The future of pressure ulcer prevention is here: Detecting and targeting inflammation early

Amit Gefen, PhD
Professor of Biomedical Engineering
The Herbert J. Berman Chair in Vascular Bioengineering
Department of Biomedical Engineering
Faculty of Engineering
Tel Aviv University
Tel Aviv 6997801,
Israel

The burden of pressure ulcers is one of the most important, yet unsolved, current medical problems. This article reviews the status of technology-based options to prevent pressure ulcers.

ABSTRACT

Pressure ulcers (PUs) are one of the largest unsolved medical complications today. The burden of PUs on society and healthcare cost continues to grow rapidly with the ageing population and spread of chronic diseases. The overall absence of advanced biomedical pressure ulcer prevention (PUP) technologies that assess risk and screen for PU formation in the clinic is concerning, especially in light of the progress being made in other fields of medicine. To develop such technologies, an in-depth understanding of the damage cascade resulting in PUs is necessary and is reviewed here in detail from a mechanobiological perspective. The paper describes the sequential and additive nature of the PU damage cascade. Specifically, the damage cascade includes the sequential damage associated with direct deformation, inflammatory response, and ischaemia. The additive nature of these damages highlights the importance of early detection of cell and tissue damage for PUP. Examples of current PUP technologies reviewed here include (i) biocapacitance measurements using a subepidermal moisture scanner, which identifies biophysical changes in tissue properties caused by early inflammation to aid in early detection and (ii) polymeric membrane dressings that prophylactically subdue the activity of nociceptive neurons to mitigate the impact and spread of inflammation. Development of these and other technology-based options to detect and mitigate PU-specific tissue changes caused by exposure to sustained deformations and the resulting inflammation and ischaemia is a timely and feasible endeavour for biomedical engineers and is anticipated to minimize the burden of PUs.

INTRODUCTION

The fastest growing segment of the human population is the elderly. With increased life expectancy, the rates of obesity, diabetes, and cardiovascular diseases climb, and the number of people with sensory or mobility impairments are rising rapidly as well. A major complication of impaired sensory and mobility capacities is the development of pressure ulcers (PUs), also known as pressure injuries in the US and Australia. Treatments for PUs are painful, lengthy, often require surgery, and impose a vast financial burden on healthcare systems worldwide. It is striking that PUs occur in 2.5 million patients annually in the US alone. Moreover, the cost estimates per single case range anywhere from $500 to $150,000 and total an inconceivable $11 billion US dollars annually.[1,2] The death toll from full-thickness or deep PUs is also devastating, totalling approximately 60,000 deaths per year in the US alone.[3] The prevalence and cost associated with PUs clearly indicate that this medical problem is far from being solved and that current clinical approaches are, at best, only partially effective in mitigating the resulting morbidity.

In recent papers, our work has suggested that a fundamental factor, which is also a barrier to improved clinical outcomes, is the lack of advanced biomedical technologies that are designated for pressure ulcer prevention (PUP) and used for both risk assessment and screening of PU formation in clinical practice.[4,5] Ideally, such technologies would facilitate cost-effective detection of cell and tissue damage, even under intact skin. Successful development and implementation of relevant technologies require, first and foremost, a deep and thorough understanding of the aetiology of PUs. This aetiology has been explored over the last two decades with the help of mechanobiol- ▶

Correspondence:
gefen@eng.tau.ac.il

Conflicts of interest:
Dr. Gefen is a scientific advisor to multiple companies in the field of pressure ulcer/injury prevention, including Bruin Biometrics LLC (CA, USA) and Ferris Mfg. Corp. (TX, USA), whose products are reviewed in this paper. The conclusions of the literature analysis presented here were not affected by this association.

