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HYPERTROPHIC SCARS AND KELOIDS: AN UPDATED REVIEW OF PATHOPHYSIOLOGY, CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS, RISK FACTORS, AND THERAPEUTIC ADVANCES

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Abstract

Hypertrophic scars and keloids are fibroproliferative disorders that arise from abnormal cutaneous wound healing and may cause pain, pruritus, functional limitations, disfigurement, and psychological distress. Although both conditions share several pathological features, they differ in their clinical presentation and natural history. Hypertrophic scars remain confined to the boundaries of the original wound and may gradually regress over time, whereas keloids extend beyond the wound margins, rarely resolve spontaneously, and are associated with a high risk of recurrence following surgical excision. This review provides an overview of the epidemiology, wound-healing mechanisms, molecular pathophysiology, clinical and histopathological characteristics, predisposing factors, diagnostic assessment, quality-of-life impact, preventive measures, and current therapeutic approaches for both conditions.

Keloid development varies across ethnic populations and frequently demonstrates familial clustering, with genetic association studies supporting an underlying hereditary susceptibility. In contrast, hypertrophic scars are more commonly associated with burns, deep dermal injuries, delayed wound healing, and increased mechanical tension. The pathogenesis of both conditions is multifactorial and involves transforming growth factor-beta (TGF-β) signalling, persistent inflammation, mechanotransduction, vascular alterations, and epigenetic mechanisms. However, much of the available mechanistic evidence is derived from experimental models and relatively small tissue-based studies. Current management strategies include silicone-based preparations and pressure therapy for prevention and early intervention, while established lesions may require intralesional corticosteroids, 5-fluorouracil, cryotherapy, or laser-based treatments. Surgical excision combined with appropriate adjuvant therapy, including radiotherapy in selected cases, may be considered for recurrent or treatment-resistant keloids. Nevertheless, comparisons of treatment efficacy remain challenging because available studies are often limited by small sample sizes, heterogeneous outcome measures, and inadequate follow-up.

Consequently, treatment should be individualized according to scar characteristics, clinical presentation, recurrence risk, and patient preferences. A combination of therapeutic approaches, validated scar assessment instruments, and long-term follow-up may help optimize clinical outcomes. Further research, particularly large-scale population-based epidemiological studies and well-designed clinical trials using standardized outcome measures, is needed to clarify disease mechanisms and establish the comparative effectiveness of emerging and existing therapeutic interventions.

Keywords: Hypertrophic scars; Keloids; Abnormal wound healing; Transforming growth factor-beta; Fibroblasts; Intralesional corticosteroids; Scar assessment; Recurrence.

Introduction

Cutaneous wound healing is a complex biological process that normally restores skin integrity and barrier function through four coordinated phases: haemostasis, inflammation, proliferation, and tissue remodelling. Successful repair generally results in a mature, flat, and pale scar [1]. However, disturbances in this tightly regulated process can lead to different pathological outcomes, ranging from chronic non-healing wounds to excessive fibrotic tissue formation. Hypertrophic scars (HS) and keloids represent two important forms of pathological scarring, characterized by excessive extracellular matrix (ECM) deposition driven by persistent fibroblast activation [2]. Although both conditions share several pathological features, their clinical characteristics and natural histories differ. Hypertrophic scars typically present as raised, erythematous, and firm lesions that remain confined to the boundaries of the original injury and may gradually regress over months or years. In contrast, keloids extend beyond the original wound margins into surrounding normal skin, rarely undergo spontaneous regression, and frequently recur following surgical excision alone. Nevertheless, the distinction between these conditions is not always straightforward. Some investigators consider them part of a broader spectrum of fibroproliferative skin disorders rather than entirely separate pathological entities. A related hypothesis suggests that chronic inflammation and mechanical stimulation within the reticular dermis contribute to the development of both conditions, with differences in disease intensity and individual susceptibility influencing their clinical expression. This continuing debate between the separate-disease and spectrum-based models remains relevant to understanding their pathogenesis and treatment response, particularly because the two conditions demonstrate different clinical behaviours despite sharing several underlying mechanisms [3]. The clinical burden of pathological scarring extends beyond its visible appearance. Hypertrophic scarring is a frequent long-term complication of burn injuries and remains an important challenge in burn management. Patients may experience persistent pain, pruritus, tenderness, and discomfort, while scars involving joints can restrict movement and impair physical function [4].

2. Epidemiology of Hypertrophic Scars and Keloids

2.1 Global Epidemiological patterns and Limitations of available data

Reliable population-based estimates of the incidence and prevalence of hypertrophic scars (HS) and keloids remain limited. Most available epidemiological data are derived from hospital-based studies, dermatology clinic populations, and specific injury cohorts, particularly patients with burn injuries. These sources may be influenced by referral patterns, selection bias, and differences in case identification and diagnostic criteria. Consequently, reported frequencies vary considerably across studies and should be

interpreted with caution rather than considered definitive estimates of disease burden. Given these limitations, providing a single pooled prevalence figure may not accurately reflect the global epidemiological situation [5].

Despite the limitations in available data, certain epidemiological patterns have been consistently observed. Keloids occur across different populations but are reported more frequently among individuals of African, Asian, and Hispanic ancestry than among those of European ancestry. This ethnic variation has been recognized in early surgical and dermatological case series and has been reiterated in subsequent reviews. However, the underlying reasons for these differences remain incompletely understood [6]. Genetic susceptibility, biological characteristics associated with skin pigmentation, variations in environmental exposures, and differences in injury patterns, including ear piercing, may all contribute to the observed distribution. Differences in healthcare access, referral practices, and patterns of healthcare utilization may also influence reported frequencies. Therefore, the relative contribution of genetic, biological, environmental, and healthcare-related factors requires further investigation [7].

2.2 Hypertrophic scars: injury-related epidemiology

HS epidemiology is better characterised in burn populations, where frequency depends on burn depth, time to healing, age, and site; reported rates vary substantially across studies. Systematic review evidence highlights heterogeneity in definitions and follow-up, which limits pooled estimates [8]. Beyond burns, HS follows surgical incisions and traumatic wounds under tension, but non-burn incidence data are limited.

2.3 Age, sex, and anatomical distribution

Keloids are generally described as presenting most often in adolescence and early adulthood, with a lower frequency at the extremes of age, a pattern linked to periods of greater skin tension, hormonal change, and injury exposure. Evidence for a consistent sex difference is weak. Some series report more female patients, which may reflect cosmetic help-seeking and ear piercing rather than biology; this remains a hypothesis [9]. Predilection sites for keloids include the sternum and presternal area, shoulders, upper back, earlobes, and the mandibular and suprapubic regions, whereas the palms, soles, and eyelids are rarely affected; these are areas that differ in skin tension and movement. Earlobe keloids frequently follow piercing, and one study linked later age at piercing with a higher frequency of keloid formation. HS predominates over flexural surfaces and joints, especially after burns [10].

2.4 Genetic and familial predisposition

Familial clustering of keloids has long been recognised. Pedigree studies suggest autosomal dominant inheritance with incomplete penetrance in some families, as well as other modes of inheritance in others. Genome-wide association work in Japanese populations identified susceptibility loci, providing evidence for polygenic contributions, and reviews summarise candidate genes and loci, noting limited replication across ethnic groups [11]. Patients with multiple-site keloids appear to differ clinically from those with a single lesion, consistent with a stronger heritable component in more extensive disease. Genetic evidence for HS is considerably weaker. Overall, the genetics literature relies on modest sample sizes, ancestry-specific cohorts, and association designs that cannot establish causal pathways [12].

2.5 Epidemiological differences between HS and keloid, and limitations

In brief, keloids show ethnic, familial, and site-specific patterns with onset that may follow minor trauma, whereas HS correlates more directly with injury type and depth (Table-1). Because many studies use inconsistent diagnostic criteria, mislabel HS as keloid or vice versa, and are performed in specialist centres, the epidemiological contrast is likely blurred [13]. The limitations of existing research (retrospective designs, hospital-based samples, absent population denominators, and poor representation of many regions) are discussed again in Section 15.

Table-1: Comparative clinical and epidemiological characteristics of hypertrophic scars and keloids

S.no.	Feature	Hypertrophic scar	Keloid	References
1.	Onset after injury	Within weeks	Weeks to years; may follow trivial injury	[14]
2.	Relationship to wound boundary	Confined to original wound	Extends beyond margins onto normal skin	[15]
3.	Growth pattern	Early growth then plateau	Slow, persistent, sometimes progressive growth	[16]
4.	Spontaneous regression	Common over months to years	Rare	[17]
5.	Ethnic and phototype pattern	Less ancestry-dependent; injury and depth driven	More frequent in people of African, Asian, and Hispanic ancestry (data limited)	[18]
6.	Familial and genetic predisposition	Weak or unproven	Supported (familial clustering; GWAS loci)	[19]
7.	Typical sites	Flexures, joints, burn sites, high-tension wounds	Presternal, shoulders, upper back, earlobes, jawline	[20]
8.	Age at presentation	Any age after deep injury; burns common in children and adults	Peak in adolescence and early adulthood	[21]
9.	Symptoms	Itch, pain, contracture	Itch, pain, tenderness; often persistent	[22]
10.	Recurrence after excision alone	Less frequent	Common	[23]
11.	Response to treatment	Generally more predictable	More resistant; multimodal regimens	[24]
12.	Quality of epidemiological data	Better for burns; limited otherwise	Hospital-based; population estimates lacking	[25]

3. Normal Wound Healing and Pathological Scar Formation

Normal repair is conventionally divided into overlapping phases [26]. Normal cutaneous wound healing progresses through four overlapping phases: haemostasis, inflammation, proliferation, and remodeling, with dysregulation of these processes potentially leading to pathological scarring (Figure-1).

