

## Review Article

# Keloids: clinical features and management.

## Part II

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**Abstract** Keloids are benign tumours of fibrous origin which clinically present as firm, flesh-coloured tumours. The exact etiology is not known; nevertheless, there are many associated dermatoses. Therapeutically, keloids are a challenging disease and no single effective therapy is available. The present review presents the clinical features and therapeutic update of this common malady.

**Key words**

Keloids, hypertrophic scars, clinical features, management.

### Introduction

Keloids and hypertrophic scars are common problems affecting 4.5% to 16% of the general population. Treatment for this skin problem is difficult. Multiple therapeutic modalities with variable success have been reported which include compression therapy, intralesional steroids, cryotherapy, surgical excision, radiation, interferons, 5-fluorouracil, bleomycin, silicon gel, UV-A<sub>1</sub> therapy, methotrexate, quercetin and laser therapy.<sup>1,2,3</sup> Many studies have used multiple treatments making it impossible to know which modality was most effective. Combination therapy underscores the importance of consistent regimens.<sup>4</sup>

### Management of keloids

*The first rule of keloid therapy is prevention<sup>1</sup>:*

- i. Avoid performing nonessential cosmetic

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surgery in patients known to develop keloids; however, do not consider patients who only have earlobe lesions.

- ii. Close all surgical wounds with minimal tension.
- iii. Incision should not cross joint spaces.
- iv. Avoid making mid-chest incisions and ensure that incisions follow skin creases whenever possible.

### **Treatment**

Different therapeutic regimens used are given as under.

#### *Dressings*

Silicone gel sheets, cream, ointment and silicone occlusive dressings have been used with varied success in the treatment of keloids. Mechanism by which these work remains unknown but some suggest that it may penetrate the skin whereas others have not found silicone within the stratum corneum.<sup>5,6</sup> There appears to be no changes in pressure, temperature and oxygen tension within the scar after treatment.<sup>5</sup>

In a study, hydration of skin was altered by the use of silicone gel sheets and evaporative water loss was one half that of normal skin. It is hypothesized that silicone sheet increases hydration of skin while reduces hyperemia and collagen synthesis in the dermis and scar hypertrophy.<sup>7</sup> Silicone ointment or gel, although more convenient to use, is less effective than silicone sheeting.<sup>6</sup> The optimal treatment time for application of the topical silicone gel sheeting has not yet been determined but different studies have shown that 12 weeks up to 12 months duration is useful.<sup>1</sup>

Non-silicone polyurethane hydroactive dressings, alone or as polytherapy, have also been used in the treatment of keloids. The success rate is variable.<sup>1</sup>

#### *Pressure therapy*

Pressure therapy has been used for hypertrophic scars since 1970's. It is effective primarily for scars which are active and of less than 6 months duration. Custom-made garments especially of elastic material with a high spandex content are advised for a year or until the scars matures. Garments should be changed every 6 to 8 weeks to maintain elasticity.<sup>8</sup> Subsequent experience by many therapists confirmed that pressure therapy is beneficial following surgical excision of keloids. To reduce recurrences, pressure must be maintained for a minimum of 4 to 6 months following surgery. Other proposed pressure devices include hard and soft cervical collars, spring pressure earring device or elastic ski-mask caps with face and ears exposed.

The speculative mechanism of action of pressure therapy involves thinning of dermis, reduction in edema and blood flow and consequent hypoxia. A hypoxic environment is hypothesized to

decrease collagen synthesis. A pressure of 25 mmHg is considered to be optimum for therapeutic results.<sup>9</sup> Drawbacks of compression therapy include its limited use in anatomic depressions, flexures, or areas of high movement, patient discomfort, occasional ulceration and hence poor patient compliance.

#### *Corticosteroids*

Intralesional corticosteroids are the mainstay of treatment in keloids, used either alone,<sup>1,2,3</sup> as an adjunct to cryosurgery<sup>10</sup> or surgical excision.<sup>11,12</sup> Various publications have reported successful treatment of a large number of keloids using intralesional triamcinolone acetonide. A broad range of recurrence rates has been reported in the follow up period.<sup>1</sup> It was found that most recurrences occurred within the first year.

Corticosteroids reduce excessive scarring by reducing collagen synthesis, altering glycosaminoglycan synthesis and reducing the production of inflammatory mediators and fibroblast proliferation during wound healing. They also enhance collagen degradation.<sup>11,12</sup> Most commonly used corticosteroid is triamcinolone acetonide (TAC) in concentration of 10 to 40 mg/ml administered intralesionally with a 25 to 27 gauge needle at 4 to 6 weeks interval till flattening of the lesion for a maximum of eight months.

