

# Keloids and Hypertrophic Scars Can Now Be Cured Completely: Recent Progress in Our Understanding of the Pathogenesis of Keloids and Hypertrophic Scars and the Most Promising Current Therapeutic Strategy

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Keloids and hypertrophic scars are fibroproliferative disorders of the skin that are caused by abnormal healing of injured or irritated skin. It is possible that they are both manifestations of the same fibroproliferative skin disorder and just differ in terms of the intensity and duration of inflammation. These features may in turn be influenced by genetic, systemic, and local risk factors. Genetic factors may include single nucleotide polymorphisms, while systemic factors may include hypertension, pregnancy, hormones, and cytokines. The most important local factor is tension on the scar. Over the past 10 years, our understanding of the pathogenesis of keloids and hypertrophic scars has improved markedly. As a result, these previously intractable scars are now regarded as being treatable. There are many therapeutic options, including surgery, radiation, corticosteroids, 5-fluorouracil, cryotherapy, laser therapy, anti-allergy agents, anti-inflammatory agents, bleaching creams and make-up therapies. However, at present, we believe that the following combination of three therapies most reliably achieves a complete cure: surgery, followed by radiation and the use of steroid tape/plaster.

(J Nippon Med Sch 2016; 83: 46–53)

**Key words:** keloid, hypertrophic scar, radiation, steroid, steroid tape

## Introduction

Keloids and hypertrophic scars are fibroproliferative disorders of the skin that are caused by abnormal healing of injured or irritated skin<sup>1</sup>. Common causes of injury and irritation are trauma, burn, surgery, vaccination, skin piercing, acne, and herpes zoster. The scars are red and elevated, and have an unappealing appearance. Moreover, they associate with intermittent pain, persistent itching, and a sensation of contraction. Some keloids can discharge due to the presence of infected inclusion cysts that arise because the follicles are obliterated by the scars. The inflammation in the scars is continuous and local, being mainly found in the reticular layer of the dermis of the skin<sup>2</sup>. In this reticular layer, there is also accelerated angiogenesis and collagen accumulation. These features suggest that the cause of keloids and hypertrophic scars is an aberrant wound healing process in the damaged reticular layer of the dermis. This implies

that more superficial damage would not elicit keloids and hypertrophic scars. Indeed, a clinical study on human volunteers showed that cutaneous injury must reach the reticular layer before it results in inflammatory scar formation<sup>3</sup>.

Many classical textbooks consider keloids and hypertrophic scars to be completely different types of scar. Clinicians define hypertrophic scars as scars that do not grow beyond the boundaries of the original wound, whereas keloids are defined as scars that spread into the surrounding normal skin. By contrast, pathologists make a histological distinction between keloids and hypertrophic scars on the basis of thick eosinophilic (hyalinizing) collagen bundles called “keloidal collagen”: these are present in the former scar type but fewer in the latter. However, there are many cases in which the scar bears the growth and histological features of both hypertrophic scars and keloids<sup>4</sup>. Indeed, it is possible that hypertrophic

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scars and keloids are manifestations of the same fibroproliferative skin disorder<sup>4</sup> and just differ in the intensity and duration of inflammation. These features may in turn be influenced by genetic, systemic, and local risk factors<sup>2</sup>.

#### **Pathogenesis of Keloids and Hypertrophic Scars**

A number of genetic, systemic, and local factors that influence the characteristics and quantity of keloids and hypertrophic scars have been identified. The genetic causes of pathological scar development may involve single nucleotide polymorphisms (SNPs): a genome-wide association study<sup>5</sup> showed that four SNP loci in three chromosomal regions associate significantly with keloid development in the Japanese population. Moreover, our study showed that one SNP associates with the clinical severity of keloids<sup>6</sup>. There are probably many other genetic factors that have not yet been identified.

