Fact or Fiction? Adipose-Derived Stem Cells and Platelet-Rich Plasma for the Treatment of Vulvar Lichen Sclerosus

Panteha Eshtiaghi, BS[1] and Leslie Ann Sadownik, MD, MEd[2,3]

Objective: The aim of the study was to summarize and review the evidence for the efficacy and safety of adipose-derived stem cells (ADSCs) and platelet-rich plasma (PRP) for the treatment of vulvar lichen sclerosus (LS).
Materials and Methods: PubMed/MEDLINE, Ovid, Web of Science, and clinicaltrials.gov were searched from inception up to May 7, 2018.
Results: Seven observational studies were identified, with a total of 98 patients. Both ADSCs and PRP were reported to improve symptoms, quality of life measures, as well as clinical and histological signs of vulvar LS. There is a strong risk of biased estimates of treatment effect.
Conclusions: Current evidence is weak for ADSCs and/or PRP as treatment for vulvar LS. Further research is needed before recommending this therapy.

Key Words: vulvar, lichen sclerosus, stem cells

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Vulvar lichen sclerosus (LS) is a chronic inflammatory dermatosis that commonly affects women in the anogenital region. The prevalence has been estimated as 1.7% in a general gynecological practice,[1] with a bimodal distribution of age, in prepuberty and perimenopause or postmenopause.[2] The etiology is unknown. Histopathologically, LS is characterized by epidermal atrophy, hyperkeratosis, and a homogenous collagen with underlying lymphocytic inflammation in the papillary dermis.[2] These changes may be associated with clinical signs such as whitening and atrophy of the skin in a figure-of-8 pattern that involves the vulva, perineum, and perianal skin. The inflammation leads to scarring and anatomical changes that include the following: clitoral phimosis, labial adhesions, and introital stenosis. Symptomatic women may report intense vulvar pruritus, dysuria, and dyspareunia. The symptoms and signs associated with vulvar LS reduce a woman's quality of life and psychosexual health.[3] The goals of therapy are (1) amelioration of itch, (2) resolution of inflammation and improvement in skin integrity, and (3) prevention of further changes to vulvar architecture.

Potent to high-potent topical corticosteroids are considered the standard first-line treatment.[4–6] Two randomized trials have reported both subjective and objective improvement with this intervention.[5] In addition, Bradford et al.[7] reported that 98% of women who were adherent with recommended maintenance steroid treatments were able to achieve symptom remission and did not report any progressive scarring. There is no cure for LS, and long-term maintenance steroid therapy has been recommended by experts.[4,7] However, topical steroid therapy is not acceptable and effective for all women with vulvar LS. Some women are concerned about the adverse effects of topical steroids, such as skin atrophy and telangiectasia. It should be noted that when topical steroids are used appropriately, these adverse effects have not been found in the long-term follow-up studies.[7]

There is a small population of women with vulvar LS whose disease is resistant to topical steroid treatment. Alternative topical, intralesional, and systemic treatments for vulvar LS have been suggested.[6] These include topical calcineurin inhibitors, topical and systemic retinoids, and systemic immunosuppressants. Phototherapy and photodynamic therapy has also been used to treat vulvar LS. The evidence for all of these treatments is weak, and more research is needed to investigate the effectiveness of these second- or third-line interventions.[6] Surgical intervention is limited to the correction of anatomical problems, such as introital stenosis, and/or treatment of premalignant/malignant lesions.[4]

Recently, a number of observational studies have reported benefit from the use of mesenchymal stem cells, adipose-derived stem cells (ADSCs), and autologous platelet-rich plasma (PRP) for the treatment of vulvar LS. Adipose-derived stem cells are purported to be able to restore and regenerate damaged tissue. Fat grafting has been previously used generally as a soft tissue filler. Now, it is considered a stem cell transplant and is purported to have tissue regenerative potential in fibrotic conditions.[8] Adipose-derived stem cells within lipoaspirates are reported to be able to proliferate and differentiate into various mesenchymal tissues.[8,9] They also have anti-inflammatory and immunomodulatory properties: these factors are hypothesized to ultimately inhibit fibrosis, promote healing, and remodel the extracellular matrix.[8,9]

