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REVIEW ARTICLE

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Acne Scar Management: Minoxidil as a Promising Approach or a Mirage?

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Abstract

Atrophic and hypertrophic scars can result from various conditions, such as acne, trauma, and surgery. Minoxidil, a medication used for the treatment of severe hypertension and hair loss, has been explored as a potential treatment for scars. This review aims to evaluate the current evidence regarding the role of minoxidil in the treatment of scars. Previously published reviews have primarily focused on the use of minoxidil in hair loss and have only briefly mentioned its potential use for scars. However, minoxidil may have a beneficial effect as an antifibrotic agent. Several studies have reported reduced collagen accumulation and fibrosis after treatment with minoxidil. The proposed mechanism of action is inhibition of the production of lysyl hydroxylases (LHs), which modify and cross-link proteins by converting lysine to hydroxylysine, making collagen more resistant to degradation. Minoxidil, as an LH inhibitor, has been shown to potentially benefit wound healing and regeneration in vitro by inhibiting the proliferation and migration of fibroblasts. To date, direct studies of the efficacy of minoxidil in treating acne scars have not been conducted; however, its inhibitory effects on fibroblast function and antifibrotic outcomes in some in vivo studies suggest that such use may be considered.(**International Journal of Biomedicine. 2023;13(3):54-58.**)

Keywords: acne • scar • treatment • minoxidil

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Introduction

Scars are a common skin condition resulting from various causes, such as acne, trauma, or surgery. Scars can be classified into two main categories based on the net change in collagen content: (1) Atrophic scars, characterized by collagen loss, are the most common type in the context of acne scars, affecting around 80% to 90% of individuals. Atrophic scars cause depressions or indentations on the skin surface, which can be both aesthetically and psychologically distressing. On the other hand, a smaller percentage of individuals develop hypertrophic scars and keloids, which involve an overgrowth of collagen. (2) Hypertrophic scars appear as raised, firm, pink formations with dense collagen bundles within the boundaries of the original injury site.[1]

Several treatment options have been explored to manage scars, including laser therapy, chemical peels, and dermal fillers. However, these treatments can be expensive and not suitable for all patients.[2] Minoxidil is a medication that is commonly used in dermatology to treat hair loss. It works by dilating blood vessels in the scalp, leading to enhanced circulation to the hair follicles and promoting hair growth.[3] However, it has also been suggested that minoxidil may have a potential role in treating scars. Previous reviews have mainly focused on the use of minoxidil for hair loss and have only briefly mentioned its potential antifibrotic role.[4,5]

This review aims to assess the existing evidence concerning the utilization of minoxidil in scar treatment. The review employs a narrative synthesis methodology and extensively searches various databases to identify pertinent studies. The inclusion criteria encompass in vitro experimental studies, randomized and non-randomized controlled trials, and observational studies that report the application of minoxidil in the treatment of fibrosis and scars.

The need for a treatment option that is both effective and safe for acne scars is significant, as it can significantly impact the quality of life of affected individuals. Scars can lead to significant psychological distress, affecting self-esteem and confidence.[6] Furthermore, managing acne scars can be challenging, with many expensive and invasive treatment

options. The potential use of minoxidil in treating scars is a promising avenue that warrants further investigation.

Scar pathogenesis

The wound-healing process involves various cells, chemical mediators, and extracellular matrix components. It advances through three distinct stages: inflammation, the formation of granulation tissue, and the remodeling of the matrix.[7]

During inflammation, the injury site undergoes vasoconstriction for hemostasis, followed by vasodilation and erythema. This stage activates various cells, such as macrophages, granulocytes, and lymphocytes. These cells release inflammatory mediators that prepare the wound site for the subsequent formation of granulation tissue,[8] which involves the repair of damaged tissues and the formation of new capillaries. Fibroblasts are stimulated to produce collagen, initially dominated by type III collagen and later shifted to type I collagen.[9]

During matrix remodeling, fibroblasts and keratinocytes play a crucial role in producing enzymes that shape the structure of the extracellular matrix. The balance between matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs is essential. An imbalance in this ratio can lead to the formation of either atrophic or hypertrophic scars.(10) Atrophic scars occur when insufficient collagen factor deposition results in depressed areas. On the other hand, hypertrophic scars form when the healing response is overly robust, leading to the development of raised nodules comprised of fibrotic tissue (Table 1).

