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# The role of collagen in wound repair

**Abstract**

Wound healing is a dynamic and complex process involving the interactions of many different cell types, matrix components and biochemical factors including chemokines, cytokines, growth factors, proteinases and proteinase inhibitors. Multiple chemokine, cytokines and growth factors are synthesised from different cell types and are thought to regulate the wound healing process. Chemokines released from neutrophils in wound site trigger the formation of granulation tissue formation. The granulation phase involves the formation of new blood vessels (angiogenesis), recruitment of fibroblasts, and the coverage with new epithelium. Contraction of the granulation tissue and remodelling of collagen and elastin fibres contribute to the maturation and conversion of the granulation tissue into scar tissue. Many chronic wounds are unable to remodel extracellular matrix (ECM) and form sufficient number of new blood vessels because excessive proteinase activity, which inhibits the delivery of nutrients and oxygen to the metabolically active newly formed tissue. Elevated levels of MMPs in the granulation tissue of chronic pressure ulcers suggest that a highly proteolytic environment contributes to the chronicity of these wounds.

Keywords: collagen, wound healing, extracellular matrix

## INTRODUCTION

Collagen is the main component of connective structures and it is the most common protein in the human body. Collagen performs an important morphogenetic and plastic repairing role. Its molecule has an helicoidal structure formed by three polypeptidic chains rich of hydroxyproline aminoacid.[1] Fibroblasts are mainly participating to the biosynthesis of collagen. The collagen tissue acts as a mould, as a precursor, as plastic material and as a cementing substance in the wound healing process.[2]

The wound healing process involves phenomena such as proliferation, migration and cells differentiation, that are influenced by the presence of collagen: in the final stage of the repair of a continuity tissue solution, the maturation of collagen takes place and collagen fibres create a bridge between the edges of the damaged tissues, aiming to form or favour a scar having elasticity and mechanical strength.

The possibility to positively influence the repair of a tissue damage has long been studied in dermatology, plastics and surgery. Owing to the repair properties of collagen, many research works were made to verify a possible acceleration of the tissue repair process by applying collagen on lesions.

The "biologic medication" represents a step forward compared to the simple traditional dressing with gauzes and various pharmacological substances.

In several clinical situations such a type of medication is required for the traumatic wounds with significant loss of substance, for the burns, for the pressure ulcers and leg ulcers.

Therefore studies were addressed to create a cover of lesions of the skin as much as possible similar to the natural one, physiological, to allow oxygen exchange, avoid loss of liquids, constitute a barrier for bacteria and then to create the conditions needed for the tissue repair.

The ideal biologic medication is the autologous skin graft that even if not lasting itself, stimulates the tissue repair. It is however obvious that this cannot be the routine medication of cutaneous lesions.

## COLLAGEN PRODUCTS

The collagen available for this use is in form of soft sponges, lyophilized, sterilized. It has been proved that the material implanted, lysed by enzymatic digestion by leucocytic proteases keeps an intimate contact with the bottom of the lesion and is embedded in the granulation process, forming a plastic scaffolding over which the fibroblasts migration takes place and then the invasion of endogenous cells with final result of physiological and natural tissue repair.[3] Its spongy network contributes to the absorption of exudate and to block eventual extensions of the wounds, stopping possible bacterial growths that would delay the healing process.[4] Moreover the pores are not so large to favour dryness nor too small to hinder granulation or gaseous exchange. It seems that heterologous collagen besides acting as mechanical support and agent of fibroblast motility, participates as a feeding substrate to the metabolic activity of the granulation tissue itself.

## MECHANISM OF ACTION

The mechanism of action of collagen can be summarized as follows:

a. Invasion of its structure by leucocytes and macrophages of blood and tissue.
b. Digestion of its proteinic scaffolding by the protease of above cells; so stimulating the plastic reconstruction of wound tissues.

