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SYMPOSIUM

Liquid Silicone to Mitigate Plantar Pedal Pressure: A Literature Review

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Abstract

Disruption of the body's plantar fat pad can occur as a result of one of three mechanisms: simple fat pad atrophy associated with age-related degeneration, steroid use, or collagen vascular disease. Actual or relative displacement in to the underlying osseous prominences may be seen in association with structural deformity of the foot. Disease states such as diabetes may alter the normal structural integrity of soft tissues through nonenzymatic glycation leading to increased stiffness and thus reduced attenuating capacity. Fat pad atrophy, regardless of the cause, is often associated with substantial emotional, physical, productivity, and financial losses. In situations where the patient is sensate, the resultant skin on bone situation is extremely painful, especially when walking.

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Introduction

Industrial chemists working for the Corning Glass Company were the first to synthesize polymethylsiloxane and recognize its potential properties. In 1962, Corning introduced the first medical-grade injectable silicone (360 grade), which was intended for coating of medical devices. Although this represented a much purified form of the previous industrial silicones, it was not until 1965 that an injectable medical-grade silicone was available from Dow Corning, referred to as MDX4-4011. Because of the reported problems associated with silicone injection, in 1964, the Food and Drug Administration (FDA) classified silicone when injected as a "new drug." To permit continued application, Corning filed for a "notice of claimed investigational exemption" so their 360 silicone medical-grade fluid could be used. Rees and Ashley[1] injected over 1300 patients, but only 408 were followed-up on; they reported only one single complication. The continued reporting of complications and lack of quality clinical data led to the criminalization of the procedure in 1975 and suspension of the drug by the FDA in 1976. Undeterred, in 1977, Corning submitted an amended exemption and received FDA approval for a new study in 1979. This newer silicone was designated an "investigational device." Conscious of the continued reported complications associated with liquid injectable silicone, the FDA requested interim clinical data in 1990; Corning had virtually no data. By 1992, the FDA investigational license had become invalid. What eclipsed

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Abbreviations: (cSt) centistoke, (FDA) Food and Drug Administration

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the concerns surrounding the use of liquid injectable silicones was the issue of breast implants culminating in a $4-billion class action lawsuit against Corning. In 1992, because of the lack of data surrounding the use of liquid injectable silicone, the FDA banned its use outside of approved investigational studies.

The physical properties of silicone make it an ideal biomaterial.[2,3] It is chemically inert, noncarcinogenic, capable of sterilization, not physically modified by soft tissue, noninflammatory, capable of resisting mechanical strains, and produces no state of allergy or hypersensitivity.[4–6] Silicone-gel-filled breast implants became available in 1962 and were implanted in 1–2 million women. Thirty years later, anecdotal reports claimed that leakage from these implants could cause immune-related or connective tissue disorders such as systemic lupus erythematosus, scleroderma, rheumatoid arthritis, or polymyositis. Patient complaints included chronic fatigue, muscle pain, joint pain, and swollen lymph nodes. Though this received unprecedented public and medical attention, epidemiological studies in the United States concluded there was insufficient scientific evidence to correlate silicone breast implants with connective tissue disease. The U.K. Department of Health arranged for their own medical devices agency and an independent expert advisory group to assess the literature for those alleged disorders. A total of 270 papers were reviewed, and no scientific evidence was found linking silicone-gel-filled breast implants with any risk of connective tissue disease or evidence of systemic pro-inflammatory effects.[7] Furthermore, there are substantial differences pertaining to potential risks between silicone breast implants and medical-grade liquid injectable silicone. Breast implants are contained within a capsule, with the potential for initiating tissue response itself. The large volume of liquid silicone contained within these units by comparison to the small volumes advised in the applications around liquid injectable silicone can be seen to promote greater safety potential.

From the late 1950s to the 1970s, thousands of women worldwide received unauthorized cosmetic silicone injections to enlarge breasts and contour various body parts. Between 750 and 2000 ml per patient was injected. These massive amounts of unknown, impure, or adulterated fluid silicone caused major infections, tissue necrosis, and, in some, the loss of breasts. In a few reported instances, intravascular injections were followed by death. This procedure, which was never approved and is now discredited, persists, as do the complications.

