The Influence of Fat Grafting on Skin Quality in Cosmetic Foot Grafting: A Randomized, Cross-Over Clinical Trial

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Abstract

Background: Pedal fat grafting is a cosmetic procedure to treat the functional and aesthetic sequelae of pedal fat pad atrophy. Fat grafting has been found to mitigate these symptoms, but the exact mechanism is unknown.

Objectives: The authors hypothesized that pedal fat grafting may improve skin quality, accounting for prolonged symptomatic improvement despite loss of grafted fat.

Methods: Patients with pedal atrophy were enrolled in a randomized crossover clinical trial. Group 1 underwent fat grafting upon enrollment with 2-year follow-up. Group 2 was managed conservatively for 1 year then placed into the fat grafting group with 1-year follow-up. Patients underwent pedal ultrasounds to determine thicknesses of the fat pad and dermis, and photographs were taken to assess skin quality.

Results: Three men and 20 women with an average age of 63 ± 6 years and an average BMI of 26.0 ± 4.6 kg/m^2 were enrolled in the study. Twenty-six feet were injected in Group 1 and 17 were injected in Group 2. Group 1 dermal thickness increased at 6 months post-injection ($P < 0.05$). This increase persisted through 24 months. Group 2 dermal thickness decreased prior to injection ($P < 0.05$) but returned to baseline after injection and through 12-month follow-up ($P < 0.05$). Fat pad thickness returned to baseline by study completion in both groups ($P < 0.05$).

Conclusions: Pedal fat grafting yielded a significant, sustained increase in dermal thickness, though grafted fat was not retained. Fat grafting may improve skin quality, which could contribute to improved clinical outcomes despite loss of grafted fat.

Level of Evidence: 2

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Pedal fat pad atrophy is a devastating condition primarily affecting adults older than 60 years.[1] The condition is characterized by foot pain that can be severe enough to limit productivity and cause emotional or physical distress. Because pedal atrophy is correlated with overuse, these patients are often high-functioning individuals who become debilitated to the point it is difficult to wear normal shoes, go barefoot, or sometimes even walk.[2-6]

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Causes of pedal atrophy are vast and include age, steroid injections, abnormal foot mechanics, underlying disease states impacting soft tissue integrity, or sequelae of surgury.[7-9] Currently, pedal atrophy is a diagnosis of exclusion because no established tissue thickness criteria define the condition.

Currently, the standard of care for treating pedal atrophy is use of external devices or augmentation with synthetic fillers. These external devices, such as orthotics and cushioning aids, are limited by mechanical or compliance issues.[10] Similarly, soft tissue fillers are limited by longevity, migration, and foreign body response.[11-13] Limitations of these modalities have sparked interest in autologous fat grafting in our research group.[14] Currently, fat grafting for treatment of pedal atrophy is not covered by insurance and is considered a cosmetic procedure.

The benefits of autologous fat grafting have been outlined previously in the plastic surgery literature.[15] In particular, previous studies have shown that fat grafting may beneficially impact surrounding tissues through increased collagen synthesis, neovascularization, and local stem cell concentrations.[16-20] Therefore, fat grafting has been applied for an ever-increasing number of indications.[21] These include soft tissue augmentation,[22,23] chronic wounds,[24] scar release,[22,25,26] radiation damage,[26,27] breast augmentation and reconstruction,[23,26,28-31] hand contractures,[32-34] and facial contouring.[21] Additionally, autologous fat grafting has been applied in specialized indications in scleroderma,[35,36] erectile dysfunction,[37] and Raynaud's phenomenon.[38] Though the mechanisms of fat graft efficacy in many of these applications are not completely understood or studied, the potential trophic effects of fat grafting clearly may positively impact the local tissue milieu. One of the proposed benefits of fat grafting is an increase in dermal thickness,[39,40] suggesting its potential utility in burn reconstruction, radiation injury, and facial rejuvenation.

Our group previously published a 1-year, randomized clinical trial on the potential applications of fat grafting to the foot to treat pedal atrophy.[14] In this study, we demonstrate an improvement in pain and quality-of-life outcomes despite loss of the grafted fat over time. In searching for the mediator of this symptomatic improvement, we hypothesize that fat grafting to the foot may increase dermal thickness, accounting for the prolonged improvement in pain and quality of life.

