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Improvement in quality of life and sexual function in patients affected by vulvar lichen sclerosus treated with combined autologous platelet-rich plasma and fat grafting

Background: Vulvar lichen sclerosus (LS) severely impairs patients' quality of life. *Objectives*: To evaluate the impact of a combined application of autologous platelet-rich plasma (PRP) and fat grafting as treatment for vulvar LS on patient quality of life. *Materials & Methods*: We reviewed the clinical charts of 72 patients affected by LS, who underwent regenerative surgery. The patients' quality of life was assessed using: the Dermatology Life Quality Index (DLQI), the Skindex-29, the Female Sexual Function Index (FSFI) and the patient-administered - Clinical Scoring System (CSS). *Results*: After reconstructive surgery, all scores improved: Skindex-29 (-31.8 [IQR: 42.1, -21.8] points; $p<0.001$), FSFI (7.6 [IQR: 2.7, 14.7)] points; $p<0.001$), Patient-administered CSS (-24 [IQR: -30, -15] points; $p<0.001$), DLQI (-9 [IQR: -17, -7] points; $p<0.001$), Physician-administered CSS (-5 [IQR: -7, -5] points; $p<0.001$), and IGA (median ΔIGA: -4, IQR: -4, -3; $p<0.001$). *Conclusion*: Combined treatment with PRP and fat grafting proved to be effective in improving the quality of life of patients with vulvar LS.

Key words: lichen sclerosus, quality of life, sexual function, autologous platelet-rich plasma, fat grafting, lipofilling

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Lichen sclerosus (LS) is a chronic inflammatory disease which mostly involves anogenital areas [1, 2]. LS more frequently affects women than men [1], and has an estimated prevalence of 1.7- 3% [3, 4]. The most common symptoms are itching, burning, and dyspareunia [1]. Long-term inflammation may lead to atrophy and scarring, resulting in changes of external genitalia, such as fusion of the labia minora to the labia majora, burying of the clitoris, and narrowing of the introitus [2]. In the worst cases, tissue anatomy is completely compromised, causing sexual and urinary impairment. Thus, LS often causes severe psychological distress in affected patients, affecting social, occupational and sexual activities, severely impairing quality of life (QoL) [5-8].

The standard of care consists of topical potent or very potent corticosteroids [1, 9]. This treatment effectively reduces itching and burning and prevents scarring if continuously used [10, 11]. Other therapeutic options include tacrolimus, pimecrolimus, systemic steroids, and photodynamic therapy [9].

In recent years, new regenerative approaches have been investigated for LS and contribute alongside standard topical therapy to improve tissue regeneration and scarring. Intradermal platelet-rich plasma (PRP) injections have been the most widely investigated technique [12-16] and to a lesser extent, fat grafting [11, 17], stromal vascular fraction (SVF)-enriched fat grafting [18], or purified adipose-derived stem cells [19]. These techniques have mostly been used separately. In 2010, our study group first proposed the combined and repeated use of PRP and fat grafting for the treatment of LS scar defects [20].

PRP has been widely used as a complement to tissue regeneration procedures. The therapeutic potential of PRP is based on growth factors (GFs) contained in the granules of platelets, such as basic fibroblast, platelet-derived, epidermal, vascular endothelial, and connective tissue GFs, which play a key role in promoting wound healing. Moreover, these GFs seem to be involved in regulating inflammation [21], mitogenesis, chemotaxis, cell differentiation and cell metabolism [22]. Initially, PRP was predominantly applied in musculoskeletal and maxillofacial fields, whereas in recent years, it has started to be used for a range of dermatological indications, including wound healing, alopecia, scar revision, and dermal volume augmentation [23].

Fat grafting is widely used in reconstructive surgery to reshape and restore the volume and function of tissues [24, 25]. Its therapeutic properties mainly reside in mesenchymal stem cells (MSC) of the stromal vascular fraction of injected fat tissue [26]. MSC can create an anti-inflammatory environment [27], secrete GFs (which turns off T-cell surveillance and chronic inflammatory processes [28]), inhibit fibrosis and promote healing, with

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beneficial effects on the remodelling of the extracellular matrix [11].
Thus, the aim of the combined use of PRP and fat grafting for the treatment of LS is to contribute to fissure healing, to reduce cutaneous sclerosis, and to restore tissue volume and function.
The aim of the present study was to evaluate improvement in QoL and sexual function in patients affected by vulvar lichen sclerosus treated with combined autologous platelet-rich plasma and fat grafting.

