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Hyaluronic Acid Filler Injections Under the Metatarsal Heads Provide a Significant and Long-Lasting Improvement in Metatarsalgia From Wearing High-Heeled Shoes

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BACKGROUND Metatarsalgia is a common overuse injury that may be caused by wearing high-heeled shoes.

OBJECTIVE To evaluate the decrease in metatarsalgia using a hyaluronic acid dermal filler.

METHODS A 6-month, open study was conducted in 15 subjects with metatarsalgia because of regularly wearing high-heeled shoes. Hyaluronic acid (20 mg/mL) with lidocaine hydrochloride (3 mg/mL) was injected under the metatarsal heads at baseline. Pain (on a 0–10 scale) under the metatarsal heads when walking in high heels was recorded in a weekly subject diary.

RESULTS At 6 months after injections, 5 subjects (33.3%) reported no metatarsalgia pain. For subjects with pain, they were able to wear high heels for significantly longer than before the injections (7.2 hours at 6 months vs 3.4 hours at baseline). Significant improvements from baseline were observed at Month 6 for time to onset of pain (3.5 hours longer), time between onset of pain and intolerable pain (1.9 hours longer), and pain sensation (−2.2 grades at onset and −3.8 grades at shoe removal). No adverse events were reported.

CONCLUSION Injection of hyaluronic acid filler to the forefeet provided a significant effective, long-lasting, and well-tolerated improvement in metatarsalgia because of wearing high-heeled shoes.

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Metatarsalgia or forefoot plantar pain is a common overuse injury with increased stress over the metatarsal head region. Affected individuals typically present with a gradual onset of pain in the forefoot (at 1 or more metatarsal heads) or radiation to the midfoot (cuboid, navicular, and cuneiform bones and the surrounding soft tissues); the pain is exacerbated by walking or running. Habitual use of high-heeled shoes is a common cause of metatarsalgia in women because high heels transfer extra weight and pressure to the forefoot, and cushioning of the fat pad is deteriorated.[1–3]

Previous studies on treating metatarsalgia with filler injections include a case report describing the unsuccessful treatment of metatarsalgia with collagen injections.[4] Silicone injections have been successfully used as a soft filler to provide cushioning of the ball of the foot by mechanical supplementation of the plantar fat pad.[5,6] Although there was no evidence of significant adverse response over long-term clinical follow-up of over 1,500 patients,[5] no silicone product for soft-tissue augmentation has been approved by the US FDA because of safety

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concerns since silicone fillers cannot easily be removed in case of an adverse event.[6]

Although there are anecdotal reports[7] on the use of hyaluronic acid (HA) dermal fillers to treat metatarsalgia, suggesting a demand for the procedure, no previous clinical studies have reported the use of HA fillers to treat metatarsalgia in the forefeet. Hyaluronic acid occurs naturally in the body and so, once injected, it will gradually break down and be absorbed by the body. Furthermore, in the event of complications, hyaluronidase may be used to degrade the HA filler and reverse the effect.[8] Hyaluronic acid dermal fillers are widely used for dermal volume depletion and soft-tissue contour defects caused by aging and have demonstrated good tolerability and longevity, as well as good resistance to deformation.[9,10] The Restylane (RES) Optimal Balance Technology (OBT) gel products are produced using an HA concentration of 20 mg/mL with different degrees of cross-linking and particle size calibration to have distinctive physical properties intended for different indications.[11] As this is the first study evaluating the use of HA dermal fillers to treat metatarsalgia in the forefeet, RES Kysse (previously CE marked in Europe under the brand name Emervel Lips) was chosen for its medium cohesivity and somewhat smaller particles to ensure good tissue integration. Although being relatively firm, but not the firmest gel, the authors predicted that this would be ideally suited to provide a cushioned effect and be optimal for the comfort of the patient. Furthermore, similar to fillers in the forefeet, fillers for lip enhancement need to resist deformation caused by strong and frequent movement of the lips and this gel had previously been shown to have good longevity in the mobile lips.[10,11] Although this gel is not approved in the United States, FDA-approved RES Defyne is produced by the same XpresHAN technology (OBT) and is also a product that provides shape and contour, albeit with slightly different gel properties than RES Kysse.

The aim of this study was to evaluate the decrease in plantar pad pain by restoring plantar pad volume and cushioning function by injection of an HA dermal filler in the forefeet of subjects with metatarsalgia caused by wearing high-heeled shoes.

