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How medical engineering has changed our understanding of chronic wounds and future prospects

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ABSTRACT

Chronic wounds which fail to progress to healing are currently considered among the most important, unsolved and expensive medical burdens, on the same scale of healthcare costs as all obesity-related problems taken together. Pressure ulcers (PUs) and diabetic foot ulcers (DFUs) make the most significant portion of these hard-to-heal wounds. Our research in the last twenty years has explained why quantitative, absolute and generic injury thresholds to predict when PUs or DFUs may occur will forever remain intangible, despite the vast efforts and resources that have been invested in allegedly discovering such injury thresholds. This perspective article explains the specific reasons for this, yet, it also describes the routes for constructive future medical engineering work which will likely lead to better prevention and treatment of PUs and DFUs, even if currently there are no simple or straight-forward injury thresholds to predict when a person may suffer a chronic wound. The role of mechanobiology, as a relatively new medical engineering discipline, is being depicted, in the context of basic and applied chronic wound research. Physical and biochemical biomarkers for early detection and for targeting prevention are also discussed, given the availability of mechanobiological approaches and methodologies to discover or test feasibility of such biomarkers towards clinical use. Finally, some inherent complexities in the prevention and treatment of PUs and DFUs are elucidated, particularly that: (i) the susceptibility to chronic wounds depend on integrated body system functions which are extremely difficult to predict in individuals, especially in seriously ill patients, and (ii) a continuum exists between prevention and treatment of wounds, and hence, in many cases, clinicians are required to treat an existing wound and protect adjacent tissues from deteriorating at the same time. This paper is an overview of our contemporary research concepts and latest published aetiological discoveries related to chronic wounds. Interested readers are encouraged to further study our cited literature for comprehensive analyses of the multiple specific topics that are briefly described here.

1. Background

Chronic wounds, namely those which fail to progress to healing as expected, are currently considered among the most important, unsolved and expensive medical burdens, being on the same scale of healthcare costs as all obesity-related problems taken together [1]. The devastating consequences of chronic wounds on health and quality of life at all ages and across all clinical settings, from neonatal to palliative care, is growing at a frightening rate of 2% annually [2], and is fueled by the aging of populations and spread of diabetes. One good example for the vast economic impact of chronic wounds on human society is pressure ulcers (PUs), also called pressure injuries, which are tissue damage events caused by sustained exposure to bodyweight or external forces, when a person is temporarily or chronically insensate or cannot respond to discomfort or pain [3]. Despite massive efforts and the immense resources that are invested in mitigating this problem, it remains the only hospital-acquired condition on the rise in the US [4], where these injuries consume difficult-to-perceive healthcare costs of at least 26.8-billion dollars per year [5]. These costs far exceed the expenditure on diseases that currently 'enjoy' better public relations, such as all dermatological cancers taken together [1]. Interestingly, and related to that point, cancer deaths are continuously declining due to restrictions on smoking, regulation on consumption of carcinogenic agents in food, movements to reduce environmental pollution, awareness and public education, together with earlier diagnosis technologies. All of the above are undoubtedly the direct results of heavy and long-term investments in biomedical and medical engineering research. In chronic wounds, these research investments have not been made to comparable

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extents, and hence the above figures. Nevertheless, there have been important and recent discoveries in the field of chronic wound research, with promising prospects for the future, which will be highlighted in this perspective article.

One of the most influential and classic medical papers which drove the 2-decades-old research interest of the undersigned in chronic wounds was that of Reswick and Rogers [6] who were the first investigators to publish a report linking the magnitude of sustained weight-bearing pressures recorded upon humans with the time of exposure to these pressures, within the context of PU prevention (PUP). Reswick and Rogers paper [6] was apparently the first attempt ever to explain how the extent and duration of bodyweight forces relate to the complex etiology of PUs. Nevertheless, the authors of that seminal paper were naïve in the sense that they intended to discover a threshold, combining the pressure magnitude and time exposure above which PUs would develop, which – in some scientific and medical forums – is still considered the 'holy grail' of PUP. Similar efforts were taken to capture the pressure-time injury threshold (often referred to as the 'pressure-time integral') above which diabetic foot ulcers (DFUs) develop [7,8]. Like PUs, DFUs are also a terrifying chronic wound type, being a complication of diabetic neuropathy and the leading cause globally for lower limb amputations, again with financial consequences that are in the multibillion-US$ range in every developed or developing country [1].

Not surprisingly, PU as well as DFU injury thresholds are still elusive, and will likely remain the 'proverbial pot of gold at the end of the rainbow', but this is because, and not despite, the important research breakthrough that we have achieved in understanding chronic wounds. In fact, our research in the last twenty years has explained, specifically, why a quantitative, absolute and generic injury threshold for either PUs or DFUs will forever remain intangible. This article put forward the reasons for this, and will pave the route for what can still be done for preventing these wounds, even if there are no simple or straight-forward injury thresholds to predict when a person may suffer a chronic wound. While this is a brief introduction to the complex topic of injury thresholds in the context of chronic wounds, interested readers are encouraged to find comprehensive models, information and data, and in-depth explanations with examples in our recent review articles and the upcoming Etiology Chapter of the International Guidelines for Pressure Ulcer Prevention and Treatment [3,9,10].

