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REVIEW

Evolution of Silicone Therapy and Mechanism of Action in Scar Management

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Abstract Silicone-based products are widely used in the management of hypertrophic scarring and keloids. This review discusses the range of products available and the clinical evidence of their efficacy in preventing excessive scarring and improving established scars. Silicone gel sheeting has been used successfully for more than 20 years in scar management. A new formulation of silicone gel applied from a tube forms a thin flexible sheet over the newly epithelialized wound or more mature scar. Results from clinical trials and clinical experience suggest that silicone gel is equivalent in efficacy to traditional silicone gel sheeting but easier to use. The mechanism of action of silicone therapy has not been completely determined but is likely to involve occlusion and hydration of the stratum corneum with subsequent cytokine-mediated signaling from keratinocytes to dermal fibroblasts.

Keywords Hydration · Hypertrophic scar · Keloid · Occlusion · Silicone gel · Silicone gel sheeting

Topical silicone therapy is widely used to improve the signs and symptoms of hypertrophic scars and keloids and to prevent the development of abnormal scarring. Over the past several years, a wide range of silicone-based products have become available for scar management.

Silicone gel sheeting (SGS) has proven effectiveness in scar management, but its use poses several limitations. Some parts of the body are not suitable for SGS use. It is impractical to use sheeting on large areas or near joints, and it cannot be used easily on the face or other areas where the contours or motility of the skin make it difficult to ensure adequate contact and coverage [21]. Taping often is needed to secure the sheeting to the skin. Also, patients may be reluctant to use the sheeting on unclothed areas during the day, and compliance with treatment is often a concern [6]. Finally, sheets must be washed carefully and often to prevent complications such as rashes and infection.

Research in product development has focused on developing silicone-based products that have the same efficacy as SGS, but are useful on more areas of the body and better accepted by patients. To that end, brands of SGS with increased durability and adhesiveness have been introduced to improve the ease of use and patient acceptability of SGS treatment [21]. Other formulations of silicone that may be easier to apply and maintain than sheeting also have been developed, and both cream containing silicone oil and silicone gel applied from a tube currently are marketed for use in scar management.

Silicone Gel Sheeting

Perkins et al. [31] first observed the potential usefulness of SGS for the treatment of burn scars and contractures in the early 1980s. Within the next few years, several uncontrolled studies documented the successful use of SGS in the treatment of hypertrophic scars and keloids [24, 30, 33]. Our group reported the first controlled comparative study demonstrating the efficacy of SGS treatment in scar management [1, 2]. Subsequently, four randomized controlled trials [6, 21, 22, 40] provided strong evidence that SGS is effective in the treatment of hypertrophic scars (Table 1).

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Table 1. Controlled comparison studies on the efficacy of silicone gel sheeting (SGS) in scar management

Study	Patients	Intervention	Scar evaluation	Outcome
Ahn et al. [1, 2]; prospective, within-subject comparison study	Study arm 1: 29 patients who underwent surgery within the past 3 months Study arm 2: 19 patients with established hypertrophic scarring	SGS treatment compared with no treatment of scars from the same or a mirror image site within a patient for 2 months (study arm 1) or up to 7 months (study arm 2)	Volume measured using negative impression mold; elasticity measured using elastomer	Scars at surgical wounds treated with SGS had significantly less volume than scars at untreated wounds SGS treatment of established hypertrophic scars produced a significant increase in scar elasticity not seen in untreated scars
Sproat et al. [40]; prospective, randomized, investigator-masked, within-subject comparison study	14 patients with poststernotomy hypertrophic scars	SGS treatment on half of scar compared with intralesional steroid injection treatment of other half of scar for 12 weeks	Appearance evaluated from photographs; length, height, and width; changes in symptoms	Patient preference, time to improvement of symptoms, and masked observers' assessment of scars based on photographs favored SGS treatment over steroid treatment
Carney et al. [6]; prospective, randomized, parallel-group comparison study	42 patients with hypertrophic scars	Cica-Care SGS treatment compared with Silastic SGS treatment, with no treatment on portions of the same scar or on different scars in the same patient for 6 months	Color, texture (hardness), extensibility	Statistically significant higher percentage of scars showed improvement in color and hardness with each brand of SGS than with no treatment; significantly greater increase in extensibility with SGS than with no treatment
Lee et al. [21]; prospective, randomized, parallel-group comparison study	26 patients with hypertrophic scars	Sil-K SGS treatment compared with Epiderm SGS treatment for 6 months	Color, texture (hardness), regularity (smoothness), elevation	Improvement in scar color, hardness, smoothness, and elevation after 6 months of treatment with each brand of SGS
Cruz-Korchin [10]; prospective, within-subject comparison study	20 women who underwent bilateral breast reduction	SGS treatment of one breast compared with no treatment of other breast for 2 months	Scar hypertrophy determined by whether scar was raised over surrounding skin	Wounds treated with SGS showed statistically significant reduction in the incidence of hypertrophic scarring compared with untreated wounds
Niessen et al. [28]; prospective, randomized, within-subject comparison study	155 women who underwent bilateral breast reduction	Sil-K or Epiderm SGS fixed with Micropore on portions of the scars compared with Micropore alone on the remaining portions of the scars	Hypertrophic scarring determined by scar height (raised above skin level); width and height measured with a ruler and using ultrasound; blood flow measured using Doppler laser flowmetry; color measured using chromameter	No difference in the occurrence of hypertrophic scarring on SGS-treated vs untreated sites

Table 1. continued

Study	Patients	Intervention	Scar evaluation	Outcome
Borgognoni et al. [5]; prospective, parallel-group comparison study	20 patients with recurring keloid who underwent another surgical excision	SGS treatment compared with no treatment for 3 months	Keloid recurrence determined by scar height (flat = no recurrence; height < 50% of excised keloid = partial recurrence; height > 50% of excised keloid = recurrence)	Reduced incidence of keloid recurrence among patients treated with SGS compared with untreated patients
de Oliveira et al. [11]; prospective, randomized, parallel-group comparison study	26 patients with 41 hypertrophic scars or keloids	SGS treatment was compared with nonsilicone gel sheeting treatment and with no treatment for 4.5 months	Length and width measured using flexible ruler to include height; hardness measured by observation and intracicatrial pressure; color; pain; itching	Statistically significant decreases in linear measurements, redness, and hardness for scars treated with either SGS or nonsilicone gel sheeting but not for untreated scars
Gold et al. [15]; prospective, randomized, parallel-group, comparison study	96 patients (46 high risk with history of abnormal scarring) who underwent skin surgery	SGS treatment in addition to normal postoperative care compared with normal postoperative care alone for 6 months	Development of abnormal scar (criteria for abnormal scar not reported)	SGS treatment reduced the incidence of hypertrophic or keloid scarring in high-risk patients
Li-Tsang et al. [22]; prospective, randomized, investigator-masked, parallel-group comparison study	45 Chinese patients with hypertrophic scars	SGS treatment in addition to deep massage compared with deep massage alone for 6 months	Thickness measured using ultrasound; pigmentation measured using spectrocolorimeter; pliability; pain; itching	Statistically significant reduced thickness and greater pliability of scars treated with SGS compared with scars not treated with SGS
Maján [23]; prospective, randomized, parallel-group comparison study	11 surgical patients	SGS (Mepiform) treatment compared with no treatment initiated from 2 weeks to 2 months after surgery	Height, pigmentation, pliability, and thickness rated on Vancouver Scar Scale	Scars treated with SGS appeared to have decreased height and pigmentation and increased pliability compared with untreated scars (results not analyzed statistically)

SGS, silicone gel sheeting

Other controlled studies [5, 10, 11, 15, 23] have shown that prophylactic treatment with SGS can be effective in preventing the development of excessive scars (Table 1). To our knowledge, Niessen et al. [28] reported the only controlled clinical study that failed to find a preventive effect of SGS treatment on hypertrophic scarring. The reasons why prophylactic SGS treatment was not effective in their study are unclear, but the investigators suggested that the SGS treatment may have been initiated too early (immediately after surgery).

A metaanalysis of 13 controlled studies reported through 2001 (including the Niessen et al. [28] study) found significant effects of SGS sheeting in reducing the incidence of hypertrophic scarring among high-risk individuals, increasing scar elasticity, and reducing redness [29]. On the whole, the controlled clinical studies that have been reported provide convincing evidence that SGS is effective in preventing and alleviating excessive scarring. The results of these studies provide an evidence-based rationale for the current widespread use of SGS in scar management.

Cream Containing Silicone Oil

The hypothesis that silicone oil leaking from SGS might be responsible for the effects of SGS on scarring [33] led to the investigation of the effects that topical formulations containing silicone oil have on scarring. In one study, treatment with a cream containing 20% silicone oil covered with gauze led to only slight improvement of hypertrophic scars or keloids in 22% of 36 patients, whereas treatment using the cream covered with an occlusive water-impermeable plastic film led to more substantial improvement of scars in 82% of 11 patients [35]. Subsequently, in an uncontrolled study investigating the effects of a cream containing 20% silicone oil, keloids of 15 Chinese patients were treated using cream covered with a self-adhesive, air-permeable, water-impermeable film (Tegaderm: 3M, St. Paul, MN) at least 12 hours daily for 6 months [44]. The treatment produced a significant decrease in scar elevation and symptoms.

These two studies suggest that silicone cream is potentially useful in scar management. However, it should be noted that silicone cream has shown good efficacy only when used with an occlusive dressing [35]. Silicone cream used without an occlusive dressing has minimal effects on scarring [35].

Silicone Gel in a Tube

A self-drying topical silicone gel was developed from the same basic long-chain silicone polymer used for SGS. The gel, available in a tube, is applied in a thin layer to the skin. It dries to form a thin, transparent, flexible, gas-permeable, water-impermeable silicone sheet that adheres to the skin and improves scarring (Fig. 1).

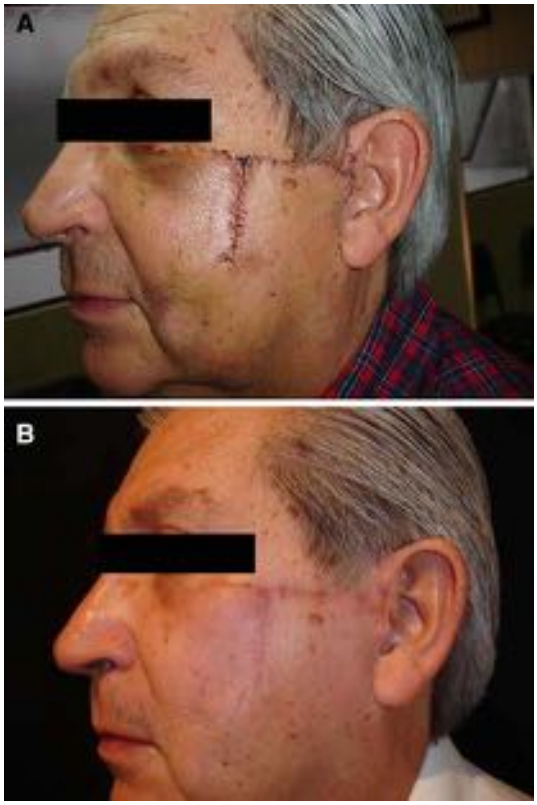

Fig. 1. Before and after views of silicone gel treatment in scar management. (**A**) Patient with full thickness surgical wound before treatment. (**B**) After 2 months of treatment with Dermatix Ultra. Photographs were kindly provided by Dr. Guerrerosantos, plastic surgeon, Guadalajara, Jalisco, Mexico.