Table 1.

The steps involved in the pathogenesis of scars.

Step	Description
1.	Injury or damage to the skin.
2.	Inflammation as part of the normal wound-healing process.
3.	Migration of fibroblasts and other cells to the injury site, collagen production to form new tissue.
4.	Remodeling Atrophic scars: Decreased number of fibroblasts and collagen production, leading to tissue thinning. Hypertrophic scars: Overexpressed healing reaction, leading to the development of raised nodules comprised of fibrotic tissue

Acne scar types

Atrophic scars

Atrophic scars are a type of skin scarring that occurs as a result of loss of tissue during the wound healing process. Several types of atrophic scars include icepick, rolling, and boxcar scars. Individual scars can have characteristics of multiple types, and treatment options may need to be tailored to address the specific features of each scar.[11] Types of atrophic acne scars are presented in Table 2.[12]

Occasionally, patients may exhibit all three types of atrophic scars, making it difficult to distinguish between them. As a result, several authors have put forth various classifications and scales. One commonly utilized qualitative grading system is the one introduced by Goodman and Baron. This classification system defines four distinct grades that can be employed to characterize an acne scar (Table 3).[13]

Hypertrophic scars

Hypertrophic and keloidal scars are associated with excessive collagen accumulation and reduced collagenase activity. Hypertrophic scars are typically present as elevated, firm, pink formations with dense collagen bundles confined within the boundaries of the initial injury site. The histological characteristics of hypertrophic scars resemble those of other dermal scars. In contrast, keloids manifest as reddish-purple papules and nodules that extend beyond the original wound borders. Histologically, keloids display thick bundles of acellular collagen arranged in the whorls. These scars are more prevalent in individuals with darker skin tones and primarily occur on the trunk.[14]

Table 2.

Atrophic depressed acne scars according to Jacob et al.[12]

Acne Scars Subtype	Clinical Features and Treatment Options
Ice-pick	Narrow (<2 mm), deep, well-defined epithelial tracts that extend vertically into the deep dermis or subcutaneous tissue. Difficult to treat due to their depth and narrowness, but options such as chemical peels and laser resurfacing may be effective in reducing their appearance.
Rolling	Dermal tethering of skin that appears relatively normal, with a width typically exceeding 4 to 5 mm. Often caused by long-term inflammatory conditions such as acne and may respond to treatment options such as subcision, microneedling, or dermal fillers.
Boxcar	Depressions with round or oval shapes and distinct vertical edges, resembling scars from chickenpox (varicella). They can be shallow (diameter <3 mm) or deep (diameter >3 mm). Boxcar scars are often caused by severe acne and may respond to treatment options such as chemical peels, laser resurfacing, and dermal fillers.

Table 3.

Acne Scar Grading System (Goodman and Baron).[13]

Grade	Clinical Features
I	Macular or erythematous scars
II	Mild atrophic scars with decreased skin texture
III	Moderate atrophic scars with a visible depression
IV	Severe atrophic scars with deep depressions and sharp edges

Treatment of acne scars

Treatment Options for Atrophic Scars

Treatment options for atrophic scars have advanced in recent years, and several new and effective treatments have emerged. Here are some of the latest updates in the treatment of atrophic scars:

Microneedling is a technique that utilizes a device equipped with small needles to create tiny punctures in the skin. This process stimulates the production of collagen

and elastin, improving the appearance of atrophic scars. A systematic review and meta-analysis of 16 randomized controlled trials conducted in 2021 demonstrated the efficacy of microneedling as a treatment for atrophic acne scars, with minimal adverse effects reported.[15]

