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REVIEW ARTICLE

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Autologous lipoaspirate as a new treatment of vulvar lichen sclerosus: A review on literature

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Abstract

Lichen sclerosus (LS) is a chronic inflammatory dermatosis that mostly affects the genital and anal skin areas. Symptoms may vary from pruritis and pain to sexual dysfunction; however, LS can also be asymptomatic. LS occurs at all ages and in both sexes. Approximately 5% of all women affected by vulvar LS will develop vulvar squamous cell carcinoma. Topical treatment is safe but less effective resulting in chronic course in most patients, who suffer from persistent itching and pain. In severe cases of therapy-resistant LS, there is no adequate treatment. Fat grafting is a novel regenerative therapy to reduce dermal fibrosis. The therapeutic effect of adipose tissue grafts for LS is already investigated in various pioneering studies. This review provides an overview of these studies and the putative mechanisms-of-action of fat grafting to treat LS.

KEYWORDS
ageing, dermal, fibrosis, lichen sclerosus, lipoaspirate, regeneration, stem cells, stromal vascular fraction, vulvar

1 | INTRODUCTION

Lichen sclerosus (LS) is a chronic inflammatory dermatosis that mostly affects the genital and anal skin areas. LS can be asymptomatic or accompanied by symptoms, for example progressive pruritis, pain, sexual dysfunction and thus, a reduced quality of life (QoL).[1,2] LS occurs at all ages and in both sexes, whereby the male-to-female ratio ranges between 1:3 and 1:10. The exact prevalence is unclear; however, vulvar LS has been found to affect one in 70 women presenting to a general gynaecology practice.[1] The incidence of histologically proven LS in women was 14.6 per 100.000 woman-years in 2011 in the Netherlands. Noticeably, approximately 5% of all women affected by LS will develop vulvar squamous cell carcinoma, for which both LS and differentiated vulvar intraepithelial neoplasia (dVIN) are additional risk factors.[3,4] Although the aetiology of LS is still unknown, it is hypothesized to be an autoimmune disorder with a genetic component.[3]

Currently, treatment of LS is mainly initiated to relieve symptoms of pruritis and pain, to reduce the progression of the skin alterations and eventually decrease the risk of cancer. Conventional treatment of LS consists of local application of corticosteroids, for example clobetasol propionate.[5] In severe cases of therapy-resistant LS, immunosuppressive agents (e.g. calcineurin inhibitors) can be administered, which inhibit T-cell activation.[6–8] However, clinical evidence

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for the efficacy of immunosuppressives as a LS therapeutic is sparse and topical treatment cannot prevent fibrogenesis of the upper dermis. Eventually, progressive fibrosis of the upper dermis culminates in persistent sexual dysfunction and a reduced QoL.[9] Therefore, innovative therapies are considered that aim to control dermal fibrosis due to LS, for example phototherapy, anti-inflammatory, anti-biotic and anti-microbial agents. In some cases, a (temporary) remission of symptoms may be achieved, but long-term relieve of symptoms is not often accomplished.[10–15] Surgery, for example vulvectomy (with or without a skin graft or gluteal fold flap reconstruction), cryosurgery and laser ablation, is considered to treat severe complications, such as severe vaginal introitus stenosis, urinary retention and synechiae vulvae.[16] Nonetheless, a surgical approach unavoidably creates scars and is characterized by a high recurrence rate of the original pathology.

In the last fifteen years, fat grafting, that is the transplantation of adipose tissue or lipoaspirate, has been developed as a novel autologous treatment modality to reduce skin fibrosis as a result of fibroproliferative diseases or post-traumatic scarring.[17] Adipose tissue harbours mesenchymal stromal cells, better known as adipose tissue-derived stromal cells (ASCs), that reside in the stromal vascular fraction (SVF) as progenitor cell types and can differentiate into, for example pericytes and supra-adventitial cells.[18,19] ASCs are able to produce and secrete a variety of growth factors, cytokines and proteins that may act as an immunomodulatory, pro-angiogenic or anti-fibrotic agent.[20–31] These paracrine effects may be beneficial in decreasing symptoms and delaying disease progression of LS.

