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## Low-Dose Enalapril in the Treatment of Surgical Cutaneous Hypertrophic Scar and Keloid - Two Case Reports and Literature Review

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### Abstract

Hypertrophic scars and keloids are 2 forms of excessive cutaneous scarring that occur in predisposed individuals. The healing process varies greatly among patients, and the risk of a bad scar evolution is unpredictable. Keloids create disfiguring scars with associated erythema and pain or pruritus or restricted range of motion, and are a major cause of morbidity. A fortuitous observation was made by the first author of this study who, at age 54, developed an erythematous and painful postsurgical abdominal keloid scar after undergoing left colectomy for colon adenocarcinoma. Four months later, after treatment with low-dose enalapril (10 mg, once a day) for mild arterial hypertension, her keloid scar rapidly improved and she eventually made a complete recovery.

A second case involved a 70-year-old female with diabetes who was affected by a long-standing postsurgical abdominal keloid scar of 2 years' duration. She was intentionally treated with the same low dose of enalapril, and, after 6 months of therapy, the bad scar showed marked improvement.

We conducted an exhaustive search of the literature pertaining to the wound healing process, specifically to determine whether angiotensin-converting enzyme (ACE) inhibitors have a healing effect on wounds. ACE inhibitors are known to induce reduction of left ventricular collagen content and to attenuate remodeling during the postinfarctual period (thus improving ventricular function), and they have been shown to exert a pulmonary antifibrotic effect. After conducting this literature search, it became apparent that no data on cutaneous scars and ACE inhibitors are available. During the posttraumatic or postoperative stage, it is useful to achieve the best possible aesthetic results and to decrease the risk of a disfiguring keloid scar, thereby avoiding revision surgery; to this purpose, an early treatment with a low dose of enalapril is a possible solution, even if further confirmatory observations are needed.

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### Introduction

It is well known that hypertrophic scars and keloids are 2 forms of excessive and aberrant cutaneous scarring (2 separate entities and not different stages of the same process) that occur commonly in predisposed individuals.[1–3] Keloids differ clinically from hypertrophic scars in that they grow beyond the original borders of the injury and, in time, do not show any trend toward resolution.[4] The healing process varies greatly from one patient to another, and the risk of hypertrophic or keloid

scar evolution is unpredictable.[1–3] Keloids (which arise after surgical operations, injury, burns, or cutaneous infections) create disfiguring and sometimes giant scars with associated redness, erythema, and pain or pruritus or restricted range of motion, and are a major cause of morbidity often distressing to patients.[2,4–8] Unfortunately, excision of hypertrophic scars and keloids results in 45%-100% recurrence.[9]

No satisfactory objective methods of clinically assessing scars have been developed, which is problematic for the evaluation of scar prevention or treatment. Similarly lacking are histologic correlates of good or bad scars. Beausang and colleagues[10] suggested a quantitative scale that is a sensitive instrument for clinical scar assessment.

A broad range of surgical treatment and diverse therapeutic measures (steroids, radiation, interferon, 5-fluorouracil, retinoid) are currently available for the management of keloids, but none has proved to be completely effective and entirely satisfactory[2,4,6,9,11–20] or without risks.[12] Intralesional interferon-gamma and interferon-alpha-2b have been used to decrease scar height and to reduce the number of postoperative recurrences[9]; yet, this treatment has also been reported to be ineffective.[21] Pretreatment with interferon-alpha-2b in keloid diathesis therapy has recently been suggested.[22] In 2002, the International Advisory Panel on Scar Management[15] concluded that the only treatments for which sufficient evidence exists to make recommendations are silicone gel sheeting and intralesional corticosteroids; moreover, it was pointed out that the new emerging therapies should undergo large-scale studies with long-term follow-up. Al-Attar and colleagues[20] recently reported that combination therapy, using surgical excision followed by intradermal steroid, appears to be the most efficacious and safe current regimen for keloid management.

