Efficacy of Injected Liquid Silicone in the Diabetic Foot to Reduce Risk Factors for Ulceration

A randomized double-blind placebo-controlled trial

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OBJECTIVE — To investigate the effectiveness of injecting liquid silicone in the diabetic foot to reduce risk factors for ulceration in a randomized double-blind placebo-controlled trial.

RESEARCH DESIGN AND METHODS — A total of 28 diabetic neuropathic patients without peripheral vascular disease were randomized to active treatment with 6 injections of 0.2 ml liquid silicone in the plantar surface of the foot or to treatment with an equal volume of saline (placebo). No significant differences were evident regarding age or neuropathy status between the 2 groups. All injections were under the metatarsal heads at sites of calluses or high pressures. Barefoot plantar pressures (pedobarography) and plantar tissue thickness under the metatarsal heads (Planscan ultrasound device) were measured at baseline and at 3, 6, and 12 months after the first injection. Injection sites were photographed at all stages, and callus formation was scored as a change from baseline. Throughout the study, patients were treated by the same podiatrist for all podiatry treatment.

RESULTS — Patients who received silicone treatment had significantly increased plantar tissue thickness at injection sites compared with the placebo group (1.8 vs. 0.1 mm) ($P < 0.0001$) and correspondingly significantly decreased plantar pressures (−232 vs. −25 kPa) ($P < 0.05$) at 3 months, with similar results at 6 and 12 months. A trend was noted toward a reduction of callus formation in the silicone-treated group compared with no change in the placebo group.

CONCLUSIONS — The results confirm the efficacy of plantar silicone injections in reducing recognized risk factors associated with diabetic foot ulceration.

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Diabetic foot disease remains one of the most serious and severe long-term complications of diabetes and is the most common cause of hospitalization for diabetic patients in Western countries. Foot ulceration occurs as a consequence of the interaction of several contributory factors: diabetic neuropathy causes changes in foot function and structure (prominent metatarsal heads) and dryness of the skin, which can lead to excessive callus formation (1,2). An important predictive risk factor for the development of foot ulceration is high plantar foot pressure (3), which usually occurs at sites with bony prominences and has been strongly associated with reduced plantar tissue thickness (4). Both plantar pressures and tissue thickness can be objectively quantitatively assessed, whereas calluses, which are more difficult to quantitatively assess, have also been reported to be predictive of foot ulceration (5). Calluses act as foreign bodies, and their removal leads to reduced plantar pressure in most cases (6). Furthermore, neuropathic ulcers are commonly found beneath plantar calluses.

Traditionally, calluses are removed when they are excessively formed under the diabetic foot; however, only 2 preliminary studies have addressed how callus buildup can be minimized (7,8). Preventive care to reduce the incidence of foot ulceration also includes the provision of pressure-reducing insoles and therapeutic footwear (9). Although effective, insoles must be replaced after they lose their cushioning properties, and padded inserts may move in the shoe. Furthermore, neither device provides any protection for noncompliant patients.

Previous reports have suggested the therapeutic use of liquid silicone injections in the foot to replace fat padding at callus sites, corns, and localized painful areas (10,11). To date, more than 20,000 injections have been given, and this has provided anecdotal evidence of reduced callus formation, reduced diabetic foot ulcer recurrence, and relief of localized pressure-related foot pain in nondiabetic patients (10,11). Only minimal side effects have been reported.

Experience with this technique to date has not only been anecdotal but also has been restricted to one center. Therefore, the present study was designed to investigate for the first time the efficacy of injecting liquid silicone in reducing risk factors for diabetic foot ulceration in a randomized placebo-controlled trial. We hypothesized that injection with silicone would lead to increased localized plantar thickness, reduced plantar pressure, and reduced callus formation.

RESEARCH DESIGN AND METHODS

— The study was approved by the local ethics committee. All patients

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Abbreviations: ABPI, ankle-brachial pressure index; CVA, cerebrovascular accident; NDS, neuropathy disability score; VPT, vibration perception threshold.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

received complete information about the study before giving their consent.

Patients

A total of 28 diabetic patients attending the Manchester Diabetic Foot Clinic (Manchester, U.K.) were enrolled in the study. Inclusion criteria were established neuropathy defined as a vibration perception threshold (VPT) of >25 V (12) or a neuropathy disability score (NDS) of >6 (13) and the presence of a callus under at least 1 metatarsal head. Patients with peripheral vascular disease (i.e., the absence of more than 1 foot pulse in both feet or an ankle-brachial pressure index [ABPI] of <0.9) and with an active or previous ulcer during the past 6 months were not selected for the study.

