Lichen sclerosus is associated with genital herpes simplex virus infection in a case-control study of 6,150 participants

Dear Editor,

Lichen sclerosus is a chronic inflammatory mucocutaneous disorder characterised by white atrophic plaques with erosions, painful ulcers, and permanent scar tissue, primarily affecting the anogenital region. Infectious organisms, including *Borrelia burgdorferi*, human papillomavirus, and hepatitis C virus, have been proposed as potential causes; however, evidence is conflicting and limited to small studies and case reports.[1] Therefore, we aimed to assess lichen sclerosus associations with preceding infectious diagnoses using a large national database.

A nested case-control study using the National Institutes of Health *All of Us* database was conducted, with participants ≥18 years with lichen sclerosus diagnosis matched with controls 1:4 by age, sex at birth, and self-reported race/ethnicity. The *All of Us* programme is a national database dedicated to the enrollment of a diverse cohort of patients in the United States.[2] We calculated multivariate logistic odds ratios for lichen sclerosus and preceding infectious diagnoses with matching by age, sex, and race/ethnicity. Infectious associations were diagnosed prior to lichen sclerosus diagnosis.

The analysis included 1,230 lichen sclerosus participants and 4,920 controls [Table 1]. Mean age of lichen sclerosus participants and controls was 68.5 years ($P = 0.99$). Among lichen sclerosus participants, 1109 participants (90.2%) were female and 941 participants (76.5%) were white, similar to controls ($P = 1$). Lichen sclerosus participants had higher odds of genital herpes simplex virus infection (OR = 3.79; 95% CI 2.64–5.45; $P < 0.001$) than controls [Table 2]. This difference persisted after stratifying the matched cohort by female lichen sclerosus participants (OR = 3.50; 95% CI 2.40–5.10; $P < 0.001$) and male lichen sclerosus participants (OR = 14.45; 95% CI 1.32–157.89; $P = 0.02$). Lichen sclerosus was not associated with chlamydia, Epstein Barr virus, gonorrhoea, hepatitis C, human immunodeficiency virus, human papillomavirus, Lyme, molluscum contagiosum, or syphilis.

Table 1: Demographic characteristics of lichen sclerosus and control participants in the *All of Us* database matched by age and self-reported race/ethnicity

	Controls (n = 4920)	Lichen sclerosus (n = 1230)	*P* value
Age, mean (SD)	68.5 (12.4)	68.5 (12.4)	0.99
Sex at birth (%)			
Male	348 (7.1%)	87 (7.1%)	1
Female	4436 (90.2%)	1109 (90.2%)	
Other	136 (2.8%)	34 (2.8%)	
Self-reported race/ethnicity count (%)			
White	3764 (76.5%)	941 (76.5%)	1
Hispanic or Latino	460 (9.4%)	115 (9.4%)	
African American	344 (7.0%)	86 (7.0%)	
Asian or Other*	352 (7.2%)	88 (7.2%)	

*Asian and Other were matched separately but were combined in this table to comply with the *All of Us* database policy prohibiting the display of any participant count less than 20. SD: standard deviation

To our knowledge, this is the first case-control study to assess for multiple potential lichen sclerosus infectious associations. Lichen sclerosus participants had an almost four-fold risk of prior genital herpes simplex virus diagnosis, which is a striking finding. This association may be potentially related to chronic trauma from recurrent genital herpes episodes, similar to other lichen sclerosus associations related to irritation and trauma, including urinary incontinence, multiparous status, and high body mass index. Additionally, occlusion, scratching, friction, surgical procedures, and injections may act as a Koebner phenomenon leading to lichen sclerosus development. Alternatively, our finding may be related to the initial misdiagnosis of lichen sclerosus as genital herpes due to overlapping clinical features, including erosions, painful ulcers, dysuria, dyspareunia, and pruritus.