Injection of triamcinolone acetonide suspension at a concentration of 10 to 40 mg/ml with luerlock control syringe or fixed-needle insulin syringe is necessary to prevent separation of the needle and syringe when injecting. To prevent clogging of the needle, 25 to 27 gauge needle should be used. The initial injection may require effort as dense untreated keloid is difficult to infiltrate. Intralesional therapy may be facilitated

by pressure jet apparatus or by cryosurgery prior to injection.<sup>1</sup> Corticosteroids are injected into the base of keloid every 4 to 6 weeks. TAC is preferred either without dilution or if the keloid is large enough when it is diluted with equal parts of 2% lidocaine. It does not relieve the initial pain of injection but does allow multiple injections with minimal discomfort and prevents postinjection pain.<sup>2</sup>

Sometimes, base of the keloid is so fibrotic that it is impossible to inject. In these cases, a needle is inserted into the keloid and triamcinolone acetonide suspension is injected into the needle tract as the needle is slowly withdrawn. The injected material is under great pressure which often leaks out. To prevent this, area around the needle site is painted with tincture of benzoin and covered with a piece of water-proof tape immediately after withdrawing the needle.

Care should be taken to inject only the base of the keloid or the lesion itself, not the surrounding tissue because injecting into surrounding areas may cause atrophy of normal tissue and cause the keloid to sink down to skin level but not flatten or become softer..

Complications e.g. infections, sloughing, hypo- and hyperpigmentation, atrophy of surrounding skin, telangiectasia, necrosis, ulceration, hemorrhage may follow intralesional steroid therapy.<sup>1,2</sup>

### *Cryosurgery*

This therapeutic modality makes use of local freezing for controlled destruction or removal of living tissues. The first true cryosurgery was performed in the late nineteenth century by a dermatologist Campbell White who used solid CO<sub>2</sub>.<sup>13</sup> Modern apparatus was developed by a

neurosurgeon, Irving Cooper in 1961.<sup>14</sup> A number of cryogens are available e.g. ethyl chloride, carbon dioxide (CO<sub>2</sub>), nitrous oxide (NO) and liquid nitrogen etc. Liquid nitrogen with a boiling point of -196°C is the most widely used. Cryogens can be delivered to the tissues in various ways e.g. cryoprobes and open spray nozzles of variable sizes with which a very fine control can be achieved. The spray is emitted from a distance of 1 to 2 cm from the target site and at a 90 degree angle to it.

Mechanisms for cellular injury include intracellular and extracellular ice formation, osmolar changes, vascular stasis, thermal shock denaturation of lipoprotein complexes and cold-induced immune recognition of remaining viral or tumor cells. These changes are dependent on several factors e.g. rate of temperature fall and rate of rewarming, solute concentration, length of time the cells are exposed to a below-freezing temperature from 0 to -50°C range and the coldest temperature reached in the target tissue.<sup>13,14</sup>

Different cells and tissues demonstrate a range of sensitivity to freezing. Rapidly growing cells, nerve cells and melanocytes are the most sensitive. Fibroblast and stromal structures are less sensitive which may be an important factor for the lack of scarring following superficial procedures. Adequate freezing in both horizontal and vertical dimensions is required for effective treatment. Depth of freeze can be gauged by an experienced operator based on the surface area of ice formation.

It is necessary to determine the amount and depth of tissue to be frozen.<sup>14</sup> The progress of freezing can be judged by the duration of freezing (freeze time), thawing of the lesion

(thaw time) and measurement of ice ball beyond the target area (lateral spread of freeze).

Cryosurgery has advantages that make it strongly competitive with other techniques.<sup>14</sup> These include:

1. Simple and safe office procedure.
2. Low cost
3. General anesthesia not required.
4. Local anesthesia optional.
5. Operative suit not required.
6. No restriction of work or sports.
7. Multiple lesions can be treated simultaneously.
8. Useful in pregnancy.
9. Minimum scarring with good cosmetic results.
10. Suitable for patients who are fearful of undergoing surgery.
11. Chances of recurrence relatively less as compared to other modalities.

Disadvantages of cryosurgery are:

1. Immediate postoperative edema and discomfort.
2. Cryo wound oozing which requires dressing for 1 to 2 weeks.
3. Permanent hypo-or depigmentation can be disfiguring.
4. Complete healing is slow to occur.
5. It can recur and long-term follow up is required.

Complications of cryotherapy may be classified as temporary or permanent.<sup>13,14,15</sup>

- Temporary complications include edema or pain during or immediately after treatment, headache, syncope, febrile reaction, vesicles, bullae, weeping, infection, delayed bleeding,

milia, pyogenic granuloma, hypertrophic scarring, hyperpigmentation or neuropathy or anesthesia.