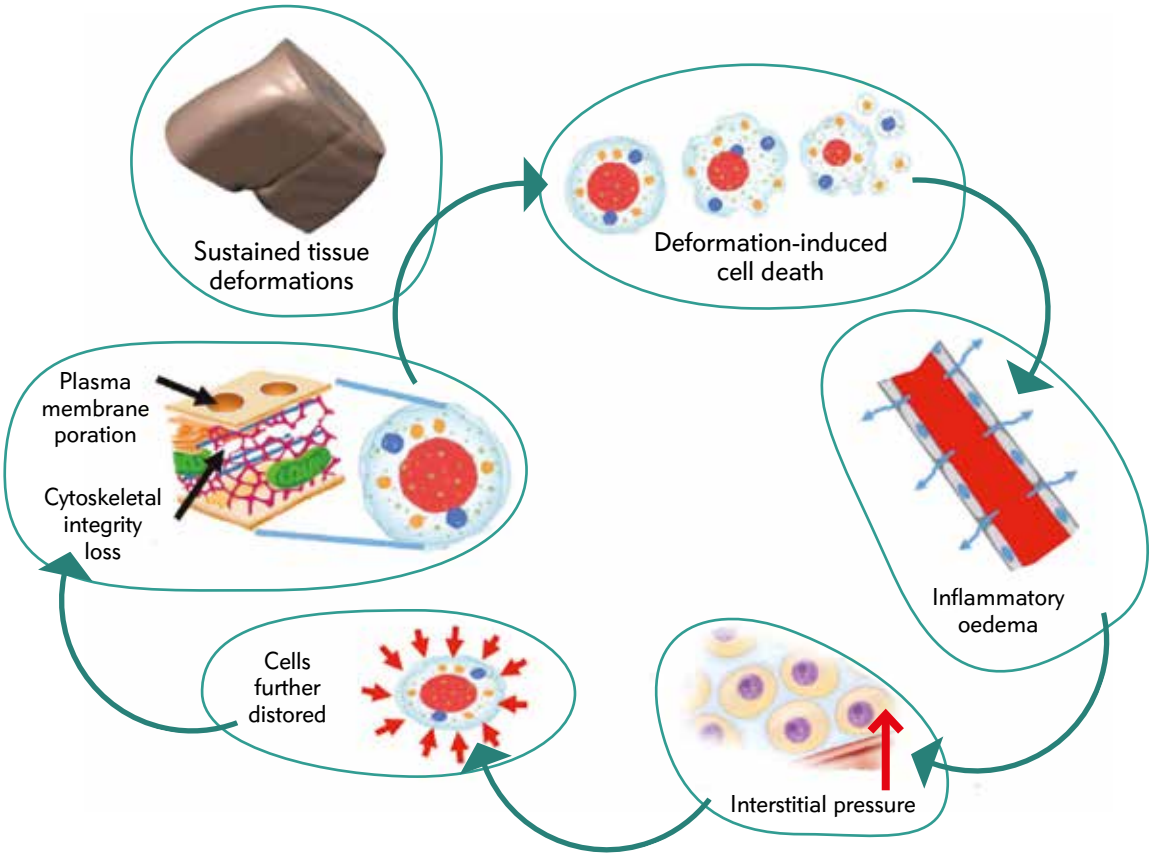

Figure 1:
The vicious cycle of deformation-inflicted and inflammation-related tissue damage in pressure ulcer formation. Sustained tissue deformations caused by bodyweight forces lead to loss of structural integrity in cells, disrupt the transport to cells via plasma membrane poration, and eventually lead to cell death. The first cell death events trigger inflammatory oedema, which increases the interstitial pressure in tissue regions confined between bones and support surfaces. This localized oedema increases cell distortion levels further, accelerating the damage pathway. At a later stage, after several hours of exposure to sustained bodyweight loads and under the influence of elevated interstitial pressure, ischaemic damage may begin to build up (not shown), further increasing the overall extent and rate of tissue damage.

ogy. Mechanobiology is an emerging field of science at the interface of engineering and biology that focuses on how physical forces and changes in the mechanical properties of cells, tissues, and their environment influence cell function and viability. As such, mechanobiology is at the heart of these recent scientific developments.