2. The role of mechanobiology in chronic wound research

The majority of the contemporary, published scientific knowledge upon chronic wound etiology and its implications to prevention, e.g. PUP, arise from mechanobiology, employing tissue-engineered and cell culture laboratory models [9,11–18]. These living model systems have demonstrated that the damage occurring to the cytoskeleton and plasma membrane when cells are chronically distorted and deformed, in a weight-bearing posture or when sustained external forces are acting on tissues (e.g. from an object as in medical device-related PUs or with regard to DFUs), is the root cause of formation of all PUs and DFUs [9,11–18].

Chronic wounds are rarely seen in individuals who are otherwise healthy, although PUs may develop in such healthy persons when they are in a transient mode of insensitivity or stationary body positions, as in operating theaters, epidural administration during labor or other states of unconsciousness or analgesia. In other common conditions, there will be a neurological or neuromuscular disease, or spinal cord or brain injury in the background, limiting or eliminating a person's ability to sense or respond to discomfort and pain. The variety of these medical conditions will impose high variability in tissue structures and compositions, neurological and immune system functions (and hence inflammatory response variations), and also, altered central or peripheral vascular function conditions. All of the above will introduce large variations in the biomechanical conditions at the meso–scale (of tissue structures) as well as at the micro-scale and nano-scale (of cells and subcellular structures). For example, the magnitudes of cell (and of course, continuum tissue) deformations will always depend on the characteristics of each individual patient, because they are functions of their internal anatomy (or patho-anatomy), tissue composition and tissue mechanical properties - which are in turn a function of age, health status and chronic conditions. The basic understanding that cell and tissue damage results, first and foremost, from exposure to internal tissue distortions and deformations, which are always different across patients (even if the forces or pressures at the body-support interface are similar), is, surprisingly, relatively new. This latter understanding has been predominantly the result of development of *in silico* modeling means (supported by the progress in computer power – from both hardware and software perspectives) to describe the multifaceted biomechanical interactions in various complex unhealthy anatomies [10,18].

External forces acting on the body (such as during lying, sitting or walking) cannot directly translate to internal tissue and cell distortions, particularly if the internal anatomy (macroscale and microscale) and tissue/cell mechanical properties are unknown and are progressively being affected by a disease or chronic conditions. It is primarily for that reason that internal tissue damage cannot be predicted based on measurements taken at the surface of the body, for example sitting interface pressure or plantar pressure measurements. While it has been known, since the early days of computer (finite element) modeling in biomechanics, that bodyweight loads may distribute in distinguishable patterns in bodies and tissues of different individuals, the consequences of these loading exposures on cell and tissue viability and function were, and still are, not fully elucidated. Our research over the last decade has taught us that depending on the internal mechanical states in tissues and cells, gradual degradation of the cytoskeleton and plasma membrane may occur, which leads to impaired control over transport through the cell's plasma membrane, and therefore, rapid loss of homeostasis [12,14,16]. The loss of control over transport is caused directly by the sustained exposure of cells and tissues to mechanical loading, and is not directly related to availability of oxygen or metabolites transported by blood circulation [12,14,16]. In other words, PUs and DFUs are caused by tissue distortions and deformations, of static or dynamic nature, respectively, and not primarily by poor blood supply, or ischemia, which was the false premise for centuries. This important discovery – that sustained or excessive tissue deformations are the primary cause of cell and tissue damage - has required the mechanobiological research approaches to induce cell distortions and monitor transport through advanced microscopy and image processing, which only became fully available in this last decade [9,11,12,14–17]. Hence, the mechanobiology perspective – which is clearly a medical engineering approach that is still considered 'special' and 'unique' in wound care research (as opposed to orthopedic, cardiovascular or cancer research) - facilitates examination of the origin of PUs and DFUs at the cell scale (rather than at the systemic level or when a wound becomes macroscopic, visual and clinically identifiable). Mechanobiology has identified the specific cell-level events that occur within minutes and up to just a few hours after the exposure to the mechanical distortions, at which time there is no 'clinically significant' tissue damage yet, but damage will become a 'chronic wound' unless interventions will be taken at that early stage already. The potential to develop new early-diagnosis and preventative means, based on cell damage markers, is a natural next step from the aforementioned bioengineering discoveries.

