New beginning for wound healing?

Healing problem in diabetes

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Approximately one in three diabetes patients develops a foot wound over the course of his life.[1] Why doesn't tissue regeneration work anymore in such cases? And can better understanding bring about new therapies?

Natural healing of a wound is a highly complex and at the same time well-organized biological process. It operates in four phases: hemostasis, inflammation, proliferation and remodeling.

From emergency care to regeneration

Following an injury, thrombocytes are activated unleashing the coagulation cascade in the area of the bleeding wound. Both form part of primary "emergency care", i.e., bleeding must be stopped. From this first step there very swiftly follows an inflammatory phase in which neutrophil granulocytes, macrophages and T-lymphocytes are sent to the wound on the very first day. They are tasked with removing bacteria and damaged tissue.[2,3] This inflammation reaction is fueled by various cytokines. It moves seamlessly into the subsequent proliferative phase in which new tissue, new blood vessels and a new extracellular matrix fill up the wound area. In this phase various growth factors and cytokines are released to support the process of rebuilding. Under the influence of epidermal or keratinocyte growth factors the migration of fibroblasts and construction of an extracellular matrix are promoted.[3] Matrix metalloproteinases (MMP) are also integrated into different stages of wound healing. They stimulate cell migration and the restoration of the epithelium. Towards the end of the healing process there is an influx of keratinocytes from the edges of the wound. The strong circulation of blood decreases, and a new epithelium forms.

The core problem – Inflammation

"These processes are extremely complex, as a great many factors also play a part," says Prof. Dr. David Armstrong of the University of Southern California/Los Angeles.[4] At least as complex are events revolving around chronic diabetic wounds, in which the described natural wound healing processes are disrupted. "This is like a sluggish computer in which various programs are active in the background," says the wound expert. "We have immune cells, inflammatory cytokines, chemokines, cell-cell interactions, none of which continue to be under control. They prevent the normal process of wound healing."[5] In fact, neutrophils, macrophages and T-cells are over-activated and the quantity of proinflammatory cytokines and tissue-reducing proteases remains permanently elevated.[3] Fibroblasts and endothelial cells do not multiply - and so the last phase of wound healing simply ceases to be. The wound remains open.

Aggressive M1 macrophages play a role

An imbalance of activated M1 macrophages and M2 macrophages plays a key role, notes Armstrong.[4] Whereas inflammation-promoting M1 macrophages are normally replaced by the "gentler" M2 macrophages at some point, the level of the aggressive M1 macrophages remains high in chronic wounds. "They then function as permanent fire accelerants," says the American expert. High levels of reactive oxygen species and the increase in free iron also characterize such open sites.[3] Lastly, stem cells, which after an injury normally differentiate into different cells in the epidermis also exhibit functional disorders, especially in the wounds of the elderly.

Bacteria create their own environment

As if that were not enough, over half of diabetic wounds are infected with bacteria.[6] In western countries these are chiefly aerobic gram-positive bacteria such as Staphylococcus and Streptococcus.[4] "Bacteria are interested in a wound remaining open. They create their own milieu, produce a biofilm and develop barriers which are meant to prevent jeopardy to this environment, i.e., an improvement in the wound," says David Armstrong. The biofilm consisting of polymeric sugar, proteins, and bacterial DNA protects the microbes from endogenous cells.[3] If the condition of the wound worsens over time, the bacterial flora also becomes more complex and more diverse. Furthermore, fungi often populate this environment too.

Supporting the healing process

People have long been trying to promote the healing of chronic wounds through a wide range of different measures. Thanks to fundamentally new scientific findings on the molecular and cellular formation process of wounds, it has been possible to develop new treatment strategies in the last few years.

Thus, attempts are being made to stimulate the production of substances and cells which promote healing by using growth factors. Gene therapy approaches are also being researched. In negative pressure wound therapy a vacuum is applied to the wound, which promotes blood vessel formation and in turn boosts the oxygen and nutrient