Till date, several pioneering studies and case reports have been published that describe the use of fat grafting as a treatment of LS.[32-40] This review provides an overview of these studies that have investigated fat grafting as a treatment of LS and summarizes the putative mechanisms-of-action of fat grafting to treat LS.

2 | MECHANISMS-OF-ACTION OF FAT GRAFTING

Autologous fat grafting has been clinically used for many decades. Originally, fat grafting was mainly used to restore volume losses due to congenital or traumatic defects.[41] Later, fat grafting became popular as a regenerative treatment modality to restore tissue damage caused by scarring due to burn wounds or trauma.[42,43] The regenerative capacity of the grafted fat can be attributed to the ASCs that reside in the perivascular niche of different tissues.[44,45] In 2001, Zuk et al. showed that the adipose tissue contains ASCs with a multilineage differentiation capacity and an extended population doubling capacity with a low occurrence of senescence.[46] Upon cell culture, these ASCs secrete a plethora of paracrine factors, for example growth factors, cytokines, proteins and exosomes that may function either in an (1) immunomodulatory, (2) pro-angiogenic, (3) anti-fibrotic or (4) in a combination of the former, fashion.[20–31] ASCs reside in the SVF. SVF harbours all non-adipocyte cell types that can be divided into blood-derived and adipose tissue-derived cells. The blood-derived cell population of SVF contains granulocytes, macrophages, lymphocytes and hematopoietic stem cells, whereas the adipose tissue-derived cell population contains supra-adventitial cells, pericytes, ASCs, fibroblasts and endothelial cells.[47] SVF can be isolated from adipose tissue either by mechanical isolation or by enzymatic isolation. Mechanical isolation utilizes shear stress to disrupt most of the adipocytes while maintaining all trophic factors or bioactive molecules present in the tissue.[19,48] Hence, mechanical isolated SVF is named tissue-SVF (tSVF). In contrast, enzymatic isolation of SVF utilizes the enzymatic digestion of adipose tissue. Enzymatic digestion of SVF yields a cellular-SVF (cSVF) that is depleted of such trophic factors as during the enzymatic isolation process both intercellular connections and extracellular matrix (ECM) are lost. As ECM is known to bind the majority of trophic factors,[48–50] it is conceivable that the therapeutic capacity of cSVF is lower than that of tSVF. Yet this postulation remains to be investigated by comparative studies and conclusive data are not available.

2.1 | Immunomodulatory actions of fat

One of the key players in inflammation and fibrogenesis is the macrophage. During normal wound healing, macrophages undergo a transition from classical M1 macrophages (pro-inflammatory phenotype) to M2 macrophages (proliferative phenotype). This phenotypic transition is important because the M1 macrophages play a crucial role in phagocytosis and protection against pathogens, whereas the M2 macrophages are important in the production of collagens and thus tissue repair. Various bioactive molecules and epigenetic factors are involved in the activation of macrophages. The Jak/STAT pathway plays a key role in macrophage transition whereby STAT1 activation promotes transition to the M1 phenotype and STAT6 activation promotes the M2 phenotype.[51,52] The M1 phenotype is activated by pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and interleukin (IL-6).[51] In contrast, the M2 phenotype is maintained by immunomodulatory cytokines such as IL-4, IL-10 and IL-13.[51,53] In chronic wounds or fibroproliferative diseases, the M1-to-M2 transition of macrophages is delayed or insufficient, which may cause a prolonged stage of inflammation. Until now, there is no conclusive evidence that LS associates with alterations in M1-to-M2 transition; however, in LS tissue, increased levels of pro-inflammatory cytokines, including IFN-γ, TNF-α and IL-1α and IL-8, are observed. Such data suggests the presence of an inflammatory state contrary to a regulatory or immunomodulatory state in LS tissue.[54-57] An in vitro study of Sun et al.[52] indicates that ASCs promote M1-to-M2 transition of macrophages by downregulating the STAT3 and STAT6 pathway. A study of Zhu et al. showed reduced inflammatory signalling after the application of human SVF subcutaneously in nude mice. On a histological level, this was measured as a decreased expression of the pro-inflammatory cytokines IL-6 and TNF-α and an increased level of the anti-inflammatory cytokine IL-10.[58] Collectively, these studies show that the application of ASCs in vivo may lead to a decreased expression of pro-inflammatory

