Medical Hypotheses 96 (2016) 51–60

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Endothelial dysfunction may play a key role in keloid and hypertrophic scar pathogenesis – Keloids and hypertrophic scars may be vascular disorders

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ARTICLE INFO

Article history:
Received 21 June 2016
Accepted 27 September 2016

ABSTRACT

Keloids and hypertrophic scars are fibroproliferative disorders (FPDs) of the skin that result from abnormal healing of injured or irritated skin. They can be called pathological or inflammatory scars. Common causes are trauma, burn, surgery, vaccination, skin piercing, folliculitis, acne, and herpes zoster infection. The pathogenesis of these scars clearly involves local conditions such as delayed wound healing, wound depth, and the tension of the skin around the scars. Scar severity is also shaped by interactions between these local factors and genetic and systemic factors such as hypertension and sex hormones. Notably, to evaluate scar severity, the Japan Scar Workshop (JSW) has established the JSW Scar Scale.

Our studies show that tension on the skin around the wound results in prolonged and/or repeated bouts of inflammation in the reticular layer of the dermis and that this inflammation generates abnormal numbers of blood vessels (as well as collagen and nerve fibers) in the dermal reticular layer. We hypothesize that local factors, such as the mechanobiology of the dermis and blood vessels, along with genetic and systemic factors promote pathological scar development by inducing endothelial dysfunction (*i.e.,* vascular hyperpermeability) during the inflammatory stage of wound healing. The continued presence of these factors prolongs the influx of inflammatory cells and factors, thereby leading to fibroblast dysfunction.

Evidence for this hypothesis includes the fact that all effective treatments of keloids, namely, radiotherapy, compression therapy, steroid administration, and long-pulsed Nd:YAG laser therapy, act, at least partly, by suppressing blood vessels.

At present, keloids are classified as strongly inflammatory scars, while hypertrophic scars are considered to be mildly inflammatory scars. However, we propose that keloids and hypertrophic scars are simply manifestations of the same skin FPD and differ only in the degree of endothelial dysfunction and therefore inflammation. We therefore suggest that these pathological scars should be classified on the basis of the factor that causes the endothelial dysfunction. Thus, primary scars are caused by congenital endothelial dysfunction (*e.g.,* a mutation prevents endothelial gaps from closing smoothly) while secondary scars are caused by endothelial dysfunction that results from aging, arterial sclerosis, and/or repeated/very strong local mechanical forces. We expect that primary keloids develop at younger ages and tend to become severe, while secondary keloids are seen in all ages and can vary in clinical severity.

Thus, abnormal blood vessel regulation may underlie keloid and hypertrophic scar pathogenesis, which suggests that inhibiting abnormal angiogenesis and vascular hyperpermeability may be an important therapeutic approach.

Characteristics of keloids and hypertrophic scars

Keloids and hypertrophic scars are fibroproliferative disorders (FPDs) of the skin [1] that are caused by abnormal healing of injured or irritated skin. They can be called pathological or inflammatory scars. They are red and elevated, and have an unappealing appearance. Moreover, they associate with intermittent pain, persistent itching, and a sensation of contraction. Some keloids also

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http://dx.doi.org/10.1016/j.mehy.2016.09.024
0306-9877/

discharge due to infected inclusion cysts that arise because of obliteration of the follicles by the scarring.

Common causes of injury and irritation are trauma, burn, surgery, vaccination, skin piercing, folliculitis, acne, and herpes zoster infection. The inflammation in the scars is continuous; it is also localized, being mainly found in the reticular layer of the dermis of the skin [2]. This reticular layer also exhibits 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 [3]. This suggests that more superficial damage would not elicit keloids and hypertrophic scars; rather, only wounds that reach the reticular layer can generate keloids and hypertrophic scars. Indeed, a clinical study on human volunteers [4] showed that cutaneous injury must reach the reticular layer before it results in inflammatory scar formation. Moreover, we have experienced cases of keloids that developed from dermal injury in the absence of epidermal injury. These cases are caused by lipoaspiration in aesthetic surgery, which can injure the dermis from the side of the fat tissue layer. Thus, epidermal injury may not be necessary for the generation of keloids and hypertrophic scars.

