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Autologous Fat Grafting: Evaluation of Efficacy in Pain Relief

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Introduction: Autologous fat grafting (AFG) has been used in reconstructive plastic surgery for over a century. Although it has obvious benefits to the aesthetic appearance of many reconstructive surgeries, less appreciated advantages of fat grafting have also been shown in potential pain reduction. This can be seen across the board from head to toe with examples ranging from facial nerve injury to pedal atrophy and foot ulcers. The purpose of this literature review is to evaluate the efficacy of AFG for pain relief in various indications and serve as a reference for clinicians to gain insight on potentially beneficial therapies for their patients.
Methods: A broad literature review was performed to analyze the various uses of AFG for pain management by various indications including postmastectomy pain syndrome, scar pain, neuromas, chronic wounds and many more. The PubMed, Science Direct and Scopus online databases were searched using keywords such as "autologous fat grafting," "reconstruction," "pain," and "therapy."
Results: At this point, there is decent evidence to support AFG's role in pain resolution in postmastectomy pain syndrome, neuropathic scar pain, and pedal injury. There is also ample low-level evidence for pain efficacy in autoimmune diseases, neuromas, vulvar lichen sclerosis, burns, and radiation-induced wounds.
Conclusions: While there is a clear lack of higher-level evidence based studies conducted on AFG for all indications, the existing literature shows a definite trend of reconstructive efficacy and pain management that can be clearly appreciated. With the increasing popularity of this procedure for reconstruction, higher-level studies are beginning to take place pertaining to AFG's efficacy not only in reconstruction, but pain management as well. *(Plast Reconstr Surg Glob Open 2022;10:e4543; doi: 10.1097/GOX.0000000000004543; Published online 1 November 2022.)*

INTRODUCTION

Fat grafting has been used in reconstructive plastic surgery for over a century.[1] Although it has obvious benefits to the aesthetic appearance of many reconstructive surgeries, less appreciated advantages of fat grafting have also been shown in potential pain reduction, although this aspect appears to be slightly controversial. This can be seen across the board from head to toe with examples ranging from facial nerve injury to pedal atrophy and foot ulcers. The purpose of the literature review is to evaluate the use of fat grafting and its effects on pain in various anatomic locations and surgical indications. The authors intend for this work to organize the use of autologous fat grafting (AFG) for pain relief by indication as to give physicians an easy reference when looking for treatment modalities for their patients.

METHODS

A broad literature review was performed to analyze the various uses of AFG and specifically its effects on pain management by various indications including postmastectomy pain syndrome (PMPS), scar pain, neuromas, chronic wounds, and many more. The PubMed, Science Direct, and Scopus online databases were searched using keywords such as "autologous fat grafting," "reconstruction," "pain," and "therapy." From there, articles were screened for relevance toward reconstructive and pain relief analysis and separated into various indications for treatment as shown in the PRISMA diagram below (Fig. 1).

Subsequent searches were performed using additional keywords specific to the indication (eg, "painful neuroma"

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or "radiation") to ensure all adequate studies would be included in this review. After removing duplicate and nonrelevant articles, these additional searches yielded eight more articles to be included making our total number of included articles 35.

Takeaways

Question: How efficacious is the use of autologous fat grafting (AFG) for pain management in various anatomic locations and surgical indications?

Findings: Moderate evidence was found to support the role of AFG in pain resolution in postmastectomy pain syndrome, pedal injury, and neuropathic scar pain. Additionally, ample low-level evidence was found for various other indications.

Meaning: Although there is a clear lack of higher-level evidence-based studies conducted on AFG for all indications, the existing studies show a definite trend toward pain management in addition to reconstructive efficacy.

