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Abstract— In recent years a specialist interest has developed
worldwide in advanced wound management for difficult to heal
chronic wounds. Further progress in advanced wound
management will require an improvement in personalized
medicine for the patient and in particular an improvement in
the availability of diagnostic tests and parameters that fulfill
clinical need in wound management decisions. However,
without easy to use sensors for nurses and carers these
potentially important near-patient diagnostic parameters will
not enter clinical diagnostics. This study focuses on a number of
metrics for wound condition and wound healing: wound fluid
pH, wound moisture, and wound matrix metalloproteinases
(MMP) enzyme activity. To observe these important markers
state of the art sensors have been developed that are based on
inexpensive sensing technologies that can be integrated within
wound dressings. These sensors will enable the wound healing
markers to be studied and profiled in clinics which will further
enhance the understanding of these markers and their
relationship in the complex healing process involved in chronic
wound healing.

I. INTRODUCTION

Chronic wounds are a growing problem worldwide with the
annual spend close to £190 million on wound dressings alone
by the National Health Service, in England, during 2011 [1].
In the USA chronic wounds accounted for 31.4% of all
direct treatment costs for dermatological diseases [2].
Chronic wounds mostly affect the over 60’s and with an
aging population this problem is set to rise on year on year [3].
The high costs associated with chronic wounds are due to
their complex healing patterns which do not follow the
standard healing path of an acute wound and result in
delayed healing. Currently there is a real lack of analytical
tools available that assess the real time state of the wounds.
At presents clinicians rely on subjective observations to
evaluate the healing of the wound and use treatments
selected from their experience on a trial and error basis to
achieve healing in chronic wounds. Clinical staff are thus
faced with a plethora of choices in dressings and treatments
with many competing manufacturers’ protocols to consider
during treatment selection. Each visual examination of a
wound to judge its stage of healing requires removal of the
wound dressing. Wearable sensors to monitor the condition
of a wound under the wound dressing will enable the state of
the wound to be observed without disturbing the wound by
removing the dressing.
The use of analytical measurement tools for measuring
healing parameters in wounds is still an emerging field in
wound management and treatment. Analytical measurements
such as wound pH, wound size, protease level and moisture
balance would enable an objective measurement of healing
to provide the clinician with the most efficient and effective
techniques to heal the wound.

These sensors will enable the wound healing markers of
moisture, pH and MMP enzyme activity to be studied
simultaneously and profiled in wound healing clinics which
will further the understanding of their relationship in the
complex healing process involved in chronic wound healing.
The real-time measurement of these parameters is important
in ensuring that the wound microenvironment is maintained
in its optimum condition for healing to occur. These
parameters, if measured and made available to clinicians, can
provide a patient-specific, personalized, data-based approach
to the selection of appropriate wound dressing and wound
management protocols.

II. MARKERS OF WOUND CONDITION

A. pH in wounds

When the skin is broken the internal pH of the body is
exposed moving the pH from the acidic skin towards the
alkali pH of the internal body. There is a large range of
reported data on pH level of wounds with the range reported
from 5.45-8.9 [4]–[6]. The large range of pH values is
interesting as the level of pH directly and indirectly affects
all of the processes that take place in the wound. The pH of a
wound varies as it heals moving from an alkaline pH towards
an acidic pH during re-epithelialization as the skin layer
reforms [7]. Research has shown that non healing wounds
and those with a high bacterial load generally have a pH
level above 7.6 [8]. The trend in recent advanced wound
dressings in reducing pH suggests that a lower wound pH
helps start the healing process of chronic wounds. In a recent
study by the authors it was found that certain wound
dressings reduced the pH of a model wound bed significantly
[9]. A lower wound pH would increase the wound oxygen,
reduce MMP levels and reduce the proliferation of bacteria.
While this trend toward lower pH may help with some
aspects of the healing process the overall role of pH in a
wound is not fully understood and further research needs to be conducted. There is currently no data to suggest the most effective pH level for wound healing. The lack of data on this subject is somewhat related to the difficulties in measuring wounds. The standard glass pH electrode is still the only effective way to measure the pH of a wound. They are expensive and difficult to sterilize. The pH electrode has not been successfully adapted into smaller and alternate packaging because the membrane that forms the selective part of the electrode, being made of silicon glass, is fragile, thus limiting manufacture, sterilization and practical application. A tool to measure pH level in an easy, cost effective and reliable way will enable the pH of a wound to be studied further to find its overall influence on the healing process and results from a prototype early device are presented in Section IV.

B. Moisture of wounds

Moisture of the wound is now accepted as a key element in the condition of the wound bed [10] based upon the evidence that cell proliferation and migration is facilitated by a moist environment. International clinical practice guidelines known as the TIME guidelines now stress the importance of moisture control in the wound healing cycle [11]. Modern wound dressings provide better control and absorbance of wound exudate, however, the actual moisture status inside the dressing at the wound surface is not known. Achieving a moist wound environment relies on clinical judgment to determine the correct therapeutic levels, since too little moisture will desiccate the wound and too much will lead to maceration of the wound bed and surrounding tissue. A study by McColl et al [12] using a new artificial wound bed and in situ moisture sensors showed some surprising results as some popular wound dressings dried out the wound and others allowed liquid to pool on the wound surface. The importance of moisture balance in wound care continues to be the subject of great interest in wound healing.