Materials and methods

We retrospectively assessed the clinical charts of 72 patients affected by vulvar LS, who underwent regenerative surgery from 2012 to 2022. All patients had severe LS with typical clinical aspects, with severe atrophy, scarring and changes of the external genitalia, and in 51% of cases, histopathological confirmation was also present in the clinical records. The enrolled patients did not obtain an entirely satisfactory clinical response to conventional chronic steroid treatment, as pruritus, burning, dyspareunia, fissuring, scarring and atrophy persisted. Each patient was treated with a combination of both autologous PRP injections and fat grafting, according to our previously published protocol [20]. Patients were repeatedly treated over time if deemed necessary. The number of procedures varied based on the clinical response. Follow-up after the last surgery lasted for three months. During the treatment period, a few patients sporadically used short courses of topical corticosteroids in case of flares, and patients could freely use emollients as needed. Clinical assessment and questionnaire administration were carried out pre-operatively and at the third follow-up visit post-operatively.
Patients affected by systemic disease (platelet disorders, thrombocytopenia, bone marrow aplasia and cancer) and local disorders (infections, areas suspicious for squamous cell carcinoma) were excluded.

Surgical procedure

A blood sample of 50 mL was drawn from the patient and was centrifuged at 1,000 rpm for six minutes to obtain platelet-poor plasma. After further centrifugation (3,000 rpm for 12 minutes), a platelet-rich plasma (approximately 5 mL) was obtained (centrifuge diameter: 52.5 cm) [20].
After sedation and local infiltration of Klein solution, liposuction was carried out with a 2-mm cannula and a 10-mL syringe from a donor region. The lipoaspirate was washed with saline solution, decanted, and injected through a 19-gauge needle into the damaged area (range: 3-9 cc fat).
Finally, 5 mL of platelet-rich plasma was injected into the intradermal/subdermal and intramucosal/submucosal compartments of the damaged tissues [20].

Questionnaires and clinical scores

Four questionnaires were administered to the patients: the Dermatology Life Quality Index (DLQI) [29] and Skindex-29 [30], which are commonly used to assess the psychological impact of dermatological conditions on patients, and the Female Sexual Function Index (FSFI) [31] and Clinical Scoring System (CSS) – patient-administered symptom score [32], which are specifically designed to investigate female sexual function and LS-associated symptoms, respectively.
The DLQI is the first and most commonly used dermatology-specific QoL instrument [29, 33]. It consists of 10 questions concerning patients' perception of the impact of their skin disease on various aspects of their QoL and has been validated for dermatology patients [33]. The total DLQI score ranges from a minimum of 0 to a maximum of 30; the higher the score, the greater the impairment of QoL [33]. Based on the total score, in order to interpret the impact of the cutaneous disorder on QoL, a banding system (consisting of five bands) has been suggested: 0-1=no effect, 2-5=little effect, 6-10=moderate effect, 11-20=very large effect, and 21-30=extremely large effect on QoL [34].
Skindex-29 is used to investigate how often (*never, rarely, sometimes, often, all the time*), during the previous four weeks, the patient has experienced the effect described for each item. Seven items address the Symptoms domain (pruritus, burning, pain, irritation and bleeding), 10 items the Emotional domain (worried, embarrassed, ashamed, frustrated, depressed), and 12 items the Functioning domain (affects relationships, stay at home, hard to work and sleep less well). Each item results in a score between 0 and 100. The average of the combined domain-specific items is the domain score, and the average of all items combined is the total score [30]. Higher scores indicate lower levels of QoL. In previous reports, a Skindex-29 total score of 19.22 was proposed as the cut-off for a significant impact on QoL and Skindex-29 scores were subdivided into four bands: "little" (0-24), "mild" (25–31), "moderate" (32-43) and "severe" (44-100) impact on QoL [8, 35].
FSFI is a reliable psychometric tool for assessing the key dimensions of female sexual function on the basis of six domains: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain [31]. Higher scores indicate higher degrees of sexual functioning. Total scores range from 2 (severe impairment of sexual function) to 36 (normal sexual function). Higher scores indicate better sexual functioning. An FSFI total score of 26.55 or less is the cut-off point for distinguishing women with sexual dysfunction from those without [36].
The Investigator's Global Assessment (IGA) (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe) and Clinical Scoring System (CSS) for lichen sclerosus [32] were used for physician-based evaluations.
CCS for lichen sclerosus is a validated patient-administered symptom score and physician-administered clinical score for the evaluation of vulvar LS [32]. The patient-administered symptom score consists of four items: pruritus, burning, soreness, and dyspareunia. Each item was scored on a numerical rating scale, ranging from 0 (no complaints) to 10 (extreme complaints), with a minimum of 0 and a maximum of 40 for the total score. The physician-administered clinical score consists of six items: erosions, hyperkeratosis, fissures, agglutination, atrophy and stenosis. Each item was scored on a three-point Likert