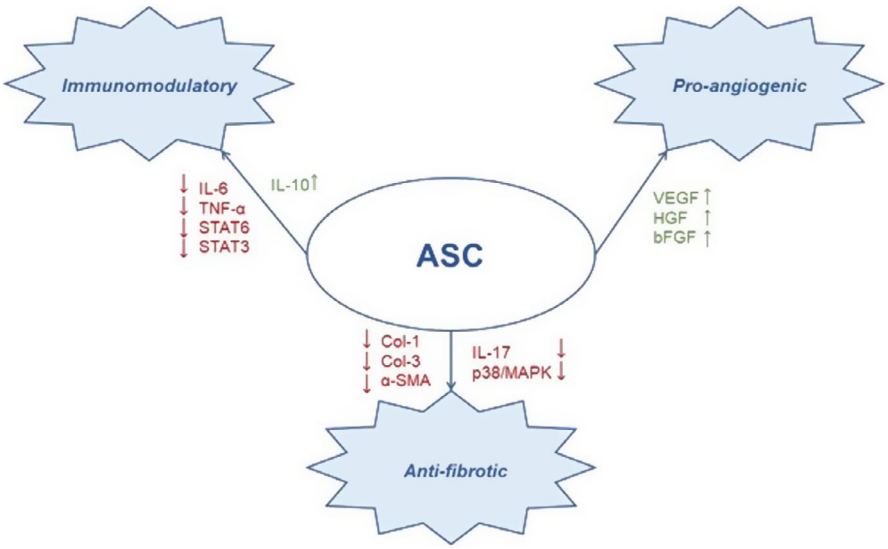

FIGURE 1 Mechanisms-of-action of an ASC; including immunomodulatory, pro-angiogenic and anti-fibrotic effects and the corresponding growth factors and cytokines.

cytokines, suggesting that ASC have an immunomodulatory capacity what might result in a faster M1-to-M2 transition of macrophages culminating in enhanced tissue repair.

2.2 | Pro-angiogenic actions of fat

Lichen sclerosus affected tissues show a lower microvessel density compared to normal vulvar tissues,[59] suggestive of tissue hypoperfusion. Insufficient microvascularization culminates in hypoxia of the surrounding tissues.[60] During a state of hypoxia, stabilization of the transcription factor hypoxia-induced factor-1 alpha (HIF-1α) results in the expression and secretion of pro-angiogenic growth factors, for example vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and hepatocyte growth factor (HGF), which eventually results in the genesis of microvessels.[61] Stabilization of the microvascularization is promoted by CD34-positive dermal dendritic cells (DDCs) or pericytes, among others. In systemic sclerosis (SSc) and hypertrophic wound healing, an elevated expression of both VEGF and HIF-1 is observed compared with healthy tissue.[61] Controversially, consistent HIF-1 accumulation alone does not result in the formation of sufficient microvasculature. The overexpression of HIF-1 correlates to an increase in the expression of pro-fibrotic factors (e.g. TGF-β1, thrombospondin-1) by fibroblasts, resulting in excessive production of collagenous matrix.[61–63] Interestingly, vulvar LS tissue shows decreased levels of VEGF[64] and a downregulation of DDCs,[65] which might contribute to a low microvessel density in LS. ASCs are shown to release angiogenic growth factors, for example VEGF, HGF and bFGF,[58,66] and they are able to differentiate into pericytes that can stabilize the adjacent microvasculature.[67-75] Different studies found that increased expression of HIF-1α promotes ASC proliferation and binding and resulted in increased angiogenesis.[67-75] Therefore, we postulate that the application of ASCs may result in increased microvessel density and stabilization of the microvasculature in LS, albeit definite proof is lacking.

