit of our hypothesis, urethral trauma/infection, cannot be proven in this cohort given the inability to accurately document remote urethra/penile trauma. However, despite these limitations, this study represents the largest to date to our knowledge to focus on the associations of chronic disease and USD. In addition, we present a 2-hit hypothesis for the development of LSUSD that may serve as a template for the future investigation of preventive and nonsurgical interventions for LSUSD that focus on the treatment of comorbid chronic inflammatory conditions.

CONCLUSIONS

In this study we analyzed the demographic and surgical data of more than 1,000 patients with consecutive anterior USD, and found that rates of chronic disease associated with

systemic inflammation, including hypertension, diabetes and obesity,are significantly higher in men with LSUSD than in those with nonLS USD. Combined with lower surgical success rates in patients with LS, these findings suggest that novel and potentially systemic approaches to managing and treating LSUSD are needed.

Abbreviations and Acronyms

BMI	body mass index
CAD	coronary artery disease
DM	diabetes mellitus
HTN	hypertension
I-PSS	International Prostate Symptom Score
LS	lichen sclerosus
LSUSD	lichen sclerosus related urethral stricture disease
MSHQ	Male Sexual Health Questionnaire
PROM	patient reported outcome measure
QOL	quality of life
SHIM	Sexual Health Inventory for Men
USD	urethral stricture disease

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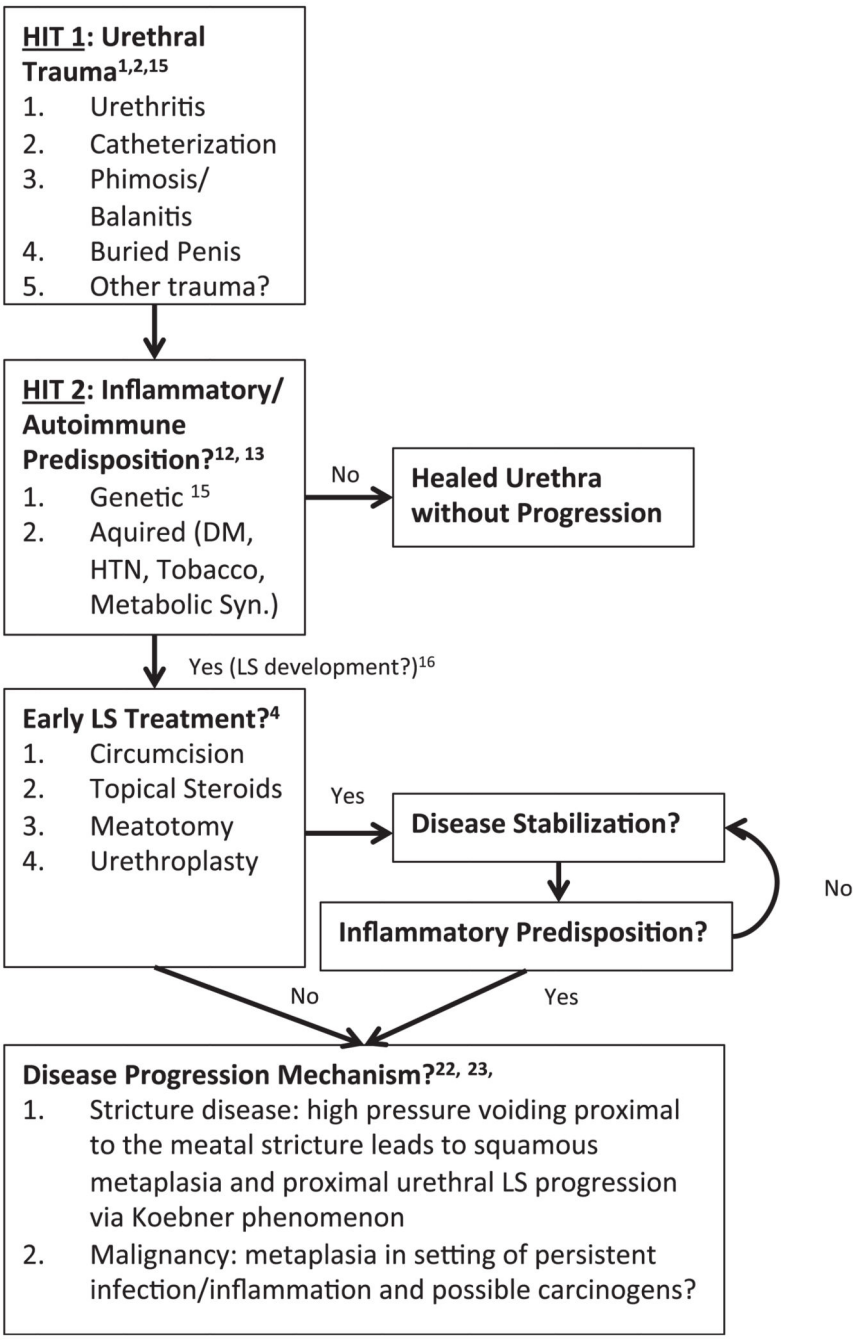