Autologous PRP contains platelets that release growth factors (GFs) thought to reduce inflammation and to promote mesenchymal cell proliferation, tissue repair, and angiogenesis.[8,10] These cells are harvested through liposuction (ADSCs) or venipuncture (PRP), then prepared through different purification methods, and subsequently injected/implanted into damaged tissue. These experimental and invasive therapies are offered at a significant cost through for-profit stem cell clinics. This literature review will summarize and evaluate the current published evidence regarding the treatment of vulvar LS with ADSCs, PRP, and both ADSCs and PRP.

MATERIALS AND METHODS

The databases PubMed/MEDLINE, Ovid, Web of Science, and clinicaltrials.gov were searched from inception up to May 7, 2018. The search strategy combined the terms "platelet-rich plasma" or "adipose-derived stem cells" with "lichen sclerosus" and "vulva*." Studies were included if they were written in English, published in a peer-review journal, and reported either ADSC or PRP for the treatment of vulvar LS. Studies were excluded if they did not meet these criteria.

STUDY RESULTS

A total of 7 studies, published between 2010 and 2018, were identified for this literature review. All were observational studies: 2 case reports[11,12] and 5 case series/cohort studies.[9,10,13–15] Two

[1]Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of British Columbia; and [3]BC Centre for Vulvar Health, Vancouver, British Columbia, Canada
Reprint requests to: Leslie Ann Sadownik, MD, MEd, University of British Columbia, 6th Floor GLDHCC, 2775 Laurel St, Vancouver, British Columbia V5Z 1M9. E-mail: leslie.sadownik@vch.ca
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TABLE 1. Clinician- and Patient-Reported Outcome Measures in Studies Evaluating Efficacy of ADSCs and PRP and in the Treatment of Vulvar Lichen Sclerosus

Study	No. patients	FU, m	Clinician-reported outcome measures		Patient-reported outcome measures	
			Assessment tool	Results	Assessment tool	Results
ADSCs and PRP treatment						
Casabonaet al.,[13] 2010	15	6–24	Unknown	- Skin and mucosa appeared more elastic and soft - Normal anatomy 15 (100%)	Unknown	15 report total disappearance of symptoms and regain of sexual activity.
ADSCs treatment						
Boero et al.,[9] 2015	36	24	Clinical examination at 1, 3, 6/12 mo	- Vulvar trophism: increased in 34/36 pts - Introital caliber and elasticity: increased in 27/36 pts - Degree burying clitoris: reduced in 18/36 pts - Volume labia: increased volume reported in 30/36 pts - Excoriations: absent 34/36 pts - White lesions: remission in 28/36 pts	DLQI at 6 mo	Improvement ($p < .0001$) *Specific values not reported*
			Biopsy at 8 mo (average)	- Hyperkeratosis: reduced in 24/36 pts - Dermoepidermal detachment: none - Dermal fibrosis: reduced in 24/36 pts - Edema: slight reduction in 12/36 pts - Presence of large caliber vessels in superficial dermis: disappearance in 16/36 pts: - Chronic inflammation: reduction in 32/36 pts	FSFI at 6 mo	Improvement ($p < .0001$) *Specific values not reported*
Onesti et al.,[14] 2015	5/8	24	Photograph	- Tissue trophism	Pain (VAS 0–10)	- Pretreatment (average): 8 Posttreatment (average): 1.2
			Biopsy	- Reduction in dermal sclerosis, dilated capillaries and inflammation	FSFI	- Pre: 12.2 (average) - Post: 35.6(average)
Tamburino et al.,[11] 2015	1	10	Clinical examination	- Improved texture and elasticity of the vulvar skin and mucosa. No score provided.	Questionnaire (0 = none to 10 = extreme): pruritus, burning soreness, dyspareunia	Decreased dryness, dyspareunia, and pruritus; restoration of sexual function. *No score provided.*
PRP treatment						
Behnia-Willison et al.,[15] 2016	28	12	Colposcopy	Lesion size not seen: 8/28 pts smaller: 17/28 pts the same: 3/28 pts	Verbal interview: soreness, discomfort, dyspareunia	No symptoms: 15/28 Intermittent symptoms: 13/28
					APF	Decrease in scores: *specific values not reported.*
					Need for steroids	No longer needed to use: 23/28 Intermittent: 5 /28

