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Authors

Blaschko, Sarah D
Gaither, Thomas W
Alwaal, Amjad
et al.

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Lichen Sclerosus Comorbidities and Complications from a National Sample of Patients Treated with Urethroplasty

Sarah D. Blaschko,* Thomas W. Gaither,* Amjad Alwaal, Catherine R. Harris, Charles E. McCulloch, Jack W. McAninch and Benjamin N. Breyer†

From the Department of Urology (SDB, TWG, AA, CRH, JWM, BNB), and the Department of Epidemiology and Biostatistics (CEM), University of California, San Francisco, San Francisco, California

Abstract

Introduction: We characterize comorbidities and inpatient complications of patients with lichen sclerosus who underwent urethroplasty from a large national patient data source.

Methods: We queried the Nationwide Inpatient Sample for patients who underwent urethroplasty between 2000 and 2010. We compared demographics, comorbidities, complications, length of hospital stay and hospital charges for patients with and without the diagnosis of lichen sclerosus.

Results: An estimated 13,700 urethroplasties were performed in the United States during the study period. Patients with lichen sclerosus comprised an estimated 3.8% of the urethroplasty population. The majority of patients with urethral stricture with lichen sclerosus were Caucasian (84%) and older, with 63% age 45 or older. Chronic hypertension, diabetes mellitus, rheumatoid arthritis/collagen vascular disease and obesity were associated with increased odds of having a lichen sclerosus diagnosis. The central East Coast (7.2%) and the Pacific Northwest (6.3%) had the highest percentage of patients treated with urethroplasty with lichen sclerosus. Patients with lichen sclerosus had longer hospital stays than those without lichen sclerosus (3.5 vs 2.6 days, $p < 0.0001$). Patients with lichen sclerosus had more complications and hospital charges than those without lichen sclerosus but these differences did not reach statistical significance.

Conclusions: A higher percentage of patients with lichen sclerosus had comorbidities, increased complications and longer hospital stays compared to patients treated with urethroplasty without lichen sclerosus. Our findings demonstrate the increased complexity that providers face when treating men with lichen sclerosus related urethral stricture disease.

Key Words: lichen sclerosus et atrophicus, urethral stricture, postoperative complications, comorbidity

Abbreviations and Acronyms

LS = lichen sclerosus

NIS = Nationwide Inpatient Sample

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* Equal study contribution.

† Correspondence: University of California, San Francisco, Department of Urology, San Francisco General Hospital, 1001 Potrero Ave., Suite 3A20, San Francisco, California 94117 (telephone: 415-206-8805; FAX: 415-206-5153; *e-mail address:* bbreyer@urology.ucsf.edu).

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Urethroplasty is a cost-effective procedure used to treat male stricture disease.[1] Although uncommon, urethroplasty failure adversely impacts patient quality of life and leads to more complex repeat repairs with higher complication rates.[2] Urethral stricture length, prior urethroplasty failure, failed endoscopic treatments and lichen sclerosus have been associated with urethroplasty failure.[3]

LS is an understudied chronic immunological disorder of unknown etiology. Patients with urethral stricture with LS often require multistage repairs, and have a risk of stricture recurrence due to disease progression and often extensive involvement of the penile urethra and beyond.[4–6] While high quality case series examining urethroplasty in patients with LS exist,[4,6,7] the current literature is limited due to small sample sizes and specific geographical populations.

We compare demographics, comorbidities and inpatient complications after urethroplasty in patients with vs without LS from a national database representing inpatient admissions. We also explore the geographic prevalence of LS to determine if distribution patterns emerge. We hypothesize that patients with LS will have different comorbidities and higher rates of urethroplasty complications than those without a LS diagnosis.