Patients were randomized to silicone treatment (n = 14) or to equal amounts of placebo treatment (n = 14) according to a random number sequence. Areas of injection were chosen under metatarsal head sites with calluses or widened skin striae.

Study design

At baseline, all patients underwent a neuropathic assessment, including the modified NDS (13) and VPT measurement on the hallux, by using a Neurothesiometer (Horwell, Nottingham, U.K.) (12), and vascular status was determined by checking foot pulses and by assessing the ABPI.

Clinical photographs were taken of the areas to be injected, and plantar pressure and tissue thickness were assessed at the chosen injection sites after calluses were debrided.

After all assessments, the first injection was given, and 5 subsequent injections were given at 2 weekly intervals. Follow-up visits were scheduled at 3, 6, and 12 months after baseline, during which all measurements of efficacy were repeated. Throughout the study, the patients were treated by the same study podiatrist, and all study patients continued to receive the same treatment that is offered to all patients at high risk for foot ulceration, including receiving specialty footwear and regular podiatry treatment as needed.

Outcome measures

Dynamic plantar pressures were measured during barefoot walking by using an optical pedobarograph (Department of Medical Physics and Clinical Engineering, Royal Hallamshire Hospital, Sheffield, U.K.), which is a pressure platform built into a 5-m walkway (14). Five steps were measured for each foot. The peak pressure of all injection sites was used for analysis. To ensure standardization, pressure was measured during the same step after initiation of gait for all subjects for all measurements.

The plantar tissue thickness was measured at each injected site by using the Planscan, which is an ultrasound device (Department of Medical Physics and Clinical Engineering, Royal Hallamshire Hospital) (15). The Planscan is a scanning platform that holds a high-resolution ultrasound probe. The ATL Ultramark 9 ultrasound scanner with a 5-MHz linear array transducer (Advanced Technology Laboratories, Bothwell, WA) was used for the assessment. The measurement was performed while the subjects stood barefoot on the platform with equal weight bearing between the 2 feet (4). The foot was placed directly above the ultrasound probe, which was attached to the frame under the top surface of the platform. Scanning the length of the foot allows more accurate and reproducible results of the minimum depth of an irregular-shaped bone prominence below the sole of the foot (15). A minimum of 3 measurements were taken of the metatarsal depth at each injected site, and these were averaged per site and were used for analysis. A combined intra- and interobserver coefficient of variation of <10% has been reported for this measurement (4).

The clinical photographs of the injected sites taken at all visits were assessed as a trend of change from baseline. A special scoring system was designed for this assessment because no other established method exists. A negative score indicates a worsening of callus formation, a score of 0 indicates no change from baseline, and a positive score indicates a reduction of callus formation. A maximum negative score of −3 was given for an ulcer or hemorrhage, and a maximum positive score of +3 was given for the complete disappearance of a callus. One score was given for each subject that represented the change in callus buildup over all injection sites per subject during the 1-year follow-up period. Thus, a composite score was given for photographs taken at 3, 6, and 12 months of follow-up when compared with the baseline photographs. Two independent observers blinded to patient groups scored all photographs, and an average of the 2 observers was used for analysis.

All outcome measurements were performed completely blinded to the treatment regimen, and all follow-up measurements were carried out without knowledge of the results from previous visits.

Method of injection

Patients were randomized according to a random number sequence just before the first injection. All investigators and patients remained blinded to the treatment regimen throughout the study, with the exception of the podiatrist administering the injections who did not participate in any of the assessments or analyses. A total of 6 injections were given per site at 2 weekly intervals. Between 1 and 5 sites were selected for injection, depending on the number of callus sites. Thus, each patient received between 6 and 30 injections. The volume of silicone or saline per injection was 0.2 ml for each site; the total maximum volume injected was 1.2 ml/injection site. An area with previous ulceration was only chosen if it had been healed for a minimum of 6 months. Before injection, all areas to be injected were debrided of calluses and were cleaned. A skin refrigerant (fluro-ethyl) was sprayed over the site of injection for 2–3 s before injection. Any discomfort was noted, and, if necessary, the needle was withdrawn, and local anesthesia was administered (mepivacaine 3%). A needle guide was attached to the syringe to assist in a more precise injection. The liquid silicone or saline was implanted subcutaneously in equal amounts beneath and within 1–2 mm of the central point of the callus. After injection, the site was covered with a sterile bandage, and the patient was advised to keep the injection site dry for 24 h and to check the site for any signs of inflammation or infection. Patients were allowed to resume regular activities immediately after injection.

