Fat Grafting Improves Fibrosis and Scarring in Vulvar Lichen Sclerosus: Results From a Prospective Cohort Study

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Objective: The aim of the study was to evaluate the effect of lipotransfer in women presenting with fibrosis and scarring due to lichen sclerosus.

Materials and Methods: This prospective cohort study included 33 women attending the vulvar clinic of a public hospital. Patients received one lipotransfer treatment. Validated measures were used prospectively to assess the sexual function (Female Sexual Function Index, Female Sexual Distress Scale); symptoms (visual analog scale for itching, burning, soreness), pain (Pain Anxiety Symptoms Scale 20); psychological status and quality of life (Hospital Anxiety and Depression Scale, Relationship Assessment Scale, Wound Management Questionnaire Revised); physician-based disease signs (Vulvar Architecture Severity Scale). Data were analyzed using paired *t* test with nonparametric Wilcoxon matched-pairs signed rank test and unpaired *t* test with nonparametric Mann-Whitney test (Prism6 Software).

Results: The mean (SD) follow-up was 12.9 (3.5) months. Sexual function improved after treatment ($p < .001$), as well as the distress associated with sexuality ($p < .0001$). A significant improvement was reported in itching ($p < .001$), burning ($p < .05$), soreness ($p < .001$), and pain ($p < .0001$). Patients reported a significant improvement in romantic relationship ($p < .05$), anxiety ($p < .0001$), and depression ($p < .0001$). Improvement was not significant in the self-care associated with self-disgust assessment ($p = .42$). The clinical physician-based score showed an overall improvement in all the treated areas to lesser or greater extent.

Conclusions: The use of fat grafting in lichen sclerosus is promising. Further studies are required to rule out a potential placebo effect and to better understand the underlying molecular mechanism of action.

Key Words: lichen sclerosus, fibrosis, vulvar scar, vulvar architecture, fat grafting, lipofilling, lipotransfer, regenerative surgery, adipose-derived stem cells, women's health

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Vulvar lichen sclerosus (VLS) is a chronic inflammatory condition that affects approximately 1 in 1000 women, and this figure may be an underestimate as mild cases often go unreported.[1] The exact etiology is unknown, but the autoimmune etiology is the most commonly accepted.[2]

The typical lesions are sclerotic porcelain-white plaques and hyperkeratosis or atrophy, often associated with areas of ecchymosis due to itching and scratching. The characteristic affected sites are the interlabial sulci, labia minora, clitoral hood, clitoris, posterior fourchette, and perineum. Genital mucosa is not involved, although muco-cutaneous junction might be affected resulting in introital narrowing.[1] Fissures and tears can develop, and the scarring process may cause the loss of normal vulvar architecture, including labia minora agglutination, clitoral phimosis, and introital stenosis.[1] Symptoms include intense itching and burning sensation. The presence of erosions, fissures, or introital narrowing can lead to significant and debilitating dyspareunia that can have a significant impact on women's psychological well-being.[3] Not all patients with lichen sclerosus (LS) have sexual dysfunction but, when present, difficulty in achieving orgasm, dyspareunia, and loss of interest in sexual activity can also have a negative effect on relationships, identity, acceptance and adjustment with anxiety, depression, and low self-esteem.[4] Standard treatment includes topical superpotent steroid to control symptoms and prevent anatomical changes and malignant transformation.[1] Surgical interventions are indicated only in the postinflammatory sequelae of the disease to correct the architectural changes and functional defects.[5]

Recently, autologous fat grafting has been proposed as an additional therapeutic option in patients experiencing the scarring sequelae of VLS despite the use of ultrapotent topical steroids.[6–8] Fat grafting is a well-established technique used on a routine basis as standard of care in plastic reconstructive surgery. It was described already in the last century to improve volumetric defects, but only in the last decade, it has been used to ameliorate dermal fibrosis in different conditions, including hypertrophic scars, burns, radiation-induced fibrosis, scleroderma, graft versus host disease, and Dupuytren contracture.[9–12]

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The authors have declared they have no conflicts of interest.

The study was conducted after obtaining ethics approval. The ethics committee that approved the study is the REC London Hampstead (Study Ref: 16/LO/1980). This study had also been approved by the research and development department of the NHS London Trust Royal Free Hospital (RFH Ref: 9576).

