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Keloid Scars: A Comprehensive Review of Pathophysiology, Aetiology, and Therapies

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ABSTRACT

This is an integrative review of the literature which analyses the studies of treatments of keloid scars, touching on the pathophysiology and aetiology of the scars. The paper explores all the different aetiology which could lead to keloid scars such as genetics, inflammatory cells and growth factors including Tenasin C, TGF-β1 and β2; all the risk factors which cause the scars; an in-depth detail of all the pathways and protein alteration of the scars such as extracellular matrix proteins and ECM-associated proteins; the epigenetics of keloid scarring including DNA methylation and histone modifications. In addition to this, the paper ended with a detailed analysis of the different treatments for keloid scarring including surgery, radiotherapy, interferons, botulinum toxins and bleomycin. These findings showed that while there are many hypotheses regarding the pathophysiology and aetiology of the keloid scars by understanding the protein alteration and pathways, many scientists have created adequate treatments for it. With the current advancement, the treatments all have their own limitations but this study aims to summarise each limitation to provide pathways to best treat the keloid scars.

KEYWORDS: Keloids, keloid scars, Treatment, Pathophysiology, Aetiology

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I. INTRODUCTION

Keloids are classified as a benign growth of dense fibrous tissues resulted from an abnormal healing response to injury on the skin, usually occurring months after the wound occurs (1). The disorder happens when the deposition of collagen extends beyond the margin of the original wound and is organized haphazardly rather than linearly (1). They appear as firm nodules, which can be skin coloured, hypopigmented or erythematous secondary to telangiectasias (2). The pathophysiology are still unclear, however it was analysed to be caused from inflammatory, proliferative, humoral or genetic (1).

Types of conventional treatments include using interferons which have a 41% keloid reduction rate but post-operative has a recurrence rate as high as 80% (1). These two treatments were teased double blindly (1). Botulinum toxins has a larger reduction at 79.2% of the keloid and a high satisfaction rate (1). No relapses at one year but a 16.6%recurrence rate. Bleomycin showing 73.3% of the lesions sowing complete recovery (1). There are other treatments such as verapamil, mytomycin and other methods such as surgery, occlusive dressings etc (2).

The limitation of this treatment lies in the re occurrence rate being so high. With surgical removements having almost 100% chance of return (1). Lowering chance of return requires wearing pressure garments for up to 20 hours a day for several months which causes discomfort. (1) after corticosteroid injections the clinical regression rates of 50%–100% after one year and recurrence rates of 33%–50% after five years. (2) There was an experiment that looked into Z Plasty for keloid scar treatment. Out of 141 only 15 cases (10.6% of the 141 lesions) were considered to be keloid recurrences. (3). However with the current treatments the pure fact that the percentage range of this re occurrence is significant does spark questions a debates on which treatment is best suited. It obvious that different treatments work dependent on how each patient reacts/inflammations.

Yet there still aren't enough studies to fully understand the lengths of these variations.

This paper aims to provide a all the limitations for each treatments that exist currently and how to best combine it to create the best treatment for keloid scar.

II. AETIOLOGY OF KELOID

The aetiology of keloids are hypothesised to be influenced by environmental and genetic factors (2). This could be analysed that keloids are to be inflammatory, proliferative and genetic in nature (1). Keloids most often develop months after a surgical or non-surgical wound, often during the healing process (2).

Keloid formation is hypothesised to be due to the prolonged inflammatory phase that often results in a overproduction of cytokines and growth factors which stimulates fibroblasts to proliferate (1). When compared to normal fibroblast, keloidal fibroblasts were shown to have a higher proliferative activity consistent with a decreased apoptosis rate - which is that reason behind the increased cytokines and collagen levels (3). Keloidal fibroblast have been shown to consists of elevated levels of growth factors, especially TGF-β1 and β2 and platelet-derived growth factor (PDGF) (1,3). There are many studies and research done on TGF-β1, to which it could be theorised that TGF-β1 is an important factor in the formation of keloids (2). TGF-β works via the SMAD pathways, prior to the transcription of mRNA, effecting the collagen synthesis (1). Studies have shown that TGF-β1 and TGF-β2 have stimulatory effects on the keloidal fibroblast hence the increased collagen production (1).

