An Evaluation of Evidence Regarding Application of Silicone Gel Sheeting for the Management of Hypertrophic Scars and Keloids

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Ancient Egyptian hieroglyphics serve as the earliest record of keloid formation. The pathogenesis of keloid formation and successful treatment still elude researchers and clinicians in dermatology and other specialties who are challenged by this problematic and refractory condition. A multifactorial etiology with interactions between genetic susceptibility and "high tension" anatomical locations are considered just a few of the potential causative factors underlying keloid formation. Keloids frequently occur in African, Hispanic, and Asian ethnicities. These lesions tend to develop in high tension anatomical sites, such as over the chest, back, and shoulders, but also routinely occur at the ear lobules, especially after piercing.[1,2]

Keloids were originally considered an inherited autosomal recessive process; however, this theory was later challenged due to the clinical observation of several syndromes that form spontaneous keloids. For example, keloids appear in Rubinstein-Taybi syndrome with additional features of beaked nose, widened phalanges of the thumbs and great toes, and mental retardation, and also in the Goeminne syndrome with associated torticollis, cryorchidism, renal dysplasia, and multiple nevi.[1,3,4] Keloid formation may occur in type 4 Ehler Danlos syndrome, following laser vaporization of genital lymphangiomas, and in the third infectious stage of yaws.[1,5,6]

How are keloids and hypertrophic scars differentiated?

Hypertrophic scars have been reported to occur in 39 to 68 percent of patients postsurgically and in 33 to 91 percent of burn patients.[7] Keloids complicate an estimated 5 to 15 percent of patients after surgery, especially in higher risk populations.[8] Initially, hypertrophic scars and early keloids can appear similar histologically. Over time, keloids can be distinguished by the more chaotic arrangement of collagen bundles. Clinically, keloids clearly widen beyond an incision site and may become lobular, while hypertrophic scars stay relatively confined within the original boundaries of the incision.[9]

What information is known about the immunomodulatory and cellular pathophysiology of hypertrophic scar formation and keloid development?

The immunomodulatory and cellular pathophysiological basis of hypertrophic scar and keloid formation stems from keloid-derived fibroblasts (KF), which have been shown to express an increase in receptors for several keratinocyte-derived cytokines including interleukin-1 (IL-1), IL-6, transforming growth factor (TGF)-beta, platelet-derived growth factor, and connective tissue growth factor.[8,10,11,12] One principal factor responsible for keloid formation is considered to be TGF-beta 1, 2. TGF-beta is secreted by monocytes, macrophages, lymphocytes, and fibroblasts as a precursor protein, and remains inactive within the extracellular matrix.[11] Studies suggest that fibroblasts in keloid formation secrete excess TGF-beta, which causes increased activation of COL1 genes and upregulation of fibrosis. COL1 is the most fibrous type of collagen and is responsible for fibrosis in hypertrophic scars, keloids, and visceral fibrosis.[13] TGF-beta deregulation occurs in a wide variety of diseases, such as hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), Loeys-Dietz syndrome, familial pulmonary hypertension, Camurati-Engelmann disease, Marfan syndrome, fibrodysplasia ossificans progressiva, multiple hamartoma syndrome

(Cowden syndrome), pulmonary fibrosis, and systemic sclerosis.[11] TGF-beta is considered one of the main factors modulated by intralesional triamcinolone injections and may prove to be a target for future pharmaceutically directed keloid treatments.[12]

What is the evidence supporting the use of intralesional corticosteroid injection for hypertrophic scars and keloids?

The ideal treatment for keloids still remains elusive. Only two evidence-based treatments are recommended by the International Advisory Panel on hypertrophic scar and keloid management: intralesional corticosteroid (triamcinolone) injection and silicone gel sheeting.[12] Intralesional corticosteroid injection is the most commonly used treatment for keloids, especially in dermatology, despite Durani et al categorizing the trials evaluating this approach with a level of evidence of 4 (LOE4). The LOE4 category includes support based primarily on case studies; low quality cohort series; nonrandomized, controlled trials; and low-quality case control trials adapted from the Oxford Centre for Evidence-based Medicine classification.[14]

Since the 1960s, intralesional corticosteroid injection has been used to treat both hypertrophic and keloidal scar formation, but the exact mechanism of action is still not fully understood.[15] Durani et al suggest that the combination treatment of cryotherapy and intralesional triamcinolone injection is the most effective treatment to prevent recurrence.[16] Repeated injection sessions are often needed depending on the size, volume, and thickness of the keloid. Importantly, patients need to be informed that intralesional corticosteroid injection does not "dissolve the keloid" and leave behind normal-appearing skin. Rather, the injected keloid will usually soften and flatten with successful intralesional injection, with symptoms of pain and pruritus usually resolving or improving as well. Adverse side effects of intralesional corticosteroid injection include cutaneous atrophy, telangiectasias, and/or permanent hypopigmentation, which reportedly occur in up to 63 percent of treated lesions.[17]

What is the evidence supporting the use of silicone gel sheeting for hypertrophic scars and keloids?