C. Protease level in wound

Chronic wound fluid contains a greatly increased level of protease activity up to 30 times that of an acute wound[13]. Matrix metalloproteinases (MMPs) are involved in every phase of wound healing [14]. In acute wound healing they act to remove necrotic tissue, promote migrations of fibroblasts and keratinocytes, regulate the activity of some growth factors, contract the wound matrix and promote angiogenesis. During the final stages of re-epithelialization they are active in remodeling the newly formed granulation tissue. As a chronic venous ulcer wound moves towards healing the activity of MMPs decreases. If the balance of the proteases is upset within a wound it can upset the cellular processes preventing healing and eventually causing further damage to the wound. It has been suggested that MMP2, MMP8 and MMP9, as they degrade type I fibrin collagen, have the biggest role in degrading the extracellular matrix and have been found at high levels in chronic wound fluid [11] [15]. The measurement and study of these important wound healing markers will enable clinicians to have a clear idea of the protease activity in the wound and tailor patent treatment accordingly.

III. METHOD OF DETECTING WOUND CONDITION

A. pH sensor

The pH sensor presented in Fig. 1 and developed by the authors is based on inexpensive screen printing technology. The sensor is based on potentiometric method of detecting pH in liquid samples. The sensor has been developed so that it can accurately measure pH accurately with as little as 10µL of wound fluid sample. The sensor has been used in a trial looking at how wound dressings influence the pH of the wound environment [9]. To test for practical use a sterile cotton bud swap was used to absorb fluid then pressed onto the sensor to transfer some liquid. During the test this method worked successfully and gave a stable pH reading over the pH range 4-10. The sensor hardware device was designed for simple operation by a nurse or carer to give accurate readings with small sample volume. The sensor could be modified to allow it to be placed within a wound dressing and provide real time pH conditions of the wound.

Figure 1. Hand held measurement device with sensor shown at top of device.
B. Moisture sensor

The author group at the University of Strathclyde have now developed a sterile, disposable moisture sensor, suitable for use in any dressing worn by a patient, which allows the dressing moisture status to be checked without the need to disturb the dressing as shown in Fig. 2. This allows clinical staff to optimally time the dressing changes and dressing type and avoids pain for the patient while reducing the risk of infection. It was released on the healthcare market in 2011 and is now in clinical use in a number of centers.

The sensor was fabricated by screen printing silver chloride ink onto a biocompatible polymer. To stop the sensor from adhering to the wound during measurements a porous, non-adherent layer of material was added to the sensor to cover the AgCl measurement electrodes.

C. Protease sensor

To move towards creating a protease sensor the authors developed an ELISA sandwich assay for measuring MMP-9 at physiologically relevant levels. Using the MMP-9 ELISA assay as a gold standard a new point of care sensor is in development to allow the user to detect the MMP level in a wound using an electrochemical based method.

IV. SENSOR PERFORMANCE

A. pH sensor response

The sensor is able to detect the pH with as little 10µL of fluid in an operational range of pH 3.5-pH 10 as shown in Fig. 3. The sensor is stable to other small molecules, such as Na⁺ and K⁺, and they do not interfere with the measurement of the pH.

Figure 3. Response of a printed pH electrode each point was recorded with a 10uL sample size of pH buffer solution.

The pH sensor was able to effectively measure pH in a horse serum mixture with measured values only within 0.04pH of a glass electrode measurement. This result indicates that the pH electrode with screen printed Ag/AgCl reference electrode is able to accurately measure the pH of human wound fluid. The sensor has also been incorporated into a different form that is capable of being placed directly in a wound. This sensor type was used to record the real-time changes that occur after application of wound dressing to a simulated wound bed model [9]. During this research it was found that certain wound dressings could change the pH of a model wound environment to low pH values. This reduction in pH will have influence on the various different molecules and processes vital to wound healing. Further research into its effects needs to be conducted to understand pH influence in wound healing.

B. protease assay performance

The MMP-9 ELISA was successfully produced to show linear results over a clinical relevant range (0.01-100ng/ml) of MMP-9 concentration (Fig. 4). Investigations into preservation solutions which will enable the ELISA plates coated in antibodies to be stored at long periods at room temperature have been investigated. The ELISA will act as a gold standard for MMP detection using a electrochemical method.

Figure 4. Results of 100ng/ml poly concentration log scale of results (n=3) averaged with average zero subtracted.
C. Wound moisture sensor

The moisture sensor has a CE mark and is currently available for sale in the European and Middle Eastern markets with the university spin out company Ohmedics. WoundSense product is a single-use, sterile, disposable, moisture sensor for sale in the European and Middle Eastern markets with the university spin out company Ohmedics. WoundSense has a CE mark and is currently available for sale in the European and Middle Eastern markets.

The moisture sensor can be read for moisture level using a small, handheld meter as required. Because the dressing is not disturbed, having read the moisture level, can take decisions as to the most appropriate time to change the dressing, decide on a change of dressing type or that the wound requires extra moisture if necessary [16]. The sensor has been trialed with a smartphone based telehealth system to provide clinician with information on moisture content and indicate when a wound dressing needs changed.

Figure 5. Moisture sensor, Ohmedics

V. CONCLUSION

Each of the sensors developed gives a window to the condition of the wound bed. These wound based metrics will allow the clinician to observe the condition of the wound and apply different treatments to ensure the wound is at its optimum healing condition. The aim of the project is to use these sensors clinically to observe the effect of pH, moisture, and protease levels affect the wound healing condition. The wound moisture monitor can already be placed in situ in a wound and with further development the pH and protease sensors will follow to enable continuous sensing of these metrics of wound condition.

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REFERENCES