Understanding the cellular and molecular events that are involved in the development of these fibroproliferative disorders will allow for optimization of the wound-healing process.[11] The mechanisms underlying keloid formation are only partially understood, and include collagen turnover, alterations in growth factors, tension alignment, and genetic or immunologic contributors.[20]

Elements of the extracellular matrix are important in tissue repair.[23] The distribution of fibrillin-1 and elastin is disrupted in a different way in normal scars than it is in hypertrophic scars and keloids: in deep dermis, the elastin volume density was higher in keloids compared with normal skin, normal scars, and hypertrophic scars.[23] Keloids are characterized by deposition of excessive extracellular-matrix collagen and increased glycosaminoglycan content (as well as increased collagen turnover), induced by abnormal fibroblasts in response to cutaneous injury; thus, epithelial-mesenchymal interactions may play a significant role in keloid pathogenesis.[9,24]

Research on wound healing over the past decades has demonstrated that transforming growth factor-beta (TGF-beta) exerts a crucial role in cutaneous scar formation and is implicated as a fibrosis-inducing cytokine in the pathogenesis of keloids.[24–26] Colwell and colleagues[27] recently reported that fibroblasts of the hypertrophic scar have increased expression of connective tissue growth factor (CTGF) after TGF-beta1 stimulation. Bayat and colleagues,[28] however, observed that TGF-beta1 plasma levels and common polymorphisms for TGF-beta1 are not involved in genetic susceptibility to hypertrophic and keloid scarring. Gira and colleagues[4] demonstrated high-level epidermal expression of the vascular endothelial growth factor (VEGF) in keloid lesions.

In 1998, Beer and colleagues[29] showed that keloids have a quantitatively reduced vascular component compared with hypertrophic scars and normally healing surgical scars, and suggested that the formation of keloids may be related to their reduced level of vascularization. On the other hand, new findings have demonstrated that keloids are angiogenic lesions, and that the overlying epidermis is the major source of this angiogenesis through an increase of VEGF.[4]

It is noteworthy that keloids and red hypertrophic scars have continuous high metabolic activity: they show increased ATP levels and contain more fibroblasts than pink or white scars.[30] In keloids, moreover, ATP content and fibroblasts seem to remain at high levels for a long time ( $\geq 10$  years after the injury).[30]

In this article, we report the experience of the one of the authors (S.I.), who observed an unexpected

and rapid recovery of a recent postsurgical keloid scar as an incidental response to low-dose enalapril treatment for mild arterial hypertension. We also describe another case of improvement of a long-standing postsurgical keloid scar in a diabetic patient, intentionally treated with the same low dose of enalapril.

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## Case Report

### Case 1

S.I. (the first author of this study), at the age of 54, underwent left colectomy for adenocarcinoma of the colon in 2002 and developed a postsurgical abdominal red keloid scar that was erythematous and painful.

After 4 months, a consulted surgeon confirmed the diagnosis of keloid because the lesion expanded in a claw-like fashion beyond the borders of the scar. He decided against surgical revision because of the risk for keloid diathesis and the high risk of recurrence associated with surgery. The patient had a preexisting hypertrophic surgical scar that was the result of 2 long-ago cesarean sections (performed 30 and 25 years before), and this scar was sometimes itchy and eczematous. In the meantime, the patient was treated for mild arterial hypertension with low-dose enalapril (10 mg, once a day), coupled with a very low dose of hydrochlorothiazide (3 mg, once a day), administered in the morning. After 15 days of this treatment, the keloid scar dramatically improved, with a nearly complete recovery. Spontaneous resolution was ruled out as the reason for this rapid improvement, and this drew attention to the effect of the drug. Moreover, the old hypertrophic scar (due to cesarean sections) completely disappeared after 3–4 months of enalapril treatment.

### Case 2

R.Z., a 70-year-old female with well-controlled diabetes who had undergone surgical removal of a tumor on her colon 2 years previously, developed a postsurgical abdominal keloid scar which, upon observation, was very prominent. The scar was red, had irregular borders, and showed increased vascularization. It is noteworthy that the patient also had a red, rounded keloid scar at the site where a drainage tube had been inserted at the time of surgery. These keloids, therefore, should be considered as long-standing lesions. The patient was intentionally treated with the same drugs as the patient in Case 1 (10 mg enalapril and 3 mg hydrochlorothiazide, once a day), administered in the morning. The keloid scars slowly improved, showing a very good response after 6 months.

The 2 patients still continue enalapril treatment, which is effective in controlling their arterial blood pressure.

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## Discussion

### General Comments

On the basis of our observations, we reviewed the available literature concerning scar or fibrous tissue production as influenced by angiotensin-converting enzyme, angiotensin II (an important modulator of collagen synthesis), and ACE inhibition.

