cosmetics

MDPI

Review

Aberrances of the Wound Healing Process: A Review

Montserrat Fernandez-Guarino [1], Jorge Naharro-Rodriguez [1] and Stefano Bacci [2,*]

[1] Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), 28034 Madrid, Spain; drafernandezguarino@gmail.com (M.F.-G.); jorgenrmed@gmail.com (J.N.-R.)
[2] Research Unit of Histology and Embriology, Department of Biology, University of Florence, Viale Pieraccini 6, 50134 Florence, Italy
* Correspondence: stefano.bacci@unifi.it

Abstract: Wound healing is a complex biological process that can lead to chronic wounds, keloids, and hypertrophic scars when disrupted. Chronic wounds result from a prolonged inflammatory phase and impaired re-epithelialization. Keloids are characterized by excessive collagen deposition beyond the original wound boundaries, driven by persistent inflammation and fibroblast hyperactivity. Hypertrophic scars, on the other hand, are confined to the wound edges and are caused by an imbalance in collagen synthesis and degradation, typically resolving over time. The therapeutic approach to wound healing impairment involves a range of strategies, including non-invasive (which focus on supporting the natural healing process), minimally invasive, and aggressive interventions (such as surgical approach, often reserved for severe or refractory cases). Emerging therapies, including stem cell treatments and botulinum toxin injections, offer new hope for improving outcomes in patients with wound healing impairments. This review highlights the distinct mechanisms underlying chronic wounds, keloids, and hypertrophic scars and discusses their respective therapeutic approaches, focusing on both established and emerging therapies. Understanding these mechanisms is crucial for optimizing treatment strategies and improving patient outcomes.

Keywords: wound healing; acute wounds; chronic wounds; keloids; hypertrophic scars

Citation: Fernandez-Guarino, M.; Naharro-Rodriguez, J.; Bacci, S. Aberrances of the Wound Healing Process: A Review. *Cosmetics* **2024**, *11*, 209. https://doi.org/10.3390/cosmetics11060209

Academic Editor: Enzo Berardesca

Received: 28 October 2024
Revised: 25 November 2024
Accepted: 26 November 2024
Published: 28 November 2024

1. Introduction

In public health, impaired Wound Healing (WH) is a significant concern because its treatment necessitates both costly and complex therapies. Millions of individuals need treatment for chronic wounds, with the associated costs amounting to billions of dollars. The increasing prevalence of age, diabetes, and other risk factors in the population is primarily responsible for the escalation of this burden. In Europe, it is anticipated that over 1.5 million individuals may be adversely affected by chronic wounds, reflecting a concerning situation. Consequently, WH is of significant interest, as seen by the multitude of fellowship programs available for various medical specialists, including vascular surgeons, nurses, dermatologists, and general practitioners. WH must adopt new technology because of existing demand. Moreover, other issues arise since a thorough comprehension of the molecular systems associated with wound healing has not yet gained widespread significance. This knowledge concentrates on specialized issues, which, unlike some academic disciplines, involve a restricted group of experts discussing the pertinent topics among themselves [1–3].

The guidelines are undoubtedly a valuable resource for wound care in clinical practice [4–6]. This is particularly pertinent given that the biofilm, accountable for 80% of infections and perpetuating the inflammatory phase of the wound, must be eradicated [5].

To gather the relevant literature for this review, a narrative search was conducted across multiple databases, including PubMed, Scopus, and Web of Science. The search was limited to articles published in English within the last ten years to ensure the inclusion of the most recent advancements in scar management. Studies included in the review

were required to focus on human subjects and specifically address the treatment of keloids, hypertrophic scars, or wound healing mechanisms. Both clinical trials and observational studies were considered, while case reports were only included if they provided significant insight into novel therapies.

2. Principal Events in the Wound Healing Process

WH has four overlapping phases: hemostasis, inflammation, proliferation, and remodeling/maturation [7–11].

2.1. Hemostasis

Endothelial cells release the von Willebrand factor during hemostasis. This factor facilitates platelet adhesion, therefore triggering the release of mediators. The release of these molecules induces the formation of a fibrin clot, which occludes the lesion, halts the hemorrhage, and averts additional injury. In reaction to elevated calcium ion concentrations, the smooth muscles contract, resulting in the fast constriction of the arteries. This thus leads to a decrease in blood flow via the arteries. When these occurrences take place, they result in the creation of vasoactive metabolites, which are responsible for the vasodilation and relaxation of arterial arteries. When it comes to completing this phase, only a few minutes are required [7–11].

2.2. Inflammation

Mast cells (MCs) facilitate vasodilation during the inflammatory phase. This is achieved by the synthesis of histamine or serotonin. In this instance, neutrophil granulocytes and monocytes (which are primed to differentiate into macrophages) engage in a process termed diapedesis. Thus, phagocytosis is promoted within the lesion to eradicate any infections or damaged cells that may exist. Cytokines and growth factors are released by leukocytes to initiate the proliferative phase of the cell cycle. Keratinocytes and various other cell types participate in this process by secreting cytokines that facilitate inflammation. In this phase, the period often spans from 0 to 3 days [7–11]. Attention must also be directed to the presence of additional chemicals during the inflammatory phase, including cytokines, matrix proteins, and enzymes. Chemokines are critically important as they predominantly attract neutrophils and lymphocytes, which orchestrate the earliest phases of wound healing [7–12].

2.3. Proliferation

Fibroblasts are involved in the process of angiogenesis and contribute to the creation of granulation tissue during the proliferative phase. They also govern the migration and proliferation of keratinocytes and can be found in the process of angiogenesis. The growth factors implicated in this process are incessantly released by macrophages and medial cells alongside the aforementioned cellular types. The duration of this phase varies from three to twelve days [7–12]. Wound contraction is induced by myofibroblasts, which are positive for Smooth Muscle Actin (SMA) and derive from fibroblasts. The key mechanisms that distinguish the maturation phase, or remodeling phase, are collagen restoration and wound contraction. A variety of growth factors govern the transitions between the mesenchymal–mesenchymal and endothelial–mesenchymal phenotypes, and they also facilitate the remodeling phase. Moreover, these modifications occur via the beta-signaling pathways of the Transforming Growth Factor (TGF) or the Notch pathways, both of which reduce cadherin production in vessels [7–12]. Beta2AR is a significant molecule implicated in the mediation of the epithelial–mesenchymal transition (EMT) process. This phase may endure for a duration ranging from three days to six months.

2.4. Remodeling/Maturation

Matrix metalloproteinases (MMPs) and their inhibitors, referred to as tissue inhibitors of metalloproteinases (TIMPs), are important in the formation of scars. The remodeling of

granulation tissue is an essential phase in scar formation. The formation of the extracellular matrix (ECM) is diminished as a result, and the constituents of the ECM undergo alterations. Specifically, type III collagen replaces type I collagen. Elastin, previously absent, is now present in the granulation tissue. Furthermore, the death of particular cell types in the granulation tissue is unquestionably an important event in the healing of wounds. Specifically, one study investigates if the fibrocytes in the dermis come from other cellular types that have evolved later in the processes described or from myofibroblastic forms that gradually lose their characteristic morphological traits [7–12]. A schematized representation of molecular mechanisms of different stages of wound healing is represented in Table 1.

Table 1. Schematized representation of mechanisms and stages of wound healing. Adapted from [7].

Phases	Time	Cells	Functions
Hemostasis	A few minutes	Platelets	Initiation of inflammatory responses, angiogenesis
Inflammatory	3–12 min to 3 days	Mast Cells	Vasodilation, inflammatory response, production of ECM
Inflammatory	3–12 min to 3 days	Neutrophils	Inflammatory response, keratinocyte proliferation, fibroblast proliferation, angiogenesis, collagen synthesis, endothelial cell activation
Inflammatory	3–12 min to 3 days	Macrophages	Inflammatory response, fibroblast proliferation, fibroblast chemotaxis, angiogenesis, ECM deposition
Inflammatory	3–12 min to 3 days	Dendritic cells, plasmacytoid dendritic cells	Inflammatory response
Inflammatory	3–12 min to 3 days	Lymphocytes	Inflammatory response, decrease in collagen synthesis, synthesis of MMPS inflammatory response
Proliferation	3 days to 12 days	Keratinocytes	Angiogenesis, proliferation of keratinocytes and fibroblasts
Maturation or remodeling	12 days–6 mounths	Fibroblasts, myofibroblasts	Chemotaxis of inflammatory cells, proliferation of fibroblasts, fibroblast differentiation

3. Alterations in the Normal Wound Healing Process

Multiple factors can lead to impaired wound healing. In general terms, the factors that influence repair can be categorized into local and systemic. Local factors are those that directly influence the characteristics of the wound itself, while systemic factors are the overall health or disease state of the individual that affect their ability to heal. About local factors, it seems important to include oxygenation, infection, foreign bodies, and venous sufficiency. About systemic factors, it seems relevant to mention age and gender, sex hormones, stress, ischemia, diseases like diabetes, obesity, medications, alcoholism and smoking, immunocompromised conditions, and nutrition [13].

3.1. Chronic Skin Lesion

According to the international literature, a skin lesion is considered a chronic wound if it does not heal after six to eight weeks. These lesions have an inflammatory response that persists over time, maintaining an imbalance between productive and degenerative

processes, but not following the traditional, orderly, and timely sequence of the repair process, or progressing through these phases without regaining the anatomical and functional integrity of the tissue [13–16].

Many factors cause the process to be delayed, which impedes it and makes it chronic in the first place. Based on probability, 1406 clinical presentations may occur [3,6,11,13–15], with 140 pathologies thought to be involved and an average comorbidity of approximately six for people over 65 (85% of the population having at least one chronic illness and 30% having three or more chronic conditions). The main causes of CWs include venous ulcers (VUs), diabetic ulcers (DUs) and pressure ulcers (PUs), all of them influenced by systemic factors such as metabolic, hormonal, venous circulation, or disability [3,13–15]. The typical clinical aspect of a venous ulcer and a diabetic foot ulcer is displayed on Figure 1A and Figure 1B, respectively.