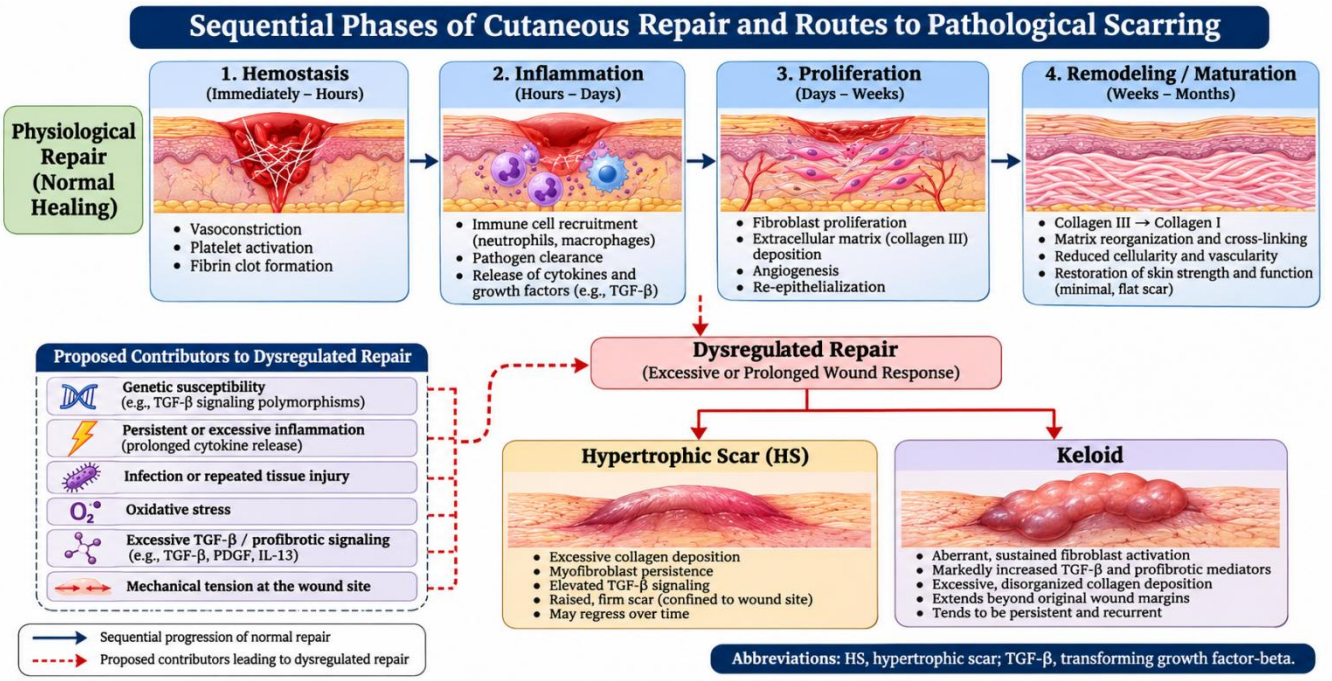


Figure-1: Schematic representation of the sequential phases of normal cutaneous wound healing and their progression towards pathological scar formation.

Cutaneous wound healing is a dynamic and coordinated biological process involving four overlapping phases: haemostasis, inflammation, proliferation, and remodeling. Initially, haemostasis occurs through platelet aggregation and fibrin clot formation, which stabilize the injured tissue and promote the release of growth factors, particularly platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β). These mediators contribute to the recruitment of inflammatory and mesenchymal cells to the wound site [27]. During the subsequent inflammatory phase, neutrophils and monocyte-derived macrophages facilitate the removal of cellular debris and microorganisms while releasing cytokines and growth factors that support tissue repair. As healing progresses, macrophage activity gradually shifts from a predominantly pro-inflammatory state towards a reparative phenotype.

The proliferative phase is characterized by keratinocyte migration across the wound surface to restore epidermal integrity, angiogenesis to support granulation tissue formation, and fibroblast activation with the synthesis of a provisional extracellular matrix (ECM), which is initially rich in type III collagen. Under the combined influence of TGF-β signalling and mechanical stimulation, a proportion of fibroblasts differentiate into contractile myofibroblasts, characterized by the expression of alpha-smooth muscle actin (α-SMA) [28]. The final phase, tissue remodelling, involves the gradual replacement of type III collagen with type I collagen, reorganization and cross-linking of the extracellular matrix, regression of newly formed blood vessels, and the removal or inactivation of myofibroblasts through apoptosis or

phenotypic transition. Together, these processes contribute to the gradual reduction in scar thickness, vascularity, and erythema. Pathological scarring may develop when the normal resolution of wound healing is disrupted. Persistent myofibroblast activity, excessive collagen synthesis, impaired extracellular matrix degradation, and sustained inflammatory and vascular signalling can collectively promote excessive fibrotic tissue formation. In hypertrophic scars (HS), these changes are generally more limited in duration, and the lesions may gradually regress over time. In contrast, keloids are characterized by more persistent fibroblast activation and excessive ECM accumulation, with fibrous tissue extending beyond the boundaries of the original wound. These differences suggest that although both conditions share several mechanisms of abnormal wound repair, they represent distinct clinical patterns of dysregulated fibrosis [29].

4. Pathophysiology of Hypertrophic Scars and Keloids

A caveat applies throughout: much mechanistic knowledge comes from cultured fibroblasts, ex vivo tissue, and animal models (keloids do not occur spontaneously in common laboratory animals), so findings must be interpreted as experimental unless confirmed in patients [30]. The interaction of inflammatory mediators, mechanical tension, vascular alterations, genetic susceptibility, and profibrotic signaling contributes to fibroblast activation and excessive extracellular matrix deposition, as illustrated in Figure-2.

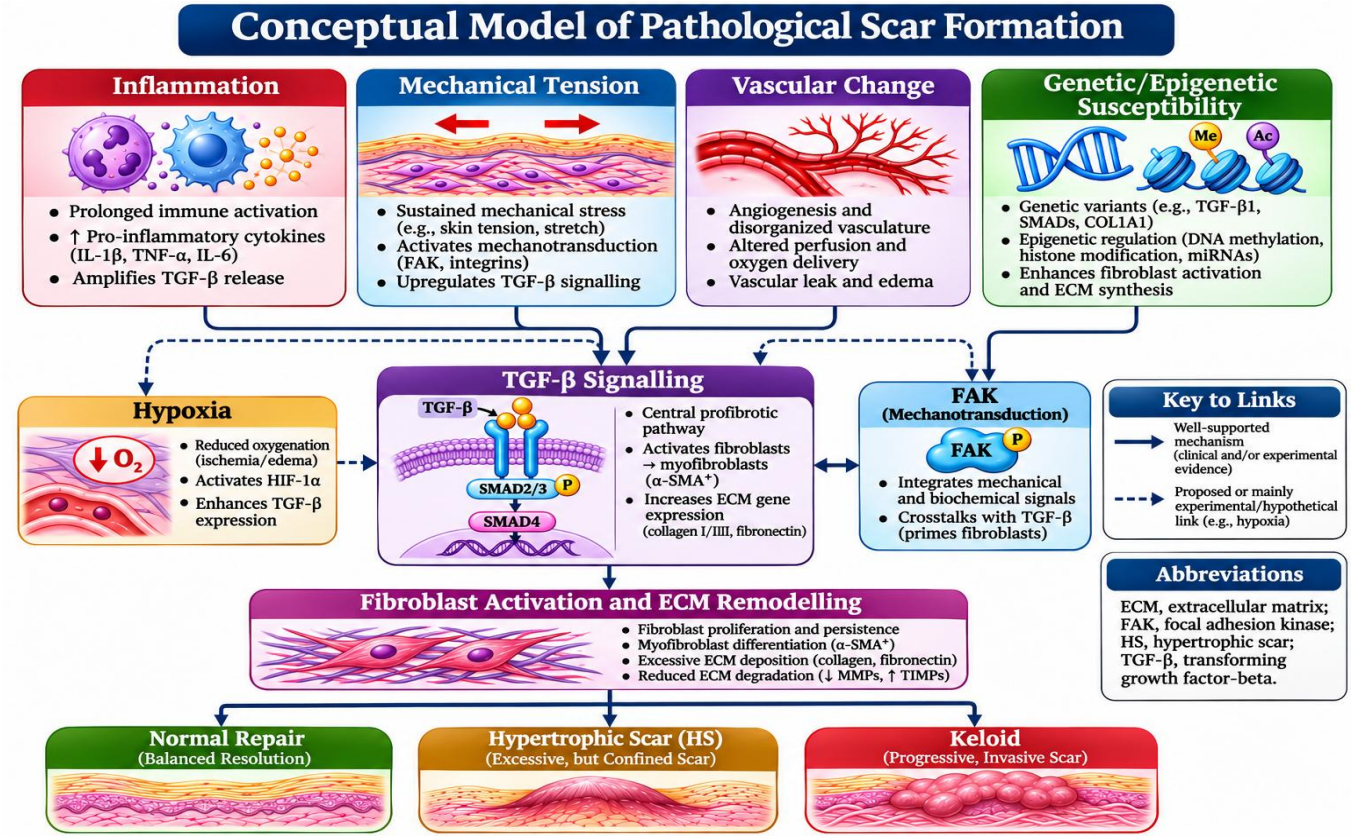


Figure 2: Conceptual overview of the molecular and cellular mechanisms underlying hypertrophic scar and keloid formation, highlighting the roles of inflammation, mechanical tension, vascular alterations, genetic susceptibility, and profibrotic signaling pathways.