ACE inhibitors are hypotensive drugs that inhibit the converting enzyme peptidyl dipeptidase, which hydrolyzes angiotensin I to angiotensin II and inhibits the degradation of a potent vasodilator, bradykinin; this mechanism, at least in part, is prostaglandin mediated.[31] ACE is present in tissues composed largely of fibrillar collagen such as heart valves, the adventitia of great vessels, and intramyocardial coronary arteries, as well as in the scar that follows myocardial infarction.[32] In experimental models that simulate primary and secondary hyperaldosteronism by administration of aldosterone or angiotensin II (which were associated with the appearance of myocardial fibrosis), Sun and colleagues[32] tested the hypothesis that ACE is related to fibrous tissue formation, whose appearance is independent of circulating renin and angiotensin peptides. It has also been reported that angiotensin II, generated by activation of the local renin-angiotensin system, is believed to play

an important role in tissue repair and remodeling, being a potent inducer of procollagen production (for example, in human lung fibroblasts) via the activation of type I receptor and, at least in part, via the autocrine action of TGF-beta.[33]

Several ACE inhibitors are currently in clinical use. Captopril is an ACE inhibitor with inhibitory action on the renin-angiotensin system and a stimulating effect on the kallikrein-kinin system.[31] It is a sulfhydryl-containing agent and is metabolized chiefly to disulfide conjugates with other sulfhydryl-containing molecules, and is distributed to most body tissues (with the exception of the central nervous system) and eliminated primarily by the kidneys, like the other ACE inhibitors. Enalapril is a prodrug that is hydrolyzed in the body and converted by de-esterification to ACE inhibitor enalaprilat; it is a non-sulfhydryl-containing agent. Lisinopril is a lysine derivative of enalaprilat, the active metabolite of enalapril. Fosinopril and ramipril, next introduced, are slowly absorbed. Losartan, on the other hand, is a nonpeptide angiotensin II antagonist.[31]

Several reports have described the effects of the ACE inhibitors captopril and enalapril on myocardial infarction (produced in diverse animals by left anterior descending coronary artery ligation), such as reduction of ventricular collagen content and attenuation of left ventricular remodeling, which improves ventricular function.[34–38] In some of these observations, scars showed less thinning and expansion with ACE inhibitors than with placebo. In a recent study involving a myocardial infarction model, long-term ACE inhibition with captopril (6 months) reduced left ventricular mass and decreased fibrosis in the viable myocardium but had no effect on cardiac expression of TGF-beta1 or CTGF mRNA and protein.[39] It is also known that some ACE inhibitors exert antifibrotic effect in pulmonary fibrosis and in some in vitro and in vivo experimental or human models of fibrotic lesions.[33,37,40–44] It has been reported that enalapril limits left ventricular hypertrophy and decreases infarct wall thickness in dogs during in vivo healing after anterior myocardial infarction.[36,38]

Infarct scars have long been considered to be inert and acellular structures, composed simply of fibrillar collagen, whose sole function is to restore structural integrity to infarcted myocardium and provide tensile strength that prevents tissue rupture. In contrast to this view, infarct scar is now recognized as a living tissue[45]; it is a dynamic structure composed of a persistent population of phenotypically transformed fibroblast-like cells (termed myofibroblasts) with contractile behavior in response to various peptides and amines. Living and dynamic infarct scar is nourished by a neovasculature.[45–48] These myofibroblasts at the myocardial infarct site are metabolically active (expressing components requisite to angiotensin peptide generation) and continue to elaborate fibrillar type I collagen.[45] Sun and colleagues[45] reported that pharmacologic intervention with ACE inhibitors is effective in attenuating scar tissue metabolic activity and minimizing adverse accumulation of fibrous tissue in noninfarcted myocardium. Some researchers have demonstrated that cultured myofibroblasts (obtained from 4-week-old scar tissue of the left ventricle of adult rats with transmural myocardial infarction) are able to generate *de novo* angiotensin I and II.[46] Angiotensin II may regulate myofibroblast collagen turnover and fibrous tissue contraction in an autocrine and/or paracrine manner.[46,47] Thus, myofibroblasts are the cells responsible for fibrous tissue formation in various injured organs, such as the heart.

### **Discussion**

We did not find any observations in the literature about the effects of ACE inhibitors on cutaneous hypertrophic scars or keloids. For this reason, we thought it would be of interest to publish the findings from our 2 cases.

It is noteworthy that the improvement of the postsurgical scar after low-dose enalapril treatment was better in the patient with a keloid lesion of short duration (4 months) than in the case with a long-standing lesion (2 years' duration), which was probably a more stable lesion. The female patient presented in Case 1, moreover, was younger and not affected by any significant diseases (aside from the surgically treated colonic neoplasm), whereas the female patient presented in Case 2 was older and affected by diabetes mellitus, a disease known to interfere with tissue healing.