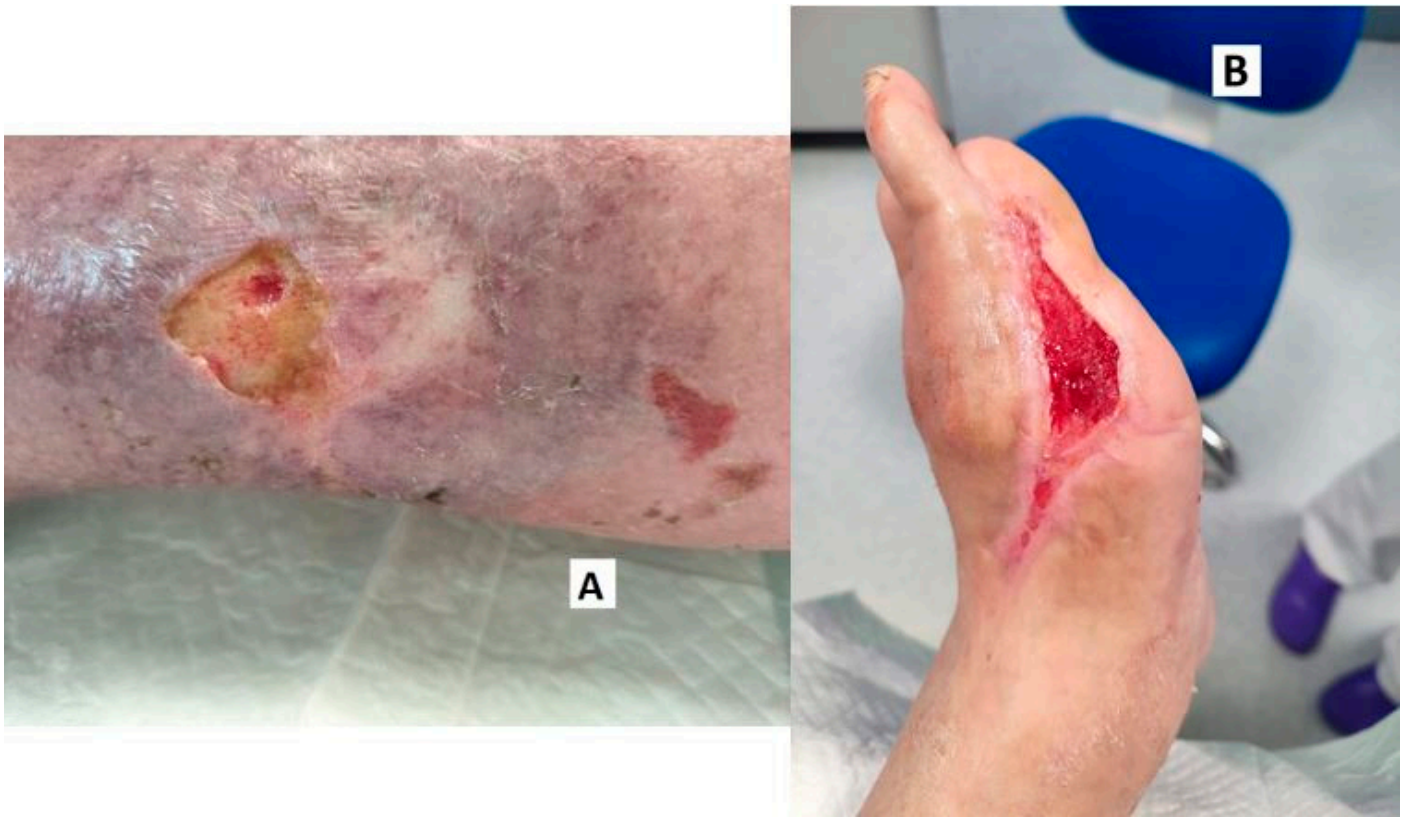

Figure 1. (**A**) Typical image of a venous ulcer in the pretibial area, secondary to chronic venous insufficiency and cutaneous sclerosis, and (**B**) typical clinical aspect of diabetic foot ulcers, provided by Dr. Almudena Cecilia-Matilla, Diabetic Foot Unit, Angiology and Vascular Surgery Department. Ramón y Cajal University Hospital.

The causes of skin ulcers include a wide range of clinical symptoms and syndromes that have been well identified and documented in the literature; however, the treatment of these conditions is outside the purview of this investigation. During the protracted inflammatory phase of ulcers, protease activity increases, leading to the breakdown of growth factors and other molecular signals that help the reparative phase. The dominance of reparative processes over destructive ones in chronic ulcers is hampered by the overproduction of pro-inflammatory cytokines and hydrolytic enzymes [3,13–15]. It has been suggested that intervention to lower protease activity can preserve endogenous growth factors and maintain the regular healing process. For the body to heal, the synthesis of new tissue and the breakdown of old tissue must happen in balance. Fibrinolytic systems and MMPs work together to remove fibrin and the damaged ECM from acute wounds.

However, it facilitates cell motility and makes the macromolecules trapped in the matrix accessible, which leads to remodeling. Chronic skin lesions have been found to have lower TIMP concentrations and higher MMP levels. This leads to a subsequent reorganization of the matrix and a worsening of its degradation [3,13–15].

Further emphasis has been placed on the formation of pericapillary fibrin sheaths, especially in diabetic lesions, and on a decrease in tissue concentrations of nitric oxide (NO), especially in conditions like malnutrition, diabetes mellitus, corticosteroid therapy, ischemia, and smoking exposure. Additionally, tissue ischemia and an increased presence of neutrophils, which leads to enhanced extracellular matrix degradation, have been highlighted [3,13–15].

The procedures involved in healing chronic wounds are similar to those involved in healing acute wounds. Chronic wounds are strongly linked to the dysregulation of MMP production, which prolongs the inflammatory phase. The primary cause of chronic wound (CW) persistent inflammation is mostly attributed to the presence of many cell types inside the cellular infiltration [4,9,13–19]. Neutrophils are widely distributed throughout the wound and release a substantial amount of MMPs. These enzymes deactivate vital proteins essential to the healing process, such as PDGF and TGFbeta, in addition to impairing the connective tissue matrix and elastase [4,13,15–18].

However, it is imperative to investigate the connections between keratinocytes and immune cells. Different signaling chemicals are secreted during this process, albeit it is still unclear exactly what role these cells have in the formation of cell walls. Genes associated with partial proliferative activation are expressed by keratinocytes in chronic wounds, which may account for the epidermal hyperproliferation surrounding the ulcer's borders. Moreover, the fibroblasts are not sensitive to TGFbeta, a migratory stimulator. This is reflected in much lower TGFbetaR levels as well as lower levels of the subsequent components of the TGFbetaR signaling cascade [4,9,13–19].

Notable is the significance of the immune system's interactions with the nervous system in controlling wound healing processes [20]. Recent research suggests that interactions between mast cells and nerve cells transmit neurotransmitters important for wound healing, including substance P (SP), protein gene product 9.5 (PGP 9.5), nitric oxide (NO), the nerve growth factor (NGF), neurokinin A (NKA), neuropeptide Y (NPY), the calcitonin gene-related peptide (CGRP), and the vasoactive intestinal peptide (VIP) [3,21,22]. The release of the ECM by fibroblasts, the elevation of TGFbeta levels, and the reaction of infiltrating cells are responsible for this outcome [17,18].

In addition, infections represent a substantial and frequent source of hindrance in the healing process: an increase in the bacterial load extends the inflammatory phase, which is marked by increased MMP levels and a subsequent escalation of the damaging processes affecting the extracellular matrix. Some bacterial species form a polysaccharide biofilm that is rich in proteins and other metabolic byproducts when they adhere to a substrate; within this biofilm, the bacteria clump together to form micro-colonies, which are protected from antibiotics by reduced penetration through the biofilm matrix as well as genetic mutations that alter their susceptibility to antibiotics [5,23].

Periodically, biofilms release single bacterial cells that can colonize new surfaces or break down the collagen matrix in healed ulcers, a process known as "re-ulceration." Within the biofilm, bacteria establish themselves, prevent the colonization of new bacteria, store energy in the polysaccharide matrix, and interact through the transfer of genetic material (a process known as quorum sensing). Variations in the conditions within the biofilm can also affect which cells remain in the colony, die, or leave. Furthermore, skin lesions are typically more subtle when they are infected. This is because the release of endotoxins and proteases by microorganisms breaks down the extracellular matrix, which triggers a significant release of mediators that worsen the local inflammatory response. This is one way that infection and the increased exudate are related. Increased levels of macromolecules, including fibrin and albumin, as well as pro-inflammatory cytokines and MMPs, inhibit growth factors in the exudate [5,23].

3.2. Therapies in Chronic Wounds

CWs represent a significant challenge in the field of medicine due to their prolonged healing time and the complex factors involved in their management. Typically, a wound is classified as chronic if fails to progress through the normal stages of healing within six weeks. CWs encompass a variety of pathologies, including venous, arterial, and mixed ulcers, diabetic foot ulcers (DFUs), and pressure injuries (also known as pressure ulcers). These wounds are often the result of underlying conditions such as vascular insufficiency, diabetes, or prolonged pressure, which inhibit normal tissue repair [4–6,15,16].

The impact of CWs is substantial, both for healthcare systems and patients. In addition to physical discomfort, CWs often led to reduced mobility, increased healthcare costs, and decreased quality of life due to the prolonged treatment. Multiple factors, including patient-specific variables like age, skin health, and the presence of comorbidities, contribute to the development and persistence of CWs. Trauma or infection can further complicate the healing process, making CWs particularly resistant to conventional treatment strategies [4–6,15,16,24–26].

The effective management of CWs requires a complex approach that addresses not only the wound itself but also the underlying conditions and patient care. Emerging therapies aim to modulate the wound environment, control infection, and promote healing, but a standardized approach remains elusive [4–6,15,16,25,26].

Venous leg ulcers (VLUs) are the most common type of chronic wound, often associated with chronic venous insufficiency. The primary treatment for VLUs is compression therapy, which remains the gold standard. However, successful management of VLUs often requires a comprehensive, multidisciplinary approach. This includes regular wound assessments, proper dressing choices, and sometimes surgical interventions like venous ablation or debridement [26]. Additionally, addressing comorbid conditions such as diabetes or arterial disease is necessary for optimizing wound healing outcomes [25].

The treatment of DFUs involves a multiple approach designed to promote healing, prevent infection, and reduce complications such as amputations. Among the most effective therapies, negative pressure wound therapy (NPWT) and platelet-rich plasma (PRP) stand out. NPWT is a therapeutic technique using a vacuum dressing to promote healing in acute or chronic wounds and enhance the uptake of medication in treated areas. It accelerates healing by applying controlled suction to the wound, removing the exudate, promoting granulation tissue formation, and improving circulation. When combined with PRP (a concentration of platelets from the patient's own blood that is injected into the wound site to promote healing and tissue regeneration, which contains growth factors that aid in reducing scar formation and enhancing tissue repair), these therapies demonstrate even greater efficacy of the CW healing rate and reduced healing time. Ultrasonic debridement (UD) is another key technique that removes necrotic tissue while promoting a clean wound environment, which enhances the effects of other therapies such as NPWT. Other innovative approaches include hyperbaric oxygen therapy (HBOT), a treatment that involves breathing pure oxygen in a pressurized environment, which improves oxygenation in hypoxic tissues, thus promoting angiogenesis and reducing infection rates [26,27].

Arterial ulcers (AUs), though less common than VLUs, are particularly challenging to treat due to their association with poor blood flow caused by peripheral arterial disease. The primary treatment goal is to restore blood circulation, typically through revascularization procedures like angioplasty or bypass surgery. In cases where revascularization is not possible, the focus shifts to wound care and pain management, avoiding aggressive debridement due to the risk of further tissue damage from poor perfusion. Moisture balance is crucial, with specialized dressings used to maintain an optimal healing environment. Adjunct therapies such HBOT may also be employed to enhance oxygenation in ischemic tissues and promote healing [28].