scale, ranging from 0 to 2, with 0 representing normal findings, 1 moderate changes, and 2 severe changes. The physician-administered total score therefore ranged from a minimum of 0 to a maximum of 12. Higher scores of the patient-administered and physician-administered CSS are associated with more severe disease.
Demographics, age at first onset of symptoms and at the time of diagnosis, symptoms (pain, burning, itching) before topical treatment and before surgery, clinical condition (erosions, hyperkeratosis, fissures, agglutination, stenosis and atrophy), functional alterations (sexual, micturition), previous topical treatments and their benefit, preoperative biopsy, number of regenerative treatments with PRP and lipofilling, were recorded.

Statistics

Categorical variables were reported as counts and percentages; continuous variables as means with standard deviation (SD) and/or medians with inter-quartile range (IQR). The McNemar test was used to detect significant changes in symptoms, and a paired t-test was used for pre-/post-intervention comparisons. The chi-square test and two-independent sample t-test or Mann-Whitney test were used to compare categorical and continuous variables, respectively, between two groups. *P* values below 0.05 were considered significant. R version 3.6.3 (2020-02-29) was used for all statistical analyses [37].
The study was approved by the local ethics review board (n° CER Liguria: 530/2021 - DB id 11787).

Results

Seventy-two female patients with a mean age of 52.7±11.8 years (range: 26-75 years) were enrolled. The median diagnostic delay was two years (IQR: 1, 5). The median disease duration at the time of enrolment was seven years (IQR: 5, 10).
The median number of procedures (PRP injections and lipofilling) was 4 (IQR: 3, 8; range: 1-10) over a median period of 2.96 years (IQR: 1.08, 4.93).
The most common preoperative symptoms were burning (98.6%) and pruritus (95.8%), while functional impairment of sexual activity was recorded in 91.3% of patients and impairment of urination in 37.7% of cases (*figure 1*).
Post-operative symptoms improved; burning and pruritus were reported by a smaller number of patients, in 69.4% and 76.4% of cases, respectively. Moreover, pruritus was moderate/severe in 83.3% of cases preoperatively and in only 2.7% of cases post-operatively. Similarly, burning was moderate/severe