The complex structural and mechanical interactions that occur at different dimensional scales between weight-bearing tissues and support surfaces or tissues that are continuously distorted by medical devices determine the loading state of tissues and cells. These interactions are affected by intrinsic factors including the tissue composition, tissue stiffness properties, and individual internal anatomy, such as the shape of bone surfaces and the thickness of soft tissue layers. These body-support interactions are further influenced by extrinsic factors such as the design, material, and mode of operation of the specific support surface in use. The pathophysiological responses to these sustained mechanical interactions are also intrinsic to the individual but can be affected by extrinsic factors such as medications. To evaluate these complex interactions in the context of PUs, mechanobiology combines the study of multiphysics, which couples multiple physical phenomena, and multi-scale perspectives, which considers processes that evolve at the micro-, meso-, and macro-scales.

PUs and other chronic injuries develop over time, even if this time is relatively short, and do not appear instantaneously. In other words, there is a gradual damage accumulation process as opposed to a traumatic wound. At their initial phase, PUs cannot be detected by the unaided eye (including by expert experienced clinicians) because damage is initiated at the microscopic scale with the death of a few cells or small groups of cells. In many cases, such cell death events may occur over very short time intervals, even within minutes, and may undergo natural and spontaneous repair by the body without evolving into a visible injury. However, in other cases, the microscopic cell death damage initiates a damage cascade that results in the initiation and progression of a clinically significant PU. A significant portion of the mechanobiology of this damage cascade has been revealed by our basic science laboratory work in the last decade and is summarized as follows.

Bodyweight forces continuously distort tissues and cause sustained cell deformations that gradually damage the integrity of the cytoskeleton, which is the complex protein