Keloidal fibroblast also exhibit an excess production of matrix metalloproteinases, which impacts the wound healing process (2). Fibroblasts are activated to repair a cutaneous defect and their activity is adequately muted to prevent excessive healing in normal scars, which appear to have a negative feedback system (2). In this way, in-vitro proliferation that can cause pathological scarring can be suppressed by fibroblasts produced from mature scars (2). This suggests that the keloidal fibroblasts' negative feedback mechanism is fundamentally flawed, leading to excessive scar formation with a predisposition to return (2).

Tenascin C and Decorin appear to have further affected keloid scar development. The TNC gene produces the glycoprotein known as tenascin C (1). Tumorigenesis, embryogenesis, and inflammatory circumstances all result in an upregulation of tenascin C. (1) Tenascin C functions as a chemokinetic agent that encourages fibroblast distribution, survival, and antiapoptotic effects. Tenascin C concentrations have been found to be greater and more persistent in keloid specimens (1). This appears to encourage fibrosis and the creation of collagen (1). Decorin appears to be another protein that affects how the fibroblasts act (1). The DCN gene produces the protein decorin (1). It has been demonstrated to reduce the effects of growth factors like PDGF, preventing the creation of keloid and hypertrophic scars as well as angiogenesis (1).

Keloids are heavily influenced by genetics (4). In addition to the DNA segment that codes for proteins (genes), mounting evidence emphasises the importance of non-coding DNA sections in phenotypic variation (5). Heritable DNA gene function and expression modifications without alterations to the gene DNA sequence are referred to as epigenetics (5). The identified epigenetic processes include histone and covalent DNA modification, control of non-coding RNA, and DNA methylation, with various gene expression changing DNA methylation and histone modification patterns (5). The heterogeneity in medication response is also impacted by this epigenetic process, in addition to the impact on cell morphologies (5). The concept of personalised medicine has been developed further with the development of newer medications that are intended to control epigenetic processes in disease states (5).

III. RISK FACTORS

Keloids are raised scars that form as a result of an overgrowth of fibrous tissue at the site of a healed skin injury. They tend to grow larger than the original injury and can become painful, itchy, or cause cosmetic concerns (6). Studies have shown that individuals with a family history of keloids are more likely to develop them, indicating a genetic predisposition to keloid formation (6). The genetic underpinnings of keloid susceptibility represent a complex and multifaceted interplay among numerous genes and their associated regulatory pathways (6). The precise mechanisms propelling keloid formation remain only partially elucidated. Nevertheless, recent advancements in research have pinpointed several candidate genes and associated genetic polymorphisms that predispose individuals to keloids. Many of these genes have pivotal roles in fundamental biological processes such as extracellular matrix (ECM) synthesis and remodeling, inflammation, and cellular proliferation (6).

The transforming growth factor-beta (TGF-β) gene exemplifies this category. Its crucial role in guiding the production of collagen and other ECM constituents during wound healing is well-established (7). Interestingly, certain polymorphisms within the TGF-β gene correlate with heightened keloid risk, underlining its potential significance in keloid scar pathogenesis (7). Moreover, other genes entwined with keloid susceptibility encompass those that encode matrix metalloproteinases (MMPs) – enzymes integral to the degradation and restructuring of the ECM – as well as an array of cytokines and growth factors which govern inflammation and cellular proliferation (8).

In the realm of genome-wide association studies (GWAS), multiple genetic loci have been spotlighted for their potential associations with keloid development (9). For instance, a recent GWAS pinpointed a noteworthy link between keloid predisposition and single nucleotide polymorphisms (SNPs) nestled on chromosome 15q21.3.

This particular chromosomal region harbors genes pivotal to skin barrier functionality and the wound healing process[4]. Such discoveries insinuate that genetic variations within these genes might be instrumental in the aberrant wound healing responses characteristic of keloids (9).