RESULTS BY INDICATION

Postmastectomy Pain Syndrome

Breast cancer affects one in eight women in the United States, many times leading to breast conserving therapy or total mastectomy.[2] Unfortunately, the treatment of breast cancer is very commonly associated with persistent pain in 24%–52% of patients.[3] Postmastectomy pain syndrome (PMPS) can be defined as chronic pain located in the chest, axilla, and/or upper arm that lasts for over 3 months postoperatively[4] that has been noted to afflict up to 65% of patients.[5] This pain is typically neuropathic with features such as tingling, burning, and aching. PMPS significantly affects the quality of life in these women who are already dealing with a cancer diagnosis and potentially

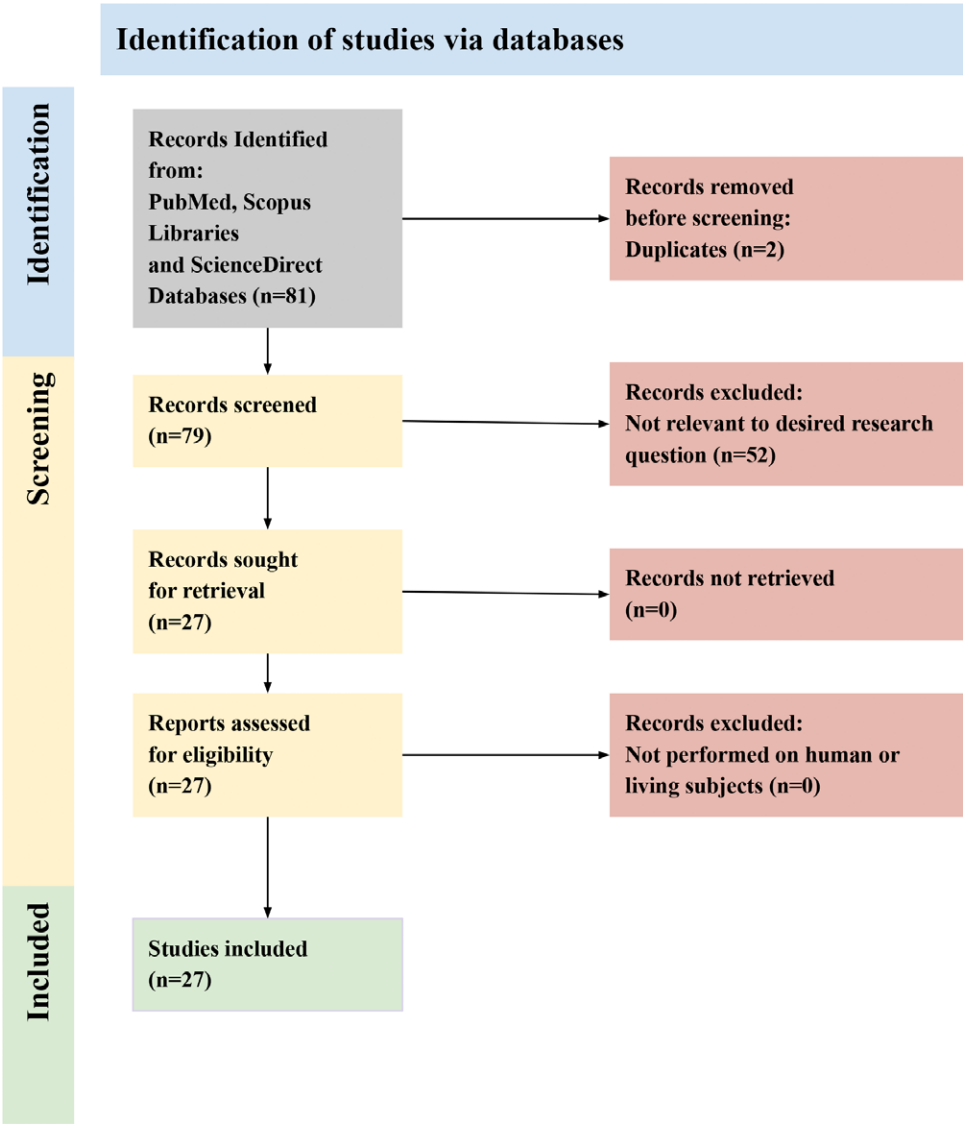

Fig. 1. PRISMA diagram of review screening process.

