Fat Grafting in Vulvar Lichen Sclerosus: Long Term Follow-Up

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Objective: The rationale for the use of autologous fat grafting in the treatment of vulvar lichen sclerosus (VLS) consists in reduction of inflammation, regeneration of tissues, volume increase, and pain fiber control. The main outcome of our study was the evaluation of patients' satisfaction after treatment. Secondary outcomes included modifications in symptoms, psychosexual wellbeing, vulvar hydration, and histology after surgery.

Methods: Eligible for this study were women aged 18–85 years with a histological diagnosis of VLS who underwent at least one autologous vulvar fat grafting at our center, between 2010 and 2019. In 2021, all women underwent a clinical reevaluation, comprehensive of vulvoscopy, vulvar biopsy, and handing out of validated questionnaires.

Results: Overall, 88.7% of patients declared themselves very satisfied/satisfied with the procedure. All symptoms were improved postsurgery; in particular, the difference was statistically significant for pruritus, burning, and dyspareunia ($p < .05$). Sexual function was also improved at time of reevaluation, as were depressive and anxiety symptoms ($p < .05$). No cases of vulvar intraepithelial neoplasia or cancer occurred during follow-up and vulvar architecture remained stable, although patients reported a significantly reduced need for topical steroids ($p < .0001$). Lastly, in postoperative biopsies, inflammatory infiltrate was stable or reduced, and the distribution of elastic fibers was comparable or restored in most patients.

Conclusions: Patient satisfaction with fat grafting is detectable up to 11 years after surgery, and as such, it may represent a valid therapeutic option in selected cases of VLS.

Key Words: fat grafting, vulvar lichen sclerosus, regenerative medicine

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Vulvar lichen sclerosus (VLS) is a chronic inflammatory dermatosis that commonly affects the anovulvar skin, leading to anatomical distortions, impaired sexual function, decreased quality of life (QoL), and increased risk of vulvar cancer.[1]

The most common symptom associated with VLS is itching, which may be accompanied by pain or burning, as well as dyspareunia-apareunia and dysuria.[2]

The main histological characteristics of VLS include hyperkeratosis, hyalinization of the upper dermis, "band-like" dermal inflammatory infiltrate, decrease of vessel density, and reduction in elastic fibers in the superficial dermis.[3] A reduction in estrogen receptor expression and an increase in CD8+ T cells are further markers of VLS.[4,5]

Topical corticosteroids (TCSs) are used as first-line treatment in all patients because they contrast inflammation as well as reducing symptoms and the risk of malignant transformation. However, they may not be as effective in treating loss of elasticity, atrophy, and permanent alterations of the vulvar architecture.[6]

Up until recent years, surgical treatment for VLS has been limited to cases of severe vaginal introitus stenosis, urinary retention, and preneoplastic and neoplastic lesions.[7,8] However, surgery could gain a new role as a regenerative treatment.

Autologous fat grafting has been used for several decades in various branches of medicine due to its regenerative and immunomodulatory properties and its negligible morbidity.[9,10] The fat graft contains mature and nonmature adipocytes, fibroblasts, hematopoietic stem cells, and adipose-derived stromal cells (ASCs). Adipose-derived stromal cells induce the production of "soft" type 1 and 2 collagen and secrete growth factors with an immunomodulatory, proangiogenic, antifibrotic, and pain fiber modulation effect.[11]

The rationale of fat grafting in VLS consists of four main mechanisms: reduction of inflammation, regeneration of tissues through an angiogenetic and antifibrotic action, volume increase by the means of a "cushion effect," which improves both vulvar morphology and dyspareunia, and pain fiber control.[8,12]

However, few studies, which are mainly based on a short-term follow-up, have reported the use of fat grafting for the treatment of VLS— alone[13–18] or in combination with platelet-rich plasma (PRP).[19–21]

On the basis of this background, the aim of our study was to evaluate the long-term efficacy of fat grafting in VLS on a large cohort of patients. The primary outcome of our study was long-term patient satisfaction. The secondary outcomes included modifications of symptoms, psychosexual wellbeing, vulvar hydration, and histological findings after surgery.

MATERIALS AND METHODS

Eligible for this observational study with a retrospective collection of data were all women aged 18–85 years, with a clinical and histological diagnosis of VLS who underwent at least one surgical treatment with autologous vulvar fat grafting at our center, between November 2010 and December 2019.

All patients had been treated with a 3-month TCS regimen at time of diagnosis and were on maintenance treatment with TCSs at time of enrollment. Women were considered candidates for surgery if they reported a persistence of symptoms, skin atrophy or anelasticity, and/or vulvar anatomical distortions despite first-line treatment. None of the patients received other kinds of medical or surgical treatment before or after fat grafting apart from steroid maintenance treatment.

All women enrolled in the study were invited to return to our center for a clinical reevaluation between November and December 2021.

The study was approved by the local ethical committee (protocol number 0037091 U, Comitato Etico di Milano Area 2, September 14, 2021) and all patients gave their consent to take part in the study.

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Fat Grafting

The surgical procedure was carried out under sedation and local anesthesia by the same plastic surgeon and gynecologist in all cases in a day surgery regimen. All women were administered ultrashort antibiotic prophylaxis and wore antithrombotic stockings before surgery.