4.1 Fibroblasts, myofibroblasts, collagen, and the extracellular matrix

Collagen is a defining abnormality: whereas normal dermis contains organised type I and III collagen in a basket-weave pattern, pathological scars have an increased type I to type III ratio during maturation and disorganized bundles [31]. Quantitative histological analysis has shown differences in collagen architecture between keloids, HS, normotrophic scars, and normal skin, with keloids showing thick, haphazardly arranged, hyalinised bundles and HS showing finer fibres oriented more parallel to the epidermis. Reduced matrix degradation (altered balance of matrix metalloproteinases and their inhibitors) is also reported but is less consistently demonstrated in vivo [32].

4.2 TGF-β signalling

TGF-β is the best-characterised profibrotic mediator in scarring. The isoforms have distinct roles: TGF-β1 and TGF-β2 are associated with fibrosis and TGF-β3 with reduced scarring, which prompted therapeutic interest in modulating isoform balance [33]. In rodent models, neutralising TGF-β1 and β2 reduced scarring. Keloid fibroblasts have been reported to show an exaggerated proliferative and collagen-synthetic response to TGF-β, altered receptor expression with increased Smad3 activation, and a role for Smad3 in epithelial–mesenchymal interactions in keloid pathogenesis. These data support a central role for TGF-β/Smad signalling, but whether TGF-β abnormalities are primary or secondary to chronic inflammation and tension is unresolved [34].

4.3 Inflammatory cytokines, growth factors, and immune dysregulation

Inflammatory cell subpopulations, including T lymphocytes, macrophages, and mast cells, are present in keloid tissue, suggesting persistent immune activity. The hypothesis that keloids and HS reflect chronic inflammation of the reticular dermis integrates these observations with the clinical observation that deeper, more inflamed wounds scar worse, and keloids have been conceptualised as chronic inflammatory disorders with some cancer-like behaviours such as local invasion and apparent autonomy [35]. Mediators implicated include interleukin-6, interleukin-1, TGF-β, platelet-derived growth factor, and connective tissue growth factor, but cytokine profiles differ between studies and sampling sites. Neurogenic inflammation, mediated by sensory neuropeptides, has been proposed to explain pain and itch these remains hypothetical [36].

4.4 Angiogenesis and vascular alterations

Vascular density and microvessel architecture differ between pathological scars and normal tissue, and stereological analysis has described distinct vascularisation patterns in HS and keloids. Occlusion of micro vessels in the keloid core and a more vascular periphery has been proposed to explain central hypoxia and peripheral growth, but this is not uniformly confirmed [37]. The erythema of immature HS and the effect of vascular-targeted lasers rest on this vascular component [38].

4.5 Mechanical tension and mechanotransduction

Mechanical load is among the most robust determinants of pathological scarring clinically: scars over the sternum, shoulders, and flexures are at greatest risk. Experimental work showed that mechanical loading of healing wounds promotes HS formation through reduced cell apoptosis, and focal adhesion kinase (FAK) has been shown to link mechanical force to fibrosis via inflammatory signalling in a murine model,

with FAK inhibition reducing scarring [39]. Keloid fibroblasts show an increased response to mechanical strain with greater focal adhesion complexes. Mechanobiological accounts propose that keloids arise where skin stretch and contraction exceed a threshold, with keloid sites corresponding to areas of high tension. Mechanotransduction is therefore a strong mechanistic and clinical rationale for tension-reducing surgery and taping, although the human randomised evidence for specific devices is limited [40].

4.6 Hypoxia and oxidative stress

Hypoxia and oxidative stress have been proposed as amplifiers of fibroblast activation, and hypoxia-induced signalling is plausible in the poorly perfused keloid core. However, direct in vivo evidence in human lesions is limited, and this area is best considered an emerging hypothesis rather than an established mechanism [41].

4.7 Genetic and epigenetic mechanisms

Beyond the germline susceptibility described above, keloid fibroblasts show epigenetic differences, including altered DNA methylation and gene expression, consistent with epigenetically altered wound healing. Such findings could explain persistence of the abnormal phenotype in culture, but sample sizes are small and tissue heterogeneity is a confounder [42].

4.8 Differences between hypertrophic scars and keloids

Proposed molecular differences include greater persistent inflammatory and TGF-β-driven activity and fibroblast autonomy in keloids, more prominent alpha-smooth-muscle-actin-positive myofibroblast nodules in HS, and different collagen organization [43]. Evidence is nevertheless contradictory, since many markers overlap, which is why some authors consider the conditions to be a continuum differing in degree and duration of the same fibro proliferative process [44]. The principal molecular and cellular mechanisms implicated in pathological scar formation, together with their respective levels of supporting evidence, are presented in Table-2.

Table 2: Key molecular and cellular mechanisms involved in the pathogenesis of hypertrophic scars and keloids.

S.no.	Mechanism	Principal findings	Relevance to HS versus keloid	Level of evidence	Reference
1.	TGF-β/Smad signalling	Isoform-dependent effects; exaggerated fibroblast response and Smad3 activation in keloid fibroblasts	Central to both; may be more sustained in keloids	In vitro, animal, tissue, limited clinical	[45]
2.	Fibroblast and myofibroblast activity	Increased proliferation, matrix synthesis, apoptosis	Myofibroblast nodules prominent in	In vitro, histology	[46]

		resistance; myofibroblast persistence	HS; keloid fibroblasts more autonomous		
3.	Collagen and ECM	Disorganised thick collagen in keloids, fine, parallel fibres in HS; altered MMP balance	Architectural contrast, overlap exists	Histology, quantitative analysis	[47]
4.	Inflammation and immune dysregulation	Persistent T cell, macrophage, mast cell infiltrates; chronic reticular dermal inflammation	Likely contributory to both	Tissue studies, hypothesis-driven	[48]
5.	Angiogenesis and vascular changes	Distinct vascularisation patterns; central hypoxia proposed in keloids	Erythema in immature HS	Stereological and histological	[49]
6.	Mechanotransduction	Tension promotes scarring; FAK links force to inflammation; strain-responsive keloid fibroblasts	Dominant in HS; contributes to keloid site pattern	Animal, in vitro, clinical observation	[40]
7.	Hypoxia and oxidative stress	Proposed amplifier of fibroblast activation	Uncertain	Largely hypothesis; limited human data	[50]
8.	Genetic susceptibility	Heritable component; GWAS loci	Mainly keloid	Family and association studies	[51]
9.	Epigenetic alterations	Altered methylation and expression in keloid fibroblasts	Mainly keloid	Small studies	[52]
10.	Neurogenic inflammation	Neuropeptide-mediated itch and pain proposed	Both	Hypothesis	[53]

5. Clinical Characteristics and Classification

5.1 Morphology and symptoms

HS are raised, firm, often pink to red scars that develop within weeks of injury, remain confined to the wound, and commonly thicken for several months before slowly softening and flattening. Keloids are firm, rubbery, often shiny nodules or plaques that extend onto normal skin with claw-like or irregular projections, may be skin-coloured, pink, or hyperpigmented, and vary from small papules to large pedunculated masses (for example on the ear). Pain, pruritus, tenderness, and burning are common in both and may be more persistent in keloids; neuropathic features are described [54].

5.2 Anatomical distribution, evolution, and course

The anatomical distribution and clinical course of hypertrophic scars (HS) and keloids differ in several respects. HS commonly develop on flexural surfaces, over joints, and at burn sites, whereas keloids are more frequently observed in the presternal region, shoulders, upper back, ears, and jawline. HS generally progress through an active proliferative phase before gradually maturing and may undergo spontaneous regression [55]. However, this process can take a year or longer and associated contractures may persist even after scar maturation. In contrast, keloids typically enlarge slowly over several months or years and may develop following relatively minor or even unnoticed skin injuries. Unlike HS, they rarely regress spontaneously, and recurrence following surgical excision alone is common [56].

5.3 Differential diagnosis

The differential includes dermatofibroma, dermatofibrosarcoma protuberans, hypertrophic lichen planus, sarcoidosis, foreign-body granuloma, and, in chronic scars, malignant change (for example Marjolin ulcer). Biopsy is considered when a lesion is atypical, ulcerates, grows rapidly, or has no clear injury history [57].

5.4 Histopathology

Histologically, keloids classically show thick, hyalinised, eosinophilic collagen bundles (so-called keloidal collagen) in a disorganised arrangement, a prominent horizontal fibrous band in the upper reticular dermis, a tongue-like advancing edge beneath normal epidermis, and relatively few nodules; HS show collagen nodules with fine fibres aligned parallel to the epidermis and often prominent vessels and myofibroblasts [58]. Studies have, however, reported overlap and inconsistent diagnostic value of individual features, and pathologists should correlate histology with the clinical picture. The characteristic histopathological features distinguishing hypertrophic scars from keloids, including collagen architecture and vascular changes, are compared in Table-4.

