Clinical, Cosmetic and Investigational Dermatology

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Diagnosis and Treatment of Keloid: Method Summary and Effect Evaluation

Yu Liu, Xiaoliang Xiong, Nan Cao, Yinlong Zhao

Nuclear Medicine Department, Jilin University Second Hospital, Changchun, Jilin Province, People's Republic of China

Correspondence: Yinlong Zhao, Email yinlong@jlu.edu.cn

Abstract: Keloid is a prevalent skin disorder characterized by the abnormal growth of keloid tissue, which usually occurs following wound healing or surgical incisions. It typically progresses through several stages: the inflammatory stage, the proliferative stage, collagen remodeling, and ultimately the formation of keloid. This review aims to summarize the diagnostic and therapeutic methods for keloid, and evaluate their effectiveness. The diagnosis of keloid is usually based on medical history and clinical manifestations such as pain, itching, erythema, and induration. Other commonly used diagnostic methods include tissue biopsy and ultrasound examination. Various treatment options for keloid exist, including physical therapy, medication, surgical treatment, and radiation therapy. Physical therapy includes pressure therapy, laser therapy, such as silicone sheets, elastic bandages, and laser irradiation. Medication treatment mainly involves the application of topical medications or intralesional injections, such as topical corticosteroids, 5-fluorouracil, and others. Radiation therapy can be administered using applicators and superficial radiation therapy, among other methods. The treatment outcomes of keloid vary from person to person and recurrence is common. Therefore, a comprehensive treatment approach may be the most effective strategy. Individualized treatment plans should consider factors such as the patient's age, gender, medical history, and the severity of the condition. In conclusion, the diagnosis and treatment of keloid require consideration of multiple factors and the implementation of individualized treatment plans. Future research should focus on identifying the molecular mechanisms underlying the occurrence and progression of keloid in order to develop more effective treatment methods.

Keywords: keloid, pathogenesis, clinical treatment

Background

Keloid is a result of abnormal skin tissue response during the healing process, which occurs when the skin is injured or a surgical incision is closed, as the body initiates the healing process to restore the structure and function of the damaged tissue.[1] Keloid is a common dermatological condition that is often believed to be associated with a specific "constitution". It is characterized by its persistent and recurring nature. In addition to its negative impact on appearance, keloid can also cause physical discomfort including itching, pain, and general discomfort. In certain instances, keloid growth can restrict limb mobility, thereby significantly affecting daily activities and work performance. Moreover, the presence of keloid can result in social and psychological distress, leading to self-consciousness and anxiety among patients. Nevertheless, the precise mechanisms underlying keloid development and its treatment methods remain incompletely understood.[2] There are a variety of treatments for keloids, but the specific effects vary from person to person, and even the same patient receiving the same treatment at different sites may have different effects. Treatments for keloids include drug therapy, surgery, laser therapy, microneedle therapy, laser therapy, photodynamic therapy, etc.[2] Each treatment has its own unique advantages and limitations. For example, medication can reduce the symptoms of keloid with topical or oral medication, but it requires long-term adherence and there may be an allergic reaction. Surgical treatment can directly remove keloid tissue, but the surgical risks and recovery period need to be carefully considered.

Epidemiology

Prevalence

Keloid is a common skin disorder. The global prevalence of keloid is estimated to be around 2–4%.[3] This means that approximately 150–300 million people worldwide suffer from keloid.

Received: 22 October 2023
Accepted: 18 December 2023
Published: 29 December 2023

Age Distribution

Keloid can occur across all age groups. In children and young adults, particularly during adolescence, the prevalence of keloid is higher.[4] This may be related to the fact that the skin of children and young adults is more prone to developing abnormal keloid.

Gender Differences

There is no significant difference in the incidence of keloids between males and females. Both males and females are equally susceptible to developing keloid.[4]

Genetic Factors

Genetic factors play a significant role in the susceptibility to keloid. Some individuals are naturally more prone to developing keloid, which may be related to their genes. There may be variations in the susceptibility to keloid among different ethnic groups. According to research findings.[5] From the perspective of affected populations, there are significant variations in the incidence of keloid among different ethnicities. The highest prevalence was reported among descendants of African descent, estimated at 4 to 6%; However, some studies put the figure as high as 16% of the adult population in Zaire. In contrast, Asian and Hispanic people have a lower prevalence, while white people have the lowest prevalence, at just 0.09% in England.[6] Multiple phenomena within families also support its genetic characteristics. Based on these observations, scientists believe that there is a close association between keloid and melanocyte-stimulating hormone. According to the research conducted by P. Omo-Dare in 1975 on 34 Nigerian pedigrees, including 11 cases of KD patients, it was found that KD exhibits an autosomal recessive inheritance pattern. However, Marneros et al,[7] through association studies on 14 KD pedigrees (comprising a total of 96 KD patients) from four different ethnicities, including African Americans, Caucasian Americans, Japanese Asians, and Caribbean Africans, proposed an autosomal dominant inheritance pattern for KD. There are discrepancies between these two research findings, which may be attributed to factors such as sample size and ethnic variations. Further research is still required to gain a more comprehensive understanding of the genetic pattern of KD.