The donor site was infiltrated using a 16-Gauge 180-mm multihole infiltration cannula with 100 mL of a solution composed of 500 mL 0.9% normal saline plus 40 mL lidocaine and 1 mL 1:500.000 adrenaline. Microfat clusters were obtained from the inner thigh, the abdomen, or the knee using a 14-Gauge 140-mm multihole cannula. The fat was then transferred into 60-mL syringes, washed with saline solution, and decanted for 10 minutes. Then, it was separated from the liquid part of the solution, which was discarded, and injected in the entire surface of the vulva using multiple needle placements (the location was the same for all patients and included the clitoral hood, the periurethral area, the labia minora, the interlabial sulci, the posterior fourchette, and the perianal area) using an 18-Gauge needle. A percutaneous release technique named "rigottomy," which consists in moving the tip of the needle in a "fan-like modality," was used. Injection modality was the same for all patients regardless of the severity of VLS. An average amount of 25 mL of fat was injected during each procedure. Women were prescribed nonopioid analgesics for 7 days after surgery.[22]

Each patient underwent the minimum number of surgical procedures deemed necessary to achieve an improvement in terms of symptoms and/or skin elasticity. Three months after each procedure, patients who reported a partial yet not complete improvement (established as a numerical rating scale [NRS] value for itching, burning, dyspareunia, and dysuria >1 and on the basis of a vulvoscopic examination for the evaluation of skin elasticity) were invited to undergo a further treatment with fat grafting, which was performed at least 4 months after the previous procedure. A maximum number of procedures per patient was not established.

Follow-Up

All patients enrolled in the study were contacted for a postoperative reevaluation that included a vulvoscopic examination, a vulvar biopsy, and handing out of validated questionnaires.

Vulvoscopy was performed to assess epithelial hydration, to rule out the presence of precancerous or invasive lesions, and to describe vulvar architecture. Vulvar architecture was graded using the CIV classification,[23] which we report as follows: grade 1: normal anatomy; grade 2: partial clitoral phimosis and/or partial involvement of one or both interlabial sulci; grade 3: total clitoral phimosis or total involvement of one or both interlabial sulci; grade 4: presence of both grade 3 criteria and/or vulvar introitus less than 2 cm; and grade 5: vulvar introitus less than 1 cm.

Vulvar biopsies were aimed at analyzing histological modifications that may have occurred after surgery and were compared with biopsies performed before surgery, when available. Each woman underwent a single postoperative 4-mm punch biopsy in the vulvar area deemed more involved by VLS on the basis of the vulvoscopic examination.

Lastly, women were asked to fill in a series of validated questionnaires, which we describe herein.

A patient satisfaction questionnaire, based on a 5-point Likert scale (1: very satisfied with the fat grafting procedure; 2: satisfied; 3: uncertain; 4: unsatisfied; and 5: very unsatisfied). Women were asked to rate their satisfaction at time of reevaluation.

A 0–10 NRS for the assessment of symptoms ("0" indicating absence of symptoms and "10" indicating the worst possible symptom intensity).[24] Women were asked to rate pruritus, burning, dyspareunia, and dysuria at time of reevaluation. Values were compared with preoperative NRS scores reported in medical records.

The Female Sexual Function Index (FSFI), a 19-item multidimensional questionnaire that assesses 6 key dimensions of sexual function (desire, arousal, lubrication, orgasm, pain, satisfaction). A total score 26.55 or lower is indicative of sexual dysfunction.[25] Women filled in 2 FSFI questionnaires at time of reevaluation; one regarding their sexual function before surgery, the other regarding their current sexual function.

The Hospital Anxiety and Depression Scale (HADS), which is divided into 2 scales, one for anxiety (HADS_A) and one for depression (HADS_D). Each scale can be scored independently. Scores range from 0 to 21, with higher scores denoting poorer psychological conditions. Women were asked to answer the questions both retrospectively, concentrating on their psychological status before surgery, and on their current status at time of reevaluation.[26]

Additional information regarding age, menopausal status, and use of steroids or other topical treatments before and after fat grafting was collected.

Histologic Analysis

Histological specimens were stained with hematoxylin and eosin to evaluate the presence or the absence of hyperkeratosis and to determine the amount of inflammatory infiltrate and of fibrosis.

Hyperkeratosis was defined as a thickening of the stratum corneum with loss of the normal "basket weave" appearance.

The inflammatory infiltrate was defined as "absent" when no inflammatory elements were found, "mild" if focal or multifocal foci of few inflammatory elements were present, "moderate" when multifocal inflammatory elements arranged in aggregates or in an interstitial pattern were evident, and "severe" when a diffuse infiltrate including several inflammatory elements and involving most of the lamina propria was detected. The quantity of CD4-positive and CD8-positive lymphocytes and of CD57-positive elements was also estimated by using immunohistochemical staining (CD4 Dako clone 4B12, CD8 Dako clone C8/144B, CD57 Dako clone TB01).

