Keloid and Hypertrophic Scars: A Review of Recent Developments In Pathogenesis And Management

Bolaji O. Mofikoya,[1] Wasiu L. Adeyemo[2] Abbas A. Abdus-salam[3]
[1]*Department of Surgery (Plastic surgery unit), Lagos University Teaching Hospital, Nigeria*
[2]*Department of Oral and Maxillofacial Surgery, College of Medicine, University of Lagos, Nigeria*
[3]*Department of Radiotherapy, College of Medicine, University of Ibadan, Nigeria*

Correspondence: **Dr. B. O. Mofikoya**

ABSTRACT

Aim: The treatment of keloid and hypertrophic scars remains a challenging clinical problem despite numerous proposed therapies reported in the literature. This is due to the fact that the mechanisms that bring about keloid/hypertrophic scars are not completely understood. This article reviews the pertinent literature regarding the pathophysiology and management of keloid and hypertrophic scars.

Material and methods: A computerized literature search using MEDLINE was conducted for published articles on keloid and hypertrophic scars. The medical subject headings "keloid" or "hypertrophic scar" were combined with "treatment" or "management" or "mechanisms" or "pathophysiology" using the Boolean operator "AND" to narrow the searches. A review of selected relevant literature was undertaken.

Results: Numerous advances have been made in understanding the process of formation of wound healing and scar formation. This increased knowledge has led to the introduction of new treatments as well as to a better understanding of how older treatments work. These include surgical excision, intralesional steroid injection, cryotherapy, laser therapy, irradiation, mechanical compression dressing, silicone sheet applications, intralesional interferon injection, or combination of techniques. Many of the treatment modalities have a defined biologic basis while others are based on anecdotal reports.

Conclusions: Presently there is still no single, reliable and effective treatment protocol for keloid and hypertrophic scars. However, surgical excision followed by postoperative intralesional steroid injection seems to provide a reasonable treatment outcome with low recurrence rate.

INTRODUCTION

Management of keloids is a well known problem in clinical practice. These aberrations of healing have never been completely understood. The earliest description of disfiguring scars was in the Edwin Smith papyrus (200 BC).[1] He described "the existence of swellings on his breasts, large spreading, and round; touching them is like touching a ball of wrappings". The Yorubas had made numerous references to keloidal lesions by the 10th century. They performed ritual facial markings and inculcated keloids into their oral art and sculptings.[2]

Jean Louis Albert described these lesions in 1806 coining the term "*chancroide*" and later changed it to "*cheloide*" to avoid the connotation of cancer.[3] This was from the Greek word 'chele' meaning 'crabs claw' and the suffix 'loid' meaning like. This was in reference to the centripetal claw like extensions of keloid growth.[3]

Keloid represents a benign growth of fibrous tissue originating from an abnormal healing response to cutaneous injury. It is one of the commonest skin lesions encountered in clinical practice particularly in Africans. Estimated incidences vary from 0.09% to 16% in some random sampling of some African populations.[4] Infants under 1 year and adults over 70 year old have also been affected. Apart from the distinct increased tendency for keloids among black populations, they also appear to have a genetically more aggressive variety. There is a strong familiar tendency and slight female preponderance among patients who present for treatment.[4]

Clinically keloids extend beyond the margins of the original injury (Fig. 1) while hypertrophic scars always remain within the confines of the original injury and show regression with time unlike a keloid. Both show predominantly extracellular matrix with predominantly types 1 and 3 collagen, though type 1 collagen predominates in keloids.[5]

Their clinical significance of keloid and hypertrophic scars lies in the distressing aesthetic problem when they occur over the exposed part of the body, irritating pruritus and tendency to suppurate.[6]

The aim of this article is to review the pertinent interature regarding the pathophysiology and management of keloid and hypertrophic scars

Aetiology of keloids

Though the aetiology of keloid is still largely unknown many associations, often anecdotal exist. In many cases however, trauma is the most frequently associated event. The observation that cutaneous lesions on the palms and soles of the feet in keloid patients do not form keloidal lesions led to "sebum autoimmune hypothesis" which proposes that intradermally secreted sebum triggers an autoimmune granulomatous response.[7] The association with hormones has also been found with increased susceptibility in acromegalics, increased growth during pregnancy, puberty and hyperthyroidism.[8]