Environmental Factors

Climate and environmental conditions do indeed vary. Cities with higher humidity may increase the risk of wound infection, as humidity favors bacterial growth. However, it is worth noting that in areas with higher humidity, the rate of decrease in the inflammatory index is faster than in areas with lower humidity.[8] This shortened duration of the inflammatory process also affects the formation of keloid. As one of the characteristics of the tumor microenvironment (TME), hypoxia also exists in keloid.[9] Hypoxia can significantly regulate cell gene expression, and it has a significant impact on Keloid proliferation, apoptosis, migration, invasion, and collagen synthesis. Therefore, being in an environment with lower oxygen content will also have a certain impact on keloid formation.

Formation Mechanisms

The formation of keloid is indeed a complex process involving the interaction of multiple cell types, signaling pathways, and molecular factors. Here are some widely accepted yet still under research mechanisms of keloid formation:

Inflammatory Response

The inflammatory response is necessary during the wound healing process, but excessive or prolonged inflammation can contribute to the formation of keloid tissue. Inflammation can trigger excessive collagen synthesis and tissue fibrosis. From skin damage to wound healing, there are five stages involved, namely hemostasis, inflammation, proliferation, reepithelialization, and remodeling.[1] Among these stages, inflammation is not only an important phase in normal healing but also closely associated with the formation of keloid tissue. Neutrophils, macrophages, mast cells, and lymphocytes participate in keloid formation, exerting varying degrees of influence on fibroblast activation. This leads to excessive production of collagen fibers, deposition in the extracellular matrix, and ultimately results in the formation of keloid

tissue. During the wound healing process, the release and regulation of cytokines and growth factors play a significant role. These factors can promote collagen synthesis and cell proliferation in keloid tissue, leading to the formation of keloid tissue. Studies have shown that in patients with keloid tissue, pro-inflammatory and fibrotic cytokines such as IL-6,[10] transforming growth factor-beta (TGF-β),[11] and tumor necrosis factor-alpha (TNF-α)[12] are upregulated, while factors that inhibit inflammation such as IL-37[13] and IL-17[14] are decreased.

Tumor Hypothesis

Keloid tissue nodules have the characteristics of continuous growth and invasion of local tissues, and they have a high recurrence rate after surgical treatment. The aerobic glycolysis level of fibroblasts in keloid tissue nodules is increased,[15] resulting in the production of more lactate, which may exhibit a Warburg effect similar to tumors.[16] Furthermore, further research has found that keloid tissue nodules exhibit inactivation of the tumor suppressor gene P53[17] and a decrease in the expression level of the tumor suppressor factor PTEN, but an increase in both factors is found in certain areas of keloid tissue nodules. These findings indicate that keloid tissue nodules have some characteristics similar to tumors, but various factors interact to confine keloid tissue nodules to a benign range. Through in-depth research, the differences and connections between the two will become clearer.

Signaling Pathways

The formation of keloid tissue nodules is associated with the remodeling and rearrangement of collagen proteins. Under normal circumstances, collagen proteins gradually organize and remodel, restoring the scarred area to a structure similar to the surrounding normal skin. However, in certain cases, the remodeling of collagen proteins may be abnormal, leading to the formation of keloid tissue nodules. There are numerous signaling pathways associated with keloid tissue nodules, and the TGF-β1/Smad signaling pathway is currently a hot topic in keloid tissue nodule signaling pathway research,[18] as it is related to various fibrotic diseases. Activation of this pathway can promote fibroblast proliferation and collagen deposition. Moreover, it has been found that by regulating genes such as FOXMI and downregulating interferon regulatory factor 3, the proliferation of fibroblasts and production of collagen can also be inhibited by suppressing the TGF-β1/Smad signaling pathway.[19] These findings indicate the important role of the TGF-β1/Smad signaling pathway in the occurrence of keloid tissue nodules. The JAK/STAT pathway is considered an important signaling pathway that transmits signals from the environment to the inside of cells. In the JAK/STAT pathway, STAT3 is the most important molecule.[14] STAT3 plays a dominant role in regulating cell proliferation, migration, the production of cytokines or chemokines, and inflammation, among other biological processes. It has been found that in keloid tissue, the expression level and phosphorylation status of STAT3 are abnormally increased,[20] suggesting its significant role in the disease process of keloid formation. In addition, integrin signaling pathways, Wnt/β-catenin signaling pathway, and others have also been found to be associated with the formation of keloid tissue nodules, and there is a connection with the TGF-β1/Smad signaling pathway.[21] EMT (epithelial-mesenchymal transition) is a critical stage in cell development,[22] describing the process of cells transitioning from epithelial cells to mesenchymal cells. EMT plays an important role in various stages of cell development. In addition to functional protein molecules, non-coding mRNA molecules such as miRNA[23] also play a significant role in regulating processes such as proliferation, differentiation, apoptosis, and invasion of keratinocytes, which has been confirmed. Further research on the signaling pathways of keloid tissue nodules is expected to provide a more solid theoretical basis for the treatment of keloid tissue nodules.

