SPECIAL TOPIC

Scientific Review

Mechanical Receptor–Related Mechanisms in Scar Management: A Review and Hypothesis

Caglayan Yagmur, M.D.
Satoshi Akaishi, M.D., Ph.D.
Rei Ogawa, M.D., Ph.D.
Ethem Guneren, M.D.

Samsun, Turkey; and Tokyo, Japan

Background: The physiopathogenesis of proliferative scarring in human skin is not well understood. Furthermore, knowledge of the precise mechanisms of action for physical treatment modalities is limited. Compression garments, occlusive/adhesive skin taping, and silicone gel sheets are applied to form an occlusion on the scar surface, reduce tension, and/or increase pressure on the scar itself. The mechanisms by which the external or superficial actions of these treatments cause remission of a protruding scar may be related to mechanoreceptor (nociceptor and cellular mechanoreceptor) responses.

Methods: Basic research studies about mechanoreceptor-related (nociceptors and cellular mechanoreceptors, separately) events are reviewed and discussed based on proliferative scarring background. Scar management–related studies were corrected from the standpoint of mechanotransduction mechanisms. The methodologic quality of the clinical trials and basic studies was evaluated and reviewed.

Results: It was suggested that many of the physical scar management methods, including compression therapy, silicone therapy, adhesive tape, and occlusive dressing therapy, are related to mechanotransduction mechanisms.

Conclusions: A unifying perspective of basic research findings and clinical observations may be obtained by considering the mechanoreceptor-related events in scar management. Moreover, a precise understanding of the roles that cellular mechanoreceptors and mechanosensitive nociceptors play in proliferative scarring may lead to the development of innovative treatment strategies and new pharmacologic therapies targeting cellular mechanoreceptors and mechanosensitive nociceptors in fibroproliferative diseases. (*Plast. Reconstr. Surg.* 126: 426, 2010.)

The physiopathogenesis of proliferative scarring of human skin, such as keloids and hypertrophic scars, is not well understood.[1,2] Extensive experience with treatments such as surgery, radiotherapy, laser therapy, brachytherapy, cryotherapy, and intralesional cytotoxic/antiproliferative regimens may add to the confusion. Several physical treatment modalities that do not result in abrupt biochemical and/or physical alterations in the scar environment, such as compression garments, occlusive and adhesive skin taping, and silicone application, can be effective for the prevention and treatment of proliferative scarring, although there are racial differences in the responses to these treatments.[3–16] The aim of the present review was to explain the unclarified mechanobiological actions of these physical treatment modalities for scarring, including mechanoreceptor-related and mechanosensitive nociceptor-related cellular events, and to provide a better explanation of the mechanisms underlying proliferative scarring.

MECHANICAL FORCE AND PROLIFERATIVE SCARRING

The sensory nerves in skin are divided into low-threshold mechanoreceptors, thermoreceptors, and nociceptors, according to their neurophysiologic

From the Departments of Plastic, Reconstructive, and Aesthetic Surgery of Ondokuz Mayis University Medical School and Nippon Medical School Hospital.
Received for publication October 5, 2009; accepted January 29, 2010.

DOI: 10.1097/PRS.0b013e3181df715d

Disclosure: *The authors have no commercial associations, supporting funds, or financial disclosures that might pose or create a conflict of interest with information presented in this article.*

characteristics.[17] Large myelinated Aβ fibers are low-threshold mechanoreceptors that are mainly related with encapsulated endings (Ruffini, Meissner, Krause, and Vater-Pacini corpuscles). Nociceptors are mainly high-threshold C fibers and Aδ fibers that transduce painful sensations.[18,19] Activation of nociceptive nerve endings (nociceptors) in the skin generates action potentials that are conducted to the spinal cord and, after processing of this nociceptive information, a sensation of pain or itch is generated in the central nervous system. Unmyelinated C fibers and lightly myelinated Aδ fibers also serve as thermoreceptors.

Unlike Aβ and Aα fibers, nociceptive C and Aδ fibers are polymodal, responding to a variable range of stimuli, including mechanical force.[17,18] Moreover, as action potentials also retrogradely invade the arborizations of the primary afferent neuron (axon reflex), C and Aδ fibers release neuropeptides from their terminals that are capable of inducing an inflammatory response (neurogenic inflammation).[18,20–25] This potential efferent function of skin afferent nerve fibers was first described by Bayliss in 1901.[26] Bayliss demonstrated that skin vasodilatation occurred after antidromic (anterograde) electrostimulation of the dorsal sensory root, and various neuropeptides responsible for this efferent function have been identified.[27–29]

Neuropeptides mediate communication among free nerve endings, immune cells, and skin cells.[23,30,31] After they are synthesized in the soma, neuropeptides are transmitted to nerve endings through accelerated axonal transport.[32] Many types of human skin cells have neuropeptide receptors, and when neuropeptides are released into the extracellular matrix, they cause capillary leakage and vasodilatation in endothelial and smooth muscle cells. The interaction of neuropeptides with mast cells and leukocyte subpopulations to release histamine and various inflammatory mediators has been reported.[24,33–35] Neurogenic inflammation may play a role in the physiopathogenesis of proliferative scarring.[20–22,36] In addition to their inflammatory role, neuropeptides also have a direct fibrinogenic effect,[24,37–39] and a change in neuropeptide metabolism or concentration may affect fibroblast proliferation and activity. In 2008, Akaishi et al.[20] used computer simulation to demonstrate the relationship between mechanical forces and the keloid growth pattern. They hypothesized that mechanical forces, including stretching of the skin, stimulate mechanosensitive nociceptors on the sensory fibers of the skin. Moreover, Chin et al.,[40] in an in vivo study, demonstrated that cyclical mechanical stretching of murine skin, using a computer-controlled system, resulted in a significant increase of neuropeptides.