In terms of systemic factors, adolescence and pregnancy appear to associate with a higher risk of developing pathological scars<sup>7</sup>. It may be that sex hormones such as estrogens and androgens have vasodilatory effects<sup>8</sup> that intensify inflammation, thereby worsening keloids and hypertrophic scars. This is supported by our unpublished data, which suggest that the incidence of keloids that are not caused by trauma suddenly increases at around 10 years of age. This implies that the increases in sex steroid levels at the start of adolescence, not a higher likelihood of trauma, are responsible for the greater risk of pathological scar development in adolescents. Moreover, our recent study showed that hypertension associates with the development of severe keloids<sup>9,10</sup>. This association may reflect the fact that hypertension damages blood vessels, thereby increasing inflammation in scar tissue<sup>9,10</sup>.

Of the many factors that contribute to pathological scar development, however, we believe that local mechanical forces play a particularly important role<sup>11-13</sup>. Several lines of evidence support this notion. First, keloids commonly adopt distinct site-specific shapes, namely, the typical butterfly, crab's claw, and dumbbell shapes on the shoulder, anterior chest, and upper arm, respectively. This, together with our visual analysis using the finite element method, suggests that keloids are largely determined by the direction of the tension that is applied to the skin around the wound site<sup>13</sup>. Second, keloids show a marked preference for particular locations on the body: they usually occur at sites that are constantly or frequently subjected to tension (such as the anterior chest and scapular

regions) but seldom in areas where stretching/contraction of the skin is rare (such as the parietal region or anterior lower leg). This is true even for patients with multiple/large keloids. Moreover, keloids are rare on the upper eyelid. This reflects the fact that eyelid skin is always relaxed regardless of whether the eyes are open or closed. An exception may be earlobe keloids: the contribution of mechanical factors to the development of these keloids may be minor (although friction from the pillow and the weight of the keloid itself can increase the risk of keloid development and progression). The most likely local cause of these keloids is the repeated attaching and detaching of the piercing, which may lead to repeated injury and infection. Both are triggers of inflammation.

At present, physicians cannot (or at least find it very difficult to) control genetic and systemic factors. However, they can reduce the mechanical forces around keloids and hypertrophic scars by using various surgical techniques (including z-plasties). Moreover, anti-inflammatory treatments such as corticosteroids or anti-angiogenesis agents (which reduce the number of blood vessels) are viable clinical strategies for the treatment of these scars.

#### **Prevention of Keloids and Hypertrophic Scars**

A burn wound that heals in less than 10 days has a 4% risk of developing into a hypertrophic scar, whereas a burn wound that takes 21 days or more to heal has a 70% or greater risk of developing into a hypertrophic scar<sup>14</sup>. This means that a deep skin injury that extends to the reticular layer of dermis needs time to heal; however, if inflammation continues for a long period, then the risk of developing a pathological scar increases. Histopathological examination of pathological scars reveals that the epidermis and papillary layer of the dermis are almost normal apart from minor inflammation, but the reticular layer shows strong inflammation with more blood vessels and greater collagen accumulation<sup>24</sup>. Thus, to prevent the formation of pathological scars, it is essential to ensure speedy wound healing. Since keloids can arise from very small injuries or from irritated skin (*e.g.*, acne, herpes zoster, insect bites, and skin injections), special care should be taken to ensure fast healing of such small wounds when treating patients with a history of keloids.

Since stretching wounds can evoke inflammation of the dermis, wounds should be stabilized as soon as the exudate from the wound surface has stopped. The wound healing of the epidermis and dermis differ completely. In the case of sutured wounds, the epidermis can regenerate

within 7–10 days, leading both the patient and the physician to believe that the wound has healed completely. In fact, it may take 3 months before the dermis recovers more than 90% of its normal strength. Thus, prolonged external mechanical support using tapes, sheets, and/or garments is recommended for scar prevention. This is supported by our study, which showed that silicone gel sheets reduce the tension on the wound site<sup>15</sup>.