Cutaneous wound healing mechanisms

Normal tissue repair represents a highly regulated interconnected sequence of events involving various cell lines, cytokines, extracellular matrix proteins as well as other mediators.[9] Fibrin rich blood which fills the site of injury

maintains homeostasis and provides a matrix for cellular migration. Infiltration by neutrophils debride the area of foreign bodies, cellular debris and bacteria. Mediators such as extracellular matrix protein (ECM), transforming growth factor ß (TGFB), and monocyte chemoattractant protein 1 (MCP1) induce a monocytic invasion of the wound with their subsequent transformation into macrophages.[9] This cell line interacts with the ECM via the integrin receptors further amplifying their phagocytic activity, stimulating the production of other mediators such as colony stimulating factor (CSF1), tumour necrosis factor á (TNFa), interleukin 1, transforming growth factor ß, IGF as well as PDGF which is intensely mitogenic for fibroblasts.[10]

The epithelial events usually begin with phenotypic alterations including retraction of intracellular tonofilaments, dissolution of intracellular desmosomes, peripheral formation of actin filaments and loosening of hemidesmosomal linkages.[11] All these occurs via the increased expression of integrins with interaction with other mediators such as vitrinectin and fibronectin in preparation for epidermal migration.[12,13] The epidermal cells begin to migrate, proliferate and dissect the wound between the scar and the viable tissue usually with the aid of collagenase activated by plasmin via plasminogen.[14] These processes are stimulated by epidermal growth factor, transfer growth factor TGFá and keratinocyte growth factor (KGF).

Within a few days new stroma begins to invade the wound space consisting of new capillaries microphages and fibroblasts this occurs under the influence of PDGF, TGF and other cytokines. At this stage there is close fibroblast and ECM interaction and modulation to synthesize deposit and remodel collagen and matrix.[15,16] At some point the fibroblast stop producing collagen with cellular matrix gradually becoming acellular with the cells undergoing apoptosis.[17] Dysregulation of this highly regulated system gives rise to abnormalities of scarring ranging from hypertrophic scar to keloid to scleroderma.

Pathophysiology of keloids

Genetic aetiology of keloid has been well investigated and both autosomal dominant and recessive types have been described. Several polymorphisms of genes encoding for TGFß and TGF receptor have been documented. Several apoptosis related genes have also been observed to be up-regulated in keloid fibroblasts. Studies have demonstrated a lower rate of apoptosis in keloidal fibroblasts.[18,19] Whatever the aetiology of the wound, the stage becomes set for keloid formation within the first 48hours of injury. Dermal fibroblasts have been used extensively to study in vitro characteristics of fibrosis. In keloids the fibroblasts have been shown to produce higher levels matrix proteins fibronectin, elastin and proteoglycan when compared to normal fibroblasts. They have also been shown to have aberrant responses to metabolic modulators such as glucocorticoid, hydrocortisone, growth factors and certain complex esters in vitro.[20,-22] This is thought to contribute significantly to the excessive collagen deposition in the keloidal scar.

The serine proteinases including plasminogen activator –plasmin and the matrix metalloproteinases (MMPs) are responsible for degradation of ECM proteins. Keloidal fibroblast has been demonstrated to have a striking increase in plasminogen activator inhibitor 1 with concomitant decreased urokinase plasminogen activator found to be expressed both at the mRNA level and at the protein synthesis levels with resultant reduction in collagen degradation and removal.[23] The keloidal fibroblast has been shown to be hyper-responsive to ECM production and plasminogen activator inhibitor PAI expression , this altered phenotype is switched on irreversibly following injury by TGFß further inhibiting ECM breakdown and removal.