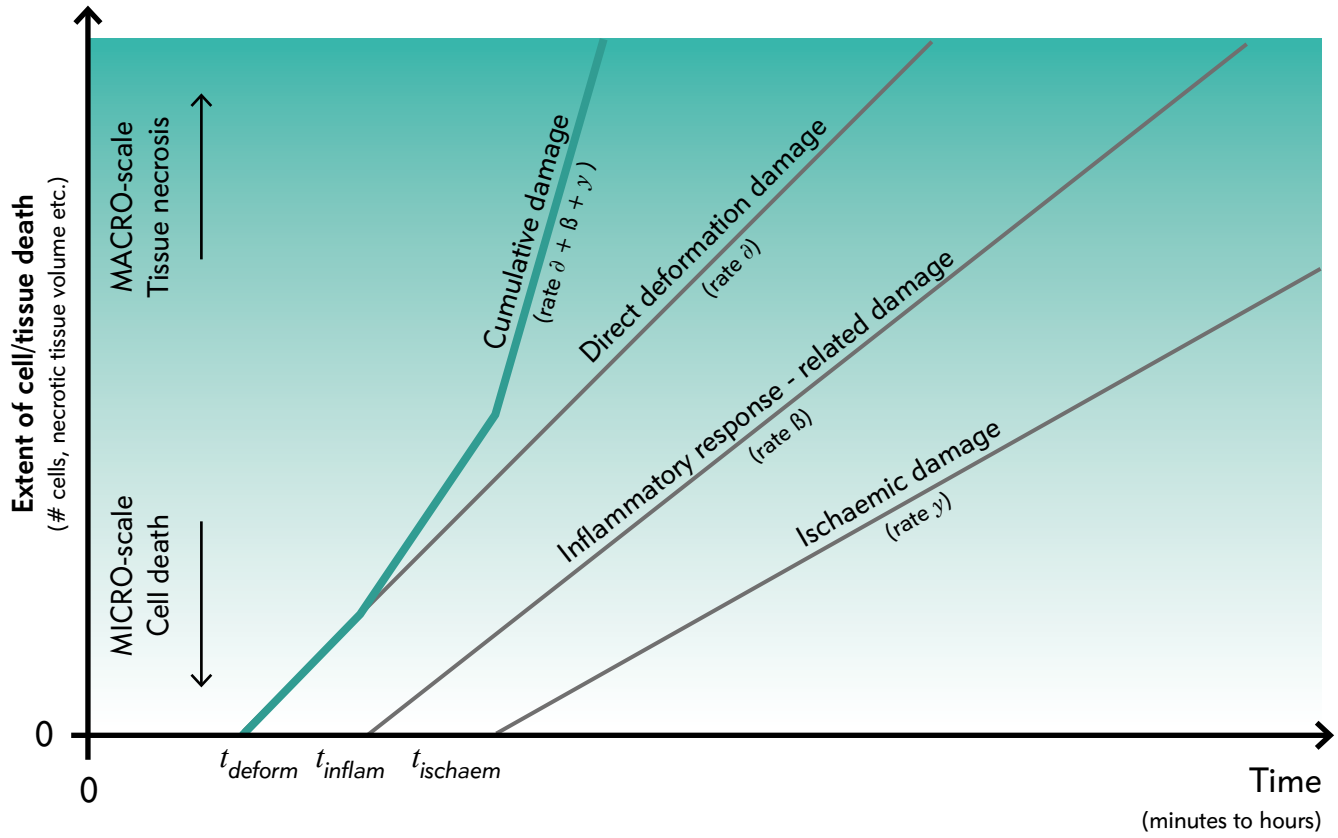

Figure 2:
There are three major contributors to cell and tissue death in pressure ulcers: direct deformation, inflammatory response, and ischaemia. (i) Direct deformation is the initial factor that begins to inflict damage at time point $t$deform and progresses at a rate α. (ii) Inflammatory response-related damage occurs second at time point $t$inflam and develops at a rate β. (iii) Finally, ischaemic damage is the last to appear at time point $t$ischaem and evolves at a rate γ. The combined contributions of these three factors at sequential time points explains the non-linear nature of the cumulative cell and tissue damage. This damage will accelerate from the micro-scale to the macro-scale and eventually exacerbate at a rate of α + β + γ.

scaffold that supports the cell structure from within.[6,7] These cell deformations cause the exterior cell walls or plasma membranes, which are structurally supported by the cytoskeleton, to lose their integrity as well. Loss of plasma membrane integrity leads to plasma membrane poration, increased plasma membrane permeability, abnormal transport patterns, and eventually loss of cell homeostasis and apoptotic cell death.[7,8,9] At the early phase of cellular damage, when small numbers of cells have died, the damaged cells release chemokines, which are inflammatory signals that attract immune cells (e.g., neutrophils, macrophages, and T-cells) to the affected site.[5,10,11] While this signalling is essential for repair of the microscopic tissue damage, inflammation itself is a potential contributor to progressive tissue damage. Specifically, the inflammatory chemokines dilate capillaries and increase the permeability of capillary walls adjacent to the damage site to allow leucocytes to leave the vasculature and migrate to the site of cell death. This causes plasma fluids to then leave the blood circulation and accumulate near the damage site, generating localized (micro-scale) oedema that gradually increases the interstitial pressure (Figure 1). Moreover, as these fluids are often confined to a limited tissue volume, such as between an internal bone surface and an external support surface or, in some cases, a medical device that is compressing the surface, there is little or no relief of the interstitial pressure that continues to build up at the initial damage site (Figure 1). Reactive oxygen and nitrogen species are then released to degrade the extracellular matrix (ECM) to relieve the pressure resulting from the accumulated fluids, further inflicting tissue damage.[12,13] The overall result is a tissue degradation spiral or 'snowball effect' where continuous tissue deformation and inflammation result in additional cell death and tissue damage that causes further inflammation and so on. Eventually, the combination of deformation caused by bodyweight or other external forces, the intensifying effects of oedema, and the associated high interstitial pressure begin to obstruct the vasculature and impair blood perfusion at the damage site. As a result, ischaemic damage may develop from that point onwards, in addition to the primary direct deformation damage and the secondary inflammatory damage. Importantly, it is critical to understand that each of these damage pathways begins sequentially at a different time point. Direct deformation damage, which is the primary cause of cell and tissue damage, begins first, followed by inflammatory-related damage, and finally evolves into ischaemic damage.