Platelet-rich plasma (PRP) therapy involves injecting the patient's own PRP into the affected area. Platelets contain growth factors that aid in tissue repair and regeneration. A review article from 2020, encompassing 13 studies, indicated that PRP therapy shows promise as a treatment for atrophic acne scars. However, further research is required to establish the optimal treatment protocol.[16]

Fractional laser resurfacing employs laser technology to create skin micro-wounds, stimulating collagen and elastin production. A systematic review and meta-analysis of 33 randomized controlled trials conducted in 2018 concluded that fractional laser resurfacing is an effective treatment for atrophic acne scars with a low risk of adverse effects.[17]

Chemical peels involve the application of a chemical solution to the skin, resulting in the exfoliation of the top layer and promoting the growth of new skin cells. A systematic review and meta-analysis of 24 randomized controlled trials conducted in 2019 established the effectiveness of chemical peels in treating atrophic acne scars. However, the optimal type and concentration of the chemical solution varied depending on the specific type of scar.[18]

Treatment Options for Hypertrophic Scars

Silicone gel is a transparent, quick-drying solution commonly used to prevent and treat hypertrophic acne scars. Its mechanism of action is not fully understood, but it is believed to increase hydration, protect the scar, and potentially affect the immune system. Clinical studies have shown a decreased scar thickness from 40% to 50%. Treatment duration varies depending on whether it is for existing scars or prevention.[19]

Intralesional steroid therapy involves injecting steroids directly into the scar tissue to reduce scar volume, thickness, and texture, as well as relieve itching and discomfort. The exact mechanisms are not fully understood, but they include anti-inflammatory properties and inhibition of collagen production. Steroid injections are usually preceded by anesthetic creams, and cryotherapy may be used to enhance drug dispersion. Adverse reactions may occur, such as hypopigmentation, skin atrophy, and infections.[20]

Cryotherapy using liquid nitrogen has the potential to greatly enhance the appearance of hypertrophic scars and keloids, possibly leading to their complete regression. By subjecting the affected area to low temperatures, cryotherapy slows down blood flow and induces thrombus formation, resulting in tissue necrosis. Cryotherapy can be combined with steroid injections to enhance effectiveness. Adverse reactions may include changes in pigmentation, skin atrophy, and pain.[21]

Pulsed dye laser (PDL) has shown promising outcomes in treating hypertrophic and keloidal scars. It reduces fibroblast proliferation, loosens collagen fibers, and decreases collagen type III deposition. PDL flattens and reduces scar volume, improves texture, and alleviates itching and pain. Multiple treatments may be necessary, and common side effects include temporary purpura and changes in pigmentation. PDL is more effective for patients with lighter skin types.[22]

Surgery options for hypertrophic scars include W-plasty to disrupt scar patterns and autologous skin grafts to close wounds with minimal tension. In facial defects requiring skin grafts, the retro- and preauricular areas, and the neck, are preferred as donor sites.[23]

Other treatment approaches may be considered, such as intralesional injection of 5-fluorouracil, radiotherapy, imiquimod, interferon, elastic compression, and bleomycin. However, their effectiveness is limited or impractical for various reasons, such as lack of clinical experience, high costs, or inefficacy. These approaches are generally more suitable for hypertrophic scars not caused by acne.[14]

Minoxidil as antifibrotic agent

Minoxidil was first introduced as an oral medication for the treatment of severe and recalcitrant hypertension in the 1970s.[24] Hypertrichosis was discovered as a side effect of chronic use of oral minoxidil in about one-fifth of patients. This observation prompted the development of a topical formulation to stimulate hair growth.[25] Topical minoxidil was FDA-approved specifically for androgenic alopecia (AGA) in 1988 as a first-line treatment for men with mild-to-moderate AGA,[26,27] subsequently for females. Topical minoxidil is used in both 2% and 5% foam and liquid solutions with varying efficacies for AGA in men and women.[28.29] Minoxidil downregulates the expression of the procollagen-lysine and 2-oxoglutarate 5-dioxygenases (PLODs) genes and their encoded catalyze lysyl hydroxylase (LH) proteins.[30] It was reported to reduce lysyl hydroxylase activity by decreasing the LH1 mRNA level.[31,32] Because the LHs modify and cross-link proteins by converting lysine to hydroxylysine, they make collagen more resistant to degradation.[33,34] Thus, limiting the supply of hydroxylysines for hydroxyallysine cross-link formation, minoxidil leads to antifibrotic effects.[32]