Table 4: Comparative histopathological features of hypertrophic scars and keloids.

S.no.	Parameter	Hypertrophic scar	Keloid	References
1.	Collagen bundles	Fine, wavy fibres oriented parallel to epidermis	Thick, hyalinised, eosinophilic “keloidal” bundles in haphazard arrangement	[59]

2.	Nodules	Collagen nodules with myofibroblasts often present	Nodules less constant; thick bundles dominate	[60]
3.	Fibrous band and advancing edge	Not typical	Horizontal fibrous band; tongue-like advancing edge beneath normal epidermis	[61]
4.	Vascularity	Prominent vessels in immature lesions	Distinct vascular pattern; peripheral predominance suggested	[62]
5.	Epidermis	Often thinned	Variable	[63]
6.	Clinical extent	Within wound	Beyond wound	[64]
7.	Clinical behaviour	May regress	Persistent, recurrent	[65]
8.	Diagnostic reliability	Overlap with keloid, no single feature pathognomonic	Same	[66]

6. Clinico-Epidemiological Differences between Hypertrophic Scars and Keloids

The principal clinical, epidemiological, and histopathological differences between hypertrophic scars and keloids, together with their overlapping characteristics, are summarized in Table-1, Table-4, and Figure-3.

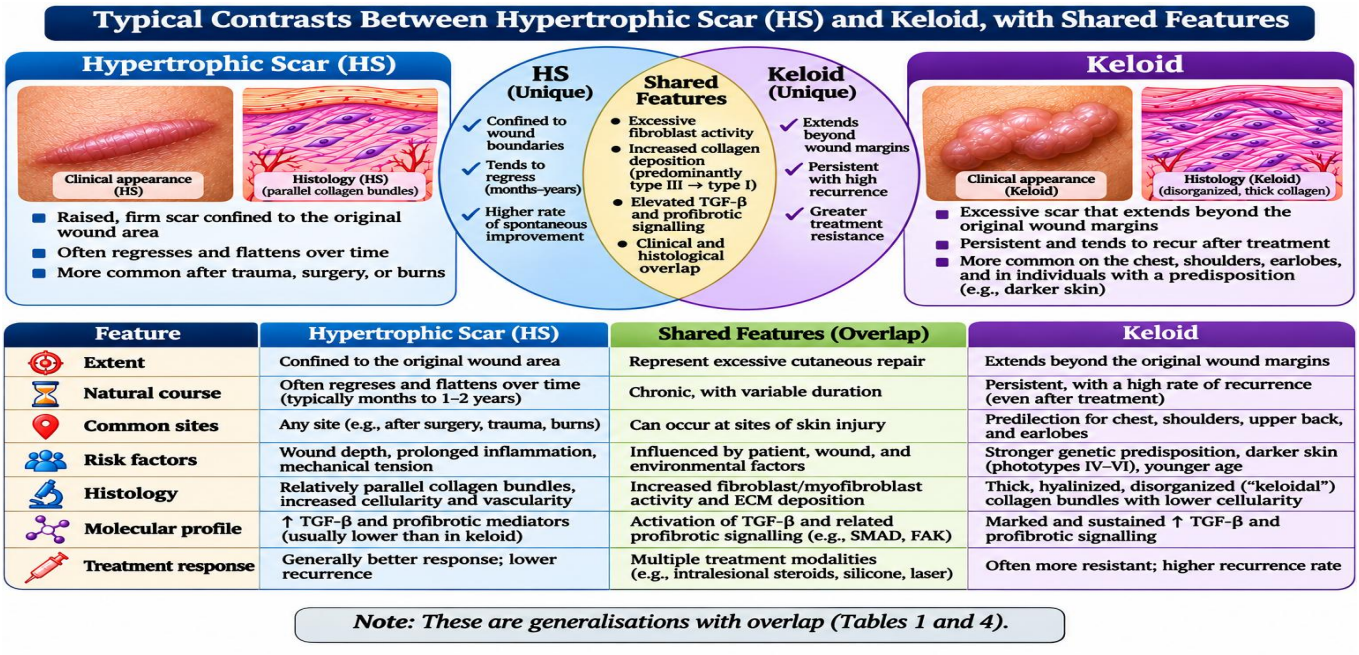


Figure-3: Comparative illustration of the clinical, histopathological, and biological characteristics of hypertrophic scars and keloids, highlighting their shared features and distinguishing characteristics.

Hypertrophic scars (HS) and keloids exhibit distinct clinical and epidemiological characteristics, particularly with respect to their onset, growth patterns, anatomical distribution, and long-term behaviour. HS typically develop within weeks of the initial injury and are commonly associated with deeper wounds, burns, and delayed wound healing. Their growth generally reaches a plateau, followed by gradual regression over time [67]. In contrast, keloids may develop several months or even years after tissue injury and can arise following relatively minor insults, including acne lesions, ear piercing, and folliculitis. In some cases, patients may not recall any preceding trauma. One of the most important clinical features distinguishing these conditions is their relationship to the original wound margins. HS generally remain confined to the boundaries of the initial injury, whereas keloids characteristically extend into the surrounding unaffected skin [68]. However, this distinction may be difficult to establish in extensive burns or large traumatic wounds, where the original wound margins are often poorly defined. Their anatomical distribution also differs. HS are more closely associated with wound depth, delayed healing, and mechanical tension, whereas keloids demonstrate a greater tendency towards familial aggregation, ancestry-related variation, and involvement of characteristic anatomical sites, particularly the presternal region, shoulders, upper back, and earlobes. Histopathological examination may reveal differences in collagen organization and tissue architecture; however, considerable overlap exists, and no single microscopic feature is sufficiently specific to establish the diagnosis independently [69].

Both conditions can cause persistent pruritus, pain, tenderness, and cosmetic or functional impairment. Nevertheless, HS generally follow a more favourable natural course, with gradual improvement during scar maturation and following the reduction of mechanical tension. Keloids, by comparison, tend to persist, may progressively enlarge, and have a substantial risk of recurrence following surgical excision, particularly when appropriate adjuvant treatment is not provided. These clinical differences are also reflected in their therapeutic responses [70]. HS generally respond more consistently to conservative measures and intralesional treatments, whereas keloids are often more treatment-resistant and may require multimodal management combining pharmacological and procedural interventions. However, comparisons of therapeutic effectiveness should be interpreted cautiously, as many clinical trials include mixed populations of patients with HS and keloids without adequately stratifying outcomes by scar subtype. This limits the reliability of condition-specific conclusions and highlights the need for more carefully designed comparative studies [71].

7. Aetiology and Predisposing Risk Factors

The major predisposing factors for pathological scarring are classified according to the strength of available clinical and experimental evidence, as illustrated in Figure-4 and summarized in Table-3.

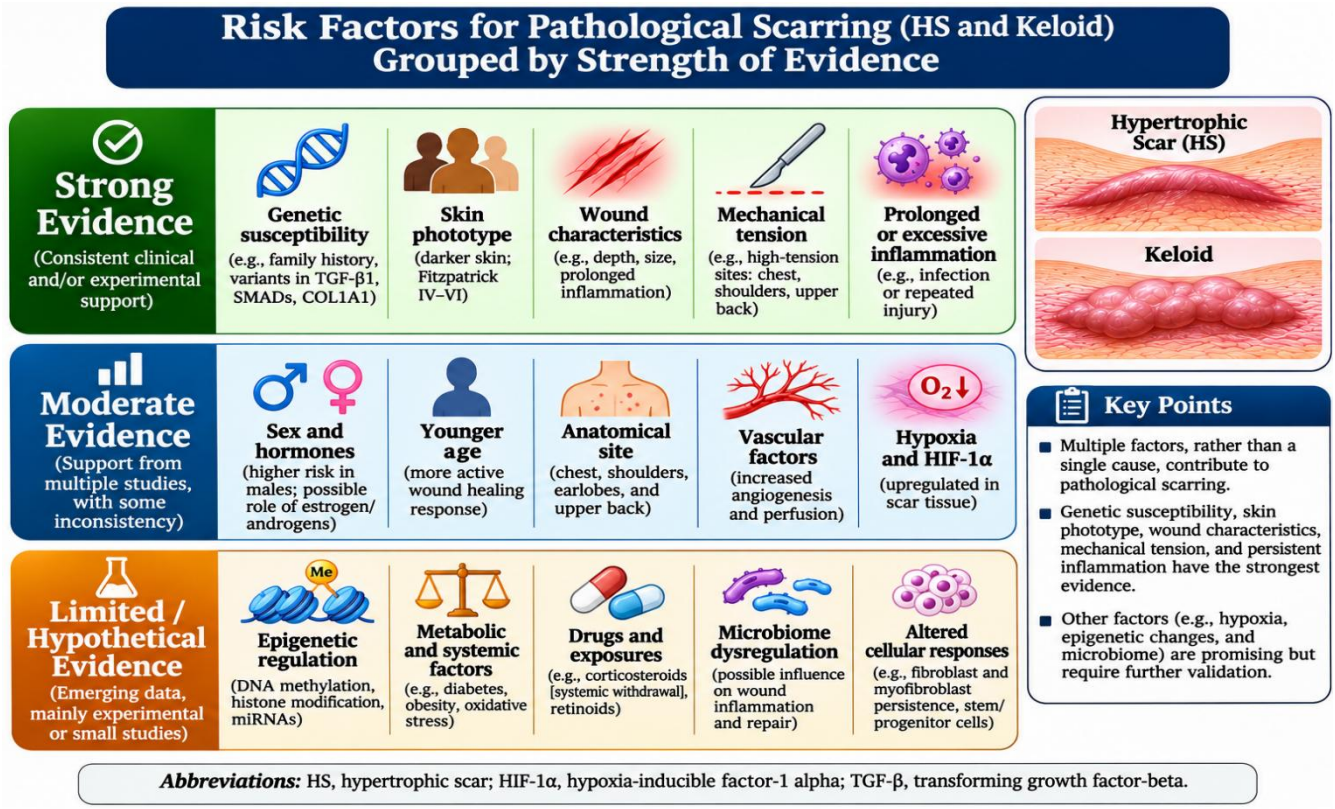


Figure-4: Major predisposing factors associated with hypertrophic scar and keloid development, categorized according to the strength of available clinical and experimental evidence.