Fibrosis was defined as "absent" when not histologically evident, "mild" when only few focal fibrotic strands were observed in the lamina propria, "moderate" when focal fusion of the fibrotic strands was detected, and "severe" when diffuse or plurifocal areas of dense fibrotic material were evident.

Edema, epidermal acanthosis or atrophy, elastophagocytosis, vasculitis (cuffing of lymphocytes around vessels), and the immunohistochemical expression of estrogen receptors in the epithelial cells were also investigated.

Elastic fibers were evaluated with orcein stain and defined as "normal" or "reduced" compared with their usual representation in normal specimens.

Estrogen receptors were defined as "expressed" even when their nuclear expression was only focal or mild.

In women in whom both preoperative and postoperative biopsies were available, a comparison between the 2 histological specimens was performed. This assessment was carried out only on the more reproducible histological features, that is, elastic fibers, inflammatory infiltrate, and estrogen receptor expression.

"Improvement" in the quantity of elastic fibers was defined as a postoperative increase in the amount of elastic fibers, whereas "worsening" was defined as the postoperative reduction in quantity.

Inflammatory infiltrate was considered "improved" when it was reduced and "worsened" when it was increased after surgery.

Estrogen receptor expression was considered "reduced" when the postoperatory biopsy showed no signs of previously expressed receptors; "stable" when the entity of the postoperative

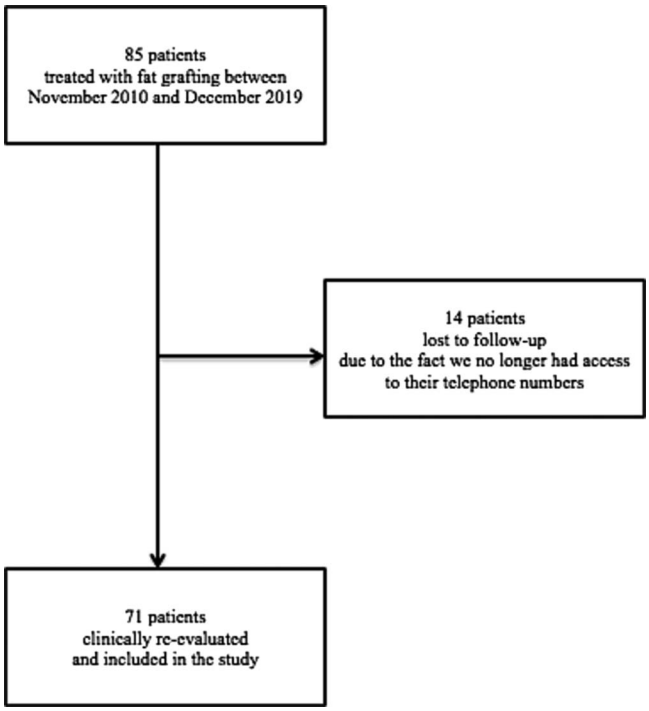

FIGURE 1. Flowchart of the selection process of patients included in the study.

receptor expression was comparable with the preoperative one and "increased" when receptor expression was present postoperatively in patients in whom it was absent before fat grafting.

Statistical Analysis

Descriptive statistics were used for demographic and medical data; continuous variables are presented as means with SDs (M ± SD), medians and interquartile ranges (IQRs), and categorical data as percentages and frequencies. The differences in the means of the NRS for the assessment of pruritus, burning, dyspareunia and dysuria, and mean of FSFI were tested using the usual *t* test.

Due to the heterogeneity in follow-up time, we divided women into 3 subgroups according to the year in which they underwent the procedure: 2016–2019 (2- to 5-year follow-up), 2013–2015 (6- to 8-year follow-up), and 2010–2012 (9- to 11-year follow-up). The categorization into 3 subgroups was used for the evaluation of patient satisfaction, symptom modifications, and sexual function.

Differences in HADS results and in the proportion of women using TCSs/other treatments were tested using the McNemar test. Differences in the proportion of very satisfied/satisfied patients were tested using the usual chi-square test.

RESULTS

A total of 85 patients with VLS were treated with vulvar fat grafting between November 2010 and December 2019. Among these, 71 were reevaluated between November and December 2021. In the remaining 14 cases, we were not able to contact patients due to the fact we no longer had access to their telephone numbers. A flowchart representing the study population is provided in Figure 1.

The VLS diagnosis was performed at a median age of 46 years (IQR = 38–57), whereas the median age at time of fat grafting was 57 years (IQR = 43–64). A total of 40 women were postmenopausal at time of reevaluation (54.9%).

Timing of fat grafting and the corresponding follow-up time were the following: 27 women underwent the procedure between 2016 and 2019 (2- to 5-year follow-up), 21 were treated between 2013 and 2015 (6- to 8-year follow-up), and 23 were treated between 2010 and 2012 (9- to 11-year follow-up).

The mean number of fat grafting procedures received by each woman was 2.2. The distribution of women according to the number of procedures was the following: 19 underwent 1 procedure (26.8%), 26 underwent 2 (36.6%), 19 underwent 3 (26.8%), 5 underwent 4 (7%), and 2 patients underwent 5 (2.8%).

