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REVIEW ARTICLE **OPEN ACCESS**

A Short Review on Keloid

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ABSTRACT

Researchers discovered that K are abnormal scars that, if not treated appropriately, may cause patients significant emotional and physical anguish. Studies have concluded that K may also occur in conjunction with other types of scars. Additionally, studies have concluded that regular scars also have the potential to become K. Studies have also concluded that the formation of K is the result of an imbalance between the increased synthesis of collagen and extracellular matrix and the reduced degradation of these products. In addition, studies have shown that doctors have been able to find new ways to prevent and treat K by using what they do know about its pathophysiology, even though it is limited. Besides this, studies have shown that doctors have looked into whether anti-inflammatory molecules and chemotherapeutic molecules can stop keloid scars from coming back. They have also done research to find the best ways to use traditional treatments like radiation and steroids. Thus, in our review, we have discussed K in terms of cause, pathology, histology, roles in formation and treatment aspects.

Key words: *K, pathology, cause, histology, roles in formation, treatment aspect.*

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INTRODUCTION

Keloidal (K) are the pathological scar tissues and fibrous proliferation of skin lesions, according to a number of previous studies.[1] Numerous studies have shown that diagnosing diabetes is extremely simple and that it often affects the limbs rather than the chest or face."[2] Studies have also concluded that K is the result of abnormal wound healing that occurs in reaction to inflammation or trauma to the skin. Studies have concluded that the formation of K is dependent on both hereditary and environmental factors. In addition to this, studies have also concluded that people with darker skin, particularly those of African, Asian, and Hispanic heritage, have a higher risk of developing this condition. Studies Overactive fibroblasts that produce excessive amounts of collagen and growth factors are believed to be the cause of K. To explain this, a lot of fibroblasts and big, strange, hyalinized collagen bundles known as K collagen have been found in normal histologic sections. Clinically, studies have shown that K appears as stiff, rubbery nodules in a region of the skin where there has been a previous lesion. In addition to this, studies have also shown that K tissue spreads beyond the original site of trauma, in contrast to typical or hypertrophic scars. Furthermore, studies have shown that patients may report experiencing burning, itching, or discomfort in their bodies. In addition to this, according to studies, there are many different therapy options available, but none of them are completely effective. However, studies have also shown that intralesional or topical steroid injections, cryotherapy, surgical excision, radiation, and laser therapy are among the most popular therapies.[3,4,5] Thus, in our review we have discussed about K.

CAUSE

Studies have also concluded that hereditary characteristics and environmental factors both have a role in the development of K. Studies have concluded that those with a genetic predisposition may develop keloid scarring as a result of any kind of skin trauma, including surgery, piercings, acne, tattooing, insect bites, burns, lacerations, abrasions, vaccinations, and any other operation that results in cutaneous inflammation. Studies have further concluded that there is some speculation that the presence of elevated tension inside a wound may potentially play a role in the development of K.[3,6,7]

PATHOLOGY

Studies say that K form when the body's collagen and extracellular matrix (ECM) are not balanced. This makes it harder for the body to break down the waste products of making more collagen and ECM.

Researchers have also found a link between making too much of inflammatory mediators like TGF- β1 and making more ECM collagen. This is thought to happen because K-fibroblasts become more active. Furthermore, studies have concluded that this would explain why TGF- β1 would play a role in the process. [8] Studies have concluded that it is suspected that the variable production of isoforms of TGF is to blame for the excessively high levels of collagen production observed in pathologic scarring, which is caused by fibroblasts. Studies have also concluded that these abnormally high levels of collagen production may be detected in the skin. [9] Overexpression of TGF-β1 and TGF-β2, as well as reduced expression of TGF-β3 result in increased fibroblast activity and ECM collagen formation.[8,9,10] Researchers found that K fibroblasts are more likely to be affected by TGF-1 because the receptor is being overexpressed. [11] Also, research has shown that matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) play a big role in the process of collagen remodeling. Additionally, studies have found that these mediators increase rather than decrease extracellular matrix (ECM) degradation. [10] According to the results of studies, TGF-1 may both raise the production of TIMP and lower the production of MMP. This would eventually lead to less collagen breakdown. [12] Furthermore, studies have concluded that it is probable that additional inflammatory proteins, such as VEGF and PDGF, may have a role in the excessive production of collagen. [13,14] Researchers discovered that the molecules may work by starting up mechano-transduction pathways, which makes fibroblasts more active. Furthermore, studies have found that mechanical stress in particular body parts, such as the sternum, shoulder, and suprapubic areas, affects the pathways. [15, 16,17] While studies have concluded that the scientific community continues to investigate the cellular mechanisms behind K formation, doctors have a range of therapies at their disposal to prevent and manage keloids, including addressing their progression, recurrence, and symptoms.[18]