Clinical observations of short-term PU development exist and have been documented in cases of relatively high sustained tissue deformations inflicted over short periods of time, such as in the operation theatre, in labour under epidural administration or with the use of spine boards.[14,15] These are much shorter timeframes than the period of several hours that has been studied in the context of repositioning regimes in the classic PU literature (e.g.[16]). For extreme support surface conditions, such as stiff spine boards, macroscopic tissue damage is initiated within tens of minutes, and tissue breakdown may occur in less than an hour, even in people with a healthy body habitus.[15] Thus, these laboratory and clinical observations[14,15] could be extrapolated to predict that patients whose tissue composition is abnormal, such as underweight or obese patients, would experience accelerated tissue breakdown in timeframes of less than an hour. In such patients, the internal mechanical stress concentrations within tissues would be especially elevated near bony prominences, even if the support surface envelopment was improved.[17] In general, the tendency for tissue breakdown would strongly depend on the internal anatomical features (curvature of bone surfaces, mass, and composition of soft tissues) and on the interaction of the individual anatomy with the specific support surface that is in use.[18,19]

The evolution of cell and tissue damage in pressure ulcers

Our cumulative body of research and the work of others demonstrates that vulnerable or fragile patients who are at a chronic (e.g. suffer a spinal cord injury) or acute (e.g. under surgery) phase of susceptibility to PUs will exhibit tissue breakdown within relatively short time periods.[6] In these at-risk individuals, the time until tissue breakdown will likely be less than the typical 2-hour interval. In fact, tissue breakdown may occur within timeframes of an hour or less, merely due to sustained tissue deformation levels.[14] As time progresses during the first several hours of damage onset, there will be additional evolving damage due to the build-up of an inflammatory process, elevated interstitial pressure, and tissue stiffness due to oedema.[20] Ischaemic damage may accompany these tissue injuries or may be slightly delayed in terms of the damage spiral. Damage related to the inflammatory response and ischaemia will exacerbate the tissue status, which has already been compromised by exposure to sustained deformations, and increase the level of damage and fragility of surrounding healthy tissues as time elapses (Figure 2).

The evolution of damage schematic, which is presented in Figure 2, describes the concept of a tissue injury threshold and demonstrates why the injury threshold is not only tissue-type specific but also patient-specific. Consistent with the presentation of the damage spiral in Figures 1 and 2, the tissue injury threshold of a given tissue type is defined by the transition from micro-scale reversible damage, which typically occurs at the level of cells or cell groups, to macro-scale irreversible tissue damage, which is visible in an imaging examination by ultrasound or MRI, if subdermal, or presents itself on the skin surface (Figure 2). As previously discussed, a tissue injury threshold strongly depends on the characteristics and health status of the individual. For instance, a person with compromised tissue perfusion (e.g., due to peripheral vascular disease, congestive heart failure, or diabetes) would accumulate ischaemic damage faster, initiating the ischaemic damage component sooner. In other words, their $t_{ischaem}$ would be shifted closer to the origin of the timescale (horizontal axis) (Figure 2). Likewise, their ischaemic damage build-up would likely occur at a higher rate (i.e., γ rate would be greater) because their tissue would have access to fewer available metabolites than a person whose vasculature is affected by exposure to the deformation but not by the biochemical stress due to a chronic vascular or metabolic disease. Another example illustrating the expected diversity in damage accumulation rates across individuals are patients with chronic inflammation, such as those seen in obese, elderly, and spinal cord injury patients. In such cases, the inflammation-related damage onset time t_{inflam} would likely be shorter due to over-stimulation of the inflammatory system, and the inflammatory damage rate β would also be greater.