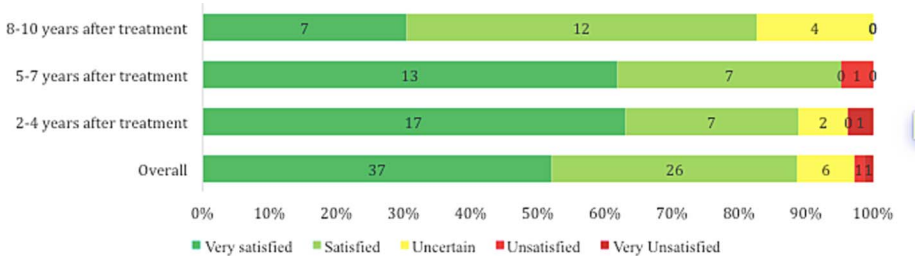

FIGURE 2. Long-term satisfaction of patients treated with vulvar fat grafting.

TABLE 1. Assessment of Subjective Symptoms and Sexual Function Before and After Treatment

	All				Period of treatment									
					2016–2019				2013–2015				2010–2012			
	N	Mean ± SD Before treatment	Mean ± SD After treatment	p^a	N	Mean ± SD Before treatment	Mean ± SD After treatment	p^a	N	Mean ± SD Before treatment	Mean ± SD After treatment	p^a	N	Mean ± SD Before treatment	Mean ± SD After treatment	p^a
Subjective symptoms (NRS)																
Pruritus	70	7.3 ± 2.8	1.4 ± 2.0	<0.0001	26	7.4 ± 2.8	1.4 ± 2.4	<0.0001	21	7.5 ± 2.8	1.7 ± 2.0	<0.0001	23	7.0 ± 3.1	1.3 ± 1.8	<0.0001
Burning	70	6.5 ± 3.3	1.3 ± 2.3	<0.0001	26	7.0 ± 3.1	1.4 ± 2.6	<0.0001	21	7.0 ± 3.1	1.5 ± 2.5	<0.0001	23	5.3 ± 3.4	1.0 ± 1.8	<0.0001
Dyspareunia[b]	55	7.3 ± 3.3	1.8 ± 2.9	<0.0001	20	8.3 ± 2.4	1.7 ± 2.7	<0.0001	15	6.9 ± 3.6	1.2 ± 2.7	<0.0001	20	6.6 ± 3.8	2.3 ± 3.2	0.0002
Dysuria	70	1.3 ± 2.8	0.6 ± 2.1	0.0129	26	1.4 ± 2.8	0.6 ± 2.1	0.0357	21	1.2 ± 3.0	0.5 ± 2.2	0.1374	23	1.4 ± 2.8	0.6 ± 2.0	0.3347
Sexual function (FSFI)																
Desire	65	2.8 ± 1.2	3.5 ± 1.3	<0.0001	26	2.6 ± 1.3	3.9 ± 1.2	0.0003	20	3.1 ± 1.2	3.5 ± 1.2	0.0828	21	2.7 ± 1.1	3.0 ± 1.4	0.3299
Arousal	44	2.9 ± 1.2	3.9 ± 1.0	<0.0001	19	2.7 ± 1.2	4.2 ± 1.1	0.0008	14	3.2 ± 1.3	3.7 ± 0.9	0.1349	11	3.0 ± 1.2	3.7 ± 1.2	0.0362
Lubrification	44	3.4 ± 1.6	4.2 ± 1.4	0.0045	19	3.3 ± 1.6	4.2 ± 1.2	0.0098	14	4.1 ± 1.7	4.3 ± 1.6	0.5964	11	3.0 ± 1.6	3.9 ± 1.5	0.1130
Orgasm	48	3.4 ± 1.5	4.4 ± 1.2	<0.0001	22	3.2 ± 1.6	4.5 ± 1.1	0.0011	14	3.8 ± 1.6	4.1 ± 1.1	0.3175	12	3.3 ± 1.5	4.3 ± 1.4	0.0251
Satisfaction	46	3.6 ± 1.3	4.6 ± 0.8	<0.0001	20	3.4 ± 1.4	4.9 ± 0.7	<0.0001	14	3.9 ± 1.3	4.4 ± 0.7	0.0951	12	3.6 ± 1.2	4.4 ± 0.8	0.0866
Pain	42	2.4 ± 1.5	4.1 ± 1.4	<0.0001	19	2.0 ± 1.4	4.4 ± 1.5	<0.0001	12	2.8 ± 1.6	4.2 ± 1.1	0.0016	11	2.7 ± 1.8	3.5 ± 1.8	0.1485

[a] t test.
[b] Patients without a sexual partner are excluded from the analysis.
FSFI indicates Female Sexual Function Index; NRS, numerical rating scale.

TABLE 2. Psychological Morbidity Before and After Treatment

Psychological morbidity (HADS)	All (N = 71)				
	Before treatment		After treatment		
	N	%	N	%	p^a
Depression					0.0029
Abnormal	9	12.7	5	7.0	
Borderline	15	21.1	10	14.1	
Normal	47	66.2	56	78.9	
Anxiety					0.0290
Abnormal	10	14.1	5	7.0	
Borderline	16	22.5	8	11.3	
Normal	45	63.4	58	81.7	

[a]McNemar test.