Methods

Study Design and Subject Selection

This study was an open-label, single-center study conducted in France in women aged 30 years and older experiencing pain under the metatarsal heads because of regularly wearing high-heeled shoes. Exclusion criteria included previous injections under the metatarsal heads or any topical treatment of the forefeet. There was no requirement for both feet to be treated.

The study was reviewed and approved by an Independent Ethics Committee and conducted in compliance with the Declaration of Helsinki, Good Clinical Practices, and local regulatory requirements. All subjects provided signed informed consent. Trial registration: ClinicalTrials.gov Identifier NCT02369380.

Treatment

This study involved unlabeled/investigational use of RES Kysse (Galderma, Lausanne, Switzerland). The injectable gel formulation consisted of 20 mg/mL of HA with 3 mg/mL of lidocaine. At baseline, in the ventral decubitus position, a single session of injections under the metatarsal heads was performed using a 25-G cannula (TSK, Tochigi-Ken, Japan). Each injection of filler treatment was preceded by an injection of local anesthetic (0.2 mL lidocaine 10 mg/mL with adrenaline). A retrograde or anterograde linear threading technique (bolus injections) was performed at the discretion of the investigator, with subdermal injection into the hypodermis.

Assessments

Assessments were performed at baseline, 1, 3, and 6 months after injection. Clinical assessments recorded in a weekly subject diary were time to onset of pain ($T_{initial}$), time to intolerable pain when shoes were removed (T_{end}), along with the respective pain sensation ($P_{initial}$ and P_{end}) on a visual analogue scale from 0 (no pain) to 10 (extreme pain). Baropodometric static examinations were performed to determine injection volume requirements under each metatarsal head, and to assess whether touch-up injections were needed (see representative images in Figure 1). Other podiatric assessments included number of callosities and severity using a 4-point severity scale, foot

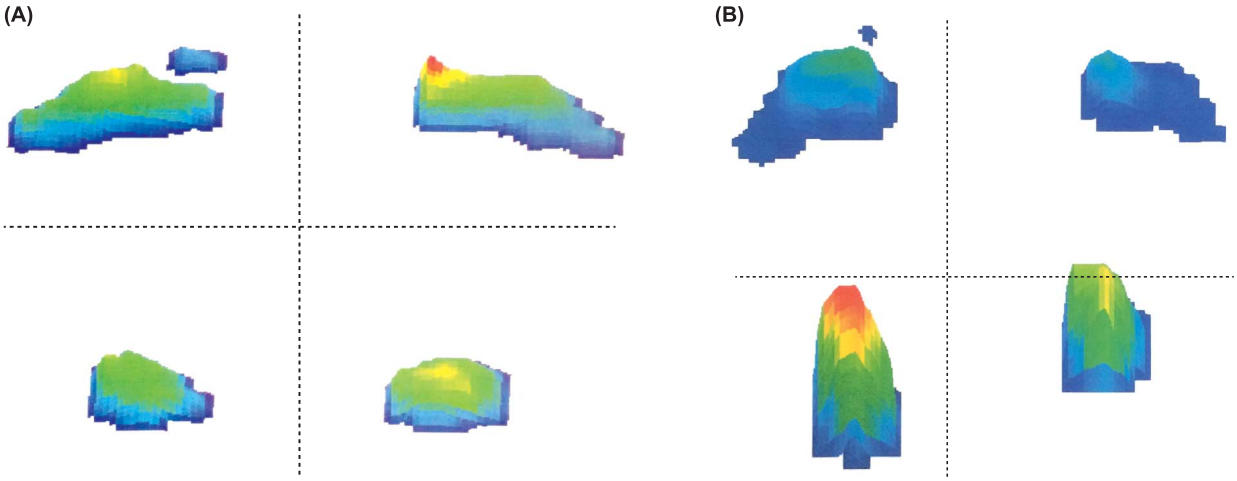

Figure 1. Representative images showing static baropodometric measurements of the mean pressure under the metatarsal heads (A) before and (B) after Injection. Red represents the highest pressure and blue the lowest pressure. The upper quadrants represent the forefeet and the lower quadrants represent the hindfeet (of the left and right feet).

morphotype (hollow or flat), and foot morphology (varus or valgus). Pain levels were assessed by the subject after the injections and adverse events were recorded throughout the study.