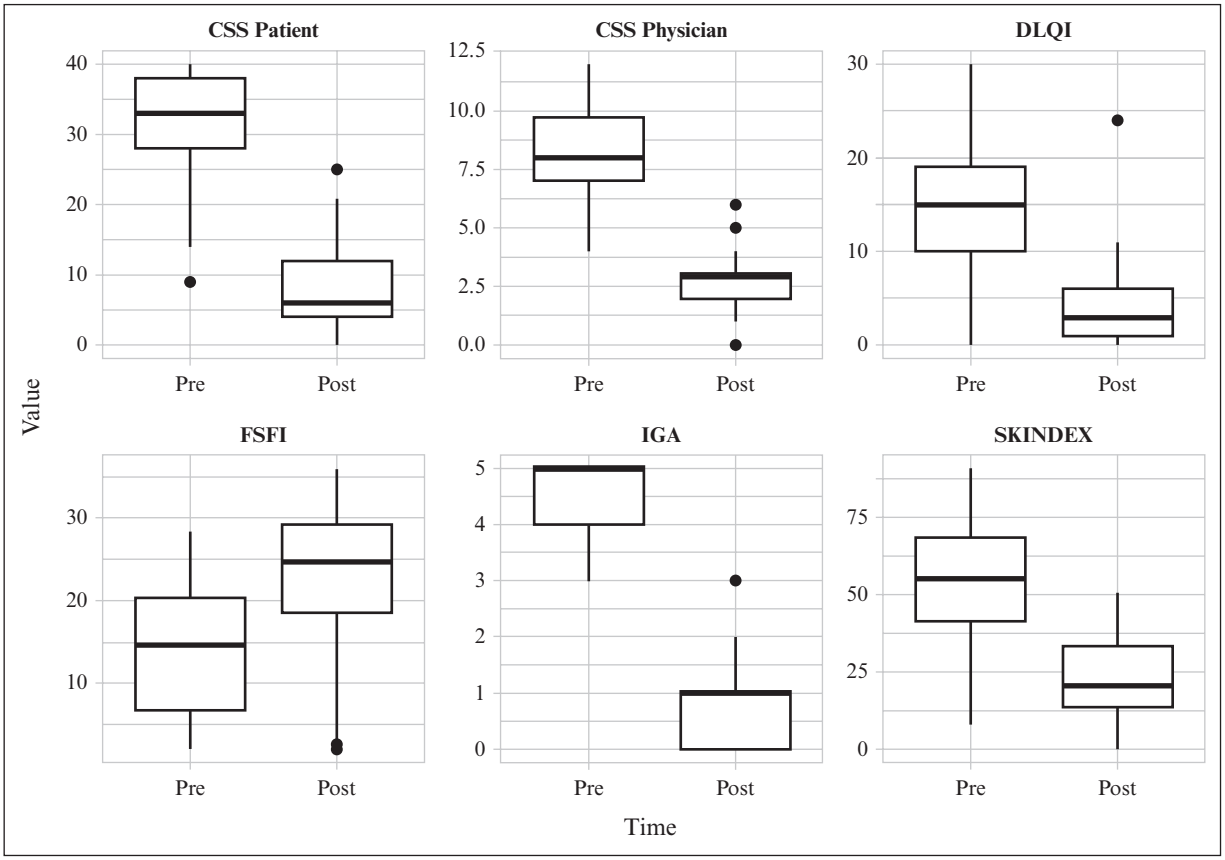

Figure 1. Boxplot summarizing average scores before and after intervention.

Table 1. Range of scores according to domains before and after surgery for SKINDEX-29, FSFI and CSS.

Sub-items	Pre-surgery Mean (SD)	Post-surgery Mean (SD)	*p*
SKINDEX-29			
Symptoms	66.87 (19.01)	25.99 (15.01)	<0.001
Emotion	55.85 (22.95)	25.04 (19.57)	<0.001
Functioning	43.42 (22.10)	17.65 (14.69)	<0.001
FSFI (items)			
Desire (1-2)	2.65 (1.15)	3.44 (1.33)	<0.001
Arousal (3, 4, 5, 6)	2.44 (1.73)	3.93 (1.93)	<0.001
Lubrication (7, 8, 9, 10)	2.32 (1.77)	3.85 (2.03)	<0.001
Orgasm (11, 12, 13)	2.43 (1.86)	3.92 (2.00)	<0.001
Satisfaction (14, 15, 16)	2.48 (1.61)	4.10 (1.77)	<0.001
Pain (17, 18, 19)	1.46 (1.56)	3.35 (2.34)	<0.001
CSS Patient			
Burning	7.61 (2.49)	1.71 (1.86)	<0.001
Dyspareunia	8.16 (2.77)	2.83 (3.15)	<0.001
Irritation	7.99 (2.27)	1.94 (1.76)	<0.001
Pruritus	7.78 (2.69)	1.94 (1.70)	<0.001

in 77.7% of cases pre-operatively and in only 4.2% of cases post-operatively.