Emerging

Recent advances in the management of CWs have significantly expanded, ranging from emerging technologies to novel therapies. Smart hydrogels, which respond to stimuli

like pH, temperature, and glucose levels, enable controlled drug release and enhance the healing of hard-to-treat wounds such as diabetic ulcers [29]. Additionally, electrical stimulation (ES) has emerged as a non-invasive strategy to promote tissue regeneration and reduce inflammation by modulating cellular migration and proliferation [30]. The integration of nanotechnology into wound dressings has also improved infection control in CWs by nanoparticles for controlled antimicrobial release and enhanced tissue regeneration [31]. Growth factors and gene therapies are also under investigation to correct disrupted cellular signaling in CW, with recent studies highlighting their potential when administered in combination [32]. Finally, advanced drug delivery systems directed to the complex microenvironment of CWs continue to be a focus, allowing for more precise and effective therapy for treating infections and promote healing [33]. CWs are challenging to treat due to microbial biofilms that resist traditional therapies. Antimicrobial biomaterials offer innovative solutions by combining WH and infection control. Materials such as hydrogels, nanofiber-based dressings, and skin substitutes can incorporate agents like silver nanoparticles, chitosan, and natural extracts to prevent biofilm formation and promote tissue regeneration. These biomaterials show promise as targeted therapies that reduce reliance on systemic antimicrobial treatments, aligning with modern wound care priorities [34].

Physical therapies have become an option as adjunct therapy in the management of CWs. Techniques such as laser therapy, photobiomodulation (PBM), and ES have been used for their ability to enhance the wound healing process. PBM, using low-level light therapy, stimulates cellular activity and nitric oxide production, helping to reduce inflammation and enhance tissue regeneration. Similarly, ES mimics the body's natural electrical fields to promote angiogenesis, reduce bacterial colonization, and accelerate healing by stimulating fibroblast proliferation [6].

4. Keloids

Around 11 million cases of keloids, a pathological condition with distinct clinical symptoms, are reported annually in wealthy countries [35]. Around 70% of cases occur in younger groups [36]. Clinically, keloid scars appear as hard, rough papules and plaques with an uneven surface. They have a wide range of colors, including pigments that are red, purple, and brown. Unlike hypertrophic scars, keloids extend beyond the original wound's boundaries and do not fade with time [37]. Because of their disruptive properties, keloids often cause symptoms like pruritus, pain, and discomfort. These symptoms can appear months or years after the initial damage. People who have keloids frequently experience psychological distress linked to negative self-perception, negative experiences, and body dysmorphic disorder [38,39]. Figure 2 shows a keloid scar secondary to ear-piercing intervention with the typical, previously described, clinical appearance.

Numerous investigations have demonstrated that a mix of systemic and local variables, including mechanical strain, hormonal imbalances, metabolic changes, and inflammatory processes, initiate the pathogenesis of keloids [36–39]. Collagen strands, specifically collagen type one and three, are primarily disorganized in these atypical scars. Keloids are fibrous, proliferative lesions that resemble noticeable scars. They are distinguished by their gradual, ongoing growth into the surrounding healthy skin beyond the boundaries of the incision. Patients with keloids may have severe pain, ongoing itching, psychological anguish, and motor limitation, all of which add significantly to their burden [36–39].

In keloid investigations, the healthy skin next to keloid scars is often ignored; yet, it has been noted to exhibit properties more in line with keloid tissue than with normal skin. This is evident in the nearby normal skin's pruritus and the increased blood flow compared to the unaffected normal skin. Heat shock protein 70 and the hematopoietic stem cell marker c-KIT are more strongly stained in the surrounding normal skin, while keloid-derived keratinocytes and fibroblasts exhibit aberrant gene expressions. The epidermal appendages that are lacking from the keloid tissue reappear in the surrounding normal skin; however, the extracellular matrix of the normal skin may become infiltrated by thick and excessive

collagen deposition. Moreover, it has been noticed that portions of the adjacent keloid's nodules penetrate the nearby normal skin [36,37].

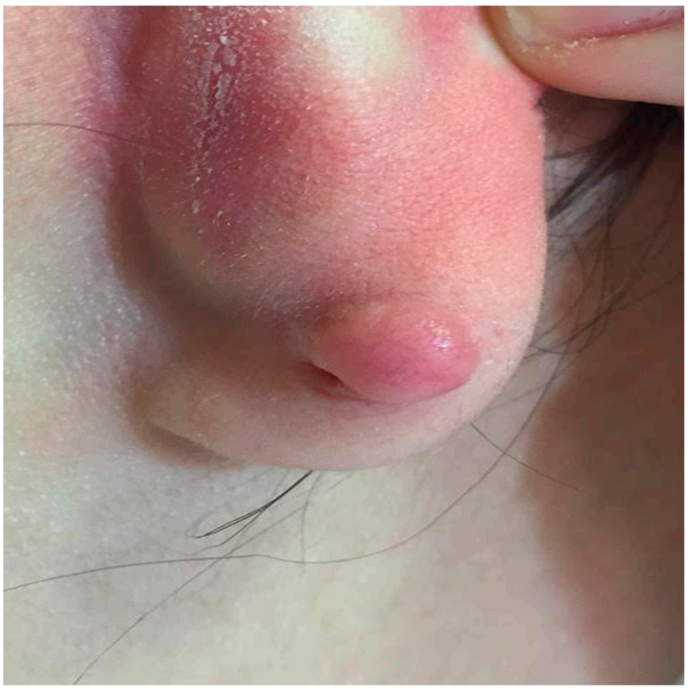

Figure 2. Image of a keloid in the ear, which appears typically after getting an ear piercing.

The proliferation and death of the surrounding normal skin differs from that of keloids. Only the nearby normal skin showed enhanced dermal proliferation and raised apoptotic keratinocyte counts; the healthy skin did not exhibit these features. Additionally, compared to keloid scars, the surrounding normal skin has more blood vessels and has higher expressions of the proliferative PCNA marker in the dermis [36,37,39].

Further inquiry is necessary since in vitro tests reveal that the normal skin in the vicinity has certain properties with the surrounding keloid. Adjacent normal skin that had been in vitro rebuilt displayed a phenotype that was more noticeable than real normal skin but less severe than the peripheral keloid models. Between genuinely unaffected normal skin and keloid scars, the surrounding normal skin showed intermediate amounts of α-SMA staining, HGF production, and collagen type IV α2 gene expression [37,39].

Most studies support the observation that keloid scars have a thicker epidermis, which is supported by micrometer measurements and the number of living cell layers. Regarding rete ridge formation, there are conflicting results from research that show normal, reduced, or nonexistent ridge creation. Several studies, including histological examinations, show a progressively thicker epidermis that has flattened. Although there appears to be little change in epidermal differentiation, there have been observations of increased activation and proliferation of the epidermis. The larger keloid epidermis underwent immunohistochemical examination, which showed normal levels of epidermal proliferation and differentiation despite the early expression of the terminal differentiation marker involucrin. Instead of epidermal hyperproliferation, the research indicates that higher epidermal thickness is associated with atypical differentiation. The expression of EMT markers is higher in keloid keratinocytes [37,39–41].

Since keloids are primarily defined by increased fibroblast proliferation, the excessive production of extracellular matrix components, and a subsequent decrease in MMPs, research on keloids has primarily focused on the role of fibroblasts in their development [37,39–42]. The formation of keloids may be influenced by inflammation-induced EGF development. Research indicates that keloids exhibit the reduced expression of E-cadherin, the ferroptosis suppressor protein 1 (FSP1), vimentin, α-SMA, TGF-β1, and

phosphorylated Smad3. In vitro studies have validated the involvement of keratinocytes in keloids. The in vitro cultivation of human hair follicle outer sheaths and epidermal keratinocytes stimulated by TGF-β1 demonstrated reduced E-cadherin expression alongside elevated FSP1 and vimentin expression. The expression of ECM-related genes, such as hyaluronan synthase 2, vimentin, cadherin-11, wingless-type MMTV integration site family member 5A, frizzled 7, ADAM metallopeptidase domain 19, and interleukin-6, was markedly elevated in keloid keratinocytes compared to normal skin keratinocytes. The inhibition of the TGFβ1 signaling pathway caused a downregulation of ECM-related genes in keloid keratinocytes, whereas the stimulation of normal skin keratinocytes resulted in the overexpression of ECM-related genes. The inhibition of the ERK1/2 or p38 MAPK pathway in keloid keratinocytes restored the altered gene expression [37,39–41].

In the context of keloid formation, cytokines, including interleukins, tumor necrosis factors, and growth factors, have been found to accelerate the formation of scar tissue by promoting fibroblast proliferation and collagen synthesis [9]. The formation of pathological scars is significantly influenced by dysregulated inflammation, which involves immune cells, inflammatory cytokines, and intracellular signaling pathways. Current and prospective therapies are designed to target these processes in order to reduce scarring [37,39–42].

Several lines of evidence support the potential connection between keloid formation and inflammatory cytokines. Keloid tissues have been found to contain elevated levels of specific cytokines in comparison to normal skin. Additionally, genetic research has identified polymorphisms in cytokine genes that are linked to an elevated risk of keloid formation. These results indicate that cytokines may have a dual function in the fibrotic response in keloids, as they may both initiate and perpetuate it. Nevertheless, the causal relationship between inflammatory cytokines and keloid formation has not been definitively established, indicating the need for additional research [37,39–41].

In vivo, hyperbaric oxygen therapy administered to patients with keloids has been shown to reduce blood perfusion and the expression of hypoxia-inducible factor-1α and vascular endothelial growth factors in keloid tissues, possibly due to the induced EMT phenomenon in keloid tissue. It has recently come to light that the immune milieu surrounding keloids plays a major role in their formation [37,39–42]. Skin fibrosis is associated with increased T cell, MC, Langerhans cell, and macrophage counts in keloids relative to normal tissues. Interactions between immune cells and keloid fibroblasts can result in a complex and synergistic regulation of the molecules and mechanisms that underlie keloid development. Macrophages play a crucial role in the healing of cutaneous wounds by controlling the microenvironment during the various stages of the healing process. M2 macrophages are found in keloids and are specifically associated with fibrosis and scarring [37,39–43].

