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Review

Up-to-date approach to manage keloids and hypertrophic scars: A useful guide

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ABSTRACT

Keloids and hypertrophic scars occur anywhere from 30 to 90% of patients, and are characterized by pathologically excessive dermal fibrosis and aberrant wound healing. Both entities have different clinical and histochemical characteristics, and unfortunately still represent a great challenge for clinicians due to lack of efficacious treatments. Current advances in molecular biology and genetics reveal new preventive and therapeutical options which represent a hope to manage this highly prevalent, chronic and disabling problem, with long-term beneficial outcomes and improvement of quality of life. While we wait for these translational clinical products to be marketed, however, it is imperative to know the basics of the currently existing wide array of strategies to deal with excessive scars: from the classical corticotherapy, to the most recent botulinum toxin and lasers. The main aim of this review paper is to offer a useful up-to-date guideline to prevent and treat keloids and hypertrophic scars.

Contents

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1. Introduction

Cutaneous scar management has relied mainly on the experience of practitioners rather than on the results of large-scale randomized, controlled trials and evidence-based studies [1].

Patients with keloids or hypertrophic scars suffer a severe impairment of quality of life, by causing physical, psychological and social sequelae [2]. Even normal visible scars may represent an important stigma [3]. The prevalence of hypertrophic scarring following burns is about 67%, but further epidemiological research is still necessary. Excessive scarring represents the first morbidity cause in burn survivors [4].

The formation of a scar is the normal physiologic response to wounding in adults. However, an alteration of extracellular matrix (ECM) metabolism – an imbalance between its destruction and deposition – may lead to excessive scarring [5]. Wound healing, and therefore scar formation, involves three distinct phases: inflammation (the first 48–72 h after trauma, supposed to be started by the release of IL-1 by keratinocytes) [6], proliferation (which may last for up to 6 weeks) and remodeling or maturation (scars mature during a period of at least 1 year [5]).

A prolonged or excessive inflammatory phase is believed to be the onset of excessive scarring, with hypertrophic scars and keloids as minor and major clinical signs (Table 1).

Still to date, it remains much more efficient to prevent excessive scars than to treat them. The most successful treatment of a hypertrophic scar or keloid is achieved when the scar is immature but the overlying epithelium is intact. In the past, the most recommended treatment strategy has been prophylaxis using silicone gel sheeting or paper tape starting on the second week after wounding, combined with other treatments, including massage, pressure therapy and intralesional corticotherapy, depending on each patient and scar's origin and type [1].

Generally, most of the therapeutic approaches may be used for both hypertrophic scars and keloids. Nevertheless, it is important to differentiate them before performing any surgery or laser treatment [5]. Briefly, keloids (Fig. 1) extend beyond the original wound borders, in contrast to hypertrophic scars (Fig. 2). Blood type A, hyper-Immunoglobulin (Ig) E syndrome (high allergy risk), hormone peaks (puberty, pregnancy), age 10–30 years old, and Hispanic, Afro-American or Asian (but not albino) background have all been associated with high risk of developing keloid scars [5,7]. Keloid pathophysiology is still complex, with both genetic and environmental factors involved. Abnormal fibroblasts have been shown to play a key role, but new lines of research have driven attention to keratinocytes and altered signaling crosstalks [8,9]. Furthermore, increased number of mast cells have been associated with enhanced HIF-1α (hypoxia inducible factor-1α), VEGF (vascular endothelial growth factor) and PAI-1 (plasminogen activator inhibitor-1) expression, all well known fibrosis promoters. TGF-β signaling with preponderance of TGF-β1 or 2 expression due to alteration of POMC (proopiomelanocortin) gene expression among other mechanisms and epithelial-to-mesenchymal transition have also been shown to play a major role in keloid formation [10,11]. Increased interleukin-6 (IL-6), PDGF (platelet derived growth factor), $\alpha_1\beta_1$-integrin and Ig A, G and M expression have all also been linked to keloid pathogenesis [3]. Besides that, keloid formation has been associated with immune alteration of sebaceous glands and enhanced androgen receptors expression with enhanced sebum secretion and lipid metabolism alteration, neurogenic inflammation, infection and mechanotransduction [12]. Regarding hypertrophic scars pathophysiology, activation of myofibroblasts has been classically reported to play a key role. This has been shown to be driven by an orchestrated interplay of platelets, macrophages, T-lymphocytes, mast cells, Langerhans cells, keratinocytes and fibroblasts. The net reported result mainly consists of an alteration of ECM (extracellular matrix) metabolism: excessive production and altered remodeling of ECM, with enhanced expression of types I and III collagen and cutaneous profibrotic pathological crosslink of collagen, in the form of pyridinoline type with increased LH2b (telopeptide lysyl hydroxylase-2b). Furthermore, hemostasis alteration (due to enhanced expression of PAI-1 and chronic fibronectin deposition), increased neovascularization and time of re-epithelialization have also been involved in hypertrophic scar pathogenesis. Decreased apoptosis and increased inflammation have also been described to play a major role. Regarding this latter, increased expression of T helper 2 cells, IL-4, IL-5, IL-6, IL-13 and IL-21, but decreased levels of IL-12 and interferon-γ (IFN-γ), have also been shown to be related in the literature [13,14]. More detailed description about both types of excessive scarring scapes from the scope of this review, which will focus on offering an evidence based description of the currently used strategies to manage