Genetic and Individual Variations

Genetic factors[24] and individual variations may also influence the formation of keloid tissue nodules. Some individuals are naturally predisposed to keloid formation, while others are not. The presence of genetic susceptibility may be due to genetic factors affecting key steps in the formation of keloid tissue, such as the synthesis, degradation, and remodeling of collagen proteins. Certain genetic variations may lead to abnormal synthesis or degradation of collagen proteins[25], thereby affecting the formation and development of keloid tissue. Certain chronic diseases or immune system abnormalities may increase the risk of keloid tissue nodules.

Diagnostic Methods

Clinical Observation

Doctors usually carefully observe the appearance of keloid tissue nodules, including their shape, color, and degree of indentation or protrusion.

Medical History Inquiry

Doctors will ask patients about trauma, surgery, or other events that may have caused the keloid tissue nodules.

Skin Biopsy

If the morphological characteristics of the keloid tissue nodules are unclear or questionable, a skin biopsy may be recommended.

Imaging Examinations

In certain cases, doctors may request imaging examinations such as superficial ultrasound or magnetic resonance imaging to assess the impact of keloid tissue nodules on deeper tissues.

Treatment and Principles

Physical Therapy

Pressure Therapy

Pressure dressings or compression garments can alleviate the redness, swelling, and overgrowth of keloid by applying moderate pressure and help flatten the keloid.[26]

Ultrasound Therapy

Ultrasound therapy is a non-invasive treatment method commonly used to improve the appearance of keloid tissue nodules. Ultrasound therapy utilizes ultrasound energy to stimulate tissues, promoting tissue repair and the reduction of keloid tissue.[27] Ultrasound therapy applies mechanical stimulation to keloid tissue through ultrasound vibrations. This mechanical action can alter the physical properties of the tissue, promoting tissue repair and regeneration. Ultrasound therapy stimulates cells within the keloid tissue, increasing collagen synthesis, regulating cellular functions, and promoting tissue repair, thereby enhancing cellular metabolism and activation.[28] However, the effectiveness of ultrasound therapy may vary depending on individual circumstances, and multiple sessions may be required.

Laser Therapy

Laser therapy can alleviate the redness, swelling, and overgrowth of keloid by stimulating collagen regeneration and disrupting abnormal vascular structures.[29] For example, intense pulsed light (IPL) passes through the skin and is absorbed by the hemoglobin in the blood vessels, causing endothelial cell damage through photothermal effects, leading to vascular occlusion and reducing the nutrient supply to keloid tissue.[30] Photothermal effects can also cause collagen damage and remodeling. The mechanism by which pulsed dye laser (PDL) causes vascular damage to keloid tissue is similar to that of IPL. Additionally, another approach of PDL treatment for keloid tissue is to inhibit fibroblast proliferation and downregulate the expression of connective tissue growth factor (CTGF).[31] The wavelength of neodymium-doped yttrium aluminum garnet (Nd:YAG) laser is close to the absorption peak of hemoglobin, which can destroy blood vessels in keloid tissue, reduce the Vancouver Scar Scale, and improve the condition of keloid tissue.[32] Laser treatment can increase the permeability of the epidermis, thereby increasing the absorption of topical medications.[33]

Cryotherapy

Liquid nitrogen cryotherapy is widely used in the treatment of skin lesions. By lowering the temperature to form ice crystals, it causes cell dehydration, denaturation, and necrosis, thereby achieving therapeutic effects.[34] Traditional contact cryotherapy may lead to side effects such as blistering and hypopigmentation, affecting the patient's aesthetics and

treatment outcomes. However, the emergence of in-lesion cryotherapy technology in recent years has addressed these shortcomings.[35] Through cryoablation probes, the cryogen is directly delivered into the lesion for treatment, preserving the appearance of the skin surface and reducing the side effects of hypopigmentation, thereby enhancing the aesthetic outcome. CC Zouboulis believes that in-lesion cryotherapy can achieve very good aesthetic results in the treatment of ear keloids, resulting in low visibility of the keloid after treatment. Therefore, it can be considered as the preferred treatment option for ear keloids.[36]

Medication Therapy

Topical Medications

Keloid Gels or Creams

These medications often contain ingredients such as silicone gel, vitamin E, chamomile extract, etc., which can help soften and improve the appearance of keloid.