Cellular mechanotransduction is the process by which cells sense mechanical forces and transduce them into intracellular biochemical and gene expression.[22,41] Many types of molecules, cellular components, and extracellular structures have been shown to contribute to mechanotransduction. These include the extracellular matrix, cell–extracellular matrix adhesions (integrins and focal adhesions), cell-cell adhesions (cadherins and gap junctions), membrane components, specialized surface processes, cytoskeletal filaments (microfilaments, intermediate filaments, and microtubules), and nuclear structures.[42–45] Perceived stimuli directly affect secondary signaling pathways, thereby altering cellular function or inducing apoptosis.[46–48]

Based on the importance of "tensional prestress" for "cell shape stability," Dr. Donald Ingber proposed that living cells use "tensegrity" (tensional integrity) architecture to control their shape and structure. Tensegrity is used by cells to mechanically integrate and stabilize the interconnecting cytoskeleton filament system (microfilaments, intermediate filaments, and microtubules).[45,49,50] Transmembrane adhesion receptors, such as integrins, mechanically couple the cytoskeletal network to the immobilized extracellular matrix molecules.[45] Integrins connect to the cytoskeleton through focal adhesions that contain multiple actin-associated proteins such as talin, vinculin, paxillin, and zyxin.[51] This interconnected structure, which is based on extracellular matrix receptors (i.e., integrin), may serve as a "tent peg" to sense the mechanical force.[49]

Stretch-sensitive membrane cation channels in mechanosensory nerves and muscle cells convert mechanical energy into electrical action potentials, which are either propagated or transformed into chemical signals.[52] For nonexcitable cells such as fibroblasts, there is increasing evidence that mechanical stimulation can be converted directly into chemical signaling.[53] Besides instant chemical signaling, mechanical strain to fibroblasts also increases fibrotic gene expression. Derderian et al., using an in vitro model consisting of cultured normal human dermal fibroblasts embedded in a type I collagen lattice, demonstrated that graded tension generates reproducible load-dependent changes in fibroblast morphology, matrix protein mRNA levels, and matrix metalloproteinase-1 secretion.[54] Wang et al., also applying in vitro mechanical strain, compared normal dermis fibroblast and keloid fibroblast cultures and demonstrated a differentially increased transcriptional response for transforming growth factor-β1 and transforming growth factor-β2 in keloid fibro-

blasts, as compared with normal fibroblasts, which was correlated with increased protein levels.[55]

Other than the numerous in vitro studies demonstrating the effect of mechanical strain on fibroblasts, Aarabi et al.[56] reported results of an in vivo study in which timed tensional load was applied to a wound model. Using this novel model in rats, they were able to obtain load-induced hypertrophic scars that featured all of the classic histopathologic characteristics of human hypertrophic scars. Furthermore, they demonstrated that increased cellularity in hypertrophic scars is attributable to decreased apoptotic pathways in vivo. Tables 1 and 2 include summary information about cited basic research studies on nociceptor-related and mechanoreceptor-related cellular events, respectively.

COMPRESSION THERAPY

Compression garments are frequently used and are the standard first-line therapy for postburn hypertrophic scars in many institutions.[3–6] Compression is reported to produce regression of hypertrophic scars in 60 to 85 percent of patients.[57] Several mechanisms of action for compression have been proposed, including the direct reduction of tissue perfusion and edema, decreased collagen synthesis, increased prostaglandin E_2 release, and increased activation and release of matrix metalloproteinases.[58–60] So far, explanations depending on a single intervening factor (e.g., cytokine, enzyme, tissue perfusion) have been inadequate for understanding the mechanism of action.

Cellular mechanoreceptors may be critical to the high success rate of compression therapy. Renò et al.[57] reported an increase in cellular apoptosis in compressed hypertrophic scars in vitro. Mechanoreceptor activity is involved in cellular apoptosis,[47,48,61,62] and mechanoreceptors are linked to the integrity of the extracellular matrix. Galbraith et al.[63] reported that focal cellular adhesions, which normally serve as mechanoreceptors, did not mature in extracellular matrix that lacked rigidity. Thus, it is likely that an increase in extracellular matrix rigidity produced by compression garments leads to a higher level of mechanoreceptor activity and increased cellular apoptosis. Moreover, as increased rigidity has been shown to affect the migration, proliferation, and differentiation of cells in vitro,[64–67] increased rigidity caused by compression may also alter or inhibit the differentiation and proliferation of scar fibroblasts in vivo. Table 3 includes summary information about cited studies.

