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REVIEW

Currently known risk factors for hypertrophic skin scarring: A review

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Summary *Objective:* The study aims to provide an overview of risk factors for hypertrophic scarring.
Background: Hypertrophic skin scarring remains a major concern in medicine and causes considerable morbidity. Despite extensive research on this topic, the precise mechanism of excessive scarring is still unknown. In addition, the current literature lacks an overview of the possible risk factors in the development of hypertrophic scars.
Methods: PubMed searches were performed on risk factors for hypertrophic scar (HTS) formation.
Results: Eleven studies suggesting nine factors associated with HTS formation were found.
Studies concerning chemotherapy, age, stretch, infection, and smoking have a moderate to high strength of evidence, but some other factors have not been studied in a convincing manner or are still disputed.
Conclusions: Risk factors for HTS formation are young age, bacterial colonization, and skin subjected to stretch. Chemotherapy, statins, and smoking seem to play a protective role in HTS formation.

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Contents

Introduction

When skin trauma occurs, rapid repair of the defect is necessary to prevent blood loss and infection in order to assure survival. Human skin achieves quick wound closure through fibrosis and contraction rather than regeneration, which results in scar formation. In a considerable number of burn as well as post-surgical wounds, hypertrophic scar (HTS) formation is a complex problem, causing both aesthetic and physical difficulties. According to literature, about 35% of surgical skin wounds result in hypertrophic scars after 1 year.[1,2] HTSs are the result of an abnormal wound healing process where an excessive amount of collagen is deposited within the wound area, causing the scar to become raised above skin surface. Besides, HTSs often appear red and shiny and cause pain, itching, and sometimes even restriction of motion when positioned above a joint, thereby causing significant morbidity.[3–5] The exact mechanism underlying HTS formation still remains unknown and a limited number of studies have been conducted for identifying conditions or risk factors associated with hypertrophic scarring. This is in contrast to the extensive literature about keloids. Like HTS, keloids arise as a result of a derailment of the normal wound healing process involving production and deposition of abundant collagen; however, the clinical appearance and behavior of keloids differ substantially from the appearance and behavior of HTS.[6,7] While HTS is defined as an excessive scar tissue located within the boundaries of the original lesion, keloids expand beyond the wound margins.[6,7] To date, no comprehensive overview of the possible risk factors for excessive scarring (HTS and keloid) is available in the literature.

The normal wound healing process comprises three successive and overlapping phases: hemostasis and inflammation, proliferation and remodeling. The clotting cascade is activated immediately after trauma in order to achieve hemostasis and temporarily seal the defect with a clot. This clot attracts inflammatory and repair cells and secretes cytokines to switch on inflammation. Inflammatory cells cleanse the wound bed in order to provide a viable environment for tissue repair. They also secrete factors for the activation of fibroblasts, keratinocytes, and endothelial cells essential for initiation of the proliferation phase. The granulation tissue is formed during the proliferation phase that commences 2–3 days after trauma: growth of blood vessels into the wound, reepithelialization, and deposition of a temporary extracellular matrix (ECM). In addition, fibroblasts differentiate into myofibroblasts to attain wound contraction. Completion of reepithelialization induces apoptosis of myofibroblasts.[8] The ECM reorganizes during the remodeling phase: Replacement of immature collagen in the granulation tissue by thicker and better-organized mature collagen fibers followed by cross-linking occurs.[9–12]

HTS is considered to be caused by a prolonged inflammatory phase and a delayed onset of epithelialization, which interferes with the resolution of granulation tissue as reflected by the higher amount of myofibroblasts and collagen present in hypertrophic scars.[13–16] In addition, remodeling is impaired in excessive scar formation, reflected by a higher amount of immature type collagen.[14]

Methods

In order to identify a collection of possible risk factors for HTS, a literature search was performed in PubMed on factors influencing wound healing. The search terms included "Cicatrix, Hypertrophic"[Mesh], "Wound Healing"[Mesh], and "Risk" [Mesh]. No time limit was instituted. All articles were examined and articles that examined or described factors other than therapies for HTS associated with HTS formation in humans, animals, or *in vitro* were selected. In addition, articles cited in the reference sections of the review articles found with the abovementioned PubMed searches were reviewed. Relevant articles were selected