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CLINICAL REPORT

A prospective pilot study to assess for histologic changes on vulvar biopsies in postmenopausal women with lichen sclerosus treated with fractionated CO_2 laser therapy

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Abstract

Objectives: To investigate the histologic characteristics of vulvar tissues before and after completion of fractionated carbon dioxide (CO_2) laser therapy (FxCO2) for vulvar lichen sclerosus (LS). The secondary objective was to assess subjective improvement in symptoms via the Skindex-16 questionnaire.

Methods: This prospective single-arm study was conducted from April 2021 to August 2022 at one academic medical center. Ten postmenopausal women with biopsy-proven LS planning FxCO2 laser treatment were enrolled. Exclusion criteria included prior transvaginal mesh for prolapse, topical corticosteroid use within 8 weeks, prior pelvic radiation, malignancy, active genital infection, or pregnancy. The vulvovaginal SmartXide2-V2-LR laser system fractionated CO_2 laser (DEKA) was utilized to treat visually affected areas of vulvar and perianal LS with a single pass. Subjects underwent three treatments 4–6 weeks apart. Subjects completed the Skindex-16 questionnaire and had vulvar biopsy at baseline and at 4 weeks after completion of fractionated CO_2 laser therapy. Blinded histologic slides were scored by one dermatopathologist (Michael A. Cardis) rating from 1 to 5 the degree of dermal sclerosis, inflammation, and epidermal atrophy. Change scores were calculated as the difference between pre- and post-treatment scores for each subject.

Results: The 10 subjects enrolled had a mean age of 61 and most were white, privately insured, and had a college/graduate-level education. Post-fractionated CO_2 laser treatment vulvar biopsies showed significant improvement in sclerosis and epidermal atrophy compared with pretreatment baseline biopsy specimens ($p < 0.05$) with no statistically significant change found in inflammation score. Skindex-16 and FSFI scores showed a trend towards improvement ($p > 0.05$ for both). A statistically significant correlation was found between change in sclerosis and Skindex-16 symptoms scores with an average change of 21.4 units in Skindex-16 symptoms score for every one-point change in histologic sclerosis score ($p = 0.03$).

Conclusions: In postmenopausal women with vulvar LS undergoing fractionated CO_2 laser, symptomatic improvements correlated with histologic change in degree of sclerosis on vulvar biopsy. These results demonstrate FxCO2 laser therapy as a promising option for the treatment of LS and suggest that further studies should assess degree of sclerosis on histopathology.

KEYWORDS

carbon dioxide laser, histology, laser therapy, lichen sclerosus, vulvar biopsy, vulvar diseases, vulvar lichen sclerosus

INTRODUCTION

Lichen sclerosus (LS) is a chronic and debilitating skin condition with a bimodal peak incidence in premenarchal and postmenopausal females with prevalence ranging between 1 in 60 to 1 in 100 in the general population,[1] or at least 1 in 70 in women seeking general OBGYN care.[2] Hypothesized to be of autoimmune origin,[3] LS causes significant changes in the architecture and appearance of the vulvar tissues leading to symptoms of discomfort, itching, vulvar pain, voiding dysfunction, and dyspareunia, and carries an increased risk of developing vulvar squamous cell carcinoma with up to 11% of women with LS affected.[1,4] Women with LS often suffer silently, enduring symptoms of significant physical discomfort, feelings of isolation, and resultant loss of intimate relationships for many years before obtaining a correct diagnosis and appropriate therapy.[5,6]

Traditional first-line therapy for managing vulvovaginal LS consists of an initial course of ultrapotent topical corticosteroid (TCS) therapy followed by intermittent use of TCS for maintenance therapy to control symptoms.[5] Compliance to TCS is variable during maintenance periods, leading to higher rates of relapse and complications, such as the development of squamous cell carcinoma.[7,8] Fractionated carbon dioxide (CO_2) laser therapy has been proposed as a novel treatment modality for patients suffering from LS. Initial studies have indicated an improvement in clinical symptoms and visible changes in vulvar skin color, elasticity, and vascularity.[9,10] A recent randomized trial performed by our group suggests that fractionated CO_2 laser resulted in greater symptomatic improvement on the Skindex-29 questionnaire when compared to TCS and more participants in the laser group rated their symptoms as being "better or much better" on the PGI-I (patient global impression of improvement) compared to participants on TCS.[11] Notably, participants in the laser treatment group were highly compliant in attending all three treatment sessions over the 6 months.