Silicone tape is better than paper tape as it prevents the epidermal injury caused by repeated taping<sup>16</sup>. Moreover, silicone tape keeps the scar surface moist. These tapes can be kept in place until they detach naturally. The patient does not need to change the tape after taking a bath/shower. In our experience, patients generally keep silicone tape in place for about 1–2 weeks. The exception is in summer: perspiration can reduce tape adherence.

If a patient has a clear history of pathological scars, then stabilization tapes should be exchanged for steroid plaster/tape about 1 month after epithelization has occurred. Steroid tape has been used to decrease inflammation of keloids; this practice is particularly common in Japan and several other countries<sup>17</sup>. Flurandrenolide tape (Cordran<sup>®</sup> tape), fludrocortide tape (Drenison<sup>®</sup> tape), and deprodone propionate tape (Eclar<sup>®</sup> plaster) are available worldwide. These steroid tapes/plasters should be changed every 24–48 hours and should be cut so that they just cover the wound, with minimal attachment (if any) to healthy skin (unpublished data). Since these tapes differ in terms of the strength of the steroid, the most appropriate tape/plaster should be selected on a case-by-case basis.

### Treatment of Keloids and Hypertrophic Scars

Over the past 10 years, our understanding of the pathogenesis of keloids and hypertrophic scars has increased markedly<sup>18</sup>. As a result, keloids and hypertrophic scars are now regarded as treatable diseases. At present, there are many therapeutic options available, including surgery, radiation, corticosteroids, 5-fluorouracil, cryotherapy, laser therapy, and make-up therapies. However, at present, we believe that the most reliable approach is a combination of three therapies, namely, surgery followed by radiation and steroid tape/plaster.

#### A. Surgery

Surgical treatment itself can result in the recurrence of keloids and hypertrophic scars, which are then often much bigger than the original lesions. Thus, unless the scar is a minor hypertrophic scar, the decision to surgically remove a pathological scar should be made very

carefully. To reduce the risk of recurrence, it is also advisable to use particular surgical techniques, namely, subcutaneous/fascial tensile reduction sutures, z-plasties, and local flap transfer.

The usefulness of subcutaneous/fascial tensile reduction sutures reflects the fact that keloids and hypertrophic scars arise from the dermis<sup>12</sup>. Dermal sutures do not effectively reduce tension on the dermis: to achieve this, we must access much deeper structures, namely, the superficial and deep fascia, and suture them. This type of suturing will elevate the wound edges smoothly while placing minimal tension on the dermis. In other words, the wound edges naturally attach to each. Only then should dermal and superficial sutures be used. It is very important to realize that dermal sutures on their own cannot reduce the tension on the dermis: this concept is the key to preventing the formation of pathological scars after surgery.

Zig-zag sutures, including z-plasties, are good for releasing linear scar contractures and tensions. A major benefit of z-plasties is that segmented scars mature faster than long linear scars. In particular, if a scar crosses a joint, zig-zag incision and suturing significantly reduces the risk of developing pathological scars.

Various local flaps are also useful for releasing scar contractures. Moreover, because local flaps expand naturally after surgery, they are not prone to postsurgical contractures. By contrast, skin grafts do not expand, which means that skin grafting tends to generate secondary contractures that result in circular pathological scars around the grafted skin. Thus, flap surgery is better for keloids. In the past, keloid reconstruction with flaps was discouraged because it was thought that the donor site could itself develop keloids. However, such donor-site keloid development can be prevented by multimodal therapy, including tension-reduction sutures and radiation therapy. This means that, especially for severe keloids, flap surgery is a highly suitable approach (Fig. 1).

#### B. Radiation

As mentioned above, the main problem of surgery for pathological scars is recurrence. However, recurrence can be controlled by using ever-improving radiation technology. In the past, superficial or orthovoltage X-rays (photons) were used<sup>19,20</sup>. However, since the safety and efficacy of radiation therapy have improved markedly in recent years, radiation is now used routinely as a highly effective postoperative adjuvant therapy. As a result, keloids can be treated with high dose rate-superficial



Fig. 1 A severe keloid case (a 63-year-old male) who was treated by flap surgery and postoperative radiation.