All the authors meet the criteria for authorship and gave their approval to the final version of the manuscript. A.A. conceived and designed the study; collected, analyzed, and interpreted the data; and wrote the paper. E.H. contributed designing the study; analyzing and interpreting the data; and reviewing the manuscript. D.B. contributed by conceiving and designing the study and writing the manuscript. N.Z. contributed by conceiving and designing the study and critically revising the manuscript. V.S. contributed by conceiving and designing the study. W.R., A.M., and P.E.M. conceived and designed the study and critically reviewed the manuscript.

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The work described in this article was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study obtained favorable ethical opinion from the ethical committee (REC Ref: 16/LO/1980; R&D Ref 9576). Written informed consent was obtained from patients before their inclusion in the study, and it is maintained by the investigators.

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So far, evidence on the efficacy of fat grafting in VLS is limited. The aim of this study was to assess with a structured methodology and validated outcome measures the clinical, sexual, and psychological outcome of fat grafting.

MATERIALS AND METHODS

Patients

The inclusion criteria are as follows: patients with biopsy-proven LS presenting with scarring, fibrosis and loss of vulvar architecture of 18 years and older, and able to provide written informed consent. The following categories were considered not eligible to participate: pregnancy; patient affected by a malignant disease or generalized infection (bacterial, viral, or fungal); and previous diagnosis of intraepithelial neoplasia or carcinoma of the vulva. Patients incapable of giving informed consent were also excluded.

Surgical Technique

The adipose tissue was harvested with a disposable cannula (Blink Medical) and centrifuged at 3000 rpm for 3 minutes. The upper fraction, containing oil and cellular debris, and the lower fraction, containing fluids and blood, were discarded. The middle layer, rich in adipose tissue, adipose-derives stem cells (ASCs), and progenitor cells, was transferred into 1 mL of Luer-Lock syringes connected to a blunt disposable cannula (Blink Medical). The purified lipoaspirate was slowly injected in multiple passages. Recipient sites included labia majora, labia minora, clitoris, posterior fourchette, and perineal area.

Patient and Public Involvement

In this study, the outcome measures were selected with the active participation of VLS patients to identify the aspects more relevant to them. Patient involvement was carried out through face-to-face meeting with patient representatives at our institution during a focus group to identify priority aspects to be included in the study as outcome measures. The patients agreed that sexual function was the most relevant aspect to be investigated, followed by symptoms and quality of life.

Outcome Measures

All the included patients were assessed prospectively before and after treatment. The primary objective of the study was to assess the sexual function measured with the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS). The FSFI questions patients on their sexual feelings and responses with the following 6 substructures that can be scored individually: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain.[13] The FSDS is composed of 13 questions ranked on a 4-point Likert scale.[14]

The secondary outcome consisted in assessing symptoms of itching, burning, and soreness with 3 visual analog scales (VASs) validated for VLS, ranging from 0 (no complaints) to 10 (extreme complaints).[15] Pain was assessed with the Pain Anxiety Symptoms Scale 20 (PASS-20); it is composed of 4 subsections with an overall score of 100 in which higher values represent more anxiety relating to experiencing pain.[16]

Other outcome measures included the psychological status carried out with validated measures of anxiety and depression—Hospital Anxiety and Depression Scale (HADS); intimacy and romantic relationship—Relationship Assessment Scale (RAS); self-care related to self-disgust—Revised Wound Management Questionnaire (WMQ-R). The HADS is composed of 14 items, 7 relating to anxiety and 7 relating to depression.[17] The RAS is composed of 7 items on a 5-point Likert scale and refers to the subjective evaluation of their romantic relationship. Questions surround satisfaction, expectations, love, problems, and needs within the relationship.[18] The WMQ was developed to assess patients' levels of disgust and how this interacts with their ability of self-management. It consists of 11 items on a 7-point Likert scale in which 1 represents strong disagreement and 7 represents strong agreement.[19]

Lastly, a physician-based clinical assessment was carried out with the Vulvar Architecture Severity Scale (VASS). The VASS is a validated scale grading the vulvar architecture in LS as follows: none, mild, moderate, and Severe.[20] Each morphological unit (labia majora, labia minora, clitoral area, posterior fourchette, perineal area, perianal area) is assessed independently.

Statistical Analysis

Intercomparisons between pretreatment and posttreatment were analyzed statistically using paired t test with nonparametric Wilcoxon matched-pairs signed rank test (Prism6 Software). Intercomparisons between subgroups (steroids versus no steroids and menopause versus no menopause) were analyzed statistically using unpaired t test with nonparametric Mann Whitney test (Prism6 Software). Tests were two-tailed with a CI of 95%. The mean and SD was calculated. Significance was described as $p < .05$.