The product acts locally without absorption and it is not involving the systemic structures of the body. Instead it enters the

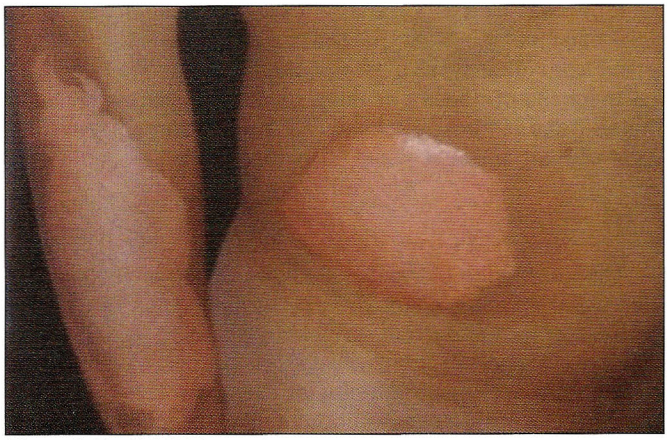

Figure 1. Partial thickness burn.

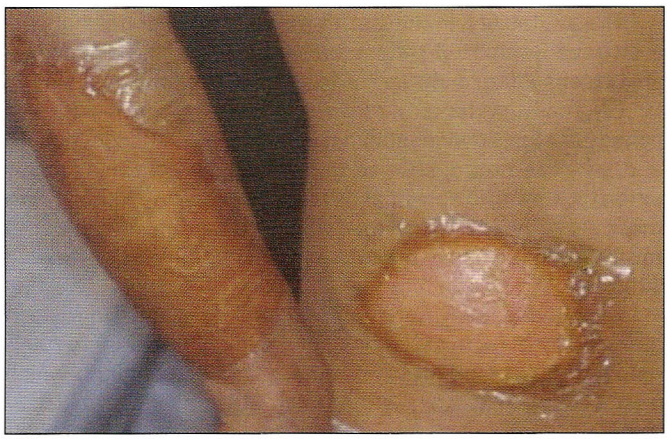

Figure 2. Burn covered with collagen film membrane.

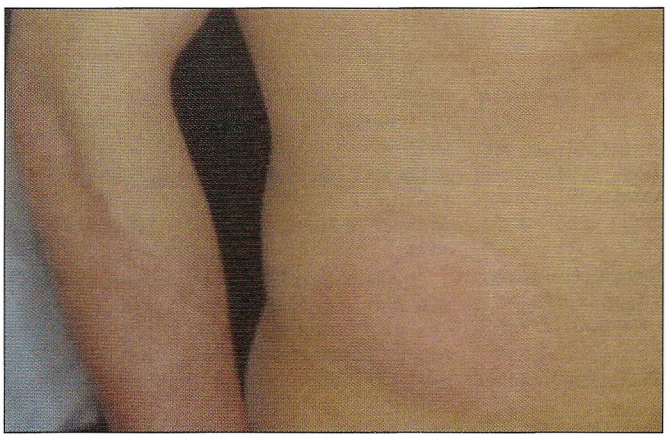

Figure 3. Final cosmetic result at 3 weeks.

fibroplastic cellular local metabolism where it acts stimulating the production of endogenous collagen which is responsible of wound healing.

In the practice of orthopedic surgery often pathologic conditions develop for which materials like the heterologous collagen can be useful, such as:

- Pressure ulcers, sacral and of the heel.
- Delays or irregularities in healing of surgical wounds in large operations on articulations.
- Ulcers of bursitis.
- Traumatic lesions of skin and tendons.
- Operative and post-operative haemorrhages.
- Superficial traumatology.
- Focuses of drying articular osteochondritis.

**The topical application of collagen acts in:**

1. Stimulating angiogenesis as well as newlyformed capillary growth.
2. Induction of histio-macrophages and lymphocytes in the granulation tissue.
3. Reducing the phlogistic crust with edematous substrate (due to superficial absorption).
4. Stimulating fibrogenesis, with presence of autologous collagen, fibroblasts activated and in line, presence of early maturation with specific colors.
5. Fibrin interacts with collagen and results in fibrogenetic activation.
6. Enrichment of the fundamental substance with presence of polysaccharides.

Skin ulcer is a continuity solution of skin with loss of substance, interesting epidermis, dermis and under-cutaneous layer. One characteristic of ulcers is that they tend not to heal spontaneously.

Ulcers are caused by trauma, dysmetabolisms, neoplasies and vascular pathogenesis. These last ulcers are frequent and represent a social problem. This is bonded to the diffusion of vascular pathology and to its continuous increase.

The yearly occurrence of new cases of peripheral arteriopathies is of 6%, diabetes often associated with ulcers of the skin is the second social sickness as frequence while the first one are the phlebopathies. About 20-25% of the population is affected by varicose veins to lower limbs and in 1-2% of venous chronic insufficiences skin ulcers are present.