Importantly, each of the factors contributing to the damage spiral—deformation, inflammation, and ischaemia—depend on individual intrinsic features as well as on extrinsic/environmental factors. Specifically, the time of appearance and rate of build-up of the primary deformation-inflicted damage, t_{deform} and α, respectively, will depend strongly on the anatomical features of the individual, including the sharpness of bony prominences, mass and composition of soft tissue, and characteristics of the bone-soft tissue interactions. Altogether, these characteristics dictate the state of mechanical loading, in terms of magnitude and distribution, at the scale of tissues and cells. The inflammation damage parameters (t_{inflam} and β) and the ischaemia parameters ($t_{ischaem}$ and γ) likewise depend on individual intrinsic and extrinsic factors. For example, the presence of intrinsic acute or chronic diseases that affect the immune and cardiovascular/respiratory systems impact the inflammation and ischaemia damage parameters, respectively. Similarly, medications that affect the immune system, such as anti-inflammatory steroids and chemotherapy, or the cardiovascular system, such as vasodilators and vasopressors, are extrinsic factors that respectively influence inflammation and ischaemia parameters as well. Accordingly, at the macro-scale phase of the PU development process, the rate of damage build-up is sensitive to each of the intrinsic

and extrinsic factors that are involved or potentially involved (e.g., the anatomy, support surface, inflammatory response time/extent, effectiveness of perfusion and level of tissue oxygenation, extracellular biochemistry including pH). Together, quantitation of the macro-scale damage rate is simplified to the sum of $\alpha + \beta + \gamma$, as shown in Figure 2. Most notably, the damage threshold of *t*issues can be defined as the transition from a microscopic (reversible) cell death event to a macroscopic clinical wound presentation and strongly depends on the individual set of time and rate parameters described above (Figure 2).

Moreover, acute events in a patient's life, or even during a relatively short hospitalization period, may temporarily affect the individual values of the aforementioned parameters. Examples of these events may include infectious diseases that influence the characteristics of the inflammatory response (e.g., extent of the response, timescale of the response) or the quality and effectiveness of perfusion (e.g., the effectiveness of perfusion would be reduced in pneumonia). Thus, injury thresholds and damage build-up rates are not only variable across populations and individuals but also dynamic in nature. In other words, the *t*issue injury threshold of the individual changes over time, potentially even during a relatively short period of hospitalization due to acute illness.

The extrinsic factors influencing all three damage build-up pathways, namely, deformation, inflammation, and ischaemia, should be discussed separately from the intrinsic factors. As an extrinsic factor, the role of support surfaces is particularly noteworthy. Theoretically, support surfaces should have a direct effect on tissue deformation levels and distributions, which is relevant to the primary deformation damage pathway. However, support surfaces may also affect the level of interstitial oedema through pressure relief and may, therefore, impact the onset and progression of inflammatory damage or the quality of perfusion related to ischaemic damage. More advanced support surface technologies are likely to influence the onset time points of tissue damage and the damage accumulation rates in the individual. For example, alternating pressure mattresses (APMs) provide periodic pressure relief, enabling the restoration of blood supply to tissues.[21,22] Thus, the value of APMs may be due to the reduction of the ischaemic component of damage accumulation, which would enhance overall tissue tolerance.[21,22] Returning to the example of a person with impaired or poor perfusion, a shorter *t*ischaem and greater *y* rate would be expected. Such a person, if not protected by an APM, would develop a PU sooner because their ischaemic damage would build up rapidly. The APM could, therefore, play an important protective role in delaying the *t*ischaem on the time axis (Figure 2), with the extent of shifting *t*ischaem depending on the specific design and technological features of the APM in use.

Despite what appears to be an extremely complex problem that, given the large number and variety of contributing and influencing factors, would make efficient risk assessment and early detection of PUs impossible (Figures 1,2), it appears that the future is quite optimistic or is perhaps already here. As the use of technological aids for PUP is on the rise, the next generation of risk assessment and early PU detection will likely be based on quantitative monitoring of individuals based on the parameters defined in Figure 2 or derivative or physiologically-linked parameters. Therefore, a next step in the evolution of PUP technologies is to integrate these parameters into new risk assessment procedures that will then become objective, standardized, and fully quantitative rather than subjective, non-standard, and qualitative, as in current practice. The vision of the author is that the *t*deform, *t*inflam, and *t*ischaem time points and the α, β, and γ parameters (Figure 2) will be evaluated and quantified for each individual based on a set of biophysical, biomechanical, and physiological measurements. This will ultimately allow PUP devices, including support surfaces and prophylactic dressings, to be evaluated, rated, and classified based on their effect on the deformation, inflammation, and ischaemia parameters. In fact, these technologies are already commercially available and now need to be put in the context of the current understanding of PU aetiology, as illustrated in Figures 1 and 2.