Patient-administered questionnaires

All patient-administered questionnaires showed significant improvement after surgery in comparison with the baseline (*table 1, figure 1*).

SKINDEX-29

Skindex-29 revealed severe QoL impairment at baseline. After reconstructive surgery, scores in all domains improved significantly (from a median score of 55.2 to 20.3, with a difference of -31.8 [IQR: 42.1, -21.8] points; $p<0.001$ [*figure 1*]; sub-domain details are reported in *table 1*).

FSFI

At baseline, more than 90% of patients had sexual dysfunction (<26.55; standard FSFI cut-off). On post-operative follow-up examination, FSFI was seen to have significantly improved (from a median score of 14.6 to 24.8, with a difference of 7.6 [IQR: 2.7, 14.7] points; $p<0.001$ [*figure 1*]; sub-domain details are reported in *table 1*).

Patient-administered CSS

Patient-administered CSS improved after treatment (from a median score of 33 to 6, with a difference of -24 [IQR: -30, -15] points; $p<0.001$ [*figure 1*]; sub-domain details are reported in *table 1*).

DLQI

The pre-operative median total score indicated significant QoL impairment. DLQI significantly improved after treatment (from a median score of 15 to 9, with a difference of -9 [IQR: -17, -7] points; $p<0.001$ [*figure 1*]).

Investigator-based scores

Investigator-based scores significantly improved after surgery (*table 1, figure 1*).

Physician-administered CSS

Physician-administered CSS significantly improved after surgery (from a median score of 8 to 3, with a difference of -5 [IQR: -7, -5] points; $p<0.001$ [*figure 1*]).

IGA

The average baseline IGA score indicated moderate/severe forms of LS. The IGA score improved significantly after treatment (pre-operatively: median=5, IQR=4, 5, range=2-5; post-operatively: median=1, IQR=0, 1, range=0-2; $p<0.001$) (median ΔIGA: -4, IQR: -4, -3) (*figure 2, 3*).

No adverse events after the surgical procedure were observed in this series of patients. All patients had moderate post-operative pain in the treated areas for 10 days after surgery. One patient developed vulvar squamous

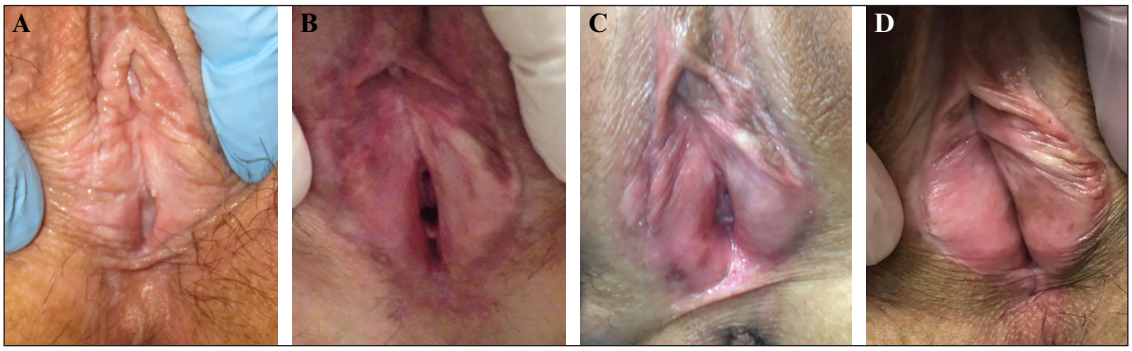

Figure 2. A) Pre-operative clinical appearance of a 28-year-old virgin patient showing fibrotic sclerosis of the whole vulva and stenosis of the introitus, with the main symptom being pruritus. **B, C)** After three treatments, improvement was seen in tissue trophism, colour and vascularization, and initial dilation of the vulvar introitus. **D)** Outcome, seven years after the last treatment, after two pregnancies and a caesarean section.