7.1 Well-supported determinants

The development of hypertrophic scars (HS) and keloids is influenced by several interacting factors, including genetic susceptibility, wound characteristics, mechanical forces, the nature of the injury, and age. Genetic and familial factors appear to have a particularly important role in keloid formation. This is supported by familial clustering, ancestry-related differences in disease occurrence, and findings from genome-wide association studies, which collectively suggest an inherited component of susceptibility [72]. Accordingly, obtaining a detailed family history is an important part of clinical evaluation, particularly when counseling individuals considering elective surgical procedures or body piercing. Wound characteristics also influence the development of pathological scars. Injuries involving the deeper reticular dermis and wounds requiring prolonged healing, particularly those taking more than two to three weeks to close, have been consistently associated with an increased risk of HS, especially following burn injuries. Persistent inflammation, wound infection, and dehiscence may further increase this risk by prolonging the tissue repair response [73].

Mechanical tension is another well-recognized determinant of pathological scarring. These scars frequently develop at anatomical sites exposed to continuous stretching and movement, while experimental findings indicate that mechanical loading can activate mechano transduction pathways involved in fibrotic tissue formation [74]. In addition, various forms of cutaneous injury, including surgical incisions, traumatic wounds, burns, and ear piercing, may trigger pathological scar formation, particularly in individuals with an underlying susceptibility. Age may also influence the development of

keloids. One observational report identified an association between older age at the time of ear piercing and subsequent keloid formation, although this finding requires further investigation. More broadly, keloids are reported more frequently during adolescence and early adulthood. The biological basis of this age-related distribution remains uncertain; however, possible contributing factors include changes in hormonal activity, increased mechanical tension, greater exposure to skin injuries, and age-related differences in fibroblast activity [75].

7.2 Plausible contributors with limited evidence

Several additional factors have been proposed to influence susceptibility to pathological scarring, although the available evidence varies in strength and consistency. Sex and hormonal influences have received attention because keloid enlargement has occasionally been reported during puberty and pregnancy, suggesting a possible role of hormonal regulation in fibroproliferative activity. However, these associations are largely based on observational findings and clinical reports, and the independent contribution of hormonal factors remains uncertain [76]. Keloids are also reported more frequently among individuals with darker skin, suggesting an association with skin pigmentation and ancestry-related susceptibility. Nevertheless, it remains unclear whether this increased occurrence is attributable to pigmentation itself, melanocyte-associated biological processes, or underlying genetic differences. Therefore, skin phototype should not be regarded as a reliable substitute for assessing individual genetic susceptibility or obtaining a detailed family history [77].

Inflammatory skin conditions, particularly acne vulgaris, may contribute to keloid development, especially in commonly affected anatomical regions such as the chest, shoulders, and upper back. Folliculitis and other inflammatory dermatoses have also been implicated as potential initiating factors, although prospective evidence establishing the magnitude of these associations remains limited. Keloid formation has additionally been documented following vaccination and other injection-related injuries, particularly in the deltoid region. Local mechanical tension may contribute to abnormal wound repair at these sites; however, evidence supporting an independent association with vaccination remains insufficient [78]. Hypertension has also been associated with increased keloid severity in observational studies. Proposed mechanisms include vascular dysfunction, endothelial alterations, and persistent inflammatory signalling, although residual confounding cannot be excluded. Furthermore, repeated tissue injury and delayed wound healing may prolong inflammatory and mechanical stimulation, potentially sustaining fibroblast activation and extracellular matrix accumulation. Despite their biological plausibility and potential clinical relevance, the independent contributions of these additional factors remain incompletely established. Well-designed prospective studies are therefore needed to clarify their associations with pathological scarring and determine their relative importance [78].

7.3 Associations requiring further investigation

Environmental and lifestyle-related factors (for example smoking, nutrition, local skin care practices, and ultraviolet exposure) lack robust evidence regarding scar abnormality [79]. Neurogenic hypotheses, hypoxia, and microbiome contributions remain hypotheses. Large prospective cohorts that record wound characteristics, tension, infection, ancestry, genotype, and treatments, and that adjudicate HS versus keloid, are needed to rank risk factors reliably [80]. The established, plausible, and emerging risk factors

associated with hypertrophic scars and keloids are summarized according to the strength of available evidence in Table-3.

Table 3: Predisposing factors and risk determinants associated with hypertrophic scar and keloid formation, classified according to the strength of available evidence.

S.no.	Risk factor	Direction of association	Strength of evidence	Comments	Reference
1.	Genetic susceptibility, family history	Increases keloid risk	Well supported	Ask in all patients	[81]
2.	Deep or slowly healing wounds, burns	Increases HS risk	Well supported	Healing time and depth key	[82]
3.	High mechanical tension, anatomical site	Increases risk	Well supported	Mechanistic and clinical support	[83]
4.	Surgical and traumatic wounds, piercing	Common precipitants	Well supported	Later age at piercing linked to keloid in one study	[84]
5.	Younger age	Higher keloid frequency	Moderate	Mechanism unclear	[85]
6.	Wound infection, delayed healing	Plausible increase	Moderate (indirect)	Sustains inflammation	[86]
7.	Sex and hormones (puberty, pregnancy)	Possible modulation	Limited	Anecdotal and observational	[87]
8.	Skin phototype, pigmentation	Higher keloid frequency in darker skin	Moderate for ancestry; weak for pigmentation per se	Poor proxy for genetic risk	[88]
9.	Acne and inflammatory dermatoses	Chest, back, shoulder keloids	Limited	Prospective data lacking	[89]
10.	Vaccination, injection sites	Reported at tension-prone sites	Limited	Independent effect unproven	[90]
11.	Hypertension	Associated with severity	Limited (observational)	Confounding likely	[91]
12.	Lifestyle and environment	Unclear	Insufficient	Requires cohort data	[92]

8. Clinical Assessment and Diagnostic Evaluation

8.1 History and examination

The clinical history should include details of the initial injury, including its date and nature, the time elapsed before scar development, subsequent progression, associated symptoms, family history, previous treatment modalities and their outcomes, as well as the patient's expectations, concerns, and treatment goals [93]. Examination records site, number, size, shape, height, color, consistency, surface changes, extension beyond the original wound margin, and the presence of contracture or restricted motion. Photographic documentation under standardized conditions allows monitoring of change over time [94].

8.2 Scar assessment instruments

The Vancouver Scar Scale (VSS) rates pigmentation, vascularity, pliability, and height, and was developed for burn scars reports of its inter-rater reliability are variable, and it does not include patient symptoms. The Patient and Observer Scar Assessment Scale (POSAS) incorporate both clinician-based observations and patient-reported assessments, providing a comprehensive approach to scar evaluation. It has demonstrated good reliability and practical applicability, with additional validation studies conducted in patients with linear surgical scars [95]. The Manchester Scar Scale is another clinical assessment tool that combines descriptive and quantitative features to evaluate scar characteristics. In addition, objective methods such as colorimetry, durometry, and ultrasonography can be used to assess specific physical properties of scars. However, systematic reviews have highlighted considerable variability and a lack of standardized protocols across these techniques, limiting their routine clinical application. Consequently, they are used predominantly in research and specialized clinical settings. No instrument is universally accepted for keloids specifically, and responsiveness to change is variable the use of both observer- and patient-reported domains is therefore advisable [96]. The commonly used clinical assessment instruments and objective measurement approaches, including their strengths and limitations, are summarized in Table-5.

Table 5: Clinical assessment tools and objective methods for evaluating pathological scars: components, applications, and limitations.