Zuurmond et al.[35] demonstrated that minoxidil treatment of cultured fibroblasts reduces LH1>>LH2b>LH3 mRNA levels depending on dose and time but has essentially no effect on the total number of pyridinoline ross-links in the collagen matrix. However, the collagen produced in the presence of minoxidil displayed some remarkable features: the hydroxylation of triple helical lysine residues was reduced to 50%, and lysylpyridinoline cross-linking was increased at the expense of hydroxylysylpyridinoline cross-linking, pointing out that the LH1 mRNA levels were the most sensitive to minoxidil treatment, and LH1 has a preference for triple helical lysine residues as substrate. The authors concluded that minoxidil is unlikely to serve as an antifibrotic agent, but confers characteristic features to the collagen matrix.

Shao et al.[36] found that the effects of minoxidil appear to be mediated at least partly through the TGF-β1/Smad3 and the MMPs/TIMPs pathways, resulting in reduced levels of lysylpyridinoline and hydroxylysylpyridinoline, resulting in a decrease in collagen biosynthesis.

In a study by Priestley et al.,[37] the effects of minoxidil in vitro were researched using fibroblasts grown from the lesional skin of patients with lichen sclerosus and morphea, and from the normal skin of healthy individuals. The proliferation of all fibroblast lines over 3 days was inhibited in

proportion to the concentration of minoxidil, being 20% or less of controls at 1mM. At 5mM, there was usually a net loss of cells. Secretion of glycosaminoglycans by normal fibroblasts showed a concentration-dependent reduction, being 25±6% of that of untreated cultures with 1mM minoxidil. In contrast, minoxidil at 0.1-1mM stimulated the proliferation of foreskin keratinocytes by up to 130%. The range of inhibitory effects of minoxidil on both normal and abnormal skin fibroblasts in vitro and stimulation of skin epithelial cells led the authors to conclude that minoxidil may provide proper topical treatment for keloids and other fibrosis.

Knitlova et al.[38] assessed the in vitro antifibrotic effects of minoxidil on clubfoot-derived cells. Minoxidil concentrations of 0.25 mM, 0.5 mM, and 0.75 mM inhibited cell proliferation in a concentration-dependent manner without causing a cytotoxic effect. Minoxidil in concentrations of ≥0.5 mM decreased collagen type I accumulation after 8 and 21 days in culture, demonstrating the potential antifibrotic effects in vivo.

A study by Freiha et al.[39] evaluated the effects of topical minoxidil 5% cream on full-thickness thermal skin burns in a Wistar rat model. The results showed that minoxidil reduced necrosis and increased wound contraction rates, resulting in positive results after one week of treatment regarding local antioxidant protection, keratinocyte migration, neo-capillarization, chronic inflammation, and fibrosis rate. However, after two weeks, the opposite results were observed.

Polo et al.[40] studied the capability of minoxidil to inhibit various fibroblast functions in vivo using an established animal model of wound contraction. Standardized cutaneous wounds were created on the dorsum of Sprague-Dawley rats. Minoxidil did not demonstrate significant inhibition of wound contraction rates that do not support the proposed use of minoxidil as an antifibrotic agent.

In conclusion, minoxidil has been shown to benefit wound healing and regeneration in vitro by inhibiting the proliferation and migration of fibroblasts. However, its potential as an antifibrotic agent for therapeutic use is still not demonstrated. It requires additional studies involving more study groups and more extended follow-up periods.