While these results are promising, a better understanding of the histologic changes in vulvar architecture in response to fractionated CO_2 laser is necessary to determine the safety and efficacy of the therapy. A recent prospective, sham-controlled study found an improvement in histopathology scale scores from baseline in women with active vulvar LS treated with fractionated CO_2 laser therapy; however, these results were not statistically significant. The group's sham treatment, which utilized some laser energy, and small sample size may have affected their results.[12] We aimed to conduct a prospective pilot study to compare the changes in histologic characteristics of vulvar tissues before and after treatment with fractionated CO_2 laser therapy in postmenopausal women with LS. Secondary objectives included assessing subjective improvement in vulvovaginal symptoms, sexual function, and lower urinary tract symptoms using validated questionnaires.

MATERIALS AND METHODS

This prospective single-arm study of 10 postmenopausal women with vulvar LS was conducted from April 2021 to August 2022 at one academic medical center within the Division of Female Pelvic Medicine and Reconstructive Surgery. Institutional Review Board approval was obtained before the start of subject enrollment.

The aim of the study was to examine histologic changes in the skin architecture resulting from fractionated CO_2 laser therapy treatment. The primary objective was to compare characteristics of vulvar biopsy specimens before and after treatment with fractionated CO_2 laser in postmenopausal women with LS. We hypothesized that fractionated CO_2 laser therapy would result in a return to more normal histologic appearance of the vulvar tissues, such as epidermal thickening, neovascularization, and restoration of rete pegs. Our secondary objectives were to assess subjective improvement in vulvovaginal symptoms, sexual function, and lower urinary tract symptoms through use of validated questionnaires administered at baseline and at the conclusion of therapy.

We aimed to recruit a pilot sample size of 10 adult women per the following inclusion and exclusion criteria. Inclusion criteria: Postmenopausal with suspected vulvar LS, English-speaking, electing to undergo fractionated CO_2 laser therapy, willing and able to undergo vulvar biopsy for diagnostic confirmation. Exclusion criteria: Prior transvaginal mesh for prolapse, active genital infection, known vulvar malignancy or active treatment for other malignancy, planning pregnancy, prior pelvic radiation therapy, TCS use on the vulvovaginal tissues within past 8 weeks. Participants were provided a $75 incentive payment with $35 provided upon enrollment and $40 upon study completion for parking costs and their time and effort in adhering to and completing the study protocol.

Upon enrollment, participants were consented, demographic data were collected (age, race/ethnicity, medical/surgical history, urogynecologic history, hormone replacement therapy use, tobacco use, prior treatment for LS), and they were asked to complete four validated questionnaires:

(1) The Skindex-16 measures the effect of skin diseases on quality of life and scores vary from 0 (no effect) to 100 (effect experienced all the time) such that a higher score indicates worse symptom severity/burden. Responses are aggregated in Symptoms (four items), Emotions (seven items), and Functioning scales (five items) that are widely utilized with

dermatologic research as a means to assess effectiveness of different treatments for skin diseases.[13,14]

(2) The Vulvovaginal Symptoms Questionnaire (VSQ), a 21-item survey focused on vulvovaginal symptoms that is comprised of four subscales including symptoms, emotions, life-impact, and sexual impact used to measure vulvovaginal symptoms in postmenopausal women.[15] A higher VSQ score indicates more vulvovaginal symptoms.

(3) The Female Sexual Function Index (FSFI) to assess domains of sexual function (e.g., sexual arousal, orgasm, satisfaction, and pain).[16] A lower score on the FSFI indicates worsening sexual function with a score of ≤26.5 indicating female sexual dysfunction.