4.1. Genetically Induced Keloids

Genetics plays a major role in the incidence of keloids, with varying prevalence rates among ethnic groups. People with darker skin tones appear to be more likely than people with lighter skin to be affected, and African Americans have the greatest incidence rate. Asian and Hispanic people are less likely to be affected, and white people are least likely to experience it. Furthermore, the presence of familial inheritance suggests that genetics contributes to the incidence of keloids [44–47]. Keloids are more common among twins, and families with several affected individuals over several generations frequently show a genetic predisposition to scarring that follows an autosomal dominant inheritance pattern. There are reports of X-linked and autosomal recessive inheritance, which suggests that more than one gene may be involved in the development of keloid formation. People who have a genetic susceptibility to keloids may acquire them at multiple anatomical sites; instances of multiple family members presenting with identical patches of keloids are common. Similarities in phenotypic expression within the same family point to a genetic inclination rather than just environmental influences. Although it has proven difficult to identify predisposing genes in familial keloids, linkage research has identified keloid susceptibility

loci in an African American and Japanese family [44–47]. Potential genes within these particular sites have been found, including the EGFR gene at chromosome band 7p11 and the TNFAIP6 gene at chromosomal band 2q23. Rubinstein–Taybi syndrome, Ehlers–Danlos syndrome Type III, X-linked Goeminne syndrome, and FLNA mutations that cause keloids, joint contractures, an elevated optic cup-to-disk ratio, and renal calculi are among the syndromes associated with keloids. To determine if these genes are really susceptibility genes for keloid formation, more investigation is needed. Two genome-wide association studies have identified four single-nucleotide polymorphisms (SNPs) in three loci linked to keloid formation. These SNPs are found in chromosomal bands 1q41, 3q22.3–23, and 15q21.3. The NEDD4 protein is crucial for animal development and survival. SNPs in the MYO1E gene, close to NEDD4, were linked to keloid formation in an African American cohort.

Environmental Factors

TGF-β, or Transforming Growth Factor beta, plays a critical role in many fibrotic illnesses, including keloids. Compared to normal fibroblasts, keloid fibroblasts exhibit higher ratios of TGF-β1 to TGF-β2 receptors, lower amounts of TGF-β3, and higher levels of TGF-β1 and TGF-β2. However, neither the previously mentioned TGFB genes nor the downstream signaling components SMAD3, SMAD6, and SMAD7 have shown any mutations or polymorphisms associated with keloids, according to the studies conducted so far [44–47]. This suggests the existence of either long-range enhancer/repressor variants of TGF-β pathway components that affect the expression of TGFB genes in keloids or upstream genes regulating TGFB genes. Tumor suppressor p53 plays a crucial role in both cell division and death; its potential dysregulation in the development of keloid tumors has been studied. It is still unclear what the TP53 gene's function is, particularly in relation to the codon 72 polymorphism. Two important studies have looked at the relationship between keloids and variations in the human leukocyte antigen (HLA). Further studies could corroborate these initial findings, identify novel or similar HLA variants in a range of ethnic groups, and elucidate the effects of these polymorphisms on the wound-healing process. In summary, keloid pathogenesis susceptibility is influenced by a number of genetic loci, albeit it is unclear which specific gene variants are involved. Keloid susceptibility is made more complex by the possibility of epigenetic control and the unclear processes underlying these genome-wide related SNPs [44–47].

4.2. Therapies for Keloids

The treatment of keloid scars remains a significant challenge due to their high recurrence rates and resistance to many traditional therapies. Various treatment strategies have been explored, each with their own advantages and limitations.

4.2.1. Noninvasive

Compression therapy and silicone sheets are noninvasive treatments for managing keloid scars. Compression garments apply consistent pressure to the scar site, which reduces the blood supply to the area, thereby decreasing collagen production and ultimately leading to scar flattening. It is particularly useful after surgical excision or cryotherapy to reduce the risk of keloid recurrence. Silicone sheets, on the other hand, work by providing an occlusive environment that hydrates the scar tissue, reducing erythema, pruritus, and promoting a softer, flatter scar [48]. Noninvasive therapies monotherapy often remains insufficient for a satisfactory treatment of keloid scars but can act as a useful adjuvant tool in this scenario.

4.2.2. Invasive

Intralesional corticosteroid injections, primarily with triamcinolone acetonide, are a first-line treatment for keloid scars due to their ability to reduce collagen synthesis, scar inflammation, and abnormal fibroblast activity. Corticosteroids are effective in reducing

the size and symptoms of keloids, although recurrence remains a significant issue post-treatment. The combination of 5-FU to corticosteroid injections is commonly used, since 5-FU inhibits fibroblast proliferation by disrupting DNA replication, while corticosteroids suppress inflammation and collagen synthesis. A study comparing intralesional 5-FU alone versus 5-FU combined with corticosteroids showed that the combination provided a significantly greater reduction in the mean keloid height and improved aesthetic outcomes [49]. In addition, the keloid response is likely influenced by lesion characteristics. Aluko-Olokun et al. compared the response of sessile vs. pedunculated lesions to TAC (10 mg) and found a lack of response by pedunculated lesions compared to the flattening of 23 of the 26 treated sessile lesions [50].

While surgical excision can remove the keloid mass, recurrence rates are notoriously high, with over 50% of excised keloids regrowing without adjuvant therapy [51]. Therefore, excision is often combined with other therapies such as corticosteroids, silicone gel sheeting, or radiation to mitigate recurrence. Silicone gel sheeting, in particular, has been widely used postoperatively and has been shown to reduce recurrence to 9% when combined with compression devices like pressure earrings for earlobe keloids [52]. The use of surgical techniques such as Z-plasty or W-plasty can also help redistribute tension across the scar, which may help in reducing the likelihood of recurrence.

Cryotherapy, the controlled freezing of keloid tissue, has been employed as a treatment modality either alone or in combination with other treatments. Cryotherapy can effectively reduce the size of keloids by destroying the scar tissue. When combined with corticosteroids, cryotherapy has been shown to enhance outcomes, but care must be taken due to the risk of hypopigmentation, especially in darker skin types, which limits its widespread applicability [49].

Laser therapy, particularly pulsed dye laser (PDL), targets the vascular component of keloid scars, reducing their redness and overall visibility. Previous articles demonstrated that PDL is effective in reducing keloid height and erythema when used in combination with other treatments like intralesional corticosteroids [53]. Non-ablative fractional lasers (NAFLs) have also been shown to be beneficial in improving the texture and pliability of keloid scars [54]. However, laser treatments alone are often insufficient, with most studies recommending their use as part of a multi-modality approach [55–57]. PDLs seem to be particularly effective for erythematous (red) keloids, as it targets the vascular component and helps reduce redness and the height of the scar. On the other hand, ablative lasers, such as CO_2 and erbium-doped lasers, are effective in reducing the thickness and improving the pliability of keloid scars by promoting collagen remodeling, and these lasers are generally more effective for larger keloids [55]. Vascular or fractional ablative lasers are often used in conjunction with corticosteroid injections. The laser treatment enhances the penetration and effectiveness of corticosteroids by disrupting the keloidal surface and reducing vascular supply. Laser therapy is commonly available with a variable cost per session depending on the country and type of laser with multiple sessions often required, which can limit its accessibility [56].

Radiotherapy is typically reserved for more severe cases of keloids, particularly post-excision. It is effective in reducing recurrence but carries a potential risk of long-term complications such as malignancy. Some studies reported that low-dose radiation therapy following keloid excision can significantly reduce recurrence rates, although its use remains controversial due to these potential risks [58].

Intralesional chemotherapy agents such as 5-fluorouracil (5-FU) and bleomycin have also been explored as alternatives to corticosteroids for keloid treatment. A study demonstrated that the combination of 5-FU with corticosteroids significantly enhances treatment efficacy while reducing adverse effects like skin atrophy [49]. Bleomycin, though effective, is limited by its potential side effects, including hyperpigmentation and systemic toxicity [49,59].

As previously mentioned, keloids frequently require combined therapies of those detailed above in order to obtain satisfactory outcomes. Figure 3 shows a schematic

representation of currently available keloid scar treatments, outlining the progression from conservative to aggressive therapies.

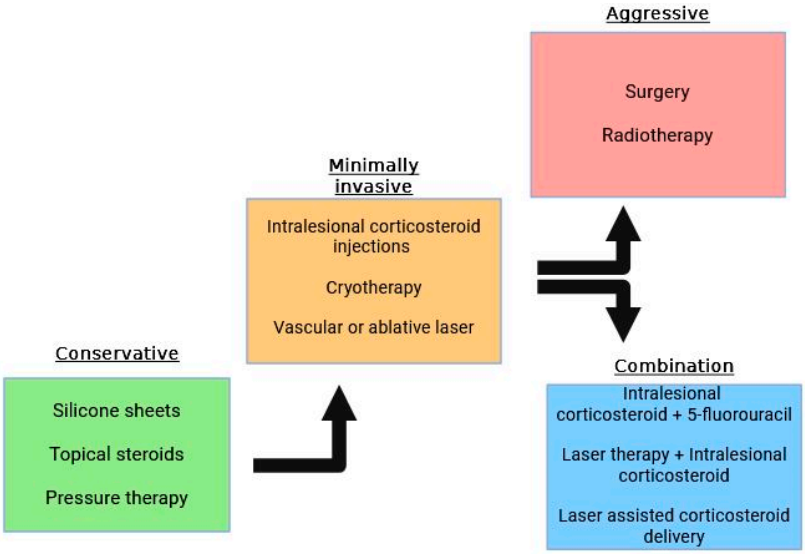

Figure 3. Flowchart depicting available therapies for keloid management and their progression from more conservative to more aggressive.

4.2.3. Emerging

Botulinum toxin type A (BTA) has recently gained attention as a treatment option for keloids, primarily for its ability to reduce muscle tension and thereby lessen mechanical forces on scars. Several studies showed that botulinum toxin not only improved keloid appearance but also reduced symptoms such as itching and pain, making it an attractive option for patients who suffer from symptomatic keloids [60–62]. Moreover, a randomized clinical trial comparing botulinum toxin with intralesional corticosteroids demonstrated fewer side effects and better patient satisfaction in the botulinum toxin group, suggesting the possibility that it may offer an advantage in long-term management [63].

Other noninvasive emerging therapies [63] include the application of a hydrogel scaffold after keloid excision, which has shown low recurrence rates. Although this treatment is still experimental and lacks randomized comparative trials, the early results are promising for reducing recurrence without significant adverse effects. Extracorporeal Shock Wave Therapy (ESWT), both with and without IL TAC, has shown similar results to IL TAC monotherapy. This suggests the potential use as an adjunct treatment for keloid scars. Further investigation is warranted to determine its role in clinical practice. Topical imiquimod applied after keloid excision has been shown to reduce recurrence, particularly for accessible lesions such as ear keloids. This represents a promising noninvasive option compared to traditional corticosteroid injections [48].

Finally, colchicine, administered orally starting one month before keloid excision, showed no recurrence in treated patients. It was well tolerated, making it a promising systemic therapy option for keloid management. However, more studies are needed to validate these findings [48].

5. Hypertrophic Scars

One common outcome of the healing process is the scar. A fibrotic hypertrophic scar may form in burn victims as a result of their wound healing processes. This scar form is characterized by a red, elevated, and stiff appearance that causes significant problems with both function and appearance [37,38]. In areas of the body with tight skin, such as the back, chest, shoulders, upper arms, elbows, and other joints, hypertrophic scars are common. Anywhere there is a wound or injury on the skin, hypertrophic scars may form [38,64–66].