METHODS

Trial Design

We enrolled patients diagnosed with fat pad atrophy of the forefoot in an IRB-approved, randomized cross-over clinical trial (ClinicalTrials.gov identifier: NCT01796808; approved by University of Pittsburgh Institutional Review Board). Patients were enrolled between January of 2014 and December of 2016. Patients were included in the study if they complained of foot pain under the metatarsal heads, had been diagnosed with fat pad atrophy by a foot and ankle specialist, and had not undergone any surgical procedures or injections within the last 6 months. Patients were excluded if they had any open foot wounds, osteomyelitis or other infection, uncontrolled diabetes mellitus (HgA1c level >7.0), cancer or active cancer treatment, known coagulopathy or systemic disease, current pregnancy, or any tobacco use within the past year.

Patients presented for an initial screening visit for thorough medical, surgical, social, and functional histories; vital sign measurements; and a complete physical exam focusing on the feet. Documentation of foot anatomy and neurovascular exam was performed. Ultrasounds measurements evaluated the subcutaneous and dermal thickness. Standardized photographs of the feet were taken to document any calluses or deformities.

Once patients provided informed consent and eligibility was determined, an independent research coordinator not involved in the trial randomized patients with the GraphSoft random number generator function (GraphPad Software, Inc. La Jolla, CA). Subjects were randomized to either the intervention protocol (Group 1) or to the standard of care protocol (Group 2).

Group 1 underwent fat grafting immediately upon enrollment with 2-year follow-up. Group 2 was managed conservatively for 1 year upon enrollment before placement into the fat grafting group with an additional 1 year of follow-up. Conservative management included orthotics, offloading, padding, and other noninvasive interventions. No control injections were performed.

Patients were followed-up at 1, 2, 6, and 12 months postoperatively, with Group 1 continuing to be monitored at 18 and 24 months.

Surgical Procedure

Fat was harvested under local anesthesia in an outpatient, office-based procedure. First, local anesthesia (lidocaine 1% with epinephrine 1:100,000) was injected at planned aspiration sites, which included abdomen, thighs, or flanks based on patient preference and physical exam findings. Tumescent solution (500 mL normal saline, 10 mL 2% lidocaine, 1 mL of 1:1000 epinephrine) was injected into the planned harvest site. Liposuction was performed using 10-mL syringes and blunt tip, multi-hole, hollow cannulas to minimize adipocyte trauma. Approximately 50 to 100 mL of lipoaspirate was obtained per patient. Donor sites were dressed with bandages.

We did not objectively quantify the number of patients who suffered from postoperative pain because the procedure was intended to treat preexisting pain. Additionally, bruising had often resolved by the initial postoperative visit and was not objectively quantified. Fat was processed by means of the Coleman method.[41] Lipoaspirate was first centrifuged at 3000 rotations per minute for 3 minutes, followed by decanting of the aqueous layer and wicking of the oil layer. The remaining fat was transferred into 1-milliliter syringes for injection into the foot.

A tibial nerve block and forefoot Mayo block was performed to anesthetize the foot with a 50:50 mixture of 2% lidocaine and 0.5% bupivacaine without epinephrine. Fat was injected through 2 puncture sites (between first and second toe and fourth and fifth toe on the plantar aspect of the foot) made with an 18-gauge needle using a blunt cannula. These access sites allowed for fat injection in a crosshatch pattern. The senior authors, a podiatric surgeon (B.R.G.) and a plastic surgeon (J.A.G.), determined the optimal areas for fat graft injection following a thorough podiatric physical exam and ultrasound imaging of forefoot subcutaneous tissue. The endpoint of injection volume was fullness of the predetermined areas on palpation and compression, which amounted to an average of 4 to 6 mL of fat. If skin blanching was noted, injection was stopped.

Postoperatively, the grafted area was offloaded with insoles and/or padding when the patient wore shoes. Barefoot walking was permitted only in the shower with flip flops and/or bathmat use. Patients were also restricted to 10 minutes of weight-bearing per hour for the initial 4 to 6 weeks postoperatively.

Measurement of Tissue Thickness

At each follow-up time point, pedal ultrasonography (Terason Ultrasound Imaging System, Version 4.7.6, Burlington, MA) was performed to determine tissue thicknesses. Images were taken over each metatarsal head, and measurements were performed by means of the native ultrasound software to measure thicknesses of the fat pad and dermis at each location.

Measurement of Pain, Function, and Quality of Life

At each follow-up visit, the Manchester Foot Pain and Disability Index (MFDI), a validated survey assessing symptoms related to foot pain, was administered to study participants.[42] The questionnaire consists of 4 categories: functionality, appearance, pain, and work/leisure; higher scores indicate increased disability. Patients completed this questionnaire at each follow-up visit.