(4) The Core Lower Urinary Tract Symptom Score (CLSS) Questionnaire score: The CLSS is an 11-item questionnaire used in male and female populations to assess lower urinary tract symptoms that specifically assesses storage symptoms, voiding symptoms, pain in the bladder/urethra, and burden.[17,18] A higher score for questions 1–10 indicate worse lower urinary tract symptoms.

Participants who did not have a baseline vulvar biopsy available underwent a vulvar biopsy. After a period of at least 2 weeks to allow healing, the patients underwent three office-based fractionated CO_2 laser treatments performed 4–6 weeks apart and then returned for a final study visit approximately 4–6 weeks following the third fractionated CO_2 laser treatment when they completed the above questionnaires again and underwent another vulvar biopsy.

Fractionated CO_2 laser is thought to work by creating small (200-micron) spots on the skin which causes the release of growth factors to recruit fibroblasts and stimulate cell division.[11] The fractionated CO_2 laser treatments were performed as follows: before the laser treatment, eutectic local anesthetic (lidocaine 2.5%, prilocaine 2.5% topical ointment) was applied for ~30 minutes then wiped off. The vulvovaginal SmartXide2–V2-LR laser system fractionated CO2 laser was used for all treatments. For the first treatment the laser was set at power 26 W, dwell time 800 microseconds, DOT spacing at 800 μm and normal scan mode and then the two additional treatments were performed with a power 30 W, dwell time 1000 μs, spacing 1000 micrometers at normal scan mode with smart pulse.[11,19] Visually affected areas of vulvar and perianal skin were treated with single pass, sparing the glans of the clitoris and clitoral hood by at least a 5 mm margin. Patients were provided eutectic local anesthetic to take home and use as needed for any additional discomfort.

Vulvar biopsy was performed at baseline and at 5 months. The vulvar tissues were cleaned with betadine or chlorohexidine, 1–2 mL of 1% lidocaine was injected and a 5 mm punch biopsy was performed of an area considered to be visually consistent with LS per provider judgment. The specimen was sent to pathology and, if needed, the biopsy site was reapproximated with dissolvable sutures or cauterized with silver nitrate. The specimens were formalin-fixed, paraffin-embedded, and sent for histologic review.

Pre- and post-treatment specimens obtained from each individual participant were compared such that each participant acted as their own control in assessing for alterations in the histologic appearance and architecture of the vulvar tissues. There is not a standardized interpretation/grading mechanism for histologic identification of LS. This qualitative analysis identified characteristics in histology comparing pre- to post-treatment vulvar biopsies, and quantitative rating was performed on a scale from 1 to 5 (with 1 being absent and 5 being most severe) for three characteristics: sclerosis, inflammation, and epidermal atrophy. One individual pathologist (Michael A. Cardis) performed the analyses on all 20 specimens for uniformity and the pathologist was blinded to patient and sample (i.e., pre- vs. post-treatment). The pathologist also performed standard clinical interpretation to describe the histology and assess degree of hyperkeratosis, epidermal thinning, loss of rete pegs, basal cell degeneration, acanthosis, and hypergranulosis. Statistical analyses were performed to determine if histologic changes correlated with participants perceived response to therapy (as assessed on validated quality of life questionnaires).

Demographic and questionnaire scores are reported as means ± standard deviations, or medians and interquartile ranges. Skindex-16, VSQ, FSFI, and CLSS scores were compared by participant from baseline to 5 months. Pre- and post-treatment continuous and categorical variables were compared using Wilcoxon signed-rank test and McNemar test, respectively. Change scores were calculated as the difference between pre- and post-treatment scores for each individual subject. A p-value less than 0.05 defined statistical significance. Logistic regression was used to control for variables identified a priori which are hypothesized to potentially influence urogenital health (i.e., estrogen supplementation, vulvovaginal moisturizer use). A sample size calculation was not performed as this study was intended to be exploratory in nature with no prior research at the time of study design available on histologic effects of fractionated CO_2 laser therapy on vulvar tissues for treatment of LS.

RESULTS

A total of 10 women with vulvar LS met inclusion criteria and were enrolled in the study. All 10 completed three treatments of Fractionated CO_2 laser therapy. Demographic characteristics as well as past medical and surgical history are reported in Table 1 for the 10 participants. The 10 subjects enrolled had a mean age of

TABLE 1 Participant demographics.