Compression garments are wrapped around the body to exert circular compression and to decrease volume. The garments may also act to decrease scar tension. The treatment usually lasts for approximately 1 year, the entire period of scar maturation.[68] During this period, the garments continuously compress and dress the scar surface, to isolate it. This isolation and decreased tension on the scar may decrease the activity of mechanosensitive nociceptors and thereby decrease neuropeptide release. Thus, decreasing mechanosensitive nociceptor activity may be an adjunctive function of pressure garments.

SILICONE THERAPY

Silicone gel sheeting has been used since the early 1980s.[7] Several randomized controlled

Table 1. Summary Information about Cited Basic Research Studies on Nociceptor-Related Cellular Events

Reference	Subject/Cultured Cell Type	Results/Outcome
Bayliss, 1901[26]	Dog, cat, rabbit	In vivo antidromic stimulation of cut dorsal nerve roots resulted in cutaneous vasodilatation.
Kilo et al., 1998[27]	Rat	Capsaicin significantly and dose-dependently increased immunoreactive CGRP release in rat hind-limb skin.
Kress et al., 1999[28]	Rat	In vitro antidromic electrical stimulation of unmyelinated nerve fibers resulted in CGRP release in rat skin.
Sauerstein et al., 2000[29]	Human, rat	In vivo transcutaneous electrical stimulation provoked neuropeptide release and vasodilatation in rat and human skin. Increased CGRP and SP levels were measured by microdialysis and compared.
Nilsson et al., 1985[38]	Human dermal fibroblast and arterial smooth muscle cell lines	Applying SP increased DNA synthesis in cell cultures. Stimulation of cell growth was inhibited by an SP antagonist (spantide).
Katayama and Nishioka, 1997[39]	Mast cell and fibroblast cell lines	Fibroblast proliferating activity of mast cell lines was diminished by different types of SP antagonists.
Delgado et al., 2003[35]	Rat	In vitro leukocytes (T lymphocytes, macrophages and neutrophils) were induced to secrete tumor necrosis factor-α, interleukin 1-β, interleukin 2, and interleukin 6 by applying SP.

CGRP, calcitonin gene-related peptide; SP, substance P.

Table 2. Summary Information about Cited Basic Research Studies on Cellular Mechanoreceptor-Related Events

Reference	Subject/Cultured Cell Type	Results/Outcome
Niland et al., 2001[47]	Human dermal fibroblast culture	Primary human fibroblasts displayed a marked reduction of apoptosis in mechanically relaxed collagen matrices in the presence of adhesion-blocking antibodies against integrins.
Tian et al., 2002[48]	Human lung fibroblast culture	The fibroblast survival signal itself (inhibition of apoptosis) was activated by β1 integrin engagement with antibody mediated by phosphoinositide 3-kinase acting through Akt/protein kinase B.
Derderian et al., 2005[54]	Human dermal fibroblast culture	Increase in load linearly induced collagen III, collagen I, and collagenase gene expression in a fibroblast-populated collagen lattice model.
Wang et al., 2006[55]	Human keloid fibroblast and normal dermal fibroblast cultures	Following mechanical strain, increased transcriptional response to transforming growth factor-β1 and transforming growth factor-β2 in keloid fibroblasts, as compared with normal fibroblasts, was demonstrated.
Aarabi et al., 2007[56]	Rat	In vivo timed tensional load is applied to a wound model. Using this model, load-induced hypertrophic scars were obtained, which have all of the classic histopathologic characteristics of human hypertrophic scars.

Table 3. Summary Information about Cited Studies on Compression Therapy

Reference	Subject/Cultured Cell Type	Results/Outcome
Niland et al., 2001[47]	Human dermal fibroblast culture	Primary human fibroblasts displayed a marked reduction of apoptosis in mechanically relaxed collagen matrices in the presence of adhesion-blocking antibodies against integrins.
Tian et al., 2002[48]	Human lung fibroblast culture	The nature of the survival signal activated by β1 integrin engagement with antibody was mediated by phosphoinositide 3-kinase acting through Akt/protein kinase B.
Szulgit et al., 2001[62]	Human	Isolated fibroblasts from specimens of normal skin, radiation ulcers, keloids, and hypertrophic scars followed by flow cytometric evaluation of integrin receptors. It was demonstrated that keloids and hypertrophic scars have marked alterations in fibroblast integrin expression and contain several distinct fibroblast populations.
Galbraith et al., 2002[63]	Fibroblast culture	Converted initial adhesions into focal complexes by applying force to β1 integrin–fibronectin connections from inside or outside the cell.
Li et al., 2007[64]	Rat portal fibroblast culture	Portal fibroblast myofibroblastic differentiation is dependent on both transforming growth factor-β1 and matrix stiffness.
Peyton and Putnam, 2005[65]	Human aortic smooth muscle cell culture	The migration speed of smooth muscle cells was reduced as ECM ligand density increased. Intrinsic mechanical properties of the ECM govern the random migration speed of primary vascular smooth muscle cells in a biphasic manner.
Leach et al., 2007[66]	Rat adrenal pheochromocytoma cell lines that were induced to a neural phenotype	By displaying a threshold response to substrate stiffness, more branched and longer neurites were formed by increased substrate stiffness. The percentage of neurite-expressing cells was shown to be low in decreased stiffness.