The results of recent comparative clinical studies [7, 9, 12, 38] indicate that silicone gel applied from a tube is as effective as SGS in the management of abnormal scarring (Table 2). A randomized, double-masked, placebo-controlled clinical trial evaluated the efficacy of silicone gel (Scarfade: Hanson Medical, Inc., Kingston, WA, also marketed as Dermatix: Valeant Pharmaceuticals International, Alison Viejo, CA) in preventing hypertrophic scarring after median sternotomy in Asian patients [7]. Half of the wound was treated twice daily with silicone gel, and the remaining half with a placebo gel. Although a hypertrophic scar or keloid developed for most patients (94%), the half of the wound treated with silicone gel typically showed less scarring than the control half of the wound.

At 3 months after surgery, the scars that developed during silicone gel treatment were significantly flatter, less

Table 2. Studies on the efficacy of silicone gel (formulated in a tube) in scar management

Study	Patients	Intervention	Scar evaluation	Outcome
Controlled comparative studies				
Chan et al. [7]; prospective, randomized, double-masked, within-subject comparison study	50 Asian patients who underwent median sternotomy	Twice-daily silicone gel on half of wound compared with placebo gel on other half of wound from postoperative week 2 to month 3	Vancouver Scar Scale scores of pigmentation, vascularity, pliability, height, pain, and itchiness	Scars that developed during silicone gel treatment were significantly flatter, less red, and more pliable and associated with significantly less pain and itching than scars that developed during placebo treatment
Signorini and Clementonil [38]; prospective, randomized, parallel-group comparison study	160 patients who underwent surgery	Twice-daily silicone gel treatment compared with no treatment initiated from 10 days to 3 weeks after surgery for 4 months	Scar quality (normal mature, slightly hypertrophic, hypertrophic, or keloid scar based on color, hardness, elevation, and relationship to wound margins)	Scar quality was significantly better in the silicone gel group than in the no treatment group at the 6-month follow-up visit: the incidence of hypertrophic or keloid scarring was 7% in the silicone gel group compared with 26% in the no treatment group
Chernoff et al. [9]; prospective, within-subject comparison study	30 patients with bilateral hypertrophic scars, keloids, or scars still in an erythematous and raised stage of healing	Silicone gel, SGS, or a combination of treatments for one scar compared with no treatment for the bilateral scar for 3 months	Elevation and texture measured using optical profilometry; erythema; pliability; severity of symptoms	Scars treated with silicone gel, SGS, or silicone gel/SGS were statistically significantly less elevated. less red, and associated with fewer symptoms than untreated scars
Fonseca Capdevila et al. [12]; prospective, parallel-group comparison study	132 patients who underwent removal of a benign skin lesion	Silicone gel treatment compared with SGS treatment initiated within 1 month of surgery	Height; redness; pliability; itching; pain/tenderness	Silicone gel and SGS were both effective in improving scar redness, hardness, elevation, pain, and itching; there were no statistically significant differences between silicone and SGS on any efficacy parameter at the month 6 follow-up
Large-scale observational study				
Sepehrmanesh [37]; prospective, open-label, noncontrolled study	1,522 patients with scars	Silicone gel typically used twice daily for at least 2 months	Height; color; pliability; itching; pain/tenderness	Improvement in scar color, pliability, height, itching, and pain/tenderness after silicone gel treatment of approximately 70% to 85% of patients
Small case series				
Murison and James [25]; prospective, noncontrolled study	6 patients with excessive scars (most at least 2 years old)	Silicone gel used for 8 weeks	Vancouver Scar Scale scores of elevation, redness, hardness, itching, tenderness; collagen content and blood flow measured using intracutaneous spectrophotometry	All scars showed improvement in redness, elevation, hardness, and itching, and pain was reduced in symptomatic scars

red, and more pliable and associated with less pain and itching than the control scars. No side effects were associated with the silicone gel treatment, and the patients self-reported a high degree of compliance, with 98% of them reporting that they usually or always applied the gel as prescribed.

A subsequent study also demonstrated that treatment with silicone gel (Dermatix) is effective in preventing abnormal scarring after surgery [38]. A hypertrophic scar or keloid developed in only 7% of the patients treated with silicone gel, compared with 26% of the patients who received no treatment. There were no side effects of silicone gel treatment, and all the patients reported that the gel was easy to apply.

A recent prospective study compared silicone gel with SGS and no treatment in the management of abnormal scarring [9]. The study enrolled 30 patients with bilateral immature scars, hypertrophic scars, or keloids. One scar of each patient was treated with silicone gel (Dermatix), SGS (Epi-derm: MatTek Corporation, Ashland, MA), or a combination of these treatments (silicone gel during the day, SGS at night), and the other scar served as an untreated control. All three silicone-based treatment regimens provided statistically significant improvement for symptoms of itching, irritation, and skin maceration compared with no treatment, and the scars in each treatment group were more pliable and less elevated and erythematous than the untreated control scars. Silicone gel was at least as effective as SGS. Patient scores for the difficulty of treatment were higher with SGS, and patient scores for their willingness to comply with treatment were higher with silicone gel.

A second prospective study compared silicone gel with SGS for the management of scarring after surgical removal of a benign skin lesion [12]. Scars treated with either silicone gel (Dermatix) or SGS showed significant improvement in redness and hardness during the study, and scar elevation, pain, and itching decreased in both treatment groups. After 6 months of treatment, there was no statistically significant difference between the treatment groups in any efficacy parameter. Patient ratings of comfort favored silicone gel over sheeting, with 88% of the silicone gel patients rating the comfort of their treatment as "good" or "very good" compared with 53% of the SGS patients.

Published noncomparative studies [25, 37] also have suggested that silicone gel is equivalent to SGS in efficacy (Table 2). A large, community-based, open-label, observational study evaluated the efficacy of silicone gel (Dermatix) for 1,522 patients with scars [37]. Scar parameters of color, pliability, height, itching, and pain/tenderness were improved after at least 2 months of silicone gel treatment in 70% to 84% of cases according to physician assessments, and in 70% to 85% of cases according to patient assessments. Both patients and physicians expressed high levels of satisfaction with silicone gel treatment with respect to ease of use, duration of treatment, cosmetic outcome, and tolerability.

A case series of six patients who had excessive scars treated with silicone gel (Dermatix) for 8 weeks also has been reported [25]. For five of the patients, the scar was at least 2 years old. All the scars showed improvement of redness, elevation, hardness, and itching after treatment, and the four scars associated with pain or tenderness also showed improvement in these symptoms. Spectrophotometric intracutaneous scope measurements obtained for five of the six patients supported the results of the clinical assessments, showing a consistent decrease in collagen content and increased blood flow in treated scars. Patients rated the efficacy of treatment as moderate (2 patients), good (1 patient), and very good (3 patients). All the patients reported that the gel was simple and easy to use.

The results of the clinical studies reported to date indicate that silicone gel and SGS have equivalent efficacy in the management of abnormal scarring after surgery, and patients may find silicone gel more comfortable to use. The evidence suggests that silicone gel, like SGS and occlusive silicone cream, is effective in softening and reducing scars, reducing redness, and improving symptoms of pain and itching in most patients.

Mechanism of Action

The mechanism of action of silicone-based products in scar management has not been completely determined, but the beneficial effects of SGS on scars are not mediated by pressure or by changes in oxygen tension or blood flow [26, 33]. Similarly, the effects likely are not attributable to silicone release and entry into scar, because biopsies of scars treated with SGS have shown no evidence of a foreign body reaction [1]. An increase in skin surface temperature could be involved because the skin surface temperature of hypertrophic burn scars under SGS is increased by 1.7°C [26], and temperature increases of this magnitude can significantly increase collagenase activity and could affect scarring [4]. Development of a static electric field also may be involved, because it has been proposed that the negative static electric field generated by friction between SGS and the skin could cause collagen realignment and result in the involution of scars [18]. In fact, cushions consisting of a silicone occlusive covering filled with silicone oil provide a stronger static electric field than SGS and are at least as effective as SGS in normalizing excessive scars [19]. However, there is no evidence currently that the static electric field produced by silicone products causes changes in the extracellular matrix of scars.

Studies have shown that SGS decreases evaporation of water from the skin and increases hydration of the stratum corneum [14, 33]. The silicone sheet that forms on the skin after application of silicone gel and the combination of silicone cream and an occlusive dressing presumably have similar effects on water loss and hydration of the stratum corneum. A growing body of evidence suggests that the beneficial effects of all silicone-based products on scars are mediated by occlusion and hydration.

In the study reported by Sawada and Sone [35] comparing silicone cream covered with gauze and silicone cream occlusive dressing, improvement in scar quality was significantly greater with the silicone cream occlusive dressing. These results suggest that occlusion is an important component in the mechanism of action of silicone-based treatment of scars.

In a subsequent study by the same investigators, silicone-free cream occluded with a water-impermeable plastic film was significantly more effective than a vaseline control in improving hypertrophic scars and keloids [36]. The results with silicone-free occlusive dressing were similar to the investigators' previous findings with silicone cream occlusive dressing, leading them to suggest that hydration and occlusion are the primary basis of silicone's therapeutic action on scars [36].

Results of other clinical studies support this suggestion. Treatment of keloids for 2 months with a water-impermeable, non–silicone-based occlusive dressing was found to be effective in reducing scar elevation, erythema, tenderness, and pruritus, suggesting that occlusion alone can be effective in the treatment of excessive scarring [3]. Moreover, in a study reported by de Oliveira et al. [11], sheets of occlusive silicone gel and occlusive nonsilicone gel appeared to be similarly effective in improving hypertrophic scars and keloids.

We have investigated the effects of SGS (Cica-Care: Smith & Nephew, Largo, FL) in a rabbit model of hypertrophic scarring [34]. As expected, SGS effectively reduced scar hypertrophy in this model system. A polyurethane dressing (Op Site: Smith & Nephew, Largo, FL) that is approximately 20% more occlusive to water, and Tegaderm, which is approximately fivefold less occlusive, did not have similar beneficial effects on scarring. Our original interpretation of these results, given the similarity in the water vapor transmission rates for the polyurethane dressing and SGS, was that the scar-reducing property of silicone gel is not dependent on the occlusive nature of the gel [34]. Further experiments, however, have led us to the belief that occlusion is indeed an essential component in the mechanism of action of silicone gel, but magnitude of occlusion is critical for effective treatment. Nonocclusive dressings are ineffective, but SGS or silicone gel, which occlude and hydrate tissue similarly, are similarly effective in reducing hypertrophic scars in the rabbit model system.

Silicone Therapy and Epidermal-Dermal Signaling

Several studies have found that silicone-related products can affect the activity and growth factor production of cultured fibroblasts from hypertrophic scars and keloids [16, 20]. Unfortunately, the relevance of these results is not clear, because in clinical silicone products are placed on the epidermis and do not have direct contact with dermal fibroblasts.

It is likely, however, that silicone products act on the epidermis to initiate signaling cascades that affect dermal fibroblasts. The epidermis has a well-known regulatory role in dermal fibroblast extracellular matrix production. Delayed epithelialization during wound healing increases the risk of hypertrophic scarring [13], and removal of the stratum corneum by tape stripping causes inflammation and activation of keratinocytes and stimulates their production of cytokines that activate dermal fibroblasts to increase collagen production [27].