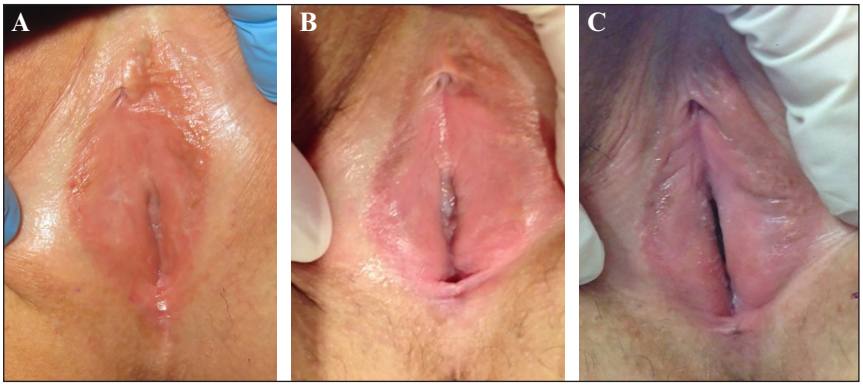

Figure 3. A) Pre-operative view showing severe deformities of vulvar anatomy (disappearance of the labia minora and majora, complete burying of the clitoris, stenosis of vulvar introitus, and splitting of the fourchette), with the main symptom being burning. The patient suffered from impaired sexual activity. **B)** After three treatments, improvement was seen in elasticity, thickness and vascularization. Upon resumption of sexual activity, the fourchette remained fragile after intercourse. **C)** Follow-up examination at three years, after four treatments, showing further improvement in tissue trophism and stabilisation.

cell carcinoma eight years after the last regenerative procedure.

Discussion

The present study confirms the efficacy of combined grafting of PRP and lipofilling in reducing patients' symptoms and improving both their QoL and vulvar anatomy.

Several studies have generically addressed QoL impairment and the severity of LS-associated symptoms in patients with LS [6-8]. However, only a few studies have specifically addressed the effects on QoL and LS-associated symptoms after PRP [12, 13] or fat grafting [11]. Moreover, only one recent study addressed the effects of combined PRP and AD-SVF on patients' QoL and LS-associated symptoms [38].

Our patients showed severe QoL impairment at baseline. Specifically, the mean baseline DLQI revealed a moderate to extremely large effect of LS on QoL, and SKINDEX-29 corroborated the impact of LS on our patients' QoL, with mean scores corresponding to severe QoL impairment. The sexual domain of QoL was especially affected, as confirmed by low baseline FSFI scores and high CSS scores. This might have been expected, since the participants showed moderate/severe treatment-resistant forms of LS.

DLQI, SKINDEX-29, FSFI and patient-administered CSS significantly improved after a mean of four surgical procedures of combined PRP and fat grafting. These data are in accordance with those from another study on the efficacy of fat grafting alone on DLQI and FSFI improvement ($p<0.001$) [11].

Notably, a recent study compared the outcomes on DLQI of AD-SVF alone vs AD-SVF supplemented by PRP in patients with LS [38]. No significant difference was noted when PRP was added. However, the study sample was small. Moreover, the use of AD-SVF substantially differs from classic fat grafting, as AD-SVF represents the extracellular fraction derived from liposuction, but no actual fat cells or adipose-derived stem cells are present in the grafted tissue. Further studies are needed to validate the superiority of single vs combined grafting techniques on improving QoL and LS-associated symptoms.

During follow-up, one of our patients developed squamous cell carcinoma of the vulva eight years after she had started treatment. The incidence of neoplastic transformation in the enrolled sample was therefore 1.39%, and thus in line with the 3-5% lifetime incidence reported in the literature in untreated women with LS [39]. For LS, the use of topical corticosteroids by compliant patients reduces inflammation and the occurrence of vulvar carcinoma [10]. Further studies are needed to investigate the effects of PRP and fat grafting on neoplastic transformation. Moreover, these techniques effectively treat mucosal atrophy, scarring and sclerosis, which cannot be properly achieved by steroid therapy alone.

Conclusions

Patients affected by vulvar LS have significant QoL impairment, particularly affecting their sexual life. The disease has a chronic course and gradually causes functional impairment. Up-to-date topical corticosteroids are the most effective therapeutic option. Treatment with PRP and fat grafting could be a valid adjuvant treatment, which is effective in promoting scar tissue regeneration, reducing symptoms, and improving the QoL of the patients treated. ■

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