ECM, extracellular matrix.

studies have demonstrated the efficacy of this therapy,[8–12] although its underlying mechanism of action is unknown (Table 4). It has been suggested that silicone therapy acts by altering the tissue oxygen level, by producing pressure and temperature changes, or by a direct action of the silicone molecule itself[69–73]; however, the most likely hypothesis is that silicone has an occlusion and hydration effect on the scar.[74,75] In his review on the evolution of silicone ther-

Table 4. Summary Information about Cited Studies on Silicone Therapy

Reference	Study Information	Results/Outcome
Carney et al., 1994[8]	Prospective controlled study comparing efficacy and safety of two different silicone gel types.	Significant improvement in silicone-treated areas relative to control areas was demonstrated. Different silicone gel types did not differ in efficacy or safety.
Lee et al., 1995[9]	Prospective randomized study comparing two different silicone gel types.	Scar color, thickness, texture, and regularity showed improvement with the use of silicone gels.
Sproat et al., 1992[10]	Prospective randomized study comparing intralesional corticosteroid injection and silicone gel sheeting in poststernotomy scar patients.	Silicone gel sheeting provided earlier symptomatic relief and a more aesthetic scar.
Li-Tsang et al., 2006[11]	Prospective, randomized, controlled study to determine the efficacy of silicone gel sheeting on severe posttraumatic hypertrophic scars among a Chinese population.	Silicone gel sheeting was effective for reducing thickness, pain, itchiness, and pliability of a severe hypertrophic scar among a Chinese population.
Borgognoni et al., 2000[12]	Prospective clinical study on keloids that recurred after surgical excision. Two treatments (surgical excision plus silicone gel sheet and surgical excision alone) were compared. Excised materials were investigated for immunophenotypic features.	Sheet applications effectively reduced recurrences after keloid excision. Excision materials from the group with silicone gel sheeting had lower rates of immune cell monoclonal antibody expression.
Musgrave et al., 2002[70]	Perfusion of hypertrophic scars and adjacent normal skin was measured using a laser Doppler with and without application of silicone gel sheets.	Applying a silicone gel sheet did not result in an acute alteration in microvascular flow within hypertrophic scars; however, applying a gel sheet produced a significant and sustained elevation in the surface temperature of the hypertrophic scar.
Chang et al., 1995[75]	In vitro two-chamber cell culture model investigating the interaction between epidermal and dermal fibroblasts.	Hydration, not silicone itself, inhibited fibroblast proliferation and collagen production.
Akaishi et al., 2009 (in press)[77]	Computer-aided visual analysis of a finite element study.	Silicone gel sheet was effective for reducing the tension at the border between the scar and normal skin, although additional tension occurred on normal skin under the lateral edge of the sheet. Silicone gel sheet appeared to transfer the tension from the scar border to the sheet edge.

apy, Mustoe[74] suggested that the occluded and hydrated environment diminishes keratinocyte stimulation, which in turn causes a decrease in fibroblast activity.

An occluded wound environment is known to prevent the stimulation of damaged nerves,[76] whereas a dry and unoccluded wound is more likely to be painful. Nociceptive nerve fibers are prominent in the area of a wound and in the epithelium and dermis of epithelized scars in the proliferative phase. Long-term application of a soft, inert, equally balanced, and occlusive material such as silicone gel sheeting to the scar surface may cause a decrease in nociceptor activity and a consequent decrease in neurogenic inflammation, leading to a reduction in scar tissue. Tensile reduction is believed to be one of the primary effects of silicone gel sheeting. The computer analysis conducted by Akaishi et al.[77] indicated that silicone gel sheeting was effective for reducing tension at the border between the scar and normal skin. Additional tension was placed on the normal skin under the lateral edge of the gel sheets, but the silicone gel sheeting transferred the tension from the border of the scar to the lateral edge of the silicone gel sheeting. Tensile reduction may decrease tension-induced neurogenic inflammation.[77]

ADHESIVE TAPE AND OCCLUSIVE DRESSINGS

Paper or plastic adhesive tape is used to prevent excessive scarring. Decreased wound tension and occlusion are thought to be important factors in their action.[4,13,78,79] Paper tapes are rigid and able to decrease wound tension[13]; however, Sawada et al.[14] reported more favorable results with a plastic occlusive transparent film dressing (Blenderm; 3M Health Care, St. Paul, Minn.).

In addition to preventing scarring, nonsilicone occlusive dressings have been reported to be effective for the treatment of excessive scarring[15,16] (Table 5). An occlusive dressing forms a "sensory isolation" to dermal and epidermal nerve endings.