Statistical Analysis

All variables were descriptively summarized for all patients treated (APT population) who received the filler treatment during the study. All variables were presented by evaluation time (time after baseline injection) in terms of change from baseline, and the Wilcoxon rank sign test was used to calculate *p*-values.

Results

Subject Disposition and Baseline Characteristics

Between November 2014 and October 2015, 15 women were enrolled and 14 completed the study; 1 subject discontinued after Week 12 at their own request. Overall, 5 subjects had at least 1 major protocol deviation of no pain evaluation at Month 3 (4 subjects) or at Month 6 (1 subject).

Subjects had a mean age of 47.7 years and they had experienced metatarsalgia for an average of 9.0 years (Table 1). At baseline, all subjects had the valgus foot, mostly of moderate grade (66.7% subjects). Most subjects (86.7%) had at least 1 foot that was pes cavus, mostly of mild (53.8% subjects) or moderate grade (30.8% subjects) (Table 1). Both feet were not necessarily affected by the same morphotype, for example, 71.4% of left feet were pes cavus and 85.7% of right feet. The mean number of callosities per subject was 1.9 (Table 1).

Efficacy

At baseline before injections, all 15 subjects had pain when wearing high-heeled shoes. At 3 and 6 months after a single-injection session, 5 subjects (33.3%; missing values are taken as having pain) reported that they had no pain at all when wearing high heels (Figure 2).

Considering only the subjects who reported that they still had pain when wearing high heels, a significant improvement from baseline in the time to onset of pain ($T_{initial}$) was observed at 3 months after injections and this was maintained at 6 months after injections (Figure 3). At 6 months after injections for subjects with pain, the mean change in time to onset of pain compared with baseline was 3.5 hours per subject ($p = .004$; Table 2).

Furthermore, the mean pain sensation at onset ($P_{initial}$) reported 6 months after injections was significantly lower than at baseline (Figure 4A). For subjects with pain, the mean change in pain sensation at onset ($P_{initial}$) between baseline and 6 months after injections was −2.2 grades ($p = .031$; Table 2).

TABLE 1. Baseline Demographic and Disease Characteristics

	Subject (N = 15), N (%)
Sex	
Female	15 (100.0)
Age (yr)	
Mean ± SD	47.7 ± 11.9
Ethnic background	
White Caucasian	14 (93.3)
Duration of metatarsalgia (yr)	
Mean ± SD	9.0 ± 6.1
Median (min, max)	7.9 (3.1, 21.9)
No. of callosities per subject	
Mean ± SD	1.9 ± 2.3
Median (min, max)	2.0 (0, 9)
Callosity maximum grade	
Mean ± SD	1.1 ± 1.1
Foot morphotype	
Valgus foot-pes valgus	15 (100)
Morphotype grade	
Mild	3 (20.0)
Moderate	10 (66.7)
Severe	2 (13.3)
Foot morphology	
Hollow foot-pes cavus	13 (86.7%)
Morphology grade	
Mild	7 (53.8)
Moderate	4 (30.8)
Severe	2 (15.4)

At baseline, the mean time between onset of pain and shoe removal (T_{end}) was 2.4 hours with a mean pain sensation (P_{end}) of 8.9. At 6 months after injections for subjects with pain, the mean time between onset of pain and shoe removal (T_{end}) had increased to 3.2 hours with a lower mean pain sensation (P_{end}) of 4.9 (Figures 3 and 4B). The mean decrease in pain sensation at shoe removal (P_{end}) between baseline and 6 months after injections was −3.8 grades per subject (p = .016; Table 2).

The mean total time of wearing high-heeled shoes, corresponding to the time of onset of pain plus the time to shoe removal ($T_{initial}$ + T_{end}), was 3.4 hours at baseline compared with 7.2 hours for subjects with pain at 6 months after injections (Figure 3). The mean change between baseline and 6 months after injections in the total time subjects with pain could tolerate wearing high-heeled shoes was an increase of 5.4 hours (p = .004; Table 2).