5-Fluorouracil Patches

This medication can be applied to keloid and helps alleviate keloid hardening and overgrowth by inhibiting cell proliferation.[37]

Injectable Medication Therapy

Steroid Injections

Corticosteroids, such as adrenal cortex hormones, can alleviate the redness, swelling, and hardening symptoms of keloid by reducing the inflammatory response in keloid tissue and inhibiting collagen synthesis.[38] Currently, some guidelines consider corticosteroid hormone therapy as the preferred method for treating keloid tissue nodules. It can be used alone for intralesional injection or in combination with other medications for intralesional injection therapy.

Hyaluronic Acid and Botulinum Toxin

Hyaluronic acid and botulinum toxin are commonly used keloid fillers.[39] They can be injected to reduce the protrusion of keloid and improve their appearance. The effects of the injections are usually immediately visible, providing significant satisfaction to patients. However, it is important to note that the effects of these fillers are not permanent and regular injections are needed to maintain the results. Typically, the effects can last for several months to a year, and patients need to receive injection treatments at certain intervals. Additionally, injections of fillers may be accompanied by some side effects. Common side effects include bruising, redness, pain, or a stinging sensation, which are usually temporary and will resolve within a few days. However, more severe side effects such as infection, allergic reactions, or improper injection techniques may occur.

5-fluorouracil belongs to a class of anti-tumor medications, and its main action is to inhibit the S phase of the cell cycle. Its mechanism of action involves inhibiting thymidylate synthase, thereby blocking the conversion of deoxyuridine monophosphate and ultimately inhibiting DNA synthesis.[40]

Bleomycin is an anti-tumor medication belonging to the class of bleomycins, and it has multiple mechanisms of action. It can inhibit DNA replication and cause DNA strand breaks, thereby affecting the cell cycle.[41] Through this mechanism, bleomycin can prevent the proliferation and growth of tumor cells. Additionally, bleomycin has the ability to disrupt collagen fiber cells, promote collagen dissolution, and cause damage to internal blood vessels, thereby reducing blood supply. This action helps inhibit tumor growth and spread. In clinical treatment, low-dose bleomycin is often used in combination with steroids for intralesional injection therapy of keloid tissue nodules. This combination therapy can improve the appearance and texture of keloid by inhibiting keloid tissue overgrowth and reducing collagen accumulation. The effects of bleomycin also include reducing the blood supply to keloid tissue,[42] thereby alleviating redness, swelling, and pain in keloid.

Antihistamines are a class of drugs that have the ability to inhibit mast cells and suppress histamine. They work by blocking the release of histamine or blocking histamine receptors, thereby reducing allergic reactions and symptoms caused by inflammation. These medications can effectively relieve symptoms of allergic conditions such as allergic

rhinitis, urticaria, and provide better relief and treatment outcomes for patients. Additionally, antihistamines are widely used in the treatment of allergic reactions, such as drug allergies and food allergies.

Novel Targeted Drugs are being explored in the laboratory to target specific factors and cellular signaling pathways involved in the pathogenesis of keloid tissue nodules.[43] However, the clinical application of these drugs still requires large-scale validation and clinical trials to ensure their safety and efficacy. Currently, these drugs are still in the research stage, but the potential therapeutic effects provide hope for future treatment of keloid tissue nodules.

Radiation Therapy

Currently, the types of radiation commonly used for the treatment of keloid tissue nodules include electron beams and photon beams. High-energy electron beams can precisely target the area, reducing redness and overgrowth of keloid. Photon radiation can inhibit cell proliferation in keloid tissue, alleviating keloid hardening and overgrowth.