Study	Design	Size	Results	Conclusion
Caviggioli et al 2011[5]	Controlled prospective trial	113 patients, 63 with AFG	Significant decrease in pain with using the VAS	AFG is considered a safe and effective treatment
Maione et al 2014[2]	Controlled prospective trial	96 patients, 69 with AFG	Significant decrease in pain using the VAS	AFG considered useful for pain treatment in this setting
Juhl et al 2016[3]	Randomized clinical trial	15 patients, 8 with AFG	Significant improvement of VAS and other measures	In support of the use of AFG
Caviggioli et al 2016[6]	Controlled prospective trial	209 patients, 131 with AFG	Significant difference in VAS reduction between treatment and control groups	Supports the role of AFG in treating neuropathic pain in women with PMPS
Lisa et al 2020[4]	Prospective multicenter study	37 patients, all with AFG	Significant reduction in VAS at 1 and 3 months post operatively	Confirms efficacy of AFG for this patient population
Sollie et al 2022[7]	Single center, double blind and randomized	35 patients, 18 with AFG	No statistically significant change in pain using the NRS	Does not support the efficacy of AFG in these patients

Fig. 2. Studies pertaining to AFG in PMPS.

the loss of one or both breasts. There have been many proposed treatments for PMPS including analgesics, antidepressants, anticonvulsants, topical medications, physical therapy, nerve blocks, and AFG.

Six total trials, as detailed in Figure 2, from 2011 to 2022 were found that investigate the role of AFG in PMPS.[2–7] All but one trial support this procedure and its efficacy in diminishing pain for this patient population. However, the most recent publication by Sollie et al denies its efficacy. This study involved a sample size of only 36 participants, 18 of whom received AFG (compared to other studies three times this size), and was the only study to not include the visual analog scale (VAS) as the measurable pain outcome. However, it was the only study to date to compare the fat grafting group with a double blinded sham operation group. With these limitations and benefits in mind and while looking at all 505 patients across these six trials, there is still strong evidence to accept fat grafting as a safe and potentially effective treatment for PMPS.

Use of the VAS among these trials increases their evidence level greatly as this is a standardized measure of pain that can easily be compared and repeated. The VAS is a validated scale for acute and chronic pain that has been commonly used for the evaluation of relief modalities since its first use in 1921.[8]

Fat grafting in these patients is many times used as a great tool for reconstruction, allowing the surgeon to create a more natural aesthetic breast. However, its potential to reduce pain in this patient population should not be overlooked. Although the exact mechanism is yet to be determined, physical components such as padding around an entrapped or inflamed nerve are very possible as well as fat tissue-provided substrates promoting the healing process and reducing inflammation.

Scar Pain

Left over scars from traumatic or minor injuries can inflict a large amount of pain and greatly decrease a patient's quality of life. Pain from scar tissue is generally described as neuropathic and has proven to be difficult for clinicians to effectively treat. Furthermore, scars create a diverse range of adverse symptoms in affected patients such as pruritus, discomfort, discoloration, stiffness, and contraction.

Injecting fat into scar tissue can loosen retractile skin, decreasing the stiffness and contracture characteristics that can contribute to pain. Furthermore, adipose tissue-containing mesenchymal stem cells have potential for propagating the healing process and decreasing inflammation. The use of AFG in the treatment of neuropathic scar pain

Study	Design	Size	Results	Conclusion
Negenborn 2016[10]	Systematic review	26 articles: 905 patients	Statistically significant improvement of scar appearance, skin characteristics and pain	Supports AFG's role in scar treatment for both aesthetics and pain
To et al 2019[9]	Systematic review	18 studies: 288 patients	233 patients responded with a reduction in pain	AFG is a promising and safe treatment of painful scars
Krastev et al 2020[11]	Systematic review and meta-analysis	45 studies: 3033 patients	Statistically significant improvement in VAS score	AFG appears to be an effective treatment for fibrosis and scar related conditions

Fig. 3. Studies pertaining to AFG in scar treatment.