While the genetic inclination towards keloids is firmly recognized, there remains a substantial gap in understanding the precise genetic variants and molecular routes culminating in keloid onset. Diving deeper into this genetic maze may illuminate pathways for targeted therapeutic interventions and prophylactic measures, aiming to ameliorate the lives of those grappling with the cosmetic and functional challenges posed by keloids (9).

The increased susceptibility to keloids among certain ethnic groups can be attributed to a combination of genetic, environmental, and cultural factors (10). Genetic predisposition exerts a substantial influence on keloid susceptibility, as underscored by the elevated incidence of keloids in families with a documented history of the condition (10). As previously delineated, myriad genes and genetic loci are implicated in predisposition to keloids. It's plausible that the allelic distribution of these genetic variants exhibits variability across different ethnic populations, thereby accounting for the observed heterogeneity in keloid prevalence among these groups. (10). Environmental factors, such as exposure to ultraviolet (UV) radiation, may also play a role in the ethnic differences observed in keloid formation. UV radiation has been shown to influence the wound healing process by modulating inflammation, collagen synthesis, and extracellular matrix remodeling. It is possible that differences in skin pigmentation and the inherent photoprotection it provides among different ethnic groups may contribute to variations in keloid susceptibility (11). Cultural factors, including traditional practices and beliefs surrounding wound care and body modification, may also contribute to the observed ethnic disparities in keloid formation (11). For example, certain cultural practices, such as ritual scarification or tattooing, may increase the risk of keloid development among specific ethnic groups. A deeper understanding of the genetic, environmental, and cultural factors underlying the increased risk of keloid formation among specific ethnic populations can help inform targeted prevention and treatment strategies. Addressing the ethnic disparities in keloid prevalence requires a comprehensive approach that encompasses personalized medicine, patient education, and culturally sensitive care (10). Keloid scars in itself don't cause physical damage to your health however it can lead to persons feeling emotional distressed (1). The possibilities in obtaining a keloid varies from insect bites to hair removals. They are formed from any sort of skin injury (1). The risks factors in being susceptible to these scars are being investigated however there are links to genetics and whether or not they play a role (2). some people are more likely to gain these keloids so the recommendation is if you've developed one you are likely to be more prone as its your skin sign of sensitivity (2).

VI. PATHWAYS AND PROTEIN ALTERATION OF KELOID

The most extensive proteomics study of keloids to date. The study produced a profile of 1359 proteins and identified 206 proteins with significantly different expression levels in keloid scars and normal skin tissues (12). The research revealed that the majority of extracellular matrix (ECM) proteins and ECM-associated proteins were significantly upregulated in keloids (12). Conversely, downregulation of keratins and cell junction-related proteins was observed in keloids. These findings are similar to a previous study that compared and contrasted keloid and healthy skin tissue samples regarding matrisome (ECM components) (12).

Further analysis of the study showed that ER stress-related pathways are overrepresented in keloids (13). Perturbations in physiological and pathophysiological conditions pose ongoing threats to ER homeostasis by influencing various physiological processes, such as the control of Ca^{2+} reservoirs and the biosynthesis of lipids and sterols (13). Under non-ER stress conditions, BiP, also known as HSPA5, is inactive and bound by the three main UPR response proteins, PERK, eIF2, and IRE1 (14). In keloids, researchers found that BiP and PDI, proteins that aid in the proper folding of proteins like P4HB, PDIA3, and PDIA6, were elevated (14). Most of the upregulated proteins were associated with XBP1, indicating that this protein plays a pivotal role in keloid development. Increased levels of active XBP1 relative to normal fibroblasts are also associated with excisional wound healing (12). The study results establish a link between XBP1 and keloid formation, suggesting it as a possible therapeutic target for keloids due to its role as a key regulator of the UPR pathway (12). However, it remains unclear precisely how XBP1 contributes to keloid formation and how it can be targeted in treatment (15). Future studies may investigate the mechanisms by which XBP1 adds to keloid formation and progression, paving the way for the development of more effective therapies that attack the fundamental molecular mechanisms of keloid formation and progression (12,16). Keloid scars are a type of pathological skin fibrosis characterized by the excessive growth of fibroblasts, resulting in the formation of raised, firm, and rubbery lesions (16). Although the exact mechanisms underlying keloid formation remain unclear, recent studies have identified several potential biomarkers associated with this condition (16). In this study, they used a proteomic approach to identify differentially expressed proteins in keloid scars and to investigate their potential roles in keloid formation (16).