The first silicone fluid injection for treatment of complicated retinal detachment was approved in the United States in 1994. Injected silicone acts as a tamponade to hold the retina in place mechanically until natural attachment occurs. Vitreal-retinal surgeons rate the procedure as 60–75% successful and as the standard care for this problem that can cause blindness. The viscosity of silicone oil used in the eye is 5000 cSt, 15 times more viscous than the fluid injected for soft tissue defects. It requires a power injector, a 19-gauge needle, and special tubing and syringes to inject the 4.5–6.0 ml of silicone needed for this procedure.

Silicone also has a long history of use as facial soft tissue filler for treatment of wrinkles and facial atrophy.[1,5] Liquid injectable silicone is considered by many to be a unique soft tissue augmenting agent that may be utilized effectively for the correction of specific cutaneous and subcutaneous atrophies. Orentreich and Leone[6] found that liquid silicone is a safe and effective method for treating human-immunodeficiency-virus-associated facial lipoatrophy and compares favorably with other methods of tissue augmentation. Zappi and coworkers[2] examined 35 skin biopsies by light microscopy. These biopsies were obtained from target areas where liquid silicone had been injected in 25 patients between 1 and 23 years prior for the correction of depressed scars on the face. The microscopic study revealed in 100% of the cases the continued presence, in significant amounts, of the silicone previously injected into the target areas, where it failed to elicit any significant adverse reaction. Although historical complications have occurred, resulting likely from the presence of adulterants and impurities,[1,5] modern purified silicone products approved by the FDA for injection into the human body may be employed with minimal complications when strict protocol is followed.

Toxicology of Silicone

Animal studies are not directly comparable with regard to injectable silicones, as they typically have a large subdermal space that can readily accommodate high volumes of silicone. In the human foot, deposition involves compact tissues space subject to high external stresses. This may contribute to an increased risk of migration and thus toxicological complication.

Andrews[7] investigated the cellular response to injection of 5-ml Dow Corning 360 medical fluid subcutaneously in mice/rats, noting no adverse effects. Ben-Hur and colleagues[8] injected a single 6-ml dose or six 1-ml doses of polymethylsiloxane subcutaneously into mice and noted

the accumulation of macrophages containing silicone in adrenal glands, lymph nodes, liver, kidney, and spleen. Death occurred at doses >7 ml polydimethylsiloxane (estimated equivalent dose 280 ml/kg). One of his co-authors, Ballantyne, published on a new treatment for facial hemiatrophy in children by injections of dimethyl-polysiloxane fluid. Nedelman[9] injected various medical-grade silicones into the subcutaneous tissue of hamsters and the jaw/palate of rabbits at dose of 0.5–2 ml. At a short-term follow-up of between 1 and 12 weeks, he reported that, save for a mild local inflammatory response at the injection site, the injection and material was well tolerated. Hawthorne and associates[10] examined the hematological effects of dimethylpolysiloxane fluid in rats. The researchers examined the white blood cell count in rats following high dose exposure to silicone. They noted no evidence of uptake within the white blood cells.

Bradley and coworkers[11,12] reported on the immuno-toxicity of 180-day exposure to polydimethylsiloxane (silicone) fluid, gel, and elastomer and polyurethane disks in mice between 10 and 180 days. In this study, none of the toxicological end points (survival, weight, hematology, serum chemistry, bone marrow cytology) were affected.

The interpretation of the available toxicological data has to be set against a number of confounding variables. The purity of the injected agent represents a major determinant of the potential toxicological end points. Complications associated with injection of material not intended for medical application, loaded with impurities, need to be set in the correct context.

Volume of material administered is not only relevant to dose-dependent complications but also pertinent to the risk of material migration and systemic uptake. A number of toxicological studies confirm increased risks with large volumes of injected silicone. None, however, discusses the relevance of the injection technique, which may play an important part in the hosts tolerance.

Fundamental differences between human and animal studies confer variation in potential dose exposure but also variation in mechanistic differences between species. The potential delay between administration and presentation of complication together with the technical limitations of older studies require consideration.

Reproductive Toxicity

There are few published data pertaining to the safety of injectable liquid silicone in pregnancy. In a review of Kennedy and colleagues,[13] they subjected several hundred rats, mice, and rabbits to a variety of medical-grade silicones at high doses, 20,200 and 12,000 mg/kg, to determine the teratological and mutagenic effects in liquid injectable silicones. No impact on gestation or embryogenesis were demonstrated.