Materials and Methods

Study Population

The Nationwide Inpatient Sample is the largest all-payer inpatient care data set designed to approximate a 20% sample of hospital admissions in the United States.[1] The NIS includes information from approximately 1,000 hospitals and 7 million hospital admissions each year.[8]

We included male patients 18 years old or older for evaluation if they had an ICD-9 code for urethral stricture and an ICD-9 procedural code for urethroplasty from 2000 to 2010. ICD-9 codes for urethral stricture include 598, 598.00, 598.01, 598.1, 598.2, 598.8 and 598.9, and ICD-9 procedural codes for urethroplasty are 58.4, 58.42, 58.44, 58.45, 58.46, 58.47 and 58.49. We grouped patients as those having ICD-9 codes for LS, 701.0, 607.81, 697.8 and 697.7, and those without a diagnosis of LS.

Predictor and Outcome Variables

From the NIS we abstracted patient age, race, comorbidities and geographic distribution of LS diagnosis. We grouped patients as having 0, 1, 2, or 3 or more NIS defined comorbidities.[8] We evaluated the prevalence of LS diagnosis by geographic region, as defined by the Department of Health and Human Services and used previously.[9] We evaluated hospital bed size and the volume of urethroplasties performed yearly at each hospital (1, 2 to 9, or 10 or more). We analyzed inpatient complications, length of hospital stay and total hospital charges by LS status.

Statistics

We compared categorical outcome variables for patients with and without the diagnosis of LS using chi-square tests, and continuous outcomes with Student t-tests. We used age adjusted logistic regression to examine the association of demographics and comorbidities with the outcome of LS diagnosis. We tested for a geographic trend from east to west using a variable coded as 1 for eastern regions (1-3), 2 for Midwest regions (4-5), 3 for central regions (6-8) and 4 for western regions (9-10).[9] Statistical analysis was performed using SAS® (version 9.2) and all analyses accommodated the complex sample survey design of the NIS. All p values less than 0.05 were considered significant.

Results

Study Population and Comorbid Risk Factors of LS

From 2000 to 2010 an estimated 13,700 inpatient urethroplasties were performed in the United States (95% CI 9,507−17,894). Of this urethroplasty population an estimated 513 patients (95% CI 201−825), or 3.8%, had LS. Patients with LS were older (years ± SD 50.4 ± 1.3) than those without a LS diagnosis (45.3 ± 0.4, p <0.0001). African-American patients had a lower odds of LS diagnosis than Caucasian patients (OR 0.28, 95% CI 0.10−0.78, table 1).

Patients treated with urethroplasty with a diagnosis of LS had a higher prevalence of all studied comorbid diseases (table 2). After adjusting for age, chronic hypertension, diabetes without chronic complications, rheumatoid arthritis/collagen vascular disease and obesity, all increased the odds of having a LS diagnosis. Patients with LS were more likely to have 1, 2, or 3 or more comorbidities

Table 1.
Multivariable analysis of patient demographics as risk factors for LS

	% Pts with LS (513)	% Pts without LS (13,187)	OR (95% CI)	p Value
Age:				
18−45	37.0	50.0	1.00 (ref)	
46−65	47.9	36.7	1.76 (1.12−2.74)	0.013
Greater than 65	15.2	13.5	1.51 (0.85−2.68)	0.16
Race:				
Caucasian	84.3	69.7	1.00 (ref)	
African-American	5.1	15.0	0.28 (0.10−0.78)	0.015
Other	10.6	15.2	0.57 (0.27−1.24)	0.15