Competing Interests

The authors declare that they have no competing interests.

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References

1. Tan J, Beissert S, Cook-Bolden F, Chavda R, Harper J, Hebert A, Lain E, Layton A, Rocha M, Weiss J, Dréno B. Impact of Facial Atrophic Acne Scars on Quality of Life: A Multi-country Population-Based Survey. Am J Clin Dermatol. 2022 Jan;23(1):115-123. doi: 10.1007/s40257-021-00628-1.
2. Connolly D, Vu HL, Mariwalla K, Saedi N. Acne Scarring-Pathogenesis, Evaluation, and Treatment Options. J Clin Aesthet Dermatol. 2017 Sep;10(9):12-23.
3. Gupta AK, Charrette A. Topical Minoxidil: Systematic Review and Meta-Analysis of Its Efficacy in Androgenetic Alopecia. Skinmed. 2015 May-Jun;13(3):185-9.
4. Choi N, Shin S, Song SU, Sung JH. Minoxidil Promotes Hair Growth through Stimulation of Growth Factor Release from Adipose-Derived Stem Cells. Int J Mol Sci. 2018 Feb 28;19(3):691. doi: 10.3390/ijms19030691.
5. Sung CT, Juhasz ML, Choi FD, Mesinkovska NA. The Efficacy of Topical Minoxidil for Non-Scarring Alopecia: A Systematic Review. J Drugs Dermatol. 2019 Feb 1;18(2):155-160.
6. Bhargava S, Cunha PR, Lee J, Kroumpouzos G. Acne Scarring Management: Systematic Review and Evaluation of the Evidence. Am J Clin Dermatol. 2018 Aug;19(4):459-477. doi: 10.1007/s40257-018-0358-5.
7. Cowin AJ, Brosnan MP, Holmes TM, Ferguson MW. Endogenous inflammatory response to dermal wound healing in the fetal and adult mouse. Dev Dyn. 1998 Jul;212(3):385-93. doi: 10.1002/(SICI)1097-0177(199807)212:3<385::AID-AJA6>3.0.CO;2-D.
8. Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. Trends Cell Biol. 2005 Nov;15(11):599-607. doi: 10.1016/j.tcb.2005.09.002.
9. Baum CL, Arpey CJ. Normal cutaneous wound healing: clinical correlation with cellular and molecular events. Dermatol Surg. 2005 Jun;31(6):674-86; discussion 686. doi: 10.1111/j.1524-4725.2005.31612.
10. Midwood KS, Williams LV, Schwarzbauer JE. Tissue repair and the dynamics of the extracellular matrix. Int J Biochem Cell Biol. 2004 Jun;36(6):1031-7. doi: 10.1016/j.biocel.2003.12.003.
11. Gupta A, Kaur M, Patra S, Khunger N, Gupta S. Evidence-based Surgical Management of Post-acne Scarring in Skin of Color. J Cutan Aesthet Surg. 2020 Apr-Jun;13(2):124-141. doi: 10.4103/JCAS.JCAS_154_19.
12. Jacob CI, Dover JS, Kaminer MS. Acne scarring: a classification system and review of treatment options. J Am Acad Dermatol. 2001 Jul;45(1):109-17. doi: 10.1067/mjd.2001.113451.
13. Goodman GJ, Baron JA. Postacne scarring: a qualitative global scarring grading system. Dermatol Surg. 2006 Dec;32(12):1458-66. doi: 10.1111/j.1524-4725.2006.32354.x.
14. Fabbrocini G, Annunziata MC, D'Arco V, De Vita V, Lodi G, Mauriello MC, Pastore F, Monfrecola G. Acne scars: pathogenesis, classification and treatment. Dermatol Res Pract. 2010;2010:893080. doi: 10.1155/2010/893080.
15. Shen YC, Chiu WK, Kang YN, Chen C. Microneedling Monotherapy for Acne Scar: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Aesthetic Plast Surg. 2022 Aug;46(4):1913-1922. doi: 10.1007/s00266-022-02845-3.