3. Biomarkers for early detection and for targeting prevention

In a world which is always short of resources for healthcare, plans for prevention of chronic wounds (which is clearly a superior strategy than just providing treatment) need to be based on the following principles: (i) early detection of patients who currently develop a chronic wound, (ii) identification of patients who are at a relatively high-risk for developing chronic wounds, (iii) effective interventions for the aforementioned patients. Biomarkers which are currently used to diagnose numerous diseases are also expected to be pivotal in upcoming breakthroughs in wound diagnosis and care. Out of the many possible biomarkers, the ones associated with the inflammatory process appear to be the ideal candidates for achieving the relevant technological advancements. Chronic wounds typically halt their healing in the inflammatory phase, which is the gateway to tissue repair: Without inflammation wound healing will not initiate, however, unleashed inflammation will lead to additional biochemical and biomechanical stress to cells, which will inflict secondary tissue damage [19].

With the deformation-inflicted death of the first cells, which lose their structural integrity and then their homeostasis, an inflammatory response is triggered, by secretion of chemokines and neurotransmitters (e.g. histamine) from the damaged cells and from nearby immune cells. The aforementioned signaling molecules dilate and increase the permeability of blood vessels to allow crossing (extravasation) and migration of additional immune cells such as phagocytes, which are recruited from the blood circulation to the tissue damage site [9,19]. This results in ongoing leakage of plasma fluids from the diluted and permeable local vasculature into interstitial spaces in the tissues in the vicinity of the forming wound, thereby forming edema (Fig. 1). That edema is first formed microscopically, and then progresses to become macroscopic. A similar response is observed in the lymphatic vessels which enlarge and become leaky, further contributing to the forming edema [20]. The clinical edema, characterized by swollen, firm and warm inflamed tissue is reached at the fully-developed phase of this inflammatory response, and is expected in any wound. If, however, for various reasons e.g. due to a dysfunctional immune system, or a chronic inflammatory state (a characteristic trait of diabetes and obesity), a stagnation in the repair process is established, the wound becomes chronic [19]. Medical engineering has recently began to target the mere onset of the inflammatory response, or signs for the inflammatory response to stagnate, as markers for the development of the wound or for the prognosis of its healing. One example is tissue biocapacitance, which is a biophysical marker for detecting initial tissue damage, based on the increased level of fluids that build-up in the interstitial space [21]. The greater interstitial fluid contents will change the biocapacitance of the affected tissues (as water has greater dielectric constant than tissue proteins), and so, biocapacitance measurements of tissues may reveal a forming microscopic injury several days before it evolves into a chronic wound [21]. The physical biomarker of biocapacitance may be used as a stand-alone biomarker, and has indeed been commercialized as a medical device called the SEM Scanner (by Bruin Biometrics LLC, BBI, Los Angeles CA, USA) [21]. An alternative approach would be to detect chemical biomarkers of cell damage in sweat, blood or urine. For example, corresponding to the subcutaneous processes that occur with inflammation, as described above, the inflammatory cytokines interleukin-1α (IL-1α) are secreted in sweat [22] but would indicate skin irritation, not necessarily deeper tissue damage. Other candidate molecular biomarkers for skin damage that have recently been proposed in the literature as related to PUP were plasminogen activator inhibitor 1 (PAI1), vascular endothelial growth factor C (VEGF-C) and heat shock protein 90α (HSP90α) [23]. The detection of these chemical biomarkers is currently more complicated and potentially more expensive than the aforementioned biocapacitance measurements, given that these biomolecular analyses require biochemical assays and blotting procedures and protocols [23], and since some of these markers e.g. IL-1α are specific to skin irritation (and do not necessarily point to subdermal tissue damage). Accordingly, such biochemical markers [22,23] are presently limited for clinical use, but may become clinically applicable in the future. Another relevant example is chemical biomarkers that point to a destruction of a specific tissue type. For instance, myoglobin and troponin levels in blood and myoglobin in urine increased in rat models of PUs where skeletal muscle tissue damage has been inflicted [24]. Regardless of whether we will observe the discovery of new chemical biomarkers which will add meaningful information to the presently, clinically available biocapacitance measurements, it is already evident that targeting inflammation is a promising approach for early detection of chronic wounds, as well as for risk assessments of PUs and DFUs. Again, mechanobiological medical engineering research is playing a key role in these discoveries and in opening new research paths.