Table 2.
Multivariable analysis of patient comorbidities as risk factors for LS

LS Status	Pts (%)	OR (95% CI)*		p Value
	Comorbidity			
Chronic hypertension:				
No	24.5	1.00	(ref)	
Yes	45.3	2.21	(1.17−4.18)	0.014
Diabetes without chronic complications:				
No	8.9	1.00	(ref)	
Yes	23.8	2.71	(1.79−4.11)	<0.0001
Rheumatoid arthritis/collagen vascular disease:				
No	0.5	1.00	(ref)	
Yes	21.1	47.95	(20.51−112.10)	<0.0001
Obesity:				
No	6.2	1.00	(ref)	
Yes	19.6	3.59	(1.96−6.59)	<0.0001
Chronic pulmonary disease:				
No	6.8	1.00	(ref)	
Yes	8.3	1.15	(0.69−1.89)	0.60
Depression:				
No	3.0	1.00	(ref)	
Yes	5.7	2.01	(0.95−4.29)	0.069
Peripheral vascular disease:				
No	0.6	1.00	(ref)	
Yes	2.8	3.33	(0.91−12.22)	0.070
Alcohol abuse:				
No	1.3	1.00	(ref)	
Yes	2.1	1.51	(0.32−7.16)	0.60
Drug abuse:				
No	1.0	1.00	(ref)	
Yes	2.1	2.20	(0.45−9.77)	0.32
Coagulopathy:				
No	0.5	1.00	(ref)	
Yes	1.9	3.55	(0.88−14.31)	0.075
Diabetes with chronic complications:				
No	0.8	1.00	(ref)	
Yes	0.9	0.85	(0.10−7.70)	0.88
	No. comorbidities			
0:				
No	60.3			
Yes	27.8	1.00	(ref)	
1:				
No	24.6			
Yes	26.9	2.38	(1.38−4.08)	0.002
2:				
No	11.1			
Yes	33.7	6.58	(3.40−12.72)	<0.0001
3+:				
No	4.0			
Yes	11.7	6.35	(2.03−19.91)	0.002

*Odds ratios adjusted for age.

compared to those without LS. Only 27.8% of patients with LS had zero comorbidities compared with 60.3% of patients who underwent urethroplasty without LS.

Complications during Urethroplasty Admission

A higher estimated percentage of patients with LS had inpatient complications (7.5%) than those without LS (6.5%, p=0.17) but these differences were not statistically significant. Patients with LS had a higher trend of percentage of complications in the genitourinary (3.9% v 2.8%), cardiovascular (2.0% vs 0.7%) and wound (1.6% vs 1.1%) complication categories than those without LS (p=0.72, p=0.22 and p=0.71, respectively).

Hospital Characteristics, Length of Stay and Charges

Hospital bed size was not associated with the prevalence of LS (data not shown). LS cases were more likely to be reported by higher volume urethroplasty hospitals. Compared to hospitals that performed 1 urethroplasty per year, those that performed 10 or more had increased odds of having patients with a LS diagnosis (OR 2.76, 95% CI 1.37−5.59, p=0.005).

Average length of stay and average hospital charges were higher for patients with vs without LS. Patients with LS stayed in the hospital longer than those without LS undergoing urethroplasty (3.51 vs 2.58 days, p <0.0001). Hospital charges were estimated to be approximately $10,000 higher for patients with vs without LS but this difference was not statistically significant (p=0.22).

Geography

The region with the highest percentage of patients who underwent urethroplasty with LS was the central East Coast (7.2% ± 0.9%), and the regions with the lowest percentage were New York/New Jersey (0%) and the North Central region (0%). In other regions the percentage of patients treated with urethroplasty with LS was Pacific Northwest 6.3% ± 2.8%, Midwest 3.9% ±0.7%, Southeast 3.7% ± 0.8%, Northeast 3.5% ± 1.8%, Southwest 3.0% ± 1.3%, Mid-Central 1.5% ± 0.6% and South Central 1.3% ± 0.7%. There was no statistically significant trend of prevalence across the United States from east to west (p=0.30, see figure).

Discussion

Our study highlights the relationship between a LS diagnosis, and associated comorbidities, immediate urethroplasty complications, hospital characteristics and geographic prevalence. A higher percentage of patients with LS had comorbidities, a longer hospital stay and higher hospital charges compared to patients treated with urethroplasty without LS. There was a trend toward increased complications in patients with LS. Our findings demonstrate the increased complexity that providers face when treating men with LS related urethral stricture disease.