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16. Long T, Gupta A, Ma S, Hsu S. Platelet-rich plasma in noninvasive procedures for atrophic acne scars: A systematic review and meta-analysis. J Cosmet Dermatol. 2020 Apr;19(4):836-844. doi: 10.1111/jocd.13331.
17. Lin L, Liao G, Chen J, Chen X. A systematic review and meta-analysis on the effects of the ultra-pulse CO2 fractional laser in the treatment of depressed acne scars. Ann Palliat Med. 2022 Feb;11(2):743-755. doi: 10.21037/apm-22-70.
18. Kontochristopoulos G, Platsidaki E. Chemical peels in active acne and acne scars. Clin Dermatol. 2017 Mar-Apr;35(2):179-182. doi: 10.1016/j.clindermatol.2016.10.011.
19. Berman B, Perez OA, Konda S, Kohut BE, Viera MH, Delgado S, Zell D, Li Q. A review of the biologic effects, clinical efficacy, and safety of silicone elastomer sheeting for hypertrophic and keloid scar treatment and management. Dermatol Surg. 2007 Nov;33(11):1291-302; discussion 1302-3. doi: 10.1111/j.1524-4725.2007.33280.x.
20. Atiyeh BS. Nonsurgical management of hypertrophic scars: evidence-based therapies, standard practices, and emerging methods. Aesthetic Plast Surg. 2007 Sep-Oct;31(5):468-92; discussion 493-4. doi: 10.1007/s00266-006-0253-y.
21. Layton AM, Yip J, Cunliffe WJ. A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids. Br J Dermatol. 1994 Apr;130(4):498-501. doi: 10.1111/j.1365-2133.1994.tb03385.x.
22. Keaney TC, Tanzi E, Alster T. Comparison of 532 nm Potassium Titanyl Phosphate Laser and 595 nm Pulsed Dye Laser in the Treatment of Erythematous Surgical Scars: A Randomized, Controlled, Open-Label Study. Dermatol Surg. 2016 Jan;42(1):70-6. doi: 10.1097/DSS.0000000000000582.
23. 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 Feb;35(2):171-81. doi: 10.1111/j.1524-4725.2008.34406.x.
24. Campese VM. Minoxidil: a review of its pharmacological properties and therapeutic use. Drugs. 1981 Oct;22(4):257-78. doi: 10.2165/00003495-198122040-00001.
25. Panchaprateep R, Lueangarun S. Efficacy and Safety of Oral Minoxidil 5 mg Once Daily in the Treatment of Male Patients with Androgenetic Alopecia: An Open-Label and Global Photographic Assessment. Dermatol Ther (Heidelb). 2020 Dec;10(6):1345-1357. doi: 10.1007/s13555-020-00448-x.
26. Cranwell W, Sinclair R. Male androgenetic alopecia. In: KR Feingold, B Anawalt, A Boyce, et al, eds. Endotext. MDText.com, Inc.; 2016.
27. Rossi A, Anzalone A, Fortuna MC, Caro G, Garelli V, Pranteda G, Carlesimo M. Multi-therapies in androgenetic alopecia: review and clinical experiences. Dermatol Ther. 2016 Nov;29(6):424-432. doi: 10.1111/dth.12390.
28. Blume-Peytavi U, Hillmann K, Dietz E, Canfield D, Garcia Bartels N. A randomized, single-blind trial of 5% minoxidil foam once daily versus 2% minoxidil solution twice daily in the treatment of androgenetic alopecia in women. J Am Acad Dermatol. 2011 Dec;65(6):1126-1134.e2. doi: 10.1016/j.jaad.2010.09.724.
29. Price VH, Menefee E, Strauss PC. Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. J Am Acad Dermatol. 1999 Nov;41(5 Pt 1):717-21. doi: 10.1016/s0190-9622(99)70006-x.