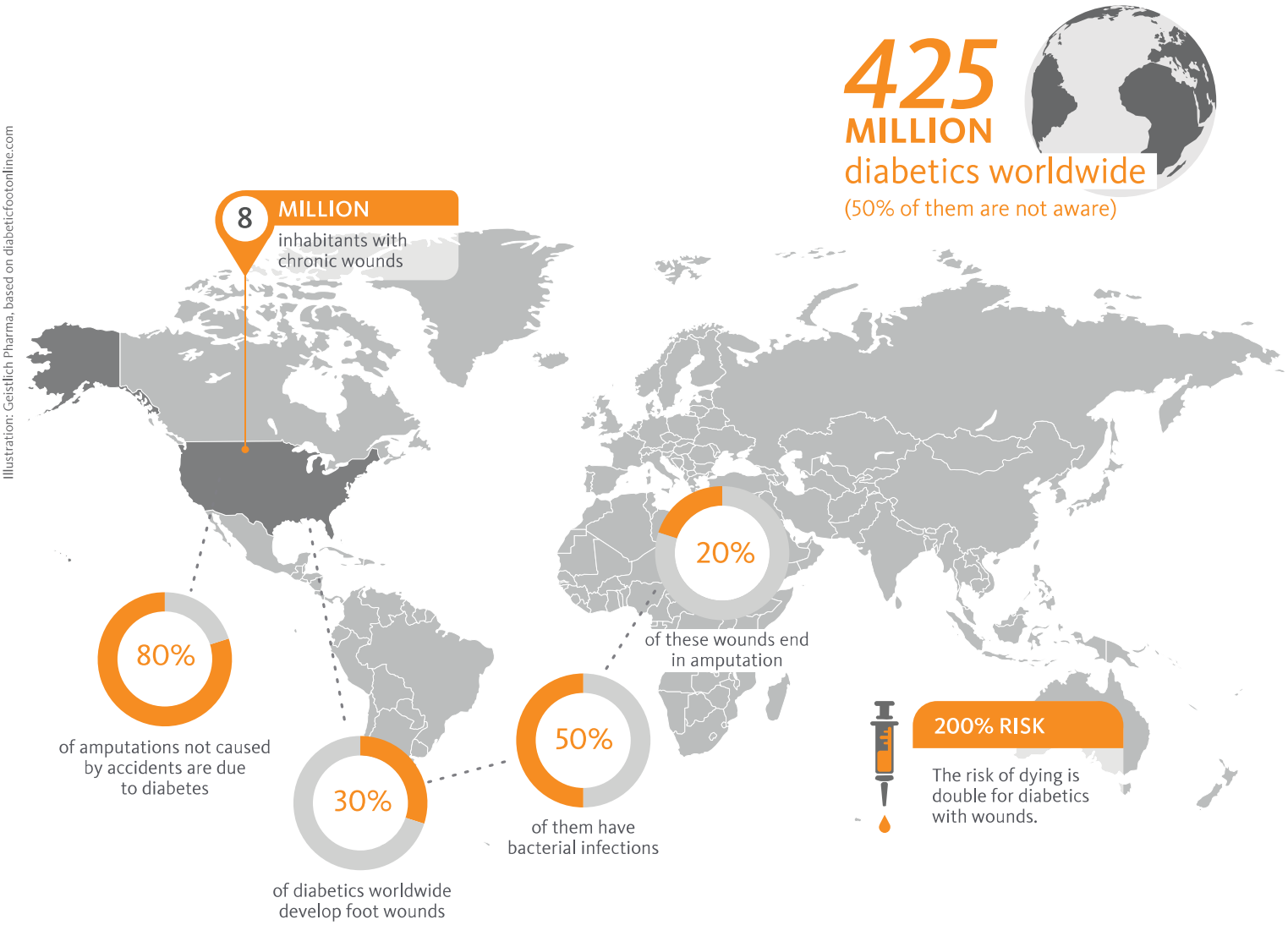

FIG. 1: Diabetes is frequent and can have severe consequences.

supply in the wound area, which can be very beneficial for wound healing.

Geistlich conducts research in this area

Geistlich developed a purified reconstituted bilayer matrix which shows very promising effects in the healing of chronic wounds.[7] The upper compact layer mimics the basement membrane and supports migration of keratinocytes. It provides for the binding of growth factors and mechanical protection of the wound. It also allows suturing of the matrix to the wound if additional fixation of the matrix is desired by the healthcare professional. The lower porous layer modulates the activity of metalloproteinases and provides an optimum structure for migration of cells. It also absorbs wound fluid readily.

In a study in patients whose wounds were an average 3.3 square centimeters in size, the median time until wound closure was 2.7 weeks with this advanced wound matrix.[7] "Geistlich Derma-Gide® provides a scaffold for a 'friendlier' environment," notes Armstrong. "This enables a new beginning for healing."

References

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