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TABLE 1. *(Continued)*

Study	No. patients	FU, m	Clinician-reported outcome measures		Patient-reported outcome measures	
			Assessment tool	Results	Assessment tool	Results
Goldstein et al.,[10] 2017	12	15	Biopsy	Inflammation: Decreased in 7/12 pts No change in 3/12 pts Minimal increase in inflammation in 2/12 pts	Pruritus and burning (VAS scale)	No significant change.
			IGA - for severity	Pre: M=2.67, SD = 0.49 Post: M = 1.83, SD = 0.83 p = .0054		
Franic et al.,[12] 2018	1	2	Biopsy	Normal epidermis and restoration of upper dermal cellularity.	ICIQ-VS	Vaginal score:Pre: 42 Post: 7Sexual score: Pre: 42 Post: 0 Quality of Life: Pre: 8 Post: 0
					FSFI	Pre: 3.6 Post: 32.6

APF indicates Australian Pelvic Floor Questionnaire (scores 0–40). Higher scores greater severity; FU, follow up; ICIQ-VS, International Consultation on Incontinence Questionnaire–Vaginal Symptoms; 0–21 score greater values indicating increased severity; IGA Investigator's Global Assessment (score: 0 [clear] to 5 [very severe disease]; VAS, visual analogue scale).

studies were published as letters to the editors.[10,13] One study used both ADSCs and PRP,[13] 3 studies used ADSCs,[9,11,14] and 3 used PRP[10,12,15] to treat vulvar LS. A total of 98 patients were recruited across all studies. There were multiple factors that limit the ability to systematically compare results across studies; thus, the results of the individual studies are summarized in Table 1 and discussed hereinafter.

Adispose-Derived Stem Cells and Platelet-Rich Plasma Study

In 2010, Casabona et al.[13] first reported the use of ADSCs and PRP to treat vulvar LS. The authors describe the results of a combined grafting of ADSCs and injection of PRP in 15 women (mean age = 54 years; age range = 27–62 years) with biopsy-confirmed vulvar LS unresponsive to steroid treatment. Both modes of therapy were administered in the intradermal-intramucosal, subdermal, and submucosal regions. Calcium chloride was added to the PRP solution for platelet degranulation. All patients had moderate pain for 10 days after the intervention. One month after intervention, all patients reported improvement (see Table 1). Four months after intervention, all patient were asymptomatic and the anatomical appearance was reported as normal. All patients resumed sexual activity. It is not clear whether these treatment outcomes were assessed subjectively or objectively, or according to specific baseline values. After procedure, biopsy was not performed. It was noted that some patients, with severe fibrosis and atrophy, underwent the procedure multiple times after 3 months with stated good results.

Adipose-Derived Stem Cells Studies

In a cohort study of 36 patients, with severe biopsy-proven vulvar LS refractory to first-line treatment, Boero et al.[9] examined the efficacy of fat grafting for: symptoms, clinical examination, and histopathology. It should be noted that 46 women (age range = 25–80) were initially recruited, but 10 were excluded because the severity of their LS required surgical intervention. The severity of the initial clinical presentation was taken into account to determine the number of procedures and the amount of adipose tissue required for each patient. Subsequent to debridement, fat tissue was injected from the epidermis to the fascial plane. The mean follow-up period was 24 months. However, the outcomes were measured at varying intervals during the follow-up period. It is unclear as to when the final results were tabulated. The authors report improvements in the clinical examination and microscopic findings as outlined in Table 1. Thirty-four (95%) patients were reported to subsequently discontinue topical corticosteroid use. Quality of life and sexual function, as assessed by Dermatology Life Quality Index (DLQI) and Female Sexual Function Index (FSFI), were reported to be statistically significantly improved; however, no specific values were provided before or after treatment; thus, one cannot comment on whether these improvements were of clinical significance.