- Permanent complications are hypopigmentation, retraction of tissues (lips, eyebrows and alae nasi), neuropathy, ulceration, tendon rupture, alopecia, ectropion, scarring, tissue defect.

Cryotherapy should not be done in conditions like agammaglobulinaemia, cold intolerance, cold urticaria, cryoglobulinaemia, cryofibrinogenaemia, Raynaud's disease, collagen vascular disease, multiple myeloma, concurrent treatment with immunosuppressives, renal dialysis, and absence of an accurate diagnosis.

#### *Surgical excision*

Excision followed by radiation therapy is a useful and effective method of keloid eradication. It alone has a high recurrence rate<sup>16</sup> and has now been relegated to non-surgical therapy. Most surgeons combine excision with adjuvant therapy such as steroid, X-ray or compression therapy which inhibit postoperative fibroplasia.<sup>17</sup> Excision followed by only skin grafting had a 59% recurrence rate. To avoid keloid formation at donor site, epithelium overlying the keloid has been used as skin graft. Care must be taken to avoid undue tissue damage at the time of excision. The recurrence rate may be enhanced by foreign material, hematoma, tissue necrosis, wound dead space, infections and wound tension. Increased tension may stimulate fibroplasia.

Most surgeons do procedures such as Z-plasty or flap repair to relieve wound tension.<sup>18</sup> Decreased recurrence rates have been reported

with excision in combination with other modalities like radiotherapy, injected interferon and corticosteroids.<sup>19</sup>

#### *Radiation therapy*

Radiation in the early post-operative period is efficacious in preventing keloid formation. X-ray treatment to prevent keloid recurrence in a dose of 250 rads, is given immediately after surgery followed by four more treatments at weekly interval.<sup>20</sup> Superficial X-ray therapy is used with or without surgery depending upon the keloidal site.<sup>21</sup> In those who received 400 rads of superficial X-ray monthly in a single dose for five or less treatments, disappearance of symptoms and keloid regression were noted in 76.5% of treated patients.<sup>22</sup> No ill-effects of radiation were observed during the second year period following completion of treatment. Continued use of radiation therapy remains controversial due to unfortunate sequelae of its extensive use in past years.

Excellent data support that ionizing radiation should not be used for a condition less serious than neoplasia. Radiation in any form is not considered for patients of keloid.<sup>1</sup>

The use of 1,500 to 1,800 rads of superficial X-ray delivered postoperatively in 5 to 6 fractions over 12 to 14 days prevents keloid recurrence.<sup>20</sup> Pigmentary changes in irradiated sites are noted in few patients.

Other forms of radiation such as electron beam and interstitial radiotherapy have been utilized in the treatment of keloid. Electron beam therapy can be given alone (1,000 to 3000 rads) or post-operatively after keloidectomy.<sup>23</sup>

In interstitial radiotherapy, post-operative radiation is delivered to the base of the sutured edges of a keloid scar. At the time of surgery, a thin plastic tube is placed into the surgical defect between cuticular and subcutaneous sutures. The ends of the tube emerge either at the ends of the scar or few millimeters beyond them. Then a radioactive iridium 192 wire is inserted into the plastic tube and remains in place for necessary time calculated for a dose of 2,000 rads to be delivered at a point 2 to 5 mm from the axis of wire opposite to its midpoint.<sup>23</sup>

#### *Laser therapy*

Ablation of keloid and hypertrophic scar using a carbon dioxide laser with an emission wavelength of (10,600 nm) in the infrared part of the electromagnetic spectrum can cut and cauterize the lesion creating a dry surgical environment with minimal tissue trauma.<sup>24</sup> When used as a single modality, the carbon dioxide laser is associated with 39% to 93% recurrence rates and when combined with postoperative injected steroid then this figure stands at 25% to 74%.<sup>25</sup> Carbon dioxide laser excision of keloidal scars is not practiced widely nowadays.

The argon laser (488 nm), similar to the carbon dioxide laser, can induce collagen shrinkage through generation of excessive localized heat. It is associated with 45% to 93% recurrence rates.<sup>25</sup>

The pulsed dye laser (585 nm) causes microvascular thrombosis. The scars become less erythematous, more pliable and less hypertrophic after treatment with the 585 nm pulsed dye laser. The findings were confirmed using objective measurements of erythema by reflectance spectrometry readings, scar height

and pliability measurements. It remains the laser treatment of choice for hypertrophic scars because of its efficacy, safety and relatively low cost.<sup>27</sup>

Nd:YAG laser (1064 nm) has been used for the treatment of keloid but has demonstrated 53% to 100% recurrence rates.<sup>6</sup>

#### *UVA1 therapy*<sup>28</sup>

Recently, UVA1 (340 to 400 nm) has been used in the treatment of keloid and other conditions like atopic dermatitis, morphea and scleroderma.