HISTOLOGY [19]

1. "Epidermis
2. Papillary Dermis
3. Tongue like
4. Horizontal fibous band in upper reticular dermis
5. Prominent fascia like a band in deep dermis.
6. Increase number of fibroblast
7. Thickened collagen bundle arranged parrallel to skin
8. Oriented blood vessel"

KEY ROLES FOR IMMUNE CELL IN K FORMATION

1. Mast Cell as Profibrotic Mediator

Studies have concluded that mast cells have a propensity to concentrate in tissue that is immediately exposed to the environment around them. In human skin, mature mast cells are found in large numbers in close proximity to the vasculature, lymphatics, nerves, and fibroblasts. These cells play a significant role in the process of wound healing by increasing angiogenesis, making it possible for re-epithelialization, and initiating inflammation.[20] It has been proposed that mast cells have a role in both the common symptoms (pruritus and erythema) associated with keloid scars as well as profibrotic chronic inflammation.[Figure 1] Studies have also concluded that silicone gel sheeting has been shown to reduce mast cell infiltration in keloid lesions, resulting in symptomatic relief.[21].

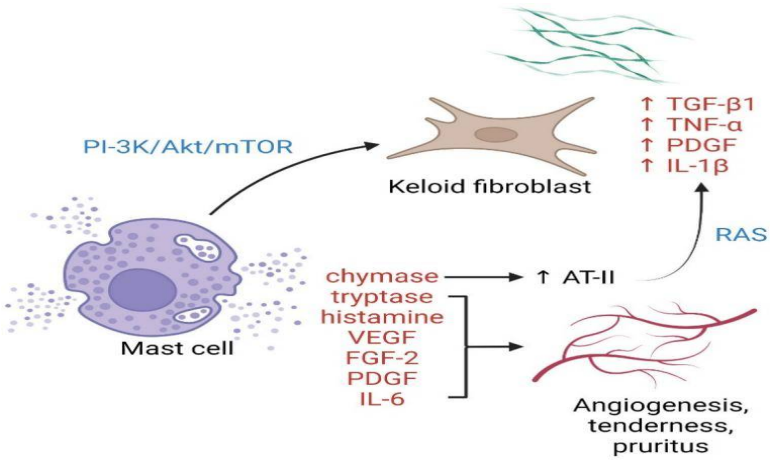

Fig. 1: Mast Cells Play a Crucial Role in K Development

Degranulated mast cells are able to connect with activated K fibroblasts thanks to the PI3K/Akt/mTOR pathway, which eventually leads to enhanced collagen synthesis. When mast cells degranulate, they create enzymes, growth factors, and cytokines. There are three different kinds of molecules that work together to turn on the RAS and cause K fibroblasts, angiogenesis, and skin symptoms. AT-II, angiotensin II; FGF-2, fibroblast growth factor 2; IL, interleukin; PDGF, platelet-derived growth factor; PI3K/Akt/mTOR, phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin pathway; RAS, renin-angiotensin system; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.[22]