Characteristic	Participants
Age	61 ± 7 (range 50–70)
Hispanic ethnicity	0 (0)
White race	9 (90)
Black race	1 (10)
Insurance type	
Govt-assisted	3 (30)
Private	6 (60)
Other/combination	1 (10)
Education	
High school or equivalent	1 (10)
Some college/Associate degree	1 (10)
College graduate	3 (30)
Graduate/Professional degree	5 (50)
Length of LS symptoms ($n = 9$)	
<1 year	0 (0)
1–3 years	4 (40)
3–5 years	3 (30)
>5 years	2 (20)
Time since LS diagnosis	
1–6 months	4 (40)
6 months – 1 year	1 (10)
1–3 years	3 (30)
3–5 years	0 (0)
>5 years	2 (20)
Medical history	
Smoker	0 (0)
Hormone therapy use	3 (30)
Diabetes	0 (0)
Heart Disease	1 (10)
High blood pressure	2 (20)
Connective tissue disorder	0 (0)
Bleeding disorder	1 (10)
Oral steroid use	1 (10)
Immunosuppressive medication use	0 (0)
Prior stress incontinence surgery	1 (10)
Prior prolapse surgery	3 (30)

Note: Data reported as *N* (%) or mean ± standard deviation (range).
Abbreviation: LS, lichen sclerosus.

61 and most were white, privately insured, and had a college/graduate-level education; 40% were diagnosed with LS within 1 month of enrollment, and 30% were on hormonal therapy. Of note, while over half of participants reported LS symptoms for >3 years, 50% reported 1 year or less since the time of diagnosis, demonstrating a >2 year time period from symptom onset to diagnosis.

Questionnaire scores showed either no significant change (VSQ and CLSS) or a trend towards improvement but no statistically significant change pre- and post-treatment in response to Fractionated CO_2 laser therapy (Skindex-16, FSFI; Table 2).

Post-treatment vulvar biopsy specimens demonstrated significant improvement in sclerosis and epidermal atrophy when compared to baseline specimens across individual participants with no statistically significant change in inflammation score (Table 3). As demonstrated in Figure 1, the pre-treatment specimen demonstrates epidermal atrophy with loss of the rete ridge pattern and prominent band-like sclerosis of the superficial dermis. There is also a brisk lichenoid lymphohistiocytic inflammatory infiltrate subjacent to the sclerosis. The post-treatment specimen in Figure 2 shows marked improvement with expansion of the epidermis and reduction in the sclerotic zone with only sparse lymphohistiocytic inflammation.

A statistically significant correlation was found between change in sclerosis rating and Skindex-16 symptoms scores with an average change of 21.4 units in Skindex-16 symptoms score for every one-point change in histologic sclerosis score ($p = 0.03$).

DISCUSSION

This small study found a significant change in degree of sclerosis on histology after treatment with fractionated CO_2 laser therapy and there was a correlation between improvement in sclerosis on histology and Skindex-16 symptom score. These results demonstrate the promise of fractionated CO_2 laser therapy for treatment and management of vulvar LS and related symptoms in postmenopausal women.

Our results are similar to those seen in our group's prior randomized trial showing improvement in vulvar LS symptoms in response to fractionated CO_2 laser therapy.[11] This previous trial was a randomized study comparing fractionated CO_2 laser therapy to TCS with clobetasol propionate 0.05% applied nightly for four weeks and then three times a week for 2 months and then as needed. The patients treated with fractionated CO_2 laser therapy showed greater improvement in Skindex-29 score at 6 months with stratified analysis showing this occurred in patients previously exposed to steroids. Significantly, 81% of participants in the fractionated

TABLE 2 Questionnaire scores.