The commonly used electron beam is beta radiation. The principle of beta radiation therapy for keloid tissue nodules is to use the energy of beta particles to promote tissue repair and improve the appearance of keloid tissue nodules.[2] Beta particles are high-speed electrons that can penetrate a few millimeters of tissue at relatively low energy levels. Beta radiation therapy uses radioactive isotopes or specific devices to generate beta particles and deliver them to the area of keloid tissue nodules. When beta particles interact with the tissue, interactions such as ionization, excitation, and ionization occur, releasing energy.[44] The therapy promotes keloid tissue repair and improvement through several aspects: ① Inhibiting collagen synthesis: The energy of beta particles can inhibit excessive collagen synthesis, reducing the hardness and protrusion of keloid tissue. ② Facilitating collagen degradation: Beta particle therapy can also promote collagen degradation, helping to flatten and alleviate keloid tissue nodules. ③ Anti-inflammatory effect: Beta radiation therapy may also alleviate inflammation and redness in keloid tissue nodules by suppressing inflammatory reactions and regulating immune responses.[45]

However, there may be some side effects to consider: Beta radiation therapy can cause skin discomfort, redness, itching, burning sensation, and desquamation. These reactions are usually temporary and gradually subside during the course of treatment.[46] It is important to note that beta radiation is a form of ionizing radiation, and if not administered properly or if the dosage is too high, it can cause irreversible damage to surrounding tissues and other parts of the body. Therefore, strict control of dosage and irradiation area is necessary during treatment to minimize radiation risks.

Surgical Treatment

For severe keloid tissue nodules, surgical intervention may be necessary to improve the appearance and functionality of the keloid. Surgical procedures such as keloid excision, skin grafting, tissue expansion, etc., may be performed.[47] Approximately 50% to 80% of patients with keloid experience recurrence after undergoing surgical treatment alone, so measures should be taken promptly after surgery to reduce the risk of keloid recurrence in the surgical area.[48] Applying silicone gel and tretinoin cream to the wound site postoperatively is a convenient method for preventing keloid recurrence. Although the effects of both are similar, for patients who cannot tolerate the burning sensation caused by tretinoin cream, silicone gel is a more suitable choice.[49]

Comprehensive Treatment

Comprehensive treatment for keloid involves using multiple methods to treat the lesions, with the most common approach being a combination of surgical treatment and radiotherapy.[50] Additionally, various other combination methods exist, such as intralesional injection combined with radiotherapy, surgical treatment combined with laser therapy, and surgical treatment combined with pressure therapy.[51] Different approaches are employed even for the same patient based on the location of the keloid. The comprehensive and individualized nature of the two-pronged treatment plan for keloid can indeed help patients achieve better therapeutic effects and improve the appearance of the keloid.[2] Local treatment methods such as laser therapy, microneedling, chemical peels, etc., provide effective means of improvement tailored to the specific characteristics of the keloid, while overall conditioning involving nutritional regulation, drug therapy, and physical therapy can promote skin regeneration and healing processes from within.