TGFß plays a key role in the cutaneous scarring as it is produced by several cells. It increases ECM fibronectin, collagen, and also increases cellular expression of matrix receptor integrin.[24] Furthermore, it regulates synthesis of PAI1 and tissue inhibitor of matrix metalloproteinase (TIMMP) is increased while plasminogen activator PA and collagenase is decreased. All these form the basis for the intense fibroplasia induced excessive TGFß. Fibroblasts in individuals with keloids respond to TGFß stimulation by further increasing their augmented rate of collagen synthesis, this response is postulated to be through a receptor or post receptor signaling.[25,26]

Hypertrophic scars have been noted to be primarily in response to the overall vector of tension exerted on wound bed. Studies have shown that fibroblasts from hypertrophic scars may represent a hyper-proliferative phenotype arising from multiple reversible stimulatory impulses such as high growth factor concentration and local wound tension.[27] This may explain tendency to resolve once the tension is released.

Treatments

Over the years, treating keloids and hypertrophic scars has proved to be challenging.[5] Numerous advances have been made in understanding the process of formation of wound healing and scar formation. This increased knowledge has led to the introduction of new treatments as well as to a better understanding of how older treatments work.[5] The limited success of 1 technique has given rise to numerous treatment protocols. However, most of these treatment protocols are plagued with spectre of recurrence.[5,28] These include surgical excision, intralesional steroid injection, cryotherapy, laser therapy, use of ionizing radiation, mechanical compression dressing, silicone sheet applications, ultrasound and heat therapy, intralesional interferon injection, or combination of techniques, and many others. Many of the treatment modalities have a defined biologic basis. However, some treatments are based on anecdotal reports. Presently there is still no single effective treatment protocol for keloids management and no consensus on the best way to treat keloids.

Surgery

Surgical excision of keloids or hypertrophic scars is a common management option. Excision of keloids hypertrophic scars is not only invasive but also marked by a high recurrence rate.[29-32] Recurrence rate of 50% to 100% have been reported.[29-33] Small keloids can be excised and closed primarily (Fig. 2), whereas larger keloids may require skin grafting. Other different techniques of closure after surgical excision like Z-plasty and healing by secondary intention have also been reported.[34,35] Excision of keloids followed by skin grafting alone resulted in 59% recurrence rate.[31] Skin grafting is also complicated by the potential of keloids development at the donor site.[5] There is no generally accepted surgical protocol for keloids excision. Both extralesional[36,37] and intralesional excisions[28,38] have been reported. Advocates of intralesional excision believe that leaving a thin rim of keloid on the wound edges avoids the risk of inducing an intense inflammatory response in the

surrounding, unaffected "keloid-prone" skin, which could lead to the formation of new and possibly bigger keloid.[28] Regardless of the surgical technique, there is further injury to the dermis that leads to proliferation of fibroblasts and extreme amounts of collagen formation, and thus, keloid scar formation.[39] Therefore, during surgical excision, it is essential that tissue trauma be minimal. Many factors may enhance the possibility of recurrences. Such factors include dead space, foreign material, haematoma, infection and wound tension.[40]

Due to high recurrence following surgical excision alone, combination therapies with intralesional steroid, cryotherapy, pressure therapy, radiotherapy, laser therapy, silicone sheet application have been advocated.[40-42]

Intralesional Steroid Injection

Therapeutic use of steroids in the management of keloids/hypertrophic scars was established in the 1960s.[43] Intralesional steroid administration has since become the most widely used and one of the most effective treatment modalities for keloid and hypertrophic scar today.[41] Intralesional steroids act by suppressing the inflammatory response, inhibit fibroblast growth, diminishing collagen synthesis, decreasing mucinous ground substance production, and inhibiting collagenase inhibitors that prevent the degradation of collagen.[5,28,44] Intralesional steroids can be used alone or as an adjuvant therapy following surgical excision of keloids.[28,41] However, the most successful treatment of keloid scars is with combined therapy involving steroids and surgical excision with cure rates of 80-100%.[28,40-42,45] Donkor[2] recently reported a success rate of 100% with a technique of intralesional excision in combination with delayed intralesional triamcinolone injection for the treatment of head and neck keloids. Combination therapy affords the opportunity to debulk the lesion, thereby preventing the tissue resistance during injection.[28] While success with surgical techniques that combine with the injection of steroid immediate after excision of keloid has been reported,[40-42] delayed injection (10-14 days after excision) prevents possible interference with wound healing.[28] Among the adverse effects of steroids are atrophy of skin, hypopigmentation, telangiectasia, necrosis, ulceration, and cushingoid effects from systemic absorption.[5,28,40]