Questionnaire	Baseline (pretreatment)	Final (posttreatment)	*p*-value
Skindex-16	58.5 ± 22.9	50.2 ± 23.1	0.3906
	(range 11–87)	(range 16–84)	
Symptoms	57.5 ± 30.9	46.3 ± 24.2	0.3438
	(range 16.7–100)	(range 12.5–83.3)	
Emotions	74.8 ± 28.6	62.4 ± 26.5	0.2422
	(range 7.1–100)	(range 19–92.9)	
Functioning	44.3 ± 35.6	43.0 ± 30.0	0.8984
	(range 0–100)	(range 0–90)	
Female Sexual Function Index (FSFI)	11.8 ± 13.4	14.4 ± 19.2	0.8711
	(range 2–40)	(range 2–58)	
Vulvovaginal Symptoms Questionnaire (VSQ)	14.0 ± 6.5	13.8 ± 5.7	0.8945
	(range 5–23)	(range 3–21)	
Core Lower Urinary Tract Symptom Score (CLSS)			
Questions 1–10	10.1 ± 5.6	9.4 ± 4.4	0.9395
	(range 2–20)	(range 2–15)	
Question 11 (mostly satisfied/ pleased/delighted)	3.5 ± 1.7	3.6 ± 1.6	0.7500
	(range 1–6)	(range 1–6)	

Note: Data reported as mean ± standard deviation (range). *p*-value obtained from Wilcoxon signed-rank test for all.

TABLE 3 Histology scores.

	Baseline (pretreatment)	Final (posttreatment)	*p*-value	Mean change
Sclerosis	3.5 ± 1.0	2.4 ± 0.7	0.0391	−1.1 ± 1.2
Inflammation	3.0 ± 1.4	2.6 ± 1.0	0.4746	−0.4 ± 1.8
Epidermal atrophy ($n = 9$)	2.9 ± 1.2	1.9 ± 0.6	0.0313	−0.9 ± 0.9
Total	9.4 ± 2.3	6.7 ± 1.7	0.0234	−2.7 ± 2.8

Note: Data reported as mean ± standard deviation. *p*-value obtained from Wilcoxon signed-rank test for all.

CO_2 laser therapy group were satisfied or very satisfied with treatment compared to 41% in the TCS group ($p = 0.011$).

Based on the wavelength of CO_2 lasers (10,600 nm, which is in the infrared spectrum), the target chromophore is primarily water leading to selective photothermolysis of the epidermis and dermis as this is composed of about 80% water.[20] The depth is superficial for the CO_2 ablative lasers.[20] The precise mechanism for tissue resurfacing and remodeling is unknown; however, collagen contraction, physical ablation of damaged tissue, and neocollagenesis have been considered as possible mechanisms.[21] We propose that this mechanism of ablative laser therapy is what produced the statistically significant improvement we saw in the histologic sclerosis and atrophy in our subjects. It may be that laser therapy for LS is more beneficial in mid to late stage or even burned-out disease where more structural abnormalities have occurred rather than early on when the inflammatory process is more prominent. As such, laser therapy would likely represent an adjunct treatment added to anti-inflammatory therapies in select patients. Identifying and treating LS in early stages is still the most important means in preventing disease progression and chronic sequelae. Laser therapy represents a possible treatment modality for the latter where not much has existed before; however, further research is needed to substantiate these preliminary findings.

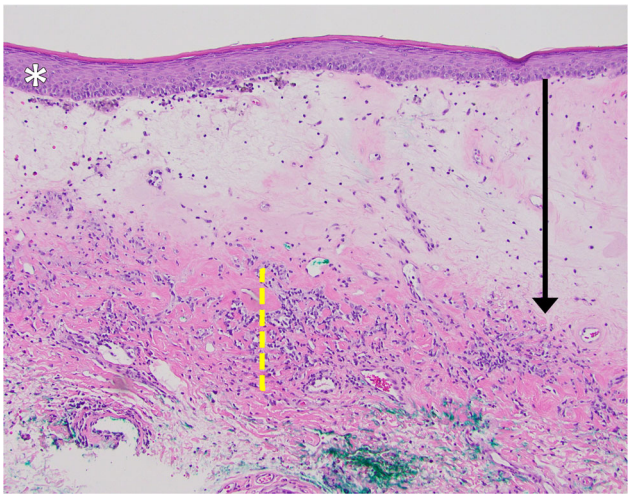

FIGURE 1 Pre-treatment (hematoxylin-eosin, original magnification x40). Pre-treatment histology demonstrating epidermal atrophy with loss of the rete ridge architecture (asterisk). There is a thick zone of dermal homogenization and pallor consistent with sclerosis with edema and telangiectasia (black arrow). Underlying the sclerotic zone is a band-like lymphohistiocytic inflammatory infiltrate (yellow bracket).