Summary and Prospect

In summary, this article has addressed the pathogenesis, epidemiological characteristics, and treatment options for keloid tissue nodules. Currently, treatment options for keloid tissue nodules are limited and demonstrate varying degrees of effectiveness. Common treatment methods encompass medication therapy, local treatments, and surgical interventions; however, these methods may not consistently yield satisfactory results and can entail side effects and risks. The high recurrence rate and refractory nature of keloid tissue nodules present significant challenges and uncertainties in treatment. The specific mechanisms underlying keloid tissue nodules are not entirely understood, further impeding the development of precise and effective treatments. Current treatment principles primarily focus on reducing redness, hardening, and overgrowth of keloid tissue, while promoting regeneration and repair of normal tissue. Clinicians must develop individualized treatment plans based on each patient's specific circumstances. Additionally, preventive measures can be implemented for individuals at high risk of keloid tissue nodules. Future research and developments will contribute to a better understanding of the pathogenesis of keloid tissue nodules and explore more effective treatment approaches. Targeted therapy for keloid tissue nodules is emerging as a promising area of research, offering more effective and personalized treatment options for patients. The aim of targeted therapy is to intervene in the abnormal skin healing process, reduce keloid tissue formation, and promote normal tissue repair. In recent years, many researchers have focused on exploring the molecular mechanisms of keloid tissue nodules and have identified potential targets. Fibroblast activation and excessive proliferation are considered key factors in the formation of keloid tissue nodules. Consequently, research efforts have concentrated on finding drugs or molecules that can inhibit fibroblast proliferation and activation. Certain cellular signaling pathways play critical roles in keloid tissue nodule formation. By intervening in these signaling pathways, it is possible to inhibit fibroblast proliferation and keloid tissue formation. Some drugs, such as small molecule inhibitors and biologics, have been utilized to inhibit the activity of specific signaling pathways, thereby reducing the formation of keloid tissue nodules. Furthermore, research has also explored therapeutic approaches involving altering gene expression to intervene in keloid tissue nodules. Gene therapy and gene editing technologies have been utilized to modulate the expression of specific genes to influence cellular behavior and tissue repair during keloid healing. However, despite the potential demonstrated by targeted therapy in keloid tissue nodules, it is still in the early stages of research. Many treatment methods require further validation and clinical trials to determine their safety and efficacy. The age of the patient, type of keloid, and treatment site are all factors that can influence the treatment outcomes. Therefore, when selecting a treatment method, it is necessary to comprehensively consider individual differences and treatment characteristics in order to achieve better therapeutic results. In the future, with the continuous advancement of medical technology, the treatment of keloid will become more personalized and precise, providing patients with more options and better therapeutic outcomes.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Rekha A. Keloids - a frustrating hurdle in wound healing. *Int Wound J*. 2004;1(2):145–148. doi:10.1111/j.1742-4801.2004.00038.x
2. Ekstein SF, Wyles SP, Moran SL, Meves A. Keloids: a review of therapeutic management. *Int J Dermatol*. 2021;60(6):661–671. doi:10.1111/ijd.15159
3. Lyons AB, Peacock A, Braunberger TL, Viola KV, Ozog DM. Disease severity and quality of life outcome measurements in patients with keloids: a systematic review. *Dermatol Surg*. 2019;45(12):1477–1483. doi:10.1097/DSS.0000000000002172
4. Liu S, Yang H, Song J, Zhang Y, Abualhssain ATH, Yang B. Keloid: genetic susceptibility and contributions of genetics and epigenetics to its pathogenesis. *Exp Dermatol*. 2022;31(11):1665–1675. doi:10.1111/exd.14671
5. Marneros AG, Krieg T. Keloids–clinical diagnosis, pathogenesis, and treatment options. *J Dtsch Dermatol Ges*. 2004;2(11):905–913. doi:10.1046/j.1439-0353.2004.04077.x
6. LeFlore IC. Misconceptions regarding elective plastic surgery in the black patient. *J Natl Med Assoc*. 1980;72(10):947–948.
7. Marneros AG, Norris JE, Olsen BR, Reichenberger E. Clinical genetics of familial keloids. *Arch Dermatol*. 2001;137(11):1429–1434. doi:10.1001/archderm.137.11.1429
8. Maibach HI, Rovee DT. *Effect of Climate in the Repair of Cutaneous Wounds in Humans*. Chicago: Year Book Medical Publishers; 1972.
9. Si L, Zhang M, Guan E, et al. Resveratrol inhibits proliferation and promotes apoptosis of keloid fibroblasts by targeting HIF-1α. *J Plast Surg Hand Surg*. 2020;54(5):290–296. doi:10.1080/2000656X.2020.1771719
10. Abdu Allah AMK, Mohammed KI, Farag AGA, Hagag MM, Essam M, Tayel NR. Interleukin-6 serum level and gene polymorphism in keloid patients. *Cell Mol Biol*. 2019;65(5):43–48. doi:10.14715/cmb/2019.65.5.7