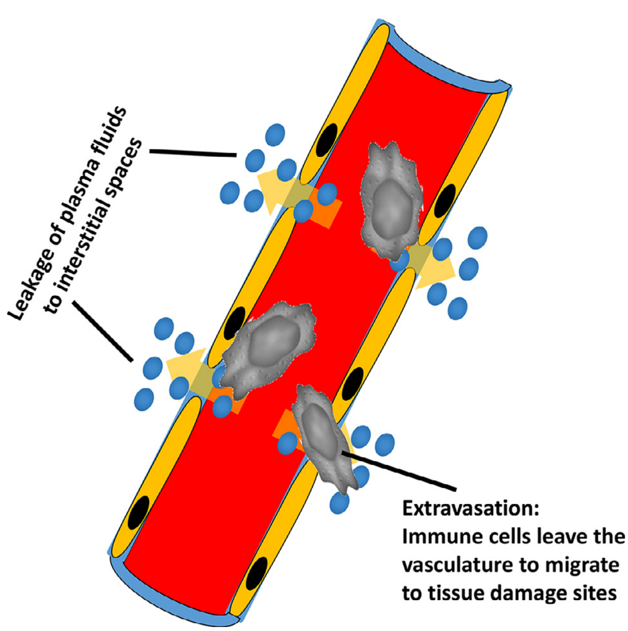

Figure 1. Illustration of the mechanism of formation of inflammatory edema. The process of extravasation, where immune cells leave the vasculature to migrate to sites of tissue damage, involves ongoing leakage of plasma fluids from the diluted and permeable vasculature into interstitial spaces in the tissues. These fluids gradually accumulate to form macroscopic edema. While still being microscopic, the edema is hidden under the skin and does not yet present itself clinically as a swollen, firmer and warmer tissue region.

4. Chronic wound risks depend on integrated body system functions

Another important factor contributing to the individual susceptibility to PUs and DFUs is the function of the cardiovascular system, and, in particular, the quality of peripheral perfusion [25]. The contribution of the cardiovascular system is not limited to supplying oxygen and metabolites to the mechanically distorted tissues, as traditionally suggested when describing ischemic damage in PUs and DFUs. It is important to understand that the vasculature is also the infrastructure for the function of the immune system and for achieving an adequate inflammatory response. The inflammatory response, as in the famous ‘Goldilocks’ principle', needs to be just right for repair of micro-damage before it becomes macroscopic, or, for healing of macro-damage if such exists while avoiding chronicity [19]. The supply of leukocytes to the damage site must not be too low, nor the permeability of the vascular walls too high, otherwise, no repair or excessive oedema, respectively, would occur. Interestingly, diabetes, which is known to contribute to the risk of chronic wounds (both DFUs and PUs), is characterized by endothelial dysfunction that increases the basal vascular permeability [26] which then exposes tissues to more acute edema events when inflammatory edema is triggered. At the same time, diabetes is associated with poor peripheral circulation [25] which limits the rate of extravasation of leukocytes that can migrate to a potential damage site (where deformation-inflicted cell death occurred). This explains why PUs and obviously DFUs are especially difficult to heal in people with diabetes. Importantly, there is strong coupling between the function of the immune system (which should kick-in after the initial deformation-inflicted cell and tissue death), and the function of the cardiovascular system upon which the immune cells and signaling systems rely, in order to respond to the cell and tissue damage. That coupling of the two body systems is not sufficiently understood. For discovery of new PU and DFU biomarkers, for quantifying the efficacy of protective means and for monitoring wound healing, further research will be required in this regard.

The ischemic (poor perfusion) damage pathway, which used to be perceived as the "one and only" cause of tissue damage in PUs, and, also, be referred to as the primary cause of DFUs, is now considered a tertiary contributor to these chronic wounds [3,9]. It is now understood that on the timescale of tissue damage accumulation, ischemic damage would occur after both direct deformation damage and inflammatory damage have already substantially compromised cell viability and tissue integrity [3,9]. Nevertheless, the complexity of the damage cascade is such that all the aforementioned damage factors – deformation, inflammation and ischemia – not only contribute as independent factors but also, though interactions [3]. High deformations will typically promote greater inflammation, but if that inflammation becomes chronic (which is driven e.g., by chronic cytokine signaling in diabetes), the extent of the inflammatory edema will escalate the deformation exposures in magnitudes and time [19]. Impaired vascular function may fuel the edema, limit the recruitment of immune cells, and hence interact with the inflammation response, which further interacts with the cell/tissue deformation state, and vice versa. This is typically a viscous cycle of 'negative' contributions to tissue health from these different factors, which eventually manifest clinically as PUs or DFUs. Referring again to the elusive nature of the injury threshold sought by Reswick & Rogers [6], the above microscopic, mechanobiological perspective that considers inflammatory and vascular processes and their interactions, points to the (perhaps somewhat disappointing?) fact that *a universal tissue injury threshold will never be found.* A person's state of tissue deformations, quality of the inflammatory response and vascular function depend on numerous factors including anatomical structure, age, nutrition and lifestyle, and any chronic or acute disease (Fig. 2). Likewise, in the unhealthy populations susceptible to PUs and DFUs, function of the inflammatory and vascular systems are also medication-dependent and will respond to, for example, antihistamines, chemotherapy, vasodilators or vasopressors (Fig. 2). All these factors will influence the integrated effectiveness of the body systems in responding to any massive cell death event, including those that precede a clinically visible lesion – a PU or DFU. The deformation, inflammatory and ischemic damage contributions with their specific onset time-points and rates of accumulation, will be superimposed together, in a highly individualized pattern which at the foreseen future, is not feasible to predict (Fig. 3). Nevertheless, continuously monitoring both the biomechanical and physiological responses of the distorted tissues, including the extent of deformations, the rate and frequency of deformation exposures, and

