Wound Medicine 8 (2015) 15–18

Contents lists available at ScienceDirect

Wound Medicine

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

Review article

The role of biomedical sensors in wound healing

P. Salvo [a], V. Dini [b], F. Di Francesco [a], M. Romanelli [b,*]

[a] Department of Chemistry and Industrial Chemistry, University of Pisa, Via Moruzzi 3, 56124 Pisa, Italy
[b] Wound Healing Research Unit, Department of Dermatology, University of Pisa, Via Roma, 67, 56126 Pisa, Italy

ARTICLE INFO

Article history:
Received 8 February 2015
Accepted 9 March 2015
Available online 26 March 2015

Keywords:
Wound healing
Sensors
Infection
Inflammation
Diagnostic
Wound management

ABSTRACT

Acute and chronic wounds have a tremendous impact on patients' life conditions. As wound healing involves a huge number of biochemical processes, biomedical sensors play a major role for wound monitoring and early detection of infections. This paper describes and discusses the sensors currently under research that can provide invaluable information on the different phases of wound healing. These sensors can allow wound healing to be continuously monitored, thus opening the path for personalized therapies and better patients' quality of life.

Contents

1. Introduction

Skin is a complex multi-layer organ that forms a barrier for exogenous agents and contributes in the body thermoregulation. When the skin is damaged, the biophysical status of the body is altered. This condition can lead to severe fluid losses or infections depending on the area and depth of the wound [1,2]. When wounds are not properly treated or when the human biochemical healing mechanism fails, wounds turn in an abnormal state and can become chronic, hard-to-heal or non-healing. The possible consequences are diabetes, arterial and venous diseases, or pressure ulcers [3].

The origin of wound treatment can be dated back to ancient and even primitive times. Curing agents were derived from vegetal, animal and mineral sources. Among the most used products, there were bark, roots, honey, fruit, blood, milk, faeces, meat, clay, arsenic and various mineral salts [4,5]. Although some medical practices were often based on erroneous or magic beliefs, and a moderate dose of luck, some of those remedies are still valid, e.g. honey. However, a deeper knowledge of the chemo-physical processes that govern wound healing has only been achieved in recent times. The progress and combination of disciplinary sectors such as medicine, electronics, chemistry and biology has led to advanced wound treatment and management that have considerably improved patient's health conditions. Examples of breakthroughs in wound treatment are the use of anti-microbial agents, the compression therapy techniques, skin grafts and the introduction of new dressings based on hydrocolloid, hydrogel, alginate and collagen [6,7]. Biomedical sensors have gained an important position in wound healing and management as they provide invaluable diagnostic and monitoring tools to clinicians. The number of wound ulcers is expected to grow dramatically in the

* Corresponding author. Tel.: +39 050 992436; fax: +39 050 551124.
E-mail address: m.romanelli@med.unipi.it (M. Romanelli).

http://dx.doi.org/10.1016/j.wndm.2015.03.007
2213-9095/

following years due to the ageing of population, with repercussion of the healthcare budget. Biomedical sensors can contribute to lower the burden of cost treatments and improve patients' quality of life by providing devices capable of early identification of infections, personalized therapies and remote monitoring of wound parameters [8].

This paper will examine the working principle, the role and future trends of biomedical sensors in the wound healing process.

2. Sensors for wound healing

Wound healing consists of four phases, namely haemostasis, inflammation, proliferation, and tissue remodelling or resolution [9]. Haemostasis is a defence mechanism that prevents bleeding and promotes blood vessel repair at the first stage of wound healing. When a wound occurs, platelets start aggregating to clot blood. The aggregation in the right place is guaranteed by the combined action of a hormone, the prostacyclin, and an enzyme, the thrombin. The healthy parts of the vessels release prostacyclin that inhibits the platelets activation. Thrombin converts fibrinogen to fibrin at the wound site. Calcium helps aggregating fibrin monomers together to form a network that stops the loss of blood cells [10].

The coagulation efficiency of blood can be tested by a coagulometer. The sensing principle can be optical or, mechanical. The optical approach can be divided in four subclasses. The first class consists of monitoring the changes in the optical density when the fibrin starts aggregating in the blood sample. In the second class, instead of the optical density, the light scattering is measured. Another optical method measures the emission of a chromophore that links to a specific protein involved in coagulation. Last optical method includes an immunological essay where an antibody anchored to a latex micro-particle binds to the protein of interest. In this case, the coagulometer measures the light absorbance that occurs when the bound if formed. During the mechanical test, the movement of a steel ball is hampered proportionally to the viscosity of coagulated blood [11]. Specific assays to monitor the activity of thrombin, fibrin and prostacyclin do exist but are beyond the scope of this paper. The interested reader can found more information in [10].