- a. Preoperative view.
- b. Removal of the axillary keloid and the flap design on the dorsum.
- c. Flap elevation.
- d. Immediately after surgery (recipient site).
- e. Immediately after surgery (flap donor site).
- f. Design of the second surgery
- g. Intraoperative view during the second operation.
- h. Immediately after the second operation.
- i. 1 year after the second operation.

This patient had severe keloids and diabetes mellitus. His ulcers and keloids were removed twice by surgery and postoperative radiation was performed. Both donor and recipient sites were irradiated. The movement of his left shoulder recovered completely after the treatment and none of the keloids recurred. The remaining keloids are being treated by applying steroid plasters.

brachytherapy (HDR-SB)<sup>21,22</sup>, as well as electron beam irradiation<sup>23-25</sup>. Depending on the shape of the surgical scar, an HDR-SB applicator can be used to ensure both the evenness and appropriate localization of the radiation to

the wound surface.

Our review of the literature revealed that to ensure maximum efficacy and safety, postoperative radiation for keloids in adults should involve the application of 10-20

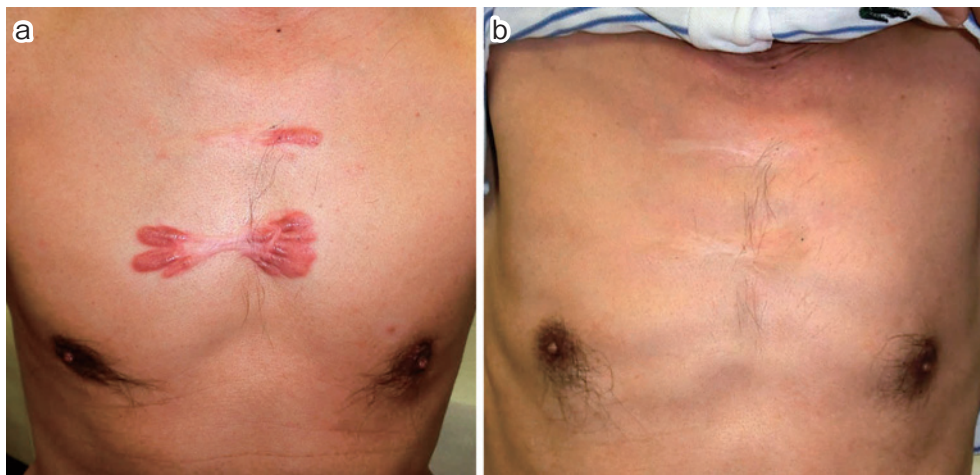


Fig. 2 A mild keloid case (a 67-year-old male) who was treated by radiation monotherapy.  
**a.** Pretreatment view.

**b.** 18 months post-treatment.

This patient had a mild chest wall keloid and was treated by high dose rate-superficial brachytherapy. A total of 25 Gy was administered in five fractions over 5 days. The inflammation resolved completely. After 1 year of treatment, both the subjective and objective symptoms had improved dramatically.

Gy *via* daily fractions of 5 Gy<sup>26</sup>. Use of the linear-quadratic model to calculate the biologically effective doses (BEDs) for various radiation regimens for keloid therapy showed that when the BED exceeds 30 Gy, the recurrence rate is less than 10%, although  $\alpha/\beta$  ratio of keloid has been considered as 10 but may have other possibilities. Moreover, the risk of secondary carcinogenesis is reduced when the BED is 30 Gy or less. Therefore, we propose that the maximum dose of postoperative radiation therapy for keloids is a BED of 30 Gy. A BED of 30 Gy can be obtained in several ways: a single fraction dose of 13 Gy, two fractions of 8 Gy, three fractions of 6 Gy, or four fractions of 5 Gy. In addition, recommended site-dependent dose protocols for the treatment of keloids are as follows: 20 Gy in four fractions over 4 days (BED=30 Gy) for the anterior chest wall, shoulder-scapular region, and suprapubic region; 10 Gy in two fractions over 2 days for the ear lobe (BED=15 Gy); and 15 Gy in three fractions over 3 days for other sites (BED=22.5 Gy).