Radiotherapy

Radiotherapy has been used as monotherapy or as an adjuvant after surgical excision for hypertrophic scars and keloids.[42] This can be delivered by tele- or brachy-therapy.[46,47] However, concern regarding the carcinogenic nature and adverse effects of radiation therapy continues to hamper its widespread use.[5,42] Radiation is believed to reduce rate of fibroblast and endothelial cell proliferation.[28] There are conflicting reports in the literature regarding the benefit of radiotherapy in the management of keloids/hypertrophic scars. It is generally accepted that irradiation alone is unreliable for the treatment of hypertrophic scars and keloids.[5] Response to radiotherapy alone is 10%-94%, with a keloid recurrence rate of 50% to 100%.[48,49] In general, radiation therapy is given during early post-surgical period.[1] Kovalic and Perez[50] reported a recurrence rates as low as 12% to 28%. A recent study using postoperative electron beam radiotherapy also reported a recurrence rate of 15%.[51] In contrast, van de Kar et al[46] showed that radiotherapy might be less efficacious for treatment-resistant keloids than suggested by other studies. A recurrence rate of 71.9% was reported within 12-35 months after surgical excision with adjuvant electron beam radiation therapy.[46] Kovalic and Perez[50] had earlier observed that patients who had received previous treatment for their keloids had a statistically significant poorer prognosis than patients for who radiotherapy was the first treatment. Among the adverse effects of radiotherapy are pigmentary alteration, radiation dermatitis (Fig. 3), and potential carcinogenesis.[5] In addition, pregnant patients, keloids located close to the thyroid gland or the female breast are considered unsuitable for adjuvant radiotherapy.[46]

Silicone Sheet Application

In 1983, Perkins et al[52] first described the use of silicone to speed the healing of burns. Since then there have been many reports of scar improvement with the use of silicone gel sheeting.[53-55] The mode of action is by increasing the temperature of the scar, thus increasing collagenase activity.[28,53] Other suggested mode of actions include increased pressure, hydration, oxygen tension.[56] Despite initial skepticism, there is good evidence of its efficacy.[42] The silicone sheet must be worn for at least 12 hours per day for several months to be effective.[5] A response rate of 79% with no evidence of recurrence after 6 months has been reported.[57] Silicone sheets may also be used as adjunctive therapy to other treatments, such as surgical excision, intralesional corticosteroids, and laser treatment.[5] The advantage of silicone gel sheeting lies in not being invasive, however, it requires prolonged application.[5]

Mechanical compression

Pressure therapy after surgical excision of hypertrophic and keloid scars has been reported to be effective in preventing recurrence.[58,59] Pressure devices have been particularly effective in following excision of earlobe keloids.[59] Mechanical compression dressing is thought to reduce oxygen tension in the wound through the occlusion of small vessels, leading to reductions in tissue metabolism, fibroblast proliferation, and collagen synthesis.[60,61] It is generally recommended that pressure be maintained between 24 and 30 mmHg for 6-12 months for this therapy to be effective.[42]

Laser Therapy and Cryotherapy

Laser therapy and cryotherapy are forms of surgical therapy that are widely used for the treatment of keloid and hypertrophic scars. In 1989, Apfelberg et al,[62] for the first time, reported the use of CO_2 lasers for the treatment, but the result was rather disappointing. Subsequently, pulsed-dye laser (PDL) has been reported to an effective tool for the treatment of keloid and hypertrophic scars.[63,64] Response rates of 57% to 83% have been reported.[63-65] Cryotherapy, when used alone, has a response rate of 51% to 74%, whereas, a response rate of 84% in combination with intralesional steroid has been reported.[66]