2.3 | Anti-fibrotic actions of fat

In LS, the expression of pro-fibrotic growth factors, for example transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF), is increased, culminating in the excessive accumulation and deposition of extracellular matrix proteins (ECM) such as collagens and especially collagen type 1 (Col-1).[60,76–78] In normal wound healing, TGF-β, CTGF and serum response factor (SRF) are secreted by platelets and macrophages to initiate fibroblast to myofibroblast differentiation and the activation of the ECM remodelling processes. Physiologically, myofibroblast undergo apoptosis and are cleared from the tissue after the remodelling process. However, if myofibroblasts persist in the tissue, myofibroblasts will continue to secrete Col-1 and excessive scar formation will occur, which is observed in hypertrophic scars.[29,79] In vitro studies have shown that the ASCsecretome—a collection term for all factors secreted by ASCsinhibit fibroblast to myofibroblast differentiation in Dupuytren nodules and keloid scar-derived fibroblasts.[20,21,80] An in vitro study of Li et al. demonstrated the inhibiting effect of ASCs on the development of hypertrophic scar tissue in both mice and men. Firstly, mice fibroblasts treated with ASC-conditioned medium (ASC-CM) showed decreased Col-1, Col-3 and alpha-smooth muscle actin (α-SMA) levels compared with the control group (no treatment). Secondly, fibroblasts obtained from human hypertrophic scar tissues showed less collagen deposition and faster wound healing after being treated with ASC-CM. The inhibiting effect on hypertrophic scar formation of ASCs seems to relate to the inhibition of the inflammatory p38/MAPK signalling pathway.[81] A more recent study of Li et al. demonstrated a decrease in the deposition of collagen, downregulated fibroblast to myofibroblast differentiation and a reduction of hypertrophic scar formation by in vitro and in vivo experiments. It was shown that ASCs release epigenetic factors (such as microRNAs) that downregulate IL-17, a pro-fibrotic protein that is known to be overexpressed in hypertrophic scar tissues.[82] Similar effects of ASCs, including the diminishment of dermal fibrogenesis and

TABLE 1 Study Characteristics, Patient Demographics, Intervention Types and Outcomes

Reference	Study type	Study population	Age (years)	Intervention
Casabona et al., 2010[32]	Prospective, non-controlled, non-blinded, non-randomized	*N* = 15, female, histologically proven LS	Range 27–62	10–15 cc lipoaspirate Co-intervention: 5 cc PRP pre-treated with 0.5 cc of calcium chloride for platelet degranulation Intramucosal, subdermal and submucosal Patients with severe fibrosis underwent one or two extra procedures, after 3 months respectively
Boero et al., 2015[33]	Prospective, non-controlled, non-blinded, non-randomized	*N* = 36, female, histologically proven LS	Range 25–80	8–15 cc lipoaspirate All perivulvar layers up to the fascia
Tamburino et al., 2016[34]	Case report	*N* = 1, female, histologically proven LS	48	40 cc lipoaspirate Co-intervention: 20 cc Nanofat Subcutaneous, intradermal
Onesti et al., 2016[35]	Prospective, non-controlled, non-blinded, non-randomized	*N* = 8, female, 1 with symptoms during menopause, 2 with vulvar scarring due to chronic GVHD and 5 affected by LS	Range 38–75	2 cc ASC-HA solution Subcutaneous of labia minora
Kim et al., 2017[36]	Case report	*N* = 1, female, affected by vaginal atrophy (no histologically proven LS)	67	36 cc lipoaspirate Co-intervention: 4 cc PRP Subcutaneous
Newman et al., 2018[37]	Prospective, non-controlled, non-blinded, non-randomized	*N* = 111, female, histologically proven LS	Range 20–76	8–15 cc tSVF Co-intervention: 2–3 cc PRP with Lidocaine with Epinephrine 1:100 000. Subcutaneous, intradermal
Stark et al., 2020[38]	Prospective, non-controlled, non-blinded, non-randomized	*N* = 10, females affected by vaginal atrophy, vulvovaginal dystrophy, and/or stress urinary incontinence	Range 30–60	8.5–32 cc (average of 24 cc) Nanofat Subcutaneous and subepithelial
Almadori et al., 2020[39]	Prospective, non-controlled, non-blinded, non-randomized	*N* = 33, female, histologically proven LS	Range 38–63	10 cc lipoaspirate In labia majora, labia minora, clitoral area, posterior fourchette, perianal area
Tedesco et al., 2020[40]	Prospective, controlled, non-blinded, non-randomized	*N* = 40, female and male, histologically proven LS	Range 43–78	15 cc tSVF Co-intervention for 20 patients: 4 cc PRP Two procedures per patient distanced over 4-months. Intradermally