Assessment of Callus Severity

At each follow-up visit, photographs of the foot were taken from the dorsal, plantar, lateral, and oblique views. Callus severity was determined with photographs from the preoperative and latest postoperative time points.

Preoperative and postoperative photographs were graded based on the presence or absence of callus. If callus was present in both photographs, an additional grade was given to indicate whether the callus had improved.

Statistical Analysis

A priori power analysis indicated that enrollment of 5 subjects would be sufficient to detect a clinically significant difference using standard conventions of $\alpha = 0.05$ and $\beta = 0.80$.

Statistical analysis was conducted by means of IBM Corporation SPSS Statistics for Windows Version 24.0 (IBM Corporation, Armonk, NY). Differences between Group 1 and Group 2 were evaluated using 2-sided Wilcoxon rank-sum tests. Statistical significance was defined as $P < .05$. Outliers (2σ) were removed prior to analyses. Correlations between dermal thickness and MFDI scores were determined by means of Pearson product-moment correlations. Fisher's exact test compared callus improvement between groups.

RESULTS

Patient Demographics

A total of 23 patients, or 43 feet, were included in the study. This cohort included 3 men and 20 women. The average age was 63 ± 6 years (range, 47-71 years), and the average BMI was 26.0 ± 4.6 kg/m^2 (range, 21.8-28.6 kg/m^2). Age and BMI did not vary between the groups ($P > 0.05$). Causes of pedal atrophy included failed neuroma surgery, prior foot surgery, steroid injections, and overuse. Group 1 consisted of 26 feet and Group 2 consisted of 17.

Surgical Procedure

In Group 1, an average 4.0 ± 2.0 mL of fat was injected into each affected foot. An average 4.6 ± 1.8 mL of fat was injected in Group 2. These values did not differ significantly between groups ($P > 0.05$). Data were generalized by averaging the thicknesses of the 5 metatarsals of each foot. These values were used for comparison.

Complications of pedal fat grafting included postprocedural pain and bruising of the feet and donor sites but no instances of infection, hematoma, seroma, or oil cysts. No patients required perioperative antibiotics or pain

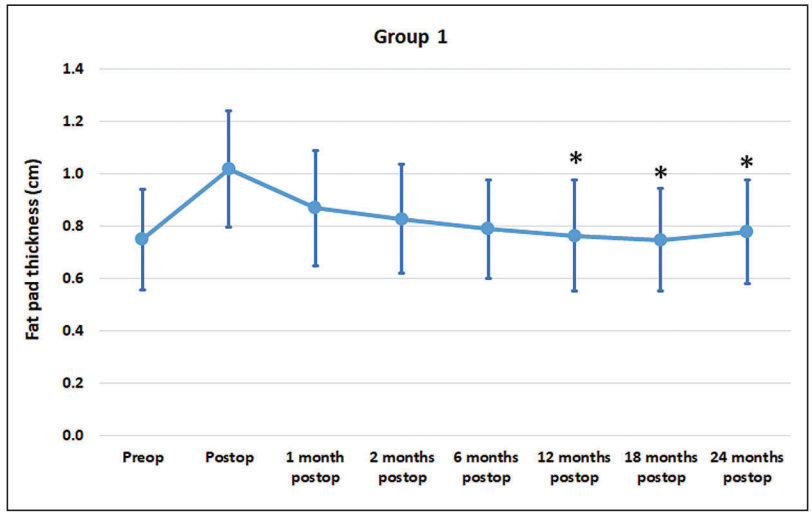

Figure 1. Fat pad thickness over time in Group 1 (*, statistically significant difference from previous measurement with $P < 0.05$).