Fewer subjects had at least 1 callosity at Month 6 than observed at baseline before injections (50.0% vs 66.7% at baseline). The mean number of callosities (±SD) under metatarsal heads decreased from 1.9 ± 2.3 at baseline to 1.0 ± 1.3 at Month 6. At Month 6, the callosities were less severe on a severity scale of 0 (no thickening of keratin layer) to 3 (marked thickening of keratin layer) than at baseline (Figure 5) and

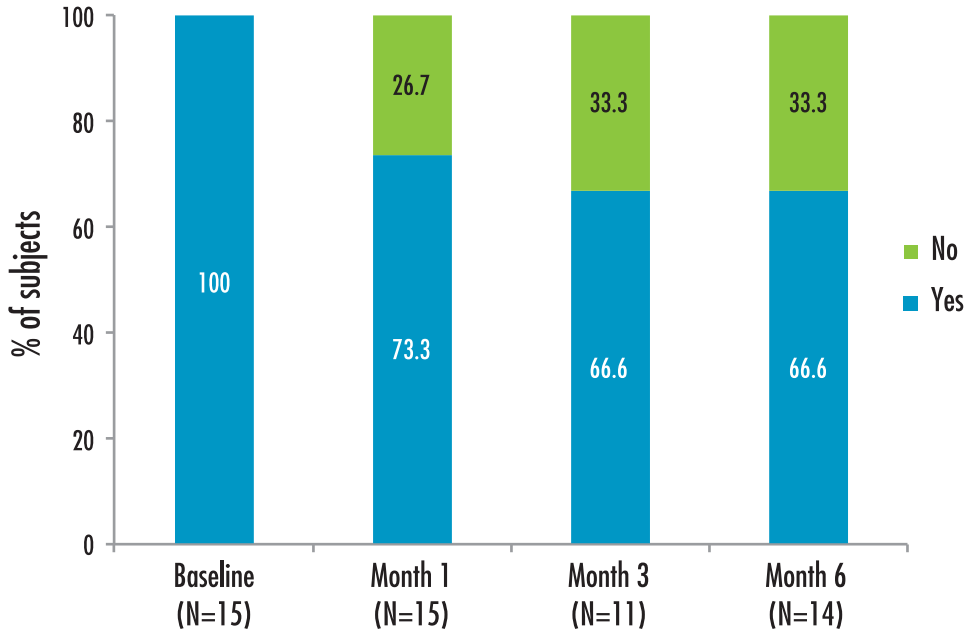

Figure 2. Proportion of subjects with pain sensation (missing values are considered as having pain).

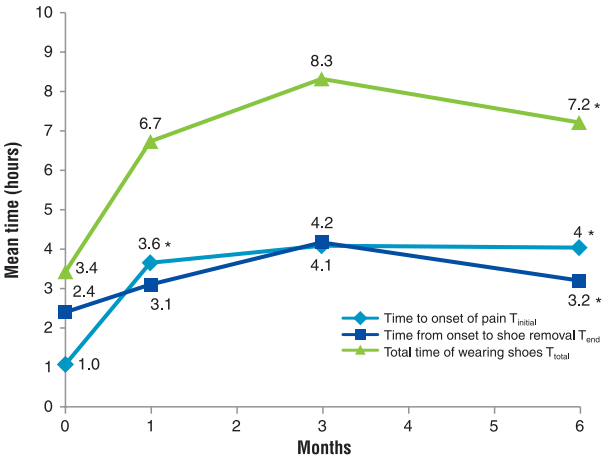

Figure 3. Mean time to onset of pain ($T_{initial}$), time between onset of pain and shoe removal (T_{end}), and total time of wearing high-heeled shoes (T_{total}) for those subjects still reporting pain.*Indicates *p*-value <.05 compared to baseline.

the mean change in maximum severity of callosities was −0.4 ± 0.5 grades at 6 months compared with baseline (p = .031).

Safety

The mean number of injections under metatarsal heads was 6.2 ± 1.7 and was equally distributed between both sides (Table 3). The mean total volume injected for both feet was 1.3 mL and was equally distributed between both sides (Table 3). One subject had no injection on the right foot and another subject had no injection on the left foot. A retrograde linear threading injection technique was used in the vast majority of subjects (93.3%); an anterograde linear threading injection technique was used for 1 subject (6.7%). Each injection of filler treatment was preceded by an injection of local anesthetic (lidocaine).

Pain sensation during injections was limited with 7 subjects (46.7%) reporting to have experienced no pain at all, and for the remaining 53.3% of subjects, the mean pain score on injection was even less than 1 (0.9) on a 0 (no pain) to 10 (extreme pain) scale (Table 3).

No subject reported any adverse event during this study.