HADS indicates Hospital Anxiety and Depression Score.

Patient satisfaction after surgery at time of reevaluation is reported in Figure 2. Overall, most patients (88.7%) declared themselves very satisfied/satisfied with the procedure. When stratifying patients according to follow-up times, differences in satisfaction were not statistically significant.

All symptoms were improved after surgery. In particular, the difference was statistically significant for pruritus, burning, and dyspareunia, as well as for dysuria among women treated in 2016–2019 (Table 1).

Mean FSFI parameters for sexual function were significantly improved at time of reevaluation except for lubrication among the 2013–2015 and the 2010–2012 groups and for arousal and orgasm in the 2013–2015 group. A total of 57 women (82.6%) declared having a sexual partner postoperatively compared with 59 (85.5%) before treatment. Results are reported in Table 1.

The reduction of both depression (from 12.7% to 7%) and anxiety (from 14.1% to 7%) after surgery was statistically significant (Table 2).

No cases of vulvar intraepithelial neoplasia or invasive vulvar cancer occurred during follow-up.

The distribution of the enrolled women according to the CIV classification before treatment was the following: 2 (3.3%) were classified as grade 1, 21 (35%) as grade 2, 23 (38.3%) as grade 3, 14 (23.3%) as grade 4, and no patients were classified as grade 5. At time of follow-up, 2 women (3.3%) were defined as grade 1, 19 (31.7%) as grade 2, 24 (40%) as grade 3, 14 (23.3%) as grade

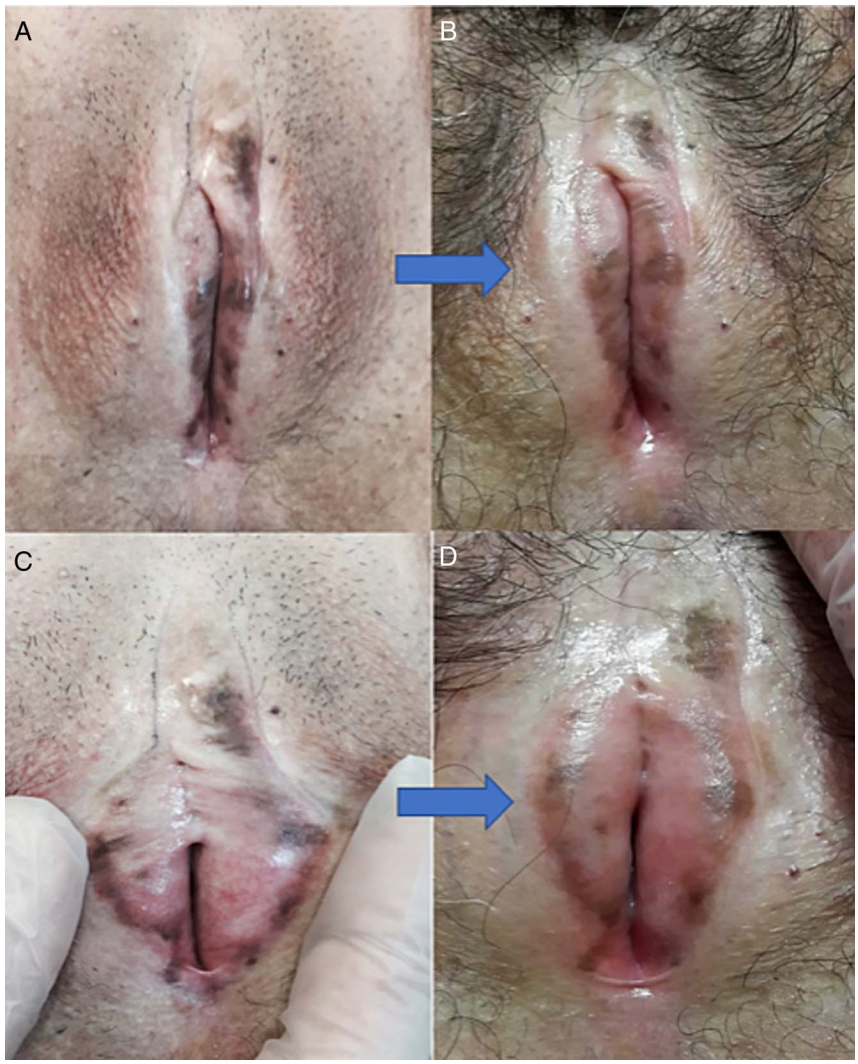

FIGURE 3. Pictures A and C represent a patient before treatment; pictures B and D represent the same patient 6 months after treatment.