Hypertrophic scars (HTSs) are associated with a number of different mechanisms, such as abnormal extracellular matrix synthesis, increased neovascularization, irregular extracellular matrix remodeling, prolonged inflammation, and extended re-epithelialization. Fibroblasts are stimulated both directly and indirectly by platelets, macrophages, T-lymphocytes, mast cells, Langerhans cells, and keratinocytes, which leads to an excess of extracellular matrix formation. Although the exact relationship between these processes and the development of atypical scar tissue is yet unknown, studies suggest that immune responses that occur shortly after damage may have a substantial impact on this result [36,42,65–67].

A large amount of evidence suggests that acute inflammation generates pro-fibrotic substances, which in turn stimulate fibroblasts and cause HTSs. Prolonged re-epithelialization and excessive angiogenesis may also delay the release of pro-fibrotic growth factors. Many biomolecules have been linked to HTSs in recent years, but the exact mechanisms underlying these associations are still not fully understood, in part due to the complex and overlapping nature of wound-healing processes. Many factors play a role in the development of a hypertrophic scar while the lesion heals. HTSs and myofibroblast activation are linked to the fibrin provisional matrix that forms following hemostasis. High-density fibrin clot deposition during the first healing phase may be predictive of the production of hypertrophic scars, although more investigation is needed to validate this relationship. During hemostasis, platelets release growth factors that promote fibrosis, such as PDGF, VEGF, TGF-β1, and CTGF, which are linked to the development of HTSs. Because it inhibits the synthesis of pro-fibrotic molecules, PRP, which is obtained from peripheral blood platelets, is thought to be an alternate treatment for hypertrophic scars (HTSs) [38,44,65–67].

The most well-known pathophysiological reason of HTS formation is excessive inflammation, and several current interventions are designed to reduce inflammation. Increased levels of pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), toll-like receptor (TLR) activation, and the infiltration of inflammatory cells at the wound site are the outcomes of severe burn wounds with severe infection and tissue necrosis [38,44,65–67].

Chemokine expression during HTSs has been inconsistently reported in research; some studies found enhanced expression for 21–35 days, while others found reduced expression for 21–56 days. Interleukins, interferon, and growth factors are among the compounds secreted by inflammatory cells. These substances activate fibroblasts and are linked to the development of HTSs. Shortly after damage, hypofibrotic diabetic wounds have been shown to have insufficient pro-inflammatory responses, which makes them prone to infection and impairs healing. More research is needed to understand why inflammatory responses are delayed during the initial healing phase after damage and how this affects the formation of hypertrophic scars [39,46,68–70]. One important cytokine that impacts the intermediate and later phases of healing, including hypertrophic scarring, is inflammation. Since IL-6 is highly expressed in HTSs, treating HTSs may involve targeting it as a therapeutic target. Other inflammatory cytokines that are being investigated as possible HTS treatment targets include IL-1β, IL-4, IL-8, IL-17, IL-13, and IL-22 [38,44,65–67].

Inflammation is impacted by alternative lipid metabolism, which can cause severe scarring. In sick HTS and HTS-derived fibroblasts, there is a reduction in the mRNA and protein expression of fatty acid synthase (FASN) and sterol regulatory element-binding protein-1 (SREBP1). It has been demonstrated that TNF-stimulated gene 6 (TSG-6) prevents scarring by suppressing the IRE1α/TRAF2/NF-κB signaling cascade [38,44,65–67].

In HTSs, the proliferative phase processes, including angiogenesis and extracellular matrix deposition, are notably active. During a high-throughput screening (HTS), pro-fibrotic growth factors, such as TGF-β, PDGF, VEGF, and CTGF, are secreted by cells such as fibroblasts, endothelial cells, and keratinocytes. Fibroblasts are stimulated to produce more extracellular matrix proteins, such as collagen, fibronectin, laminin, periostin, fibrillin, and tenascin, when the environment is pro-fibrotic. However, there have been reports of altered or decreased expressions of certain extracellular matrix proteins, such as decorin, dermatopontin, and hyaluronic acid [38,44,65–67].

HTSs may be exacerbated by endothelial dysfunction and the altered expression of angiogenic genes, such as endothelin-1, angiopoietin-1, angiopoietin-2, and angiogenin, according to endothelial cells obtained from pig burn wounds. Hypertrophic scarring may also result from keratinocytes' dysregulation of Notch signaling. Patients with hypertrophic scars had significantly higher levels of expression in their epidermis for Notch 1 signaling and intracellular domains, such as Hes1 and Jagged1 [38,44,65–67].

The balance between ECM synthesis and remodeling is upset in HTSs. In HTSs, fibroblasts and myofibroblasts continue to deposit collagen I and III. Scarring results from the accumulation of excess fibrous collagen I brought on by the irregularities in apoptosis, which maintain the presence of myofibroblasts over time. Hypertrophic scars are characterized by nodules that include myofibroblast HTSs. HTS development can be aided by the differentiation of fibroblasts into myofibroblasts, which can be induced by mechanical strain and TGF-β [38,44,65–67].

During the formation of HTSs, MMPs—including MMP1 and MMP7—are downregulated. This results in a reduced breakdown of ECM components such as collagen I, collagen III, and fibronectin. It has been shown that an MMP1 injection is effective in improving the appearance of scars. TIMP1 and TIMP2, two TIMPs, reduce the activity of matrix MMPs during the development of hypertensive heart disease. In HTSs, there is an increase in MMP2, MMP9, and MMP13 expression. The delivery of decorin, a matricellular protein involved in the structure of collagen fibers, has been effective in reducing the formation of HTSs. Furthermore, via modifying TGF-β1 activity, blocking the lysyl hydroxylase enzyme, which is involved in the formation of pyridinoline cross-links, reduces fibroblast proliferation [38,44,65–67].

HTSs are caused by the activation of many genes required for the formation of extracellular matrix and fibroblast proliferation by the IL-6/STAT3 pathway. Those with hypertrophic scarring had lower levels of IL-10, an anti-inflammatory cytokine and possible therapeutic agent, than those without hypertrophic scarring. Based on certain research, fibroblasts are directly impacted by IL-10 through stimulation of the AKT or STAT3 signaling pathways. It has been shown that IL-10 inhibits the TLR4/NF-kB pathway in dermal fibroblasts, which reduces the production of scars. To fully understand IL-10's function in inhibiting the formation of HTSs, more research is required [46,68].

One theory that is put forth to explain the genesis of keloids is genetic causes. Mutations and polymorphisms in genes can interfere with the signaling pathways that are necessary for the later stages of the wound healing process. The pathophysiology of abnormal scarring may involve multiple pathways, including the TGF-B1/Smad pathway, the MAPK kinase pathway, IGF-I and its receptor, plasminogen activator inhibitor-1, the urokinase plasminogen activator, gene polymorphisms of the vitamin D receptor and the ADAM33 gene, and the aberrant expression of suppressor genes. Additionally, the effect on type 2 hyaluronidase synthase and heat shock protein expression was shown. Clarifying the genetic basis of hypertrophic scar formation may contribute to a thorough comprehension of their pathophysiology and provide important therapeutic benefits, ultimately leading to the development of effective treatment approaches [46,68].

5.1. Therapies for Hypertrophic Scars

Hypertrophic scars are a common concern in dermatology, and several treatments have emerged to address their development, severity, and aesthetic impact. The main differences between normal skin, keloids, and hypertrophic scars are summarized in Table 2. Understanding these differences is crucial for selecting the most appropriate treatment strategy and management.

Table 2. Differences between normal skin, hypertrophic scars, and keloid scars.

Feature	Normal Skin	Hypertrophic Scars	Keloids
Collagen Arrangement	Organized, parallel bundles	Excessive collagen, parallel arrangement	Disorganized, haphazard arrangement
Collagen Type	Predominantly Type I and III	Increased Type I	Increased ratio of Type I to Type III
Growth Beyond Wound	No	Confined to wound boundaries	Extends beyond wound boundaries
Fibroblast Activity	Normal	Increased, but regulated	Hyperactive, unregulated
Vascularity	Normal	Increased, leading to redness	Increased, leading to persistent redness
Recurrence after Treatment	N/A	Low	High
Response to Treatment	N/A	Good response to corticosteroids and pressure therapy	Variable response, often requires combination therapies
Pruritus and Pain	Absent	Common during scar maturation	Often severe and persistent
Elastic Fibers	Normal density and distribution	Reduced	Significantly reduced or absent
Common Locations	All skin areas	Areas of high tension (e.g., shoulders)	Earlobes, chest, shoulders, upper back
Tendency to Regress	N/A	Tends to regress over time	Rarely regresses, may continue to grow

5.1.1. Noninvasive

Silicone gel sheeting remains a cornerstone in the management of hypertrophic scars. It functions primarily by maintaining moisture and exerting pressure on the scar tissue, which helps reduce collagen proliferation [69]. Studies have shown that silicone sheets effectively improve scar texture, pigmentation, and overall appearance. Shen et al. demonstrated that the use of silicone gel in combination with other treatments like elastic sleeves significantly reduced the severity of hypertrophic scars in pediatric patients with burn injuries [70]. The Vancouver Scar Scale (VSS) scores in patients using silicone gel were significantly better than those who did not use the gel, supporting its role as a first-line treatment for hypertrophic scars.

5.1.2. Invasive

Laser therapies, particularly fractional CO_2 lasers and pulsed dye lasers (PDLs), have gained popularity for treating hypertrophic scars due to their ability to remodel collagen and improve scar appearance [56]. Fractional CO_2 laser therapy targets both the dermis and epidermis, promoting collagen remodeling and reducing scar height and thickness. In a study conducted by Ge et al., patients with hypertrophic scars saw significant improvements in scar texture, pliability, and pigmentation after several sessions of fractional CO_2 laser treatments. These lasers also proved effective in reducing postoperative pain and improving patient satisfaction, with most patients reporting smooth skin and reduced scar visibility [71].

Similarly, Yang et al. highlighted the efficacy of PDLs in reducing vascularity and pigmentation in hypertrophic scars. The study demonstrated that patients treated with PDLs showed significant improvements in the visual appearance of their scars, particularly in reducing redness and scar height. The study also noted that PDL treatments were generally well tolerated, with minimal side effects [53].

Microneedling has emerged as a promising treatment for hypertrophic scars, especially when combined with other modalities like PRP or chemical peels. This technique involves using tiny needles to create controlled micro-injuries in the skin, stimulating collagen production and scar remodeling. A study conducted by Ali et al. compared the effects of microneedling alone versus microneedling combined with Jessner's solution peeling in patients with hypertrophic scars. The combined treatment showed superior outcomes, with more significant improvements in scar texture and pigmentation [72].

Microneedling is particularly favored for its low risk of post-inflammatory hyperpigmentation, making it suitable for patients with darker skin tones. An et al. further supported the efficacy of microneedling when combined with radiofrequency and topical polylactic acid. Their randomized controlled trial demonstrated that this combination significantly improved scar smoothness, size, and overall appearance compared to monotherapy. These findings suggest that microneedling, particularly in combination with other treatments, can offer significant improvements in the management of hypertrophic scars [73].