Long-Term Efficacy and Safety

Numerous studies have confirmed that there can be a significant delay between injection of liquid silicone and the manifestation of complications. Wallace and associates[14] reported on the histological host response to liquid silicone injections for prevention of pressure-related ulcers to the human foot in 49 postmortem patients who had previously received injection of liquid injectable silicone into the foot. Histological evaluation consisted primarily of delicate-to-robust fibrous deposition and histiocytic phagocytosis, with eventual formation of well-formed elliptic fibrous pads. No sign of granulomas, chronic lymphoplasmacytic inflammation, or granulation tissue formation were seen, with only rare foreign-body giant cells present. The authors concluded that liquid injectable silicone resulted in a histologically stable and biologically tolerated host response.

Balkin[15] reported on the long-term follow-up of injectable silicone, examining both the clinical and the histological outcomes. In this long-term study, there was no evidence of significant adverse response, and histological specimens revealed no inflammation, infection, allergy, or granulomas.

Pedal Silicone Implantation

It is well-documented that plantar pressure is directly proportional to plantar tissue thickness.[16,17] Historically, corns and calluses have been treated with a myriad of palliative measures and by surgical intervention. Fat pad atrophy is common among persons with collagen vascular disease and diabetes, particularly in the forefoot. The loss of fatty tissue has been noted to be the fundamental mechanism associated with pressure-related foot disorders. Therefore, augmentation of this high-risk area with an inert viscoelastically robust substance such as silicone has the potential benefit to mitigate pressure.

Credit for the introduction of this modality into podiatric medicine rests with Balkin,[18–26] who published over a dozen papers on the technique of liquid silicone for the prevention and treatment of pedal pathology. The commonly used unit for viscosity of fluids is the centistoke (cSt), with water having a centistoke value of 1.02. Silicone fluid used to replace soft tissue has a viscosity of 350 cSt (similar to that of light motor oil) and can be injected easily using a 25-gauge needle and a standard Luer lock syringe. The rationale for considering injectable silicone in the foot is that, regardless of the causes leading to increased digital or plantar pressure, there is an associated loss of subcutaneous fatty tissue. Development of essentially inert silicone fluids has provided the potential of augmenting the body's own soft tissue by injection.

An injection procedure has been developed by which silicone fluid is implanted to form a stable subdermal cushion between skin and weight-bearing bone. The internal pad eliminates or reduces pain and frequency of care for most patients. It also reduces the incidence of pressure ulcers. Trademarked PodiSil (Richard-James, Inc., Peabody, MA), a 350 cSt injectable silicone has been approved for the prevention of diabetic foot ulcers.[27] Previous studies suggest significant improvement in soft tissue thickness and subsequent profound reduction in plantar pressure. The availability and production of liquid injectable silicone and medical-legal factors have reduced the potential for widespread implementation. Previous reports suggest a positive therapeutic use of liquid silicone injections in the foot to replace fat padding at callus sites, corns, and localized painful areas.[26]

Silicone Injection Pressure/Ulceration

Balkin[24] injected silicone (Dow Corning Corporation's 360 Medical Fluid, 350 cSt) beneath corns and calluses in 1585 patients and gathered surgical and postmortem specimens for histological analysis. No inflammation, infection, allergy, or granulomas were noted after the specimens were studied by two pathology departments. Long-term clinical follow-up also found no evidence of significant adverse responses. Balkan concluded that medical fluid silicone appears to be safe, effective, and stable biomaterial for treating weight-bearing loss of plantar fat.

Van Schie and coworkers[27] investigated the effectiveness of liquid silicone injections in the diabetic foot to reduce risk factors for ulceration in a randomized double-blind placebo-controlled trial. A total of 28 diabetic neuropathy patients without peripheral vascular disease were randomized to active treatment with six injections of 0.2 ml liquid silicone in the plantar surface of the foot or to the placebo treatment with an equal volume of saline. No significant differences were evident regarding age or neuropathy status between the two 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. Patients who received silicone treatment had significantly increased plantar tissue thickness at injection sites compared with the placebo group (1.8 versus 0.1 mm) ($p < .0001$) and correspondingly significantly decreased plantar pressures (–232 versus –25 kPa) ($p < .05$) at 3 months, with similar results at 6 and 12 months.[5] A trend was noted toward a reduction of callus formation in the silicone-treated group compared with no callus reduction in the placebo group. The results of this study further confirm the efficacy of plantar silicone injections in reducing recognized risk factors associated with diabetic foot ulceration.