The 2001 International Advisory Panel for hypertrophic scar and keloid management concluded that silicone gel sheeting for hypertrophic scars, immature keloids, and mature keloids is a viable first-line treatment choice.[15] Silicone gel sheeting was first used in 1981 for the treatment of hypertrophic scarring for burns at an Australian pediatric hospital; however, poor trial design and truncated follow-up times related to keloid recurrence have skewed the outcome data.[8] Few randomized, controlled trials have been conducted for many of the methodologies used for keloid treatment, such as intralesional bleomycin injection, topical imiquimod application, pressure dressing, radiotherapy, and intralesional verapamil injection. Follow-up time for recurrence of keloids varies in trials from six months to one year. However, keloids can develop from six months to two years after an inciting cause, suggesting that follow-up trial times in most studies are inadequate.[15] Recently, Davison et al followed five patients with refractory keloids of the chest wall. All five patients were supplemented with silicone gel and silicone gel sheeting. Davison et al reported follow up for recurrence, which ranged from 7 to 65 months. Two patients were followed to at least 64 months with no recurrence. The extended and more appropriate follow-up time utilized by Davison et al is one exception from the majority of research examining keloid recurrences.[16] Examination of the quality of trials looking at topical silicone-based therapies for keloids were categorized with a LOE2. LOE2 designation includes trial designs, such as low-quality, randomized, controlled trials and systematic review of cohort studies utilizing the Oxford Centre of Evidence-Based Medicine classification.[14] There were no trials rated with a LOE1 for keloid treatment reported by Durani et al. Importantly, Durani et al acknowledges the literature and guidelines that support the most commonly practiced treatment modalities for keloids and hypertrophic scars, but emphasizes that levels of evidence were not uniformly reported from these trials. It is also important to emphasize that recurrence of keloids appears to be more common than complete resolution with all treatment types.[14] More thorough studies investigating the combination of several therapies and the use of silicone gel sheeting would be advantageous.

Importantly, silicone gel sheeting does not tend to completely resolve keloids, but it is evident that this therapy modulates keloid formation and can reduce thickness and induration.[18] Silicone gel sheeting has few associated adverse effects and can serve as an adjunct to other therapies or can be used as a preventative treatment for patients with a history of hypertrophic scar or keloid formation. Current data do suggest that patients with a history of hypertrophic scarring and keloid

formation respond to silicone gel sheeting. Patients who scar normally do not receive any benefit from gel sheeting treatment, such as an enhanced healing time. Silicone gel sheeting should be restricted only to patients with a history of pathological healing.[14,19,20]

Basic science research evaluating the pathogenesis of keloid formation has proven cumbersome. Organotypic epidermal-dermal models simulating the wound-healing process have been developed to study keloid formation, but are fraught with limitations. In fact, no animal model existed to evaluate keloid formation until recently.[19,20] In a recent study, the rabbit ear model was assessed with punch biopsy of several areas on rabbit ears. The study removed the skin and perichondrium from the ear allowing healing only through granulation rather than contraction, which is the main mechanism for animal skin healing. The rabbit ear model results showed silicone gel sheeting plus five sheets of Tegaderm (3M) occlusion reduced hypertrophic scar formation by 80 percent. Although design flaws are evident, silicone gel sheeting, unlike cryotherapy and intralesional triamcinolone injection, has few adverse side effects. More research is needed to adequately understand and optimally treat hypertrophic scars and keloids with different modalities, both monotherapy and combination therapy.

Recent literature reviews have concluded that silicone gel sheeting is a helpful treatment for peri-incisional pruritus and hyperpigmentation. Silicone gel sheeting applied after complete reepithelization for at least 12 hours a day, over a duration of 2 to 3 months, is the recommended regimen for treatment of hypertrophic scars and keloids.[21,22]

Although the exact mechanism is unknown, silicone gel sheeting has proven to initially improve texture, then pigmentation, then height of keloids.[22] Previous studies determined no correlation between temperature, pressure, silicone incorporation into epidermis, or oxygen tension as mechanisms by which silicone gel sheeting treats keloid formation.[22] One theory suggests that hydration of the stratum corneum is the major influencing factor contributing to the successful treatment of the keloid lesion. Hydration is believed to augment cytokine production and regulation, although the specific factors influenced by silicone gel sheeting have not been determined.[22,23] One study showed hydration alone reduced both IL-8 and fibronectin while silicone decreased only fibronectin concentrations.[22]