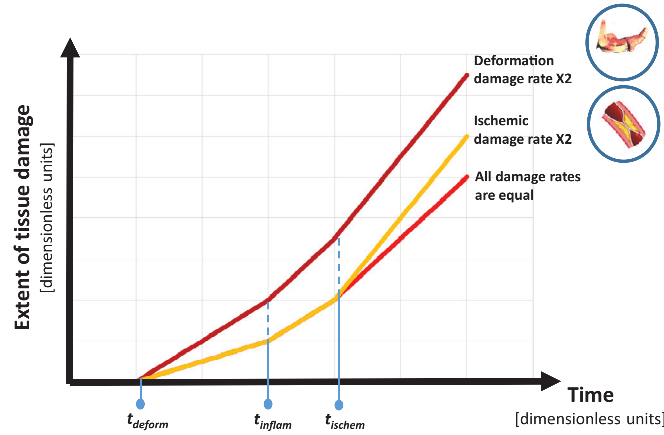

Figure 2. Simulations of the growth in tissue damage over time (in dimensionless units), based on the mathematical modeling of tissue damage accumulation described by Gefen in [9], where (i) the rates of damage accumulation due to deformation, inflammatory edema and ischemia are assumed to be equal (lower curve), (ii) the ischemic damage rate is doubled to reflect poor circulation and/or low blood oxygenation (middle curve), (iii) the deformation damage rate is doubled to reflect an anatomy with sharp bony prominence (e.g. sacrum) and/or low soft tissue mass covering the bone (top curve). The modeling in [9] demonstrated the following: (1) The damage rate associated with the deformation-inflicted damage and the time of onset of the deformation-inflicted damage (t_{deform}) have the greatest influence on the cumulative tissue damage. This is due to t_{deform} being the first event in the damage cascade, occurring before inflammatory edema-related damage (which onsets at time t_{inflam}) and prior to the ischemic damage (which initiates at time t_{ischem}). (2) Since the susceptibility of individuals to deformation-inflicted tissue damage, as well as to inflammatory and ischemic damage varies substantially, it is not feasible to determine universal injury thresholds for prevention of pressure ulcers or diabetic foot ulcers, or predict the injury.

functional markers e.g., skin temperature, perfusion rate, oxygenation distribution and inflammatory mediators, is a promising direction towards prevention. Multiple sensors for measuring these parameters can be embedded in footwear, orthoses and prosthetic sockets, support surfaces and body positioners, socks, clothing and underwear, diapers and bedsheets. Big databases of these measures, analyzed through machine learning, will then facilitate data analytics useful for risk assessments at first examination, and for monitoring tissue health of individuals over time, by seeking significant changes from their baseline tissue status levels, as done in current blood tests.

5. The continuum between prevention and treatment of wounds

In the world of wound care, which has been traditionally focused on treatments, prevention is a relatively new concept. Indeed, from a medical perspective, prevention and treatment are (still) often being considered two separate worlds, whereas, in fact, there is a physiological and clinical continuum between prevention and treatment. Cell death and tissue damage occur constantly and continuously throughout life, and clearly, in unhealthy individuals with fragile tissues, tissue tolerances are lower and, therefore, tissue damage develops easily and spreads faster. Nevertheless, a clinically significant tissue damage event, diagnosed as a PU or a DFU, will be an event where the rate and extent of tissue damage exceeded those that the body systems were able to repair timely (in a process that starts with inflammation, as explained above). Effective prevention, according to this view, is therefore to always maintain the balance between damage rate versus repair rate in favor of that of repair. Even if a chronic wound exists already, prevention is still fundamentally relevant for protecting the peri–wound tissues from the mechanical factors (forces, pressures and shear) that caused the original wound, and which further threat

