Research in Biotechnology, 2(6): 37-43, 2011 ISSN: 2229-791X
www.researchinbiotechnology.com

Mini Review

Aetiology of Keloids – An Overview

R. Devika* and S. Nazareth Arockiamary

Aarupadai Veedu Institute of Technology, Paiyanoor- 603 104, Tamil Nadu, India
E- mail Id: vineeth_2001@yahoo.com; nazi.mary20@gmail.com

Keloids are firm, rubbery lesions or shiny, fibrous nodules, and can vary from pink to flesh-coloured or red to dark brown in colour, benign, non-contagious, and sometimes accompanied by severe itchiness and pain, which affects the movement of skin. Keloids scar formation is nearly 1000 years old aetiology and pathogenesis is still poorly understood. Current paper is an overview of the aetiology, formation and the severity of keloids. It also gives the complete information of the prevailing treatment and its complications, and few case studies to strengthen the current strategy.

Key words: Aetiology, collagen, fibroblast, hypertrophic scars, keloids,

Skin is well recognized as an important somatic mirror of ones emotion and a site for the discharge of ones anxieties. According to Sobanko and Alster (2009) a complex array of reparative tissue mechanism occurs in the skin after epithelial barrier distruption and develops abnormal healing responses that result in inadequate restoration of the cutaneous surface. Hypertrophic scars and keloids are common problems after injury and cause functional and cosmetic deformities (Wang *et al.,* 2009)

As per Meenakshi *et al.,* (2005a) keloids are dermal fibromatosis disorders unique to human that occurs following trauma, inflammation, surgery, burns which are characterized by excess deposition of collagen in the dermis and subcutaneous tissues.

Keloid scar formation is nearly 1000 years old aetiology and pathogenesis is still poorly understood (Sullivan *et al.,* 1996) and the evidence of keloids scar are found in the tenth century writings of Yoruba tribe of Nigeria (Oluwasanami, 1974). The first scientific description of keloids was represented by Reitz (1790) and stated in the lesions represented herniation of subcutaneous fat.

Keloids was described by Egyptian surgeons around 1700 BC, Baran Jeas Louis Albert(1768-1837)who coined as cancroids and later changed it as "Cheloide" to avoid confusion with cancer which was derived from the Greek word chele meaning 'hoof' in the sense of crab pincers' and suffix 'oid' meaning "like". The classic definition of keloids scar is that which progressively invades surrounding tissues whereas hypertrophy scars remain confined to the area of tissue damaged by the initial injury and which increases in size by pushing out the margins of the scar and not by the invasion of the surrounding normal tissue (Muir, 1990).

Keloids may be accounted into two subgroups as 'True keloids '(spontaneous lesions arising arising without previous trauma) and false or cicatrical keloids (keloids from the site of previous injury (Sullivan *et al*., 1996).

Keloids (spot like) have been called "Cancroids" (cancer like or crab like) and "Cheloids" (claw like) because of their characteristic aggressive and expansive nature (Cohen and Peacock, 1990).

According to Dubato – Brown (1990) keloids thick scar of human skin or cornea, produced by deposition of excessive amounts of collagen over prolonged period. Keloids represent an example of cutaneous scarring and partially considered as benign tumors. It is characterized by excessive deposition of collagen upon cutaneous injury, cocktails of chemokines, cytokines and growth factor and secreted temporally and spatially to direct appropriate responses from neutrophil, keratocytes and fibroblast (Lim *et al*., 2006).

Incidence:

An increased incidence of keloids and hypertropic scars in dark skinned races has been documented, greater melanocyte stimulating hormone (MSH) activity and few other observations are seem to substantiate as

1. Deeply pigmented people are more prone to keloid formation.
2. Keloid formation occurs at the site where melanocyte content is high
3. Incidence of keloids is higher during increased pituitary activity as in puberty and pregnancy (Dubato and Brown, 1990).

Keloids occur in individuals with a familial disposition among the 13 lakhs, Hispanics and orientals (Meenakshi *et al*., 2005b). There are evidences of fifteen times higher frequency of occurrence in highly pigmented people of both sexes equally, but young female patients has been reported to be higher than in young males.

Spontaneous development of keloids are reported among West African and Southern Indian origin which had greatest risk of keloid or hypertrophic scar in many areas of the body (Cosman *et al*., 1969; Ramakrishnan *et al*., 1974). Fair skinned individuals traveling to tropical areas have increased risk of keloid formation not as great as that of the indigenous population Murray *et al*., 1981). Evidence of increased susceptibility to keloid formation resulted due to hereditary factors like autosomal dominant (Murray *et al*., 1981), autosomal recessive (Bloom, 1976) and cross linked recessive (Gominne, 1968).

Scars on certain areas of the body progress to hypertrophic or keloid scars, particularly the surgical area, the back the ears, the neck (Davey, 1968) and cornea (Lemasters and Notz, 1986). Keloid formation is very rare in the eyelids, penis and areola of the breast (Dubato and Brown, 1990).

