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Assessment of surgical strategies for addressing keloids: An optimization problem☆

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ABSTRACT

This paper deals with the optimization of keloid surgery strategies. The phenomenological interpretation of the medical/biological system under consideration leads to the modeling of the growth of a keloid and to the assessment of an objective functional, the minimization of which identifies the aforesaid strategy.

1. Introduction

Keloids are fibroproliferative lesions, which are characterized by increased deposition of collagen and growth beyond the borders of an original skin wound also affecting adjacent normal tissue [1,2]. No single unifying hypothesis adequately explains keloid formation, but they seem to be linked to a genetic predisposition. A keloid can develop following a vast array of traumatic events including but not only reserved to burns, surgery, piercing, skin lacerations, acne, and insect bites. Keloids are present most often on the chest and shoulders suggesting a tensile stress-related pathophysiological mechanism [3].

Keloids do not follow the same pattern of evolution, stabilization, and involution of hypertrophic scars [4,5]. They can be distinguished clinically by their growth pattern and histologically by the presence of thick eosinophilic (hyalinosis) collagen bundles, which are absent in hypertrophic scars. Keloids can develop directly after an initiating event or some years later, arising from a mature scar, or can occur as spontaneous lesions and rarely regress over time [5].

Numerous therapeutic strategies exist to address keloids, however, because of inconsistencies among studies with regard to race, age, and sex of recruited patients; the anatomical area that is affected; its size; varying choice of outcome parameters, evaluation of response rates, and follow-up terms, the clinical and scientific support for their efficacy varies [6–8]. Combination therapies are said to be most effective and usually comprise surgical excision with adjuvant treatment forms [9].

In this paper, we focused on the surgical excision as primary form of its treatment [10,11]. Surgical excision can be performed extralesionally or intralesionally, see Fig. 1. Intralesional excision denotes the central excision of a keloid, which ignores the peripheral borders of the keloid, and leaves this portion of the keloid in the wound. Extralesional excision describes the entire removal of a keloid inclusive of its borders, resulting in a larger scar. Currently, both forms of surgical excision of keloid scars are readily performed by surgeons [9].

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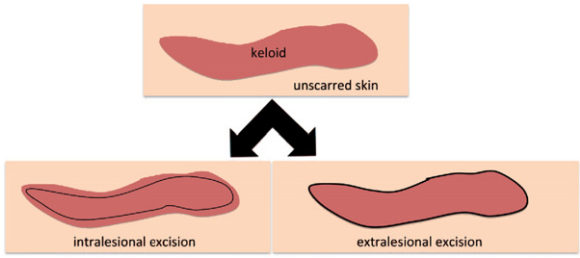

Fig. 1. Illustration of types of surgical excision on a random keloid form.

In vitro studies have demonstrated that the central subpopulation of fibroblasts in keloid scars have lower rates of apoptosis as compared to the superficial and deep borders, supporting the practice of intralesional excision [12]. Additionally, it is hypothesized, that the intralesional excision with lateral undermining of the wound provides a rim of the keloid scar that serves as a splint in order to reduce the tensile stress, possibly reducing the stimulus for increased collagen synthesis. In contrast to that a pathological study reviewing keloid specimens and correlating them with 6–12 months patient follow-up revealed that incomplete surgical excision was associated with higher recurrence rates, and therefore favored an extralesional approach [13]. No clinical studies comparing the effectiveness of intralesional versus extralesional excision are currently available.

From a mathematical point of view, the problem, that has been outlined above, can be regarded as an optimization problem. It is worth stressing, that the problem is dealt with using simple geometries for the shape of the keloid, while more sophisticated approaches need to be employed for the nontrivial mathematical calculations. More precisely, Section 2, provides a phenomenological description of the clinical problem from a modeling point of view. Section 3 presents the mathematical description of the optimization problems. Further perspectives are discussed in the last section.

2. Abnormal wound healing: keloids from empirical data to modeling

This section provides a phenomenological model by which the course of the growth of a keloid can be predicted based on empirical data. A phenomenological description is useful to pursue the aforesaid objective.

Wound healing, or *wound repair*, is an intricate process, in which the skin (or any other tissue) repairs itself after the afore injury [14–16]. More precisely, the term wound is defined as a disruption of the normal anatomical structure, and more importantly, of its function. Healing is a complex and dynamic process, that normally results in the restoration of anatomical continuity and function. Skin wounding triggers a highly complex cascade of local and systemic events, which follow a characteristic time sequence and can be categorized into four distinct, but overlapping phases: hemostasis, inflammation, proliferation and remodeling. A normal healing response results in scar formation. It is similar to a fine hyper- or hypopigmented line related to the neighboring healthy skin, without any irregularities in texture or contractures distorting the adjacent tissue. However, in case of disequilibrium of reparative processes, wound healing can be altered in the direction of a surplus production of connective tissue resulting in hypertrophic scars or keloids. Both types of scars begin with a similar morphology: an increasing deposition of collagen and proteoglycans within the dermis and subcutaneous tissue. Nevertheless, their clinical, histological, and biochemical entities are quite different [4,5].

Clinically, hypertrophic scars are typically red or pink in color, often pruritic, elevated but remain within the confines of the original wound. Its time course is considerably prolonged in comparison to a normal wound healing process. However, after a steep increase in size, a static phase begins which spontaneously passes into a regression period.

Keloid scars do not follow the same pattern of evolution, stabilization, and involution of normal or hypertrophic scars. First of all, they invade adjacent normal skin. For this reason, Alibert in 1806 developed the term "keloid" from the Greek word "crab claw" to underline the way the lesion expanded laterally from the original scar into normal tissue [17]. Furthermore, a keloid may appear directly after an initiating event or start to grow some years later arising from a mature scar. Keloids present with increased fibroblast proliferation rates. The continuous proliferation surpasses the growth of hypertrophic scars and exceeds in size by indefinite progression. As a result, they are characterized by exuberant and erythematous scars, which can become painful or pruritic. Major keloids show elevation levels of 0.5 cm or above the skin surface. An inactive keloid shows cessation of scar growth, but no degeneration of the elevated tissue.

Factors generally regarded as key components for keloid formation include the following

- *Genetic predisposition.* Studies have consistently demonstrated that persons of certain ethnic groups are more susceptible to keloid scar formation (e.g. of African or Asian origin) [9,18].
- *Immune system dysfunction or deregulation.* In keloids, for example, fibroblasts fail to undergo physiologically programmed cell death (apoptosis) and, thus, continue to generate connective tissue beyond a normal and timely limited scarring response. Moreover keloids are associated with particular human leukocyte subtypes. An inherited abnormal immune response to dermal injury opens up another perspective in the pathogenesis of keloid formation [12,19].
- *Tensile forces.* Mechanical tension on a healing wound further stimulates fibroblast proliferation and increases the synthesis and deposition of collagen, predisposing certain body regions for keloid predilection [20].