The only study that seems to support our observations is that of Sun and colleagues.[47] These authors, using a granuloma pouch model (whereby a subcutaneous air sac was created, followed by

injection of croton oil) and collecting pouch tissue on Days 4, 7, 14 and 21, tested whether fibroblasts (wound-healing fibroblast-like cells) and the locally generated angiotensin II are involved in repairing tissue. In the pouch tissue, They found that ACE and angiotensin II receptor binding was evident at Day 4 (and remained unvaried on Days 7, 14, and 21), the predominant angiotensin II receptor subtype expressed was AT1, myofibroblasts expressed ACE and AT1 receptors, and lisinopril and losartan significantly attenuated pouch weight and accumulation of collagen. Thus, in this model of cutaneous repair, the appearance of myofibroblasts was associated with angiotensin II generation, which regulates fibrogenesis by AT1 receptor binding, whereas signals involved in the appearance of myofibroblasts remain uncertain.

It is noteworthy that, in 1990, Ward and colleagues[40] demonstrated that collagen (hydroxyproline) and mast cell accumulation are decreased in irradiated rat lung, and that, in irradiated rats, the ACE inhibitor captopril, in addition to ameliorating acute lung damage, also induced reduction of chronic skin manifestations – both benign (epilation and moist desquamation) and malignant (fibrosarcomas and squamous cell carcinomas) – thus demonstrating a useful effect in cutaneous reactions.

### ***Are All ACE Inhibitors Equally Effective in the Treatment of Keloid Scars?***

Captopril, which contains a sulphhydryl (SH) radical in its moiety, was reported to be the most efficient drug in protecting the lung parenchyma from the inflammatory response and subsequent fibrosis.[44] The observation that ACE inhibitors containing the sulphhydryl radical are more effective than those without it led to the question of whether this protective effect is related to inhibition of angiotensin II synthesis or rather to some of the collateral properties of these drugs, such as antioxidation or protease inhibition.[44] In the study by Ward and colleagues,[40] captopril inhibited radiation-induced pulmonary fibrosis in rats, showing cytostatic effect not attributable to ACE inhibition. In another research, the ability of captopril to inhibit 3H-thymidine incorporation was not reversed by exogenous angiotensin II and was not mimicked by the non-thiol ACE inhibitor, lisinopril.[41] In another study, penicillamine, a thiol compound with no ACE-inhibitory activity, also reduced fibroblast 3H-thymidine incorporation, indicating that the antimitotic action of captopril may represent a nonspecific sulphhydryl effect.[41] Nevertheless, enalapril, which is a non-sulphhydryl-containing agent, exerts effects similar to those of captopril.[36,37] Moreover, Marshall and colleagues[33] recently demonstrated that, after bleomycin-induced lung injury, administration of ramipril (another ACE-inhibitor without sulphhydryl radical) reduced the increase in TGF-beta1 expression and lung collagen deposition. On the other hand, the angiotensin II receptor blockers are reported to be equally effective in antifibrotic capacity to any ACE inhibitor with or without SH-radical, reaffirming the role of angiotensin II in the modulation of collagen synthesis.[44] Thus, the mechanism of ACE inhibitors remains to be clarified.

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## Conclusion

On the basis of the fortuitous observation of a beneficial effect of enalapril on recent and long-standing postsurgical keloid scars and confirmatory data from the literature, ACE inhibitors and angiotensin-receptor antagonists (largely used in clinical practice) should be regarded as potentially useful therapeutic agents for patients with fibrotic diseases (such as lung fibrosis and postinfarction left ventricular remodeling) and, perhaps, also for healing bad cutaneous scars and repairing tissue.

Obviously, our observation is only a preliminary one, and our results should be compared to those observed with similar keloids *not* treated with enalapril.

During the posttraumatic or postoperative stage, it is difficult to achieve the best possible aesthetic when treating cutaneous scars. The proliferative phase occurs during the first few months, and pharmaceutical intervention can help to decrease the risk of aesthetically disfiguring hypertrophic or keloid scars, thereby avoiding revision surgery. Furthermore, surgically removed keloids commonly recur within the excision sites. Therefore, the precocious treatment with low-dose enalapril, which is not associated with side effects (except in patients with acute renal failure or chronic renal insufficiency and those with collagen vascular disease), is a possible solution; however, further confirmatory observations are needed.

## Footnotes

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