2. Macrophage polarization (MP) & Chronic Inflammation(CP)

According to studies, there are two well-established subgroups of macrophages: M1 macrophages, which are activated in a traditional manner and are positive for CD68; and M2 macrophages, which are activated in an alternate manner and are positive for CD163. Studies have concluded that the first phenotype has an effect that is pro-inflammatory, while the second phenotype has an effect that is anti-inflammatory.[23] Furthermore, studies have shown that these two phenotypes have features that are diametrically opposite to one another and have attributes that are diametrically opposed to one another. Studies have also concluded that an imbalance between M1 and M2 macrophages has been identified in a variety of chronic inflammatory illnesses,[24] one of which is rheumatoid arthritis. Studies have also found that a normal wound heals by moving smoothly from the early stages of inflammation, which are controlled by M1, to the restoration stages, which are controlled by M2. This shift may be divided into two distinct phases if necessary. Additionally, studies have found that a dysfunctional form of this system will either cause prolonged inflammation, which will then cause a delay in the healing of wounds, or it will cause more scarring. Additionally, research has shown that M2 macrophages are disproportionately high in keloid lesions.[25,26,27,28,29] This may be because of the high concentration of Th2 cytokines in the area. Researchers have also found a possible link between M2 predominance and macrophages being able to sense mechanical signals like skin tension and stiffness,[30] but this link has not been proven yet. TGF-β1 is made by M2 macrophages, which are immune cells that cause inflammation. It strongly supports the growth of fibroblasts and their change into myofibroblasts.[31] Additionally, studies have found that M2 macrophages are responsible for the production of TGF-β1, which starts the wound closure process. Also, research has shown that M2 macrophages help regulatory T cells (Tregs) grow by making more FOXP3 in CD3+ T cells that are floating around in the blood.[32] [Figure 2] Additionally, according to studies, it is noteworthy to note that despite the clear presence of M2 predominance, the expression of genes and proteins related to both M1 (inducible nitric oxide synthase [iNOS], IL-12) and M2 (IL-10, TGF-β1) is elevated in keloid lesions compared to normal skin.[32]

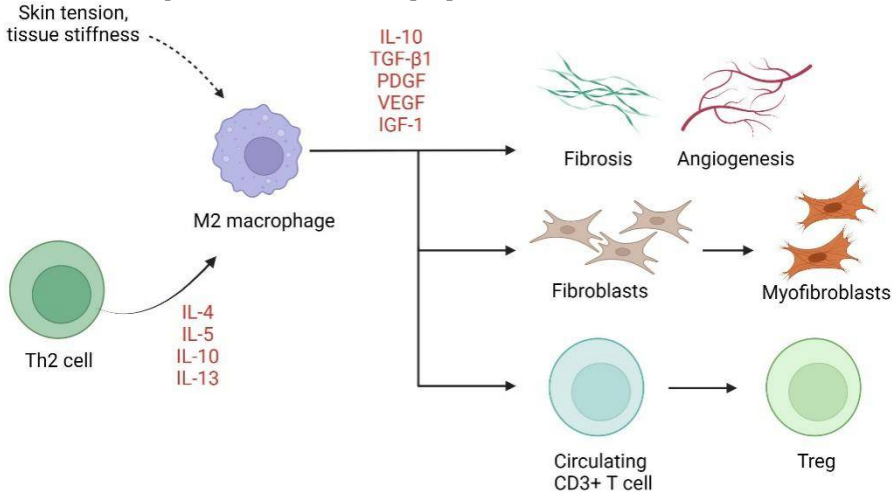

Fig. 2: The role that macrophages play in the development of keloids and their pathogenesis Keloids are different because they have an abnormally high number of M2 macrophages. These macrophages activate keloid fibroblasts, help Treg cells mature, and lead to fibrosis and angiogenesis. IL stands for interleukin, PDGF stands for platelet-derived growth factor, and TGF-β1 stands for transforming growth factor 1. IGF-1 stands for insulin-like growth factor 1. VEGF stands for Vascular Endothelial Growth Factor, Th stands for T cells that support and regulate other T cells, and Treg stands for T cells that control other T cells.[22]