In vitro studies using co-cultures of keratinocytes and fibroblasts or monocultures of fibroblasts and conditioned medium from keratinocytes have shown that keratinocytes release substances, presumed to be cytokines, that stimulate fibroblast proliferation and inhibit their synthesis of collagen [13, 17]. In an *in vitro* two-chamber cell culture model investigating the interaction between epidermis and dermal fibroblasts, fibroblast proliferation and collagen and glycosaminoglycan production in the bottom chamber were significantly inhibited when keratinocytes that had formed a differentiated epithelium in the upper chamber were exposed to Hanks solution rather than air on their apical surface [8]. Importantly, exposure of the epithelium to silicone oil did not have a similar inhibitory effect on fibroblasts. These results suggest that hydration, rather than silicone itself, can modulate the effect of keratinocytes on skin fibroblasts by affecting their production of soluble factors [8].

Potential Role of Occlusion and Hydration in Silicone Therapy

The function of the skin epithelium is to conserve water and serve as a barrier to microbial infection. The stratum corneum normally contains a gradient of water and is responsible for water conservation, but its function is disrupted when the skin is wounded. After a full-thickness wound, transepidermal water loss (TEWL) is increased and can take longer than 1 year to recover to basal levels [41].

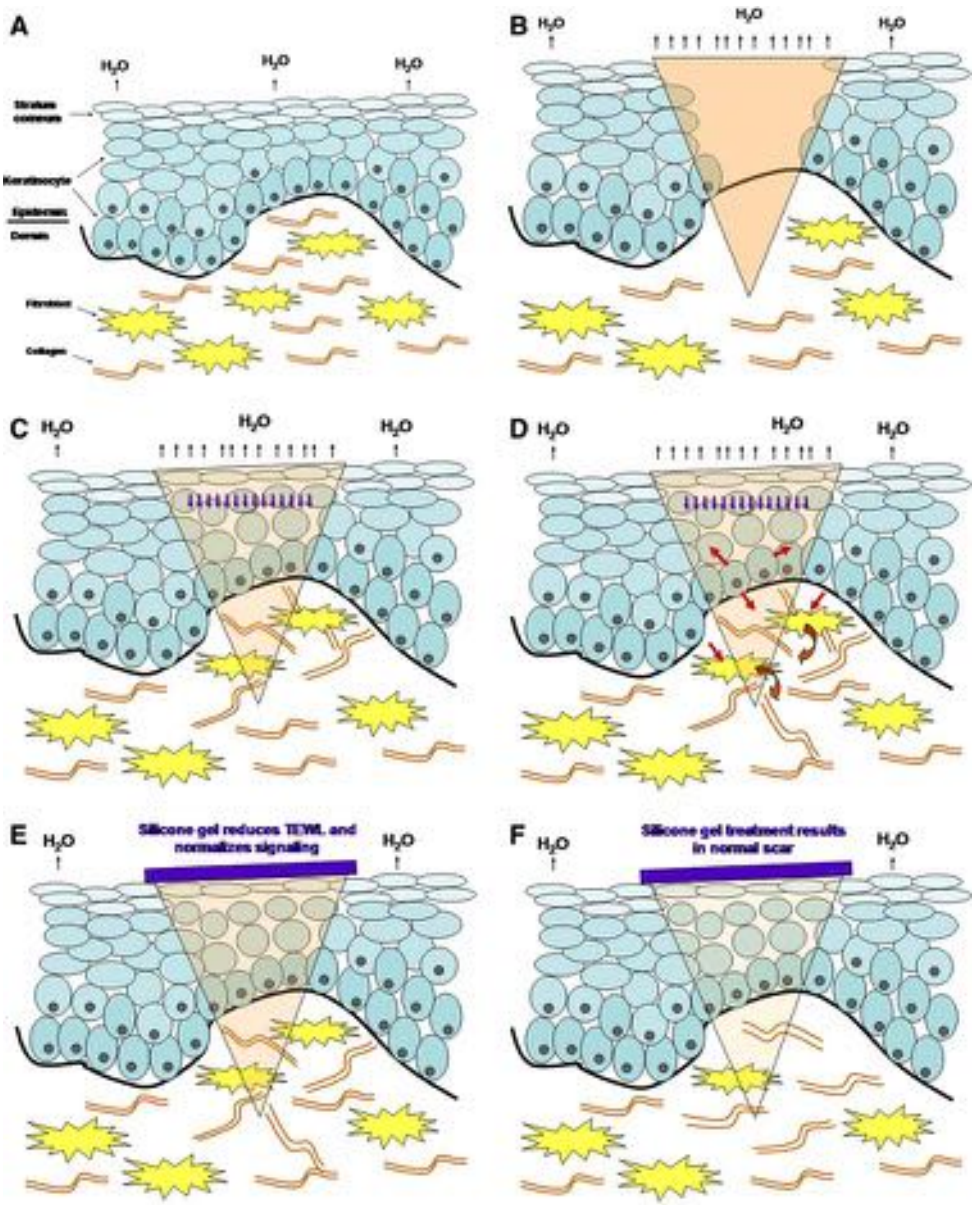

Fig. 2. Proposed mechanism of action of silicone gel in scar management. (**A**) Normal skin with mature stratum corneum and minimal transepidermal water loss (TEWL). (**B**) Partial- or full-thickness injury. (**C**) At 1 to 2 weeks after wounding, reepithelialization is completed, but the stratum corneum is immature and allows abnormally high levels of TEWL. Dehydration of the stratum corneum is signaled (*blue arrows*) to keratinocytes, perhaps via an osmotic gradient. (**D**) Keratinocytes are stimulated to produce cytokines (*red arrows*), which in epidermal-dermal signaling activate dermal fibroblasts to synthesize and release collagen. Excessive collagen production leads to abnormal scarring. (**E**) Treatment of the reepithelialized wound or the scar with silicone gel restores the barrier function of the stratum corneum, reducing TEWL and turning off the stimulation of keratinocytes. Keratinocytes stop producing cytokines that activate dermal fibroblasts. (**F**) After 2 to 3 months of silicone gel treatment, collagen deposition has normalized, and there is no scar hypertrophy.

In addition, TEWL is greater with hypertrophic scars and keloids than with atrophic scars or normal skin [41]. An increase in superficial skin water content measured by high-frequency conductance has been reported for these abnormal scars [41], although the changes in TEWL are more reliable and substantial. The stratum corneum of hypertrophic scars and keloids absorbs water more readily than normal skin [41], suggesting that the reservoir of water normally hydrating keratinocytes may be depleted. Abnormally high levels of water loss from the epidermis and dehydration of keratinocytes might stimulate these cells to produce cytokines that lead to changes in the dermis and increased collagen production by fibroblasts. In fact, in cultured keratinocytes exposed to a solution with high osmolarity (a model system for keratinocyte dehydration/dessication that occurs when the epidermal barrier is disrupted and TEWL is elevated), levels of proinflammatory interleukin mRNAs are increased [43]. These findings suggest a mechanism by which the hydration state of keratinocytes that could lead to signaling that affects fibroblasts production of collagen.

Although application of SGS to skin causes hydration of the stratum corneum, the extent of hydration is less than that produced by a plastic film, and the increase in hydration compared with normal skin decreases after repeated treatment [42]. These results have been interpreted to suggest that the semi-occlusive nature of SGS improves scars by providing adequate but not excessive hydration [42]. A plausible explanation for the mechanism of action of silicone-based products, therefore, is that occlusion causes a decrease in TEWL and normalizes the hydration state of keratinocytes, which then signal dermal

fibroblasts to downregulate extracellular matrix production (Fig. 2). This explanation is consistent with clinical findings that occlusion is essential for the efficacy of silicone cream and can have beneficial effects on abnormal scars even in the absence of silicone, and with *in vitro* findings of the interactions between keratinocytes and dermal fibroblasts.

If this hypothesis is correct, any product that provides occlusion may be beneficial in wound management, but the magnitude of occlusion may be critical and may differ between silicone products and other occlusive dressings, or even among silicone products. Dressings that are too permeable to water may be ineffective on scars because they fail to block water loss and restore homeostasis and normal epithelial-dermal signaling, whereas dressing that are too occlusive may cause skin maceration. Clinical studies [33] and studies using our rabbit hypertrophic scar model [34] may have found that occlusive dressings were less effective than SGS in scar management because the dressings used were more occlusive than SGS.

This suggested mechanism of action is consistent with the reported ability of silicone therapy to improve both old and new scars. Normal scars generally mature in 6 months, but hypertrophic scars take longer to mature, and keloids may continue to evolve for many years. To our knowledge, the time course for recovery of TEWL to basal levels in hypertrophic scars and keloids has not been studied, but it is likely to take years for TEWL to normalize in abnormal scars [41]. If TEWL remains abnormal throughout the course of scar maturation and the therapeutic effects of silicone therapy are mediated by occlusion, hydration, and normalization of TEWL, silicone products would be predicted to be effective in improving excessive scars that are several years old.

Perspective and Conclusions

Results from clinical trials and the rabbit hypertrophic scar model suggest that occlusive silicone-based products are similarly effective in reducing and preventing excessive scarring. The mechanism of action of these products is likely to be occlusion, and the similar occlusive properties of silicone gel and SGS explain their equivalent efficacy in scar management.

The similar mechanisms of action of silicone gel and SGS have been confirmed in the rabbit model. Although few comparative clinical data are available for many of the silicone-based products, to the extent that they have similar occlusive properties, their efficacy can be predicted to be similar, and indeed, the reported clinical studies suggest that silicone gel is at least as effective as SGS in scar management. All the products are safe. Minor side effects such as rash sometimes associated with SGS can be avoided by appropriate hygiene and care of the sheets. Therefore, factors beyond efficacy and safety that might be excepted to increase patient compliance with treatment and improve scar outcomes [39], such as greater ease of use, better acceptability to patients, and lower cost, should be considered when clinicians are choosing among the various products. Our clinical experience with silicone products has suggested to us that silicone creams with a sticky consistency are not well accepted by patients, but we have used silicone gel and SGS successfully with many patients.

Silicone gel currently is the preferred silicone therapy because silicone gel has fundamental advantages over SGS. For effective treatment, occlusion must be achieved by close apposition of the silicone product and the scar, and that is easier to achieve and more practical with silicone gel than with SGS, especially near joints and on areas with contours. Many patients object to the appearance of SGS and do not want to use it on visible areas not covered by clothing. In contrast, silicone gel is well accepted by patients because it forms a nearly invisible sheet and dries fairly quickly when applied correctly in a thin layer. The ability to use makeup over silicone gel to camouflage scars also is an advantage of the gel formulation for some patients.

Silicone therapy has a primary role in scar management. Although it may not be uniquely useful in this respect (non–silicone-based occlusive dressings also may be useful), a silicone-based product may represent the easiest way to achieve an effective level of occlusion in an inexpensive, nonirritating manner. The magnitude of occlusion provided by silicone therapy appears to be critical, because other occlusive treatments such as vaseline and plastic film have been shown to be ineffective in scar management, presumably because they do not provide an appropriate level of occlusion. Few studies have investigated the effects of moisturizers on abnormal scars. Notably, however, treatment of hypertrophic scars and keloids with a moisturizer has been reported to have no effect on scar elevation or erythema [32]. These findings lend support to the hypothesis that normalization of the skin's barrier function, and not simply hydration of the stratum corneum, may be an important component of the mechanism of action of silicone therapy in reducing abnormal scarring.