It is important to emphasize that although occlusion and hydration may be achieved by other products, silicone gel sheeting has been clinically proven to also address pruritus, skin pigmentation changes, and primary prevention. Other hydrating products are unable to match these claims.[22] One study examined use of hydrocolloid keloid prevention and found no effect on scar appearance. However, because of poor research design and the unknown *in-vivo* contributing factors to keloid formation, no individual theory is solidly supported.[22] Transepidermal water loss (TEWL) and skin barrier homeostasis are emerging as proposed fundamental pathophysiological factors for many skin conditions, such as eczematous dermatoses, rosacea, and psoriasis. Silicone gel sheeting is able to simulate the physiological skin barrier and decrease TEWL.[23–25]

What is the reported utilization of silicone gel sheeting among plastic surgeons and dermatologists?

A survey conducted in 2005 through the *Aesthetic Surgery Journal* found 18 percent of plastic surgeons polled reported use of hypertropic scar and keloid augmenting products. Of the products used, 79 percent were silicone gel sheeting products. Also, 40 percent of plastic surgeons reported beneficial effect of products in 50 to 75 percent of their treated patients.[20] The authors are not aware of similar data being collected among dermatologists.

What are the types of silicone-based topical products used to treat hypertrophic scars and keloids? What is the efficacy of these products?

Many of the topical products that contain silicone, including gel, adhesive sheets, ointment, and combinations containing a topical corticosteroid, are available over the counter (OTC). Specifically, silicone gel sheeting has been demonstrated through randomized, controlled trials to reduce incidence of hypertrophic scars. However, several studies comparing silicone gel and silicone gel sheeting suggest that silicone gel has a higher compliance than gel sheeting, due primarily to ease of use and convenience.[26] A few studies have suggested no significant difference between the gel and gel sheeting. Recently, Perez et al examined tolerability and efficacy of an OTC preparation of 0.5% hydrocortisone, silicone, and vitamin E lotion (HSE). The study followed 30 subjects with keloids or hypertrophic scars. Seven of 12 subjects using HSE had improved investigator cosmetic assessment, lesion induration, pigmentation, and erythema.[27]

Additionally, only silicone gel sheeting received international recommendation by a consensus panel in 2001 for hypertrophic scar management. It is important that clinicians be aware of available preparations their patients may access. Very few side effects from silicone gel sheeting treatment have been reported and include local irritation secondary to occlusion.[19]

What was the consensus reported by the International Advisory Panel to manage hypertrophic scars and keloids?

The International Advisory Panel in 2001 suggested a combination of intralesional corticosteroid injection and silicone gel sheeting employed for up to 12 months. If keloid scarring is refractory to treatment, research supports surgical excision of the keloid in combination with silicone gel sheeting.[15] Silicone gel sheeting can be effectively utilized postoperatively, after complete reepithelialization, and for mature keloids.[15] Silicone gel sheeting immediately after surgery without allowing reepithelialization is ineffective.[25]

What conclusions can be drawn from the available evidence of silicone gel sheeting and the management of hypertrophic scars and keloids in dermatology?

Few randomized, double-blind, clinical trials have been published that evaluate the efficacy of silicone gel sheeting for hypertrophic scars and keloids. The few trials that do exist are associated with limited follow-up time, given the nature of keloid behavior, which can emerge up to two years after an inciting traumatic event. Despite the obvious need for more precisely designed research, it is apparent from the limited data that silicone gel sheeting of hypertrophic scars and keloids does benefit patients with a history of hypertrophic scar or keloid formation, and or burn injury, with little risk of adverse effects to the patient. Silicone gel sheeting is also an excellent treatment option for pediatric patients who may not be able to tolerate intralesional corticosteroid injection.[15]

Silicone gel sheets can be washed and reused, limiting financial burden to the patient over the 2- to 3-month treatment course. Application of silicone gel sheeting is a conservative measure that is routinely utilized by the Maricopa County Burn Center in Phoenix, Arizona, and this product makes up 79 percent of keloid treatment products utilized by 18 percent of plastic surgeons surveyed in 2005.[20]

Although additional studies are needed with all therapies used to treat hypertrophic scars and keloids, silicone gel sheeting can be employed, especially as an adjunct in combination with other hypertrophic scar and keloid treatments. As with any therapy, responses may vary, although available data and clinical experience support that many patients may experience a reduction in induration, dyschromia, thickness, and symptomatology associated with hypertrophic scars and keloids after proper use of silicone gel sheeting.

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