Abnormal calcium homeostasis has been reported to exist in keloid fibroblasts, and in our study, we found that

CALU, RCN3, and RCN1, which are members of the CREC protein family involved in calcium homeostasis and secretory cargo sorting, were significantly upregulated in keloids (17). CALU localizes to the entire secretory pathway, including the ER, Golgi apparatus, and the extracellular matrix, and appears to exert different functions when localized in different sites (17).

RCN3 has been associated with the maturation of alveolar epithelial type II cells during alveogenesis and contributes to cell survival and wound healing (18). The overexpression of RCN3 in keloids was also highlighted in a study of familial keloids (18).

RCN1, which is uniquely present in keloids, can suppress ER stress-induced apoptosis and is related to tumorigenesis. These findings suggest that CALU, RCN3, and RCN1 may be associated with keloid formation and could be novel potential biomarkers of keloids (12). Another uniquely expressed protein in keloid scars is PDGFRL, which could be considered as a potential candidate for the diagnosis and treatment of keloids (12). Although the biological function of PDGFRL is still under debate, it has been reported to inhibit the proliferation and invasion of colorectal cells and to contribute to the maintenance of the proliferating chondrocytes phenotype. PPI network analysis identified 10 key regulators of the genes that were coexpressed with PDGFRL, including FN1, FBLN1, APP, CLU, PDGFRB, COL1A1, LMO2, GRB2, TFAP2C, and DBN1. These proteins are involved in ECM assembly, cell migration, wound healing, and various signaling pathways, and their dysregulation may contribute to keloid formation (12). In particular, TFAP2C, LMO2, GRB2, and DBN1 have been implicated in tissue regeneration and cell–cell communication, while CLU and APP have been associated with neurodegenerative diseases and epidermal wound repair, respectively (12).

V. PATHWAYS AND PROTEIN ALTERATION OF KELOID EPIGENETICS OF KELOID

Epigenetics delves into changes in gene expression that occur without alterations to the underlying nucleotide sequence. This field has come to the forefront in elucidating the intricate nature of diseases like cancer, diabetes, and fibrosis (19). Epigenetic modifications encompass a wide spectrum of mechanisms, including DNA methylation, histone modifications (such as methylation, acetylation, phosphorylation, ubiquitination, and SUMOylation), and those driven by non-coding RNAs, including microRNAs, long non-coding RNAs, and circular RNAs (19).

Multiple variables, both internal and external, as well as genetic predisposition, have been linked to accelerated wound healing and chronic inflammation, which can lead to keloid formation. In the intricate web of relationships between genes and environmental hazards, epigenetics may serve as a connecting link (19).

Investigating the molecular pathogenesis of keloids has revealed a new and exciting area of study: epigenetic changes such as DNA methylation, histone modifications, and non-coding RNA regulations (20). The activation of fibroblasts in keloids is thought to be initiated and maintained in part by epigenetic alterations. An imbalance in the repair and regeneration of scar tissue may arise from epigenetic dysregulation. Pathogenesis of keloids is still poorly known, despite the fact that the epigenetic mechanisms of other diseases are well-established (20). Excessive proliferation of fibroblasts and myofibroblasts leads to the development of keloids, which are benign skin lesions (21). Although the precise cause of keloids is unknown, researchers think a mix of genetic and environmental factors play a role in their development (21). Epigenetic alterations have only recently been recognized as key players in the development of keloids (21).