RESULTS

Demographic Data

A series of 33 patients with VLS presenting vulvar fibrosis and scarring were included (Table 1). Of the 33 patients, 48.48% (n =- 16) were under concurrent use of topical steroids, and 51.51% (n = 17) were not; 48.48% (n = 16) were in menopause, and 51.51% (n = 17) were not. Patients received 1 lipotransfer treatment and the mean (SD) follow-up was 12.9 (3.5)months. Overall, patients received injection of 10 (2) mL of centrifuged lipoaspirate. The mean (SD) amount injected in each of the vulvar morphologic subunit was as follows: 4 (2) mL in labia majora; 2 (1) mL in labia minora; 1 (0.5) mL in clitoral area; 1 (0.5) mL in the posterior fourchette; and 2 (1) mL in the perineal area.

Sexual Outcome

After treatment, patients reported a significant improvement in the overall sexual function measured with the FSFI ($p < .001$). The different items composing the FSFI were also analyzed separately,

TABLE 1. Demographic Data

No. patients	**33**
Age, mean (SD)	50.5 (12.5)
No. treatment	1
Follow-up, mean (SD), mo	12.9 (3.5)
Duration of LS, mean (SD), y	14 (6)
Concomitant topical steroid treatment	
None	51.51% (n = 17)
Topical steroid	48.48% (n = 16)
Main treatment:	
Dermovate	81.25% (n = 13)
Nerisone forte	18.75% (n = 3)
Hormonal status	
Menopause	48.48% (n = 16)
Not in menopause	51.51% (n = 17)

The table illustrates the demographic data of the patients included in the study.

and significant improvement was reported after fat grafting in the following subitems: desire ($p < .001$), orgasm ($p < .05$), satisfaction ($p < .01$), and pain ($p < .01$). Results showed nonsignificant improvement in the subitems arousal ($p < .69$) and lubrication ($p < .52$) (Table 2). A significant reduction in the distress associate with sexual life was also reported by the FSDS ($p < .001$) (Table 2).

The score change did not highlight significant differences in patients using concurrent topical corticosteroids compared with patients who did not, neither in the sexual function ($p = .71$) nor in the sexual distress ($p = .55$) (Table 2). Similarly, the hormonal status did not have an effect on the outcome: patients who were in menopause did not reported significant differences in the outcome compared with patients who were not in menopause, both in the sexual function ($p = .69$) and sexual distress ($p = .40$) (Table 2).

Symptoms Outcome

All the symptoms evaluated with the VAS improved after lipotransfer: itching ($p < .001$); burning ($p < .05$); and soreness ($p < .001$). A significant improvement was also reported in pain measured with the PASS-20 ($p < .0001$) (Table 2). The symptoms