Statistical analysis

The change from baseline was used for data analysis of the plantar tissue thickness and pressures to eliminate the effect of natural differences in baseline plantar thickness and pressures at different sites. Data are medians (interquartile ranges). The changes in peak plantar pressure and tissue thickness per injected site were averaged over the total number of injected sites per patient because treatment was randomized per patient and not per injection site. The average change per patient was then used for further analysis by using the Mann-Whitney U test for differences between the 2 treatment groups at each follow-up visit. An intention-to-treat analysis was carried out by using a conservative carry forward analysis in which miss-

Table 1—*Demographic and neurological characteristics of patients by treatment group*

	n	Sex (F/M)	Age (years)	Diabetes duration (years)	Type of diabetes (1/2)	History of ulceration	NDS	VPT (V)	ABPI
Silicone	14	5/9	58.1 ± 12.3	10.5 (9.3–17.8)	5/9	8	8.0 (7.3–9.5)	29.5 (25.3–41.5)	1.23 (1.0–1.28)
Placebo	14	3/11	55.0 ± 7.8	15.0 (7.3–22.0)	6/8	7	8.0 (8.0–10)	28.0 (25.0–34.8)	1.18 (1.11–1.38)

Data are *n*, means ± SD, and medians (interquartile ranges). No significant differences were observed between the 2 groups in any variable.

ing data in both the silicone-treated and placebo groups were considered to be no different from baseline.

The scores of the clinical photographs were averaged for the 2 observers and were subsequently analyzed by using the Mann-Whitney *U* test. SPSS software (Chicago) was used for the statistical analysis.

RESULTS — No significant differences were evident in baseline characteristics between the 2 groups (Table 1). Not all follow-up visits were completed by all patients because of foot ulcers (n = 2), development of malignancy (n = 1), cerebrovascular accident (CVA) (n = 1), repeatedly missed appointments (n = 1), technical problems with equipment (n = 3), and inability to analyze data (n = 1). Tissue thickness data are missing for 2 silicone and 5 placebo follow-up visits, and plantar pressure data are missing for 3 silicone and 8 placebo follow-up visits (from a total of 84 follow-up visits).

A total of 62 sites were chosen for injection, of which 34 sites were injected with silicone, and 28 were injected with saline (treatment was randomized per patient). Between 1 and 5 sites (median 2) per patient (depending on the number of callus sites) were selected for injection. Treatment was ceased at 3 sites (after 1 or 2 injections, all in the silicone-treated group) because of the development of an ulcer on the same foot as 2 of the sites and 1 site that looked fragile and seemed likely to ulcerate according to the medical staff.

A nonsignificant difference was evident in mean ± SD baseline thickness in the silicone-treated group (0.66 ± 0.21 cm) compared with the placebo group (0.85 ± 0.26 cm) (P = 0.06). The difference in thickness was caused by the different number of first and fifth metatarsal heads chosen as injection sites. The ratio of first/fifth metatarsal head injection sites was 7/12 for the silicone-treated group and 11/7 for the placebo group.

The median (interquartile range) plantar tissue thickness had substantially increased from baseline with 1.8 mm (1.0–2.5), 2.0 mm (0.9–2.6), and 1.3 mm (0.9–1.6) at 3, 6, and 12 months, respectively, in the silicone-treated group compared with no change in plantar tissue thickness (0.08 mm [–0.3 to 0.5], 0.2 mm [–0.2 to 0.6], and 0.25 mm [0.0 to 0.6], respectively) in the placebo group ($P < 0.005$) (Fig. 1).

A significant decrease in peak plantar pressures from baseline was measured in the silicone-treated group at 3, 6, and 12 months (−232 kPa [–372 to −84], −182 kPa [–227 to 13], and −216 kPa [–300 to −30], respectively), whereas no change or a slight increase was evident from baseline in the placebo group (−25 kPa [–146 to 97], 58 kPa [–67 to 99], and 145 kPa [–136 to 220], respectively) ($P < 0.05$) (Fig. 2).