Study	Design	Size	Results	Conclusion
Vaienti 2010[13]	Case Report	1 patient	Pain relief in radial nerve neuroma	Supports AFG by this indication
Vaienti 2012[14]	Retrospective analysis	7 patients	Mean 27% decrease in VAS score	Supports AFG for painful neuromas
Vaienti 2013[15]	Retrospective analysis	8 patients	Mean 23% decrease in VAS, not significant	Supports AFG for painful neuromas
De Jongh 2020[16]	Case Report	1 patient	Pain relief in neuroma of the hand	Supports AFG in this population

Fig. 4. Studies pertaining to AFG in painful end neuromas and other neuropathic pain.

has been very widely researched. And as such, there have been many studies on this treatment modality leading to systematic reviews and meta-analyses. For the purposes of this article, we decided to only include these previously conducted larger view projects as a means of gaining a fuller understanding of AFG in this patient population.[9–12]

Systemic reviews by both To and Negenborn reported positive results in regard to both pain reduction and aesthetic outcome when treating scars with AFG.[9,10] These studies included 288 and 905 patients, respectively, giving a significant generalizability of these results. Furthermore, a recent significant systemic review and meta-analysis done by Krastev et al in 2020 included 45 studies with 3000+ patients with scar pain being included.[11] Their results showed a statistically significant decrease in VAS score with the use of AFG for this condition. These larger-based, higher-level analyses show the credibility of AFG in pain relief for these patients and are highlighted in Figure 3.

Two of three of these reviews highlighted the therapeutic level of their included studies ranging from level I to level V with the average being III–IV.[9,10] This points to the larger limitation of most studies surrounding AFG lacking larger-based randomized controlled trials. However, having multiple systematic reviews and meta-analyses pointing toward the same conclusion does show strength in the use of this technique and justifies future research and practice of AFG in scar therapy.

Painful End Neuromas and Other Neuropathic Pain

A neuroma is a benign nerve growth commonly characterized by severe debilitating pain. As with many difficult to treat conditions, there are a multitude of therapy modalities in use by clinicians with none remaining as the gold standard of care. To this point, there is only low-level evidence, including studies of limited patient size and largely from one center, to support the role of AFG in this population.

Study	Design	Size	Results	Conclusion
James et al 2021[18]	Prospective randomized	13 patients	Foot pain, function and appearance all significantly improved with controls at 6 and 12 months	In support of AFG for rejuvenation of heel
Maione et al 2019[19]	Case series	7 patients	Resolved pain in all patients	Supports AFG for treatment of calcaneal post-surgical chronic ulcer
Minteer et al 2018[20]	Prospective, randomized, crossover, single center	18 patients	Pain improved immediately following fat grafting in both groups and lasted through follow-up	Supports AFG due to long lasting improvements in pain and function
Raposio and Calderazzi 2017[21]	Prospective study	8 patients	Statistically significant decrease in pain scales at 6 months post-op	Promotes AFG for the relief of weight bearing foot pain

Fig. 5. Studies pertaining to AFG in pedal injury.

Five publications, as described in Figure 4, were found pertaining to the use of AFG mainly in neuromas and also neuropathic pain from herpes zoster virus. All articles spoke to the effectiveness of this technique.[13–17] Although this is a mix of lower- and medium-level evidence, it does suggest that more research is needed to fully determine the usefulness of AFG in painful neuromas. The suggested most likely mechanism for reduction of pain includes fat acting as a protective barrier around the sensitive nerve endings.

Pedal Injury

Foot pain can be very debilitating for patients for obvious reasons including impaired ambulation and decreased ability to care for oneself. This can be due to various reasons such as pedal fat pad atrophy and chronic wounds on the base of the foot. Recently, work has been done, as detailed in Figure 5, to attempt to relieve this pain with AFG.[18–20]

It is reasonable to assume there would be some pain management with increased padding on the weight bearing areas on the sole of the foot. However, these studies are even finding adequate pain relief once the thickness of the foot has returned to preprocedure baseline.[18,20] This continued pain relief suggests an additional mechanism contributing to analgesia and validates the use of AFG over a simple shoe pad for more significant results.

Autoimmune Conditions

Autoimmune diseases, specifically systemic scleroderma, are life altering conditions commonly associated with pain and minimal treatment options. Scleroderma consists of malfunction of connective tissue causing stiffness and thickening of the skin as well as manifestations in other organ systems. Skin involvement of the facial region can cause significant distress to patients by way of both disfiguration and loss of function including eating, drinking and speaking. The hands can also become very affected by scleroderma causing great pain and digital ulcers.

The rationale behind the use of AFG in these patients lies in its potential for decreasing collagen depositions and increasing elasticity and vascularization.[23] This can improve motion in the face and hands as well as support the healing process of ulcers. Four studies, as shown in Figure 6, were included that show promising results in both pain modification and reconstruction using AFG in these patients.