PRP therapy, which utilizes concentrated platelets from the patient's own blood, is known for its regenerative properties and has been increasingly used to treat hypertrophic scars. PRP is rich in growth factors that promote collagen remodeling and tissue healing, making it a suitable adjunctive therapy for scar management [74–76]. A systematic review by Mujahid et al. indicated that combining PRP with other treatments, like microneedling or laser therapy, enhanced scar reduction outcomes. Patients receiving PRP combined with fractional CO_2 laser therapy reported faster recovery times, reduced erythema, and overall better clinical outcomes compared to those receiving laser treatment alone [77]. However, while PRP shows promise, its efficacy as a standalone treatment for hypertrophic scars remains debated. Studies suggest that PRP is more effective when used in conjunction with other treatments, particularly those that target collagen remodeling at a deeper level [78]. In this regard, PRP may be a better tool for atrophic scars or to prevent excessive atrophy derived from other therapies such as corticosteroid infiltration.

Corticosteroid injections, particularly intralesional triamcinolone acetonide, are a well-established treatment for hypertrophic scars. The mechanism involves reducing inflammation and inhibiting fibroblast proliferation, which in turn reduces collagen synthesis. This treatment is most effective when administered in the early stages of scar formation, helping to prevent excessive collagen buildup [79]. According to some articles, corticosteroid injections were found to be equally effective as botulinum toxin injections in reducing hypertrophic scar volume and improving pliability, while being better tolerated by patients [62].

However, corticosteroid therapy is often associated with side effects such as skin atrophy and telangiectasia, which limits its long-term use in some cases. The combination of corticosteroids with other therapies has also proven beneficial. Studies have demonstrated that combining corticosteroids with 5-fluorouracil (5-FU) or botulinum toxin can enhance treatment efficacy. For example, a study highlighted in the review found that the combination of triamcinolone with 5-FU resulted in a significant reduction in scar thickness and a decrease in recurrence rates after surgical excision [49]. This combination therapy, while effective, requires multiple treatment sessions and careful monitoring for potential adverse effects, such as local skin irritation or allergic reactions.

5.1.3. Emerging

Several emerging therapies hold promise for the future treatment of hypertrophic scars, highlighting botulinum toxin injections, stem cell therapy, and novel laser technologies.

BTA, commonly known for its use in cosmetic procedures, has been shown to reduce the mechanical forces on wounds, thus preventing the exacerbation of hypertrophic scars [80]. Botulinum toxin's ability to paralyze muscles surrounding the scarred area may reduce tension on the wound, leading to better healing outcomes [81].

Stem cell therapy is another innovative treatment being explored for hypertrophic scar management. Mesenchymal stem cells (MSCs) have regenerative properties that can aid in tissue repair and reduce fibrosis. Preliminary studies have indicated that MSCs can decrease collagen production and improve the quality of scar tissue. However, this therapy is still in the experimental stages, and more research is required to understand its long-term efficacy and safety [82]. This innovative treatment application for hypertrophic and keloid scars is still under research, and availability is limited to specialized clinics in the context of clinical studies. In addition, elevated cost will probably be an aspect to consider [82].

Lastly, advancements in laser technology, such as fractional ablative lasers combined with growth factors, or picosecond lasers, are showing promise in enhancing the remodeling of scar tissue. These treatments not only target the scar itself but also promote healing through the stimulation of surrounding healthy tissue. Research conducted by Xi et al. indicated that these advanced lasers, when used in conjunction with other treatments, can lead to significant improvements in the texture, thickness, and appearance of hypertrophic scars [83].

Dupilumab, an IL-4 receptor-α monoclonal antibody that blocks type 2-driven inflammation, has been explored for hypertrophic scars. It has shown varying effects, including

reduced symptoms and improvements in scar quality in some cases, though results have been inconsistent. A phase IV clinical trial is underway to further investigate the role of dupilumab in treating hypertrophic scars [48].

6. Conclusions

This review was born from the need of the authors to give a significant and comprehensive picture of the complex process related to wound healing; a process that causes millions of deaths a year should not be considered superficial. In the case of failure to heal, wound healing causes suffering in the individual as well as changes in aesthetics. Suffering therefore turns out to be the essential point of reference for the authors who have been experts in this sector for years. This document therefore offers an updated vision of the cellular mechanisms involved in wounds and their failure to heal, such as chronic wounds. Attention is also given to keloids and hypertrophic scars. The authors also finally show a current reflection on therapies. From all this emerges the awareness of the seriousness of these issues and the need to transform these types of studies into global, and not just niche, topics.

Future research in wound healing should prioritize the development of more accessible and cost-effective treatments, particularly for challenging conditions like chronic wounds, keloids, and hypertrophic scars. Innovative therapies such as stem cell treatments, gene therapy, and advanced drug delivery systems hold immense potential but require more clinical trials to validate their efficacy and safety. Collaborative, interdisciplinary research efforts are needed to deepen our understanding of wound healing mechanisms and to translate experimental therapies into standardized clinical practices that improve patient outcomes and quality of life.

This review contributes to the recognition that wound healing is a complex biological process, and a failure to heal can lead to significant physical, psychological, and aesthetic consequences. Chronic wounds, keloids, and hypertrophic scars present considerable challenges due to their prolonged healing times and complex pathophysiology. Understanding the cellular and molecular mechanisms of wound healing is crucial for developing effective treatments and improving patient outcomes. Established therapies may be shadowed by emerging treatments in the future, but further clinical validation of the latter is still required.

7. Limitations

The review described by the authors takes on meaning only if viewed in perspective. The cellular and molecular processes of wound healing must necessarily be considered as important as the therapies used. Indeed, the use of new therapies, an example for all is the photobiomodulation induced by certain devices [84,85], which takes on relevance only if the proposed studies are accompanied by the study of possible effects. It is therefore the task of the doctor and the biologist to assume a unitary vision that takes into account these limits. The fact that the authors reflect on these issues also means that they have been forced to pay greater attention to numerous topics and do not exclude the lack of a systematic methodology in the review process.

Author Contributions: Conceptualization, M.F.-G., J.N.-R., and S.B.; Investigation, M.F.-G., J.N.-R., and S.B; writing—review and editing, M.F.-G., J.N.-R., and S.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

Denomination	Acronym
Wound Healing	WH
Mast Cells	MC
Smooth Muscle Actin	SMA
Transforming Growth Factor	TGF
Epithelial-Mesenchymal Transition	EMT
Matrix Metalloproteinases	MMPs
Tissue Inhibitors of Metalloproteinases	TIMPs
Extracellular Matrix	ECM
Venous Ulcers	VU
Diabetic Ulcers	DU
Pressure Ulcers	PU
Nitric Oxide	NO
Chronic Wound	CW
Platelet Derived Growth Factor	PGDF
Substance P	SP
Protein gene product 9.5	PGP 9.5
Nerve Growth Factor	NGF
Neurokinin A	NKA
Neuropeptide Y	NPY
Calcitonin Gene-Related Peptide	CGRP
Vasoactive Intestinal Peptide	VIP
Diabetic Foot Ulcers	DFU
Venous leg ulcers	VLUs
Negative Pressure Wound Therapy	NPWT
Platelet-Rich Plasma	PRP
Ultrasonic Debridement	UD
Hyperbaric Oxygen Therapy	HBOT
Arterial Ulcers	AU
Electrical Stimulation	ES
Photobiomodulation	PBM
Epidermal Growth Factor	EGF
Ferroptosis Suppressor Protein 1	FSP1
Epidermal growth factor receptor	EGFR
Single-Nucleotide Polymorphisms	SNPs
Human Leukocyte Antigen	HLA
Pulsed Dye Laser	PDL
Non-Ablative Fractional Lasers	NAFL
Botulinum toxin type A	BTA
5-fluorouracil	5-FU
Hypertrophic Scars	HTS
Connective Tissue Growth Factor	CTGF
Pathogen-Associated Molecular Patterns	PAMPs
Damage-Associated Molecular Patterns	DAMP
Toll-Like Receptor	TLR
Interleukin	IL
Fatty Acid Synthase	FASN
TNF-stimulated gene 6	TSG-6
Vascular Endothelial Growth Factor	VEGF
Pulsed Dye Lasers	PDLs
5-fluorouracil	5-FU
Mesenchymal stem cells	MSCs