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REVIEW ARTICLE

Hypertrophic Scars and Keloids—A Review of Their Pathophysiology, Risk Factors, and Therapeutic Management

Dolores Wolfram, MD,* Alexandar Tzankov, MD,† Petra Pülzl, MD,* and Hildegunde Piza-Katzer, MD*

BACKGROUND Hypertrophic scars and keloids result from an abnormal fibrous wound healing process in which tissue repair and regeneration-regulating mechanism control is lost. These abnormal fibrous growths present a major therapeutic dilemma and challenge to the plastic surgeon because they are disfiguring and frequently recur.

OBJECTIVE To provide updated clinical and experimental information on hypertrophic scars and keloids so that physicians can better understand and properly treat such lesions.

METHODS A Medline literature search was performed for relevant publications and for diverse strategies for management of hypertrophic scars and keloids.

CONCLUSION The growing understanding of the molecular processes of normal and abnormal wound healing is promising for discovery of novel approaches for the management of hypertrophic scars and keloids. Although optimal treatment of these lesions remains undefined, successful healing can be achieved only with combined multidisciplinary therapeutic regimens.

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Hypertrophic scars and keloids are a problem that mainly dermatologists and plastic surgeons encounter. Especially in the head and neck region, these lesions are conspicuous and not easy for patients to conceal. Patients typically present with cosmetic concerns, although hypertrophic scars and keloids can also cause pruritus, pain, or pressure.[1] This article reviews various treatment modalities for aberrant wound healing and the updated findings of molecular scar biology.

Hypertrophic Scar Versus Keloid

Hypertrophic scars and keloids are abnormal wound responses in predisposed individuals and represent a connective tissue response to trauma, inflammation, surgery, or burns.[2] The first challenge to scar therapy begins with the simple identification and diagnosis of the problematic abnormal wound healing.[3] Hypertrophic scars are typically raised, red or pink, and sometimes pruritic but do not exceed the margins of the original wound, whereas keloids infiltrate into surrounding normal tissue and rarely regress (Figures 1 and 2). Hypertrophic scars usually subside with time, whereas keloids continue to evolve over time, without a quiescent or regressive phase.[2–5]

Aside from clinical features, histologic characteristics also help distinguish between hypertrophic scars and keloids. Normal skin contains collagen bundles running parallel to the epithelial surface. In hypertrophic scars, the primarily type III collagen bundles are flatter, with the fibers arranged in a wavy pattern but predominantly oriented parallel to the epithelial surface.[6–9] Furthermore, nodular structures in which alpha-smooth muscle actin (α-SMA)-expressing myofibroblasts, small vessels, and fine collagen fibers are present characterize hypertrophic scars

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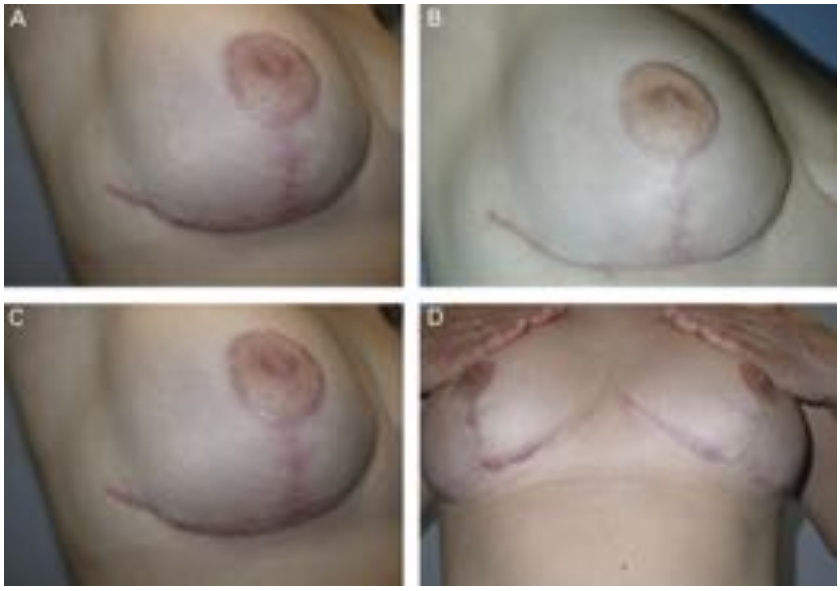

Figure 1. (A) Hypertrophic scars with intense itching 5 months after reduction mammoplasty. (B) 1 month after scar excision and suturing without resorbable suture. (C) 9 months postoperatively, the scars were hypertrophic again and were treated with corticosteroid injections. (D) Result after five cycles of corticosteroid therapy—25 months after surgery.

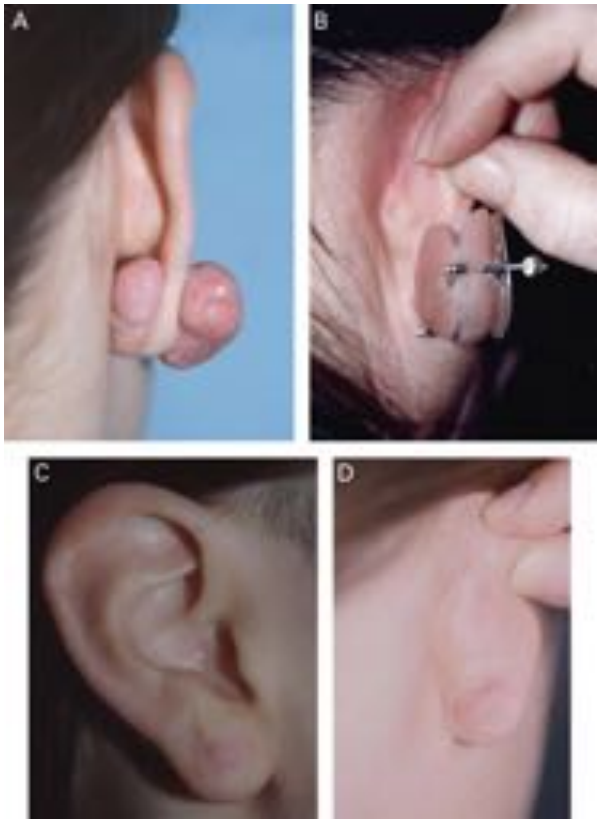

Figure 2. (A) Massive keloid formation after ear piercing. (B) Pressure therapy after keloid excision with a pressure clip. (C and D) Results 3 years after successful therapy.

(Figure 3A). In contrast, in keloids, collagen bundles are virtually nonexistent, and the collagen type I and III fibers lie in haphazardly connected loose sheets (Figure 3B) randomly oriented to the epithelial surface.[10,11] Overproduction of fibroblast proteins like transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF) in both abnormal wound responses suggests pathologic persistence of wound healing signals or failure of the appropriate down-regulation of wound-healing cells[12,13] (Table 1).

Normal Wound-Healing Process

Understanding the normal sequence of wound healing is important in understanding the pathophysiology and treatment of hypertrophic scars and keloids. Normal wound healing occurs in three phases: (1) the inflammatory phase, (2) the proliferative or granulation phase, and (3) the maturation or remodeling phase.

The initial inflammatory phase begins at the time of wounding, when activation of the coagulation cascade causes a release of cytokines that stimulate chemotaxis of unspecific immune cells (e.g., macro-

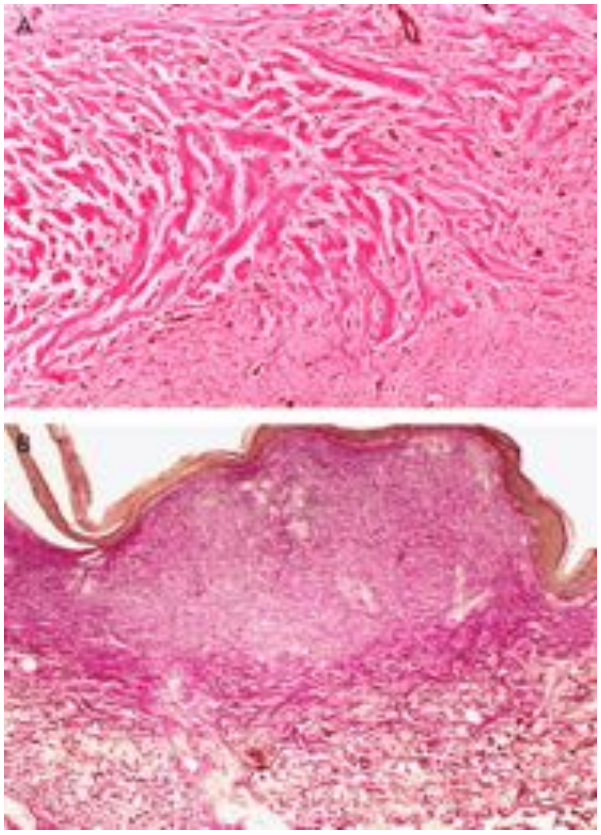

Figure 3. (A) Hypertrophic scar, overview, Van Gieson stain, × 20. Note a raised, nodular structure consisting of parallel collagen bundles. (B) Keloid, detail, hematoxylin and eosin stain, × 100. Note thick, haphazardly lying, nonoriented collagen bundles.

TABLE 1. Clinical Features of Hypertrophic Scars and Keloids

Hypertrophic Scars	*Keloids*
Develop soon after surgery	May develop months after the trauma
Usually improve with time	Rarely improve with time
Remain within the confines of the wound	Spread outside the boundaries of the initial lesion
Occur when scars cross joints or skin creases at a right angle	Occur predominantly on the ear lobe, shoulders, sternal notch, rarely develop across joints
Improve with appropriate surgery	Are often worsened by surgery
Are of frequent incidence	Are of rare incidence
Have no association with skin color	Are associated with dark skin color

phages and neutrophils) into the wound for early wound debridement. After 48 to 72 hours, the inflammatory process passes into the proliferative phase, which lasts for 3 to 6 weeks. Fibroblasts are attracted into the wound to synthesize granulation tissue. This granulation tissue is composed of procollagen, elastin, proteoglycans, and hyaluronic acid and forms a structural repair framework to allow vascular ingrowth. Myofibroblasts containing myofilaments (α-SMA, desmin) are responsible for physiologic wound contraction, and once a wound is closed, the immature scar can move on to the final maturation phase, which can last several months.[13–15]

A multitude of signaling molecules, including growth factors [TGF-β, PDGF, vascular endothelial growth factor (VEGF)], mitogen-activated protein (MAP) kinases, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs), regulate this complex process of wound healing on the molecular level (Figure 4). The effector molecules that link these regulatory signals and the various phases of wound healing are incompletely understood,[16–19] although it is known that a derailment in this complex wound-healing process contributes to hypertrophic scars and keloid formation.[3]

Pathophysiology of Hypertrophic Scars and Keloids

In the normal maturation phase, the nodularity and redness of the wound soften and flatten due to ongoing simultaneous collagen synthesis and degradation and the connective tissue elements regress after the third week.[2] In keloids, the collagen synthesis is approximately 20 times as great as that in normal unscarred skin and three times as great as in hypertrophic scars.[20,21] Abergel and colleagues showed that not only is collagen production high in hypertrophic scars and keloids, but the ratio of type I to type III collagen is also high.[22] Friedman and colleagues postulated that, in keloids, the downregulation of type I collagen synthesis is inefficient.[23] This collagen overproduction can be attributed to the stronger proliferating activity of keloid