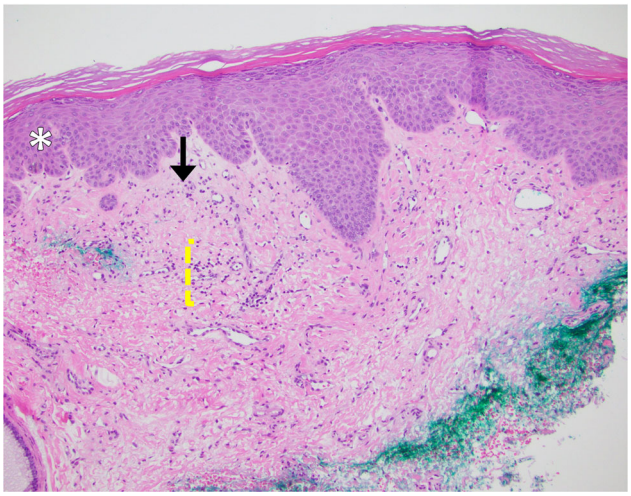

FIGURE 2 Post-treatment (hematoxylin-eosin, original magnification x40). Post-treatment histology revealed expansion of the epidermis with a retained rete ridge pattern (asterisk). There is a significant reduction in the degree and extent of the sclerotic zone (black arrow). Only a sparse lymphohistiocytic inflammatory infiltrate is present (yellow bracket).

Another recent randomized trial by Mitchell et al. published in June 2021 that examined vulvar biopsy specimens pre- and post-fractionated CO_2 laser therapy found a small reduction (improvement) in histopathology scale for women treated in the active treatment arm, but the change was not statistically significantly different from the small increase (deterioration) in histopathology scale for women treated with sham laser.[12] The histopathology scores showed improvement in the active treatment arm and deterioration in the sham arm indicating therapeutic effect of fractionated CO_2 laser therapy but did not meet the study criteria for change which was set by the investigators. Thus, the investigators concluded that fractionated CO_2 laser therapy showed no meaningful improvement in histopathologic changes. However, these results seem to confirm that laser does have a potential therapeutic effect and the authors' conclusions may be related to two important factors: (1) this trial used a control "sham" laser treatment that used enough energy "to create the spots, smoke, and odor so that both the patients and investigator remained blinded" thus leaving the possibility of some therapeutic effect in sham-treated patients,[12] and (2) the histopathology scale utilized a 0–6 point rating scale for loss of rete pegs, dermal homogenization, and chronic inflammation. However, the latter is nonspecific and can be seen in many conditions. An accompanying editorial noted that future research should aim to determine the histologic parameters that correlate to clinically important outcomes.[22] Our trial utilized a specific sclerosis score which was found to correlate with subjective symptoms on the Skindex-16 in our small pilot study so future studies should include sclerosis as a specific outcome when assessing histologic response to fractionated CO_2 laser therapy.

Strengths of this study include the use of histologic and subjective measures to assess the effects of fractionated CO_2 laser therapy and provide a comprehensive assessment of disease improvement and treatment efficacy. Limitations of our study include the small sample size and the homogeneity of the participant pool. The reliance on self-reported, subjective symptom scores introduces the possibility of a reporting bias or placebo effect. The use of an objective histologic measure that was blindly scored reduces dependency on subjective reports.

CONCLUSION

In postmenopausal women diagnosed with vulvar LS undergoing fractionated CO_2 laser therapy, histologic changes in degree of sclerosis are seen on vulvar biopsy and these changes correlate with symptomatic improvement. These results demonstrate fractionated CO_2 laser therapy as a promising option for the treatment of LS, suggesting the need for further studies to assess its safety and efficacy, and to include outcomes assessing effects on degree of sclerosis in pre- and post-treatment vulvar biopsies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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