Table 5. Summary Information about Cited Studies on Adhesive Tape and Occlusive Dressings

Reference	Study Information	Results/Outcome
Sawada et al., 1998[14]	Prospective, randomized study to compare results obtained by prophylactic use of paper tape and occlusive film dressing in sutured incisional wounds.	Better cosmetic results were achieved in the areas treated with occlusive film dressing.
Atkinson et al., 2005[13]	Prospective, controlled, randomized study to observe the efficacy of paper tapes for preventing hypertrophic scars after cesarean delivery.	The results provided evidence for the effectiveness of paper tape for reducing scar volume and preventing hypertrophic scar formation following cesarean delivery.
Bieley and Berman, 1996[15]	Prospective, randomized study to evaluate the effects of a water-impermeable nonsilicone-based occlusive dressing on keloids.	Non–silicone-based occlusive dressing worn continuously for 8 wk was effective in the majority of keloids treated, indicating that the presence of silicone is not required for an occlusive dressing to have salutary effects on keloidal tissue.
de Oliviera et al., 2001[16]	Prospective, randomized, controlled study to compare silicone and nonsilicone gel dressings in the treatment of keloids and hypertrophic scars.	All of the measured scarring parameters were significantly reduced in the silicone and non–silicone-treated groups, as compared with the control, with no significant differences between them.

A reduction of tensile forces by adhesive dressings may also diminish nociceptor activity. These two effects are synergistic, and the mechanism of action may be related to a decrease in neuropeptide release and neurogenic inflammation.

OCCLUSIVE DRESSING THERAPY

Little is known about the cellular mechanisms that mediate proliferative scarring treatments, and the mechanisms underlying occlusion of the epithelialized (water-impermeable) surface and remission of the deep layers of a protruding scar remain an enigma. Using an in vitro cell culture model, Chang et al.[75] demonstrated that the effect of keratinocytes on fibroblasts after silicone application was modulated by hydration. Mustoe suggested that hydration of the scar surface by an occlusive silicone dressing induces "epidermal-dermal cellular signaling," which in turn regulates cell (i.e., fibroblast) function to diminish scarring.[74]

The effects of hydration and dehydration on the interplay between keratinocytes and other skin cells seem reasonable, but the role of free nerve endings in the dermis and epidermis should not be overlooked. Free nerve endings in the skin connect the surface of a scar to deeper layers in a transmissive manner. Furthermore, when stimulated, free nerve endings release neuropeptides, which have inflammatory and fibrinogenic potential. Isolation of free nerve endings from external stimuli, sensory occlusion of the scar surface, and decreased tension on the scar may in time impair neuropeptide-related cellular responses. It is useful to consider the mechanism of action of compression garments, silicone gel sheeting, and adhesive tapes from this perspective.

DISCUSSION AND FUTURE PERSPECTIVES

Wound healing is a continuous and complex process of dynamic intercellular and cell-matrix interactions.[80,81] Among these interactions, the importance of cellular mechanoreceptors and mechanosensitive nociceptors cannot be underestimated. Excessive scarring can be described as a wound-healing complication, and the possible involvement of these receptors in its pathophysiology and treatment must be considered.

Cellular mechanoreceptors and membrane neuropeptide receptors are functionally related to membrane ion channels, particularly the calcium-transporting channels. Calcium influx and calcium-mediated intracellular signaling in fibroblasts as a response to mechanical stimulation has been observed in a number of studies.[82–84] Hayakawa et al.[85] reported that stimulation of mechanoreceptors (cytoskeletal actin stress fibers and focal cellular adhesions) activated mechanosensitive calcium channels, which in turn increased the intracellular calcium level. Moreover, neuropeptide receptor agonists have been reported to directly increase intracellular calcium.[17] Calcium plays a central and diverse role in the complicated process of wound healing. As calcium acts as a vital intracellular messenger and effector in most cells, including fibroblasts, it can be inferred that a decrease of intracellular calcium would impair intracellular signaling in response to mechanoreceptor and neuropeptide receptor activity. This may be an additional action of intralesional calcium channel blockers on proliferative scarring.

Besides hypertrophic scars and keloids, there are many other fibroproliferative diseases of the human body, including Dupuytren contracture, aggressive fibromatoses (desmoid tumors), and Ledderhose disease. Therapeutic considerations for these diseases may benefit from efforts that explain the mechanisms of action of proliferative scar treatments. In conclusion, a more precise understanding of the roles that cellular mechanoreceptors and mechanosensitive nociceptors play in proliferative scarring may lead to the development of innovative treatment strategies and new pharmacologic therapies targeting cellular mechanoreceptors and mechanosensitive nociceptors in fibroproliferative diseases.

Caglayan Yagmur, M.D.
Ondokuz Mayis University Medical School
Department of Plastic, Reconstructive, and Aesthetic Surgery
55200 Kurupelit, Samsun, Turkey
caglayanyagmur@gmail.com