In presence of venous insufficiency, pathologies which more frequently are associated with ulcer, are the post-phlebitic syndrome and primitive varices.[5] In both the cause is venous hypertension. Phlebostatic ulcer is typically localized above internal malleolus, has irregular edges, is surrounded by edema, cyanotic with haemosiderinic pigmentation. Often, touching with a doppler examination reveals the presence of an incontinent perforating action in correspondence of the ulcer.

**Topical treatment of skin ulcers is based on three phases:**

1. Detersion of the ulcer.
2. Sterilization.
3. Cicatrization.

It is not possible to obtain cicatrization of an infected ulcer or showing necrotic debris. Necrotic material present in the ulcer and particularly the necrotic adipose tissue, is a factor causing local infections and represents a rich soil of bacterial culture. It is for this reason that cleansing of the ulcer is fundamental, without it one cannot sterilize nor heal. The removal of necrotic tissue must be done until vital bleeding tissues are reached. Cleansing can be made surgically or enzymatically using proteolytic enzymes which, demolishing the insoluble macromolecules in smaller molecules, allows the removal without trauma or damaging vital tissues.

It is also necessary to administer antiseptics locally and in the most serious cases, systemic antibiotics in order to stop infection by opportunistic germs with low pathogenic power, but able to stop the tissue repair process. Once the removal of hindering factor is obtained, appropriate techniques of medication able to favour the tissue repair process are followed.

**A good medication must:**

1. Create a barrier to bacterial contamination.
2. Be permeable to gas ($O_2$, $CO_2$) and vapours (transpiration). →

3. Adhere to the ulcer and be easily replaceable.
4. Be of low cost and easy handling.

The meaning of the first point is clear: the permeability to gases is needed to favour the gas exchange on the bed of the lesion to avoid additional necrosis and/or development of anaerobic colonies.

Referring to the mechanical properties of medications these are: adhesion to the wound, good adsorbent capacity of exudates, be adaptable to irregularity of the wound, maintaining the wound moistured without maceration.

Heterologous collagen, besides having all the above properties, has the peculiarity to be, as a natural molecule, involved in the tissue repair process.[6]

**The role of collagen in healing is remarkable and depends on the action on various aspects of this process:**

a. Haemostatic action per interaction with clotting factors and platelets.
b. Enhances liberation of growth factors as an example of the interaction with platelets (PAGF and others).
c. Induces concentration of fibronectine, with a role in developing intracellular contacts, then of diapedesis.
d. Modulates the activity of growth factors.

The capacity of healing of a lesion is bonded to the capacities of biosynthesis of collagen and to its availability. From what is said above, it is derive that the possibility to apply heterologous collagen, has strong theoretical basis.[7] As mentioned the medication must have specific chemical-physical properties.

Heterologous collagen is presented as a microporous soft sponge constituted by non denaturated filamentous proteins.

It behaves as a very absorbent sponge mechanically traction-resistant.[8] It is clear that the use of collagen is deeply different from other types of wound dressings, due to its biological mechanism inducing healing. It is a real precursor of plastic material and cementing substance, having the property to stimulate cellular and vascular proliferation.[9]

## CONCLUSION

The knowledge of the use of collagen in the treatment of ulcers and lesions is not recent: the surgeon was often in need to use surfaces of dermic connective tissue to be applied as support in big hernia or laparocele. This practice was replaced by tantalum nets or polyglycolic or polygalactic acid meshes while the use of autologous or homologous connective, requiring a certain preparation of "bench surgery" type is no longer popular.

The availability, in the last 15 years, of soft sponges of heterologous lyophilized collagen allowed an increase in its use also in consulting rooms for the treatment of wounds and ulcers.

Originally, collagen was used only as haemostat. It happened later that sponges applied on the wounds tended to adhere and, when removed, showed to have promoted a rich granulation tissue and in some cases also re-epithelialisation. From these facts the idea developed to use collagen as biomaterial to stimulate the tissue process in presence of difficult healing situations.

Simple use, easy handling and clinical results in a standardized form were at the base of the idea: therefore our scientific committment to evaluate the activity mechanisms which define collagen as a true stimulator and adjuvant of cicatrization. ■

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