Intralesional Interferon Injection

The lack of effective therapy and suspected role of growth factors in keloids pathogenesis have lead to novel treatment strategies such as interferons that modulate growth factor composition.[67] Interferons are cytokines that exhibit antiproliferative, antifibrotic, and antiviral effects in multiple cell types.[68] Interferons are used in keloid management because of their ability to interfere with collagen synthesis and fibroblast proliferation, and thereby produce an antifibrotic

effect that has been speculated to be mediated through transforming growth factor-β1 modulation.[67] Tredget et al[69] found that interferon alpha-2b injections three times weekly resulted in significant mean rates of improvement of hypertrophic scars versus control and also reduced serum transforming growth factor-β levels that continued after treatment. However, several other clinical studies have failed to demonstrate a long-term efficacy of intralesional interferon in the management of keloids.[67,70-72] Davison et al[67] concluded that the findings from their trial, along with cumulative conclusions from earlier studies and the adverse side effects, suggest that further clinical investigation of interferon for therapy of keloids might not be warranted.

Other Modalities of Treatment

Several other treatment modalities have also been reported in the literature.[39,40,42,73] These include: ultrasound and heat therapy, and intralesional injection of antihistamine, mitomycin C, 5-fluorouracil or bleomycin.[39,40,42,74,75] Many of these treatments have a defined biologic basis, while some are based on anecdotal reports.

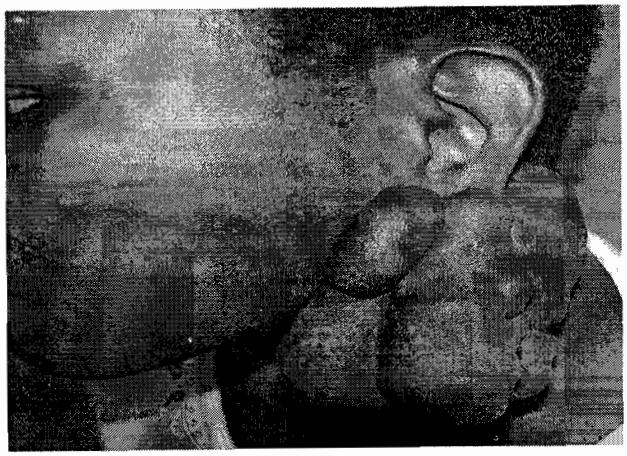

Figure 1: A 17-year-old girl with an extensive keloid of the left ear lobe

CONCLUSIONS

The treatment of keloids and hypertrophic scars remains a challenging clinical problem despite numerous proposed therapies reported in the literature. While hypertrophic scars are amenable to a wide range of therapies, presently there is no consensus on the best way to treat keloids, because adequate studies on this subject are sparse. In addition, most studies are retrospective or uncontrolled prospective studies. There is a need for further work to clarify the mechanisms that bring about keloid/hypertrophic scar, in order to aid our understanding of the disease and facilitate the development of more evidence-based treatment strategies. However, surgical excision followed by intralesional steroid injection seems to provide a reasonable treatment outcome with low recurrence rate, and appears to be the most widely used and most effective treatment modality for keloids and hypertrophic scar. Due to fear of morbidity associated with ionizing radiation, surgical excision followed by radiotherapy is best reserved for situations where previous treatments have failed.