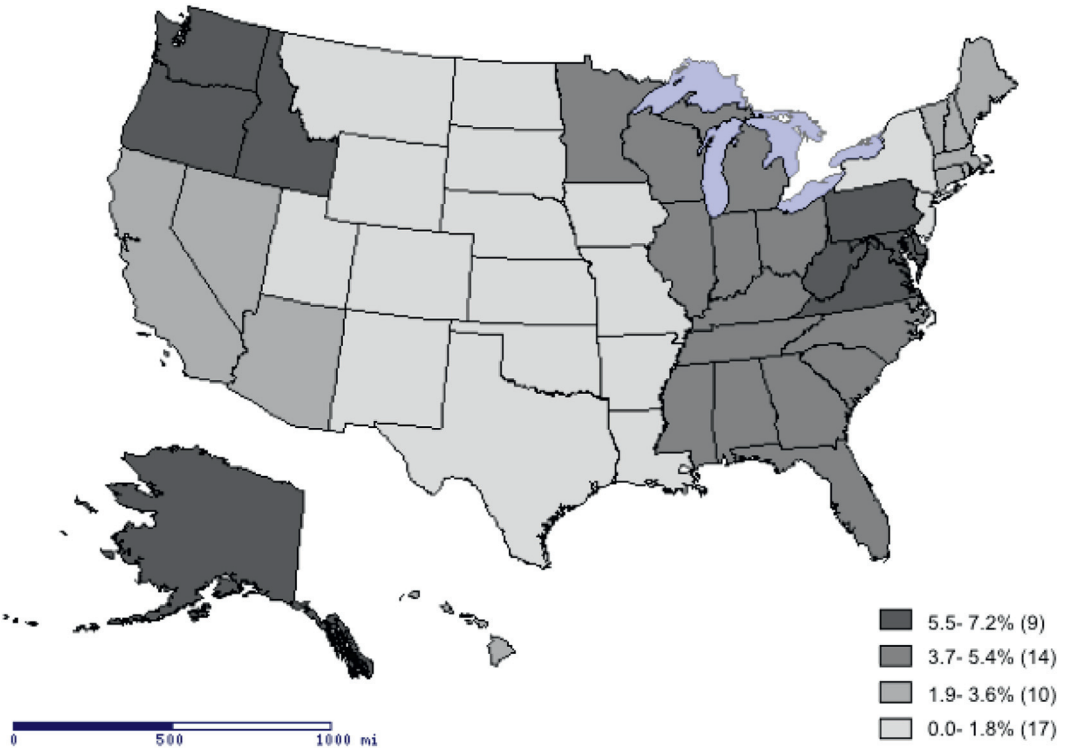

Figure. Geographic distribution of patients with LS treated with urethroplasty. Map shaded by percentage of patients with urethroplasty with LS (number of states in each shaded region). Trend for significance from east to west p=0.30.

Several demographic and comorbid conditions were associated with LS in the NIS cohort. Patients with LS were older and mostly Caucasian. These findings are similar to those of Nelson and Peterson, who identified 604 men with LS from across the United States.[9] They found that LS was more likely among men age 40 to 60 and Caucasian.

Comorbidities with a significant association with LS include chronic hypertension, diabetes mellitus, rheumatoid arthritis/collagen vascular disease and obesity. Diabetes mellitus has a known association with LS.[10,11] In addition to diabetes mellitus, Hofer et al showed LS in men was associated with obesity as well as coronary artery disease and tobacco use.[10] These findings suggest that direct microvascular compromise or metabolic disturbances may contribute to the development of LS.

Pathophysiology

Although the pathophysiology of LS is unknown, there is increasing evidence to support an autoimmune mechanism.[12] LS is more prevalent in women, as is common for most autoimmune disorders.[13] Many patients with LS have comorbid autoimmune disease or a family history of autoimmune disease.[12] IgG autoantibodies targeting extracellular matrix 1 protein have been found to be significantly higher in men and women with anogenital LS than controls.[14,15] Genetic factors have also been linked to LS.[12] In a large cohort of women with LS 12% had a family history of LS.[16] It has also been suggested that trauma or chronic irritation might have a role in the pathogenesis as genital jewelry, trauma and instrumentation have been associated with LS.[17] No strong link has been found between LS and an infectious agent.[12]