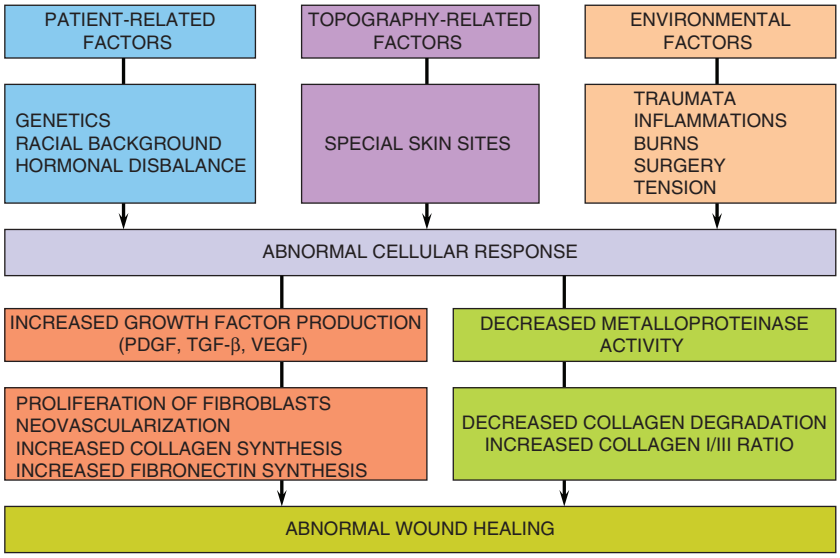

Figure 4. Pathogenesis of abnormal wound healing.

fibroblasts.[24] Aside from high collagen synthesis and proliferation of fibroblasts in keloids, Oliver and colleagues and Babu and colleagues found that keloid-derived fibroblasts show a rate of fibronectin biosynthesis that is as much as four times as high as that of fibroblasts from normal scars and normal dermis.[25,26]

Recent studies investigated the influence of various growth factors in scar and keloid formation. TGF-β and PDGF have been shown to play an integral role in the formation of hypertrophic scars and keloids. The majority of cells involved in wound healing express TGF-β in an inactive form that strongly promotes the chemotaxis of fibroblasts to the site of injury. Moreover, this growth factor plays a critical role in fibroblast proliferation and collagen production.[27] When wound repair is completed, the activity of TGF-β is normally turned off. In keloidal tissue, TGF-β is overproduced and poorly regulated through normal autocrine signaling mechanisms. At the same time, keloid fibroblasts have greater numbers of growth factor receptors and respond more intensely to growth factors such as TGF-β and PDGF.[15,28] Less synthesis of molecules that promote matrix breakdown (e.g., MMPs) may also explain the lack of scar regression seen in keloids.[13]

Furthermore, disturbed apoptosis mechanisms are discussed in the development of hypertrophic scars and keloids. Messadi and colleagues and Luo and colleagues demonstrated a significantly higher rate of apoptosis in normal skin fibroblasts than in keloidal fibroblasts.[29,30]

Etiology

Factors that play a major role in keloid development are genetic predisposition and some form of skin trauma.[2] Skin or wound tension has also been implicated as a critical factor in hypertrophic scars and keloids, as have been incisions beyond the relaxed skin tension lines.[31,32] Scars that cross joints or skin creases at a right angle are predisposed to form hypertrophic scars because of the constant tension forces that occur.[33] Although keloids can occur at any age, they tend to develop more readily during and after puberty.[2] Davies explained this fact by stating that younger individuals are more frequently subjected to trauma and their skin is more elastic than the skin of elderly persons.[34] The fact that keloids are 15 times as likely to occur in darker-skinned individuals points to genetic influences.[35] Keloid formation mainly occurs in parts of the body with high concentrations of melanocytes, and it is

rare on the soles and palms. Keloid formation has also been associated with endocrine factors. Menopause also prompts the recession of keloids, whereas women report keloid onset or enlargement during pregnancy.[21,36]

Prevention and Treatment

The most important factor in hypertrophic scar and keloid formation is prevention. Avoiding all unnecessary wounds, especially in keloid-prone patients, remains an obvious but imperfect solution.[3] All surgical wounds should be closed with minimal tension, incisions should not cross joint spaces, midchest incisions should be avoided, and incisions should follow skin creases whenever possible.[3,33,37] Especially in head and neck surgery, the esthetic subunits of the face must be considered for incision sites.[38] An atraumatic operation technique should be used, followed by efficient hemostasis, and wound closure should include eversion of the wound edges. It is also crucial to properly débride contaminated wounds and limit foreign bodies in the form of polyfilamentous sutures.[3] Particularly in the face, subcutaneous sutures should be used only when necessary. Furthermore, wound healing and the esthetic outcome of scar formation can be improved with massage or greasing ointments[38] (Figure 5).

Surgery for Hypertrophic Scars

For patients with hypertrophic scars from complicated (e.g., infected) wounds or delayed closure, simple excision is the therapy of choice. Scar revision as a treatment achieves two aims: excision and narrowing of scars as done for wide-spread scars and Z- or W-plasty designed to change the direction of the scar.[2,39] The extension of a reduced distance is the main principle of Z-plasty, and this surgical scar disruption turns the main axis of the scar parallel to

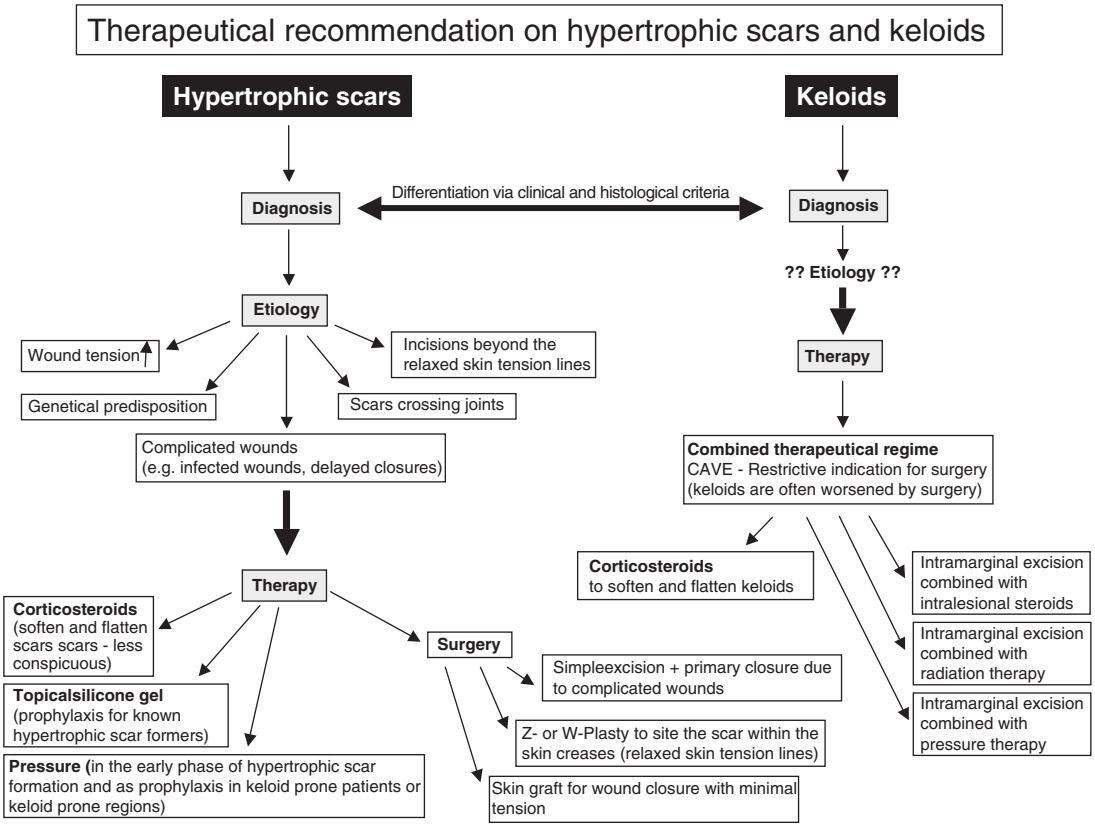

Figure 5. Therapeutic recommendation for hypertrophic scars and keloids.

skin creases.[2,39,40] Z-plasty is ideal in patients with hypertrophic scars crossing joints or wrinkle creases at a right angle, because this technique brings the new scar within the relaxed skin tension lines,[39] which ultimately improves healing. For the correction of facial scars, W-plasty seems to be optimal because every other scar shank can be positioned within the skin creases.[2,39,41] This therapeutic procedure causes a disruption of the scar that makes the lesion less conspicuous. Unfortunately, not all wounds after scar excision can be closed per primam. Especially in facial surgery, autologous skin transplants, namely full-thickness skin transplants or composite fat-skin grafts, are another valuable alternative to achieve wound closure with minimal tension.[42] The preferred donor sites for skin grafts used for facial defects are the retro- and preauricular sites, as well as the neck or the upper lid. From an esthetic point of view, the color match and texture of these near facial regions is superior to those of the upper arm and other donor sites[42] (Figure 1A–D).

Surgery for Keloids

Simple total excision of a keloid stimulates additional collagen synthesis, thus sometimes prompting quick recurrence of a keloid even larger than the initial one.[43,44] For this reason, intramarginal surgical excision of keloid tissue is recommended in order not to stimulate additional collagen synthesis.[45] Surgical excision of a keloid alone is associated with a high recurrence rate.[46–48] Thus, surgical therapy should be combined with adjuvant treatment such as pressure, corticosteroids, and radiotherapy. Kauh and colleagues demonstrated that surgical excision combined with steroid injection into the wound bed causes down-regulation of type I collagen gene expression without compromising wound healing.[49] If intralesional steroids are used postoperatively, we recommend leaving the sutures 3 to 5 days longer to prevent wound dehiscence. Nevertheless, surgical therapy for the treatment of keloids has been relegated mainly to second-line therapy for lesions unresponsive to steroids or pressure[20] (Figure 2A–D).

Pressure

The use of pressure to treat keloids was initially described in 1835,[50] although compression therapy was not popularized until the 1970s, when physicians noted that pressure stockings used on lower extremity burns resulted in scars that matured more rapidly, with less erythema and thickness.[51] The compression phenomenon is not well understood, but theories include the following:[50]

(1) a decrease in blood flow with a resultant decrease in α_2-macroglobulin and a subsequent increase in collagenase-mediated collagen breakdown, normally inhibited by α_2-macroglobulin,

(2) hypoxia leading to fibroblast degeneration and collagen degradation,

(3) lower levels of chondroitin 4-sulfate, with a subsequent increase in collagen degradation,

(4) decreased scar hydration, resulting in mast cell stabilization and a subsequent decrease in neovascularization and matrix production.

Histologic examination showed that pressure therapy in hypertrophic scars partly restores the extracellular matrix organization, like that observed in normal scar tissue, and induces the disappearance of α-SMA-expressing myofibroblasts, probably by apoptosis.[11] Recent studies have investigated presence of epilysin (MMP-28), a proteolytic enzyme expressed by keratinocytes in response to injury, in normal and hypertrophic scars and evaluated the effect of in vitro compression on its expression. Immunohistochemistry revealed a slight protein presence in normotrophic scar keratinocytes and strong positivity in hypertrophic scar keratinocytes, whereas compression therapy induced a significant reduction in this protein in hypertrophic scars.[52] Other experimental studies were able to show that tumor necrosis factor-α (TNF-α) release, which is significantly enhanced in hypertrophic scars, can be diminished with compression therapy, whereas the apoptosis rate can be strongly increased in hypertrophic scars with pressure.[53]

The part of the face most amenable to the use of pressure dressings is the ear lobe (Figure 2), and pressure clips are in common use for patients with ear lobe keloids.[54,55] Pressure therapy should be started immediately after reepithelialization of the wound, and patients should wear these pressure devices for continuous 8 to 24 hours a day for the first 6 months of scar healing.[2,3,56] The success rate depends largely on patient compliance.