TABLE 2. Patient-Reported Outcome

Item	Preop	Postop	Score change overall	Significance[a]	Score change steroid subgroup ($n = 11$)	Score change no steroids subgroup ($n = 13$)	Significance[b]	Score change menopause subgroup ($n = 12$)	Score change not in menopause subgroup ($n = 12$)	Significance[b]
Sexual function overall (FSFI)	14.9 (7.3)	19.4 (8.8)	4.5 (5.0)	***	4.2 (4.2)	4.9 (5.7)	NS	4.2 (5.8)	4.9 (4.2)	NS
Desire (FSFI)	2.4 (1)	3.4 (1.1)	1 (1)	***	0.1 (0.8)	1.1 (1.1)	NS	1 (1)	1 (1)	NS
Arousal (FSFI)	2.9 (1.8)	3.1 (1.8)	0.2 (1.4)	NS	0.4 (1.5)	0.7 (1.1)	NS	0.2 (1.8)	0.1 (1.2)	NS
Lubrication (FSFI)	2.4 (2.2)	2.7 (2.3)	0.4 (1.7)	NS	0.6 (1.6)	0.1 (1.7)	NS	0.1 (1.6)	0.4 (1.3)	NS
Orgasm (FSFI)	2.5 (2.2)	3.3 (2.4)	0.8 (1.5)	*	0.6 (1.6)	1.1 (1.4)	NS	1 (1.6)	1.1 (0.9)	NS
Satisfaction (FSFI)	2.7 (1.3)	3.7 (1.4)	1 (1.3)	**	1.1 (1.3)	1 (1.4)	NS	1 (1.7)	1.1 (0.9)	NS
Pain (FSFI)	2.1 (1.4)	3.3 (1.9)	1.1 (1.4)	**	1.3 (1.1)	0.9 (1.7)	NS	1.1 (1.8)	1.1 (0.9)	NS
Sexual distress (FSDS)	40.7 (10.1)	31. (13.2)	9.7 (8.6)	***	10.5 (8.8)	8.8 (7.9)	NS	10.9 (10.6)	8.4 (5.3)	NS
Itching (VAS)	6.5 (2.8)	3.7 (2.7)	2.8 (2.1)	***	2.8 (2.1)	2.8 (2.2)	NS	3.1 (2.6)	2.5 (1.6)	NS
Burning (VAS)	4.8 (2.8)	3.2 (2.8)	1.6 (2.5)	*	1.5 (2.6)	1.8 (2.4)	NS	1.5 (3.4)	1.8 (1.1)	NS
Soreness (VAS)	7.1 (2.6)	4.5 (2.6)	2.5 (2.3)	***	2.6 (2.2)	2.5 (2.4)	NS	2.8 (2.6)	2.4 (2)	NS
Pain (PASS-20)	62.1 (12.8)	48.4 (11.5)	13.4 (9.3)	***	14.6 (9.9)	13.1 (9)	NS	10.7 (5.4)	17.1 (11.5)	*
Anxiety (HADS-A)	11.8 (4)	8.1 (3.07)	3.7 (3.1)	***	3.4 (2.4)	4 (3.7)	NS	3.6 (4)	3.8 (2.2)	NS
Depression (HADS-D)	9.3 (3.7)	5.8 (3.5)	3.5 (3.2)	***	3.3 (3.1)	3.6 (3.4)	NS	3.8 (3.9)	3.1 (2.7)	NS
Romantic relationship (RAS)	21.8 (5)	24.2 (3.7)	2.4 (3.6)	*	2.6 (5.3)	4.8 (5.7)	NS	1.3 (2.1)	3.4 (5.6)	NS
Self-care tot (WMQ-R)	54.5 (11.4)	56.7 (12.1)	2.1 (6.2)	NS	4.3 (4.8)	0.1 (6.1)	0.04	2.1 (7)	2.2 (5.2)	NS
Preoccupation (WMQ-R)	19.7 (5.2)	19.8 (5.1)	0.1 (3.8)	NS	0.2 (4.5)	0 (2.9)	NS	−0.2 (4.1)	0.4 (2.6)	NS
Avoidance (WMQ-R)	34.7 (7.3)	36.4 (8.5)	1.7 (4.7)	NS	3.5 (4.5)	0.1 (3.9)	*	1.6 (5.6)	1.8 (4.2)	NS

The table illustrates: sexual function overall (FSFI), by each individual item of the FSFI, and sexual distress (FSDS); symptoms including itching (VAS), burning (VAS), soreness (VAS), and pain (PASS-20); psychological status and quality of life including anxiety (HADA-A), depression (HADS-D), romantic relationship (RAS), self-care overall (WMQ-R), and by each individual item of the WMQ-R. Results are represented overall in all the included patients, in the different concurrent treatment subgroups (topical steroids vs no topical steroids), and in the different hormonal sub-groups (menopause vs not in menopause).

[a]Paired *t* test (nonparametric Wilcoxon matched-pairs signed rank test).

[b]Unpaired *t* test (nonparametric Mann-Whitney test).

NS indicates not significant.

outcome was not affected by the concurrent use of topical corticosteroids ($p > .01$) or hormonal status ($p > .01$) (Table 2).

Psychological and Quality of Life Outcome

Overall patients reported an improvement in psychological status after lipotransfer (Table 2). A significant improvement was recorded in HADS Anxiety (<0.0001) and HADS Depression ($p < .0001$). Romantic relationship measured with the RAS was improved after treatment ($p < .05$). Improvement was not statistically significant in the self-care associated with self-disgust scores measured with the WMQ-R ($p = .42$). This score is composed of 2 subitems, preoccupations and avoidance. Neither one showed statistically significant improvement ($p = .93$ and $p = .35$; Table 2).