Concomitant genital herpes simplex virus infection and lichen sclerosus have been rarely reported in the literature and poses a therapeutic challenge, since topical corticosteroids may reactivate genital herpes and delay herpes simplex virus

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Table 2: Infectious associations with lichen sclerosus in the *All of Us* database in a combined dataset of male and female patients

Associations (n, %)	Controls (n = 4920)	Lichen sclerosus (n = 1230)	OR (95% CI)	*P* value
Genital herpes simplex virus	66 (1.3%)	59 (4.8%)	3.79 (2.64–5.45)	< **0.001**
Chlamydia	≤20*	≤20*	1.76 (0.54–5.67)	0.34
Epstein Barr virus	≤20*	≤20*	3.58 (0.48–26.35)	0.21
Gonorrhoea	≤20*	≤20*	0.58 (0.10–3.2)	0.54
Hepatitis C	117 (2.4%)	≤20*	0.67 (0.40–1.1)	0.12
Human immunodeficiency virus	49 (1.0%)	≤20*	0.52 (0.22–1.21)	0.13
Human papilloma virus	91 (1.8%)	31 (2.5%)	1.21 (0.79–1.86)	0.36
Lyme	72 (1.5%)	≤20*	1.04 (0.62–1.73)	0.86
Molluscum contagiosum	≤20*	≤20*	0.71 (0.08–6.26)	0.76
Syphilis	22 (0.4%)	≤20*	0.88 (0.32–2.40)	0.81

Infectious diagnoses preceded lichen sclerosus diagnosis. Statistical analyses were conducted using R (version 4.40).
Goodness-of-fit test: Chi-squared = .1304, degrees of freedom (df) = 0, p = 0.
Boldface indicates significance ($P < 0.05$).
*Prevalence values are concealed in order to comply with the *All of Us* database policy prohibiting the display of any participant count less than 20.
OR: Odds ratio, CI: Confidence interval.

lesion healing.[3] In one case report of a lichen sclerosus patient with genital herpes simplex virus infection, treatment with systemic acyclovir 400 mg three times daily for seven days and topical clobetasol propionate 0.05% cream for ten days, followed by acyclovir 400 mg twice daily and clobetasol propionate 0.05% cream for one month resulted in lesion resolution after 30 days.[3]

We did not find lichen sclerosus association with human papillomavirus. The role of human papillomavirus in lichen sclerosus pathogenesis is controversial, with one study of 88 male lichen sclerosus cases reporting the presence of human papillomavirus deoxyribonucleic acid in biopsy specimens of 37.5% of cases, most commonly human papillomavirus type 16.[4] In another case series of 329 patients, there was no correlation between male genital lichen sclerosus and human papillomavirus.[5]

We did not find lichen sclerosus association with Lyme disease. In a prospective study[6] of 61 lichen sclerosus cases and 118 controls, *Borrelia* species was detected in 63% of lichen sclerosus specimens and was absent in all negative controls. In contrast, borrelial deoxyribonucleic acid was not detected in any serological studies or skin biopsy specimens in a prospective study[7] of eight lichen sclerosus patients.

We did not find lichen sclerosus association with hepatitis C. A lipidomic and metabolomic analysis demonstrated that vulvar lichen sclerosus correlated with an abnormal antiviral response due to the presence of hepatitis C virus poly-U/UC sequences.[8] In contrast, in a prospective study[9] of 61 male patients with genital lichen sclerosus, no patients had hepatitis C virus seropositivity.

Limitations include lack of histopathologic confirmation of lichen sclerosus and herpes simplex virus confirmation via viral culture, potential disease misclassification, inability to measure time between herpes simplex virus infection and lichen sclerosus diagnosis, exclusion of pediatric participants in the database, and small male sample size. Strengths include an overall large sample size and a case-control design.

In conclusion, we demonstrate a novel finding of lichen sclerosus association with genital herpes simplex virus infection. Our data argues against previously hypothesised infectious associations with human papillomavirus, Lyme disease, and hepatitis C. Studies utilising histopathology and viral culture for diagnostic confirmation are needed to corroborate these findings. We recommend that dermatologists elicit history of genital herpes simplex virus infection and perform a complete examination of the anogenital area for herpes simplex virus infection and lichen sclerosus. Consideration of antiviral suppressive therapy in patients with recurrent herpes simplex virus infection might prevent worsening of lichen sclerosus.

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