Topical Silicone Gel

Topical silicone gel sheeting has enjoyed much popularity in the treatment of abnormal scars. First reported in the early 1980s, silicone therapy has recently been marketed for at-home use to improve the appearance of any scar.[3] It is recommended that these silicone sheets be worn at least 12 hours a day for a minimum of 2 months. The mechanism of action is unknown, but it has been suggested that the greater wound hydration achieved using occlusive therapy (silicone and non-silicone based) affects local keratinocytes to alter growth factor secretion and, secondarily, influences fibroblast regulation.[57–59] It is also believed that hydration decreases capillary permeability, inflammatory and mitogenic mediators, and collagen synthesis.[50] In patients who are known to be hypertrophic scar formers, topical silicone gel sheeting has a distinct effect in impeding the formation of abnormal scars in surgical incisions. Application of silicone gel sheets should begin as soon as reepithelialization is finished, and daily application for at least 12 hours is recommended,[54] although the exact duration needed for maximum benefit is unknown and requires further investigation.

Radiation

Debeurmann and Gougerot first described the use of X-rays for the treatment of keloids in 1906.[60] Later evidence showed that radiation therapy alone is inadequate for the treatment of keloids;[61] therefore, Cosman and colleagues introduced the use of post-excision radiation therapy as an adjunct to surgical excision.[62] The reported efficacy rate varied between 65% and 99% compared with excision alone.[63,64] It is suggested that radiation directly affects fibroblast proliferation by inducing apoptosis. The total dose recommended for the treatment of keloids varies from 15 to 20 Gy fractionated over five to six treatments.[3] The main drawback of radiation therapy, aside from hyperpigmentation, is the risk of radiation-induced malignancy, although only a few cases have been described, and large treatment cohorts with extensive follow-up have provided no evidence to substantiate the risk of carcinogenesis.[65,66] Nevertheless, radiation therapy is contraindicated in children, as well as in areas of high carcinogenic potential, namely the breast and thyroid.

Laser Therapy

Many laser types, including the carbon dioxide laser and the pulsed dye laser (PDL), have been tested for treatment of hypertrophic scars and keloids, with varied results.[67,68] The carbon dioxide laser, which is commonly used for skin resurfacing, has not been proven to be more effective in treating problem scars than are other methods.[3] The PDL is considered to be the criterion standard for vascular lesions, such as port wine stains, initial hemangiomas, and facial telangiectasias. Additionally, this laser type is often successfully used for non-vascular indications, such as keloids or hypertrophic scars.[69] Currently, the PDL wavelengths 585 and 595 nm are most frequently used for therapeutic purposes. Alster reported an average improvement of 57% after the first treatment and 83% after the second treatment with PDL for hypertrophic surgical and traumatic scars. In addition to a reduction in erythema, flattening, a clear reduction in itching and pain, and optimization of the skin texture have been observed.[70] The entire scar in each patient was exposed to PDL at a wavelength of 585 nm, a pulse duration of 0.45 ms, and a fluence of 6.5 to 7.25 J/cm^2. Recent biochemical studies suggest that 585-nm PDL treatment alters signaling pathways to favor collagen degradation and fibroblast apoptosis.[71,72] In contrast to the above-cited results, Chan and colleagues failed to show any clinical improvement using PDL

for hypertrophic scars. In 27 hypertrophic scars, one side of each of which was treated (585 nm, 7–8 J/cm^2, 2.5 ms, 5 mm), the authors documented no superiority of the treated half after three to six treatments regarding thickness and elasticity, although pain and touch sensitivity were far better on the treated side.[73] Several reports have shown a trend toward better clinical improvement using low to moderate fluences,[69] although laser therapy has not shown a clear advantage over cold scalpel excision, especially in keloids.[74,75]

Corticosteroids

Intralesional corticosteroid injections have become a mainstay in the treatment of hypertrophic scar and keloids, alone or in combination with other therapeutic procedures.[76] Corticosteroid application can soften and flatten keloids but cannot narrow hypertrophic scars or eliminate keloids.[2] Intralesional corticosteroid injection decreases fibroblast proliferation, collagen synthesis, and glycosaminoglycan synthesis and suppresses pro-inflammatory mediators.[40,50] We recommend beginning with direct serial intralesional corticosteroid injections in an already-developing keloid or hypertrophic scar. The most commonly used drug for steroid injection is triamcinolone acetonide (TA) at a dose of 5 to 10 mg/mL, which should be injected with a 25- to 27-gauge needle into the upper dermis of a developing hypertrophic scar[54] every 3 to 6 weeks. Injections are discontinued when the scar is stable, when surgical intervention is indispensable, or if side effects such as tissue atrophy, hypopigmentation or telangiectasia develop.[5] The treatment of preexisting keloids should begin with three monthly, intralesional injections of TA at a dose of 40 mg/mL mixed with equal parts of 2% lidocaine.[33,54] Some authors also recommend the addition of hyaluronidase, which helps to disperse the injection.[32]

Because tissue absorption through intact or sutured skin is poor, the use of topical steroids is indicated only for superficial lesions, such as those occurring from dermabrasion.[77]

Other Pharmacologic Therapies

5-Fluorouracil

Intralesional injection of the pyrimidine analog 5-fluorouracil (5-FU) has been investigated for the regression of keloids and hypertrophic scars. 5-FU targets rapidly proliferating fibroblasts in dermal wounds responsible for excessive collagen production.[27] 5-FU has been shown to be effective in the treatment of hypertrophic scars, whereas studies of intralesional 5-FU application have provided mixed results in keloids.[3] The injection can be painful, and purpura and ulcers have been documented.[39,78] 5-FU can also be combined with corticosteroids; Fitzpatrick was the first to report improved efficacy and less painful injections by mixing corticosteroids (triamcinolone acetonide) with 5-FU.[79] Apikian and Goodman found that the combination of 5-FU with corticosteroids has fewer undesirable side effects than intralesional corticosteroid injection alone.[80] This combined therapy provides also more rapid response.[81]

Imiquimod 5% Cream

Imiquimod 5% cream, a topical immune response modifier, is approved for the treatment of genital warts, basal cell carcinoma, and actinic keratoses.[82] Imiquimod stimulates interferon α, a proinflammatory cytokine, which increases collagen breakdown. Additionally, imiquimod alters the expression of apoptosis-associated genes.[83] Therefore, it has been used in an attempt to reduce keloid recurrence after excision. Berman and Kaufman reported positive effects on the recurrence rate of keloids after postoperative application in 12 patients.[84] By contrast, Malhotra and colleagues showed a complete recurrence of presternal keloids after keloid excision and after imiquimod therapy.[85] The role of imiquimod in the prevention of hypertrophic scars is under evaluation.

Onion Extract

Allium cepa, or onion extract, is found in numerous scar treatment products.[83] This "botanical" ingredi-

ent exhibited antiinflammatory, bacteriostatic, and collagen down-regulatory properties[86] and improves collagen organization in a rabbit ear model,[87] but three major clinical studies in the United States evaluating the effects of onion extract on human wound healing showed no evidence that this extract could be beneficial in improving hypertrophic scars. Products containing onion extract did not improve scar cosmesis or symptomatology any more than a petrolatum-based ointment.[83]

Interferons

Interferons are cytokines secreted by T-helper cells that, apart from other functions, suppress fibrosis. All interferon isoforms (α, β, γ) have been shown to reduce collagen and extracellular matrix production while increasing collagenase level but have been applied only experimentally and predominantly in small numbers of patients. Furthermore, the use of interferons is also associated with severe side effects, including fever, chills, night sweats, fatigue, myalgia, and headache.[88,89]

Immunotherapy

Immune modulators and antibody therapies are new in the context of problem scars. Commercial drugs like tacrolimus and sirolimus are known to affect cytokine activation, TNF-α, interferons, and interleukins, with wide-ranging effects on inflammation and cell-cycle regulation. Topically used, these drugs may suppress fibroblast activity and increase the apoptosis rate in keloids.[84] Anti-TGF-β antibody application use in animal models decreased scar hypertrophy and collagen contraction.[90] Further molecular investigations will yield more specific, probably gene-based, therapies that are designed not only to treat, but also to prevent problem scars.

Conclusion

The development of hypertrophic scars and keloids is a frustrating problem for the patient and the physician. Despite decades of research, the pathophysiology of aberrant wound healing remains incompletely understood, and the therapeutic interventions for such lesions often give inconsistent and suboptimal results. The appropriate planning of incisions and gentle handling of the tissue is indispensable in keloid prevention. A better understanding of growth factor functions, wound matrix degradation, and immune regulatory processes is beginning to elucidate the complex process of scar formation. These investigations will help to develop more specific therapies for treating and preventing problem scars.

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Topical treatments for hypertrophic scars

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Hypertrophic scars represent an abnormal, exaggerated healing response after skin injury. In addition to cosmetic concern, scars may cause pain, pruritus, contractures, and other functional impairments. Therapeutic modalities include topical medications, intralesional corticosteroids, laser therapy, and cryosurgery. Topical therapies, in particular, have become increasingly popular because of their ease of use, comfort, noninvasiveness, and relatively low cost. This review will discuss the properties and effectiveness of these agents, including pressure therapy, silicone gel sheeting and ointment, polyurethane dressing, onion extract, imiquimod 5% cream, and vitamins A and E in the prevention and treatment of hypertrophic scars. (J Am Acad Dermatol 2006;55:1024-31.)

The wound healing process consists of 3 stages—inflammation, granulation, and matrix remodeling.[1,2] The first phase, inflammation, produces exudate from damaged vessels that fills the wound. Neutrophils trigger an inflammatory cell cascade and macrophages phagocytose cellular and foreign debris. Subsequently, in the granulation phase, macrophages secrete cytokines that promote granulation tissue formation consisting of re-epithelialization, formation of an appropriate blood supply, and reinforcement of the injured tissue. In the final stage of wound healing, matrix remodeling, fibroblasts proliferate and deposit new collagen and matrix materials at the wound site. The remodeling process of collagen synthesis and lysis can last up to 2 years after tissue injury.

Hypertrophic scars, by definition, represent an exaggerated proliferative response to wound healing that stays within the boundaries of the original wound, in contrast to keloids, which have a more aggressive life cycle and extend beyond the original borders. Because the collagen found is in a disorganized, whorllike arrangement rather than in the normal parallel orientation, hypertrophic scars are indurated, elevated, and poorly extensible.[3] Hypertrophic scars are also characterized by hypervascularity, hence, their erythematous appearance.

Clinically, hypertrophic scars are raised, red, nodular lesions that occur most commonly in areas of thick skin. They frequently develop within 6 weeks of a burn, wound closure with excess tension, wound infection, hypoxia, or other traumatic skin injury.[1,3] Their normal course involves a rapid growth phase for up to 6 months that may be followed by regression during the next 12 to 18 months.[3]

Early recognition of the potential development of the hypertrophic scar is critical in its management. Because hypertrophic scars are often painful and difficult to treat, several treatments have been developed in the past several years in an effort to minimize tissue growth and wound contraction. This review will focus on pressure therapy, silicone gel sheeting and ointment, polyurethane dressing, onion extract, imiquimod 5% cream, and vitamins A and E in the management of hypertrophic scarring. A summary of these therapies and a selection of common commercial products can be found in Tables I and II, respectively.