S.no.	Instrument or method	Components	Strengths	Limitations	References
1.	Vancouver Scar Scale (VSS)	Pigmentation, vascularity, pliability, height	Simple widely used, especially in burns	Observer-only, variable inter-rater reliability, no symptoms	[97]
2.	POSAS	Observer scale plus patient scale (pain, itch, colour, stiffness, thickness, irregularity)	Patient perspective, reliability and feasibility reported	Not keloid-specific; scoring interpretation requires care	[98]

3.	Manchester scar scale	Clinical scale with visual and quantitative elements	Includes quantitative components	Less widely adopted	[99]
4.	Objective devices (colorimetry, durometry, ultrasound)	Colour, stiffness, thickness	Quantitative; useful in research	Standardisation lacking; availability limited	[100]
5.	Ultrasonography and dermoscopy	Thickness, depth, vascular patterns	Surgical planning; non-invasive	Diagnostic accuracy poorly defined	[101]
6.	Histopathology	Collagen architecture, nodules, fibrous bands	Excludes malignancy and mimics	Invasive; may provoke lesions, not fully specific	[102]
7.	HRQoL assessment	Generic and dermatology-specific measures	Captures burden	Scar-specific tools not universally adopted	[103]

8.3 Imaging and histopathology

High-frequency ultrasonography can estimate lesion thickness and depth and may assist surgical planning, and dermoscopy can show vascular patterns, but their role in routine care is not defined and evidence for diagnostic accuracy is limited. Biopsy is indicated when the diagnosis is uncertain, the lesion is atypical, ulcerated, rapidly growing, or lacks a clear injury history, or when malignancy is suspected [104]. A biopsy site in a keloid-prone patient can itself provoke a new lesion, so the decision should be considered carefully and discussed with the patient.

9. Complications and Impact on Quality of Life

Symptoms are frequent and under-recognised. Pain and pruritus can be persistent and sleep-disrupting, and both are commonly reported by patients with keloids and HS. Scars crossing joints, the neck, the axilla, or the hands can cause contracture and functional restriction, particularly after burns. Cosmetic disfigurement, especially on the face, ears, chest, and shoulders, is a major source of distress [105].

Quality-of-life studies indicate substantial burden [105]. In a German study, patients with keloids and HS reported impairment across physical and psychosocial domains, with higher distress in those with more visible or symptomatic scars. Reviews of skin scarring have emphasized the “hidden cost” of scars, including emotional, social, and functional effects, and the limited attention they receive. A cross-sectional assessment of health-related quality of life (HRQoL) in keloid patients found a measurable burden across several domains. Psychological consequences reported include anxiety, depression, body image dissatisfaction, self-consciousness, and avoidance of social situations. These studies are cross-sectional, rely on self-report, and often draw from clinic samples, so the magnitude of burden in the

community and the causal contribution of scars versus other factors cannot be quantified reliably [106]. Generic and dermatology-specific HRQoL measures are used; scar-specific patient-reported outcome measures are developing, and none is yet universally adopted. Because symptoms and psychosocial impact may not correlate with scar size or observer ratings, patient-reported assessment is essential when prioritizing treatment [107].

10. Prevention of Hypertrophic Scars and Keloids

Prevention remains the most appropriate approach to managing pathological scarring, as established keloids are often difficult to treat and have a considerable risk of recurrence. International clinical recommendations, largely informed by expert consensus, available clinical evidence, and practical experience, emphasize early risk identification, appropriate wound management, and the timely use of preventive interventions such as silicone therapy and pressure application where indicated [108]. The prevention of hypertrophic scars (HS) and keloids largely depends on proper wound care, minimizing mechanical tension, and initiating early interventions in individuals predisposed to abnormal scar formation. Gentle tissue handling, prompt identification and treatment of wound infections and avoidance of excessive tension during wound closure are important preventive measures. Whenever possible, surgical incisions should be aligned with relaxed skin tension lines. Similarly, layered wound closure can help distribute mechanical forces and minimize tension along the epidermal margins. The importance of mechanical tension in abnormal scar formation has also supported the use of subcutaneous and fascial tension-reducing sutures, as well as flap-based surgical techniques, particularly in patients at increased risk of pathological scarring [44]. However, despite their clinical rationale, high-quality randomized evidence establishing the superiority of particular wound-closure techniques, especially in individuals predisposed to keloid formation, remains limited. Timely wound healing is another important consideration. Early surgical closure may be appropriate for deep burns and other injuries that are unlikely to heal within an acceptable timeframe. Among topical preventive approaches, silicone gel and silicone sheeting are widely recommended in clinical guidelines for preventing and managing early abnormal scars. Their proposed mechanism involves maintaining hydration and occlusion of the stratum corneum, which may indirectly influence keratinocyte–fibroblast interactions and subsequent scar development. Although silicone products are generally well tolerated and widely used in clinical practice, a Cochrane review identified methodological limitations in the available trials, making the overall certainty of evidence regarding their effectiveness relatively low [109].

Pressure therapy, particularly through pressure garments, is another commonly used approach in burn rehabilitation to limit excessive scar formation. However, findings from meta-analyses indicate that its preventive effectiveness remains uncertain. In addition, practical challenges, including discomfort, increased local temperature, and difficulties maintaining long-term adherence, may further influence treatment outcomes [110]. Preventive measures are particularly important in individuals with a previous history of keloid formation, a positive family history, or wounds located in anatomically high-tension areas. Before undergoing elective surgery or body piercing, such individuals should be informed about their increased susceptibility and the potential risk of abnormal scar development. Depending on individual risk factors, a preventive strategy may include tension-reducing wound closure, early silicone therapy, intralesional corticosteroids in selected cases, and adjuvant radiotherapy following keloid excision when clinically indicated. Regular postoperative follow-up is equally important, as it allows

early recognition of abnormal scar development or recurrence and facilitates timely intervention. Finally, patient education should be an integral part of preventive care. Patients should understand that although appropriate wound management and early preventive interventions can reduce the risk of pathological scarring, they cannot completely prevent its occurrence, particularly in individuals with an underlying predisposition [1].

11. Current Therapeutic Approaches

Most evidence consists of small randomized trials with different comparators, mixed HS and keloid populations, short follow-up and non-standard outcome measures, and for many modalities the best evidence is observational [111].

11. A Conservative approaches

Silicone gel and sheets and pressure therapy are described above. Massage and supportive scar care (moisturisation, sun protection, and gentle mobilization) are widely advised, a literature review concluded that massage may improve scar pliability and symptoms, but trial evidence is limited and methodologically weak. Supportive care is inexpensive and low-risk and serves as the foundation to which other treatments are added [112].

11. B Intralesional pharmacological treatments

Intralesional corticosteroids remain the most commonly used first-line injectable therapy for keloids and symptomatic hypertrophic scars (HS). Their therapeutic effects are attributed to several mechanisms, including suppression of inflammation, inhibition of fibroblast proliferation and collagen synthesis, and local vasoconstriction. Triamcinolone acetonide is commonly administered at concentrations of approximately 10–40 mg/mL, with injections repeated at intervals of several weeks depending on the lesion's size, location, and clinical response [113].

Clinical trials and observational studies have demonstrated beneficial outcomes with intralesional corticosteroid therapy, although treatment responses vary among patients and recurrence may occur after treatment is discontinued. Meta-analyses and systematic reviews have also supported the use of corticosteroids and other intralesional agents, while highlighting considerable heterogeneity in treatment protocols and reported outcomes. Common adverse effects include injection-site pain, dermal atrophy, telangiectasia, and hypopigmentation, whereas systemic corticosteroid-related effects are uncommon [114]. These complications warrant particular consideration when treating facial lesions and individuals with darker skin tones. The major conservative and pharmacological treatment options, together with their proposed mechanisms of action, clinical indications, and limitations, are summarized in Table 6.

Table 6: Conservative and intralesional pharmacological treatment options for hypertrophic scars and keloids: mechanisms of action, clinical applications, and limitations.

S.no.	Treatment	Mechanism (proposed)	Main indication	Evidence summary	Adverse effects and limitations	References
1.	Silicone gel and sheets	Hydration and	Prevention and early	Consensus first-line;	Skin irritation,	[115]

		occlusion; modulated signalling	treatment of HS and keloid	trial quality poor (Cochrane)	adherence	
2.	Pressure therapy	Tissue compression, reduced perfusion	Burn scars, ear keloid adjunct	Limited evidence of benefit	Discomfort, heat, poor adherence	[116]
3.	Massage and supportive care	Mechanical softening, hydration	Adjunct for symptoms and pliability	Weak evidence	Minimal	[117]
4.	Intralesional triamcinolone	Anti-inflammatory; reduces fibroblast activity	Keloid and symptomatic HS	Trials and series; response variable; recurrence after stopping	Atrophy, telangiectasia, hypopigmentation, pain	[118]
5.	Intralesional 5-FU	Antimetabolite	Keloid and HS, alone or combined	Series and small trials	Pain, ulceration, hyperpigmentation	[119]
6.	TAC plus 5-FU	Dual mechanism	Resistant lesions	Small trials suggest advantage over TAC alone	Same as components	[120]
7.	Intralesional verapamil	Possible effect on collagen metabolism	Alternative injectable	One small comparative trial	Limited data	[118]
8.	Intralesional bleomycin	Cytotoxic; effect on fibroblasts	Refractory lesions	Small series	Pain, pigment change, rare necrosis	[121]

5-Fluorouracil (5-FU) is an antimetabolite with antiproliferative properties that inhibits fibroblast activity and is increasingly used as an intralesional treatment for hypertrophic scars (HS) and keloids. It is commonly administered at a concentration of approximately 50 mg/mL. Evidence from clinical trials and case series suggests that 5-FU can improve scar characteristics. Its therapeutic potential has also been evaluated in a randomized comparative study involving triamcinolone acetonide (TAC), 5-FU, and pulsed dye laser (PDL) in patients with sternotomy scars [122]. However, its use may be associated with local adverse effects, including injection-site pain, ulceration, and hyperpigmentation. Combining TAC with 5-FU has produced encouraging results in several small randomized studies. Some findings suggest that this combination may provide greater clinical improvement than TAC alone while potentially reducing corticosteroid-related adverse effects. A triple-modality approach combining TAC, 5-FU, and PDL has also been explored as an alternative treatment strategy. Nevertheless, the available studies are generally limited by small sample sizes, short follow-up periods, and inadequate blinding, making it difficult to establish whether combination therapy is consistently more effective than individual treatments [123].