Abbreviations: (t)SVF, (tissue or mechanically isolated) stromal vascular fraction; ASCs, adipose-derived stromal cells; DLQI, dermatology life quality index; FSDS, female sexual distress scale; FSFI, female sexual function index; GVHD, graft versus host disease; HA, hyaluronic acid; HADS, Hospital Anxiety and Depression Scale; LS, lichen sclerosus; PASS-20, Pain Anxiety Symptom Scale Short Form 20; PRP, platelet rich plasma; QoL, quality of life; RASS, Richmond Agitation-Sedation Scale; VASs, Visual Analogue Scale; WMQ-R, Wound Management Questionnaire.

Follow-up	Results	Complications
Questionnaires (non-validated), photographic and physical evaluation up to 24 months postoperative. No specific index parameters were mentioned	After 15 days symptoms started to improve. Itching and burning disappeared within one month. Four months after surgery, all patients reported total disappearance of pain, regained sexual activity and normal appearance of anatomical features of the vulva. No statistical analysis	No adverse events were observed. All patients had moderate pain in the treated areas for 10 days after surgery
Vulvoscopic examination and DLQI and FSFI questionnaires up to 24 months postoperative. Histological evaluation through punch biopsies preoperative and 8 months postoperative	94% showed improved vulvar trophism of the skin and mucosa. QoL was significantly improved for both DLQI ($p < 0.0001$) and FSFI ($p < 0.0001$). On a histological level, reduction of hyperkeratosis (67%), reduction of chronic inflammation (89%), reduction of fibrosis (67%), increased angiogenesis (44%) and reduction of dermal oedema (33%)	No adverse events were observed. 30% of patients had pain for 10 days after surgery
Questionnaires (not validated) up to 8 months postoperative. No specific index parameters were mentioned	Decreased symptoms and anatomical features of LS with the greatest improvement in the first two months postoperative and maintained up till 8 months. No specifications were mentioned	Not described
Histological, FSFI questionnaires and physical evaluation up to 24 months postoperative	All patients mentioned pain reduction and improved sexual function. Histological examination in LS patients showed significantly reduction of dermis sclerosis, less dilated capillaries and reduced inflammatory infiltrate. No statistical analysis	Not described
Physical evaluation up to 12 months postoperative. No specific index parameters were mentioned	Relieve of vaginal pruritis and irritation, restoration of labia majora contour. White patchy lesions improved	No adverse events were observed
Questionnaires (not validated) up to 3 months postoperative. No specific index parameters were mentioned	All patients experienced improvement of symptoms, with a significant decrease per symptom of 38%–68% ($p < 0.001$)	No serious complications were described. Side effect, such as swelling, bruising, burning and discomfort were noted
Physical evaluation up to 12 months and questionnaires (not validated) up to 24 months. No specific index parameters were mentioned	All patients reported an improvement of symptoms after 6–16 months, differing from sexual activity, improved vaginal appearance and itching. No statistical analysis	No adverse events were observed
FSFI, FSDS, VASs, PASS-20, HADS, RAS and WMQ-R questionnaires up to a mean follow up of 12.9 months postoperative	Improvement of sexual function ($p < 0.001$), as well as the distress associated with sexuality ($p < 0.0001$), romantic relationship ($p < 0.05$), anxiety ($p < 0.0001$) and depression ($p < 0.0001$). Decrease of symptoms such as itching ($p < 0.001$), burning ($p < 0.05$), soreness ($p < 0.001$), pain ($p < 0.0001$)	Not described
Physical examination during every visit and DLQI questionnaires up to 6 months follow up	Significant improvement of QoL was observed in both groups after one month. After 6 months the SVF-group showed a significant improvement of QoL, the SVF-PRP combination group little improvement compared to pre-operative QoL	No severe or mild side effects were observed during and after the procedure