Burn Injury

Burns can be very dangerous and deadly pathologies affecting a broad range of patients every year. Experiencing a burn can be a traumatic experience that can be taxing on not only the patient, but their family and healthcare providers as well. Up to 29% of burn patients may experience chronic neuropathic pain.[27] Current research suggests a role for AFG in the treatment of burn patients. It has been found to accelerate revascularization and reduce fibrosis found in thermal injuries as well as support wound healing with the induction of mesenchymal stem cells found in adipose tissue.

As seems to be the case throughout AFG research, there have been multiple low-level studies performed that are

Study	Design	Size	Results	Conclusions
Strong et al 2021[24]	Retrospective analysis	10 patients	Subjectively and qualitatively improved perioral skin quality, facial animation, hand ROM and hand pain	Supports AFG in patients with systemic scleroderma
Bene at al 2014[25]	Prospective	9 patients with 15 treated ulcers	Complete healing in 10 ulcers, 6 patients with reduced pain	Supports treatment with AFG in systemic sclerosis
Del Papa 2019[26]	Randomized Controlled trial	38 patients	Significant reduction in pain intensity after 4 and 8 weeks	Strongly supports AFG's effectiveness in treating scleroderma induced digital ulcers
Pignatti at al 2020[23]	Prospective	25 patients	Pain reduced while perception of disability improved	Supports treatment of AFG in systemic sclerosis

Fig. 6. Studies pertaining to AFG in autoimmune conditions.

making way for larger randomized control trials. We have included two smaller based retrospective analyses as well as the first higher evidence-based trial of this kind investigating the role of AFG in burn patients, as can be seen in Figure 7.

Although the work by Ahmed did not include any specific outcome measure pertaining to pain, a great increase in quality of life can be seen.[29] Furthermore, an impressive and significant difference in opioid use is a very strong indication of pain relief in these patients. Not only is decreased need for pain medications and decreased hospital stay beneficial for quality of life but it also is a decreased financial burden on the patient and family.

Radiation Injury

Radiation injury and its various treatment modalities are another well-debated topic among clinicians. Once again, we see a large amount of case studies and retrospective studies pointing towards the efficacy of AFG in this pathology. One comprehensive systematic review pulls all these studies together and advocates for the future trials that need to take place.[30] The details of these included studies can be seen in Figure 8.

Although the available literature is not fully robust yet, a great potential can be seen with AFG in radiated tissue. Improvements can be seen in tissue quality pertaining to liability and vascularization after grafting. Furthermore, pain seems to be reduced across the board, regardless of radiation injury location, removing some of the disability from these patients.

Vulvar Lichen Sclerosus

Vulvar lichen sclerosus (VLS) presents with very painful fibrosis and scarring of the vulvar area. In severe cases, this can greatly decrease quality of life by fibrosis impairing the anatomy of the vagina. Studies on the treatment of VLS with AFG have shown significant increases in relief of itching, pain, soreness and burning as well as improved sexual function and less distress.[36] Currently, there are not many studies dedicated to this treatment modality, but the two included articles shown in Figure 9 are promising for the future direction of this treatment.

DISCUSSION

Pain is a notoriously difficult to treat and potentially debilitating condition even with whole fields of medicine dedicated towards treating it. The prospect of AFG in the treatment of pain has been a promising development in plastic and reconstructive surgery. Another benefit of this treatment modality is a low complication rate; AFG is generally considered a very safe procedure.[19,25]

AFG has been greatly developed over the course of a century. Starting in 1899 for the treatment of scars, the process has been refined immensely, leading to the start of the Coleman method in 1994.[1] The Coleman method includes aspiration of the fat tissue by means of a blunt cannula under low negative pressure suction to avoid unnecessary trauma to the cells. The lipoaspirate is then centrifuged to obtain the purest form of the fat.[1]

Study	Design	Size	Results	Conclusions
Fredman et al 2016[27]	Retrospective case review	7 patients	6 patients had improvement in neuropathic pain	AFG can safely be used in these patients and may improve pain symptoms
Byrne et al 2016[28]	Retrospective analysis	13 patients	Improvements in total active movement, daily living and satisfaction of the Michigan Hand Outcome Q. No significant improvement in pain score.	Supports AFG in improvement of skin quality and reduction of tightness
Ahmed 2021[29]	Prospective, open label single center, randomized clinical trial	100 patients	A significant difference in opioid use was found with 98% use in the control group and only 22% in the AFG group	AFG in acute burn wounds was associated with significant clinical improvement including lower hospital stay and use of skin grafting

Fig. 7. Studies pertaining to AFG in the treatment of thermal injuries.