In a 2016 study, Onesti et al.[14] reported on the results of a clinical trial of the use of ADSCs to treat women with vulvovaginal atrophy, vulvar graft-versus-host disease and vulvar LS. Eight women were recruited; the average age was 56.5 years of age (range = 38–75 years). Five of these women had vulvar LS. Within 3 months, 2 treatments were performed and patients were followed on 5 occasions at varying intervals, up to 2 years after intervention. Adipose tissue was harvested through liposuction and ADSCs were then isolated, cultured, and supplemented with hyaluronic acid in preparation for injection. Tissue trophism, histological changes, symptoms, and sexual satisfaction were assessed before and afterward. All these outcomes improved after intervention (see Table 1). Of note was the marked improvement in sexual function as measured by the FSFI. No additional information is provided regarding possible confounding variables, i.e., additional treatments used during the follow-up period such as local systemic hormone replacement therapy, use of sexual lubricants, or counseling.

Finally, in 2015, Tamburino et al.[11] reported on the effect of nanofat grafting, in addition to standard lipofillng, in a symptomatic 48-year-old woman with biopsy-confirmed vulvar LS and severe anatomical distortion and sexual dysfunction. After surgical revision of her clitoral scarring, nanofat was prepared from emulsified lipoaspirate using the Tonnard technique. The solution was then injected intradermally into the introitus and clitoris. Betamethasone was applied for 1-week postoperatively. Within 10 months after the procedure, the patient self-reported decreased symptoms, as well as improvement of sexual function and quality of life. It was noted that the partial recurrence of the clitoral phimosis occurred postoperatively, in which benefits were

secondary to the lysis of periclitoral adhesions versus the nanofat grafting is unclear. Although a specific scoring system was outlined for the clinical examination and patient's symptoms, no final scores were provided. Postprocedural biopsy was not performed.

Platelet-Rich Plasma Studies

Behnia-Willison et al.[15] investigated PRP treatment in 28 patients (aged 22–88 years) with vulvar LS, 26 of whom had biopsy-confirmed lesions, unresponsive to topical steroid treatment. Three PRP treatments were administered 4 to 6 weeks apart and then at 12 months to affected areas. Steroid use was discontinued for the duration of the study. Patients were interviewed and examined after each treatment. Objective and subjective improvement was noted by all patients (see Table 1). Patients reported mild to moderate pain after the procedure; however, no adverse outcomes (e.g., infection, bleeding) were reported. The study did not evaluate posttreatment histopathological changes.

In a 2017 Letter to the Editor, Goldstein et al.[10] reported a pilot study to examine the efficacy and safety of subdermal and intradermal PRP injections in 12 patients with biopsy-confirmed vulvar LS. The 2 treatments were 6 weeks apart, and all other medications were discontinued. Six weeks after treatment, improvement in histopathology was noted in 7 (58%) of 12 patients. Clinically, the severity of the disease was decreased significantly after treatment, as assessed by Investigator's Global Assessment (IGA). However, the change in subjective scores for burning and pruritus was not significant.

Finally Franic et al,[12] in a 2018 case report, described the outcome of a 38-year-old premenopausal woman with biopsy-confirmed vulvar LS, refractory to standard treatment, who was administered PRP subdermally twice for 2 months. The second PRP treatment was combined with an acellular matrix, hyaluronic acid (HA). One month after the procedure, the patient reported absence of symptoms and increased quality of life and sexual health as assessed by International Consultation on Incontinence Questionnaire–Vaginal Symptoms and FSFI instruments (see Table 1). Posttreatment biopsy demonstrated nearly normal epidermis and restoration of upper dermal cellularity.