TABLE 2 Intervention Types, Advantages and Disadvantages

Method	Advantages	Disadvantages
Monotherapy using fat or nanofat	• Fat grafts and nanofat grafts are easily obtained and used • Increasing soft tissue volumes	• The consistence and cellular proportions differ per patient's fat tissue and processing method • Graft retention rates are variable
Combination therapy of fat with PRP	• Increasing soft tissue volumes • PRP contains platelets that release growth factors that promote ASC proliferation	• Additional venipuncture and PRP purification method required • High concentration of PRP might decrease the regenerative effects of ASCs; however, the optimal ratio is unclear • Number of platelets is highly variable due interpatient variation, intra-day variation and different reabsorption rates • PRP might result in hyperplasia
Combination therapy of SVF with PRP	• SVF contains a high concentration of ASCs and therefore a potential larger regenerative effect than conventional fat grafting • PRP contains platelets that release growth factors that promote ASC proliferation	• Additional SVF isolation method required • High concentration of PRP might decrease the regenerative effects of ASCs; however, the optimal ratio is unclear • Number of platelets is highly variable due interpatient variation, intra-day variation and different reabsorption rates • PRP might result in hyperplasia
Combination therapy of ASCs with HA	• Single cell suspension with a controllable number of cells • A high concentration of ASCs and therefore a potential larger regenerative effect than conventional fat grafting • Addition of HA reduces the risk of migration of ASCs • Transplanted cells in hydrogels is thought to result in long-term protection of the cells in vivo	• An expensive and time-consuming method • The optimal ratio is unclear

Abbreviations: ASCs, adipose-derived stromal cells; HA, hyaluronic acid; LS, lichen sclerosus; PRP, platelet rich plasma; SVF, stromal vascular fraction.

enhanced wound healing in different disease models, for example SSc and Peyronie's disease, were demonstrated by others.[22–28,83–97]

In conclusion, ASCs can secrete a plethora of growth factors and cytokines, which may have immunomodulatory, pro-angiogenic and anti-fibrotic effects on the surrounding tissues (Figure 1). Since the pathology of LS comprises a state of chronic inflammation and persistent fibrogenesis of vulvar tissues, the application of ASCs to LS affected tissues could be a symptom-controlling and disease-delaying therapy for LS.

3 | FAT GRAFTING THERAPIES FOR LICHEN SCLEROSUS

Clinically, LS usually presents as white, polygonal papules that coalesce into shiny porcelain-white plaques in the perivaginal and perianal area. LS can lead to obliteration (fusion) of the labia minora and stenosis of the introitus. Even though most clinicians diagnose LS based on clinical aspects, the gold standard to diagnose LS is punch biopsy followed by histological examination.[98-104] Histologically, a combination of (A) ectatic (dilated) or sclerotic blood vessels, (B) infiltration of lymphocytes, epidermal atrophy and (C) basement membrane thickening, is found in LS tissue. This could be explained by (A) poor angiogenesis and lack of stabilization of the existing microvasculature, (B) chronic inflammation and (C) increased fibrogenesis. Progression of LS will lead to replacement of the upper dermis by dense fibrotic tissue with insufficient microvasculature.[55,76,105,106] Since adipose tissue has shown to harbour a regenerative potential, that is immunomodulatory, pro-angiogenic and anti-fibrotic actions, several clinical studies examined whether fat grafting may ameliorate the pathogenesis of LS, using either (1) fat grafting, (2) a combination of fat grafting with platelet-rich plasma (PRP), (3) a combination of tSVF with PRP and (4) a combination of ASCs with hyaluronic acid (HA) (Tables 1 and 2).