A significant correlation existed between the percentage change in peak plantar pressure and plantar tissue thickness after injection with silicone. The correlation coefficients were −0.37, −0.34, and −0.39 at 3, 6, and 12 months of follow-up, respectively ($P < 0.05$).

Intention-to-treat analysis

The results of the intention-to-treat analysis showed a significant increase in tissue thickness (1.8 mm [1.0–2.5], 1.8 mm [0.8–2.5], and 1.2 mm [0.9–1.6] at 3, 6, and 12 months, respectively) in the silicone-treated group compared with the placebo treatment group (0.08 mm [–0.3 to 0.5], 0.10 mm [–0.2 to 0.5], and 0.09 mm [0.0 to 0.4], respectively) ($P < 0.008$).

The reduction in peak plantar pressure, by using the intention-to-treat analysis, was significantly greater in the silicone-treated group at 12 months (−170 kPa [–296 to −7]) compared with the placebo group (0.0 [0.0 to 183] kPa) ($P <$ 0.02) and almost reached significance at 3 and 6 months (silicone vs. placebo −225 kPa [–370 to −21] vs. −25 kPa [–146 to 97] [P = 0.06] and −172 kPa [–220 to 10] vs. 3.7 kPa [–35 to 89] [P = 0.09] at 3 and 6 months, respectively).

Callus

A nonsignificant trend was noted toward a reduction in callus formation in the sili-

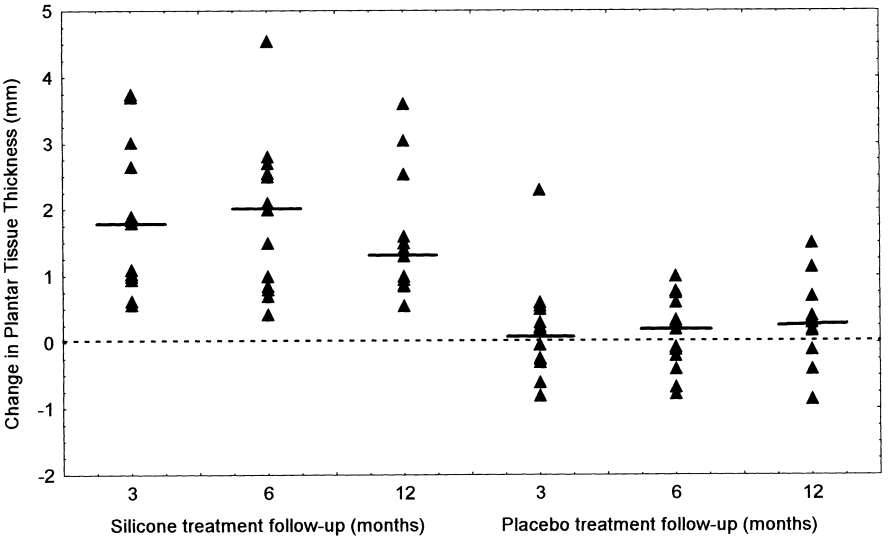

Figure 1—*Changes in plantar tissue thickness (in millimeters) from baseline. The bars represent the median values. Silicone treatment vs. placebo,* $P < 0.0005$ *at 3 and 6 months and* $P < 0.005$ *at 12 months of follow-up.*

