

## Mini Review

# Risk Factors of Keloids: A Mini Review

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## Abstract

Keloid is a benign fibrous growth, which presents in scar tissue of predisposed individuals. It is a result of irregular wound healing, but the exact mechanism is unknown. However, it is possible that several factors such as age of onset, sex, cause of scarring, blood groups, anatomical site, presence of family history and number of injured sites (multiple/single) have an important role in keloid formation and consequentially in predicting keloid's behavior in response to treatment and prognosis. In this mini review, we have demonstrated these risk factors of keloids in detail.

**Keywords:** Keloids; Risk factors; Family history; Melanin; Blood groups; Cause of scarring; Anatomical site; Multiple sites; Sex; Age of onset

## Introduction

Keloid is a benign fibrous growth, presents in scar tissue of predisposed individuals, extends beyond the borders of the original wound, doesn't usually regress spontaneously, and tends to recur after excision. It is a result of irregular wound healing following skin insults (trauma, inflammation, surgery, burns...etc.), but sometimes occur spontaneously. Most keloids develop within 3 months of the injury, but some may occur up to 1 year after skin insults [1]. First described in the Edward Smith papyrus in Egypt around 1700 BC [2]. Keloids appear as firm, mildly tender, boss elated tumors with a shiny surface. In the Caucasian patient, keloids tend to be erythematous and telangiectatic; they are often hyperpigmented in darker-skinned individuals. Keloids are often pruritic and painful, in addition to significant effects of patient's quality of life, both physically and psychologically, especially in excessive scarring [3,4].

The main differential diagnosis of keloid is hypertrophic scar, also called pseudokeloid. Differential diagnosis is important, since treatment procedures differ between these two types of scar disorders. Hypertrophic scars, which defined as raised scars that remained within the boundaries of the original lesion, often regressing spontaneously after the initial injury and rarely recurring after surgical excision. In contrast, a keloid scar is defined as a dermal lesion that spreads beyond the margin of the original wound, continues to grow over time, does not regress spontaneously and commonly recurring after excision [1].

The process by which keloid develops is poorly understood, but it is known to be induced by skin insults in predisposed individuals. There are several theories of keloid etiology, most of them are related to fibroblast dysfunction. Keloid fibroblasts, when compared with fibroblasts isolated from a normal wound, have excessive deposition of extracellular matrix components, especially collagen, fibronectin, elastin, proteoglycans. In addition, these cells have lower rates of apoptosis [2,5].

## Risk Factors of Keloids (Epidemiology and Etiology)

Several factors play a significant role in keloids formation. The

genetic predisposition is the most important factor; other factors are blood groups, melanin, the anatomical site, the type of skin injury, the age of onset, and sex [1].

### Genetic predisposition

There is a clear genetic component given the correlation with family history, which supported by the following phenomena: (a) some patients with keloids report a positive family history. 19.3% of Syrian patients had a family history [1], 50% of Afro Caribbean patients [6], and 36.4% of Nigerian patients [7]. (b) High occurrence in identical twins [6,8,9]. (c) There are higher predisposition in Blacks, Hispanics and Asians, less frequently in Caucasians [6]. (d) Increased incidence of keloids in patients with some genetic syndromes like Turner syndrome, Opitz-Kaveggia syndrome, Rubinstein Taybi syndrome and Ehlers Danlos syndrome [10].

Proposed inheritance patterns include autosomal recessive, autosomal dominant with incomplete penetrance, and variable expression [8,11]. Several genes are considered responsible for keloid disease, but no single gene mutation has thus far been found to be responsible [12].

(a) Genome wide association study in Japanese population has shown that four SNP (Single Nucleotide Polymorphism) loci in three chromosomal regions (1q41, 3q22.3-23 and 15q21.3) exhibit significant associations with keloids [13]. (b) Marneros and colleagues studied two families with an autosomal dominant inheritance pattern of keloids (Japanese family and African American one). They identified linkage to chromosome 2q23 (maximal two-point LOD score of 3.01) for the Japanese family. The African-American family showed evidence for a keloid susceptibility locus on chromosome 7p11 (maximal two-point LOD score of 3.16) [14]. (c) Brown and colleagues found a genetic association between HLA-DRB1\*15 statuses and the risk of developing keloid scarring in white individuals [15]. (d) Also, carriers of HLA-DQA1\*0104, DQB1\*0501 and DQB1\*0503 have been reported to be have an increased risk of developing keloid scarring [3].