Physician-Based Clinical Assessment

The treated patients presented an overall improvement of the dermal fibrosis and overall architecture (see Figures 1, 2). The physician-based assessment with the VASS showed that all the anatomical vulvar units improved after treatment to a lesser or greater extent. The improvement rate in each unit was as follows: labia majora, 57.6%; labia minora, 84.8%; clitoris, 72.7%; posterior fourchette, 87.8%; perineal area, 45.5%; and perianal area, 30.3%.

The level of improvement was grouped as "3 level improvement" (from severe to none); "2 level improvement" (from severe to mild or from moderate to none); and "1 level improvement" (from severe to moderate, from moderate to mild, or from mild to none). The highest improvement was reported in the posterior fourchette, with 33.3% of patients presenting a "2 level improvement," and 54.5% with "1 level improvement" (see Figure 3).

DISCUSSION

This study shows that autologous lipotransfer might have a role in improving the vulvar fibrosis and architecture, with a positive effect on sexual functions, symptoms, and overall quality of life. The efficacy and safety of lipotransfer to ameliorate dermal fibrosis are already well established in different conditions. The rationale of this treatment is on one hand to increase the subcutaneous tissue bulk by injecting the lipoaspirate ("padding effect") and on the other hand to ameliorate the fibrotic tissues via a paracrine effect probably mediated by progenitor cells such as the ASCs ("regenerative effect").

In this series, we found that sex function improved after treatment, likely for the combined effect of soft tissue augmentation in the posterior fourchette and skin fibrosis improvement, allowing penetrative intercourse (see Figure 1). This improvement was paired with an overall improvement in quality of life including romantic relationships.

In addition, we found that the use of corticosteroid cream/ointment or the hormonal status (menopause) did not have an effect on the outcome; there was no difference in the response in the different subgroups, suggesting that the concurrent use of topical steroids and different hormonal status do not affect the outcome. This should support inclusive criteria in future treatment protocols.

Vulvar lichen sclerosus is an extremely distressing condition causing significant morbidity to affected patients.[1] Impaired sexual function and relationship dissatisfaction can contribute to avoidance behavior, sexual intercourse avoidance, relationship breakdown, and reduced engagement in social activities. These can be associated with increased feeling of low self-esteem, depression, and anxiety. Despite the major impact on affected patients, a definitive cure for VLS is currently lacking and no effective treatment is available to reverse the vulvar fibrosis associated with LS. Mainstream treatment consists in topical steroids that are known to inhibit chronic inflammatory processes. The use of topical steroids may be helpful to slow the disease progression, to keep symptoms under control, and to prevent anatomical changes and malignant transformation. However, randomized controlled trials to support one ultrapotent steroid over another and indication regarding the length of treatment are lacking, and the treatment needs to be individualized.[1]

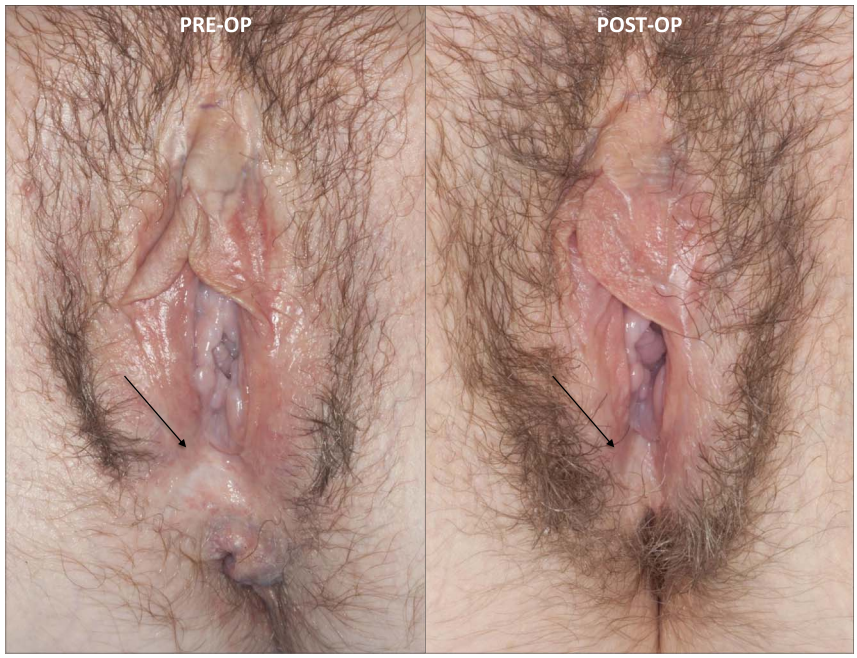

FIGURE 1. Lichen sclerosus: representative case #1. The image illustrates a patient with VLS localized mainly in the posterior fourchette, before and after lipotransfer treatment. Main issue preoperatively was the presence of fibrosis and scarring in the posterior fourchette (arrow), associated with severe dyspareunia and fissuring during penetrative sexual intercourse. After treatment, the fibrosclerotic area was improved (arrow) and the patient reported improvement in sexual function.