REFERENCES

1. Butler PD, Longaker MT, Yang GP. Current progress in keloid research and treatment. *J Am Coll Surg.* 2008;206:731–741.
2. Atiyeh BS. Nonsurgical management of hypertrophic scars: Evidence-based therapies, standard practices, and emerging methods. *Aesthetic Plast Surg.* 2007;31:468–492; discussion 493–494.
3. Esselman PC, Thombs BD, Magyar-Russell G, Fauerbach JA. Burn rehabilitation: State of the science. *Am J Phys Med Rehabil.* 2006;85:383–413.
4. Mustoe TA, Cooter RD, Gold MH, et al. International clinical recommendations on scar management. *Plast Reconstr Surg.* 2002;110:560–571.
5. Nedelec B, Ghahary A, Scott P, Tredget E. Control of wound contraction: Basic and clinical features. *Hand Clin.* 2000;16:289–302.
6. Ward RS. Pressure therapy for the control of hypertrophic scar formation after burn injury: A history and review. *J Burn Care Rehabil.* 1991;12:257–262.
7. Perkins K, Davey RB, Wallis KA. Silicone gel: A new treatment for burn scars and contractures. *Burns Incl Therm Inj.* 1983;9:201–204.
8. Carney SA, Cason CG, Gowar J, et al. Cica-Care gel sheeting in the management of hypertrophic scarring. *Burns* 1994;20:163–167.
9. Lee SM, Ngim CK, Chan YY, Ho MJ. A comparison of Sil-K and Epiderm in scar management. *Burns* 1996;22:483–487.
10. Sproat JE, Dalcin A, Weitauer N, Roberts RS. Hypertrophic sternal scars: Silicone gel sheet versus Kenalog injection treatment. *Plast Reconstr Surg.* 1992;90:988–992.
11. Li-Tsang CW, Lau JC, Choi J, Chan CC, Jianan L. A prospective randomized clinical trial to investigate the effect of silicone gel sheeting (Cica-Care) on posttraumatic hypertrophic scar among the Chinese population. *Burns* 2006;32:678–683.
12. Borgognoni L, Martini L, Chiarugi C, Gelli R, Reali UM. Hypertrophic scars and keloids: Immunophenotypic features and silicone sheets to prevent recurrences. *Ann Burns Fire Disasters* 2000;8:164–169.
13. Atkinson JA, McKenna KT, Barnett AG, McGrath DJ, Rudd M. A randomized, controlled trial to determine the efficacy of paper tape in preventing hypertrophic scar formation in surgical incisions that traverse Langer's skin tension lines. *Plast Reconstr Surg.* 2005;116:1648–1656.
14. Sawada Y, Urushidate S, Nihei Y. Hydration and occlusive treatment of a sutured wound. *Ann Plast Surg.* 1998;41:508–512.
15. Bieley HC, Berman B. Effects of a water-impermeable, non-silicone-based occlusive dressing on keloids. *J Am Acad Dermatol.* 1996;35:113–114.
16. de Oliveira GV, Nunes TA, Magna LA. Silicone versus non-silicone gel dressings: A controlled trial. *Dermatol Surg.* 2001;27:721–726.
17. Roosterman D, Goerge T, Schneider SW, Bunnett NW, Steinhoff M. Neuronal control of skin function: The skin as a neuroimmunoendocrine organ. *Physiol Rev.* 2006;86:1309–1379.
18. Boulais N, Misery L. The epidermis: A sensory tissue. *Eur J Dermatol.* 2008;18:119–127.
19. Lumpkin EA, Caterina MJ. Mechanisms of sensory transduction in the skin. *Nature* 2007;445:858–856.
20. Akaishi S, Akimoto M, Ogawa R, Hyakusoku H. The relationship between keloid growth pattern and stretching tension: Visual analysis using the finite element method. *Ann Plast Surg.* 2008;60:445–451.
21. Akaishi S, Ogawa R, Hyakusoku H. Keloid and hypertrophic scar: Neurogenic inflammation hypotheses. *Med Hypotheses* 2008;71:32–38.
22. Ogawa R. Keloid and hypertrophic scarring may result from a mechanoreceptor or mechanosensitive nociceptor disorder. *Med Hypotheses* 2008;71:493–500.
23. Scholzen TE, Brzoska T, Kalden D, et al. Effect of ultraviolet light on the release of neuropeptides and neuroendocrine hormones in the skin: Mediators of photodermatitis and cutaneous inflammation. *J Investig Dermatol Symp Proc.* 1999;4:55–60.
24. Zegarska B, Lelińska A, Tyrakowski T. Clinical and experimental aspects of cutaneous neurogenic inflammation. *Pharmacol Rep.* 2006:58;13–21.
25. Papp A, Valtonen P. Tissue substance P levels in acute experimental burns. *Burns* 2006;32:842–845.
26. Bayliss WM. On the origin from the spinal cord of the vasodilator fibres of the hindlimb, and on the nature of these fibers. *J Physiol (Lond.)* 1901;32:1025–1043.
27. Kilo S, Harding-Rose C, Hargreaves KM, Flores CM. Peripheral CGRP release as a marker for neurogenic inflammation: A model system for the study of neuropeptide secretion in rat paws skin. *Pain* 1997;73:201–207.
28. Kress M, Guthmann C, Averbeck B, Reeh PW. Calcitonin gene-related peptide and prostaglandin E2 but not substance P release induced by antidromic nerve stimulation from rat skin, in vitro. *Neuroscience* 1999;89:303–310.
29. Sauerstein K, Klede M, Hilliges M, Schmelz M. Electrically evoked neuropeptide release and neurogenic inflammation differ between rat and human skin. *J Physiol.* 2000;529:803–810.
30. O'Sullivan RL, Lipper G, Lerner EA. The neuroimmunocutaneous-endocrine network: Relationship of mind and skin. *Arch Dermatol.* 1998;134:1431–1435.
31. Schmelz M, Petersen LJ. Neurogenic inflammation in human and rodent skin. *News Physiol Sci.* 2001;16:33–37.
32. Slominski A, Wortsman J. Neuroendocrinology of the skin. *Endocr Rev.* 2000;21:457–487.

