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INDUSTRY EDUCATION

Scars and Keloids

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As with all other organs in the body, the skin plays many integral roles including serving as a protective barrier from external chemical and physical factors, regulation of body temperature, and prevention of excessive water loss from the body. Needless to say, the skin plays a major role in our health and wellbeing, and damage, injury or complications can negatively affect one's quality of life. How then, can we improve the quality of life of those plagued by common skin ailments such as keloid formation and hypertrophic scarring?

THE INTEGUMENTARY SYSTEM

The integumentary system consists of three layers, the epidermis, dermis, and subcutaneous tissue, each of which is comprised of different cell types playing a unique role. [1]

The outer layer of the skin, known as the epidermis, is further subdivided into four layers, namely, the stratum basale/germinativum, the stratum spinosum, the stratum granulosum, and the stratum corneum. With thicker areas of skin, there is a fifth layer known as the stratum lucidum. The ever-renewing nature of the epidermis is due to stem cells present within the stratum basale, which undergo mitosis and produce new cells known as keratinocytes which move into the stratum spinosum, at which point they lose their mitotic ability. When the skin is functioning optimally, the rate at which these stem cells become new keratinocytes is equal to the rate at which the outer layer of the skin, the stratum corneum, sheds corneocytes from its surface.

Each layer of the epidermis contains keratinocytes in different forms/arrangements. Within the stratum spinosum, keratinocytes are densely arranged and contain melanosomes in their cytoplasm. In the stratum granulosum,

the keratinocytes contain keratohyalin granules which play a role in the production of profilaggrin ,and subsequently filaggrin, in the stratum corneum as well as the production of hydrophobic glycophospholipids which ensure permeability of the epidermis. Profillagrin ensures the joining together of keratin fibres within the outer layer of the skin. The corneocytes within the stratum corneum are differentiated keratinocytes [4] which have an internal structure made up solely of keratin fibres. [2] Further, the epidermis consists of melanocytes which are responsible for melanin production, Langerhans's cells which play a role in protecting the skin from harmful pathogens, and Merkel's cells which are thought to play a role in the reception of sensation/touch. [2]

Beneath the epidermis lies the dermis, which plays the largest role in ensuring the elasticity and strength of the skin. Within this layer lie fibroblasts which give rise to collagen type I and III proteins, as well as elastic and reticular proteins. (3) Additionally, below the dermis lies the subcutaneous tissue which is mostly comprised of fatty tissue among nerves, vessels, and muscle tissue. The subcutaneous layer plays a role in insulation and protection of underlying muscles as well as housing metabolic energy.

WOUND HEALING AND SCAR FORMATION

Following a wound causing injury or damage to the skin, the skin initiates and undergoes a cascade of wound healing phases which may occur in an overlapping manner. The first phase, responsible for the cessation of bleeding, known as haemostasis, involves various steps including vascular constriction, platelet activation, activated platelet binding to exposed collagen, subsequent release of inflammatory mediators, growth factors and cytokines through platelet binding, platelet thrombus formation, the initiation and progression of the coagulation cascade, discontinuation of clotting and elimination of the clot.

During the inflammatory phase of wound healing, inflammatory cells continue to move to and occupy the wound site enabled by mast cells which cause vasodilation through the release of proteins such as histamine and in turn make it easier for the cells to reach the wound. Neutrophils are first in line to arrive at the wound site, attracted to and engulfing the bacteria and dead tissue that are present, which in turn causes the wound to exude pus. Macrophage turned monocytes continue the clean-up efforts and remove other cell components as well as the neutrophils which have completed their role. The macrophages further release inflammatory cytokines like platelet-derived growth factor and fibroblast growth factor which trigger angiogenesis in the next phases of wound healing. Epidermal growth factor is also released by macrophages and are in this sense essential for wound healing.

The next phases (which focus on restoring the missing tissue) rely on the inflammatory phase to create a clean wound bed which can then be repaired. The proliferative phase focuses on repairing the vasculature at the wound site through angiogenesis and granulation tissue production. Granulation tissue serves a vital role in the repair and restoration of the wound, due to the richness of vasculature in this connective tissue. Collagen production and epithelialisation also take place. Angiogenesis is triggered by a lack of oxygen in the area which signal endothelial cells of the vasculature to release nitric oxide, which in turn stimulates the release of endothelial growth factor. Once angiogenesis is activated, the wound receives oxygen and other necessary components, which decrease the release of factors that initially stimulated angiogenesis. The regulation of angiogenesis in this manner prevents excessive collagen production which could lead to abnormal scarring. The reason the excessive production of collagen could occur, is due to the fact that fibroblasts migrate into the area and produce collagen and elastin fibres which make up the new extracellular matrix that serves as a support for the new vasculature and granulation tissue that must be produced to restore the wounded skin.