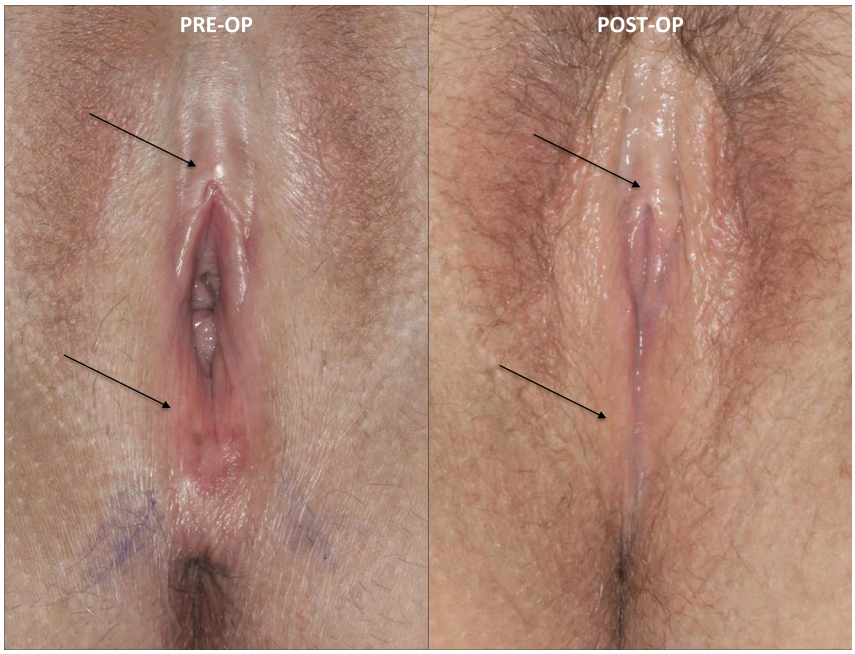

FIGURE 2. Lichen sclerosus: representative case #2. The image illustrates a patient presenting VLS-associated loss of vulval architecture, before and after lipotransfer treatment. Main issues preoperatively were the presence of tight skin in the clitoral hood with clitoral phimosis; labia minora agglutination; and multiple episodes of erosions and scarring in the posterior fourchette. After treatment, the clitoral hood skin is more elastic and nonphimotic; the labia majora and labia minora present increased volume, allowing closure of vaginal opening; and the skin quality in the posterior fourchette is improved.

Despite the large and consolidated use of fat transfer in reconstructive surgery, its use in VLS is relatively new and sound evidence on safety and efficacy in this condition is currently lacking. The antifibrotic effect of fat grafting is attributed to the anti-inflammatory properties of the ASCs, which are a multipotent population of cells within the adipose tissue able to exert paracrine proangiogenic, anti-inflammatory, and immunomodulatory effects.[21] It has been suggested that ASCs have antifibrotic properties through secretion of antifibrotic factors and matrix metalloproteinase and by decreasing profibrotic factors.[22–24] Despite these recent findings, the actual role of the ASCs is not clear and the antifibrotic effect might be mediated by other components of the lipoaspirate or by a combined effect of different cell populations including progenitor cells, endothelial precursors, pericytes, and T-regulatory cells.[21]

In this study, the surgical technique used to harvest, process, and inject the adipose tissue was the standardized lipostructure technique. Overall, a mean (SD) amount of 10 (2) mL of adipose tissue was injected in the vulva. From the literature, it is well established that the fat graft survival is inversely related to the amount of the injection; preclinical and clinical studies demonstrated that the injected adipose tissue is able to obtain nutrition through