Other intralesional agents, including verapamil and bleomycin, have also been investigated for the management of pathological scars. Verapamil, a calcium channel blocker, is thought to influence collagen metabolism and extracellular matrix regulation. Although a small comparative study reported clinical improvement with verapamil and fewer adverse effects than TAC, further evidence is needed to establish its therapeutic value [120]. Similarly, intralesional bleomycin has demonstrated potential in reducing scar size in small clinical series. However, its use may be associated with injection-related pain, pigmentary changes, and, rarely, tissue necrosis. Overall, these alternative injectable treatments offer additional therapeutic possibilities for patients with hypertrophic scars and keloids, particularly when conventional approaches provide inadequate results. However, their clinical effectiveness, long-term safety, and comparative advantages remain insufficiently established. Larger, well-designed randomized controlled trials with standardized treatment protocols and longer follow-up are therefore necessary before their routine clinical use can be more firmly recommended [124].

11. C Cryotherapy

Cryotherapy is another treatment option for hypertrophic scars (HS) and keloids. It works by inducing tissue necrosis and vascular damage, which may also reduce fibroblast viability and activity. Conventional contact cryotherapy has shown variable clinical outcomes across different case series. However, its application is often limited by adverse effects such as pain, blistering, and hypopigmentation, with pigmentary complications being a particular concern in individuals with darker skin tones [125]. Therefore, this approach is generally more suitable for smaller or relatively thin lesions.

To overcome some of these limitations, intralesional cryotherapy has been developed using a needle-based device that delivers freezing directly into the scar tissue while attempting to preserve the overlying epidermis. Prospective studies and clinical case series have reported reductions in scar volume, with potentially fewer pigmentary complications than conventional contact cryotherapy. Nevertheless, the available evidence is largely based on uncontrolled studies, limiting definitive conclusions regarding its effectiveness and long-term outcomes [126]. Cryotherapy may also be combined with intralesional corticosteroids to improve treatment response; however, comparative evidence supporting the superiority of this combination over individual therapies remains limited.

11. D Laser-based treatments

The pulsed dye laser (PDL) primarily targets hemoglobin within cutaneous blood vessels and has been shown to improve erythema, scar pliability, and associated symptoms, particularly in patients with sternotomy scars. However, subsequent comparative studies have reported variable treatment responses, with some suggesting that PDL may not offer greater benefits than intralesional corticosteroid injections in certain clinical settings [127].

Ablative and non-ablative fractional lasers, including fractional carbon dioxide (CO_2) lasers, represent another approach to scar management. These techniques produce microscopic treatment zones within the scar tissue, promoting collagen remodelling and improving skin texture. They can also facilitate the delivery of topical or intralesional medications, particularly corticosteroids, through laser-assisted drug delivery. An expert consensus report supports the use of laser-based interventions, including ablative fractional resurfacing, for the management of traumatic and burn scars. Similarly, a systematic review suggested that early laser treatment may help limit scar formation, although the available studies vary considerably in their methodology, treatment protocols, and overall quality of evidence. In keloid management, laser monotherapy is generally associated with a risk of recurrence, therefore, lasers are more commonly incorporated into combination treatment protocols alongside intralesional corticosteroids or other injectable agents [128]. Treatment-related adverse effects vary according to the laser modality and may include procedural pain, purpura following PDL treatment, and pigmentary alterations. Ablative procedures may additionally cause delayed wound healing and increase the risk of infection.

11. E Surgical treatment

Surgical excision of HS is indicated mainly for contractures, extensive or functionally limiting scars, and failed conservative therapy, and uses tension-reducing designs. Simple excision of keloids has a high recurrence rate and can provoke a larger lesion, which has been recognised since the earliest surgical series [129]. Surgery for keloids is therefore reserved for selected lesions (for example pedunculated or ear lesions, or those refractory to injectables) and is combined with adjuvant therapy: perioperative intralesional corticosteroid, pressure, silicone, or radiotherapy. Intralesional or core excision with preservation of a rim of tissue can reduce wound tension [130].

11. F Radiotherapy

A meta-analysis compared recurrence by modality and fractionation, and a systematic review of excision with adjuvant irradiation concluded that the evidence is limited by heterogeneity and a lack of randomized trials. Safety is a central concern: the risk of radiation-induced carcinogenesis is considered low but not zero, and radiotherapy is avoided in children and over radiosensitive sites (thyroid, breast, gonads) unless alternatives have failed, with careful dose and field planning [131]. Radiotherapy should be offered after multidisciplinary discussion. Procedural and surgical approaches, including cryotherapy, laser treatment, surgical excision, and postoperative radiotherapy, is compared in Table-7.

Table 7: Procedural and surgical treatment modalities for hypertrophic scars and keloids: indications, advantages, limitations, and recurrence considerations.

S.no.	Intervention	Indications	Advantages	Limitations and adverse effects	Recurrence considerations	References
1.	Contact cryotherapy	Small or thin lesions	Low cost, office-based	Pain, blistering, hypopigmentation	Variable	[132]
2.	Intralesional cryotherapy	Thicker keloids	Epidermal sparing, volume reduction	Specialised device, mostly uncontrolled data	Data limited	[133]
3.	Pulsed dye laser	Erythematous, immature scars	Improves colour, symptoms	Purpura, benefit variable	Moderate evidence	[134]
4.	Fractional ablative laser and laser-assisted delivery	Pliability, texture, burn and traumatic scars	Remodelling; enhanced drug delivery	Pain, pigment change, infection; keloid recurrence risk if used alone	Use with adjuncts	[135]
5.	Excision of HS	Contracture, functional limitation	Releases tension	Needs tension-reducing design	Lower than keloid	[136]
6.	Keloid excision alone	Pedunculated or small selected lesions	Removes bulk	High recurrence, may enlarge lesion	High	[137]
7.	Excision plus adjuvant steroid or silicone/pressure	Selected keloids	Reduces recurrence	Adherence, adverse effects of steroids	Reduced, not eliminated	[138]
8.	Postoperative radiotherapy	Refractory or recurrent keloids	Best-established adjuvant	Carcinogenesis risk (low); avoid in children and sensitive sites	Dose and timing important	[139]

11. G Emerging therapies

Botulinum toxin type A has attracted interest as a potential treatment for pathological scarring because of its ability to reduce local muscle activity and mechanical tension, with possible additional effects on fibroblast function. A small clinical study involving patients with keloids reported encouraging results, while a placebo-controlled study evaluating facial wound healing suggested improvements in scar appearance following treatment [140]. Nevertheless, evidence supporting its effectiveness in established hypertrophic scars (HS) and keloids remains limited, and further clinical evaluation is needed. Interferon-based treatments, particularly intralesional interferon alfa-2b administered after surgical excision, have also been investigated for their potential to reduce keloid recurrence. Although some studies have reported favorable outcomes, their clinical application remains limited by high treatment costs, flu-like adverse effects, and insufficient supporting evidence. Similarly, topical imiquimod, an immunomodulatory agent, has been examined in pilot studies following keloid excision. Preliminary findings suggest a possible reduction in recurrence; however, the available evidence is not yet sufficient to establish its effectiveness in routine clinical practice [141].

Several other therapeutic approaches are currently being explored to improve the management of pathological scars. These include targeting transforming growth factor-beta (TGF-β) and focal adhesion kinase (FAK) signaling pathways, investigating anti-vascular endothelial growth factor (VEGF) agents, and evaluating tacrolimus, gene-based interventions, cell-based regenerative therapies, and advanced drug-delivery systems. Most of these approaches remain at the preclinical or early clinical stage. Overall, these emerging therapies offer promising opportunities for developing more targeted approaches to scar management [142]. However, their clinical benefits, optimal treatment protocols, and long-term safety profiles need to be established through larger, adequately powered, and well-designed controlled clinical trials before they can be considered for routine clinical use.

12. Comparative Treatment Strategies

The treatment approach for hypertrophic scars (HS) and keloids should be guided by their differences in natural history, clinical presentation, and recurrence patterns. Hypertrophic scars may gradually regress over time, making conservative management a reasonable initial approach in selected patients. Measures such as silicone therapy, regular scar massage, reduction of mechanical tension, and clinical monitoring may be sufficient in less severe cases [143]. However, persistent symptoms or prominent scar elevation may warrant intralesional injections or laser-based interventions. Surgical treatment is generally reserved for cases involving functional limitations, particularly contractures. Keloids, on the other hand, rarely undergo spontaneous regression and often require more active treatment, frequently involving a combination of therapeutic approaches. Surgical excision is considered in carefully selected patients, usually alongside additional measures to reduce the risk of recurrence [144]. Published treatment algorithms, including updated versions of established recommendations, emphasize selecting interventions according to scar characteristics, anatomical location, and individual recurrence risk. Nevertheless, many of these recommendations continue to rely on expert consensus and observational findings, as high-quality comparative clinical evidence remains limited.