Finally, in the last phase of wound healing, namely maturation, a process of remodelling and wound constriction occurs. The collagen that was previously laid down now undergoes a process of interlinking, and the type III collagen is replaced by type I collagen. Type I collagen is found in healthy skin, whereas type III collagen is what is initially produced by fibroblasts and is a thinner, less mature type of collagen. The nature of the wounded skin becoming stronger as it heals, is due to the replacement of the type III collagen with type I collagen and how the presence of type I collagen increases. Furthermore, the nature of wounded skin to contact, is thought to be a mechanism whereby the skin reduces the area that has to be repaired and restored. In the final stages of

maturation, the skin continues to heal by epithelial cells migrating from the edge of the wound inwards, and under normal circumstances a scar will remain, which will be firm initially , and red due to the increased vasculature, as well as raised due to the increased collagen content. The scar should become softer, flatter, and decrease in redness over time. (5) But this is not true for some individuals. This is where abnormal scarring takes place.

HYPETROPHIC SCARS AND KELOIDS

For some, the terms “hypertrophic scar” and “keloid” are interchangeable, however these are in fact different conditions with different presentations. Hypertrophic scars tend to develop rapidly for up to six months after the skin injury, and then spontaneously subside over time. Keloids on the other hand do not need a skin injury to occur, for them to make an appearance, but can develop for up to several years after a minor skin injury. Keloids however are not believed to spontaneously subside after any period of time. Taking a further look at the differences between keloids and hypertrophic scars, it should be noted that keloid scars tend to be mildly tender, firm and can have a shiny surface appearance. The epithelium of the keloid is usually thinner than other areas of skin and appears in hues of pink or purple with irregular border outlines. A hypertrophic scar in contrast is usually linear but does have a similar appearance. Both scar types tend to present with itching, but it is usually keloids that involve symptoms of sensitivity to touch as well as significant pain.

The development of keloids and hypertrophic scars can be attributed to some sort of abnormality in the wound healing process. It is thought that a dysregulation of wound healing signals and cells could contribute to the increased levels of collagen present in both scar types, as well as increased fibroblast proteins. Either the signals that up regulate wound healing, or the signals that down regulate wound healing are dysregulated.

It is thought that when the inflammatory period/response is exaggerated in wound healing, this leads to abnormal scar formation. [6] For example, if there is an increased expression of pro-inflammatory and pro-fibrotic growth factors, this would lead to increased chance of hypertrophic scarring. Prolonged stages within the proliferation phase of wound healing are thought to be another culprit of abnormal scarring, for instance the extended period of re-epithelialisation due to prolonged keratinocyte activation has been observed in hypertrophic scars. Further, in the remodeling or maturation phase, excess fibrous/type I collagen is deposited due to prolonged activation of fibroblasts and myofibroblasts and lack of apoptosis of myofibroblasts. [7] In fact, normal skin fibroblast cultures have twice as much the percentage of apoptotic cells than what keloid fibroblasts do. [8] Hypertrophic scars have excess type III collagen arranged parallel to the underlying epithelial tissue, along with many myofibroblast containing nodules, large extracellular collagen filaments and an abundance of acidic mucopolysaccharides. Keloids in contrast, have a disorganised arrangement of type I and III collagen along with hypocellular collagen bundles but no nodules and no excess myofibroblasts. [6]

SILICONE THERAPY

Taking the above into account, the prevention, management, and treatment of abnormal scarring is becoming increasingly important and sought-after. One therapy gaining attention is the use of silicone gels for the reduction of hypertrophic scars and keloids. Silicone gel has shown significant efficacy in the treatment of abnormal scarring, and results in the reduction of height, colour, and texture of scars.

Silicone gels are thought to be effective in the treatment of scars for several reasons. Firstly, their ability to increase hydration of the external skin surface/stratum corneum is believed to regulate fibroblast and collagen production. It in turn results in a flatter and softer scar. Moreover, the ability of the silicone gel to contribute to protecting the skin against bacterial invasion, prevents the excessive production of collagen which would be induced by the presence of bacteria at the wound site. Interestingly, it also modulates the expression of growth factors, namely, fibroblast growth factor beta (FGF β) and tumour growth factor beta (TGF β). TGF β is responsible for stimulating fibroblasts to produce collagen and fibronectin. FGF β normalises the production of collagen production in the scar and regulates the amount of proteins that break down excess collagen (collagenases). Silicone gels therefore regulate the balance between collagen production and breakdown. Finally, the itching associated with scarring is relieved using silicone gel.

Further benefits of silicone gel therapy include the fact that it is easy to use, lightweight and suitable for many different areas of the skin, unlike silicone sheets or other therapies which may not be suitable for areas such as joints which are constantly moving and bending. [9]

Nourisil is one such silicone gel, and an excellent one at that. It targets the loss of moisture in the scar tissue caused by abnormal levels of trans-epidermal water loss which is a signal for keratinocytes to produce cytokines which in turn leads to changes in the dermis that result in the production of excess collagen. By creating a silicone barrier to the environment, Nourisil allows moisture to be removed from the surface of the skin at a much more normal rate, and thereby reducing the moisture-associated signals that cause excess collagen production, and in turn reducing the severity of the scars appearance.

As a blend of 5 silicones and vitamin E oil (which further enhances the silicone's efficacy and harbors antioxidant activity), that is quick drying, easy to use, suitable for all skin types, including sensitive skin and pediatric skin, when used for prevention and treatment.

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