Olaitan (2009) estimated that out of one hundred and thirty one keloid cases, fifty five (42%) of the patients had keloids in conspicuous parts of the body alone (ie) hand, forearm, head and neck, fifty four (41.2%) on non – conspicuous parts, while twenty two (16.8%) had swelling on both conspicuous and non – conspicuous parts of the body.

There are evidences of people of all ages suffered from these conditions, in which the patients are young and healthy and become burdened with an activity limiting lesion or psychosocial stresses associated with a perceived esthetic defect (Jones *et al*., 2006).

Age:

Children under 11 are less likely to develop keloids and the incidence may develop from pseudofolliculitis barbae, continued shaving, when one has razor bumps (cancerous growth in future) and it is also speculated that this may be hereditary and may be passed down from generation to

generation. Tougher individuals are more prone to trauma and younger skin possess greater tension where as older skin is less elastic and has more redundancy.

Development of keloid formation:

Keloid formation is found in most regions of the body where there is skin tension in all conceivable direction with greatest at relaxed skin tension lines (rdtl) which is referred to as Langers. They represent the lines of skin tension in rigor mortis in living person in supine position with extremities in extension where in collagen fibres follow the same direction as RSTL (McCarthy, 1990; Hunt *et al.*, 1978). Keloids and hypertrophic scars develop most often when the wound axis is at right angles to RSTL. If an incision is made parallel RSTL two forces develop

1. The distracting force of the wound which is in a longitudinal direction and
2. The force imposed by the lines of skin tension is in a transverse direction.

The arrangement of collagen fibres goes across the wound resulting in smaller and weaker scar formation perpendicular to RSTL, (Distracting force and the force of skin tensions are in the same direction). If an increased force is translated into a stimulus for increased inflammatory reaction and increased amount of collagen running in same direction leads to stronger and thicker scars (Cohen and Peacock, 1990). Increased occlusion of microvessels by endothelial cells proliferation and perivascular myofibroblast contraction may also contribute to increased microvascular occlusion significantly leading to hypoxia resulting in hypertropic scars and keloids.

Meenakshi *et al.*, (2005a) reported that keloids and HSC have collagen bundles that appear relaxed and are arranged in a random array which appear and aligned in the same plane as the epidermis. The collagen bundles are thicker and more abundant in keloids and form acellular node like structures in the deep dermal portion.

Several biochemical and molecular composition studies of keloids and HSC were carried out and illustrated keloid tissue showed high level of collagen, proteoglycan, water and HSC showed high pepsin soluble (Rghow, 1994; Needlec *et al.*, 1996). Ando and Jense (1993) illustrated that angiogenesis is stimulated by endothelial chemo attractants and mitogens which are released by mast cells, neutrophils, macrophages and kerotinocytes and within the wound bed EGF, TGF-b, vaccinia growth factor and IGF-1 showed enhancement (Kiristy and Lynch, 1993).

The release of TGF-b by platelets localizes it in the wound environment very soon after injury, where it acts as a chemo-attractant. The auto induction of TGF- b production by fibroblasts in the wound may contribute to fibrosis and wound contraction by increasing the production of collagen, fibronectin and proteoglycans (Bassols and Massague, 1988; Ignotz and Massague, 1986), decreasing the production by fibroblasts in the wound environment may contribute to fibrosis and wound contraction by increasing the production of tissue inhibition of matrix metalloproteinases (TIMP) I and II and a2 macroglobulin (Edward *et al.*, 1986). *In vivo* stimulation of granulation tissue formation and enhanced connective tissue response support the role of TGF- b in normal wound healing, however the prolonged and excessive presence of TGF-b contributes to the development of keloids and HSC (Ghahary *et al.*, 1998; Peltonen *et al.*, 1991).

Treatment

Silicone sheeting - Silicone sheeting is safe and effective in reducing existing scars and helping to prevent new scars in anyone age 3 and up.

Surgery – This procedure requires great care during and after the operation.

Keloids that return after being excised may be larger than the original. There is a 50% chance of recurrence after surgical removal. However, keloids are less likely to return if surgical removal is combined with other treatments.

Silicone Gel or silastic- This treatment is safe and painless, some are even helpful in alleviating the itching often associated with keloids.

Steroid injections- A series of injections with triamcinolone acetonide or another corticosteroid may reduce keloid size and irritation. The treatment area can become very painful as the anesthetic wears off.

Cryosurgery – It is an excellent treatment for keloids for small and lightly pigmented skin. It freezes the skin and causes sludging of the circulation beneath, effectively creating an area of localized frostbite.

Radiation therapy- Radiation treatments reduce scar formation if they are used soon after a surgery while the surgical wound is healing.

Laser therapy — This is an alternative to conventional surgery for keloid removal and it produces a superficial peel but often do not reduce the bulk of the keloid.