3. Tregs derived TGF-β1 & Collagen Expression

According to studies, it has been shown that an increased number of Tregs is present in patients who have keloid lesionn.[32,33] Studies have also concluded that in chronically inflamed skin, regulatory T cells, also known as Tregs, are able to multiply provided the right conditions are met. These conditions

include the presence of IL-15 and cellular contact with dermal fibroblasts (116). In addition, research has shown that they make it easier for collagen III to build up in keloids when anti-CD3/CD28 is present, which is mentioned in reference number.[33] Another finding from studies is that when Tregs were brought into the area around multiple keloid scars, the number of circulating CD4+ CD25high FOXP3+ Tregs lowered. In addition to this, studies have also concluded that this was identified in people who had several keloid scars on their bodies. Other than this, studies have also concluded that, since it is not clear if the seemingly excessive number of local tregs is detrimental or just a response to the inflammation, the issue is yet unsolved. Important cytokines produced by regulatory T cells include TGF-β1 and IL-10.[34,35] Furthermore, studies have concluded that these two cytokines have an autocrine effect on each other. The first one boosts the production of immunoglobulin by B cells and lowers the activity of proinflammatory macrophages. The second one boosts the production of matrix proteins and IL-6 by mast cells.[36] [Figure 3] Studies have also shown that it is important to remember that TGF-β1, not IFN-γ, is what stops TGF-β1 from working on keloid fibroblasts.[37,38] Researchers have also found that regulatory T cells, or Tregs, may gather in damaged muscle and control the change of macrophages from M1 to M2 polarization. [39] This is the case in damaged regions of muscle. When it comes to the process of wound healing, it is quite probable that they take on a coordinating role of a similar sort. Thus, we need to do more research to find out how much tregs affect the balance between M1 and M2 macrophages and how they contribute to the formation of keloidogenesis. This may be done by determining the degree to which tregs affect the equilibrium between M1 and M2 macrophages.

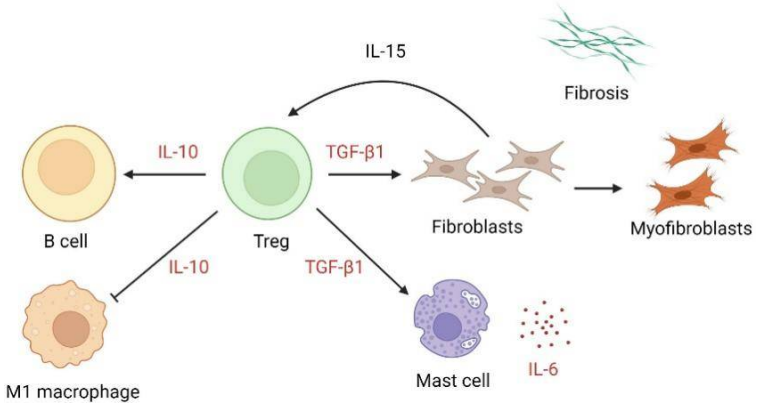

Fig. 3 : Role Of Regulatory T cell in K Pathogenesis

Tregs work by affecting IL-10 and TGF-1, which stops M1 macrophages from working, turns on mast cells, and causes keloid fibroblasts to make IL-6. TGF-1, Tregs, regulatory T cells; IL

4. Dendritic cell

Studies have also concluded that dermal invasion of FXIIIa-positive DCs is greater in keloid scars than hypertrophic and mature scars. Potent antigen-presenting cells may play a role in pathogenic interactions in K,[40] and DC-derived TGF-β1 may facilitate Treg differentiation.[40] Thus, studies have concluded that sequencing RNA showed that there were more DC markers (CD80 and CD86) and atopic DC markers (OX40L+ and FCR1+) in both lesional and nonlesional skin from people with K. DCs are implicated in mast cell activation and Th2, Th17, and Th22 differentiation in atopic dermatitis,[41,42] but their role in K formation is unknown.[41,42]

5. Natural Killer cell

Studies have concluded that K single-cell suspensions have shown unusually abundant NK cells. It's not completely clear what role NK cells play in the formation of keloid tumors, but they do show the NKG2A/CD94 complex on their surface and are connected to the NKG2A-sHLA-E axis.[43] In addition to this, studies concluded that K environments that are high in TGF and always swollen may stop NK cells from working, which can cause cancer to grow out of control because NK and cytotoxic T cells are worn out.[44]

DIFFERENTIAL DIAGNOSIS [19]