A higher percentage of patients with LS have rheumatoid arthritis and collagen vascular disease (21.1%) than those who underwent urethroplasty without LS (0.5%). Although the connection between LS and autoimmune disorders is well documented,[12] to our knowledge this is the first study showing an association between LS in men with stricture disease, and rheumatoid arthritis and collagen vascular disease. The large 95% CI associated with the rheumatoid arthritis and collagen vascular disease odds ratio reflects the small number of patients with the diagnosis in our cohort. This large increased risk may reflect a true association or may be due to a coding issue in the NIS data set such as coders considering LS a collagen vascular disease. Nevertheless, additional research into the association between rheumatoid arthritis and collagen vascular disease may be warranted. Lastly, a previous study showed that a family history of diabetes mellitus, vitiligo, alopecia areata and thyroid diseases were independent risk factors for LS in men.[11] These autoimmune diseases were not available in the NIS data set.

A higher percentage of patients with LS had a complication (7.5%) than those without LS (6.5%) in the immediate postoperative period, but this was not statistically significant. The trend toward increased complications in patients with LS may be due to increased comorbidities, average older age or more complicated urethroplasty procedures. Overall patients with LS presenting for urethroplasty require complex care, as seen with the increased comorbidities, complications, referral to high volume centers, length of stay and hospital charges. Future studies are warranted to understand factors important to patients (ie voiding location, number of procedures, costs etc) so that physicians can best counsel these patients about complication risks and outcomes.

Similar to other epidemiological reports we found a high prevalence of LS in the Northwest.[9] Although the Northwest had the second highest prevalence of LS (6.3% ±2.8%) in our study, we did not find a significant geographic trend from east to west (p=0.30). Whether the higher prevalence in the Pacific Northwest is significant to the etiology of LS is not known but may support the autoimmune etiology of LS. Less sunlight induced vitamin D may have a role in the development of autoimmune disease as many autoimmune diseases are more prevalent in Northern latitudes.[18] These findings may also be explained by genetic factors in these locations, such as the founder effect. LS has been shown to be familial in approximately 12% of cases[16] and has been associated with antigens of the human leukocyte antigen system.[19]

Although we found a correlation between obesity and LS, the geographic distribution of patients with LS did not match the general geographic distribution of obesity in the United States.[20] However, the widespread prevalence of obesity in the United States may limit a correlation between geographic obesity and LS distribution.

Limitations

Our study approach has limitations. These data represent a single hospital admission and long-term outcomes are not available. Long-term complications of urethroplasty in patients with LS are not captured in this data set and patients who underwent outpatient urethroplasty procedures are not included in the study. We rely on ICD-9 coding, which does not account for complexity of the urethral stricture or urethroplasty and cannot verify LS diagnosis with pathology. However, we think it is unlikely that patients with no obvious LS or no LS pathology diagnosis would be misclassified as having LS.

Furthermore, some cases of LS may not be coded for LS or may be miscoded and, therefore, are not included in our query. There may be geographic differences in ICD-9 coding that account for the geographic differences noted in LS cases. Cases of subclinical LS may also have been missed, likely causing bias toward the null.[21] It is possible that men seeking urethroplasty may have more of a disease burden and, thus, have more comorbidities and procedural complications than those with LS not presenting for urethroplasty.

Conclusions

A higher percentage of patients with LS had comorbidities, increased complications, longer hospital stays and greater hospital charges compared to patients treated with urethroplasty without LS. Our findings demonstrate the increased complexity that providers face when treating men with LS related urethral stricture disease.