33. Foreman JC. Substance P and calcitonin gene-related peptide: Effects on mast cells and in human skin. *Int Arch Allergy Appl Immunol.* 1987;82:366–371.
34. Furchgott RF, Cherry PD, Zawadzki JV, Jothianandan D. Endothelial cells as mediators of vasodilation of arteries. *J Cardiovasc Pharmacol.* 1984;6:S336–S343.
35. Delgado AV, McManus AT, Chambers JP. Production of tumor necrosis factor-alpha, interleukin 1-beta, interleukin 2, and interleukin 6 by rat leukocyte subpopulations after exposure to substance P. *Neuropeptides* 2003;37:355–361.
36. Scott JR, Muangman P, Gibran NS. Making sense of hypertrophic scar: A role for nerves. *Wound Repair Regen.* 2007;15: S27–S31.
37. Younai S, Nichter LS, Wellisz T, Reinisch J, Nimni ME, Tuan TL. Modulation of collagen synthesis by transforming growth factor-beta in keloid and hypertrophic scar fibroblasts. *Ann Plast Surg.* 1994;33:148–151.
38. Nilsson J, von Euler AM, Dalsgaard CJ. Stimulation of connective tissue cell growth by substance P and substance K. *Nature* 1985;315:61–63.
39. Katayama I, Nishioka K. Substance P augments fibrogenic cytokine-induced fibroblast proliferation: Possible involvement of neuropeptide in tissue fibrosis. *J Dermatol Sci.* 1997; 15:201–206.
40. Chin MS, Lancerotto L, Helm DL, et al. Analysis of neuropeptides in stretched skin. *Plast Reconstr Surg.* 2009;124: 102–113.
41. Ingber DE. Tensegrity-based mechanosensing from macro to micro. *Prog Biophys Mol Biol.* 2008;97:163–179.
42. Furuichi T, Tatsumi H, Sokabe M. Mechano-sensitive channels regulate the stomatal aperture in *Vicia faba. Biochem Biophys Res Commun.* 2008;366:758–762.
43. Hayakawa K, Tatsumi H, Sokabe M. Actin stress fibers transmit and focus force to activate mechanosensitive channels. *J Cell Sci.* 2008;121:496–503.
44. Yoshimura K, Usukura J, Sokabe M. Gating-associated conformational changes in the mechanosensitive channel MscL. *Proc Natl Acad Sci USA.* 2008;105:4033–4038.
45. Ingber DE. Cellular mechanotransduction: Putting all the pieces together again. *FASEB J.* 2006;20:811–827.
46. Chen CS. Mechanotransduction: A field pulling together? *J Cell Sci.* 2008;121:3285–3292.
47. Niland S, Cremer A, Fluck J, Eble JA, Krieg T, Sollberg S. Contraction dependent apoptosis of normal dermal fibroblasts. *J Invest Dermatol.* 2001;116:686–692.
48. Tian B, Lessan K, Kahm J, Kleidon J, Henke C. Beta 1 integrin regulates fibroblast viability during collagen matrix contraction through a phosphatidylinositol 3-kinase/Akt/protein kinase B signaling pathway. *J Biol Chem.* 2002;277:24667–24675.
49. Ingber DE. Cellular tensegrity: Defining new rules of biological design that govern the cytoskeleton. *J Cell Sci.* 1993; 104:613–627.
50. Ingber DE. Tensegrity I: Cell structure and hierarchical systems biology. *J Cell Sci.* 2003;116:1157–1173.
51. Geiger B, Bershadsky A, Pankov R, Yamada KM. Transmembrane crosstalk between the extracellular matrix-cytoskeleton crosstalk. *Nat Rev Mol Cell Biol.* 2001;2:793–805.
52. Chiquet M, Renedo AS, Huber F, Fluck M. How do fibroblasts translate mechanical signals into changes in extracellular matrix production? *Matrix Biol.* 2003;22:73–80.
53. Chiquet M, Gelman L, Lutz R, Maier S. From mechanotransduction to extracellular matrix gene expression in fibroblasts. *Biochim Biophys Acta* 2009;1793:911–920.
54. Derderian CA, Bastidas N, Lerman OZ, et al. Mechanical strain alters gene expression in an in vitro model of hypertrophic scarring. *Ann Plast Surg.* 2005;55:69–75.
55. Wang Z, Fong KD, Phan TT, Lim IJ, Longaker MT, Yang GP. Increased transcriptional response to mechanical strain in keloid fibroblasts due to increased focal adhesion complex formation. *J Cell Physiol.* 2006;206:510–517.
56. Aarabi S, Bhatt KA, Shi Y, et al. Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. *FASEB J.* 2007;21:3250–3261.
57. Renò F, Sabbatini M, Lombardi F, et al. In vitro mechanical compression induces apoptosis and regulates cytokines release in hypertrophic scars. *Wound Repair Regen.* 2003;11: 331–336.
58. Kischer CW, Shetlar MR, Shetlar CL. Alteration of hypertrophic scars induced by mechanical pressure. *Arch Dermatol.* 1975;111:60–64.
59. Baur PS, Larson DL, Stacey TR, Barrat GF, Dobrkovsky M. Ultrastructural analysis of pressure-treated human hypertrophic scars. *J Trauma* 1976;16:958–967.
60. Renò F, Grazianetti P, Cannas M. Effects of mechanical compression on hypertrophic scars: Prostaglandin E2 release. *Burns* 2001;27:215–218.
61. Ruoslathi E, Reed JC. Anchorage dependence, integrins and apoptosis. *Cell* 1994;77:477–478.
62. Szulgit G, Rudolph R, Wandel A, Tenenhaus M, Panos R, Gardner H. Alterations in fibroblast alpha1 beta1 integrin collagen receptor expression in keloids and hypertrophic scars. *J Invest Dermatol.* 2002;118:409–415.
63. Galbraith CG, Yamada KM, Sheetz MP. The relationship between force and focal complex development. *J Cell Biol.* 2002;159:695–705.
64. Li Z, Dranoff JA, Chan EP, Uemura M, Sevigny J, Wells RG. Transforming growth factor-beta and substrate stiffness regulate portal fibroblast activation in culture. *Hepatology* 2007; 46:1246–1256.
65. Peyton SR, Putnam AJ. Extracellular matrix rigidity governs smooth muscle cell motility in a biphasic fashion. *J Cell Physiol.* 2005;204:198–209.
66. Leach JB, Brown XQ, Jacot JG, Dimilla PA, Wong JY. Neurite outgrowth and branching of PC12 cells on very soft substrates sharply decreases below a threshold of substrate rigidity. *J Neural Eng.* 2007;4:26–34.
67. Lo CM, Wang HB, Dembo M, Wang YL. Cell movement is guided by the rigidity of the substrate. *Biophys J.* 2000;79: 144–152.
68. Linares HA, Larson DL, Willis-Galstaun BA. Historical notes on the use of pressure in the treatment of hypertrophic scars or keloids. *Burns* 1993;19:17–21.
69. Quinn KJ, Evans JH, Courtney JM, Gaylor JDS. Nonpressure treatment of hypertrophic scars. *Burns* 1985;12:102–108.
70. Musgrave MA, Umraw N, Fish JS, Gomez M, Cartotto RC. The effect of silicone gel sheets on perfusion of hypertrophic burn scars. *J Burn Care Rehabil.* 2002;23:208–214.
71. Ahn ST, Monafo WW, Mustoe TA. Topical silicone gel: A new treatment for hypertrophic scars. *Surgery* 1989;106:781–787.
72. Wolfram D, Tzankov A, Pülzl P, Piza-Katzer H. Hypertrophic scars and keloids: A review of their pathophysiology, risk factors, and therapeutic management. *Dermatol Surg.* 2009; 35:171–181.
73. Zurada JM, Kriegel D, Davis IC. Topical treatments for hypertrophic scars. *J Am Acad Dermatol.* 2006;55:1024–1031.
74. Mustoe TA. Evolution of silicone therapy and mechanism of action in scar management. *Aesthetic Plast Surg.* 2008; 32:82–92.