TABLE 3. Histological Features After Treatment

	All (N = 57)	
	N	%
Hyperkeratosis		
Absent	35	61
Present	22	39
Edema		
Absent	47	82.5
Present	10	17.5
Inflammatory infiltrate		
Absent	14	24.6
Mild	34	59.6
Moderate	9	15.8
Severe	0	—
Epidermal changes		
Acanthosis	47	82.5
Atrophy	10	17.5
Elastophagocytosis		
Absent	57	100
Present	0	—
Vasculitis		
Absent	55	96.5
Present	2	3.5
Elastic fibers		
Normal	22	39
Reduced	35	61
Fibrosis		
Absent	39	68.4
Mild	15	26.3
Moderate	3	5.3
Severe	0	—
Estrogen receptor expression		
Absent	37	65
Present	20	35
CD4 and CD8		
Not evaluable	2	3.5
CD4 > CD8	2	3.5
CD8 > CD4	8	14
CD4 = CD8	45	79
CD57		
Absent	18	31.6
Present	39	68.4

4, and 1 as grade 5 (1.7%). The overall mean difference in CIV values before and after fat grafting was 0.1 (SD = 0.9, $p = .58$). When dividing women according to time of follow-up, differences remained non-statistically significant. An example of the clinical result of the treatment with fat grafting is reported in Figure 3.

The need for TCSs was significantly reduced at time of follow-up ($p < .0001$, McNemar test). In particular, the use of TCSs 2 times or more a week decreased from 28 women (39%) preoperatively to 8 women (11.3%) postoperatively, whereas the number of women declaring they never used TCSs or used TCSs only on demand rose from 43 (60.6%) to 63 (88.7%).

A total of 57 women underwent a vulvar biopsy after fat grafting. In 16 cases, a preoperative biopsy was also performed. The histological features of the postoperatory biopsies are shown in Table 3, whereas the comparison between preoperative and postoperative specimens is reported in Table 4 and in Figure 4. Inflammatory infiltrate, elastic fibers, and estrogen receptor expression were stable or improved after surgery in most cases (68.8%, 75%, and 87.5%, respectively).

DISCUSSION

Although high-potency topical steroids reduce symptoms in as many as 70% of women,[8] they are generally not effective in the treatment of anatomical distortions once these occur. Moreover, a common adverse effect of TCSs is atrophy, which may aggravate the thinning of tissues induced by VLS.[27]

The benefit of autologous regenerative treatments in VLS has been reported in an increasing number of recent studies, although the evidence is still limited due to exiguous study populations, heterogeneous treatment types, and short follow-up periods.[8,13–22,28,29]

In 2015, Boero et al. treated 36 women with VLS with fat grafting. Among these, 75% reported improved caliber and elasticity of the vaginal introitus, 83% reported an increased volume of labia majora and minora, and 94% no longer presented scratching lesions. Improvement in QoL and in sexual function was significant, and histopathological parameters were improved in 94% of cases at a 24-month follow-up.[13]

Similar results were found by Almadori and coworkers, who carried out a 13-month follow-up on 33 women with VLS treated with fat grafting. Symptoms were significantly decreased and sexual function was significantly improved after treatment in all patients. Moreover, women reported a significant improvement in intimate contact, anxiety, and depression.[14]

In our current series, the reduction of symptoms and improvement in QoL after fat grafting persisted up to 11 years after treatment. Moreover, women reported a significant reduction in the use of TCSs, and no cases of vulvar intraepithelial neoplasia or cancer were diagnosed during follow-up. A further important result of our study is represented by the significant improvement in sexual function, which may be impaired by VLS in 3 ways. Firstly, skin atrophy may cause tearing; secondly, pain and the fear of pain may reduce arousal and lubrication and cause a contraction of the pelvic muscles. Lastly, anatomical distortions may represent a mechanical obstacle to penetrative intercourse.[30]

In their case control study, Van de Nieuwenhof et al. compared QoL and FSFI of 187 female patients with VLS with 61 healthy controls. Among all domains of the QoL questionnaire, VLS interfered the most with sexual functioning, and patients

TABLE 4. Changes in Histological Features After Treatment

	All (N = 16)	
	N	%
Inflammatory infiltrate	7	43.8
Stable		
Improvement	4	25.0
Worsening	5	31.3
Elastic fibers	8	50.0
Stable		
Improvement	4	25.0
Worsening	4	25.0
Estrogen receptor expression	10	62.5
Stable		
Improvement	4	25.0
Worsening	2	12.5