References

1. Rourke KF and Jordan GH: Primary urethral re-construction: the cost minimized approach to the bulbous urethral stricture. J Urol 2005; **173:** 1206.
2. Blaschko SD, McAninch JW, Myers JB et al: Repeat urethroplasty after failed urethral reconstruction: outcome analysis of 130 patients. J Urol 2012; **188:** 2260.
3. Breyer BN, McAninch JW, Whitson JM et al: Multivariate analysis of risk factors for long-term urethroplasty outcome. J Urol 2010; **183:** 613.
4. Levine LA, Strom KH and Lux MM: Buccal mucosa graft urethroplasty for anterior urethral stricture repair: evaluation of the impact of stricture location and lichen sclerosus on surgical outcome. J Urol 2007; **178:** 2011.
5. Pugliese JM, Morey AF and Peterson AC: Lichen sclerosus: review of literature and current recommendations for management. J Urol 2007; **178:** 2268.
6. Barbagli G, Mirri F, Gallucci M et al: Histological evidence of urethral involvement in male patients with genital lichen sclerosus: a preliminary report. J Urol 2011; **185:** 2171.
7. Peterson AC, Palminteri E, Lazzeri M et al: Heroic measures may not always be justified in extensive urethral stricture due to lichen sclerosus (balanitis xerotica obliterans). Urology 2004; **64:** 565.
8. HCUP: Overview of the National (Nationwide) Inpatient Sample. Rockville, Maryland: Agency for Healthcare Research and Quality 2011. Available at www.hcup-us.ahrq.gov/nisoverview.jsp.
9. Nelson DM and Peterson AC: Lichen sclerosus: epidemiological distribution in an equal access health care system. J Urol 2011; **185:** 522.
10. Hofer MD, Meeks JJ, Mehdiratta N et al: Lichen sclerosus in men is associated with elevated body mass index, diabetes mellitus, coronary artery disease, and smoking. World J Urol 2014; **32:** 105.

11. Bjekic M, Sipetic S and Marinkovic J: Risk factors for genital lichen sclerosus in men. Br J Dermatol 2011; **164:** 325.

12. Fistarol SK and Itin PH: Diagnosis and treatment of lichen sclerosus: an update. Am J Clin Dermatol 2013; **14:** 27.

13. Meyrick Thomas RH, Ridley CM, McGibbon DH et al: Lichen sclerosus et atrophicus and autoimmunity—a study of 350 women. Br J Dermatol 1988; **118:** 41.

14. Oyama N, Chan I, Neill SM et al: Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. Lancet 2003; **362:** 118.

15. Edmonds EV, Oyama N, Chan I et al: Extracellular matrix protein 1 autoantibodies in male genital lichen sclerosus. Br J Dermatol 2011; **165:** 218.

16. Sherman V, McPherson T, Baldo M et al: The high rate of familial lichen sclerosus suggests a genetic contribution: an observational cohort study. J Eur Acad Dermatol Venereol 2010; **24:** 1031.

17. Bunker CB: Male genital lichen sclerosus and tacrolimus. Br J Dermatol 2007; **157:** 1079.

18. Staples JA, Ponsonby AL, Lim LL et al: Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. Environ Health Perspect 2003; **111:** 518.

19. Marren P, Jell J, Charnock FM et al: The association between lichen sclerosus and antigens of the HLA system. Br J Dermatol 1995; **132:** 197.

20. Le A, Judd SE, Allison DB et al: The geographic distribution of obesity in the US and the potential regional differences in misreporting of obesity. Obesity (Silver Spring) 2014; **22:** 300.

21. Liu JS, Walker K, Stein D et al: Lichen sclerosus and isolated bulbar urethral stricture disease. J Urol 2014; **192:** 775.

Editorial Commentary

We know precious little about lichen sclerosus. We do know that it can "cause" urethral strictures—or is it just associated with urethral stricture? (No one knows.) LS strictures most often start at the meatus and progress proximally, requiring glanular and penile urethroplasties, which tend to be more technically difficult than bulbar urethroplasty, and surely have higher complication and failure rates. LS also often causes long and difficult panurethral strictures. Now from this study we know that LS significantly increases hospital stay after urethroplasty, surely reflecting this tendency toward its well-known association with 1) long, 2) panurethral and 3) penile strictures, all complicating factors in urethroplasty. This series also showed higher complications and hospital charges in patients with LS (although not statistically significant). It's clear that LS is a bad actor when complicating urethroplasty. It will be up to us to further characterize the negative effects of LS on urethroplasty outcomes and work toward fixes to overcome them.

Richard A. Santucci
Detroit Medical Center
The Center for Urologic Reconstruction™
Michigan State College of Medicine
Detroit, Michigan