References

1. Sen, C.K. Human Wound and Its Burden: Updated 2020 Compendium of Estimates. *Adv. Wound Care* **2021**, *10*, 281–292. [CrossRef] [PubMed]
2. Bacci, S. Cellular Mechanisms and Therapies in Wound Healing: Looking toward the Future. *Biomedicines* **2021**, *9*, 1611. [CrossRef] [PubMed]
3. Grandi, V.; Corsi, A.; Pimpinelli, N.; Bacci, S. Cellular Mechanisms in Acute and Chronic Wounds after PDT Therapy: An Update. *Biomedicines* **2022**, *10*, 1624. [CrossRef] [PubMed]
4. Gupta, S.; Andersen, C.; Black, J.; de Leon, J.; Fife, C.; Lantis Ii, J.C.; Niezgoda, J.; Snyder, R.; Sumpio, B.; Tettelbach, W.; et al. Management of Chronic Wounds: Diagnosis, Preparation, Treatment, and Follow-up. *Wounds* **2017**, *29*, S19–S36. [PubMed]
5. Babalska, Z.Ł.; Korbecka-Paczkowska, M.; Karpiński, T.M. Wound Antiseptics and European Guidelines for Antiseptic Application in Wound Treatment. *Pharmaceuticals* **2021**, *14*, 1253. [CrossRef] [PubMed]
6. Fernández-Guarino, M.; Bacci, S.; Pérez González, L.A.; Bermejo-Martínez, M.; Cecilia-Matilla, A.; Hernández-Bule, M.L. The Role of Physical Therapies in Wound Healing and Assisted Scarring. *Int. J. Mol. Sci.* **2023**, *24*, 7487. [CrossRef]
7. Fernández-Guarino, M.; Hernández-Bule, M.L.; Bacci, S. Cellular and Molecular Processes in Wound Healing. *Biomedicines* **2023**, *11*, 2526. [CrossRef]
8. Tyavambiza, C.; Meyer, M.; Meyer, S. Cellular and Molecular Events of Wound Healing and the Potential of Silver Based Nanoformulations as Wound Healing Agents. *Bioengineering* **2022**, *9*, 712. [CrossRef]
9. Raziyeva, K.; Kim, Y.; Zharkinbekov, Z.; Kassymbek, K.; Jimi, S.; Saparov, A. Immunology of Acute and Chronic Wound Healing. *Biomolecules* **2021**, *11*, 700. [CrossRef]
10. Rodrigues, M.; Kosaric, N.; Bonham, C.A.; Gurtner, G.C. Wound Healing: A Cellular Perspective. *Physiol. Rev.* **2019**, *99*, 665–706. [CrossRef]
11. Wilkinson, H.N.; Hardman, M.J. Wound healing: Cellular mechanisms and pathological outcomes. *Open Biol.* **2020**, *10*, 200223. [CrossRef] [PubMed]
12. Peña, O.A.; Martin, P. Cellular and molecular mechanisms of skin wound healing. *Nat.Rev. Mol. Cell. Biol.* **2024**, *25*, 599–616. [CrossRef] [PubMed]
13. Guo, S.; Dipietro, L.A. Factors affecting wound healing. *J. Dent. Res.* **2010**, *89*, 219–229. [CrossRef] [PubMed]
14. Tottoli, E.M.; Dorati, R.; Genta, I.; Chiesa, E.; Pisani, S.; Conti, B. Skin Wound Healing Process and New Emerging Technologies for Skin Wound Care and Regeneration. *Pharmaceutics* **2020**, *12*, 735. [CrossRef] [PubMed]
15. Falanga, V.; Isseroff, R.R.; Soulika, A.M.; Romanelli, M.; Margolis, D.; Kapp, S.; Granick, M.; Harding, K. Chronic wounds. *Nat. Rev. Dis. Primers* **2022**, *8*, 50. [CrossRef]
16. Han, G.; Ceilley, R. Chronic wound healing: A review of current management and treatments. *Adv. Ther.* **2017**, *34*, 599–610. [CrossRef]
17. Corsi, A.; Lecci, P.P.; Bacci, S.; Cappugi, P.; Pimpinelli, N. Early activation of fibroblasts during PDT treatment in leg ulcers. *G. Ital. Dermatol. Venereol.* **2016**, *151*, 223–229.
18. Grandi, V.; Bacci, S.; Corsi, A.; Sessa, M.; Puliti, E.; Murciano, N.; Scavone, F.; Cappugi, P.; Pimpinelli, N. ALA-PDT exerts beneficial effects on chronic venous ulcers by inducing changes in inflammatory microenvironment, especially through increased TGF-beta release: A pilot clinical and translational study. *Photodiagnosis Photodyn. Ther.* **2018**, *21*, 252–256. [CrossRef]
19. Haensel, D.; Dai, X. Epithelial-to-mesenchymal transition in cutaneous wound healing: Where we are and where we are heading. *Dev. Dyn.* **2018**, *247*, 473–480. [CrossRef]
20. Steinman, L. Elaborate interactions between the immune and nervous systems. *Nat. Immunol.* **2004**, *5*, 575–581. [CrossRef]
21. Grandi, V.; Paroli, G.; Puliti, E.; Bacci, S.; Pimpinelli, N. Single ALA-PDT irradiation induces increase in mast cells degranulation and neuropeptide acute response in chronic venous ulcers: A pilot study. *Photodiagnosis Photodyn. Ther.* **2021**, *34*, 102222. [CrossRef] [PubMed]
22. Nardini, P.; Notari, L.; Magazzini, M.; Mariani, B.; Rossi, F.; Rossi, S.; Van Aardt, E.; Marszalek, K.; Grandi, V.; Corsi, A.; et al. Neuroimmunomodulatory effect of Nitric Oxide on chronic wound healing after photodynamic therapy. *Photodiagnosis Photodyn. Ther.* **2024**, *47*, 104078. [CrossRef] [PubMed]
23. Kadam, S.; Nadkarni, S.; Lele, J.; Sakhalkar, S.; Mokashi, P.; Kaushik, K.S. Bioengineered Platforms for Chronic Wound Infection Studies: How Can We Make Them More Human-Relevant? *Front. Bioeng. Biotechnol.* **2019**, *7*, 418. [CrossRef] [PubMed]
24. Garcia, A.D.; White Chu, E.F. The challenge of chronic wounds in older adults. *Clin. Geriatr. Med.* **2024**, *40*, 367–373. [CrossRef]
25. Crous, C.; Pretorius, J.; Petzer, A. A review of the current trends in chronic wound and scar management. *Wound Manag.* **2024**, *70*. [CrossRef]
26. Bernatchez, S.F.; Eysaman-Walker, J.; Weir, D. Venous Leg Ulcers: A Review of Published Assessment and Treatment Algorithms. *Adv. Wound Care* **2024**, *11*, 28–41. [CrossRef]
27. OuYang, H.; Yang, J.; Wan, H.; Huang, J.; Yin, Y. Effects of different treatment measures on the efficacy of diabetic foot ulcers: A network meta-analysis. *Front. Endocrinol.* **2024**, *15*, 1452192. [CrossRef]
28. Federman, D.G.; Dardik, A.; Shapshak, D.; Ueno, C.M.; Masterson, L.; Hopf, H.W.; Abdullah, N.; Junkins, S.; Mostow, E.N. Wound Healing Society 2023 update on guidelines for arterial ulcers. *Wound Repair. Regen.* **2024**, *32*, 619–629. [CrossRef]
29. Fan, Y.; Wang, H.; Wang, C.; Xing, Y.; Liu, S.; Feng, L.; Zhang, X.; Chen, J. Advances in Smart-Response Hydrogels for Skin Wound Repair. *Polymers* **2024**, *16*, 2818. [CrossRef]

30. Preetam, S.; Ghosh, A.; Mishra, R.; Pandey, A.; Roy, D.S.; Rustagi, S.; Malik, S. Electrical stimulation: A novel therapeutic strategy to heal biological wounds. *RSC Adv.* **2024**, *14*, 32142–32173. [CrossRef]
31. Nasra, S.; Pramanik, S.; Oza, V.; Kansara, K.; Kumar, A. Advancements in wound management: Integrating nanotechnology and smart materials for enhanced therapeutic interventions. *Discov. Nano* **2024**, *19*, 159. [CrossRef] [PubMed]
32. Mullin, J.A.; Rahmani, E.; Kiick, K.L.; Sullivan, M.O. Growth factors and growth factor gene therapies for treating chronic wounds. *Bioeng. Transl. Med.* **2023**, *9*, e10642. [CrossRef] [PubMed]
33. Aljamal, D.; Iyengar, P.S.; Nguyen, T.T. Translational Challenges in Drug Therapy and Delivery Systems for Treating Chronic Lower Extremity Wounds. *Pharmaceutics* **2024**, *16*, 750. [CrossRef] [PubMed]
34. Miron, A.; Giurcaneanu, C.; Mihai, M.M.; Beiu, C.; Voiculescu, V.M.; Popescu, M.N.; Soare, E.; Popa, L.G. Antimicrobial Biomaterials for Chronic Wound Care. *Pharmaceutics* **2023**, *15*, 1606. [CrossRef]
35. Huang, C.; Ogawa, R. Keloidal pathophysiology: Current notions. *Scars Burn. Heal.* **2021**, *7*, 2059513120980320. [CrossRef]
36. Barone, N.; Safran, T.; Vorstenbosch, J.; Davison, P.G.; Cugno, S.; Murphy, A.M. Current Advances in Hypertrophic Scar and Keloid Management. *Semin. Plast. Surg.* **2021**, *35*, 145–152. [CrossRef]
37. Limandjaja, G.C.; Niessen, F.B.; Scheper, R.J.; Gibbs, S. The Keloid Disorder: Heterogeneity, Histopathology, Mechanisms and Models. *Front. Cell Dev. Biol.* **2020**, *8*, 360. [CrossRef]
38. Berman, B.; Maderal, A.; Raphael, B. Keloids and Hypertrophic Scars: Pathophysiology, Classification, and Treatment. *Dermatol. Surg.* **2017**, *43* (Suppl. 1), S3–S18. [CrossRef]
39. Andrews, J.P.; Marttala, J.; Macarak, E.; Rosenbloom, J.; Uitto, J. Keloids: The paradigm of skin fibrosis—Pathomechanisms and treatment. *Matrix Biol.* **2016**, *51*, 37–46. [CrossRef]
40. Zhang, M.; Chen, H.; Qian, H.; Wang, C. Characterization of the skin keloid microenvironment. *Cell Commun. Signal.* **2023**, *21*, 207. [CrossRef]
41. Yuan, F.L.; Sun, Z.L.; Feng, Y.; Liu, S.Y.; Du, Y.; Yu, S.; Yang, M.L.; Lv, G.Z. Epithelial-mesenchymal transition in the formation of hypertrophic scars and keloids. *J. Cell. Physiol.* **2019**, *234*, 21662–21669. [CrossRef] [PubMed]
42. Ogawa, R. Keloid and Hypertrophic Scars Are the Result of Chronic Inflammation in the Reticular Dermis. *Int. J. Mol. Sci.* **2017**, *18*, 606. [CrossRef] [PubMed]
43. Nangole, F.W.; Agak, G.W. Keloid pathophysiology: Fibroblast or inflammatory disorders? *JPRAS Open* **2019**, *22*, 44–54. [CrossRef] [PubMed]
44. Glass, D.A. Current Understanding of the Genetic Causes of Keloid Formation. *J. Investig. Dermatol. Symp. Proc.* **2017**, *18*, S50–S53. [CrossRef]
45. Kim, H.J.; Kim, Y.H. Comprehensive Insights into Keloid Pathogenesis and Advanced Therapeutic Strategies. *Int. J. Mol. Sci.* **2024**, *25*, 8776. [CrossRef]
46. Libersky, S.; Marczak, D.; Migdalski, A. The influence of genetic factors on the pathogenesis of hypertrophic scars and keloids. *J. Educ. Health Sport* **2018**, *8*, 313–321.
47. Sadiq, A.; Khumalo, N.P.; Bayat, A. Genetics of Keloid Scarring. In *Textbook on Scar Management: State of the Art Management and Emerging Technologies*; Téot, L., Mustoe, T.A., Middelkoop, E., Gauglitz, G.G., Eds.; Springer: Cham, Switzerland, 2020; Chapter 8. Available online: https://www.ncbi.nlm.nih.gov/books/NBK586075/ (accessed on 10 November 2024).
48. Frech, F.S.; Hernandez, L.; Urbonas, R.; Zaken, G.A.; Dreyfuss, I.; Nouri, K. Hypertrophic Scars and Keloids: Advances in Treatment and Review of Established Therapies. *Am. J. Clin. Dermatol.* **2023**, *24*, 225–245. [CrossRef]
49. Arno, A.I.; Gauglitz, G.G.; Barret, J.P.; Jeschke, M.G. Up-to-Date Approach to Manage Keloids and Hypertrophic Scars: A Useful Guide. *Burns* **2014**, *40*, 1255–1266. [CrossRef]
50. Aluko-Olokun, B.; Olaitan, A.A.; Ladeinde, A.L. Sessile and Pedunculated Facial Keloid Scar: A Comparison of Response to Intralesional Triamcinolone Injection. *Eur. J. Plast. Surg.* **2014**, *37*, 255–258. [CrossRef]
51. Garg, S.; Dahiya, N.; Gupta, S. Surgical Scar Revision: An Overview. *J. Cutan. Aesthetic Surg.* **2014**, *7*, 3. [CrossRef]
52. Gold, M.H.; Berman, B.; Clementoni, M.T.; Gauglitz, G.G.; Nahai, F.; Murcia, C. Updated International Clinical Recommendations on Scar Management: Part 1—Evaluating the Evidence. *Dermatol. Surg.* **2014**, *40*, 817–824. [CrossRef] [PubMed]
53. Yang, L.; Li, N.; Cheng, J.; Han, J.T.; Hu, D.H. A prospective randomized controlled clinical study on the optimal treatment interval of pulsed dye laser in treating hypertrophic scar after burn. *Zhonghua Shao Shang Za Zhi* **2021**, *37*, 57–63. [CrossRef] [PubMed]
54. Taudorf, E.H.; Danielsen, P.L.; Paulsen, I.F.; Togsverd-Bo, K.; Dierickx, C.; Paasch, U.; Haedersdal, M. Non-ablative Fractional Laser Provides Long-term Improvement of Mature Burn Scars—A Randomized Controlled Trial with Histological Assessment. *Lasers Surg. Med.* **2015**, *47*, 141–147. [CrossRef] [PubMed]
55. McLaughlin, J.; Branski, L.K.; Norbury, W.B.; Bache, S.E.; Chilton, L.; El-Muttardi, N.; Philp, B. Laser for Burn Scar Treatment. In *Total Burn Care*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 648–654. ISBN 978-0-323-47661-4.
56. Lin, M.J.; Dubin, D.P.; Torbeck, R.L.; Bernstein, D.M.; Nabatian, A.; Dolan, C.K.; Bacigalupi, R.; Zade, J.; Zheng, Z.; Desman, G.; et al. Early Fractional Ablative Laser for Skin Cancer Excision Scars: A Randomized Split-Scar Study. *Dermatol. Surg.* **2023**, *49*, 338–342. [CrossRef]
57. Karmisholt, K.E.; Banzhaf, C.A.; Glud, M.; Yeung, K.; Paasch, U.; Nast, A.; Haedersdal, M. Laser Treatments in Early Wound Healing Improve Scar Appearance: A Randomized Split-Wound Trial with Nonablative Fractional Laser Exposures vs. Untreated Controls. *Br. J. Dermatol.* **2018**, *179*, 1307–1314. [CrossRef]