UVA1 stimulates collagenase enzyme production by fibroblasts. Its advantages include deep penetration into the skin which allows treatment of deeper tissues and less DNA absorption than that occurs with shorter, more erythemogenic UV radiation which results in decreased risk of burns and cancer formation. It can cause transient hyperpigmentation of the skin immediately surrounding the irradiated field.

Improvement in keloid is evident as early as the third week of UVA1 treatment and after six weeks, marked softening and flattening were noted by both dermatologists and patients. If this treatment proves to be effective on larger scale controlled study, then it will be of great help to patients with large scars such as burn scars for whom surgical remodeling or intralesional corticosteroid injection can be difficult.

It remains to be seen whether the combination of UVA1 with other treatment modalities e.g. intralesional injections of corticosteroids or surgical intervention will offer further benefits.

#### *5-Fluorouracil*<sup>29</sup>

It is a pyrimidine antimetabolite that resembles uracil, with a fluorine atom substituted for the 5-methyl group.

5-Fluorouracil (5-FU) inhibits thymidylate synthetase enzyme activity, interfering with the synthesis of deoxyribonucleic acid and ribonucleic acid. These effects are more marked in atypical, rapidly proliferating cells. Cytotoxicity of 5-FU is due to its effects on both DNA and RNA.

Keloidal scars are treated with intralesional 5-fluorouracil (5FU) more than 5000 units at intervals ranging from 2 to 3 injections per week every 2 to 3 weeks. A cream in a concentration of 1% to 5% applied twice a day for 1 to 4 weeks can be used to treat areas of skin that have a large number of keratoses including keloids. A pronounced inflammatory reaction develops which can be reduced by using topical steroids. Treatment may be repeated at a later date if any lesion persists after the inflammatory phase has regressed.

The reaction can be largely avoided if 5-fluorouracil is applied weekly over a prolonged period. The results are excellent. Response is less impressive on the hands and forearms than on the face and scalp. Addition of keratolytics or topical vitamin A acid may be of value in this situation. 5-FU may also be given in combination with cryotherapy.

Adverse effects of local 5-FU include pain, pruritus, burning sensation, tenderness and post-inflammatory hyperpigmentation.

### *Bleomycin*<sup>30</sup>

It is an antineoplastic antibiotic produced by *Streptomyces verticillus*. It appears to act through binding to DNA which results in single and double strand breaks following free radical formation and inhibition of DNA synthesis. The fragmentation of DNA seems to be due to oxidation of a DNA bleomycin-Fe II complex and leads to chromosomal aberrations.

Doses of bleomycin are given in units or in milligrams. One milligram contains 1.5 to 2 units. Injections are very painful and preceding local anesthesia should be considered. Between 2 to 5 treatments are required at 1 to 4 months intervals. Total dosage is 15 mg.

Adverse effects of bleomycin therapy include lethal anaphylactoid reaction, high incidence of fever with or without chills (fever may result in dehydration and hypotension), anorexia, blister formation, hyperkeratosis of the palms, pulmonary fibrosis in old patients, nail loss or dystrophy following periungual injection, Raynaud's phenomenon in treated fingers, and local urticaria.

### *Methotrexate*<sup>31</sup>

Being a folic acid antagonist, it is a potent inhibitor of enzyme dihydrofolate reductase and thus inhibits the formation of dihydrofolate and tetrahydrofolate from folic acid. Tetrahydrofolic acid is the precursor of N-methylene tetrahydrofolic acid which is necessary in the conversion of deoxyuridic to thymidilic acid.

It inhibits synthesis of DNA by competitive inhibition of dihydrofolate reductase, an antimetabolic action on epidermis. It also inhibits

neutrophil chemotaxis and inflammation caused by C<sub>5a</sub>.

For the treatment of keloids, oral or parenteral methotrexate is given a week prior to surgery and continued for 4 months in a single dose of 15 to 20 mg repeated at 4-day intervals.

Methotrexate is contraindicated in anemia, thrombocytopenia, acute infection, leucopenia, peptic ulceration, ulcerative colitis, alcoholism and immunodeficiency.

Major side effects include myelosuppression, hepatotoxicity, mucocutaneous and gastrointestinal effects.