There are many proposed therapeutic mechanisms for the efficacy of fat grafting. Although a simple physical padding of the area seems to have obvious benefits, more complex mechanisms of the components in adipose tissue may reveal the true analgesic effects. Fat contains many elements that have potential to benefit the wound healing process such as extracellular matrix, collagens, laminin, fibronectin, adipocytes, and stem cells.[5] Adipose-derived stem cells have the capability to differentiate into multiple cell lineages including all three germ cell layers.[38] They also serve to secrete multiple restorative growth factors and chemicals that suppress inflammation.[38] These properties in the presence of damaged tissue seem to give way to an environment prone to healing. Potentially, these mechanisms are more effective in certain areas of the body which could be why there is more complete evidence for PMPS, whereas it is lacking for other indications such as autoimmune diseases. Without uniformity throughout the studies it is difficult to give a conclusive answer; however, the current data do show a trend toward more adequate pain relief in indications related to neuropathic pain as seen in PMPS, scars, and neuromas.

Histological studies have given a basis of evidence for the healing effects of fat grafting by showing neovessel formation and improved hydration within the treatment of radiation injury.[32] Further studies have even shown new collagen formation, dermal hyperplasia, and local hypervascularity.[34] Increasing blood flow to a damaged area greatly increases its likelihood to heal and thereby decrease pain. One of the included studies on scleroderma also gave evidence of this in showing newly formed capillary beds in patients with debilitating digital ulcers treated by AFG using nailfold video capillaroscopy to visualize the capillaries in addition to histology.[26]

Another proposed mechanism lies within AFG decreasing the inflammatory response. Keyser's work found inhibition of NK cell proliferation and T cell activation by fat grafting.[39] The inhibition of T cell activation could be explained by Huang's work showing adipose cells secreting interleukin-10 which adamantly inhibits both CD4 and CD8 found on T cells.[40] Furthermore, mesenchymal stem cells also found in adipose tissue are known to decrease inflammation by inhibiting the generation and release of inflammatory cytokines.[6]

LIMITATIONS

As was continually noted, there is a clear lack of higher-level evidence-based studies conducted on AFG for all indications. The available nonrandomized and nonblind data leave many opportunities for bias, namely selection and measurement biases. However, in the existing case studies and series, retrospective reviews and prospective investigations, a definite trend of reconstructive efficacy and pain management can be clearly appreciated.

To gain an encompassing view of the level of evidence available at this point in research, the included studies were evaluated using the GRADE tool.[41] The number of studies found to be in each category can be seen below in Figure 10.

Study	Design	Size	Results	Conclusions
Jackson et al 2001[31]	Case report	1 patient	Cosmetically acceptable result following a large volume deficit	AFG successfully added volume and decreased skin tightness
Rigotti 2007[32]	Prospective analysis	20 patients	Systematic improvement or remission of symptoms in all evaluated patients	This surgical procedure is a low-invasive therapeutic approach for resolving the late side effects of radiotherapy
Phulphin et al 2009[33]	Retrospective	11 patients	Improvement in the quality of the irradiated skin	Functional and aesthetic improvements from AGF
Klinger et al 2018[34]	Case series	3 patients	Improvement of pain in all patients as well as decreased fibrosis and retraction	AFG is a promising treatment for radiation induced orbit injuries
Vyas et al 2021[35]	Case report	1 patient	19 month nonhealing ulcer treated with AFG showed near complete healing 10 months later	AFG is useful for chronic non healing radiation induced wounds
Kenny 2021[30]	Systematic review	22 studies	Current clinical evidence suggests that AFG reduces pain, and improves cosmetic and functional outcomes.	More higher level trials need to be conducted

Fig. 8. Studies pertaining to AFG in radiation injury.