In the inflammatory phase, neutrophils, macrophages, and lymphocytes invade the wound site and stimulate keratinocytes, fibroblasts, and angiogenesis to promote tissue regeneration. In the proliferative phase, fibroblasts and endothelial cells start the re-epithelialization, which is completed in the remodelling phase where the scar tissue is formed and the vascular density returns to normal. Most of the exudate produced by the wound occurs in the inflammatory and proliferative phases. Exudate is a fluid that contains a plethora of component among which there are electrolytes (e.g. sodium), urea, creatinine, fibrinogen, matrix metalloproteinases (MMPs), and proteins such as tumour necrosis factor (TNFα) and C-reactive protein (CRP) [12]. Although there are no specific sensors that measure electrolytes on wound sites, it is worth mentioning the research works on wearable sensor described in Bandodkar et al. and Coyle et al. [13,14]. Bandodkar et al. have presented a promising tattoo potentiometric sensor that can be applied onto skin to measure sodium in sweat. This sensor has been tested in the range 0.1–100 mM and has withstood stretching strains up to 26% and bending cycles of 180°. Coyle et al. have reported a sodium selective electrode with a polymeric membrane made of a polypyrrole, a plasticizer, an ionophore, and an ion exchanger. This sensor has been fabricated on a Kapton® surface and is intended to be applied onto skin. Although at a research level, both these epidermal sodium sensors have the potentiality to be integrated in a bandage and used for point-of-care and personalized therapies for wound treatment.

A decrease in uric acid concentration in exudate can be associated with the risk of bacterial colonization of the wound. Sharp et al. have proposed carbon fibres-based electrodes to be integrated in a bandage to monitor uric acid in wounds. The electrodes surface has been coated with cellulose acetate barrier to avoid fouling of extracellular components, e.g. proteins and fats. This sensor has shown a linear response in the range of approximately 0–500 μM of uric acid [15].

A recent study has found that creatine phosphokinase (CPK) present in exudate may be act as an indicator of the severity for deep tissue injuries, which are deep muscle injuries that rapidly deteriorate to stages III and IV pressure ulcers. Incisions were made on eight rats and the injury was created by applying a metal plate in the sub-peritoneal region at controlled pressure. Although further studies are necessary, preliminary results have shown an increase in the CPK level on days 2 and 3 when compared with the CPK level in serum [16].

A novel method for monitoring wound healing has been reported by Pan et al. who have proposed conventional fluorescence imaging to monitor the conversion of fibrinogen into fibrin. Human fibrinogen has been labelled with near infrared dye (HiLtye FluorTM 750 SE). This work has found that the fibrin formation continues for up to 24 h after blood loss has stopped [17].

MMPs take part in the inflammatory phase. They are a family of zinc-dependent endoproteinases that contribute in the degradation of extracellular matrix (ECM) components. The MMPs are also involved in the removal of the devitalized tissue, and are therefore believed to play an important role in normal wound healing and remodelling. As for the repair phase, MMPs are necessary for angiogenesis, wound matrix contraction, migration of fibroblasts and keratinocytes, and epithelialization. However, several papers suggest that elevated levels of active MMPs impair wound healing [18,19]. The common approaches to detect MMPs are immunoassays (e.g. antibodies labelled with fluorescent dyes) or the measurement of the enzymatic activity [20]. A novel approach has been presented by Song et al. with a graphene oxide-based fluorescence resonance energy transfer (FRET) biosensor. A fluorescein isothiocyanate-labelled peptide (Pep-FITC) was bound onto graphene oxide surface for detecting MMP-2 in complex serum samples. This biosensor has achieved a detection limit of 2.5 ng/mL and high selectivity even in presence of other MMPs [21].

Tumour necrosis factor-alpha (TNFα), a monocyte-derived cytokine, is mainly involved in the inflammatory phase of wound healing. Although there are some contradictory studies, TNFα seems to accelerate wound epithelialization and neovascularization, whereas excessive amounts are associated with inflammatory diseases and non-healing wounds [22–24]. Battaglia et al. have developed a fibre-optic surface plasmon resonance (SPR) sensor to detect the concentration of TNFα in non-healing wounds. Specific TNFα antibodies have been bound to 200 μm-diameter optical fibres that have been connected to a light source and a spectrometer. Although the system portability should be improved, the sensor achieved a limit of detection of 0.77 ng/mL with a root mean square error of calibration of 0.89 ng/mL [25].

CRP plays a major role during the inflammation phase. In response to injuries and presence of bacteria, the immune system triggers the synthesis of CRP, which promotes the action of macrophages to remove necrotic and apoptotic cells and bacteria [26,27]. Pasche et al. have developed a CRP sensor that can be integrated in wound dressing. A waveguide is modified with a CRP sensitive compound. A light source emits a white light that propagates to the chip and is reflected at specific wavelengths according to the amount of CRP. The sensor has detected changes in the concentration of CRP between 1 and 100 μg/ml [28].