### *Retinoic acid*<sup>32</sup>

Also known as tretinoin, it is the acid form of vitamin A. It has several effects on epithelial tissues. It stabilizes lysosomes, increases ribonucleic acid polymerase activity, increases prostaglandin E<sub>2</sub>, cAMP and cGMP levels and increases the incorporation of thymidine into DNA. It is insoluble in water but soluble in many organic solvents. It is susceptible to oxidation and ester formation when exposed to light. When applied topically it remains in the epidermis, only less than 10% is absorbed into the circulation which is metabolized by the liver and excreted in bile and urine.

Retinoic acid 0.05% solution is used in the treatment of keloids and hypertrophic scars which is applied daily for about 3 to 22 months which reduces the bulk of keloid and diminishes pruritus. Most common adverse effects of topical retinoic acid are erythema and dryness.

### *Interferon therapy*<sup>33</sup>

Recently, intralesional interferons have been used in the treatment of keloids and hypertrophic scars. In various studies, it has been demonstrated that interferon- $\alpha$ , interferon- $\beta$  and interferon- $\gamma$  reduce keloidal fibroblast production of collagen I, III and VI which results in decreased levels of cellular messenger RNA.

Interferon- $\alpha$  and - $\beta$  also reduce fibroblast production of glycosaminoglycans which forms the scaffolding for deposition of dermal collagen and interferon- $\gamma$  enhances glycosaminoglycans production. Interferon- $\alpha$ , - $\beta$ , and - $\gamma$  all increase collagenase enzyme activity. Interferon- $\gamma$  also modulates p53 apoptotic pathway by inducing apoptosis related genes. p53 is a protein synthesized as a result of DNA damage. Once damage is repaired, p53 protein is degraded. Mutations in this protein cause cells to proliferate which results into keloid formation. p53 is also a potent suppresser of interleukin-6 which is implicated in hyperproliferative and fibrotic conditions.

Interferon injected into suture line of keloid excision sites may reduce recurrence prophylactically. Recurrence of few keloids after postoperative treatment using interferon  $\alpha$ -2 in a total dose of 5 million units (one million units injected per centimeter of scar into keloid excision sites) was 18% whereas in excision alone it was 51.1% and at triamcinolone acetonide treated sites it was 58.4%. The common complications of interferon- $\alpha$  to be therapy include flu- like symptoms of headache, fever and myalgias.

### *Imiquimod*<sup>34</sup>

Recently, 5% imiquimod cream topically has been used in keloid therapy. Imiquimod is an immune response modifier capable of inducing interferon- $\alpha$ , tumor necrosis factor- $\alpha$  and interleukins-1, 6 and 8. It was applied over the excisional suture line for 2 months. Patients were examined at weeks 4, 8, 16 and 28 for local erythema, erosions, pigment alteration and recurrence of keloid. Eleven of the keloids evaluated at 24 weeks, none recurred.

### *Quercetin in the treatment of keloids*<sup>35</sup>

Quercetin, rutin and rubinin are flavonoid glycones found in diet. The richest sources of quercetin are onions, apples and red wine. It is also identified as an active ingredient of medicinal plants.

It has a wide range of biological activities. It inhibits sodium-potassium ATPase, protein kinase C, tyrosine kinase and human immunodeficiency virus reverse transcriptase enzymes. It is also a potent inhibitor of enzymes involved in the proliferation of signalling pathways including phosphatidylinositol-3-kinase (PI-3K) and 1-phosphatidylinositol-4 kinase. It also causes the cell cycle arrest and apoptosis.

Insulin-like growth factor-I (IGF-I) and II are potent mitogens and inhibitors of apoptosis for cell types. Insulin growth factor-I stimulates fibroblast proliferation and enhances collagen synthesis. Both insulin growth factor-I and II bind to type I insulin growth factor receptor (IGF-I-R). Insulin growth factor (IGF)/insulin growth factor receptor (IGF-I-R) signal mediates the invasiveness of keloid fibroblasts (KF). Insulin growth binding activates insulin growth

factor- IR which then phosphorylates phosphatidylinositol-3K (PI-3K) and Ras/Raf/Mitogen activated protein kinase (MAPK) which play important roles in IGF-I-R induced cellular proliferation and the inhibition of apoptosis. IFGs also bind with high affinity to specific IGF binding proteins which modulate activity.

Treatment of keloid fibroblasts with quercetin leads to growth inhibition. The key proteins involved in IGF signal cascades and their basal phosphorylation and collagen are inhibited by it. Quercetin blocks collagen expression by KF through its ability to inhibit the expression of several key proteins in the IGF signalling pathway such as AKT-I, MAPK, C-Raf and EIK-I.

Quercetin is used in concentrations from 10 to 50 micrograms/ml.

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