DISCUSSION

The previous reviewed case reports, case series, and cohort studies report favorable short-term clinical and patient-reported treatment outcomes. Both ADSCs and PRP administration improved patient symptoms, quality of life measures, and clinical and histological signs of vulvar LS—many of whom were reported to be refractory to steroid treatment. However, the quality of the reviewed evidence is weak. Confidence in the effect of ADSCs and PRP treatment is limited by the inherent weaknesses in these observational studies, which include lack of the following: sample characteristics, control/comparison groups, placebo groups, random assignment, and nonblind treatment evaluation. The method of recruitment was not explicitly discussed in these studies, and the small sample sizes include a preponderance of postmenopausal women. In addition, although patients enrolled in the studies were characterized as refractory to steroid treatment, limited information was provided with regard to specific treatments (drug, dose, regimen, duration of therapy) previously tried and adherence to previous therapies. Furthermore, most studies did not explicitly state that women discontinued all other treatments during the study period. Finally, given the intervention is available at a cost to patients, there is a potential for selective reporting and publication bias.

The lack of a standardized intervention also limits the ability to summarize the results. The method of preparation, use of adjuvant, quantity, frequency, delivery, and activation of ADSCs and PRP differs within and among the different studies. For example, Casabona et al.[13] combined both ADSCs and PRP injections, restricting the ability to determine which of these interventions provided the reported beneficial results. Furthermore, Casabona et al.[13] used calcium chloride for platelet degranulation and subsequent release of GFs from α-granules, although there was no formal activation step in other treatment protocols before PRP administration. The activation strategy for optimal release of GFs is an area under investigation.[16]

In the studies by Tamburino et al.[11] and Onesti et al.,[14] ADSCs were purified for use, whereas Boero et al.[9] did not isolate for ADSCs before injection of fat tissue. As injection of adipocytes can aid in volume filling and thus improve tissue trophism in vulvar LS, it is not clear then whether the observed clinical improvement is due to volume correction or stem cell activity. The Tonnard technique of nanofat grafting, used by Tamburino et al.,[17] is a way to filter ADSCs from adipocytes, which isolate ADSCs for their regenerative properties. Furthermore, Tonnard's technique mechanically processes the lipoaspirate; the induced shear stress has been reported to up regulate endothelial progenitor cell types with regenerative potential.[16]

Administration of ADSCs is a surgical procedure requiring sampling of fat tissue under local anesthesia, with potential scar revision under general anesthesia.[11] Therefore, the treatment comes with operative risks and convalescence. The entire procedure was a day surgery in 2 of the reports,[9,11] whereas multiple sessions were required in the study by Onesti et al.[14] for a single vulvar injection. Boero et al.[9] noted that the total number of procedures is dependent on preprocedure clinical severity and resolution of signs and symptoms.

The positive clinical results of PRP treatment in treating vulvar LS may also be confounded by the method of injection. Behnia-Wilson et al.[15] reported that the PRP injection was performed in a fanning motion to break up the sclerotic tissue. Therefore, regardless of the substance injected, this breakdown of scars and fibrotic tissue may increase intrinsic tissue healing that may not be necessarily attributable to PRP.[15] Platelet-rich plasma injections are prone to early washouts because autologous products have high reabsorption rates.[18] Scaffolds are frequently used in tissue engineering to support proliferation, differentiation, and vascular supply of tissue substitutes.[19] Use of HA by Franic et al.[12] as a tissue scaffold in 1 of the 2 treatments of PRP is inconsistent, whereas the rest of the studies lack this adjunct. Recipient site retention is also a concern with ADSCs. Although Onesti et al.[14] used HA, there is no indication of scaffold use in the other studies to potentially increase retention of ADSCs. Survival of a graft in vivo is also associated with neovascularization, a characteristic that decreases with age.[20]

Another major limitation of these studies, of all treatment studies of LS,[21] is the lack of standardized treatment outcome measures. Primary and secondary outcome measures differed between the studies, as did validated tools for their measurement and follow-up periods. The tools used have not been validated for a population of women with LS. For example, the Australian Pelvic Floor questionnaire, as used by Behnia et al.,[15] was tested and validated in a population of women with varying pelvic floor disorders.[22] The individual studies reported between 1 and 4 different outcomes in their results. Only 2 studies[9,10] explicitly reported a primary outcome measure. It should be noted that a postprocedure biopsy was not performed routinely to evaluate histological changes as an outcome measure. In the 2 studies that compared histopathology before and after treatment with PRP, the restoration of upper dermal cellularity was observed,[10,12] a key feature associated with LS.[23] Aside from histological evidence, it is also important to determine whether the molecular signature of vulvar tissue has been positively affected by PRP.