It has been reported that of 10,000 individuals between 18 and 64 years of age who are subjected to whole body irradiation composed of 1 Gy, 670 (6.7%) will acquire skin cancer<sup>27</sup>. In general, skin cancer kills one in 500 patients. Thus, the mortality rate associated with 1 Gy of whole body irradiation would be  $6.7\% \times 1/500 = 0.0134\%$ ; namely, one in 7,500 people. If this reasoning is applied to earlobe keloid radiotherapy, where 0.05% of whole body skin is irradiated with 10 Gy, the incidence

of skin cancer associated with this treatment would be  $6.7 \times 10 \times 0.05/100 = 0.0335\%$ , namely, one in 3,000 people. The mortality rate of secondary carcinogenesis of earlobe keloid treatment would be  $0.0335/500 = 0.000067\%$ , namely, one in 1,500,000 people. We believe that this risk is clinically acceptable if informed consent is obtained from the patients after they have been advised of the benefits and side effects of this type of treatment.

We have used primary radiation (radiation monotherapy) to treat older patients or patients with severe huge keloids (Fig. 2). The total radiation dose in these cases is higher than that used for postoperative radiation. In such cases, it is necessary to apply the radiation carefully to prevent secondary radiation carcinogenesis. It is also important to obtain informed consent. However, the risks of primary radiation therapy should be weighed against its tremendous benefits: it causes subjective symptoms such as pain and itching to decrease immediately. Moreover, over the following year, it causes the color and thickness of the scars to progressively normalize.

### C. Corticosteroid Tapes/Plasters

Corticosteroid injections rapidly reduce the volume of a scar<sup>28</sup>. However, the downsides of corticosteroid injections include pain (caused by the injection itself) and difficulties associated with contraindications such as pregnancy, glaucoma, or Cushing's disease. In our experience, to prevent menstrual irregularities, the maximum dose of

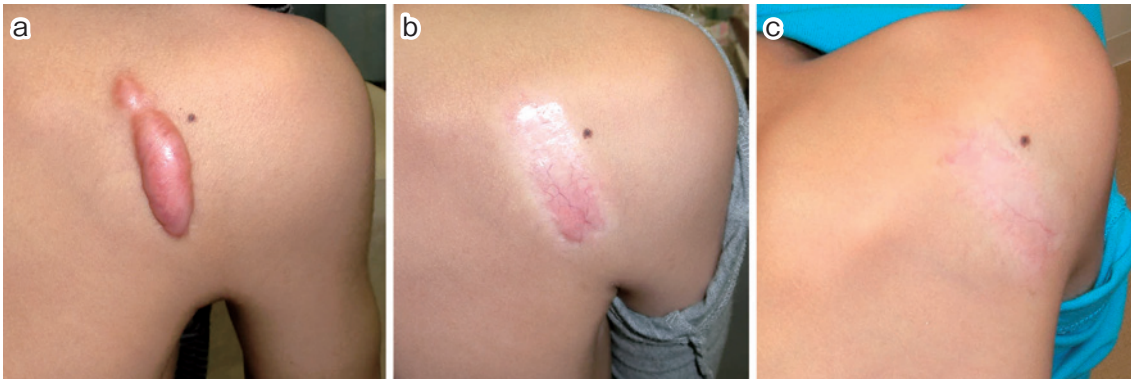


Fig. 3 A mild keloid case (a 9-year-old boy) who was treated by steroid tape.

a. Pretreatment view.

b. After 16 months of treatment.

c. After 26 months of treatment.