PRESSURE THERAPY

Pressure therapy has been the preferred conservative management of scars since the 1970s, especially in treating hypertrophic scarring after burn injury. Pressure therapy is influential primarily while the scar is active and, therefore, loses some efficacy after 6 months of treatment.[4] The garments are typically custom-made from an elastic material with a high spandex content and are intended to be worn for approximately 1 year until the scar matures.[5] To prevent a decrease in elasticity, garments should be changed every 6 to 8 weeks. Drawbacks of compression therapy include its limited use in anaerobic depressions, fissures, or areas of high movement; patient discomfort; the need to be

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Table I. Topical scar therapies

Product	Preparation	Use	Pros	Cons	Summary of literature findings	Overall efficacy
Pressure therapy[4,11]	Custom-made elastic compression garment	Worn all day until scar is mature; new garment made every 6-8 wk	Low cost	Limited use on face, anatomic depressions, or high-motion areas; low patient compliance; subjective pressure measurements; side effects of local skin maceration	Long-standing preferred conservative management but few studies have documented optimal pressures and dose	+
Silicone gel sheeting[5,14,15]	Soft, extensible fabric, or nonfabric gel sheet	12-24 h/d for 2-4 mo	Easy to use, more effective than silicone gel alone	Cumbersome application, especially in areas of movement; side effects of superficial maceration	Strong evidence supporting effectiveness in preventing and treating hypertrophic scars	+ +
Polyurethane dressing[16-20]	Self-adhesive, flexible polyurethane pad	12-24 h/d for 2-4 mo	Breathable	Cumbersome application, especially in areas of movement	Equivocal evidence supporting effectiveness in preventing hypertrophic scars and some evidence that improves mature scars	+/−
Onion extract[21-24]	Transparent topical gel	3-4 times/d for 8 wk on new scars (after wound closure) and 2-6 mo on old scars	Good for exposed areas, widespread availability	Few documented effects on scars	Long-term use in Europe but studies in United States show no benefit in scar appearance	−
Imiquimod 5% cream[25-27]	Cream	Once every 1-4 d for 8 wk	Infrequent application	Side effects of acute inflammatory reaction (pruritus, erythema, burning); prescription only; costly	Strong evidence in treating keloids with preliminary data showing similar effects in hypertrophic scars	+
Topical vitamin A[28-31,33]	Various creams	Daily application; no established duration	Easy to use, good for exposed areas	Potential systemic absorption causing hypervitaminosis or birth defects	Limited data that may improve hypertrophic scarring but side effect profile limits use	+/−
Topical vitamin E[28-31,37]	Various creams	Daily application; no established duration	Easy to use, good for exposed areas	Side effects of contact dermatitis and theoretic scar widening	Moderate evidence that does not improve or may worsen appearance of scars	−

Studies have shown −, no adequate benefit; +/−, equivocal results; +, some benefit; + +, marked benefit.

worn at all times and occasional skin ulceration from uneven pressure distribution. For these reasons, patient compliance can be a major problem, with reports of noncompliance ranging from 8.5% to 59%.[4,7]

Pressure treatment is believed to accelerate wound maturation by several mechanisms, namely a thinning of the dermis, decrease in edema, and a reduction of blood flow and oxygen.[4] The hypoxic environment is hypothesized to decrease collagen formation and increase collagen lysis and loosen the collagen fibrils aligned to the skin surface, thereby more closely approximating the elastic requirements

of the skin.[4,5,8,9] This hypothesis remains controversial, however, as other studies have shown that qualitative improvements in scar tissue receiving pressure therapy correlate with increased blood flow.[4,10]

A fair body of evidence supports the use of compression therapy but literature is generally lacking in reports on effectiveness and optimal pressures. The consensus is that an applied pressure of 25 mm Hg may represent ideal loading,[11] but more recent studies suggest that good clinical results may be achieved at much lower compression levels.[12] However, given that most often this measurement is made clinically by the therapist together with feedback from the patient, pressure measurements are subjective and not standardized.[13] Overall, there is some evidence to support that compression therapy may be effective but more definitive research is needed to evaluate the most optimum parameters.

SILICONE GEL SHEETING AND OINTMENT

Silicone, a soft, semiocclusive scar cover, is composed of cross-linked polydimethylsiloxane polymer that has extensibility similar to that of skin. Since its introduction in 1982, topical silicone gel sheeting and ointment have been used widely to minimize the size, induration, erythema, pruritus, and extensibility of pre-existing hypertrophic scars and to prevent the formation of new ones. Numerous formulations exist, in addition to several gels and ointments (Table II).

The therapeutic effect of topical silicone gel sheeting on pre-existing hypertrophic scars is well documented.[3,14-26] Although there have been several uncontrolled clinical reports stating that silicone gel sheeting promotes resolution of hypertrophic scars,[5,16,21-26] a number of more valid controlled studies exists.[14-17,19,20,26,28] For example, in a controlled trial of 20 patients who had either evolving hypertrophic scars or keloids, silicone gel sheeting stopped the development of and softened evolving hypertrophic lesions in 85% of cases.[15] Silicone gel sheeting has also been shown to significantly improve elasticity of old scars between 1 and 6 months after treatment when compared with untreated scars.[14,16]

Silicone sheeting also helps minimize new hypertrophic scarring when applied about 2 weeks after wounding.[15,16,19,20,26,27,29] Gold et al[27] showed that in patients at high risk—those who had a significant history of hypertrophic scar or keloid formation after a surgical procedure—29% developed hypertrophic scars after silicone gel sheeting whereas 44% developed hypertrophic scars after routine postoperative care. This finding provided only marginal evidence ($P = .072$) that the proportion of patients developing abnormal scars was lower in the topical silicone gel sheeting group. However, of those patients at high risk who underwent scar revision there was a significant statistical difference ($P = .035$) that topical silicone sheets are effective in reducing the development of abnormal scars after surgical excision. Katz[21] supported these findings in an examination of 14 patients with 14 hypertrophic scars less than 3 months old. Nine patients had long-standing hypertrophic scars that were completely excised and sutured with silicone sheeting soon after re-epithelialization. Five patients had a history of hypertrophic scar formation and were given silicone sheeting within 2 months of operation to prevent recurrence. In 11 of these cases (79%), hypertrophic scars did not recur after at least 6 months of follow-up.

The mechanism of silicone gel sheeting remains unclear, although several hypotheses exist. Studies have shown that silicone sheets do not change pressure, temperature, or oxygen tension at the wound site.[30,31] Silicone sheets have an evaporative water loss almost half that of skin and have been compared with the stratum corneum. Most researchers believe that silicone acts by creating a hydrated, occluded environment that decreases capillary activity, thereby reducing fibroblast-induced collagen deposition and scar hypertrophy.[32,33,35] Silicone sheets decrease hyperemia and eliminate fibroblast production of collagen and promote wound flattening.[20] Interestingly, the use of silicone cream alone compared with silicone cream with occlusive dressing showed 22% and 82% scar improvement, respectively, with respect to erythema, tenderness, pruritus, and hardness.[35] These results supported that occlusion may be synergistic in wound healing and suggested that silicone gel alone may not be as effective as silicone sheeting.

Wounds treated with silicone gel sheeting have negligible amounts of silica in histologic sections. Therefore, the presence of silicone fluid may not be necessary.[1,2,19] A randomized controlled study showed that silicone gel dressings and nonsilicone gel dressings were equally effective in improving size, induration, and color of hypertrophic scars.[37] In another study comparing a silicone-free cream and occlusive dressing with petrolatum alone, scar improvement was significantly greater in the cream-occlusive dressing group with respect to pruritus, pain, hardness, elevation, and erythema,[38] further supporting this hypothesis.

In summary, silicone gel sheeting is efficacious, both in minimizing the severity of hypertrophic scars in fresh wounds and in promoting the resolution of pre-existing hypertrophic scars. Silicone ointment

Table III. Selected products and features

Type	Product	Features	Product size
Silicone gel sheets	Cica-Care gel sheeting (Smith and Nephew, Largo, Fla)	Thin, self-adhesive flexible gel sheets	5- × 2.375-in sheet, 1 count
	Epi-derm (Biodermis, Las Vegas, Nev)	Soft, semitransparent sticky sheets; variety of configurations available (standard and large sheets, areola circles, mastopexy strips, C-strips)	Various sizes
	Scar solution (Neosporin, Morris Plains, NJ)	Skin-toned, thin, self-adhesive sheets that last 4 d	2.75- × 1.5-in sheets, 28 count
Silicone gel	Kelo-cote (Advanced Bio-Technologies, Silverdale, Wash)	Odorless, thick, colorless, fast-drying clear gel; once-daily application; suitable under cosmetics	15-g tube
	Scarfade Scar Gel (Nielsen-Medical, Kingston, Wash)	Oily transparent gel	15-g tube
	ScarGel (Derma, Weir, Tex)	Oily transparent gel	15-g dispenser
Silicone ointment	Xeragel Ointment (Biodermis)	Designed to work in conjunction with Epi-Derm sheets and SilquaClenz scar and sheet cleanser	10-cm^3 tube
	Pro-all (Biodermis)	Similar to Xeragel, but in glide-on compact applicator	4.25-g stick
Polyurethane dressing	Scar therapy (Derma, Wilton, Conn)	Self-adhesive, flexible, and breathable pads; available in skin-toned or clear formulations	2.75- × 1.5-in sheets, 20 count
	Cuticura thin dressing (Smith and Nephew)	Self-adhesive, flexible, breathable, semitransparent pads; maintain a moist wound environment and help prevent bacterial contamination	6- × 8-in pads, 3 count
Onion extract	Mederma (Merz Pharmaceuticals, Greensboro, NC)	Greaseless, pleasant-smelling clear gel; new separate lid-friendly preparation	20- or 50-g tube
	Scar gel (Derma E, Simi Valley, Calif)	Light-textured gel	56-g container
Imiquimod 5% cream	Aldara	Pleasant-smelling cream	By prescription

or gel, although more convenient and suitable for exposed areas, is less effective than silicone sheeting.

POLYURETHANE DRESSING

Polyurethane dressing is a self-adherent, flexible, hydroactive pad that should be worn 12 to 24 h/d for a minimum of 8 consecutive weeks.[30] Advantages of this form of treatment are its availability as clear pads for use on exposed areas such as the face or hands and low incidence of skin maceration because of the pads' evaporative properties. Polyurethane occlusive dressings act by creating a moist wound-healing environment that may promote re-epithelialization and dermal extracellular matrix synthesis and, hence, decrease scarring.[31,32] Despite the theoretic risk that a moist environment is associated with a higher risk of wound infection, studies have shown that occlusive dressings do not increase the incidence of infection.[33,34]

Hydroactive dressings have been shown to prevent the formation of hypertrophic scars.[30,35] A pilot study of 60 patients noted significant improvements in microcirculation and surface qualities in patients who were treated with polyurethane dressing for

6 weeks after surgical incisions when compared with other patients who were randomized to receive either dry gauze dressing until removal of the sutures, hydroactive dressing until removal of the sutures, or dry gauze dressing until removal of sutures followed by hydroactive dressing for 6 weeks.[35] In another study of 60 patients with acute facial lacerations, a 5-day course of polyurethane dressing after acute skin injury—despite initially showing significantly improved comfort, less erythema, and less potential for scarring when compared with dry gauze—showed negligible differences between the dry gauze control group after 2 months.[35] This suggested that the magnitude of benefit from occlusive dressings may depend on long-term treatment.