There is importance of the cause and anatomical site in the added heredity of keloids. 76% of patients with family history have keloids located in the same anatomical sites of the relative, and 66% of them

have keloids caused by the same cause [1]. Also, there is predisposition to heredity spontaneous keloids, which usually appears in the second decade, presternal and shoulder keloids [1]. In addition, family history is strongly associated with the formation of keloid scars in multiple sites as opposed to a single anatomical site [6].

### Blood groups

People with blood group A have high probability to develop keloids compared with other blood groups, that may be partly explained by the association between the effect of red cell antigens A (which present on the membrane surface of red blood cells and certain epithelial cells) and other factors in these patients [1,9]. A study by Shaheen [1] revealed association between spontaneous keloids and blood group A ( $p = 0.01$ ), which confirms the effect of red cell antigens A in development of keloids. (This finding has not been previously reported).

### Melanin

There is a relationship between keloid formation and skin color, as supported by the following phenomena: (a) Colored skin people such as the Negroid and Mongoloid races have a greater tendency to suffer from keloid compared to the Whites (the Caucasian race). The comparative ratio between Blacks and Whites who suffer from keloid varies extensively, ranging from 5 up to 18.7 to one. On the other side, evidently keloid is not found among albino which is a condition where there is absent or minimal melanin pigment [5,6,16-18]. (b) The incidence of pathological scarring varies across different parts of the body even in the same individual; for example, fewer keloids develop in the palm and thenar eminence, where melanocytes are less common [17,19]. (c) Adolescents and pregnant women, who are subjected to increased hormone secretion and skin pigmentation, are more susceptible to developing keloids [17]. Based on these facts, it becomes apparent that the incidence of keloid is strongly related to skin color. Melanin is the most important pigment which determines variations in skin color of the various races in the world [2,20].

The relationship between melanin and keloid formation have been assumed by several theories: (a) During wound healing, melanocytes from the stratum basal contact or interact with fibroblasts from the dermal layers after the basal membrane is damaged, which in turn facilitates fibroblast proliferation and the secretion and deposition of collagen [2]. (b) High levels of melanin cause decreasing of histologic PH, which inhibit collagenase, that disrupts collagen degradation process [20].

### Causes of keloids (Type of skin injury)

Keloids may develop following any skin injury like non-inflammatory conditions such as burn, trauma, surgery, piercings, or inflammatory skin conditions such as acne vulgaris, folliculitis, varicella infection, or vaccinations (particularly BCG vaccination) [3,19], but not all such insults lead to a keloid scar even in the susceptible individuals [6]. This means all types of skin injuries could cause keloids, but each patient is affected by specific type of injuries. That indicate to the role of type of skin injury in keloid formation, which supported by the higher prevalence of single keloid more than multiple keloids, although the patient is exposed to other injuries that may cause keloid. On other hand, there are very few patients have keloids caused by two different causes [21].

The most common cause of keloid differs according to conditions of study's society. Syrian [1] and Iranian studies [22] found that keloids could follow any form of skin injury, but burns were the most common. Bayat [6] found that laceration was the most common cause in Afro Caribbean patients. However, the occurrence of a keloid or hypertrophic scar following BCG vaccination is not uncommon and is likely more to the inflammatory nature of the injection response rather than the size of the wound [19]. Causes have almost coordinated distribution in males and females, but males have higher predisposition to develop acne keloids compared to female, because only males have acne keloidalis nuchae, and the severity of acne is higher in them [1].

Spontaneous keloid is a rare condition, and it is controversial whether it is in fact spontaneous. The scar tissue may form after an insignificant inflammatory reaction or injury which the patient has no recollection of. Syrian study [1] found 13.4% of spontaneous keloids, which was similar to Togo study 13.13% [21], but lesser than an Iraqi one 34% [23]. As we said before, some patients have hereditary of spontaneous keloids, while others have association with blood group A [1]. There is confirmed evidence of the association between spontaneous keloid formation and different diseases such as Dubowitz syndrome, Rubenstein-Taybi syndrome, and Noonan syndrome. In addition, Spontaneous keloid has been reported in siblings and in people with allergic diseases [24].