DNA methylation refers to the addition of a methyl group to a cytosine residue in the DNA strand, which in turn alters the expression of genes. Evidence suggests that keloid cells display abnormal DNA methylation patterns, including the hypermethylation of some genes and the hypomethylation of others (22). DNA methylation was discovered to be involved in the regulation of gene expression in keloids, specifically in genes involved in extracellular matrix remodeling and fibroblast activation (22). The accessibility of DNA to transcription factors and the subsequent regulation of gene expression can be affected by histone modification, which is the covalent alteration of histone proteins that package DNA in the nucleus (23). The writers explain how acetylation, methylation, and phosphorylation of histones play a part in controlling gene expression in keloids (23). They point out that elevated fibroblast activation and extracellular matrix (ECM) remodeling are both linked to specific histone alterations in keloid tissues (23).

The function of non-coding RNAs (ncRNAs) is to control gene expression but not by encoding proteins (24). MiRNAs, lncRNAs, and circRNAs are all discussed in relation to keloid development and growth (24). Many microRNAs (miRNAs) have been found to be out of whack in keloid tissues, and they point out that lncRNAs and circRNAs may have a hand in controlling fibroblast growth and migration (24). The complicated interplay between genetics, environment, and epigenetics in the onset and progression of keloids calls for more study. Epigenetic alterations are a potential causal factor in keloid development. However, more research into epigenetic modifications in keloids could lead to better diagnosis and treatment choices for patients with this disease.

VI. TREATMENTS

As the aetiology of keloid scars are still relatively unclear, there continues to be many different therapies including, surgical excision, radiotherapy and various

pharmaceutical drugs (25). Albeit, none of these treatments and therapies are able to instantly restore the skin to its original state, nor can it permanently remove keloid scar - which could be evident in the high recurrence rates (25).

Table 1. Keloids treatment efficacy and recurrent rate

Types of treatment	Keloid reduction rate	Keloid recurrence rate
Surgical excision	~100%	100%
Radiotherapy	70-90%	15-23%
Interferons	41%	51%
Botulinum toxin	79.2%	16.7%
Bleomycin	73.3%	50%

In some cases, if the keloid scar occurs over a large surface area, surgeons may recommend using a reconstructive technique to remove the scars (26). An example of this technique would be the skin expansion which allows for the surgeon to replace the damaged tissues (26). Nevertheless, surgical excision is considered to be an ineffective monotherapy as recurrence rate ranges from 45%-100%, even though the reduction rate can come close to 100% (25). It is typically recommended that those who did surgical removal of the scar continues to receive more conservation treatment such as Radiation therapy, steroid injections or chemotherapeutics (25) **(Table 1.)**.

Radiation therapy for keloid scars uses carefully measured doses of radiation to target the scars by damaging the cells and stopping the development (27). Nonetheless, radiation therapy on it own is not as effective. Radiation is normally recommended to patients who are at risk of recurrence, mostly effective to those who had just previously removed their scar via surgery (27). Different forms of radiation can be used such as electrons (up to 6 MeV), x-rays (70-130kV) and iridium-192 brachytherapy with either implants or surface application (25). Electrons are the most common form of radiation therapy as it allows shallow dose to penetrate the skin to stunt the development of keloid tissues (25). It has be shown that radiation therapy can lower recurrence from 100% to only 15-20% (25).

Interferons are a relatively new treatment. (3) Interferons are a group of cytokines that exert immunoregulatory, antiproliferative & antifibrotic functions. (3) IFN-alpha-2b and IFN-γ are therapeutic to keloids, however no regimen had been recorded for IFN-alpha-2b. (3) IFN-γ may influence regulation of collagen by inhibiting the synthesis of Type 1and 3 collagen. (3) It may mitigate the stimulatory effect of TGF-β. (3) A case series on intralesional injections of interferons-γ treatment shows a reduced rate of recurrence to 28%. (3) Intralesional injections of IFN-γ 3 times a week for 3 weeks can reduce keloid by 30.4%, as this causes reduction in thickened collagen bundles and active dermal fibroblast. (6) Double-blind RCT shows local IFN-γ did not reduce recurrence rate (26). A short-term in vivo study that involves 2 intralesional of interferons α-2b into progressively enlarging keloid, study shows 41% reduction in keloid area (3). A post-operative comparative study of post-operative intralesional injections of interferons α-2b showed a reduced rate of recurrence compared with excision site alone, recurrence rate was 18% vs 51%. (3)