Polyurethane dressing also reduces color, prominence, and hardness of mature hypertrophic scars.[36,38] In a comparative study in which 82 patients were randomized to 4 groups (hydroactive polyurethane dressing alone, polyurethane plus compression, silicone sheeting plus compression, and compression alone for 24 h/d for 6 weeks), the most pronounced effects were achieved with either polyurethane dressing plus compression or silicone sheeting plus compression.[35] Polyurethane plus compression was slightly superior to silicone plus compression in reduction of surface roughness. These effects lasted for at least 1 year after the termination of therapy. Furthermore, polyurethane dressing alone was found to provide functional and structural improvement in scar tissue that was slightly superior to that obtained from compression alone. It was speculated that scar dressings and compression may promote dynamic shear forces needed for tissue reorganization.

Currently, polyurethane dressing has unclear effects on the development of new hypertrophic scars but has been shown to improve the prominence and appearance of mature scars in a small randomized trial. Further studies are necessary to elucidate its role in hypertrophic scar treatment.

ONION EXTRACT

Allium cepa, or onion extract, is found in a number of scar treatment products. Patients, in particular, value this remedy because of its ease of use, relatively low cost, "botanical" ingredients, and widespread availability. Onion extract exhibits anti-inflammatory, bacteriostatic, and collagen down-regulatory properties[36] and improves collagen organization in a rabbit ear model.[39]

Documented clinical studies of onion extract have shown that onion extract does not improve hypertrophic scarring. To date, there have been 3 major controlled clinical studies in the United States on the effect of onion extract on human wound healing.

One clinical trial evaluating onion extract in the prophylactic treatment of 17 scars after Mohs micrographic surgery showed no statistically significant difference between pretreatment and posttreatment evaluations of erythema and pruritus after 1 month of 3-times daily applications of onion extract gel.[38] In fact, a significant reduction in scar erythema was demonstrated in control patients who used a petrolatum-based ointment for 1 month, possibly because of the effects of petrolatum on scar hydration.

Another randomized, double-blinded trial evaluating 57 patients with new and old scars who were assigned to a Mederma treatment group or placebo gel control group for 2 months showed similar results. Scar changes were measured using 6 categories of scar size, overall improvement, noticeable appearance, elevation, erythema, and softness. The only significant advantage in the treated group was the patient-reported improvements of a softer, less noticeable scar at 2 months.[39] There were no notable differences with respect to physician-measured appearance and also nor patient-measured erythema and elevation. More patients in the placebo group than treated group reported improvement with a less noticeable scar at 1 week and a less red scar after 1 month. The study's short follow-up time of 2 months, however, was a limitation of this study.

The most recent randomized, double-blinded, split-scar study of 24 patients with new surgical wounds also demonstrated that onion extract gel did not improve scar appearance, erythema, and hypertrophy when compared with a petrolatum-based ointment.[40] Before enrollment, each patient tested negatively for an allergic reaction to both treatments by a 48-hour patch test on the forearm. Each scar half then received either the onion extract or petrolatum ointment 3 times daily for 8 weeks. The scars were evaluated by blinded investigators and patients at 2, 8, and 12 weeks after initiation of treatment and by blinded patients at 11 months postoperatively. None of the scars became hypertrophic at 11 months, but it was uncertain whether the patients would have developed abnormal scarring without treatment. One limitation of this study, however, was that all the patients were elderly Caucasians, a group inherently at lower risk for hypertrophic scarring than patients who are younger and have darker skin.

In summary, despite the wide use of onion extract by patients, there is no evidence that it is beneficial in improving hypertrophic scars. In the few studies conducted to date, more patients in the petrolatum control group reported greater improvements in

wound healing when compared with those who used onion extract.

IMIQUIMOD 5% CREAM

Imiquimod 5% cream, a topical immune response modifier, is approved for treatment of genital warts, basal cell carcinoma, and actinic keratoses.[41] Imiquimod stimulates proinflammatory cytokines, especially interferon-α, which generate a cell-mediated immune response. Interferon-α increases collagen breakdown. In addition, imiquimod alters the expression of genes associated with apoptosis.[41] Therefore, imiquimod has been used in an attempt to reduce keloid recurrences after excision.[42,43]

Because of the success of imiquimod 5% cream in lowering keloid recurrences after operation, its role in the prevention of hypertrophic scars is currently under evaluation. A recent randomized, double-blinded study of 15 patients investigated the use of imiquimod 5% cream in the prevention of hypertrophic scarring after breast operation.[44] Treatment with imiquimod consisted of gently rubbing the cream over the scar for 3 to 5 minutes once every 3 to 4 days for a period of 8 weeks. At 24 weeks postsurgery, imiquimod treatment improved scar quality, especially color and elevation, when compared with two control groups (no treatment and treatment with petrolatum.) There was an absence of hypertrophic scars and keloids in the imiquimod group, although this might have been related to the small sample size. Of note, all patients in the treatment group experienced an inflammatory response characterized by erythema, local pain, and pinpoint bleeding. This response allowed "blinded" physicians to distinguish between treatment and control groups that may have biased the results.

In summary, imiquimod has been shown to improve hypertrophic scar quality after operation in a preliminary small, randomized, prospective clinical trial, but additional studies with a larger sample size and longer follow-up are necessary to determine the role of imiquimod 5% cream in hypertrophic scar therapy.

VITAMIN A

Vitamin A is required to maintain the integrity of epithelial and mucosal surfaces. Based on the observation that oral vitamin A improved the appearance of keloid scars,[45] it has been tested in the form of 0.05% retinoic acid in wound healing. Daily application of retinoic acid to intractable hypertrophic and keloid scars has been shown to reduce size and pruritus[46] and cause scar softening, flattening, and fading of color.[47] In a randomized, double-blind study, Daly et al[48] demonstrated a statistically significant 30% reduction in scar size in the 0.05% retinoic acid treatment group compared with the base cream control group. A more recent study of a different form of vitamin A, 0.25% tocopheranyl retinoate, showed marked decreases in the size, stiffness, erythema, and pruritus in all mature hypertrophic scars.[49] Only 4 hypertrophic scars were examined, however, making these data preliminary.

Vitamin A treatment has its downsides, however. As topical retinoids may be absorbed systemically, hypervitaminosis and teratogenicity are potential complications of this form of therapy and, therefore, limit its use, especially in pregnant women and people who take oral vitamin supplements.

In general, sufficient data are lacking on the efficacy of topical vitamin A on hypertrophic scarring and its use may be associated with side effects. Vitamin A should, therefore, not be recommended.

VITAMIN E

Vitamin E (tocopherol), a lipid-soluble antioxidant, has complex effects on wound healing.[50] It has been shown to penetrate into the reticular dermis and reduce the formation of oxygen radicals that impede healing and damage DNA, cellular membranes, and lipids. Vitamin E also alters collagen and glycosaminoglycan production and inhibits the spread of peroxidation of lipids in cellular membranes, thereby acting as a membrane-stabilizing agent.[50,51]

Despite numerous anecdotal reports claiming that vitamin E speeds wound healing and improves the cosmetic appearance of scars, little scientific evidence exists to support these claims. Jenkins et al,[52] in an attempt to reduce scarring after reconstructive surgery in patients with burn, used topical vitamin E in the postoperative period. No significant differences were found in range of motion, scar thickness, change in graft size, and overall cosmetic appearance between the vitamin E treatment group and base cream control group 1 year after surgery. In addition, 20% of patients reported local reactions to the vitamin E cream. A subsequent double-blind, placebo-controlled clinical trial evaluating patients who applied emulsion with vitamin E and emollient alone to each half of their scar from Mohs micrographic surgery (twice daily for 4 weeks starting soon after surgery) also demonstrated similar results. Twelve weeks after surgery, vitamin E did not help in improving the cosmetic appearance of scars or was detrimental in appearance in 90% of cases.[53] A high incidence (33%) of contact dermatitis was noted. Limitations of the study included the use of the d-α-tocopheryl form of vitamin E, which has been widely associated with contact dermatitis, and

the potentially diluted concentration of topical vitamin E (one crushed capsule of 320 IU in 1 g of emollient).

The use of vitamin E in scar management has other theoretic limitations. Because of its ability to inhibit collagen synthesis, the use of vitamin E early in scar therapy may reduce scar tensile strength and, hence, lead to the development of widened scars and even wound dehiscence.[illegible]

When used in conjunction with silicone gel sheets, however, vitamin E has been shown to improve pre-existing hypertrophic scars. In all, 38 patients (95%) who received silicone gel sheets with added vitamin E improved by at least 50% with respect to color, size, and cosmetic appearance, whereas only 30 patients (75%) using silicone gel sheets alone improved at least 50% after 2 months of treatment.[illegible] This study led to the conclusion that the combination of vitamin E and silicone gel sheeting is beneficial in hypertrophic scar treatment, possibly as a result of a synergistic effect.

In conclusion, the evidence that topical vitamin E alone improves the cosmetic appearance of scars is poor. It is also associated with a high incidence of contact dermatitis. The use of vitamin E should, therefore, be discouraged.

DISCUSSION

Studies of scar treatments to date are limited for a number of reasons. A suitable animal model is lacking. Many studies on scar treatments did not use controls,[illegible] used other confounding methods such as pressure or intermittent corticosteroid injections,[illegible] or applied different methods of scar assessment, making it difficult to evaluate the precise effects of each topical treatment. The studies also varied in the ages of scars studied and used different control protocols, such as no treatment or emollient massage. Another long-standing issue has been the difficulty to quantitatively measure certain subjective scar parameters, such as color, induration, or pruritus. Given the long-term and sometimes cumbersome nature of scar treatment, patient compliance has also been problematic. Finally, because of the unclear clinical distinction between hypertrophic scars and keloids, several studies combined the two entities[illegible]; however, these two scar types have very different histologic features, growth patterns, and responses to treatment. On this note, because hypertrophic scars sometimes spontaneously regress, the beneficial qualities attributed to the various treatments may actually be partially caused by natural healing.

Several other topical treatments that are occasionally used in an attempt to minimize hypertrophic scars lack enough scientific data regarding their effect on this type of scar. Such topical therapies include aloe vera, vitamin C, corticosteroids, and tacrolimus. A new patent-pending product, a botanical QR340 formula (Quigley Pharma, Doylestown, Pa), has preliminarily demonstrated higher efficacy than Mederma and placebo in hypertrophic scar improvement. Further studies are necessary to determine these products' role in hypertrophic scarring.

In conclusion, there is no single, optimal modality that can eliminate or prevent hypertrophic scarring. Currently, the most accepted treatment for old and new hypertrophic scars is silicone gel sheeting. Silicone ointment or gel alone, however, is less effective than silicone sheeting. Pressure therapy has demonstrated some efficacy but is cumbersome and not standardized. Polyurethane dressing has equivocal effects on the development of new hypertrophic scars but may improve the appearance of mature scars. Products in the United States containing onion extract do not improve scar cosmesis or symptomatology when compared with a petrolatum-based ointment. Imiquimod 5% cream has been shown to improve the quality of new hypertrophic scars after surgery in a preliminary clinical trial, but further studies are necessary. Vitamin A lacks sufficient data and may be associated with side effects, especially in pregnant women. Finally, vitamin E alone may be detrimental to wound healing and often leads to contact dermatitis; it should, therefore, not be recommended.

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