11. Hu HH, Chen DQ, Wang YN, et al. New insights into TGF-β/Smad signaling in tissue fibrosis. *Chem Biol Interact*. 2018;292:76–83. doi:10.1016/j.cbi.2018.07.008
12. Pop VV, Seicean A, Lupan I, Samasca G, Burz CC. IL-6 roles - Molecular pathway and clinical implication in pancreatic cancer - A systemic review. *Immunol Lett*. 2017;181:45–50. doi:10.1016/j.imlet.2016.11.010
13. Khattab FM, Samir MA. Correlation between serum IL 37 levels with keloid severity. *J Cosmet Dermatol*. 2020;19(9):2428–2431. doi:10.1111/jocd.13290
14. Lee SY, Kim EK, Seo HB, et al. IL-17 induced stromal cell-derived factor-1 and profibrotic factor in keloid-derived skin fibroblasts via the STAT3 pathway. *Inflammation*. 2020;43(2):664–672. doi:10.1007/s10753-019-01148-1
15. Ueda K, Furuya E, Yasuda Y, Oba S, Tajima S. Keloids have continuous high metabolic activity. *Plast Reconstr Surg*. 1999;104(3):694–698. doi:10.1097/00006534-199909010-00012
16. Ichioka S, Ando T, Shibata M, Sekiya N, Nakatsuka T. Oxygen consumption of keloids and hypertrophic scars. *Ann Plast Surg*. 2008;60(2):194–197. doi:10.1097/SAP.0b013e318053ec1d
17. De Felice B, Wilson RR, Nacca M, Ciarmiello LF, Pinelli C. Molecular characterization and expression of p63 isoforms in human keloids. *Mol Genet Genomics*. 2004;272(1):28–34. doi:10.1007/s00438-004-1034-4
18. Li T, Zhao J. Knockdown of eIF3a inhibits TGF-β1-induced extracellular matrix protein expression in keloid fibroblasts. *Mol Med Rep*. 2018;17(3):4057–4061. doi:10.3892/mmr.2017.8365
19. Mun JH, Kim YM, Kim BS, Kim JH, Kim MB, Ko HC. Simvastatin inhibits transforming growth factor-β1-induced expression of type I collagen, CTGF, and α-SMA in keloid fibroblasts. *Wound Repair Regen*. 2014;22(1):125–133. doi:10.1111/wrr.12136
20. Zhou Y, Sun Y, Hou W, et al. The JAK2/STAT3 pathway inhibitor, AG490, suppresses the abnormal behavior of keloid fibroblasts in vitro. *Int J Mol Med*. 2020;46(1):191–200. doi:10.3892/ijmm.2020.4592
21. Wang M, Chen L, Huang W, et al. Improving the anti-keloid outcomes through liposomes loading paclitaxel-cholesterol complexes. *Int J Nanomed*. 2019;14:1385–1400. doi:10.2147/IJN.S195375
22. Satish L, Evdokiou A, Geletu E, Hahn JM, Supp DM. Pirfenidone inhibits epithelial-mesenchymal transition in keloid keratinocytes. *Burns Trauma*. 2020;8:tkz007.
23. Wu J, Fang L, Cen Y, Qing Y, Chen J, Li Z. MiR-21 regulates keloid formation by downregulating Smad7 via the TGF-β/Smad signaling pathway. *J Burn Care Res*. 2019;40(6):809–817. doi:10.1093/jbcr/irz089
24. Glass DA. Current understanding of the genetic causes of keloid formation. *J Investig Dermatol Symp Proc*. 2017;18(2):S50–S53. doi:10.1016/j.jisp.2016.10.024
25. Nyika DT, Khumalo NP, Bayat A. Genetics and epigenetics of keloids. *Adv Wound Care*. 2022;11(4):192–201. doi:10.1089/wound.2021.0094
26. Ghassemi P, Shupp JW, Travis TE, Gravunder AJ, Moffatt LT, Ramella-Roman JC. A portable automatic pressure delivery system for scar compression therapy in large animals. *Rev Sci Instrum*. 2015;86(1):015101. doi:10.1063/1.4904842
27. Guo R, Xiang X, Wang L, Zhu B, Cheng S, Qiu L. Quantitative assessment of keloids using ultrasound shear wave elastography. *Ultrasound Med Biol*. 2020;46(5):1169–1178. doi:10.1016/j.ultrasmedbio.2020.01.010
28. Huang SY, Xiang X, Guo RQ, Cheng S, Wang LY, Qiu L. Quantitative assessment of treatment efficacy in keloids using high-frequency ultrasound and shear wave elastography: a preliminary study. *Sci Rep*. 2020;10(1):1375. doi:10.1038/s41598-020-58209-x
29. Ravanfar P, Alster TS. Laser earlobe revision. *Dermatol Surg*. 2013;39(7):1056–1061. doi:10.1111/dsu.12223
30. Erol OO, Gurlek A, Agaoglu G, Topcuoglu E, Oz H. Treatment of hypertrophic scars and keloids using intense pulsed light (IPL). *Aesthetic Plast Surg*. 2008;32(6):902–909. doi:10.1007/s00266-008-9161-7
31. Zhu R, Yue B, Yang Q, et al. The effect of 595 nm pulsed dye laser on connective tissue growth factor (CTGF) expression in cultured keloid fibroblasts. *Lasers Surg Med*. 2015;47(2):203–209. doi:10.1002/lsm.22334
32. Pan L, Qin H, Li C, Zhang G, Yang L, Zhang L. Efficacy of the neodymium-doped yttrium aluminum garnet laser in the treatment of keloid and hypertrophic scars: a systematic review and meta-analysis. *Aesthetic Plast Surg*. 2022;46(4):1997–2005. doi:10.1007/s00266-021-02716-3
33. Ali FR, Al-Niaimi F. Laser-assisted drug delivery in dermatology: from animal models to clinical practice. *Lasers Med Sci*. 2016;31(2):373–381. doi:10.1007/s10103-015-1853-z
34. Zouboulis CC. Kryochirurgie in der Dermatologie [Cryosurgery in dermatology]. *Hautarzt*. 2015;66(11):834–848. German. doi:10.1007/s00105-015-3703-0
35. Har-Shai Y, Har-Shai L. Minimally invasive technologies for the treatment of hypertrophic scars and keloids: intralesional cryosurgery. In: Téot L, Mustoe TA, Middelkoop E, Gauglitz GG, editors. *Textbook on Scar Management: State of the Art Management and Emerging Technologies*. Cham (CH): Springer Copyright 2020, The Author(s); 2020:235–241.
36. Zouboulis CC, Weidmann MJ, Har-Shai Y. Keloidbehandlung mit intraläsionaler Kryochirurgie [Intralesional cryosurgery in the treatment of keloids - a differentiation of keloid types for the improvement of patient selection]. *Laryngorhinootologie*. 2019;98(8):536–544. German. doi:10.1055/a-0960-6100
37. Hietanen KE, Järvinen TA, Huhtala H, Tolonen TT, Kuokkanen HO, Kaartinen IS. Treatment of keloid scars with intralesional triamcinolone and 5-fluorouracil injections - a randomized controlled trial. *J Plast Reconstr Aesthet Surg*. 2019;72(1):4–11. doi:10.1016/j.bjps.2018.05.052
38. Huang C, Ogawa R. Pharmacological treatment for keloids. *Expert Opin Pharmacother*. 2013;14(15):2087–2100. doi:10.1517/14656566.2013.826651
39. Bi M, Sun P, Li D, Dong Z, Chen Z. Intralesional injection of botulinum toxin type a compared with intralesional injection of corticosteroid for the treatment of hypertrophic scar and keloid: a systematic review and meta-analysis. *Med Sci Monit*. 2019;25:2950–2958. doi:10.12659/MSM.916305
40. LaRanger R, Karimpour-Fard A, Costa C, Mathes D, Wright WE, Chong T. Analysis of keloid response to 5-fluorouracil treatment and long-term prevention of keloid recurrence. *Plast Reconstr Surg*. 2019;143(2):490–494. doi:10.1097/PRS.0000000000005257
41. Guo R, Xuan W, He X, Xu K, Zhang F. Clinical efficacy and safety of pulsed dye laser combined with pingyangmycin on hyperplastic scar after acne. *Mediators Inflamm*. 2022;2022:3305107. doi:10.1155/2022/3305107
42. Gao QH, Zheng GJ, Wang XY, et al. 平阳霉素白蛋白微球诱导兔耳中央动脉闭锁的实验研究 [Effects of Pingyangmycin albumin microspheres on sclerostenosis of the rabbit central auricular arteries]. *Shanghai Kou Qiang Yi Xue*. 2005;14(1):42–47. Chinese.
43. Guo QG, Yao M. 瘢痕疙瘩病灶内药物注射治疗的研究进展 [Advances in the research of drug intralesional injection therapy in keloid]. *Zhonghua Shao Shang Za Zhi*. 2018;34(6):415–418. Chinese. doi:10.3760/cma.j.issn.1009-2587.2018.06.024