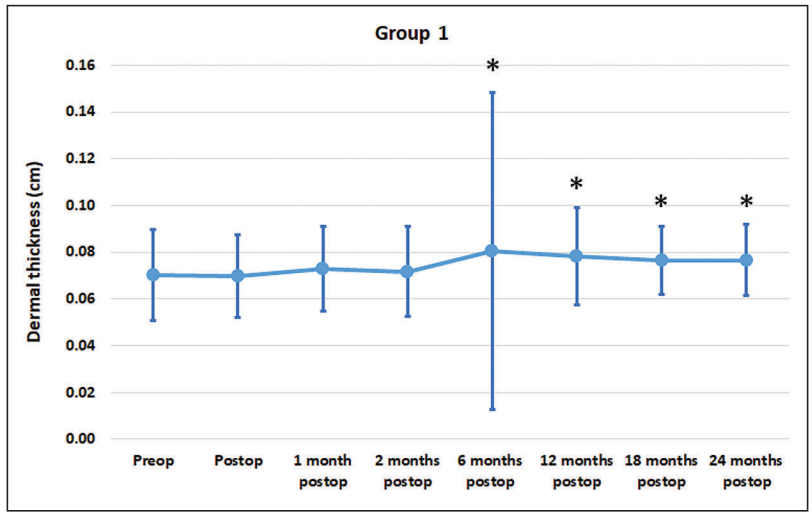

Figure 2. Dermal thickness over time in Group 1 (*, statistically significant difference from previous measurement with $P < 0.05$).

medications, and no serious unanticipated or adverse events occurred. Three subjects requested a second round of fat grafting at the end of the 2-year clinical trial owing to symptomatic improvement.

Tissue Thickness Outcomes

The average preoperative fat pad thickness, 0.75 ± 0.19 cm in Group 1 and 0.74 ± 0.20 cm in Group 2, did not differ significantly between groups ($P > 0.05$). The average dermal thickness, 0.07 ± 0.02 cm in Group 1 and 0.08 ± 0.02 cm in Group 2, also did not differ significantly between groups.

In Group 1, fat pad thickness returned to the baseline of 0.76 ± 0.21 cm by 12 months postinjection after reaching a maximal thickness of 1.02 ± 0.22 cm immediately postoperatively (Figure 1). Dermal thickness increased by 6 months postinjection to 0.08 ± 0.07 cm (Figure 2). This increase persisted through 24 months, when dermal thickness measured 0.08 ± 0.02 cm.

In Group 2, fat pad thickness decreased to 0.71 ± 0.17 cm while patients underwent conservative management but increased to a baseline thickness of 0.83 ± 0.20 cm by 2 months postinjection (Figure 3). Dermal thickness also decreased to 0.07 ± 0.02 cm during conservative management but increased to a baseline of 0.08 ± 0.02 cm after fat injection and through 12-month follow-up (Figure 4).

Symptomatic Outcomes

MFDI scores did not differ in any category (pain, function, appearance, and work leisure activities) between groups at the preoperative time point ($P > 0.05$).

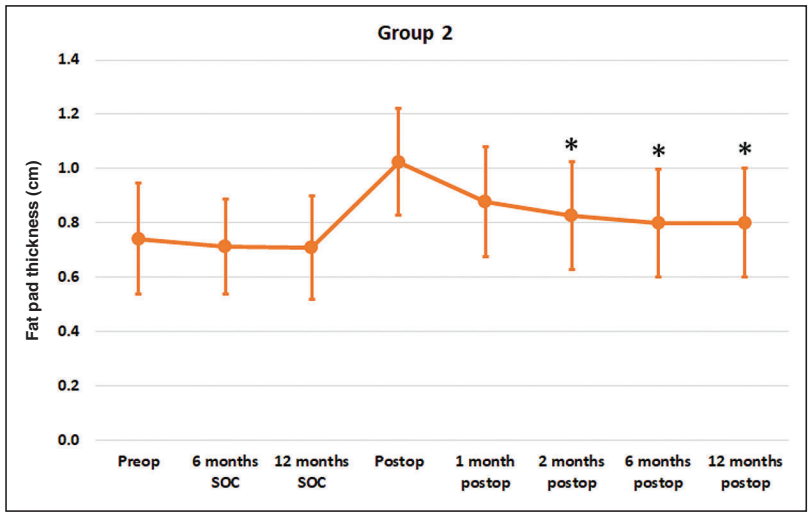

Figure 3. Fat pad thickness over time in Group 2 (*, statistically significant difference from previous measurement with $P < 0.05$). SOC, standard of care.