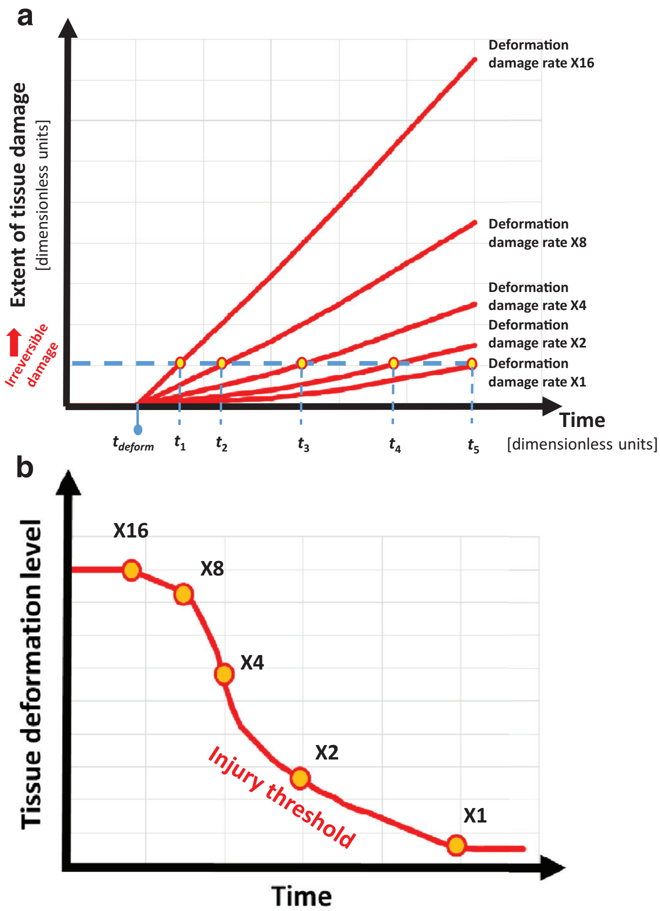

Figure 3. Tissue tolerances to sustained bodyweight forces or to external mechanical loads, in the context of pressure ulceration or diabetic foot ulceration, vary considerably across individuals. One of the most important factors influencing the soft tissue tolerances to load exposures in a person is their (internal) anatomy. (a) Based on the mathematical modeling of Gefen [9], we examine here computer simulation cases where individuals with different sacral bone structures accumulate deformation-inflicted tissue damage at different rates, from a time point t_{deform} onwards. Soft tissues under sharper sacral bones in some hypothetical patients will be exposed to greater tissue stress concentrations, and, therefore, will accumulate damage faster than tissues under more blunt sacral bones in other hypothetical individuals. Accordingly, each individual will cross the level of irreversible (clinically significant) tissue damage (which is arbitrarily determined here) at a different time point t_i (where $i = 1,2,3, \ldots$). (b) Plotting the tissue deformation levels at which each individual has crossed the aforementioned 'irreversible damage' level against the corresponding time point t_i at which that has occurred, yields the tissue injury threshold curve for the deformation-inflicted damage. Obtaining such tissue injury thresholds empirically, for human patients, is impossible, not only due to ethical considerations but also, because, as demonstrated in this paper, there is strong coupling between deformation-inflicted damage, inflammation-related damage and ischemic damage. The latter implies that tissue injury thresholds cannot be generic, and, at this time, are unpredictable in individual patients. Units are dimensionless for the purpose of explaining the above concepts.

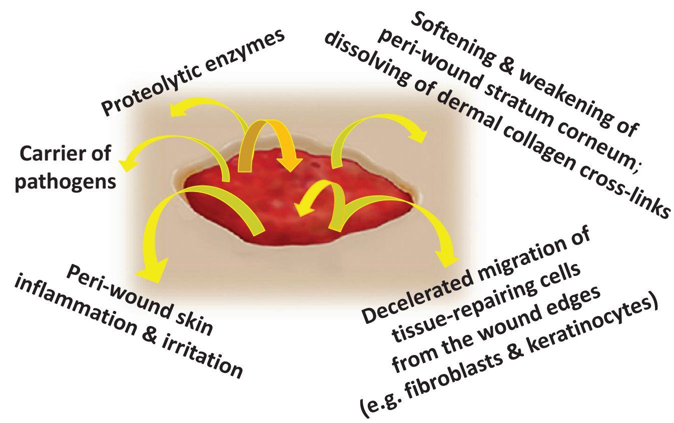

Figure 4. Various factors that are associated with excess wound exudate and which compromise the integrity and viability of peri–wound tissues.

adjacent non-injured tissues. Moreover, in an existing wound, the ongoing inflammatory process adds risk to peri–wound tissues.

As a result of the increased vascular permeability which is part of the inflammatory process (Fig. 1), excess fluids enter the wound bed. These fluids, called exudate, contain proteins, nutrients, inflammatory mediators, digestive enzymes, growth factors, waste products, immune cells (primarily neutrophils and macrophages) and platelets [27]. The exudate has several important roles in the healing process. First, it prevents the wound bed from drying out. Second, it makes the medium for migration of immune cells (e.g. for reducing bacterial burden) and for motility of tissue-repairing cells. Third, it facilitates nutrient diffusion to the aforementioned cells and to the cells in the wound bed. Fourth, it allows diffusion of signaling molecules and growth factors that are required for repair, e.g. inflammatory mediators such as histamine and vascular growth factors for angiogenesis [27]. Despite these critical roles that exudates fulfill in a normal healing process, secretion of excess exudates or specific exudate composition and properties (e.g. highly acidic exudates) may compromise the viability of peri–wound tissues. Specifically, in infected wounds, exudates may carry pathogens to adjacent skin sites, or cause additional inflammation and irritation for example, due to their pH levels, which typically differ from those of healthy skin and may be highly acidic or alkaline (Fig. 4) [28–30]. In addition, the prolonged exposure to moisture and wetness causes softening and weakening of the stratum corneum at the peri–wound skin, which progressively dissolves dermal collagen and detaches collagen cross-links around the wound bed [31–34]. Chronic wound exudates, in particular, typically contain proteolytic enzymes that aggressively disintegrate collagen and skin matrix [35]. Lastly, acidic wound exudate environments decelerate migration of tissue-repairing cells such as fibroblasts and keratinocytes from the wound edges [13]. For all these reasons, the aforementioned discussion of the role of biomarkers of tissue status in the context of PU and DFU prevention, is also highly relevant in regard to treatment and healing of chronic wounds.