Studies have concluded that when assessing a patient who may have keloids, it is difficult to make a differential diagnosis because of the presence of the keloids. However, in order to establish whether or not lesions need a skin biopsy, it is essential to make a note of the critical characteristics that are present in the lesion. Studies have also concluded that this will allow one to decide whether or not a skin biopsy is required. As was said before, studies have also concluded that hypertrophic scars are the consequence of

trauma to the skin and may appear quite similar to keloids. Keloids are the more common kind of scar. In comparison to keloids, studies have been proving that hypertrophic scars are typically less noticeable and are typically isolated to the region where the damage happened. This is in contrast to keloids, which may continue to expand and get involved with the skin that is around them. Studies have also concluded in addition to above that dermatofibroma is a kind of abnormal scar response that typically manifests as a flesh-colored or hyperpigmented papule or nodule on the skin. This medical condition is known as dermatofibroma. It is called the "dimple sign," and it is referred to as the "classic clinical hallmark of these lesions." The central depression that emerges as a consequence of applying lateral pressure is what is known as the "dimple sign." An uncommon spindle cell tumor called dermatofibrosarcoma protuberans may strike young people at some point. This kind of tumor is known to be aggressive in its immediate surroundings, and it may exhibit itself on the trunk as well as the proximal extremities. These lesions, in contrast to keloids, were not caused by a previous trauma and have margins that are more asymmetrical. The look of keloids may help identify them from these lesions. Keloidal variants include scleroderma and morphea. These patients would have a disease that develops even in the absence of a known inciting incident, and they may also display additional symptoms that they are suffering from a disease of the connective tissue. This is due to the fact that these patients have a disease that continues to worsen, even though the origin of the disease is unclear. Xanthoma disseminatum is a fairly uncommon histiocytic growth that may produce skin lesions that may be mistaken for keloids. Acute lesions frequently present themselves in a form that is both diffuse and symmetrical. Diabetes insipidus may develop over time if the condition is systemic. Last but not least, the fungus Lacazia loboi both causes and contributes to the serious fungal illness known as lobomycosis. This condition may prove to be lethal. There is a link between having contact with dolphins or the rural soil in Central and South America and the development of a nodule on the distal extremities that resembles a keloid. This link has been shown to be statistically significant. When measured in terms of its rate of development, the nodule is moving forward at a very sluggish pace.[19]

TREATMENT

Researchers discovered that “K continues to be a challenge for medical treatment. Not only are they difficult to heal, but insufficient treatment may lead to a keloid deteriorating and expanding in size. Furthermore, studies have concluded that K-scars can be quite uncomfortable. Therefore, studies have concluded that the major focus should be on prevention. Additionally, studies have concluded that individuals who are predisposed should, if at all possible, refrain from undergoing elective treatments, notably ear piercings and tattoos. Studies have concluded that there are strategies to lessen the risk of developing a K scar and, in some cases, even prevent its formation, in the event that an accidental trauma or surgical intervention is necessary. Furthermore, studies have concluded that it is essential to minimize the wound's tension as much as possible in order to lower the likelihood of keloid formation. On top of that, studies have shown that the two most important things for tension-free wound closure are enough hemostasis and fast primary closure. Additionally, studies have concluded that the use of silicone sheeting to stabilize wounds for an extended period of time may also help alleviate tension in the wounds. Compression treatment, with pressures of 15 to 45 mmHg advised for more than 23 hours per day for at least 6 months, is said to minimize the formation of keloids, according to research published in medical journals”.[19]

Studies have also proved that, several other modalities are present which alleviate the symptoms on its use, that are as follows:-[19]

1. “Corticosteroid
2. Cryotherapy
3. Surgical Excision
4. Radiotherapy
5. Laser”

CONCLUSION

Researchers discovered that recent success from innovative treatments is promising, adding to the growing number of therapies available for the prevention and treatment of K. Studies have also concluded that clinicians' familiarity with the various injectable treatments and devices mentioned in the literature will allow for more consistent data collection. Studies have also found that there aren't any large, high-quality studies that compare the effectiveness of different keloid treatments, so there aren't any standardized guidelines for how to treat keloid scars. Studies have also found that there isn't a set standard way to treat keloid scars because there isn't an academic or regulatory body that backs them up.

Thus, there is a need for more comparative studies of treatment modalities to be conducted using a consistent experimental design.

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