This patient had a mild right scapular keloid and was treated by fludrocortide tape (Drenison® tape). The tape was placed on the keloid 24 hours a day and was changed daily. The inflammation resolved completely. After 26 months of treatment, both the subjective and objective symptoms of the patient had improved dramatically.

triamcinolone should be 5 mg per session. This is actually a very small dose compared to the doses used in other reports. This dose also does not cause hypopigmentation or skin atrophy, and effectively reduces the thickness of pathological scars if the area to be treated at each intervention is small. Lidocaine (1%) can be used to dilute the triamcinolone if used over a wide area. A narrow needle (30 Gauge) and warming the solution can help to reduce the pain associated with the injection. Moreover, the injection should be placed into the edge between the scar and normal skin: if the injection is performed in the scar, the thick tissue hampers the infiltration of the steroid solution. This in turn results in increasing pressure in the wound during the injection, which causes severe pain. When these tips are used, the patients can generally tolerate monthly steroid injections for a few months, even a year. However, this is generally not long enough to achieve a complete cure. Thus, steroid injections may be less promising than other methods in terms of curative ability.

This problem can be overcome by using steroid tapes/plasters. Adults between the ages of 18 and 64 years can be treated with a combination of steroid injections and treatment with these tapes/plasters: once the entire thickness of a pathological scar has been reduced by several steroid injections, this effect can be maintained and augmented by using steroid tapes/plasters that the patients can apply themselves. Most pediatric and older patients can be treated by steroid tapes/plaster alone because they have much thinner skin, which means that the ster-

oids are easily absorbed. This is particularly important in relation to the pediatric cases because children are more sensitive to radiation than adults. This reflects the fact that their cells are actively dividing at a greater rate. Moreover, because they are young, the effects of radiation-induced damage may have more time to manifest themselves. Thus, radiation therapy is contraindicated in pediatric patients (less than 18 years of age). This means that, in most cases, surgery is also not indicated because surgery alone associates with a high rate of keloid recurrence. Children are also more responsive to steroid tapes/plasters. Thus, steroid tapes/plasters are a reasonable first-line therapy for keloids and hypertrophic scars in all children (Fig. 3) as well as for minor keloids in adults.

Interestingly, in our experience, contact dermatitis (which is common among adult patients who use tapes) does not tend to occur in children. This may also reflect the fact that children have thinner skin through which the steroid is easily absorbed and/or the smaller sebum secretion in children.

#### Follow-up of Keloids and Hypertrophic Scars

It is important that sequentially-treated keloid and hypertrophic scar patients are followed up over the long-term and that they are appropriately educated about scar management. If patients develop pathological scars in the first place, it suggests that they may be particularly prone to recurrence or the development of new pathological scars in response to minor stimulation. Thus,

these patients should be educated in the self-management of their wounds. In particular, they should be encouraged to apply steroid tape/plasters during the early stages of scar development. This will rapidly reduce the inflammation in the scar and improve its appearance. Moreover, laser therapy, anti-allergy agents including tranilast, anti-inflammatory agents, bleaching creams and make-up therapies can be used case-by-case basis.

### Conclusions

Our impression is that physicians in non-Caucasian societies often avoid actively treating keloids and, if they do treat these scars, they tend to prefer using steroid injections as the first-line therapy. However, surgery, radiation, and steroid tape/plaster therapy successfully manage keloids and hypertrophic scars, and are increasingly being used, especially in Japanese populations. Thus, there is now sufficient evidence on which to base a standard international algorithm for treating pathological scars. Treatments are likely to improve significantly as our knowledge of scar biology increases, higher quality clinical trials are performed, and new agents are developed.

**Conflict of Interest:** The authors declare no conflict of interest.

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(Received, February 29, 2016)

(Accepted, March 11, 2016)