There was a study showed that Botulinum toxin type A showed a significant effect in treating keloid lesions, especially in children. It was discovered that botulinum toxin acted via the mechanism of action called neuronox (25). Essentially, the fibroblast that had been treated with botulinum toxin type A was able to inhibit the TGF-β release - thus inhibiting the development of hypertrophic and keloid scars (25) According to the results from the study, the group that was treated with the neuronox mechanism showed a significant improvement after the first session and increased gradually after each section (25). Statistically, the results ranged from 51%-100% regarding the scarring and improvement (25). It was further observed that the injection was devoid of side effects and contributed to the alleviation of symptoms, including itching and erythema (25).

Bleomycin is another known chemotherapeutic agent to treat keloids (3). Bleomycin functions as a cytotoxic antibiotic that has many properties to induce apoptosis as it delays certain aspects of the cell cycle (6). In a study, patients were treated with 0.1mL of 0.15IU bleomycin injections using the dermojet technique which resulted in significant reduction of the scars (6). However, in a single-blinded study showed that intralesional bleomycin injection did not produce any significant reduction, compared with the dermojet method (6). Nevertheless, the results from both studies showed that bleomycin treatment resulted in very good improvement - however the therapeutic effects varies depending on the keloid scar itself (6).

VII. FUTURE PERSPECTIVE AND RECOMMENDATIONS

Keloids manifest as thick, elevated scars due to excessive collagen deposition during wound healing. Although not life-threatening, their presence can detract from aesthetic appearance and lead to symptoms such as pain, itchiness, and discomfort, thereby considerably affecting an individual's quality of life (28). To address keloid management and research in the future, several key recommendations can be made (28). A deeper understanding of keloid pathogenesis is crucial. Research should focus on the cellular and molecular mechanisms involved in keloid

formation, potentially leading to targeted therapies that can prevent or treat keloids more effectively (29). Personalised treatments could also prove beneficial since keloids can have different characteristics and responses to treatment. By identifying individual risk factors and genetic predispositions, treatments could be tailored to each patient's unique needs (29). Continued research into innovative therapies, such as gene therapy, stem cell therapy, or immunotherapy, may lead to more effective treatments with fewer side effects (30). Developing non-invasive or minimally invasive treatments should be prioritized, as they may offer better cosmetic outcomes and fewer complications. Examples include advanced laser therapies, cryotherapy, and high-frequency ultrasound (30). A multidisciplinary approach involving dermatologists, plastic surgeons, and other medical professionals can provide comprehensive care for patients with keloids, potentially leading to better treatment outcomes and increased patient satisfaction. Increasing patient knowledge about keloids, their risk factors, and available treatment options can help individuals make informed decisions about their care. This can be achieved through patient-centered educational materials and outreach programs (30). More long-term studies are needed to evaluate the effectiveness and safety of various keloid treatments, helping guide future treatment recommendations and refine current approaches. Research into effective prevention strategies should also be prioritised, as preventing keloid formation is often easier than treating existing keloids (30,31). This could involve early intervention, such as pressure therapy or silicone gel sheeting, after an injury or surgery in at-risk individuals (31). The psychosocial impact of keloids should not be underestimated (32). Addressing the psychological well-being of patients with keloids, including providing support and counseling, can improve overall quality of life and treatment outcomes (32). Finally, the establishment of international collaborations between researchers and clinicians can foster the sharing of knowledge, resources, and best practices, helping drive innovation and improve the overall management of keloids worldwide (32).

CONCLUSIONS

The management of keloids presents an ongoing challenge, largely attributable to their complex pathophysiology, diverse clinical presentations, and significant recurrence rates. Currently, an integrated approach - marrying surgical intervention with adjunctive therapies - is posited as the most efficacious treatment modality. Future research imperatives include a deeper exploration of the molecular mechanisms implicated in keloid pathogenesis and a thorough assessment of the effectiveness of targeted biological therapies.

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