30. Shao S, Zhang X, Duan L, Fang H, Rao S, Liu W, Guo B, Zhang X. Lysyl Hydroxylase Inhibition by Minoxidil Blocks Collagen Deposition and Prevents Pulmonary Fibrosis via TGF-β1/Smad3 Signaling Pathway. Med Sci Monit. 2018 Nov 27;24:8592-8601. doi: 10.12659/MSM.910761.
31. Hautala T, Heikkinen J, Kivirikko KI, Myllylä R. Minoxidil specifically decreases the expression of lysine hydroxylase in cultured human skin fibroblasts. Biochem J. 1992 Apr 1;283 (Pt 1)(Pt 1):51-4. doi: 10.1042/bj2830051.
32. Murad S, Walker LC, Tajima S, Pinnell SR. Minimum structural requirements for minoxidil inhibition of lysyl hydroxylase in cultured fibroblasts. Arch Biochem Biophys. 1994 Jan;308(1):42-7. doi: 10.1006/abbi.1994.1006.
33. van der Slot AJ, van Dura EA, de Wit EC, De Groot J, Huizinga TW, Bank RA, Zuurmond AM. Elevated formation of pyridinoline cross-links by profibrotic cytokines is associated with enhanced lysyl hydroxylase 2b levels. Biochim Biophys Acta. 2005 Jun 30;1741(1-2):95-102. doi: 10.1016/j.bbadis.2004.09.009.
34. Remst DF, Blaney Davidson EN, Vitters EL, Blom AB, Stoop R, Snabel JM, Bank RA, van den Berg WB, van der Kraan PM. Osteoarthritis-related fibrosis is associated with both elevated pyridinoline cross-link formation and lysyl hydroxylase 2b expression. Osteoarthritis Cartilage. 2013 Jan;21(1):157-64. doi: 10.1016/j.joca.2012.10.002.
35. Zuurmond AM, van der Slot-Verhoeven AJ, van Dura EA, De Groot J, Bank RA. Minoxidil exerts different inhibitory effects on gene expression of lysyl hydroxylase 1, 2, and 3: implications for collagen cross-linking and treatment of fibrosis. Matrix Biol. 2005 Jun;24(4):261-70. doi: 10.1016/j.matbio.2005.04.002.
36. Shao S, Fang H, Duan L, Ye X, Rao S, Han J, Li Y, Yuan G, Liu W, Zhang X. Lysyl hydroxylase 3 increases collagen deposition and promotes pulmonary fibrosis by activating TGFβ1/Smad3 and Wnt/β-catenin pathways. Arch Med Sci. 2019 Jan 16;16(2):436-445. doi: 10.5114/aoms.2018.81357.
37. Priestley GC, Lord R, Stavropoulos P. The metabolism of fibroblasts from normal and fibrotic skin is inhibited by minoxidil in vitro. Br J Dermatol. 1991 Sep;125(3):217-21. doi: 10.1111/j.1365-2133.1991.tb14743.x.
38. Knitlova J, Doubkova M, Plencner M, Vondrasek D, Eckhardt A, Ostadal M, Musilkova J, Bacakova L, Novotny T. Minoxidil decreases collagen I deposition and tissue-like contraction in clubfoot-derived cells: a way to improve conservative treatment of relapsed clubfoot? Connect Tissue Res. 2021 Sep;62(5):554-569. doi: 10.1080/03008207.2020.1816992.
39. Freiha M, Achim M, Gheban BA, Moldovan R, Filip GA. In Vivo Study of the Effects of Propranolol, Timolol, and Minoxidil on Burn Wound Healing in Wistar Rats. J Burn Care Res. 2023 Apr 26:irad057. doi: 10.1093/jbcr/irad057.
40. Polo M, Hill DP Jr, Carney G, Ko F, Wright TE, Robson MC. Minoxidil and wound contraction. Ann Plast Surg. 1997 Sep;39(3):292-8. doi: 10.1097/00000637-199709000-00012.