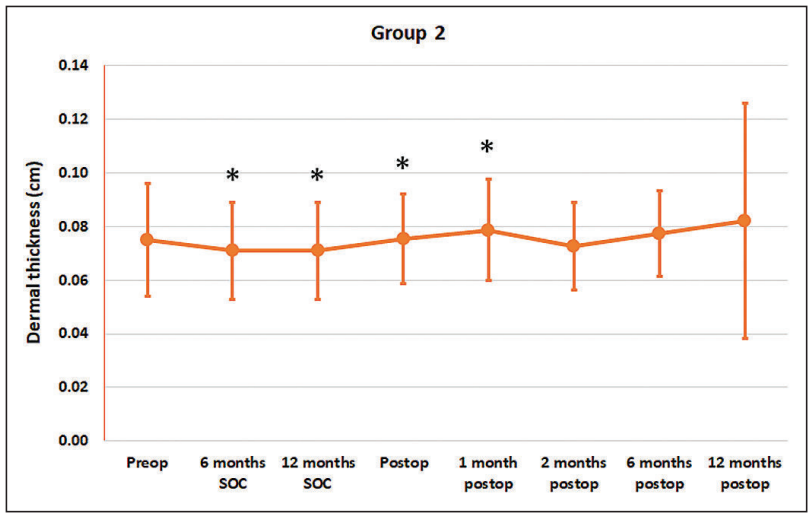

Figure 4. Dermal thickness over time in Group 2 (*, statistically significant difference from previous measurement with $P < 0.05$). SOC, standard of care.

In Group 1, overall MFDI scores significantly improved by 1-month postinjection and were maintained through 24 months. In Group 2, overall MFDI scores improved by 2 months postinjection and were maintained through 12 months.

There were strong, negative correlations between MFDI scores and dermal thicknesses for pain (r = -0.66, $P < 0.05$), function (r = -0.57 $P < 0.05$), and work/leisure (-0.54, $P < 0.05$) in Group 1 and for function (r = -0.75, $P < 0.05$), appearance (-0.71, $P < 0.05$), and work/leisure (r = -0.80, $P < 0.05$) in Group 2. Note that lower MFDI scores indicate improvement in pain, function, appearance, and work/leisure. Therefore, negative correlations in scores imply a positive correlation between dermal thickness and improvement of reported symptoms.

Skin Quality Outcomes

Most patients experienced callus improvement in both groups: 17 feet in Group 1 and 7 feet in Group 2 experienced improvement, whereas 3 feet in Group 1 and 5 in Group 2 had no improvement. Figure 5 depicts one patient's improvement in callus severity and skin quality between the preoperative visit (5A) and the 2-year follow-up visit (5B).

Fisher's exact test confirmed that improvement in callus did not differ between groups ($P > 0.05$).

DISCUSSION

Fat grafting for pedal fat pad atrophy significantly impacts dermal thickness. In patients who underwent fat grafting