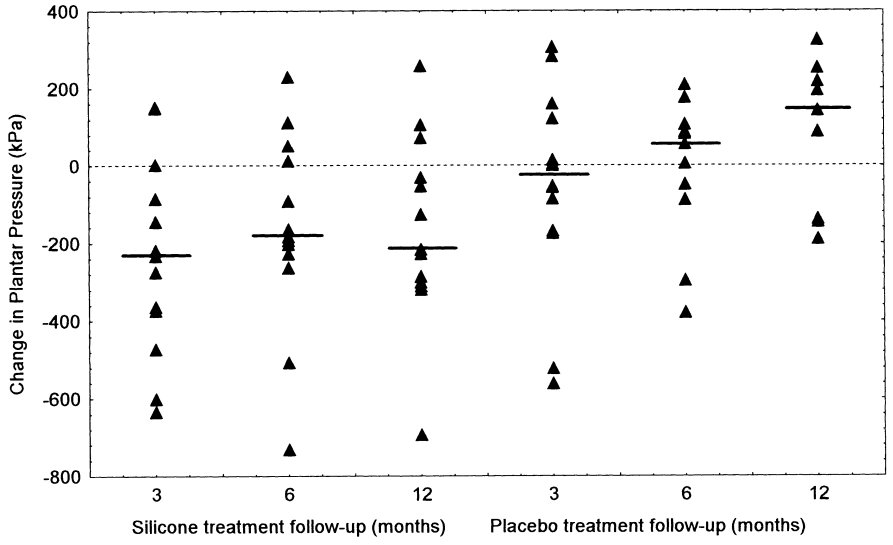

Figure 2—*Changes in peak plantar pressure (in kilopascals) from baseline. The bars represent the median values. Silicone treatment vs. placebo,* $P < 0.05$ *at 3 and 12 months and* $P = 0.11$ *at 6 months of follow-up.*

cone-treated group compared with the placebo group. The median score for change in callus buildup from baseline was 0.5 (0.0 to 1.0) in the silicone-treated group compared with 0 (−1.25 to 0.75) in the placebo group ($P = 0.3$).

Adverse events

A total of 7 patients developed foot ulcers during the course of the study. A total of 3 placebo and 3 silicone-treated patients developed ulcers at noninjected sites (toes, between digits, toe nails, heels, and Achilles tendons), whereas 1 placebo patient developed an ulcer at an injection site. A total of 2 patients from the placebo group developed unrelated diseases (CVA and malignancy). No clinical evidence of any migration of injected silicone was observed throughout the study.

CONCLUSIONS — This study confirms the efficacy of injecting liquid silicone in the diabetic foot in this first randomized double-blind placebo-controlled trial. Even with a conservative intention-to-treat analysis (assuming no change from baseline for all missing data), the increase in plantar tissue thickness and the reduction in peak plantar pressure were significantly greater in the silicone-treated group than in the placebo group.

Because this is the first study reporting on objectively measured parameters before and after liquid silicone injections, comparing our data with the anecdotal reports of Balkin (10,11) is extremely difficult. Furthermore, note that the only other center that used this technique injected individually tailored volumes; however, in the present study, we used a standardized volume.

No significant side effects were reported in this study, and only minimal side effects have been reported by the only other center that has experience with injecting silicone in the foot (10,11). Asymptomatic fluid migration has been reported as the main adverse response (10,11); however, this has only been observed in early cases when larger volumes were injected per single callus (>3.0 ml). No such migration was evident in any of our study patients. No infection, rejection, inflammation, or allergic reaction has been reported. Morphological studies have confirmed that medical-quality liquid silicone injected in the foot is a safe procedure (10,11). In the present climate, silicone is still a controversial topic, but no overt proof has been uncovered linking silicone implants and any chronic medical condition.

In this study, the cushioning effect of the injected silicone was still significant at 12 months after the first injection, but how long this effect remains or whether it will decline is not known. Anecdotal evidence suggests that most patients stay free of calluses and pain for many years (10,11), although ~50% of plantar injection sites will require booster injections at a later date (11).

Whether the amount of pressure reduction and the increase in plantar tissue thickness is enough to prevent future foot ulceration is not known. However, a median pressure reduction of 30%, as reported in this study, is similar to the results of insole material and shoe design studies (16–19). Thus, the injected silicone provides an amount of cushioning similar to the more conventional methods of pressure relief; however, silicone has the advantage of not being removable, thus offering cushioning continuously.

The highly subjective nature of the assessment of change in callus buildup (scoring of clinical photographs) and consequently high variability of this method combined with the fact that calluses were scored per patient (and not per site) may have contributed to the nonsignificant difference in callus buildup between the 2 treatment groups.

In conclusion, the results of this study have shown for the first time that the injection of liquid silicone in the diabetic foot can substantially increase plantar tissue thickness and reduce plantar peak pressures, thus adding a new treatment method to diabetic foot care. Whether this method can reduce foot ulceration remains to be answered in larger trials. No side effects were reported in this study. Thus, a reduction of risk factors strongly associated with foot ulceration has been observed, and we believe that injection with liquid silicone may represent a potential preventative intervention to reduce the incidence of neuropathic foot ulcers in high-risk diabetic patients. Further large-scale studies are now indicated to confirm this observation.

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