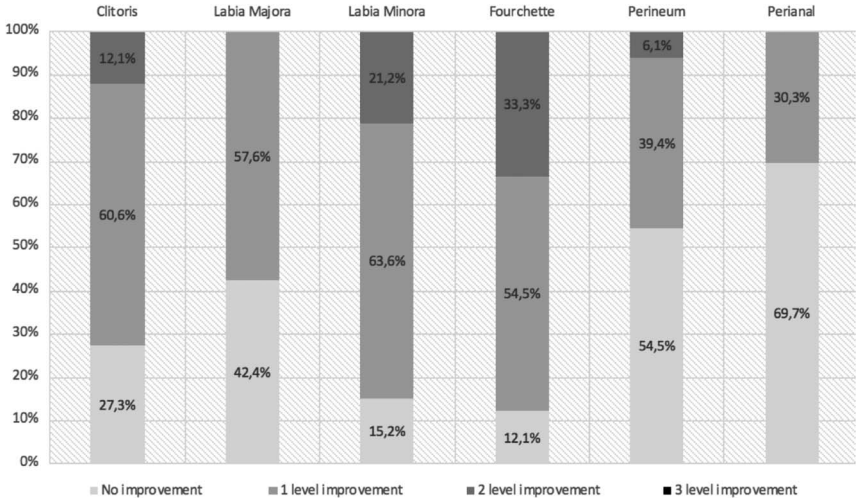

FIGURE 3. Disease signs improvement after treatment. The bar chart illustrates the physician-based assessment of the disease graded with the VASS. Each anatomical unit is assessed independently as none, mild, moderate, and severe. The improvement extent is illustrated as "no improvement"; "1 level improvement"; "2 level improvement"; "3 level improvement."

plasmatic imbibition approximately at 1.5 mm from the vascularized tissue.[25] Therefore, injection of small aliquots of fat is more effective than large-volume injection for lipoaspirate survival. Others techniques to process the adipose tissue are available, such as the microfat[26] and nanofat grafting.[27,28] However, to this date, there is no evidence supporting one technique over another for the antifibrotic effect; hence, we adopted the standardized lipostructure technique.

The main strengths of the study consist in the strong patient and public involvement component and robust patient-reported outcome measures. The patient and public involvement is important to ensure that only important aspect that are priorities for patients is included and there is no waste in research resources.[29] Patient-reported outcome measures are standardized, validated questionnaires to systematically gain meaningful subjective accounts from patients. In the past, the approach was that outcomes should be mainly assessed by professionals, and reports from patients were viewed as subjective and unreliable. Significant evidence, however, has accumulated that patient-reported outcome are not only a reliable source of information but also one of the most important.[29,30]

Results from this study support the efficacy and safety of lipotransfer in VLS. In addition, the study is valuable because it provides information useful to design future studies, including the following: preliminary data allowing a formal power and sample size analysis; study design with inclusive criteria in term of concurrent use of topical steroids and hormonal status; and appropriateness of items to be included as outcome measures.

Despite its strengths, this study presents the following limitations: it is a single-arm study without a control group therefore a potential placebo effect cannot be excluded; the follow-up is limited to 12.9 months and the long-term durability of the effect is unclear; the sample size is small; need to explore further the skin fibrosis with an objective assessment; and the underlying molecular mechanism of action has to be clarified.

CONCLUSIONS

Autologous lipotransfer offers a potentially effective regenerative option to treat vulvar fibrosis in LS. Despite the encouraging finding shown in this study, the mechanism of action responsible for the trophic effect is not clear yet, and laboratory-based studies should be encouraged to clarify the molecular mechanism of action. The use of a standardized core of outcome set is encouraged in future clinical studies to allow comparison of results among different surgical techniques.