44. Supe SS, Supe SJ, Rao SM, Deka AC, Deka BC. Treatment of keloids by 90Sr-90Y beta-rays. *Strahlenther Onkol*. 1991;167(7):397–402.
45. Chen Y, Dong F, Wang X, et al. Postoperative carbon ion radiotherapy for keloids: a preliminary report of 16 cases and review of the literature. *Wounds*. 2014;26(9):264–272.
46. Ji J, Tian Y, Zhu YQ, et al. Ionizing irradiation inhibits keloid fibroblast cell proliferation and induces premature cellular senescence. *J Dermatol*. 2015;42(1):56–63. doi:10.1111/1346-8138.12702
47. Shockman S, Paghdal KV, Cohen G. Medical and surgical management of keloids: a review. *J Drugs Dermatol*. 2010;9(10):1249–1257.
48. Daurade M, Breton P, Rouard N, Lorchel F, Ibrahim B, Sigaux N. Efficacy of surgical excision and brachytherapy in the treatment of keloids: a retrospective cohort study. *Adv Skin Wound Care*. 2020;33(11):1–6. doi:10.1097/01.ASW.0000717228.02752.4e
49. Kwon SY, Park SD, Park K. Comparative effect of topical silicone gel and topical tretinoin cream for the prevention of hypertrophic scar and keloid formation and the improvement of scars. *J Eur Acad Dermatol Venereol*. 2014;28(8):1025–1033. doi:10.1111/jdv.12242
50. Deng K, Xiao H, Liu X, Ogawa R, Xu X, Liu Y. Strontium-90 brachytherapy following intralesional triamcinolone and 5-fluorouracil injections for keloid treatment: a randomized controlled trial. *PLoS One*. 2021;16(3):e0248799. doi:10.1371/journal.pone.0248799
51. Walsh LA, Wu E, Pontes D, et al. Keloid treatments: an evidence-based systematic review of recent advances. *Syst Rev*. 2023;12(1):42. doi:10.1186/s13643-023-02192-7