75. Chang CC, Kuo YF, Chiu H, et al. Hydration, not silicone, modulates the effects of keratinocytes on fibroblasts. *J Surg Res.* 1995;59:705–711.
76. Emflorgo CA. The assessment and treatment of wound pain. *J Wound Care* 1999;8:384–385.
77. Akaishi S, Akimoto M, Hyakusoku H, Ogawa R. The tensile reduction effects of silicone gel sheeting. *Plast Reconstr Surg.* (in press).
78. Atiyeh BS. Nonsurgical management of hypertrophic scars: Evidence-based therapies, standard practices, and emerging methods. *Aesthetic Plast Surg.* 2007;31:468–492.
79. Reiffel RS. Prevention of hypertrophic scars by long-term paper tape application. *Plast Reconstr Surg.* 1995;96:1715–1718.
80. Robson MC. Growth factors as wound healing agents. *Curr Opin Biotechnol.* 1991;2:863–867.
81. Clark RA. Biology of dermal wound repair. *Dermatol Clin.* 1993;11:647–666.
82. Kang Y, Lee DA, Higginbotham EJ. In vitro evaluation of antiproliferative potential of calcium channel blockers in human Tenon's fibroblasts. *Exp Eye Res.* 1997;64:913–925.
83. Glogauer M, Arora P, Yao G, Soklohov I, Ferrier J, McCulloch CA. Calcium ions and tyrosine phosphorylation interact coordinately with actin to regulate cytoprotective responses to stretching. *J Cell Sci.* 1997;110:11–21.
84. Wu Z, Wong K, Glogauer M, Ellen RP, McCulloch CA. Regulation of stretch-activated intracellular calcium transients by actin filaments. *Biochem Biophys Res Commun.* 1999;261:419–425.
85. Hayakawa K, Tatsumi H, Sokabe M. Actin stress fibers transmit and focus force to activate mechanosensitive channels. *J Cell Sci.* 2008;121:496–503.