REFERENCES

1. Breasted JH. The Edwin Smith surgical papyrus Vol 1. Hieroglyhic text translation and commentary Chicago. Chicago, University press, 1930; 403-6.
2. Omodare P. Yoruba contributions to the literature on keloids. J Natl Med Assoc 1973;65:367-72.
3. Addison T. On the keloid of Alibert and on true keloid Med-Chir Trans 1854;37:27-47.
4. Alhady SM, Aivanankaraja K. Keloids in various races: a review of 175 cases. Plast Reconstr Surg 1969; 44:564-72.
5. Mafong E, Ashinoff R. Treatment of hypertrophic scars and keloids. Aesthet Surg J 2000;20:114-20.
6. Onwukwe MF. The suppurative keloid. J Dermatol Surg Oncol. 1978:4;333-335.
7. Bucman D, Cosman B. Histologic basis of keloid and Hypertrophic scar differentiation. Arch Pathol 1966;82:65-71.
8. Monstafa MFH, Abdel fatah AF. The presumptive of the presumptive evidence of pregnancy estrogen on keloid growth: case report. Plast Recon Surg 1975; 56:450-3.
9. Brown EG. Phagocytosis. Bioassays 1995;17:109-17.
10. Rappolee DA, Mark D, Banda MJ, Werb Z. Wound macrophages express TGFa and other growth factors in vivo: analysis by mRNA phenotyping . Science 1988; 241:708-12.
11. Golider PA, Paul D. Wounding alters epidermal connexin expressions and gap junction mediated intercellular communication .Mol Bio Cell 1995;6:1491-501.
12. Clark RAF. Fibronectin matrix deposition and fibronectin receptor expression in healing and normal skin. J Inves Derm.1990; 49 suppl;128s-134s.
13. Clark RAF, Ashcroft GF, Spencer MF Larjava M, Ferguson FWJ. Re-epithelization of normal human excisional wounds is associated with a switch from ab5 toab6 integrins. Br J Dermatol.1996;135:46-51
14. Mignatti P, Rifkin DB, Welgus HG, Parks WC. Proteinases and tissue remodeling. In Clark RAF, Henson P, ed. The molecular and cellular biology of wound repair.2nd ed. New York, Plenum Publishing Co., 1996; 427-74.
15. Clark RAF ,Nielsen FD, Welch MP, Mc pherson JM . Collagen matrices attenuate the Collagen synthetic response of cultured fibroblasts to TGFB. J Cell Sci 1995; 108:1251-61.
16. Welch MP, Oldam GF, Clark RAF. Temporal relationships of F-actin bundle formation, collagen and fibronectin matrix assembly and fibronectin receptor expression to wound contraction. J Cell Bio 1990;110:133-45.
17. Desmouliere A, Redard M, Darby M, Gabbiani G . Apoptosis mediates the decrease in cellularity during transition between granulation tissue and scar. Am J Path 1995;146:56-66.
18. Messadi DV, Le A, Berg S, Hung G, Zhuang W, Bertolami CN. Effect of TGF-beta 1 on PDGF receptors expression in human scar fibroblasts. Front Biosci 1998;15:a16-22.
19. Sayah DN, Soo C, Shaw WW, Watson J, Messadi D et al. Down regulation of apoptosis-related genes in keloid tissues. J Surg Res 1999, 87:209-16.
20. Babu, M., Diegelmann, R. Oliver, N. Keloid fibroblast