At a two-year follow up, the plantar tissue thickness in the silicone group that was noted to have increased by a mean 1.6 ± 0.9 mm ($p = .001$) and remained increased at 24 months (1.1 ± 0.7 mm, $p = .003$).[27] However, the peak plantar pressure in the silicone group that was reduced at 12 months (–165.0 ± 253.5 kPa, $p = .03$) was not noted at 24 months.

The reduction in the pressure time integral in the silicone group did not reach significance at 12 months (–0.71 ± 1.17 kPa/s, $p = .055$). Although pressure time integral returned to baseline at 24 months for the silicone group, it was significantly increased in the placebo group (0.64 ± 0.37 kPa/s, $p = .043$), suggesting that silicone may still exhibit some pressure-reducing properties after 24 months. The results indicate that, at 24 months postinjection, the cushioning properties of injected silicone have reduced, suggesting that booster injections may be required in certain patients.[28]

Tollafield and colleagues[29] in a single-blind randomized trial evaluated 31 subjects who presented with plantar keratoma. Comparison was made between saline (control) and 350 cSt polydimethicone. Total volumes used were not identical between the groups of subjects ($p = .05$), although the maximum volume was no greater than 1.5 ml in any subject. Outcome measures included Harris–Beath ink mat, visual analogue scale, alteration

in frequency of treatment, and subjective analysis of reduction in lesions before and after by color photography. Ten patients were lost to follow-up. Essential histopathology was undertaken on 11 subjects. Granulomatous reactions were only positively identified in one case. Nine matched pairs showed no statistically significant difference between the two treatments ($p = .082$).

Fluid Migration

The migration of this silicone fluid remains the most significant, single adverse response ever since silicone foot injection fluid drifts were first reported.[17] Despite findings that even relatively small amounts of silicone can migrate and, in rare instances, require surgical excision, it has been long assumed that fluid migration was due to overinjection. Such movement may be seen as a thick silicone skin tag proximal to weight-bearing metatarsal heads, at times with a fine keratotic leading edge, but are typically asymptomatic.

It is reported that from 1964 to 1995, 1350 patients, 986 female and 364 male, mean age 60.8 years, received silicone injection. Most were over the soles; however, lesser toes, the hallux, heels, and bases of the first and fifth metatarsals were also silicone implanted. Among this group, 885 received plantar injections beneath 1879 metatarsal heads. Of these 885 patients, 17 (1.92%) developed a soft to firm mass of migrant fibrous silicone tissue over the dorsum at 21 sites. Four patients had a single migratory site bilaterally. These were all observed on pressure-bearing only and were painless upon firm palpation. This unusual response has been reported previously.[29] The earliest postinjection appearance was noted at 15 months and at 13 years, an average of 5 years. Four out of these 885 patients (0.45%) experienced sufficient discomfort in shoe wear (footwear) to warrant surgical removal, which was uneventful and without recidivation.

Migration from beneath a first or fifth metatarsal head tends to travel proximal medial or proximal lateral, respectively. In all instances where silicone migrated from plantar to dorsal, it followed implants beneath a second, third, or fourth metatarsal head. It is unknown why this type of migration was not observed or detected in earlier cases when larger amounts were injected. The 17 cases reported here received total amounts ranging from 0.4 to 4.1 ml (mean 1.46 ml). Of the 17 patients with dorsal migration, 16 (94%) were women. The lymphatic role in transporting silicone droplets, altered biomechanics induced by women's shoes, which considerably increase forefoot pressure, appears to be contributory. Silicone implanted at metatarsal heads two, three, or four may migrate distally or proximally, as can a natural fat pad under weight-bearing conditions.

Regardless of fluid migration, in most patients, the originally injected calluses remained improved or resolved, indicating that a further reduction of injected silicone might be desirable. Considering the inordinate forces to which feet are subjected, it may be impossible to prevent migration in every case.

The greatest amount of fluid injected into a patient at a single plantar site was 17.8 ml. This massive amount was 10–15 times greater than is currently suggested for a callus and is remarkable for its size and appearance. Yet over a 30-year course, it has remained asymptomatic. Silicone migration following lesser toe implantation can also occur. Similar to plantar migration, such movement is infrequent and rarely symptomatic. Though silicone injections for a corn may make the toe appear fuller, this is absent any inflammation characteristics, such as heat, redness, swelling, or pain. In several hundred treated small toes, a need for surgical excision of migrant silicone due to discomfort was rare, estimated at less than 0.5%. But even in these rarely seen cases, as with plantar migration, the original painful keratosis often resolved.