3.1 | Monotherapy using fat or nanofat

Thus far, four studies have investigated the effect of fat grafting or nanofat (an emulsified mixture of fat grafting and infiltration fluid) for therapy-resistant LS in a total of 60 female patients.[33,34,38,39] The largest study used fat grafting to treat 36 patients suffering from LS. In this study, 94% of patients reported a clinical improvement, which was associated with histopathological improvements. Clinically, 75% of the patients reported improved caliber and elasticity of the vaginal introitus, 50% reported reduced clitoris burying degree, 83% reported increased volumes of labia majora and minora, 94% had a complete disappearance of scratching lesions and 78% of the patients showed complete remission of white lesions on clinical and vulvoscopic evaluation. Improvement in QoL was

significant for the Dermatology Life Quality Index (DLQI) and the Female Sexual Function Index (FSFI) after 24 months follow-up.[33] Two studies in 2020 showed comparable results with the aforementioned study.[38,39] Almadori et al. used fat grafting to treat 33 patients suffering from LS with a mean follow-up of 12.9 months. Symptoms such as itching, burning, soreness and pain were significantly decreased, and sexual function was significantly improved after fat grafting in all patients. Moreover, patients showed significant improvement in intimate contact, anxiety and depression. However, no histological analysis was performed. Moreover, the potential placebo effect cannot be excluded because it was a single-arm study without a control group.[39] Stark et al. used nanofat to treat 10 patients suffering from vulvar dystrophy caused by LS with a mean follow-up of 6 to 16 months. All patients reported a decrease of their symptoms without any sequelae. Unfortunately, assessment strategies and statistical analysis are not mentioned in this study, and no patients with histologically proven LS were included.[38] In a case report of Tamburino, one patient suffering from LS was treated with nanofat and showed improvement in texture and elasticity of vulvar skin and mucosa one month after application. This was demonstrated by decreased dryness and dyspareunia measured with a non-validated questionnaire.[34]

3.2 | Combination therapy of fat with platelet-rich plasma (PRP)

Thus far, two studies used a combination therapy of fat grafting with application of PRP to treat a total of 16 female patients suffering from LS.[32,36] PRP contains platelets that release growth factors to reduce inflammation and to promote mesenchymal cell proliferation, tissue repair and angiogenesis.[107,108] Nevertheless, the number of platelets is highly variable due interpatient variation, intra-day variation and different reabsorption rates[109,110] and PRP might result in hyperplasia.[111] In the study of Casabona et al. 15 patients were treated with a combination of fat grafting and PRP. Symptoms of itching and burning disappeared in all patients within one month. The vulvar skin and mucosa became more elastic and softer with a normal colour as assessed by the investigators. After 4 months, all patients reported total disappearance of pain and regained sexual activity; however, no statistical analysis was performed.[32] Adding to this, a case report of a 67-year-old female patient with vaginal atrophy showed decreased sensation of vaginal itching and irritation and improved vulvar contours one year after administration of fat grafting with PRP.[36]