58. Zainib, M.; Amin, N.P. *Radiation Therapy in the Treatment of Keloids*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
59. Ziade, M.; Domergue, S.; Batifol, D.; Jreige, R.; Sebbane, M.; Goudot, P.; Yachouh, J. Use of Botulinum Toxin Type A to Improve Treatment of Facial Wounds: A Prospective Randomised Study. *J. Plast. Reconstr. Aesthetic Surg.* **2013**, *66*, 209–214. [CrossRef]
60. Goodman, G. The Use of Botulinum Toxin as Primary or Adjunctive Treatment for Post Acne and Traumatic Scarring. *J. Cutan. Aesthetic Surg.* **2010**, *3*, 90. [CrossRef]
61. Chang, C.-S.; Wallace, C.G.; Hsiao, Y.-C.; Chang, C.-J.; Chen, P.K.-T. Botulinum Toxin to Improve Results in Cleft Lip Repair: A Double-Blinded, Randomized, Vehicle-Controlled Clinical Trial. *PLoS ONE* **2014**, *9*, e115690. [CrossRef]
62. Shaarawy, E.; Hegazy, R.A.; Abdel Hay, R.M. Intralesional Botulinum Toxin Type A Equally Effective and Better Tolerated than Intralesional Steroid in the Treatment of Keloids: A Randomized Controlled Trial. *J. Cosmet. Dermatol.* **2015**, *14*, 161–166. [CrossRef]
63. Ramadan, H.; Saber, M.; Salah, M.; Samy, N. The Effectiveness of Long Pulsed Nd:YAG Laser Alone for Treatment of Keloids and Hypertrophic Scars versus Its Combination with Bleomycin. *J. Cosmet. Dermatol.* **2021**, *20*, 3899–3906. [CrossRef]
64. Carswell, L.; Borger, J. *Hypertrophic Scarring Keloids*; StatPearls Publishing: Treasure Island, FL, USA, 2024. Available online: https://www.ncbi.nlm.nih.gov/books/NBK537058/ (accessed on 23 October 2024).
65. Choi, C.; Mukovozov, I.; Jazdarehee, A.; Rai, R.; Sachdeva, M.; Shunmugam, M.; Zaslavsky, K.; Byun, S.; Barankin, B. Management of hypertrophic scars in adults: A systematic review and meta-analysis. *Australas. J. Dermatol.* **2022**, *63*, 172–189. [CrossRef] [PubMed]
66. Lingzhi, Z.; Meirong, L.; Xiaobing, F. Biological approaches for hypertrophic scars. *Int. Wound J.* **2020**, *17*, 405–418. [CrossRef] [PubMed]
67. Mony, M.P.; Harmon, K.A.; Hess, R.; Dorafshar, A.H.; Shafikhani, S.H. An Updated Review of Hypertrophic Scarring. *Cells* **2023**, *12*, 678. [CrossRef] [PubMed]
68. Thomas, A.; Farah, K.; Millis, R.M. Epigenetic Influences on Wound Healing and Hypertrophic-Keloid Scarring: A Review for Basic Scientists and Clinicians. *Cureus* **2022**, *14*, e23503. [CrossRef] [PubMed]
69. Poelchow, F.; Codde, J.; Kendell, R.; Edgar, D.W.; Wood, F.M. A Randomised Investigation of Film-Forming Silicone Gel in Superficial Partial Thickness Face and Neck Burn Patients: Indication of Improved Early Scar Pigmentation Outcomes. *Burns* **2024**, *50*, 1605–1613. [CrossRef]
70. Shen, Y.; He, J.; Liu, J.Z.; Zhang, X.F.; Tan, J.; Tang, W.J.; Yang, H.; Chen, X.; Luo, X.W. A randomized controlled trial on the effect of early eschar dermabrasion combined with antimicrobial soft silicone foam dressing in the treatment of deep partial-thickness burn wounds in children. *Zhonghua Shao Shang Yu Chuang Mian Xiu Fu Za Zhi* **2024**, *40*, 342–347. [CrossRef]
71. Ge, X.; Sun, Y.; Lin, J.; Zhou, F.; Yao, G.; Su, X. Effects of Multiple Modes of UltraPulse Fractional CO_2 Laser Treatment on Extensive Scarring: A Retrospective Study. *Lasers Med. Sci.* **2022**, *37*, 1575–1582. [CrossRef]
72. Ali, B.; ElMahdy, N.; Elfar, N.N. Microneedling (Dermapen) and Jessner's Solution Peeling in Treatment of Atrophic Acne Scars: A Comparative Randomized Clinical Study. *J. Cosmetic Laser Ther.* **2019**, *21*, 357–363. [CrossRef]
73. An, M.K.; Hong, E.H.; Suh, S.B.; Park, E.J.; Kim, K.H. Combination Therapy of Microneedle Fractional Radiofrequency and Topical Poly-Lactic Acid for Acne Scars: A Randomized Controlled Split-Face Study. *Dermatol. Surg.* **2020**, *46*, 796–802. [CrossRef]
74. Heitmiller, K.; Wang, J.V.; Murgia, R.D.; Saedi, N. Utility of Platelet-rich Plasma for Treatment of Striae Distensae: A Current Exploration. *J. Cosmet. Dermatol.* **2021**, *20*, 437–441. [CrossRef]
75. Ibrahim, Z.A.E.; El-Tatawy, R.A.; El-Samongy, M.A.; Ali, D.A.M. Comparison between the Efficacy and Safety of Platelet-rich Plasma vs. Microdermabrasion in the Treatment of Striae Distensae: Clinical and Histopathological Study. *J. Cosmet. Dermatol.* **2021**, *14*, 336–346. [CrossRef] [PubMed]
76. Ebrahimi, Z.; Alimohamadi, Y.; Janani, M.; Hejazi, P.; Kamali, M.; Goodarzi, A. Platelet-rich Plasma in the Treatment of Scars, to Suggest or Not to Suggest? A Systematic Review and Meta-analysis. *J. Tissue Eng. Regen. Med.* **2022**, *16*, 875–899. [CrossRef] [PubMed]
77. Mujahid, N.; Shareef, F.; Maymone, M.B.C.; Vashi, N.A. Microneedling as a Treatment for Acne Scarring: A Systematic Review. *Dermatol. Surg.* **2020**, *46*, 86–92. [CrossRef] [PubMed]
78. Leo, M.S.; Kumar, A.S.; Kirit, R.; Konathan, R.; Sivamani, R.K. Systematic Review of the Use of Platelet-rich Plasma in Aesthetic Dermatology. *J. Cosmet. Dermatol.* **2015**, *14*, 315–323. [CrossRef]
79. Manuskiatti, W. Treatment Response of Keloidal and Hypertrophic Sternotomy Scars: Comparison Among Intralesional Corticosteroid, 5-Fluorouracil, and 585-Nm Flashlamp-Pumped Pulsed-Dye Laser Treatments. *Arch. Dermatol.* **2002**, *138*, 1149. [CrossRef]
80. Meretsky, C.R.; Polychronis, A.; Schiuma, A.T. A Comparative Analysis of the Advances in Scar Reduction: Techniques, Technologies, and Efficacy in Plastic Surgery. *Cureus* **2024**, *14*, e66806. [CrossRef]
81. Elhefnawy, A. Assessment of Intralesional Injection of Botulinum Toxin Type A Injection for Hypertrophic Scars. *Indian J. Dermatol. Venereol. Leprol.* **2016**, *82*, 279. [CrossRef]
82. Wang, M.; Xu, X.; Lei, X.; Tan, J.; Xie, H. Mesenchymal Stem Cell-Based Therapy for Burn Wound Healing. *Burn. Trauma* **2021**, *9*, tkab002. [CrossRef]
83. Xi, W.J.; Zhang, Z.; Li, J.; Su, W.J.; Li, H.; Pu, Z.M.; Zhang, Y.; Feng, S.Q.; Zhang, Y.X. Clinical effect of fractional carbon dioxide laser in the treatment of contracture scars. *Zhonghua Shao Shang Za Zhi* **2021**, *37*, 711–717. [CrossRef]

84. Rossi, F.; Magni, G.; Tatini, F.; Banchelli, M.; Cherchi, F.; Rossi, M.; Coppi, E.; Pugliese, A.M.; Rossi degl'Innocenti, D.; Alfieri, D.; et al. Photobiomodulation of Human Fibroblasts and Keratinocytes with Blue Light: Implications in Wound Healing. *Biomedicines* **2021**, *9*, 41. [CrossRef]
85. Hernández-Bule, M.L.; Naharro-Rodríguez, J.; Bacci, S.; Fernández-Guarino, M. Unlocking the Power of Light on the Skin: A Comprehensive Review on Photobiomodulation. *Int. J. Mol. Sci.* **2024**, *25*, 4483. [CrossRef]