Transcriptome analysis may help understand PRP's mechanism of action in tissue regeneration.

Given that vulvar LS is a chronic condition that requires years of management, a longer follow-up period is needed to document the effectiveness of any single intervention. There were no reports of serious short-term adverse events after injections in any of the studies. However, with respect to PRP, as platelets provide GFs, there are theoretical concerns over that PRP may cause hyperplasia and tumor growth.[24] Long-term potential for hyperplasia and tumorgenesis cannot be ruled out until investigated. Although angiogenic properties of ADSCs have been proposed, it is not clear what concentration of stem cells in lipoaspirate will result in appropriate angiogenesis for graft survival.[20]

There is little known about the natural history of vulvar LS, including the consequences of no therapy. The available evidence, though limited, supports topical steroids as an effective, noninvasive, and inexpensive treatment of vulvar LS, with appropriate use. Tailoring its application to the lowest potency steroid effective for the severity of the disease has been shown to prevent steroid-induced skin atrophy.[25] Furthermore, research of the ideal steroid preparation, potency, and dose regimen needed to achieve disease remission would also be helpful for clinicians. Finally, there is weak evidence that topical steroid therapy may reduce the risk of developing invasive squamous cell carcinoma in women with vulvar LS.[7] A large randomized controlled trial with a sample size of 984 treated and 984 untreated participants has been suggested to evaluate whether a treatment can halve the 5% risk of developing squamous cell carcinoma in women with vulvar LS.[5]

There remains a small population of patients with vulvar LS refractory to steroid treatment whose quality of life is greatly reduced. Given the well-documented efficacy of topical steroids, it is prudent to determine whether there are other underlying factors contributing to their symptoms such as superinfections, premalignancy, or alternate diagnoses (e.g., atrophy).[26] Before second- or third-line, invasive, and costly experimental therapy is recommended as treatment for vulvar LS, factors that affect patient acceptance and adherence to standard topical steroid therapy (e.g., concerns about drug safety, side effects, cost, complicated dosing regimen, etc.) should also be explored and addressed.

For those women with treatment-resistant vulvar LS alternative topical (e.g., calcineurin inhibitors, calcipotriol, retinoids), intalesional (e.g., steroids, adalimumab), and systemic (e.g., cyclosporine, methotrexate, hydroxycarbamide, cycloferon) have been recommended in guidelines; however, the level of evidence and grade of recommendations are very low for most of these therapies.[25] The current evidence to recommend ADSCs or PRP as an effective alternative treatment for vulvar LS is also weak. The future role of these therapies as alternative treatments for vulvar LS is uncertain at this time. Although results in these observational trials are promising, these outcomes need to be validated by unbiased well-designed research trials that address the inherent study weaknesses in the reviewed trials. In general, more well-designed research of all treatment options for vulvar LS is needed. The last Cochrane review included only 7 randomized controlled trials, with a total of 249 participants, and included only 6 different treatments.[5]

CONCLUSIONS

In conclusion, 7 observational studies report a positive subjective and objective effect of ADSCs and PRP on women with vulvar LS. However, the current evidence regarding the novel use of ADSCs and PRP in the treatment of vulvar LS is weak, and further research is required to substantiate these outcomes. There is a clear need for comparative randomized controlled trials and long-term data on efficacy and safety for second-line therapies such as ADSCs and PRP for vulvar LS. Further studies are also required to determine optimal ADSC and PRP harvest, purification, injection, and retention techniques. There is currently no standardization for ADSCs and PRP treatment dose, technique, and/or technology. Given the current unregulated costly therapy, it is imperative to ensure long-term treatment efficacy and patient safety before recommending autologous therapy.

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