Discussion

All study subjects were regular wearers of high-heeled shoes who experienced pain during their daily activities while wearing high-heeled shoes before receiving the study treatment. At baseline, all subjects had the valgus foot and most subjects (86.7%) had at least 1 foot that was pes cavus. Valgus foot (pes valgus pronated foot) deformity is a condition in which the

TABLE 2. Mean Change in Pain Levels and Time of Wearing High-Heeled Shoes Between Baseline (Before Injections) and 6 Months After Injections for Those Subjects Still Reporting Pain

	Baseline (N = 15)	*Month 6 (N = 9)*	*Change Between Baseline and Month 6 (N = 9)*	*p*
Time to onset of pain ($T_{initial}$)				
min	62.7 ± 59.3	240.0 ± 187.3	208.9 ± 188.5	.004
h	1.0	4.0	3.5	
Pain level at onset ($P_{initial}$), mean ± SD	5.6 ± 2.8	3.8 ± 1.8	−2.2 ± 2.2	.031
Time between onset of pain and shoe removal (T_{end})				
min	143.3 ± 131.8	193.3 ± 181.9	114.4 ± 156.1	.047
h	2.4	3.2	1.9	
Pain level at time of shoe removal (P_{end}), mean ± SD	8.9 ± 1.2	4.9 ± 2.7	−3.8 ± 3.3	.016
Total time of wearing high heels (T_{total})				
min	206.0 ± 177.8	433.3 ± 272.9	323.3 ± 251.1	.004
h	3.4	7.2	5.4	

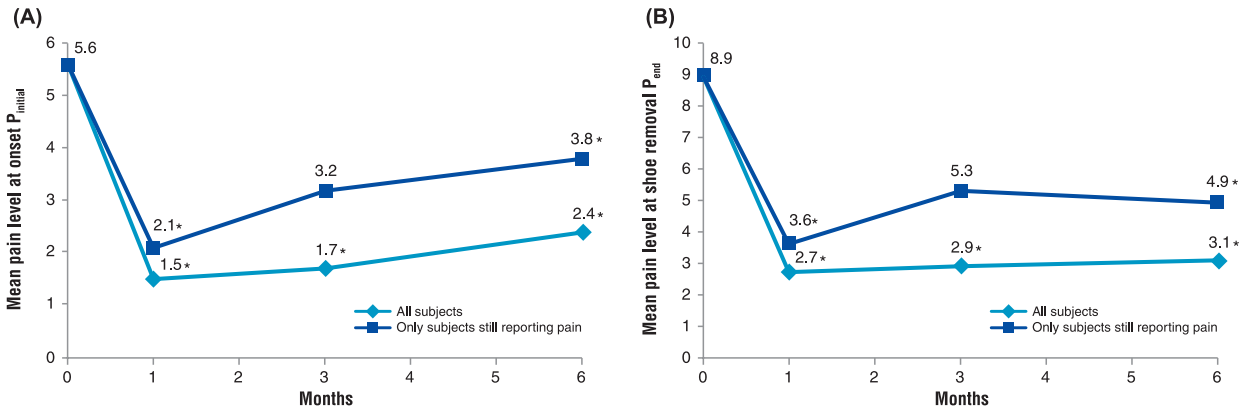

Figure 4. Pain sensation level (A) at onset and (B) at shoe removal.*Indicates *p*-value <.05 compared to baseline.

bone segment distal to a joint is angled outward, away from the midline of the body. Pes cavus is a descriptive term for a foot morphology characterized by high arch of the foot that can cause increased weight bearing for the metatarsal heads and associated metatarsalgia and callosities.

At 3 months after a single-injection session comprising an average of 6.2 injections and totaling 1.3 mL of HA filler for both feet, one-third of subjects reported no pain at all and this was maintained at 6 months after injections. Furthermore, even for those subjects still experiencing pain while wearing high-heeled shoes at 6 months after injections, there was a statistically significant reduction in pain (at onset and at shoe removal) and significant increase in mean total time of wearing high-heeled shoes (7.2 hours vs 3.4 hours at baseline).

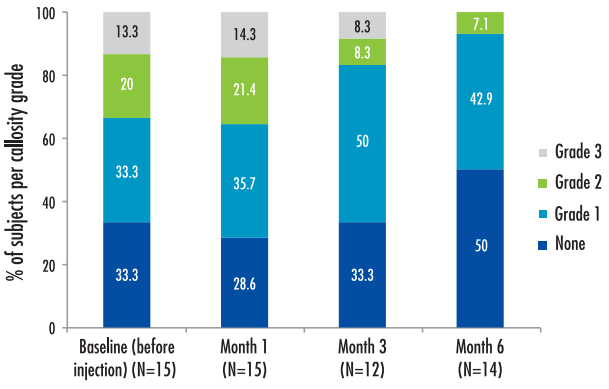

Figure 5. Change in severity of callosities between baseline (before injection) and 6 months after injections, on a 0 (no thickening of keratin layer) to 3 (marked thickening of keratin layer) severity scale.