There are very few patients have keloids caused by two different causes [1]. They are only 2.32% of patients in Syrian study [1], 83.3% of them had surgical keloids, so we have to be careful when performing surgery for a patient who had a previous keloid. On other hand, this percentage is higher in dark skin patients 15.9% [21], maybe because developing keloid is more common in Blacks than in Whites.

Keloids could follow any skin insults, but there is association between anatomical sites and specific injuries. Shaheen [1] found that burn was the most common cause of keloid formation in uncovered sites (face (35%), neck (50%), upper limbs (44.29%, lower limbs (66.66%), and chest wall (27.59%)), and less affected sites (lower back (37.5%), button (50%), genitalia (50%), palm and sole (66.66%)), which disagree partly with the Japanese study, found that trauma was the most common cause of extremities keloids [25]. Ear piercing is the most common cause for earlobe keloid [1,6,25]. Acne is the most common cause for scalp keloids [1,6]. More than quarter of shoulder keloids were caused by acne [1,25]. The Syrian study [1] found that Most sternum keloids were spontaneous (35.82%), or followed surgery (37.13%), while most sternum keloids were caused by trauma in Jamaican study [6], or acne in Japanese study [25]. At last, abdominal keloids followed by surgery in several study, more than half of abdominal keloids followed surgery in the Syrian study [1], while all abdominal keloids followed surgery in the Japanese study [25].

### Anatomical site

Several studies indicated to the role of anatomical site in keloid formation, which supported by the following phenomena: (a) Genetically susceptible individuals form keloids after wounding but not at every body site [6]. (b) Generally keloids tend to occur on highly mobile sites with high tension such as shoulders, neck, and presternum [26,27]. (c) There are familial patterns of keloid distribution [11].

Anterior chest, shoulders, earlobes, upper arms and cheeks have a higher predilection for keloid formation. Eyelids, cornea, palms, mucous membranes, genitalia and soles are generally less affected [3]. The most common anatomical site for developing keloids differs according to race, traditions and conditions of study's society. Shaheen [1] indicated that upper limb 20% followed by sternum 19.17% were the most common sites for developing keloids in Syrian patients. Similarly, Abas Mouhari Toure [21] noted that sternum 28.95%, upper limb 15.8% and head 16.7% were the most common sites in dark skin patients. Conversely, ear 23% was the most common one in Bayat's study [6]. On other hand, most of studies agree that genitalia, buttock, palm and sole are the rarest sites for developing keloids [1,6,7,21].

Few studies discussed the development of keloids in single versus multiple anatomical sites and its correlation with patient's clinical feature and prognosis [1,6]. Shaheen [1] found that 19.3% of patients had keloids in multiple anatomical sites, where upper limb was the most common site for developing keloids in them 46%, and burn was the most common cause 38.2%. Bayat [6] demonstrated that 42.2% of patients had keloids in multiple anatomical sites, where earlobe was the most common site in multiple 24% sites, and ear piercing was the most common cause. Although all causes tend to develop keloids in multiple sites, only burn and acne have association with developing keloid in multiple sites in Syrian patients ( $p = 0.029$ ) ( $p = 0.0002$ ) respectively, which means there is high probability to develop acne or burn keloids in another anatomical site in a patient who had a previous acne or burn keloid respectively, because both acne and burn could affect multiple sites more than other causes, which is more located [1]. Female sex, younger age at presentation and the presence of a positive family history are associated with the development of keloid scars in multiple anatomical sites in Afro Caribbean individuals [6]. A previous study reported that 1.93% of patients have keloids caused by two different causes, and distributed on multiple anatomical sites. This may be indicate that very few people have a high predisposition to develop keloids, but this finding needs more research.