Combining different treatment modalities has gained considerable attention because approaches targeting separate biological mechanisms may produce complementary effects. Such combinations may also help improve treatment outcomes while limiting the adverse effects associated with higher doses of individual

agents. Small clinical studies have reported encouraging results with combined intralesional therapies and the use of laser treatment alongside injectable agents. However, the available evidence is still insufficient to establish the consistent superiority of combination therapy over monotherapy [145]. Direct comparisons between treatment options remain relatively uncommon, and many existing studies are limited by small sample sizes and inadequate statistical power. In clinical practice, silicone-based preparations and supportive scar care are commonly recommended for prevention and early management. Intralesional corticosteroids remain a first-line treatment option for established keloids and symptomatic HS in many treatment guidelines. Depending on the clinical presentation, lesion location, skin type, and patient preferences, additional or alternative interventions may include 5-fluorouracil, verapamil, cryotherapy, and laser therapy. Surgical excision, sometimes combined with postoperative radiotherapy, may be considered for selected lesions [146]. Patients with recurrent or treatment-resistant keloids may benefit from a multidisciplinary approach involving surgical management, adjuvant radiotherapy, or more intensive intralesional treatment. Before initiating therapy, clinicians should also identify and address factors that may contribute to persistent scar activity, including mechanical tension, wound infection, and poor treatment adherence [147].

13. Recurrence and Long-Term Prognosis

Recurrence remains one of the major challenges in the management of keloids. From a biological perspective, surgical excision creates a new wound in an individual already predisposed to abnormal scar formation. The resulting tissue injury, mechanical tension, and inflammatory response may stimulate renewed fibroblast activity, while residual abnormal fibroblasts along the wound margins can contribute to regrowth of the lesion. Several factors have been associated with an increased risk of recurrence, including anatomical location, larger lesion size, multiple keloids, a positive family history, excessive wound tension, infection, and inadequate postoperative treatment [148].

Recurrence is particularly common following surgical excision alone. Although additional treatments, such as intralesional corticosteroids and postoperative radiotherapy, can reduce this risk, they do not guarantee permanent resolution. Reported recurrence rates vary considerably across studies because of differences in patient populations, treatment protocols, follow-up periods, and definitions of recurrence. Clinical observations suggest that most recurrences develop within the first one to two years after treatment, highlighting the importance of regular postoperative monitoring throughout this period and, ideally, beyond it [149]. Patient adherence to postoperative treatment is another important factor influencing clinical outcomes. Compliance with recommended measures, including silicone application, pressure therapy, scheduled intralesional injections, and postoperative radiotherapy appointments, may affect treatment success. However, adherence is not consistently evaluated or reported in clinical studies. Therefore, outcome assessment should extend beyond changes in scar size or appearance and include validated scar assessment scales, symptom evaluation, and patient-reported quality-of-life measures. Patients should also receive realistic counseling regarding the possibility of recurrence, as long-term freedom from keloid formation cannot always be guaranteed, even with combined treatment approaches [150].

14. Emerging Research and Future Perspectives

Advances in genetic and epigenetic research have raised the possibility of developing molecular biomarkers to support risk stratification and precision-based management of hypertrophic scars (HS) and keloids. In the future, such markers may help identify individuals who could benefit from intensified preventive measures or require additional counseling before elective surgical procedures. However, no biomarker is currently validated for routine clinical decision-making [151]. Most candidate markers have been identified in relatively small, ancestry-specific cohorts and require independent validation in larger and more diverse populations. Similarly, distinguishing inflammatory, mechanically driven, and genetically influenced scar phenotypes may eventually support mechanism-based treatment selection, although this approach remains conceptual. Fibroblast-targeted therapies and modulation of transforming growth factor-beta (TGF-β) signaling represent another important area of investigation. Despite a strong preclinical rationale for targeting this pathway, translation into effective clinical treatments has been limited, partly because TGF-β also contributes to normal tissue homeostasis and wound repair. An alternative strategy involves targeting downstream or mechanosensitive pathways, including focal adhesion kinase (FAK) [152].

Novel drug-delivery systems and regenerative approaches are also being explored to improve treatment effectiveness and tolerability. Laser-assisted drug delivery, microneedling, and sustained-release or topical formulations aim to enhance local drug penetration while potentially reducing injection-related pain and complications such as tissue atrophy. Gene-based, cell-based, and other regenerative strategies are under early investigation; however, their long-term safety, durability, and suitability for individuals prone to keloid formation have not yet been established [153]. Complex, recurrent, or treatment-resistant keloids may benefit from coordinated input from dermatologists, plastic surgeons, and radiation oncologists, with psychological support when scarring causes substantial emotional or social distress. Future clinical trials would also benefit from a standardized core outcome set incorporating both clinician-assessed and patient-reported measures, clearly defined recurrence criteria, and prespecified follow-up periods. Greater consistency in outcome reporting would facilitate comparisons across studies, improve evidence synthesis, and support the development of more reliable treatment recommendations. Emerging therapeutic strategies and research directions, including molecular targeting, regenerative approaches, and precision assessment, are summarized in Table-8.

Table 8: Emerging therapeutic approaches and future research directions in the management of hypertrophic scars and keloids.

S.no.	Approach	Rationale	Current evidence	Key uncertainties	References
1.	Botulinum toxin A	Tension reduction, fibroblast effects	Pilot and small controlled studies	Dose, duration, durable benefit	[154]
2.	Interferon alfa-2b	Antifibrotic cytokine	Limited reports	Cost, side effects, efficacy	[155]

3.	Imiquimod	Immune modulation	Pilot study	Efficacy and tolerability	[156]
4.	TGF-β modulation	Central profibrotic pathway	Preclinical; limited clinical	Safety, pleiotropy	[157]
5.	FAK or mechanotransduction inhibitors	Link force to fibrosis	Animal data	Human translation	[158]
6.	Gene and cell-based approaches	Correct or regenerate	Early stage	Safety, durability, cost	[159]
7.	Novel delivery (laser-assisted, sustained release)	Improve penetration and reduce adverse effects	Early clinical	Standardization	[160]
8.	Biomarkers and genetic risk stratification	Precision prevention	Candidate markers	Replication	[161]
9.	AI-based scar assessment	Objective monitoring	Not validated for keloids	Bias across skin tones	[162]

15. Research Gaps and Clinical Implications

Population-based incidence and prevalence data for keloids and HS are lacking, so burden estimates rely on selected samples. Diagnostic definitions are inconsistent, and studies often combine HS and keloids, which prevents treatment effects from being attributed to either. Assessment instruments are heterogeneous, and few have been validated specifically for keloids. There is no standardized treatment protocol, and many commonly used practices rest on limited comparative evidence. Long-term, head-to-head randomized trials with adequate follow-up are scarce, and populations most affected by keloids are underrepresented in research [163]. Prospective multicentre cohorts and pragmatic trials are needed, together with research on cost-effectiveness and patient-reported priorities [164].

For clinicians, the implications are fourfold. First, identify patients at risk before elective surgery, piercing, or other injury, using family history and anatomical site, and discuss realistic prevention. Second, distinguish HS from keloid using history, boundary behavior, and, when needed, histology, because prognosis and management differ. Third, individualize treatment using conservative measures, injectable, and procedural options, weighing the limits of the evidence and the patient's priorities. Fourth, plan long-term follow-up, since late recurrence and symptom persistence are common [165].

16. Conclusion

Hypertrophic scars (HS) and keloids are closely related but clinically distinct fibroproliferative conditions that develop through the combined influence of tissue injury, genetic predisposition, inflammation, and mechanical tension. Although both involve excessive collagen deposition, their clinical behavior differs considerably. Keloids demonstrate a stronger association with familial susceptibility, may extend beyond

the boundaries of the original injury, and are particularly prone to recurrence. In contrast, HS generally develop following deeper tissue injury or wounds exposed to increased mechanical tension and may gradually regress over time. Early identification, appropriate assessment of risk factors, accurate differentiation between the two conditions, and effective wound management remain central to reducing the burden of pathological scarring. Available treatment options include silicone-based preparations, intralesional corticosteroids, 5-fluorouracil, cryotherapy, laser-based interventions, surgical excision with adjuvant treatment, and radiotherapy. However, differences in study design, treatment protocols, and reported outcomes limit reliable comparisons between these approaches. Consequently, treatment decisions should be individualized, often incorporating multiple therapeutic modalities and long-term follow-up using validated scar assessment tools. Future research should focus on strengthening population-based epidemiological evidence, establishing standardized outcome measures, and conducting well-designed clinical trials that investigate the underlying biological mechanisms of scar formation and treatment response. Greater attention should also be directed towards patient-reported outcomes and health-related quality of life to ensure that future management strategies address not only the physical characteristics of pathological scars but also their broader impact on patients' daily lives.

LIST OF ABBREVIATIONS

Abbreviation	Full form
5-FU	5-Fluorouracil
BED	Biologically effective dose
ECM	Extracellular matrix
FAK	Focal adhesion kinase
HS	Hypertrophic scar
HRQoL	Health-related quality of life
PDL	Pulsed dye laser
POSAS	Patient and Observer Scar Assessment Scale
PIH	Post-inflammatory hyperpigmentation
TAC	Triamcinolone acetonide
TGF-β	Transforming growth factor-beta
VSS	Vancouver Scar Scale

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