6. Conclusions

Mechanobiology, the medical engineering approach and methods of examining the interplay between cell and tissue mechanics and the biological function at the cellular and tissue scales, has developed and is now well accepted as a new biomedical subfield. Mechanobiology complements our understanding of the etiology of PUs and DFUs, and their prevention and treatment [3,15]. It is mechanobiological research that was able to explain the colossal failure of generations of researchers who were seeking the holy grail of universal injury threshold values to be able to predict PUs and DFUs in individuals. That failure was manifested for example in guesstimating a pressure of 32 mm of mercury as the 'safe' exposure to skin surface loading, which was, embarrassingly, very common in the medical device industry for many years as a selling point for allegedly 'good' support surfaces. Other various attempts to find alternative values of pressure, shear or any other body surface loads or time-integrals of such loads for predicting PUs or DFUs are also doomed to fail. We now understand that for risk assessments and early detection of chronic wounds in an individual, we need to monitor the tissue anatomy – and their exposure to internal tissue deformation in particular [36], and also, their local tissue physiology at the vulnerable body sites [37,38]. We will need to seek trends of changes in wound biomarkers with respect to historical or reference values, particularly focusing on inflammatory mediators, the production of which is triggered by the body in response to the first event of massive cell death [3,37,38]. This is not surprising when we think of how blood tests are currently being analyzed, for example, with regard to glucose or lipid levels. Biomarkers targeting individual tissue deformation extents and tissue inflammation responses, in particular, are expected to lead to new breakthroughs in PU and DFU prevention [3,9,37].

Declaration of Competing Interest

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Ethical approval

Not required.