Although PU detection and PUP technologies have been recently developed, and new technologies are underway, the time point at which their implementation will be the most effective and allow for the least progression of the damage cascade warrants further discussion. Identifying the very first deformation-inflicted cell death events that occur exactly at the time point *t*deform may not be feasible in the foreseen future, particularly considering that damage may, and likely will, evolve in subdermal and deep *t*issues. Moreover, cell death events occurring near the *t*deform time point may be fully reversible if the body is able to repair the damage. Therefore, detecting damage at or very near to the *t*deform time point may be too early and, in fact, create many 'false alarms', or false positives (i.e. low specificity), in a technological implementation method which targets *t*deform. Accordingly, the inflammation response to these initial deformation events, which is initiated at time point *t*inflam, is very likely the next best option. Nevertheless, identifying cell and tissue damage as early or as close to the *t*inflam time point as possible, or perhaps slightly before *t*inflam, is still critically important. Altogether, inflammation is the candidate event

that presently needs to be targeted by PUP strategies and technologies. Examples for currently available technologies that intervene in the vicious cycle depicted in Figure 1 or target the damage evolution parameters described in Figure 2 are provided below.

Examples of novel and available technologies that target early inflammation.

The subepidermal moisture (SEM) scanner

The SEM scanner (Bruin Biometrics LLC, Los Angeles, CA, USA) is a hand-held device that measures the biocapacitance of tissues at a depth of several millimetres under the skin (the SEM scanner is CE-marked, pending US Food and Drug Administration decision, and not available for sale in the US). tissue biocapacitance rises when extracellular water content, also called SEM, increases due to the localized micro-oedema that forms shortly after the $t$inflam time point (Figure 2). According to the physics of capacitance, water has a high dielectric constant of 80 compared to dry collagen, which is the major structural component of the ECM and has a much lower dielectric constant of four. As localized (micro-scale) oedema builds up (Figure 2), the effective dielectric constant (EDC) of the tissue region affected by the developing PU rises linearly in relation to the percentage of water in the $t$issue.[4,5] For example, if the ECM:water content in a healthy $t$issue region is 40:60, then the EDC of that $t$issue is the weighted average of the individual dielectric constants, or (0.4 x 4) + (0.6 x 80) =~ 50. An abnormal increase in the water content would change that ratio to 20:80 and would then increase the EDC of the affected tissue to (0.2 x 4) + (0.8 x 80) =~ 65, which is 30% greater than the healthy EDC value. Thus, the time point at which the EDC began to deviate from the normative value and the rate of change in the EDC with the progressive development of $t$issue damage are biophysical measures indicative of $t$inflam and β, respectively (Figure 2). In other words, the SEM scanner technology directly targets the early inflammatory response/damage pathway in the damage cascade (Figure 2) and uses the biophysical changes associated with the onset and formation of localized micro-oedema, or SEM, as an effective biophysical marker for early detection of PUs.

Polymeric membrane dressings

Polymeric membrane dressings (PolyMem®, Ferris Mfg. Corp., Fort Worth, TX, USA) are multifunctional dressings that focus and control inflammation and oedema. These dressings subdue the intensity and spread of the inflammatory response and minimize potential secondary oedema-related damage (Figures 1,2). The mitigation of secondary damage increases the likelihood for reversal of the initial injury and self-healing. Published experimental evidence suggests that the design and structure of the PolyMem® dressing material inhibits the activity of nociceptive neurons, which produce neurogenic inflammatory signals through release of calcitonin gene-related peptides.[11,23,24] As the immune and peripheral nervous systems are strongly coupled, inhibition of nociceptive neurons has considerable prophylactic value. Prophylactic use of the PolyMem® dressing may help control and contain the inflammatory response, including the formation of oedema and associated damage.[11] Thus, prophylactic use of the PolyMem® dressing would shift the onset of inflammatory damage, $t$inflam, to the right (future) and reduce the rate of inflammatory-related damage, β.