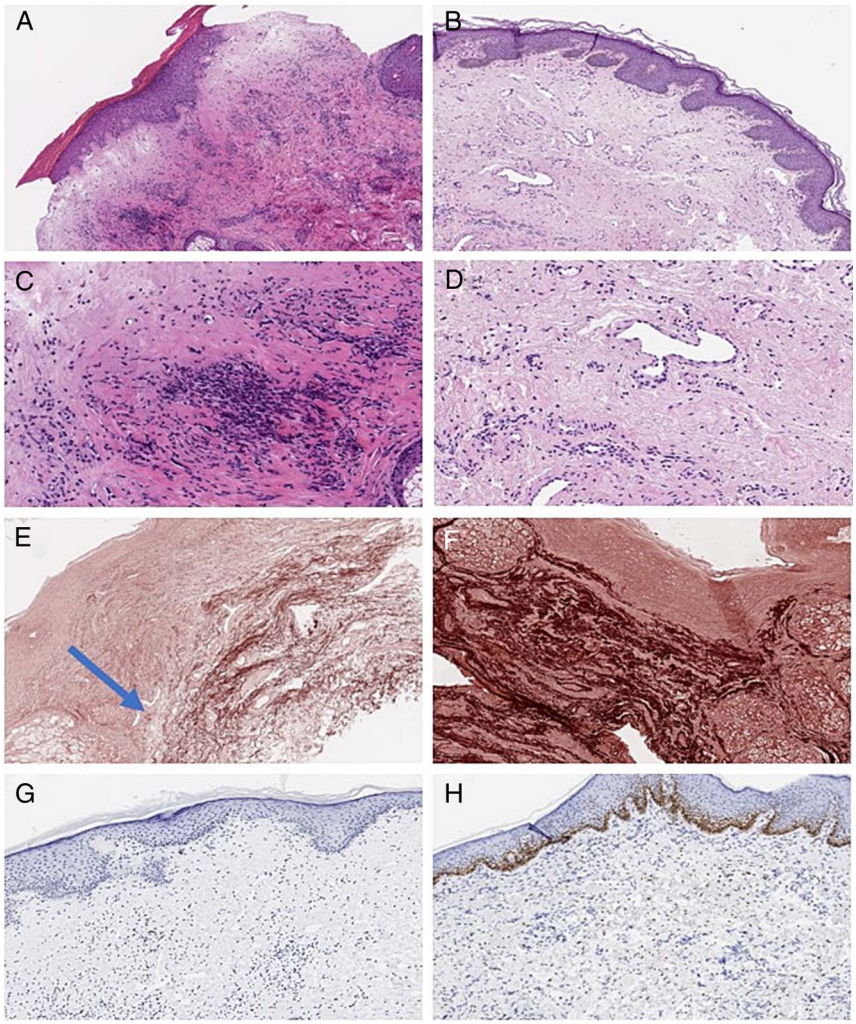

FIGURE 4. The left column shows images of histological samples taken before treatment, the right column shows samples taken after treatment in the same patients. A, Hematoxylin-eosin preparation showing acanthosis, hyperkeratosis, collagenization of the subepithelial chorion, and moderate-grade inflammatory infiltrate. B, Hematoxylin-eosin preparation showing no evidence of collagenization of the subepithelial chorion, absence of inflammatory infiltrate. C, Detail of the inflammatory infiltrate. D, Detail of the absence of inflammatory infiltrate. E, Orcein preparation showing a band of rarefaction/absence of elastic fibers. F, Orcein preparation showing the presence of elastic fibers at the immediate subepidermal site. G, Immunohistochemical staining for estrogen receptors showing absence of significant expression in the epidermal site and in the subepithelial chorion, in a premenopausal patient before treatment. H, Nuclear expression of estrogen receptors in the epidermal site and in subepithelial chorion in a premenopausal patient after treatment.

significantly scored lower on all subscales of the FSFI. The smallest difference was on the subset "desire."[30]

Similar results were found in our current series, in which sexual function was improved for all subsets postoperatively. The most relevant difference regarded pain (from 2.4 to 4.1 FSFI points), whereas the less relevant difference regarded desire (from 2.8 to 3.5 FSFI points). Although an improvement was found in all groups, statistical significance decreased with lengthening of follow-up time. This may be explained by the fact that postmenopausal vulvovaginal atrophy may have subsequently occurred. Moreover, the percentage of women declaring they had a sexual partner was reduced at time of reevaluation, also due to the fact they no longer had a life partner.

The comparison of anatomical distortions before and after surgery showed an almost absent progression of architectural modifications, even in women whose follow-up time was the longest. This result is extremely encouraging, considering the chronic and progressive nature of VLS.

Most patients presented with mild or absent inflammation and fibrosis postoperatively, whereas elastic fiber reduction and absence of estrogen receptors were found in more than half of patients after surgery. When comparing preoperative and postoperative biopsies, inflammatory infiltrate was stable or reduced in nearly two thirds of patients. The distribution of elastic fibers was comparable or restored in most patients, and estrogen receptor expression was stable or improved in nearly 90% of patients. Considering that VLS is a chronic disorder, the evidence of stable or improved histological features in most cases was not expected.

The main strengths of our study consist in its considerable sample size, compared with that of other studies, and in the length of follow-up time. Moreover, our postoperative evaluation also included a histological analysis, although a comparison of preoperative and postoperative specimens was possible only in a limited percentage of cases. Further limitations are represented by the monocentric nature of the study, the heterogeneity in follow-up time and in the number of surgical procedures performed on each

patient, and the retrospective collection of data regarding sexual function and psychological wellbeing before treatment. Lastly, a control group, which would have conferred greater strength to our results, was not included in our analysis.

CONCLUSIONS

In our case series, most patients with VLS were satisfied with fat grafting, and satisfaction rates remained elevated up to 11 years after surgery. After first-line treatment with TCSs, fat grafting may provide an added value in terms of an improvement in sexual function and in psychological wellbeing. It may also prove useful in reducing the need for TCSs when used as part of maintenance treatment.