Keloids could develop at any anatomical sites, but there is association between type of skin injury and specific anatomical sites. Syrian study [1] found that 80% of spontaneous keloids were located on sternum and shoulders, this agree partly with a previous study, which demonstrated that sternum was the most common site for spontaneous keloids [28]. Also, 45% of burn keloids were located on extremities (lower and upper) in that study [1], while a Japanese study found that all burn keloids were located on chest wall and lower limbs [25]. About 40% of sharp wound keloids were located on upper limbs, and 50% of surgical keloids were located on sternum and abdominal wall [1,25]. Sternum and shoulder are the most common site for acne keloids. Syrian study [1] found that about half of acne keloids were located in these sites, while most acne keloids were located in these sites in the Japanese study [25]. 37% of trauma keloids were located on face and upper limb in Syrian patients [1], which agree partly with the Japanese study [25], which found that most trauma keloids were located on extremities (upper and lower).

### Epidemiologic variances (sex and age)

Incidence of keloids is usually equal in females and males [9,21,23,29], but sometime there is higher incidence in female [6,29]

(it could be related to the higher rate of earlobe piercing in females), or in male (it could be related to acne keloidalis nuchae, especially in Blacks) [7]. In general, both sexes develop keloids in the same anatomical sites, and followed to the same injuries, but sometimes there is preference for one gender to develop keloids in specific site, following specific cause, at specific age. Males who are older than forty could develop keloids more than females in the same age (as we will discuss later). Also, males have higher predisposition to develop acne and scalp keloids compared to female, because only males have acne keloidalis nuchae, also, the severity of acne is higher in them [1]. As we said before, Female sex is associated with the development of keloid scars in multiple anatomical sites in Afro Caribbean individuals [6].

Although keloids could occur at any age, they are rare in first decade, because people in this decade are not stimulated by sexual hormones (higher incidence of keloid formation during puberty) [1,3,16]. Most likely to occur in second and third decades and tend to decrease in older [1,6,9,17], which supported by the following phenomena: (a) younger people may have a higher frequency of trauma, their skin is more elastic than the skin of elderly people [29], (b) they have higher level of sexual hormone than older people (Keloid growth may also be stimulated by various hormones, as indicated by some studies in which results have suggested a higher incidence of keloid formation during puberty and pregnancy, with a decrease in size after menopause, that related to localized hyper androgen metabolism which may play a causal or at least contributory role in the pathogenesis of keloids, or elevated androgen receptor levels exist in clinical active keloid tissue [30,31]) [1,3,16,19]. Also, younger age is associated with the development of keloid scars in multiple anatomical sites [6]. Each decade has preference to develop keloids in specific site, following specific cause. Burn is the most common cause for developing keloids in first decade compared with other decades, especially on upper and lower limbs. This is a logical result, because most of burn accidents exist in younger children especially on extremities [1]. Occurrence of acne keloids is higher in second decade compared with other decades, because the peak in prevalence and severity of acne occurs in second decade. High frequency of sharp wound accidents and earlobe piercing in second decade explain the higher incidence of these keloids in this decade [1]. Also, development of scalp keloids is higher in second decade compared with other decades, because most cases of acne keloidalis nuchae occur in persons aged 14-25 years (most cases of scalp keloids are caused by keloidalis nuchae) [1]. There is absence of acne keloids in fourth decade, because frequency of acne extremely decrease in this decade [1]. At last, development of surgical keloids is higher in fifth, sixth and seventh decades compared with other decades, especially on sternum. These results reflect an increase of open heart surgeries in older people, especially for males who are older than forty compared to females in the same age [1].

**Note:** The above risk factors are unmodifiable factors, but there are modifiable factors like delayed healing [32], and hypertension [33].

### Delayed healing

This usually occurs as a result of wound infection or if wound edges are not apposed. This will lead to healing by second intention as the defect fills gradually with granulation tissue and restoration of epidermal continuity may take a considerable time. Healing by second

intention usually results in prolonged healing, excessive fibrosis and an ugly puckered scar as opposed to healing by first intention which occurs following the meticulous apposition of the edges of clean incised skin. This leaves a narrow epidermal defect which can be bridged easily resulting in a fine hairline scar. Thus healing by second intention is more likely to develop keloids especially if healing time is greater than three weeks [32].

### Hypertension

There is relationship between hypertension and development of severe keloids. Blood pressure associated significantly and positively with both keloid size and number (both  $p < 0.0001$ ). This association may reflect the fact that hypertension damages blood vessels, thereby increasing inflammation in local tissue [33].