3.3 | Combination therapy of stromal vascular fraction (SVF) with PRP

Thus far, two studies examined the effect of tSVF with PRP on therapy-resistant LS in a total of 151 female patients.[37,40] In contrast to the combination therapy of the previous paragraph, the relative concentration of ASCs should be higher when SVF is used instead of fat. The largest study treated 111 patients suffering from LS with tSVF whereby most patients were concomitantly treated with PRP. However, the exact number of patients treated with a combination treatment of tSVF and PRP was not mentioned. A significant decrease of symptoms, for example discomfort, pain, fissures, tearing and fusing, was observed after 3 months, varying from 38% to 68% per symptom and all patients showed improvement of one or more symptoms. No validated questionnaires were used and a long-term follow-up was not reported for this trial.[37] A smaller study investigated the effect of tSVF with or without PRP in 40 female and male patients with histologically proven LS. Significant improvement of QoL was observed in both groups after one month using the validated DLQI questionnaire. After 6 months, the tSVF-group (mixed female and male patients) still showed a significant improvement of QoL, but the tSVF and PRP group showed only limited improvement compared with the pre-operative QoL,[40] suggesting that PRP may mitigate the beneficial effects of tSVF. Willemsen et al. demonstrated a concentration-related effect of PRP to the regenerative capacity of ASCs. This in vitro study showed that PRP promoted endothelial sprouting and survival in a dose-dependent manner; however, when a higher concentration of PRP was added to the ASC-CM, the beneficial effect disappeared or the endothelial sprouting even reduced.[112] More research is necessary to investigate the effects of a combination therapy of tSVF or fat with PRP and which concentration is most effective to treat vulvar LS.

3.4 | Combination therapy of ASCs with hyaluronic acid (HA)

One study used a combination therapy of ASCs with synthetic HA to treat eight female patients suffering from vulvar discomfort, which were affected by LS ($n = 5$), or had vulvar scarring do to chronic graft versus host disease (GVHD) ($n = 2$) or symptoms during their menopause ($n = 1$).[35] HA is a natural glycosaminoglycan believed to function as both a filler and a scaffold that provides support for cell ingrowth.[113] Furthermore, the transplantation of cells in hydrogels is thought to result in long-term protection of the cells in vivo.[114] From obtained lipoaspirate, SVF was isolated and subsequently ASCs were cultured and added to HA. Application of ASC-HA solution into the subcutaneous plane of labia minora resulted in pain reduction and improvement of sexual function in all patients, which was assessed using the validated FSFI questionnaire. This effect was maintained up to two years postoperative. Furthermore, postoperative biopsy specimens indicated that sclerosis of the dermis was reduced, capillaries were less dilated and the inflammatory infiltrate was reduced compared with pre-operative histological examinations. However, the time period of the obtained postoperative biopsy specimens was not mentioned, and the histological findings were not objectively measured.[35] It would be interesting to get a better understanding

of the percentages of reduction of dermal sclerosis and quantity and quality of microvasculature, for example.

4 | CONCLUSIONS

Fat grafting is a novel regenerative treatment modality to treat therapy-resistant LS, wherein the endogenous regenerative capacity of the fat tissue is employed to mitigate the mechanisms underlying the pathophysiology of LS. Various pioneering studies have already applied fat grafts to vulvar LS tissue, and they all report promising results regarding the relieve of clinical symptoms and an improvement of QoL. The proposed mechanisms-of-action of the fat grafting to mitigate the pathophysiology of LS include immunomodulatory, pro-angiogenic and anti-fibrotic effects; however, in these clinical studies, these proposed mechanisms have hardly been investigated. Therefore, we recommend that future studies should validate these initial findings and should use validated outcome measurements and histological examinations before and after treatment, in order to elucidate the mechanisms-of-action, which are currently elusive.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

NS, ECAHS and JD performed the research. ECAHS, GK, BL and MHMO designed the research study. Nobody contributed essential reagents or tools, since this article is a review article. NS, ECAHS, GK and JD analysed the data. NS wrote the paper. All authors have read and approved the final manuscript. Anyone who contributed to the study and/or manuscript preparation, but who does not meet the authorship criteria is listed in the acknowledgments.

DATA AVAILABILITY STATEMENT

The data sharing is not applicable to this article as no new data were created or analysed in this study.

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