REFERENCES

1. Krapf JM, Mitchell L, Holton MA, et al. Vulvar lichen sclerosus: current perspectives. *Int J Womens Health* 2020;12:11–20.
2. Lewis FM, Tatnall FM, Velangi SS, et al. British Association of Dermatologists guidelines for the management of lichen sclerosus, 2018. *Br J Dermatol* 2018;178:839–53.
3. Robboy SJ, Mutter GL, Prat J, et al. Lichenoid dermatoses, from vulvar dermatoses and infections. In: *Robboy's Pathology of the Female Reproductive Tract*. London: Elsevier, Churchill Livingstone; 2009:32–4.
4. Lagerstedt M, Huotari-Orava R, Nyberg R, et al. Reduction in ERRα is associated with lichen sclerosus and vulvar squamous cell carcinoma. *Gynecol Oncol* 2015;139:536–40.
5. Bao Y, Li Z, Liu W, et al. Study of Langerhans cells and T lymphocytes in vulvar lichen sclerosus lesions. *Australas J Dermatol* 2021;62:e217–22.
6. 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.
7. Lee A, Fischer G. Diagnosis and treatment of vulvar lichen sclerosus: an update for dermatologists. *Am J Clin Dermatol* 2018;19:695–706.
8. van der Sluis N, Scheers ECAH, Krenning G, et al. Autologous lipoaspirate as a new treatment of vulvar lichen sclerosus: a review on literature. *Exp Dermatol* 2022;31:689–99.
9. Krastev TK, Schop SJ, Hommes J, et al. Autologous fat transfer to treat fibrosis and scar-related conditions: a systematic review and meta-analysis. *J Plast Reconstr Aesthet Surg* 2020;73:2033–48.
10. Shauly O, Gould DJ, Ghavami A. Fat grafting: basic science, techniques, and patient management. *Plast Reconstr Surg Glob Open* 2022;10:e3987.
11. Evans BGA, Gronet EM, Saint-Cyr MH. How fat grafting works. *Plast Reconstr Surg Glob Open* 2020;8:e2705.
12. Cuomo R, Giardino FR, Nisi G, et al. Fat graft for reducing pain in chronic wounds. *Wound Repair Regen* 2020;28:780–8.
13. Boero V, Brambilla M, Sipio E, et al. Vulvar lichen sclerosus: a new regenerative approach through fat grafting. *Gynecol Oncol* 2015;139:471–5.
14. Almadori A, Hansen E, Boyle D, et al. Fat grafting improves fibrosis and scarring in vulvar lichen sclerosus: results from a prospective cohort study. *J Low Genit Tract Dis* 2020;24:305–10.
15. 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.
16. Stark L, Razzaque M, Yoon J, et al. Safety and feasibility of autologous micro-fragmented adipose tissue injections for the treatment of vaginal atrophy, vulvovaginal dystrophy, and stress urinary incontinence: an observational case series. *EMJ Urol* 2020;8:29–37.
17. Monreal J. Safety and efficacy of stromal vascular fraction enriched fat grafting therapy for vulvar lichen sclerosus. *Cureus* 2020;12:e7096.
18. Newman N, Rogowski RN, Newman D, et al. Autologous adipose-derived stem cell treatment for women with genital lichen sclerosus. *Gynecol Reprod Health* 2018;2:1–4.
19. 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–1e.
20. Kim SH, Park ES, Kim TH. Rejuvenation using platelet-rich plasma and lipofilling for vaginal atrophy and lichen sclerosus. *J Menopausal Med* 2017;23:63–8.
21. Gutierrez-Ontalvilla P, Giner F, Vidal L, et al. The effect of lipofilling and platelet-rich plasma on patients with moderate-severe vulvar lichen sclerosus who were non-responders to topical clobetasol propionate: a randomized pilot study. *Aesthetic Plast Surg* 2022;46:2469–79.
22. Nguyen PS, Desouches C, Gay AM, et al. Development of micro-injection as an innovative autologous fat graft technique: the use of adipose tissue as dermal filler. *J Plast Reconstr Aesthet Surg* 2012;65:1692–9.
23. Boero V, Liverani CA, Brambilla M, et al. The "CIV classification," a new proposal for the architectural grading of vulvar lichen sclerosus. *J Low Genit Tract Dis* 2021;25:291–5.
24. Paul SM, Zelman DC, Smith M, et al. Categorizing the severity of cancer pain: further exploration of the establishment of cutpoints. *Pain* 2005;113:37–44.
25. 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.
26. Costantini M, Musso M, Viterbori P, et al. Detecting psychological distress in cancer patients: validity of the Italian version of the Hospital Anxiety and Depression Scale. *Support Care Cancer* 1999;7:121–7.
27. Ayhan A, Guven S, Guvendag Guven ES, et al. Topical testosterone versus clobetasol for vulvar lichen sclerosus. *Int J Gynaecol Obstet* 2007;96:117–21.
28. Tedesco M, Bellei B, Garelli V, et al. Adipose tissue stromal vascular fraction and adipose tissue stromal vascular fraction plus platelet-rich plasma grafting: new regenerative perspectives in genital lichen sclerosus. *Dermatol Ther* 2020;33:e14277.
29. 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.
30. Van de Nieuwenhof HP, Meeuwis KA, Nieboer TE, et al. The effect of vulvar lichen sclerosus on quality of life and sexual functioning. *J Psychosom Obstet Gynaecol* 2010;31:279–84.