Many classical textbooks consider keloids and hypertrophic scars to be different types of scar. In fact, keloids are sometimes referred to as benign tumors. 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 [3,5]. By contrast, pathologists make a histological distinction between keloids and hypertrophic scars: if a scar has multiple thick eosinophilic (hyalinizing) collagen bundles called keloidal collagen, it is considered to be a keloid. Hypertrophic scars have fewer keloidal collagen bundle [3,5]. However, the validity of these classification systems is challenged by the fact that there are many cases of scars that bear the growth and histological features of both hypertrophic scars and keloids (Fig. 1). Indeed, our histological studies [3,5] show that keloids can contain both keloidal collagen bundles and the dermal nodules that are considered to be characteristic of hypertrophic scars. Moreover, we have observed that hyalinized collagen fibers appear to start from the surrounding dermal nodules. In addition, key features of inflammation, such as the presence of microvessels, fibroblasts, and inflammatory cells, all decrease gradually from the periphery to the center of the keloids (Fig. 2). This indicates that, although there is continuous intense inflammation at the edges of keloids, the center has much lower levels of inflammation; indeed, the degree of inflammation resembles that seen in classical hypertrophic scars. Thus, we hypothesize that hypertrophic scars and keloids may be successive stages of the same FPD of skin [3,5] and that the differing degrees of inflammation in these scars merely reflect the extent of skin FPD risk factors. As will be described further below, these risk factors include genetic, sys-

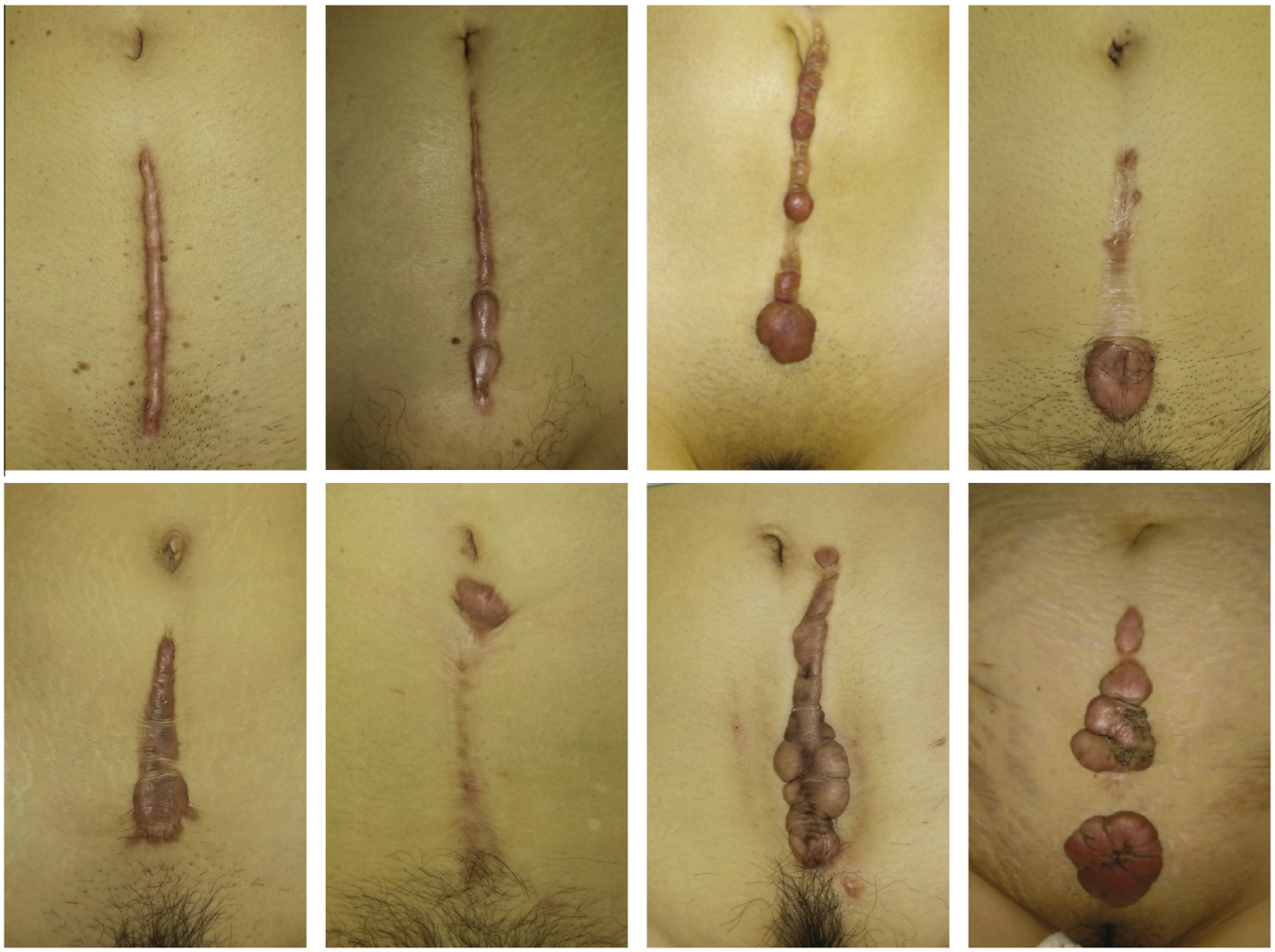

Fig. 1. Clinical appearance of keloids and hypertrophic scars. There are many cases of scars that bear the growth and histological features of both hypertrophic scars and keloids.