Although the average of all studies was between low and moderate, it is important to note that this varied greatly by section. For instance, more established categories such as PMPS, scar pain, and pedal injury had averages between moderate to high, while the indications for treatment earlier in the research stages such as VLS and painful end neuromas ranged from low to very low.

FUTURE DIRECTIONS

With the limitations in mind, it is imperative that continued research be done on AFG to help us unlock its full potential. Although much of this work has yielded promising results, future studies should be performed in a uniform manner to gain higher-level evidence for AFG in pain relief.

One study improvement could include scales for pain severity such as the VAS[8] and other standardized measures for pain symptoms. The use of objective outcomes in this way will allow researchers and clinicians to analyze and compare the efficacy of pain relief throughout all of the proposed indications. The authors hope to see future studies moving away from case reports and series and toward high-level controlled trials.

Study	Design	Size	Results	Conclusions
Almadori et al 2020[36]	Prospective cohort	33 patients	Significant improvements in VAS for itching, burning, soreness and pain	Supports AFG for this indication and also reports improvements in psychosocial aspects of life
Boero et al 2015[37]	Prospective cohort	36 patients	Reduction of chronic inflammation in 89% of cases. Reduction of fibrosis in 67%. Disappearance of scratching lesions in 94%	Promotes the role of AFG in the treatment of refractory VLS

Fig. 9. Studies pertaining to AFG in VLS.

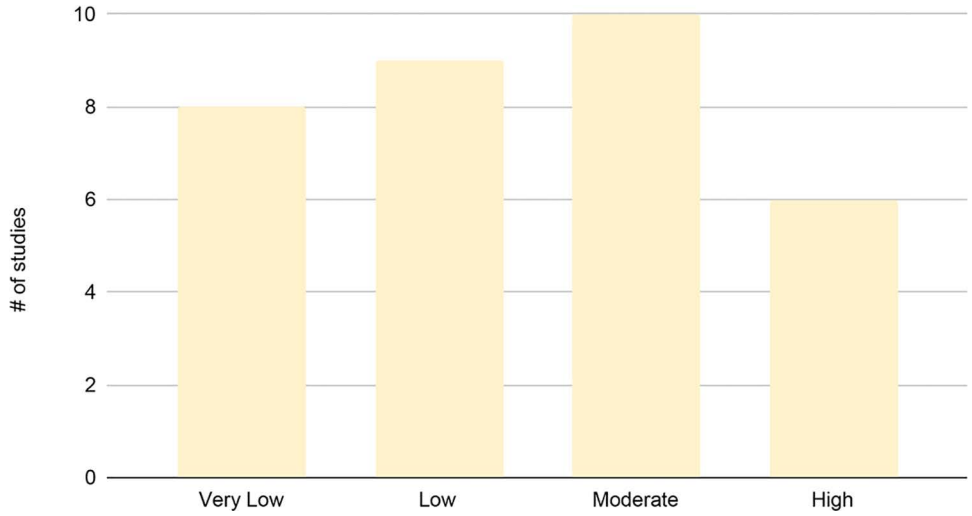

Fig. 10. GRADE ratings of included studies.

CONCLUSIONS

Although there is a clear lack of higher-level evidence-based studies conducted on AFG for all indications, the existing case studies and series, retrospective reviews, and prospective investigations show a definite trend of reconstructive efficacy and pain management that can be clearly appreciated. With the increasing popularity of this procedure for reconstruction, higher-level studies are beginning to take place pertaining to AFG's efficacy not only in reconstruction, but pain management as well.

At this point, there is decent evidence to support its role in pain resolution in PMPS, neuropathic scar pain and pedal injury. Although more higher-level studies need to be conducted for every indication, we can see ample low-level evidence for pain efficacy also in autoimmune diseases, neuromas, vulvar lichen sclerosis, burns, and radiation-induced wounds.

There are many proposed reasons for why this relief may come with AFG. For instance, the introduction of multipotent mesenchymal stromal cells found in adipose tissue may increase vascularity and promote healing. Additionally, the increased volume alone could act as a protective barrier against noxious stimuli. Perhaps, the combination of this and other factors is the source of pain relief that can be seen throughout various indications and across all areas of the body.

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