REFERENCES

1. Neill SM, Lewis FM, Tatnall FM, et al, British Association of Dermatologists. British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. *Br J Dermatol* 2010;163:672–82.
2. Powell JJ, Wojnarowska F. Lichen sclerosus. *Lancet* 1999;353:1777–83.
3. van Lankveld JJ, Granot M, Weijmar Schultz WC, et al. Women's sexual pain disorders. *J Sex Med* 2010;7(1 Pt 2):615–31.
4. Yesudian PD, Sugunendran H, Bates CM, et al. Lichen sclerosus. *Int J STD AIDS* 2005;16:465.
5. Paniel BJ, Rouzier R. Surgical procedures in benign vulvar disease. In: Neill S, Lewis F, eds. *Ridley's the Vulva*. Oxford: England Wiley-Blackwell; 2009:233.
6. Casabona F, Priano V, Vallerino V, et al. New surgical approach to Lichen sclerosus of the vulva: the role of adipose-derived mesenchymal cells and platelet-rich plasma in tissue regeneration. *Plast Reconstr Surg* 2010;126: 210e–1.
7. Boero V, Brambilla M, Sipio E, et al. Vulvar lichen sclerosus: a new regenerative approach through fat grafting. *Gynecol Oncol* 2015;139: 471–5.
8. Giuseppina Onesti M, Carella S, Ceccarelli S, et al. The use of human adipose-derived stem cells in the treatment of physiological and pathological vulvar dystrophies. *Stem Cells Int* 2016;2016:2561461.
9. Griffin MF, Almadori A, Butler PE. Use of lipotransfer in scleroderma. *Aesthet Surg J* 2017;37(suppl 3):S33–7.
10. Griffin MF, Drago J, Almadori A, et al. Evaluation of the efficacy of lipotransfer to manage radiation-induced fibrosis and volume defects in head and neck oncology. *Head Neck* 2019;41:3647–55.
11. Kan HJ, Selles RW, van Nieuwenhoven CA, et al. Percutaneous aponeurotomy and lipofilling (PALF) versus limited fasciectomy in patients with primary Dupuytren's contracture: a prospective, randomized, controlled trial. *Plast Reconstr Surg* 2016;137:1800–12.
12. Spiekman M, van Dongen JA, Willemsen JC, et al. The power of fat and its adipose-derived stromal cells: emerging concepts for fibrotic scar treatment. *J Tissue Eng Regen Med* 2017;11:3220–35.
13. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;26:191–208.
14. Derogatis L, Rosen R, Leiblum S, et al. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *J Sex Marital Ther* 2002;28:317–30.
15. Günthert AR, Duclos K, Jahns BG. Clinical scoring system for vulvar lichen sclerosus. *J Sex Med* 2012;9:2342–50.
16. McCracken LM, Dhingra LA. Short version of the Pain Anxiety Symptoms Scale (PASS-20): preliminary development and validity. *Pain Res Manag* 2002;7:45–50.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
18. Dicke A, Hendrick C. The Relationship Assessment Scale. *J Soc Pers Relationships* 1998;15:137–42.
19. Elliott D, Bluebelle Study Group. Developing outcome measures assessing wound management and patient experience: a mixed methods study. *BMJ Open* 2017;7:e016155.
20. Almadori A, Zenner N, Boyle D, et al. Development and validation of a clinical grading scale to assess the vulvar region: the Vulvar Architecture Severity Scale (VASS). *ASJ* 2020. In press.
21. Salgado AJ, Reis RL, Sousa NJ, et al. Adipose tissue derived stem cells secretome: soluble factors and their roles in regenerative medicine. *Curr Stem Cell Res Ther* 2010;5:103–10.
22. Almadori A, Griffin M, Ryan CM, et al. Stem cell enriched lipotransfer reverses the effects of fibrosis in systemic sclerosis. *PLoS One* 2019; 14:e0218068.
23. James I, Bourne D, Silva M, et al. Adipose stem cells enhance excisional wound healing in a porcine model. *J Surg Res* 2018;229:243–53.
24. Waldner M, Zhang W, James IB, et al. Characteristics and immunomodulating functions of adipose-derived and bone marrow-derived mesenchymal stem cells across defined human leukocyte antigen barriers. *Front Immunol* 2018;24:1642.
25. Mashiko T, Yoshimura K. How does fat survive and remodel after grafting? *Clin Plast Surg* 2015;42:181–90.
26. Serratrice N, Bruzzese L, Magalon J, et al. New fat-derived products for treating skin-induced lesions of scleroderma in nude mice. *Stem Cell Res Ther* 2014;5:138.
27. Tonnard P, Verpaele A, Peeters G, et al. Nanofat grafting: basic research and clinical applications. *Plast Reconstr Surg* 2013;132:1017–26.
28. Tamburino S, Lombardo GA, Tarico MS, et al. The role of nanofat grafting in vulvar lichen sclerosus: a preliminary report. *Arch Plast Surg* 2016;43:93–5.
29. Lohr KN, Zebrack BJ. Using patient-reported outcomes in clinical practice: challenges and opportunities. *Qual Life Res* 2009;18:99–107.
30. Jenkinson C, Morley D. Patient reported outcomes. *Eur J Cardiovasc Nurs* 2016;15:112–3.