Wang *et al.* (2009) explored antimitotic drugs such as steroid injection 5 –FU, mitomycin C and bleomycin which targeted the fibroblasts in scar tissue and scar prevention after surgery. In the past, several drugs were in existence for the purpose of inhibiting collagen synthesis and to remove the excessive collagen deposition in the keloids and HSC which includes cross linking inhibitors, b– amino proprionitrile (BAPN) and penicillamine, the antimicrotubular agent colchicine and corticosteroids which has interference with protein synthesis (Pannu *et al.*, 1995). Meenakshi *et al.* (2005b) stated that keloid surgery followed by radiation was very effective and almost all cases treated did not show any reoccurrence.

The Therapeutic Management of hypertrophic scars and keloids includes occlusive dressings, cryotherapy, intralesional (Lahiri *et al.,* 2001) corticosteroid injections, compression therapy (Gailloud *et al.,* 1999) intralesional 5FU (Gupta and Karla, 2002; Nanda and Reddy, 2004) radiation therapy (Ragoowansi *et al.,* 2003) laser therapy (Connell and Harland, 2000; Kumar *et al.,* 2000) interferon therapy (Berman and Flores, 1997) Bleomycin taltooing has been used for the treatment of hypertrophic scars and keloids (Bodok *et al.,* 1996; Espana *et al.,* 2001).

Case reports:

Sanjiv *et al.* (2009) reported that 42 year old female patient had a vague history of skin lesions in the form of cotton threads buried under the skin, crusted plague, multiple keloids and rusted pin buried through the skin in the accessible areas of the body. She was reported to have multiple hyper pigmented keloid lesions and hypopigmented atrophic scars involving the abdomen in a bizarre pattern. She was been treated with 40mg of fluoxetine and 1mg of risperidone per day for 2 weeks and the Hamilton Depression Rating Scale Score (HDRS) was during admission and came down to11 after 2 weeks and then prescribed with anti depressed drugs after her discharge from the hospital.

Ahmed *et al.* (2009) identified 20 patients with keloids and classified them into two groups according to the different clinical treatment one with triaminolone acetomide (20 mg/ml) and other by cryotherapy spray technique. They were under observation for six sessions for period of one year, skin biopsies were taken before and after treatment. Histopathologic examinations revealed a remarkable resolution of the nodular arrangement of collagen in group I and no significant difference in cryotherapy treatment.

Zammer *et al.* (2009) investigated 5 keloid patients and compared with alveolar damage, bronchiolitis obliterans and reported that the proliferative activity in fibroblasts of diffuse alveolar damage was significantly higher than that of fibroblasts in skin scars. One hundred and thirty one keloid cases were studied out of which 61 males and 70 females between ages ranging between 14 and 66 years with an average of 34 years (Olaitan, 2009). One hundred and ten patients (83.97%) had swelling on the skin for more than two years, while 24 (18.32%) had swelling since childhood.

A 30 year old female was reported to have an enlarged scar at the posterior ear lobe due to excessive formation of collagen and it was removed by plastic surgery followed by single dose of radiotherapy by the surgeons of Essex country hospital. Forty five patients with hypertrophic scars or keloids were divided into two groups as Group A (23 patients) who were treated with bleomycin taltoo and Group B (22 patients) were treated with cryotherapy and triamcinolone injection. The patients were followed up for three months where in the therapeutic response was 88.3% ± 14% in Group A and 67.4 ± 22.5% in Group B (Fatemi *et al.*, 2005). On the basis of the above study, a few other reports also discussed about the efficacy of bleomycin in keloids and hypertrophic scars (Bodok *et al.*, 1996; Espana *et al.*, 2001) recommended bleomycin as appropriate treatment and economically suitable for all the patients.

A Hindu male child aged 6 years has been reported an out growth sized 3cmX1.5cm with clear sclera from limbus onwards who had a case history that the child suffered from chicken pox six months before the growth. A study was carried out with 20 Egyptian patients (10 females and 10 males) and the keloids were graded according to the size into three categories small (<5 cm), medium (5-15 cm) and large (>15 cm) [Shukla *et al.*, 1975). Twenty patients were randomly assigned into two groups as Group I who received intralesional triamcinolone acetonide (20mg/ml) and Group 2 received cryotherapy spray technique (with liquid nitrogen). The treated patients had significant difference in VEGF expression before and after therapy and the patients subjected to intralesional steroids showed better clinical response and less side – effects than cryotherapy.

Conclusion:

Keloids are being described as more cosmetic nuisance and they are symptomatic and have significant psychosocial burden for the patients. For centuries, keloids have been an enigma and management is seem to be difficult and frustrating both to the patient and the physician, since the mechanism underlying are only partially understood for nearly 1000 years old, and pathogenesis is yet to be determined. Keeping the above concepts in mind the present study paves the way to treat keloids using medically valuable herbs in mere future.

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