References

[1] Schreml S, Berneburg M. The global burden of diabetic wounds. Br J Dermatol. 2017;176(4):845–6.
[2] Healogics, Inc. Chronic wound epidemic cited in u.s. Electr. Compon. News Mag., https://www.ecnmag.com/news/2016/06/chronic-wound-epidemic-cited-us, accessed in June 23rd, 2019.
[3] Gefen A. (Leader) and members of the small working group – etiology. Int Guidel Press Ulcer Prev Treat 2019 in press.
[4] Agency for Healthcare Research & Quality (AHRQ) National scorecard on hospital-acquired conditions updated baseline rates and preliminary results 2014–2017, http://www.ahrq.gov, accessed in June 17th, 2019.
[5] Padula WV, Delarmente BA. The national cost of hospital-acquired pressure injuries in the united states. Int Wound J. 2019;16(3):634–40 in press (available online). doi:10.1111/iwj.13071.
[6] Reswick JB, Rogers JE. Experience at rancho los amigos hospital with devices and techniques to prevent pressure sores. Bed sore biomechanics. Kenedi RM, Cowden JM, editors, London: Palgrave; 1976. Strathclyde Bioengineering Seminars.
[7] Borg J, Mizzi S, Formosa C. Peak pressure data and pressure-time integral in the contralateral limb in patients with diabetes and a trans-tibial prosthesis. Gait Posture 2018;64:55–8.
[8] Fernando ME, Crowther RG, Pappas E, Lazzarini PA, Cunningham M, Sangla KS, Buttner P, Golledge J. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. PLoS One 2014;9(6):e99050.
[9] Gefen A. The future of pressure ulcer prevention is here: detecting and targeting inflammation early. EWMA J 2018:7–13.
[10] Gefen A, Alves P, Creehan S, Call E, Santamaria N. Computer modeling of prophylactic dressings: an indispensable guide for healthcare professionals. Adv Skin Wound Care 2019;32(7S Suppl 1):S4–S13.
[11] Gefen A, van Nierop B, Bader DL, Oomens CW. Strain-time cell-death threshold for skeletal muscle in a tissue-engineered model system for deep tissue injury. J Biomech. 2008;41(9):2003–12.
[12] Slomka N, Gefen A. Relationship between strain levels and permeability of the plasma membrane in statically stretched myoblasts. Ann Biomed Eng 2012;40(3):606–18.
[13] Topman G, Lin FH, Gefen A. The influence of ischemic factors on the migration rates of cell types involved in cutaneous and subcutaneous pressure ulcers. Ann Biomed Eng. 2012;40(9):1929–39.
[14] Leopold E, Gefen A. Changes in permeability of the plasma membrane of myoblasts to fluorescent dyes with different molecular masses under sustained uniaxial stretching. Med Eng Phys. 2013;35(5):601–7.
[15] Gefen A. The mechanobiology of wounds: the science of preventing pain and suffering. Med Eng Phys. 2016;38(9):827.
[16] Gefen A, Weihs D. Cytoskeleton and plasma-membrane damage resulting from exposure to sustained deformations: a review of the mechanobiology of chronic wounds. Med Eng Phys. 2016;38(9):828–33.
[17] Toume S, Gefen A, Weihs D. Low-level stretching accelerates cell migration into a gap. Int Wound J. 2017;14(4):698–703.
[18] Bader DL, Worsley PR, Gefen A. Bioengineering considerations in the prevention of medical device-related pressure ulcers. Clin Biomech (Bristol, Avon) 2019;67:70–7.
[19] Cutting K, Gefen A. PolyMem and countering inflammation made easy. Wound Int 2019:1–6.
[20] Schwager S, Detmar M. Inflammation and lymphatic function. Front Immunol. 2019;10:308.
[21] Ross G, Gefen A. Assessment of sub-epidermal moisture by direct measurement of tissue biocapacitance. Med Eng Phys. 2019 in revision.
[22] Worsley PR, Stanger ND, Horrell AK, Bader DL. Investigating the effects of cervical collar design and fit on the biomechanical and biomarker reaction at the skin. Med Devices (Auckl) 2018;11:87–94.
[23] Nakai A, Minematsu T, Tamai N, Sugama J, Urai T, Sanada H. Prediction of healing in category i pressure ulcers by skin blotting with plasminogen activator inhibitor 1, interleukin-1α, vascular endothelial growth factor C, and heat shock protein 90α: a pilot study. J Tissue Viability 2019;28(2):87–93.
[24] Traa WA, Strijkers GJ, Bader DL, Oomens CWJ. Myoglobin and troponin concentrations are increased in early stage deep tissue injury. J Mech Behav Biomed Mater 2019;92:50–7.
[25] Goodall RJ, Langridge B, Onida S, Davies AH, Shalhoub J. Current status of non-invasive perfusion assessment in individuals with diabetic foot ulceration. J Vasc Surg. 2019;69(2):315–17.
[26] Wardle EN. Vascular permeability in diabetics and implications for therapy. Diabetes Res. Clin. Pract. 1994;23(3):135–9.
[27] Chambers T, Bradley P. Wound exudate. Br J Nurs 2018;27(20):S28–32.
[28] Schreml S, Meier RJ, Weiß KT, Cattani J, Flittner D, Gehmert S, Wolfbeis OS, Landthaler M, Babilas P. A sprayable luminescent pH sensor and its use for wound imaging in vivo. Exp Dermatol. 2012;21(12):951–3.
[29] Schreml S, Meier R, Kirschbaum M, Kong S, Gehmert S, Felthaus O, Küchler S, Sharpe J, Wöltje K, Weiß K, Albert M, Seidl U, Schröder J, Morsczeck C, Prantl L, Duschl C, Pedersen S, Gosau M, Berneburg M, Wolfbeis O, Landthaler M, Babilas P. Luminescent dual sensors reveal extracellular pH-gradients and hypoxia on chronic wounds that disrupt epidermal repair. Theranostics 2014;4(7):721–35.
[30] Vowden P, Bond E, Meuleneire F. Managing high viscosity exudate. Wounds International 2015;6(1):14–18.
[31] Gefen A. How do microclimate factors affect the risk for superficial pressure ulcers: a mathematical modeling study. J Tissue Viability 2010;20(3):81–8.
[32] Gefen A, Kottner J, Santamaria N. Clinical and biomechanical perspectives on pressure injury prevention research: the case of prophylactic dressings. Clin Biomech (Bristol, Avon) 2016;38(Oct):29–34.
[33] Woo KY, Beeckman D, Chakravarthy D. Management of moisture-associated skin damage: a scoping review. Adv Skin Wound Care 2017;30(11):494–501.
[34] Schwartz D, Katsman Magen Y, Levy A, Gefen A. Effects of humidity on skin friction against medical textiles as related to prevention of pressure injuries. Int Wound Journal 2018;15(6):866–74.
[35] Palolahti M, Lauharanta J, Stephens RW, Kuusela P, Vaheri A. Proteolytic activity in leg ulcer exudate. Exp Dermatol. 1993;2(1):29–37.
[36] Gefen A. Time to challenge the continued use of the term ‘pressure ulcer’? Br J Nurs 2017;26(15):S4–5.
[37] Gefen A. Managing inflammation by means of polymeric membrane dressings in pressure ulcer prevention. Wounds Int 2018;9(1):22–8.
[38] Gefen A. The sub-epidermal moisture scanner: the principles of pressure injury prevention using novel early detection technology. Wounds Int 2018;9(3):30–5.