Hypothesized 2-hit mechanism for LSUSD. Question marks (?) indicate area in need of further study. *Syn*, syndrome.

Table 1
Frequency and age adjusted odds ratios of systemic conditions

	LS	NonLS	p Value*	Age Adjusted OR (95% CI)	p Value†
No. HTN (%)	43 (53)	325 (30)	<0.0001	2.028 (1.206, 3.411)	0.0007
No. hyperlipidemia (%)	25 (31)	197 (18)	0.0062	1.455 (0.838, 2.527)	0.1805
No. DM (%)	17 (21)	128 (12)	0.0183	1.705 (0.948, 3.067)	0.0746
No. CAD (%)	11 (14)	91 (9)	0.1212	1.047 (0.487, 2.248)	0.9067
No. peripheral vascular disease (%)	2 (2)	15 (1)	0.4426	1.458 (0.320, 6.647)	0.6263
No. active tobacco use (%)	30 (35)	282 (26)	0.037	1.982 (1.345, 3.398)	0.0391
Mean ± SD pack yr history	22.31 ± 20.84	13.07 ± 17.1	0.0303	1.018 (0.994, 1.044)	0.1443
Mean ± SD kg/m^2 BMI	34.59 ± 7.92	29.55 ± 6.65	<0.0001	1.089 (1.050, 1.130)	<0.0001

*Determined using the chi-square test for categorical variables and the unpaired t-test for continuous variables.

†Bivariate logistic regression adjusting for age.

Table 2
Comparison of preoperative and postoperative PROM scores

	LS (45)	NonLS (547)	p Value*
Mean ± SD Preop PROM			
SHIM	18.20 ± 16.00	18.59 ± 7.21	0.7248
MSHQ	11.41 ± 5.96	12.01 ± 5.71	0.5382
I-PSS	18.29 ± 10.00	18.38 ± 8.72	0.9560
I-PSS QOL	4.34 ± 1.26	4.26 ± 1.38	0.7414
Mean ± SD Postop PROM (excluding recurrences)			
SHIM	19.44 ± 6.96	18.53 ± 7.40	0.5332
MSHQ	14.79 ± 5.97	14.45 ± 5.94	0.7676
I-PSS	8.63 ± 8.08	5.67 ± 6.40	0.0392
I-PSS QOL	2.32 ± 1.49	1.42 ± 1.53	0.0079

* Unpaired t-test $p < 0.05$ statistically significant.

Table 3

Comparison of stricture characteristics and type of urethroplasty performed for LS vs nonLS strictures

	LS	NonLS	p Value
No. location (%):			
Penile only	33 (41)	145 (14)	<0.0001*
Bulbar only	5 (6)	736 (69)	
Penile + bulbar	36 (44)	95 (9)	
Other	7 (9)	94 (9)	
Mean ± SD stricture length	8.41 ± 5.30	3.36 ± 2.68	<0.0001†
No. repair type (%):			
Excisional	0 (0)	438 (41)	<0.0001*
Substitutional	23 (28)	394 (37)	
Perineal urethrostomy	32 (40)	52 (5)	
Other/combined	26 (34)	186 (17)	

*Chi-square analysis (testing equal distribution).

†Unpaired t-test.