exhibits an altered response to TGF-b. J Invest Dermatol 1992; 99:650–55.
21. Myles M E. Keloid fibroblasts are refractory to inhibition of DNA synthesis by phorbol esthers. J Biol Chem. 1992;267:9014-9020.
22. Younai S. Modulation of collagen synthesis by transforming Growth factor b in keloid and hypertrophic scar fibroblasts. Ann Plast Surg 1994;33:148-154.
23. Tuan T L. Elevated levels of plasminogen activator I may account for the altered fibrinolysis by keloid fibroblasts. J Invest Dermatol 1996;106: 1007-11.
24. Roberts AB, Sporn M B . Transforming growth factor b. In peptides growth factors and their receptors. Handbook of experimental pharmacology. 95th ed., 1990, Springer-Verlag, 419-72.
25. Derynck R, Zhang Y. Intracellular signaling: the mad way to do it. Curr Biol 1996;10:1226-9.
26. Geinnell F. Fibroblasts, myofibroblasts, and wound contraction. J Cell Biol 1994;124:401-4.
27. Sussman M D. Effect of increased tissues traction upon tensile strength of cutaneous incisions in rats. Proc Soc Exp Biol Med 1996:123:38-41.
28. Donkor P. Head and neck keloids: treatment by core excision and delayed intralesional injection of steroid. J Oral Maxillofac Surg 2007;65:1292-6.
29. Darzi MA, Chowdi NA, Kaul SK, Khan M. Evaluation of various methods of treating keloids and hypertrophic scars: a 10-year follow-up study. Br J Plast Surg 1992;45:374-9.
30. Lawrence WT. In search of the optimal treatment of keloids: report of a series and a review of the literature. Ann Plast Surg 1991;27:164-78.
31. Cosman B, Crikelair GF, Ju DMC, Gaulin JC, Lattes R. The surgical treatment of keloids. Plast Reconstr Surg 1961;27:335-58.
32. Apfelberg DB, Maser MR, Lash H. The use of epidermis over a keloid as an autograft after resection of the keloids. J Dermatol Surg Oncol 1976;2:409-411.
33. Berman B, Bieley HC. Keloids. J Am Acad Dermatol 1995;33:117-23.
34. Craig RD, Pearson D. Early post-operative irradiation in the treatment of keloid scars. Br J Plast Surg 1965;18:369-
35. Norris JE. Superficial x-ray therapy in keloids management: A retrospective study of 24 cases and literature review. Plast Reconstr Surg 1995;95:1051-
36. Ogawa R, Mitsuhashi K, Hyakusoku H, Miyashita T. Postoperative electron-beam irradiation therapy for keloids and hypertrophic scars: Retrospective study of 147 cases followed for more than 18 months. Plast Reconstr Surg 2003;111:547-
37. Ship AG, Weiss PR, Mincer FR, Wolkstein W. Sternal keloids: Successful treatment employing surgery and adjunctive radiation. Ann Plast Surg 1993;31:481-
38. Ollstein RN, Siegel HW, Gillooley JF, Barsa JM. Treatment of keloids by combined surgical excision and immediate postoperative X-ray therapy. Ann Plast Surg 1981;7:281-
39. Sanders KW, Gage-White L, Stucker FJ. Topical mitomycin C in the prevention of keloid scar recurrence. Arch Facial Plast Surg 2005;7:172-5.
40. Murray JC, Pollack SV, Pinnell SR. Keloids and hypertrophic scars. Clinics in Dermatology 1984;2:121-33.
41. Jalali M, Bayat A. Current use of steroids in management of abnormal raised skin scars. Surgeon 2007;5:175-80.
42. Mustoe TA, Cooter RD, Gold MH, Hobbs FD, Ramelet AA, Shakespeare PG et al. International clinical recommendations on scar management. Plast Reconstr Surg 2002;110:560-71.
43. Ketchum LD, Smith J, Robinson DW, Masters FW. The treatment of hypertrophic scar, keloid and scar contracture by triamcinolone acetonide. Plast Reconstr Surg 1966;38:209-18.
44. Kill J. Keloids treated with topical injections of triamcinolone acetonide (kenalog). Immediate and long-term results. Scand J Plast Reconstr Surg 1977;11:169-
45. Al-Attar A, Mess S, Thomassen JM, Kaufmann CL, Davison SP. Keloid pathogenesis and treatment. Plast Reconstr Surg 2006;117:286-300.
46. Van de Kar AL, Kreulen M, van Zuijlen PP, Oldenburger F. The results of surgical excision and adjuvant irradiation for therapy-resistant keloids: A prospective clinical outcome study. Plast Reconstr Surg 2007;119:2248-54.
47. De Lorenzi F, Tielemans HJ, van der Hulst RR, Rhemrev R, Nieman FH, Lutgens LC, Boeckx WD. Is the treatment of keloid scars still a challenge in 2006? Ann Plast Surg 2007;58:186-92.
48. Borok TL, Bray M, Sinclair I, Plafker J, Labirth L, Rollins C. Role of ionizing radiation irradiation for 393 keloids. Int J Radiat Oncol Biol Phys 1988;15:865-70.
49. Lawrence WT. In search of the optimal treatment of keloids: Reports of a series and a review of the literature. Ann Plast Surg 1991;27:164-
50. Kovalic JJ, Perez CA. Radiation therapy following keloidectomy: a 20-year experience. Int J Radiat Oncol Biol Phys 1989;17;77-80.
51. Bischof M, Krempien R, Debus J, Treiber M. Postoperative electron beam radiotherapy for keloids: objective findings and patient satisfaction in self-assessment. Int J Dermatol 2007;46:971-75.
52. Perkins K , Bruce DR, Wallis KA. Silicone gel: a new treatment for burn scars and contracture. Burns Incl Therm Inj 1983;9:201-4.
53. Cheng JC, Evans JH, Leung KS et al. Pressure therapy in the treatment of post-burn hypertrophic scar- A critical look into its usefulness and fallacies by pressure monitoring. Burns Inc Therm Inj 1984;10:154-
54. Gold MH. A controlled clinical trial of topical silicone gel sheeting in the treatment of hypertrophic scars and keloids. J Am Acad Dermatol 1994;30:506-
55. Fulton J. Silicone gel sheeting for the prevention and management of evolving hypertrophic and keloid scars. Dermatol Surg 1995;21:945-
56. Quinn KJ. Silicone gel in scar treatment. Burns 1987;132:33-40.
57. Katz VE. Silicone gel sheeting in scar therapy. Cutis 1995;56:65-67.
58. Stanley MJ, Richard RL. Use of pressure to treat hypertrophic burn scars. Adv Wound Care 1997;10:44-
59. Brent B. The role of pressure therapy in management of earlobe keloids: preliminary report of a controlled study. Ann Plast Reconstr Surg 1978;1:579-81.
60. Sawada Y, Sone K. Hydration and occlusive therapy for hypertrophic scars and keloids. Br J Plast Surg 1992;45:599-603.