Histopathology

The morphologic cellular responses and end fate of silicone have also been analyzed microscopically. In Balkin's[15] study, 33 surgical biopsies and 124 postmortem specimens from 32 patients were conducted. Of these, 58 were digital and 66 were plantar. The earliest postinjection tissue examined was at 1 month, and the oldest was at 29 years. Regardless of time since injection, each specimen showed the presence of silicone. The fluid was noted to be well retained at the deposit site by two essentially noninflammatory tissue responses—histiocytosis and fibrosis. Histiocytes phagocytize foreign matter and are part of the body's scavenger system. The silicone is engulfed and retained within the histiocyte cell body as countless microscopic droplets.

The second key reaction to silicone fluid is that it stimulates the production of collagen fibers. The newly formed mesh of fibrous tissue acts like a web to further entrap and retain silicone fluid where deposited. Microscopic findings also show that numerous droplets envelop microneural and microvascular structures.

By thickening skin and encircling nerves with this resilient fibrous silicone coating, neural impingement by the bone is decreased, thereby reducing stress and pain. Similar encirclement of tiny blood vessels at pressure points appears to spare or protect vascularity by this cushioning mechanism. This benefits the patient population where neuropathic skin suffers from pressure due to unrecognized callus or tight shoes. They are less likely to shift body weight as seen when nerves are intact, and these longer periods of unrelieved stress, when standing, walking, or at rest, can diminish or stop local circulation.

Pathologists search for lymphocytes, eosinophils, fibroblasts, or plasma cells to detect the occurrence of any inflammatory process. These are characteristic of chronic inflammation but are infrequently seen in silicone-injected tissue. Postmortem specimen gathering has also afforded an opportunity to study inguinal nodes in 11 patients, including 4 in whom other lymph node systems were studied, as well as all major viscera. Although the body does not reject silicone fluid, microscopic droplets are transported into the groin lymph nodes without clinical signs or symptoms. Other deep nodal systems and viscera revealed no silicone. Histopathological findings suggest that medical-quality silicone injected into the foot is a safe procedure.[15]

Summary

Chemical and biomedical engineering advances have provided the health care industry with implantable polymeric biomaterials capable of repairing or replacing body parts. One such polymer, silicone fluid, is an implantable material that can augment soft tissue and be remarkably well retained. For the foot, this means that a quick, outpatient, injectable procedure can control or eliminate a patient's most common painful foot affliction—corns and calluses. In patients with diabetic neuropathy, this procedure can help eliminate the formation of ulcers. The debate over the legitimacy of silicone as a safe tool for soft-tissue augmentation has spanned well over half a century. Proponents concede that injections of questionable purity and/or of massive quantities have produced unfavorable outcomes. They assert that, in experienced hands with "injectable-grade" silicone, there are very few problems. Despite these claims, the literature is replete with disastrous outcomes following silicone fluid injection, often many years after the initial treatment. Unfortunately, as recently as 2006, reports in *The New England Journal of Medicine* and *The New York Times* failed to distinguish between the use of medical-grade silicone injected by trained practitioners in the microdroplet technique and the use of large volumes of industrial-grade products injected by unlicensed or unskilled practitioners. Injected silicone fluid has been found to be safe and effective as facial dermal filler and as a soft-tissue substitute for treating pressure-induced foot disorders, based on several independent evaluations and studies. Constant long-term patient review and extensive microscopic analysis have found no serious complications. No tumors or systemic responses were noted. Additionally, injected silicone does not impair healing nor impede venous or arterial circulation.

All beneficial drugs and medical devices have some degree of risk, and silicone foot injections are no different. The current level of scientific evidence supporting weight-bearing pain relief far outweighs the risk of painless fluid migration or the rare need for surgical removal. For patients with diabetes, the fluid can prevent insensitive digital or plantar ulceration, and with that, there is the extraordinary further potential of preventing toe, foot, or leg amputation. By breaking the chain of events of increased pressure leading to ulcer, disastrous diabetic foot complications and their social and economic costs can be dramatically mitigated. Further confirmation of these most favorable findings through official investigation, followed by silicone approval and appropriate usage, could herald a new and exciting era in the history of foot care.

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