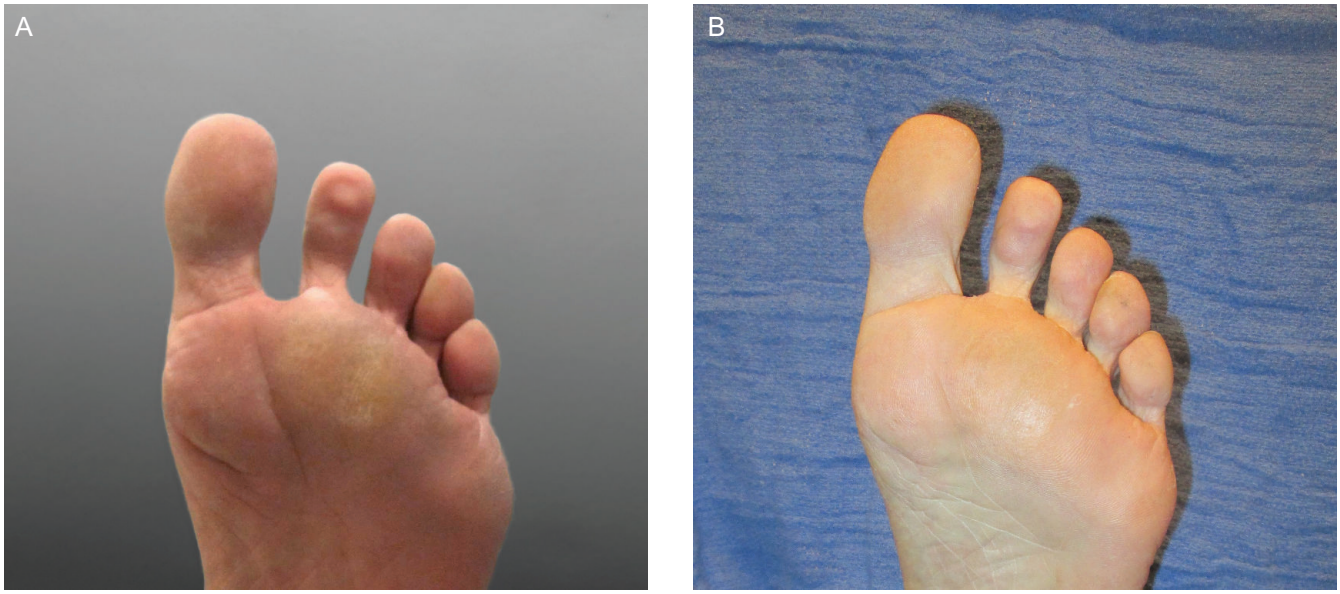

Figure 5. Representative photographs of this 61-year-old woman depict callus severity and skin quality (A) at the preoperative visit and (B) at the 2-year postoperative follow-up visit.

immediately upon enrollment, the measured increase in dermal thickness persisted through the 2-year duration of the study, whereas fat pad thickness returned to baseline after just 6 months. In patients who underwent 1 year of conservative management prior to fat grafting, dermal thickness returned to baseline after fat grafting following an initial decrease prior to injection. Similarly, the increase in dermal thickness lasted for the remaining 1-year follow-up, whereas fat pad thickness returned to baseline after only 2 months.

We also found that patients who were managed conservatively for 1 year experienced decreased fat pad and dermal thickness prior to fat grafting. This finding illustrates the natural history of pedal fat pad atrophy, which is a progressive decrease of thickness of the fat pad and dermis that occurs despite conservative management. Importantly, we found this decrease in dermal thickness is reversible within under 6 months with pedal fat grafting.

Previous studies from our group have evaluated the impact of fat grafting on foot pain, function, and quality of life. These studies demonstrated that Group 1 experienced significant improvement in these measures as soon as 1 month following fat injection, and this increase persisted through the duration of the study. Group 2 also experienced significant improvement by 2 months following fat grafting, which also persisted through 12-month follow-up. Importantly, improvement in many of these symptoms was strongly correlated with dermal thickness.

We propose that symptomatic improvement despite loss of grafted fat may be attributed to the impact of increased dermal thickness. The observed increase in dermal thickness, which occurred in the absence of fat graft retention, has been previously described following autologous fat grafting. One study by Mojallal et al investigated mouse skin biopsies 8 weeks following fat injection. They found a significant increase in dermal thickness, which they attributed to fat graft stimulation of native fibroblast function and collagen production.[39] A human study by Charles-de-Sa et al found that fat grafting resulted in increased organization of dermal cells and dermal vascularity, resulting in a rejuvenating effect.[40] In all, these findings suggest that grafted fat has a regenerative effect that improves skin softness, elasticity, vascularity, healing capacity, and overall quality. Our observation that calluses improved after fat injections further supports the potential beneficial impact of fat grafting on skin quality. Although calluses may not resolve completely, they often can occur with less frequency, requiring less podiatric care and causing less pain. The mechanism of this effect has yet to be elucidated but is presumed to be secondary to the presence of adipose stem cells in the grafted fat.[15] To further assess this hypothesis, investigation of stem cell characteristics obtained from patients' leftover adipose tissue is currently underway. Findings of these studies may have implications in other areas such as facial rejuvenation, cutaneous radiation damage, or scar management.

Limitations of our study include the variability in fat graft injection patterns. We individualized fat graft distribution in each patient based on their unique patterns of atrophy. Though this approach adds an element of heterogeneity in our intervention, we felt it was important to offer our study patients the appropriate treatment for their individual deformity. Another limitation is our inability to confirm patient compliance with postoperative weight-bearing and offloading instructions. However, our study maintains "real world" applications because patient compliance can be neither dictated nor confirmed. Finally,

ultrasound measurements illustrate the tissue thickness at only a single point over each metatarsal; meanwhile, fat may disperse around the metatarsal rather than completely resorb, which our measurements would suggest. Further 3-dimensional magnetic resonance imaging studies are underway to investigate whether this dispersion occurs. These analyses will also allow for quantification of fat graft retention, which we were not able to determine based on the 2-dimensional measurements in our study.

CONCLUSIONS

Pedal fat grafting has a significant, positive impact on dermal thickness and overall symptoms, although results did not indicate the volume of the grafted fat was retained. These results may suggest an increase in dermal thickness could mediate symptomatic improvement and provide further evidence that fat grafting can improve dermal thickness and overall skin quality. Our study further supports the role that aesthetic plastic surgeons may play by offering pedal fat grafting in their cosmetic practices, thereby positively impacting the lives of individuals suffering from pedal atrophy.

Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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