61. Carr-Collins J. Pressure techniques for the prevention of hypertrophic scar. Clin Plast Surg 1992;19:733-43.
62. Apfelberg DB, Maser MR, White DN, Lash H. Failure of carbon dioxide laser excision of keloids. Lasers Surg Med 1989;9:382-88.
63. Alster TS, Nanni CA. Pulsed-dye laser treatment of hypertrophic burn scars. Plast Reconstr Surg 1998;102:2190-95.
64. Alster TS. Laser treatment of hypertrophic scars. Facial Plast Surg Clin North Am 1996;4:267-74.
65. Dierickx C, Goldman MP, Fitzpatrick RE. Laser treatment of erythematous/hypertrophic and pigmented scars in 26 patients. Plast Reconstr Surg 1995;95:84-90.
66. Babin RW, Ceilley RI. Combined modalities of in the management of hypertrophic scars and keloids. J Otolaryngol 1979;8:457-60.
67. Davison SP, Mess S, Kauffman LC, Al-Attar A. Ineffective treatment of keloids with interferon alpha-2b. Plast Reconstr Surg 2006;117:247-52.
68. Edwards L. The interferons. Dermatol Clin 2001;19:139-46.
69. Tredget EE, Shankowsky HA, Pannu R, Nedelec B, Iwashina T, Ghahary A, Taerum TV, Scott PG. Transforming growth factor-beta in thermally injured patients with hypertrophic scars: Effects of interferon alpha-2b. Plast Reconstr Surg 1998;102:1317-28.
70. Berman B, Duncan MR. Short-term keloid treatment in vivo with human interferon alfa-2b results in a selective and persistent normalization of keloidal fibroblast collagen, glycosaminoglycan, and collagenase production in vitro. J Am Acad Dermatol 1989;21:694-702.
71. Al-Khawajah MM. failure of interferon alpha-2b in the treatment of mature keloids. Int J Dermatol 1996;35:515-17.
72. Wong TW, Chiu HC, Yip KM. Intralesional interferon alpha-2b has no effect in the treatment of keloids. Br J Dermatol 1994;130:683-85.
73. Adeyemi-Doro HO. Keloid: the natural history. Afr J Med Med Sci 1976;5:93-100.
74. Espana A, Solano T, Quintanilla E. Bleomycin in the treatment of keloids and hypertrophic scars by multiple needle punctures. Dermatol Surg 2001;27:23-7.
75. Fitzpatrick RE. Treatment of inflamed hypertrophic scars using intralesional 5-FU. Dermatol Surg 1999;25:224-32.