Furthermore, relieving the pressure under the metatarsal heads by cushioning with HA filler injections led to a reduction in the number and severity of calluses with the mean number of callosities per subject decreasing from 1.9 at baseline to 1.0 at Month 6, by which time no subject had Grade 3 callosities. There can be multiple causative factors that lead to the development of metatarsalgia. One or more of the metatarsal heads may become painful and/or inflamed, usually because of excessive pressure from poorly fitting footwear, such as high-heeled shoes and other restrictive footwear, as well as atrophy of the metatarsal fat pad. Although corns and calluses are not usually a cause of metatarsalgia, the repeated friction and pressure that caused the metatarsalgia can also lead to the development of callosities, which are relatively thick, toughened areas of skin that may become painful after an extended period. Hence, it may be expected that by treating the metatarsalgia with filler injections and thus eliminating the source of friction or pressure, the callosities would also disappear.

The HA filler injections were safe and well tolerated with no adverse events reported during the study. Almost half the subjects (46.7%) reported having experienced no pain at all during the injections, with the remaining subjects reporting very low levels of pain, presumably because local anesthetic was administered before the filler and the filler product itself contains lidocaine anesthetic.

Limitations of this study include the small sample size, absence of a control group, and the use of only 1 filler.

TABLE 3. Baseline Injections

	Right	*Left*	*Subjects (N = 15), n (%)*
Injection on metatarsal head I			
Yes	13 (86.7%)	14 (93.3%)	15 (100.0)
Injection on metatarsal head II			
Yes	8 (53.3%)	11 (73.3%)	12 (80.0)
Injection on metatarsal head III			
No	15 (100.0%)	15 (100.0%)	15 (100.0)
Injection on metatarsal head IV			
Yes	11 (73.3%)	8 (53.3%)	12 (80.0%)
Injection on metatarsal head V			
Yes	14 (93.3%)	14 (93.3%)	15 (100.0)
No. of injections			
Mean ± SD	3.1 ± 1.2	3.1 ± 1.1	6.2 ± 1.7
Median (min, max)	3.0 (0, 4)	3.0 (0, 4)	6.0 (3, 8)
Total volume injected (mL)			
Mean ± SD	0.63 ± 0.29	0.66 ± 0.30	1.29 ± 0.53
Median (min, max)	0.60 (0.0, 1.3)	0.70 (0.0, 1.2)	1.20 (0.5, 2.5)
Injection technique			
Linear threading anterograde			1 (6.7)
Linear threading retrograde			14 (93.3)
Pain sensation during injection			
0			7 (46.7)
1			4 (26.7)
2			2 (13.3)
3			2 (13.3)
Mean ± SD			0.9 ± 1.1
Median (min, max)			1.0 (0, 3)

Baropodometric measurements were taken before and after the procedure to determine injection volume requirements under each metatarsal head and provide information on the distribution of mechanical stress, as well as posture. However, as this was the first clinical study to evaluate the decrease in plantar pain and the baropodometric pressure measurements were exploratory, the absolute baropodometric values were difficult to interpret because of the large volume of data obtained and further experiments are warranted to provide objective evidence of changes in pressure. Nevertheless, despite having suffered from metatarsalgia for a long time (mean duration of 9 years), the pain assessment results of all subjects consistently demonstrated that the HA filler injections alleviated the pain and discomfort associated with wearing high-heeled shoes and this effect was maintained over 6 months. Although pain assessments are inherently subjective in nature and results are not clinically visible, it is noteworthy that a third of subjects reported that they felt no pain at all when wearing high-heeled shoes at 6 months after the HA injections, clearly illustrating the effectiveness of the HA filler injections.

Conclusion

Volume restoration of the plantar pad with a single-injection session of HA dermal filler under the metatarsal heads provides a nonsurgical, long-lasting, well-tolerated, and efficient treatment to alleviate the pain and discomfort associated with metatarsalgia because of wearing high-heeled shoes. In addition to pain assessments, further baropodometric experiments are warranted to provide objective evidence of changes in pressure to corroborate these promising results and an important area for future research is to study other fillers.

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