### Treatment

No single therapeutic modality is best for all keloids. The location, size, and depth of the lesion; the age of the patient; and the past response to treatment determine the type of therapy used. There are several options in keloid treatment [34].

#### Standard treatments

These include occlusive dressings, compression therapy, and intralesional corticosteroid injections. Occlusive dressings include silicone gel sheets and dressings, nonsilicone occlusive sheets, and cordran tape. These measures have been used with varied success. Antikeloidal effects appear to result from a combination of occlusion and hydration, rather than from an effect of the silicone. Compression therapy involves pressure, which has long been known to have thinning effects on skin. Reduction in the cohesiveness of collagen fibers in pressure treated hypertrophic scars has been demonstrated by electron microscopy. Cellular mechanoreceptors may have an important role of compression therapy. Mechanoreceptors induce apoptosis and are involved in the integrity of the extracellular matrix. Corticosteroids, specifically intralesional corticosteroid injections, have been the mainstay of treatment. Corticosteroids reduce excessive scarring by reducing collagen synthesis, and reducing production of inflammatory mediators and fibroblast proliferation during wound healing. The most commonly used corticosteroid is Triamcinolone Acetonide (TAC) in concentrations of 10-40mg/mL administered intralesionally at four to six week intervals. Intralesional steroid therapy as a single modality and as an adjunct to excision has been shown to be efficacious in various studies.

#### Cryotherapy

Cryosurgical media like liquid nitrogen affects the microvasculature and causes cell damage *via* intracellular crystals, leading to tissue anoxia. Generally, 1, 2, or 3 freeze-thaw cycles lasting 10-30 seconds each are used for the desired effect. Treatment may need to be repeated every 20-30 days.

#### Excision

Decreased recurrence rates have been reported with excision in combination with other postoperative modalities, such as radiotherapy, injected IFN, or corticosteroid therapy.

#### Radiotherapy

Radiation destroys fibroblasts in the wound, prevents neovascularization, which ultimately leads to a decreased production

of collagen.

#### Laser therapy

Ablative lasers (carbon dioxide 10,600nm, Erbium: Yttrium Aluminum Garnet Laser Er: YAG 1064nm, and Argon 488-nm laser). Nonablative lasers (Pulsed-dye laser 585nm): it provides photothermolysis, resulting in microvascular thrombosis. The PDL remains the laser treatment of choice for keloids hypertrophic scars.

Intralesional/topical apply of following drugs: IFN injections, 5-Fluorouracil, Doxorubicin (Adriamycin), Bleomycin, Verapamil, Retinoic acid, Imiquimod 5% cream, Tamoxifen, Tacrolimus, and Botulinum Toxin A.

#### Other promising therapies

The antiangiogenic factors, including the Vascular Endothelial Growth Factor (VEGF) inhibitors (e.g. Bevacizumab). Phototherapy (Photodynamic Therapy - PDT), UVA-1 therapy, narrow band UVB therapy. Tumor Necrosis Factor (TNF) alpha inhibitor (etanercept). Recombinant Human Interleukin (rhIL-10) which are directed at decreasing collagen synthesis [34].

### Conclusion

It is possible that several factors have an important role in keloid formation and consequentially in predicting a keloid's behavior in response to treatment and prognosis. The genetic predisposition is the most important factor, but no single gene mutation has thus far been found to be responsible. People with blood group A have high probability to develop keloids compared with other blood groups. There is a relationship between keloid formation and skin color, Blacks have a greater tendency to suffer from keloid compared to the Whites. All types of skin injuries could cause keloids, but each patient is affected by specific type of injuries, which indicate to the role of type of skin injury in keloid formation. Genetically susceptible individuals form keloids after wounding but not at every body site, which indicate to the role of anatomical site in keloid formation. There is importance of the cause and anatomical site in the heredity of keloids. Burn, acne, female sex, younger age at presentation and the presence of a positive family history are associated with the development of keloid scars in multiple anatomical sites. Males who are older than forty could develop keloids more than females in the same age. Also, males have higher predisposition to develop acne and scalp keloids compared to female. Although keloids could occur at any age, they are rare in first decade, most likely to occur in second and third decades and tend to decrease in older. There are modifiable factors like delayed healing, and hypertension.

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