Summary and conclusions

The burden of PUs appears to be one of the most important yet unsolved current medical problems, and its impact grows continuously with the ageing of populations and spread of chronic diseases and conditions. As such, it is surprising that advanced biomedical technologies for clinical PUP, risk assessment, and screening are sorely lacking. The vicious cycle of deformation-inflicted and inflammation-related tissue damage in PU formation (Figure 1) has been described in this paper. Sustained tissue deformations, caused by either bodyweight forces or external sources (e.g., a ventilation mask tightened to the face), lead to loss of structural integrity in cells, disrupt the transport to cells via plasma membrane poration, and eventually lead to cell death. Importantly, all of these events may transpire within a relatively short time, in the order of tens of minutes to approximately an hour.[7] The first cell death events trigger inflammatory oedema, which increases the interstitial pressure in tissue regions confined between bones and support surfaces.[11] This oedema further increases cell distortion levels, accelerating the deformation damage pathway and so on and so forth. After several hours, the combined effect of deformation forces and increased interstitial pressure begin to impact vascular function, which can adapt in the short term (e.g., via vasodilation) but not over prolonged periods of exposure.[25] At that time, ischaemic damage is initiated and builds, adding to the overall extent of tissue damage. The step-wise additive nature of the damage contributors, deformation, inflammation, and ischaemia, makes the damage development process (and the relationship of damage extent versus time) highly non-linear (Figure 2).

In bioengineering terms, the theory developed here to describe the damage evolution breaks the damage process down into three major sequential contributors to cell and tissue death in PUs, as follows (Figure 2). (i) Direct deformation damage, which begins first at time point $t$deform and progresses at a rate α. (ii) Inflammatory response-related damage, which occurs second at time point $t$inflam and develops at a rate β. (iii) Ischaemic damage, which is the last to appear at time point $t$ischaem and evolves at a rate γ. Together, these variables explain the non-linear nature of the cumulative damage, which is generally expected

to accelerate from the micro-scale to the macro-scale and eventually to a full-scale rate of $\alpha + \beta + \gamma$. The non-linear accelerating nature of the damage curve highlights the necessity of early detection at the soonest possible stage followed by appropriate intervention to relieve tissue deformation and halt the damage aggravation process. Inflammation markers are promising for early detection, as they appear relatively quickly in the damage spiral, while cell death is still contained to the microscopic level, near time point $t$inflam.

Targeting early cell and tissue damage for early PU detection and PUP interventions must be based on an in-depth understanding of the mechanobiological damage cascade. Moreover, these interventions need to be evaluated or classified by the damage development theory that has been detailed here. Recent early detection and intervention advances using the SEM scanner and PolyMem® dressing, respectively, have been discussed in the context of the damage evolution process described in Figures 1 and 2. The SEM scanner identifies biophysical changes in affected tissue (biocapacitance) that have resulted from events near the $t$inflam time point and enables early detection between the $t$deform and $t$inflam time points. On the other hand, prophylactic use of the PolyMem® dressing to mitigate the impact and spread of inflammation past the $t$inflam time point is an example of an effective intervention strategy. Development of a selection of these technology-based options for early detection of events near the $t$deform to $t$inflam time points (Figure 2) and effective intervention as close as possible to the time of detection is necessary to reduce the human suffering and financial burden associated with PUs. Furthermore, it appears that the most opportune time for early detection and intervention is indeed the $t$deform to $t$inflam time range (Figure 2), as opposed to post-$t$ischaem. At these later time points, the direct deformation damage and inflammation-related damage have already occurred, and damage begins to progress at a full rate of $\alpha + \beta + \gamma$. Finally, a major focus of bioengineers should be to work closely with clinicians and basic scientists to bring PUP into the era of science and technology in an effort to solve this unacceptable problem. Development of portable or hand-held systems for detecting multiple biomarkers of inflammatory and PU-specific changes that indicate early cell death is a timely and feasible mission and will ultimately minimize the heavy burden of PUs.

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