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The complex interplay between mechanical forces, tissue response and individual susceptibility to pressure ulcers

Amit Gefen, Ph.D.

Department of Biomedical Engineering, Faculty of Engineering, Tel Aviv University, Tel Aviv, Israel; Skin Integrity Research Group (SKINT), University Centre for Nursing and Midwifery, Department of Public Health and Primary Care, Ghent University, Ghent, Belgium; Department of Mathematics and Statistics, Faculty of Sciences, Hasselt University, Hasselt, Belgium.

***Address for correspondence:**

Amit Gefen, Ph.D.
Professor of Biomedical Engineering
The Herbert J. Berman Chair in Vascular Bioengineering
Department of Biomedical Engineering
Faculty of Engineering
Tel Aviv University
Tel Aviv 69978, Israel
Tel: +972-3-6408093
Fax: +972-3-6405845
E-mail: gefen@tauex.tau.ac.il

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Abstract

Objective:

The most recent edition of the International Clinical Practice Guideline for the Prevention and Treatment of Pressure Ulcers/Injuries was released in 2019. Shortly after, in 2020, the first edition of the SECURE Prevention expert panel report, focusing on device-related pressure ulcers/injuries, was published as a Special Issue in the *Journal of Wound Care*. A second edition followed in 2022. This article presents a comprehensive summary of the current understanding of the causes of pressure ulcers/injuries (PUs/PIs) as detailed in these globally recognized consensus documents.

Method:

The literature reviewed here specifically addresses the impact of prolonged soft tissue deformations on the viability of cells and tissues in the context of PUs/PIs related to bodyweight or medical devices.

Results:

Prolonged soft tissue deformations initially result in cell death and tissue damage on a microscopic scale, potentially then leading to development of clinical PUs/PIs over time. That is, localized high tissue deformations, or mechanical stress concentrations, can cause microscopic damage within minutes, but it may take several hours of continued mechanical loading for this initial cell and tissue damage to become visible and clinically noticeable. Superficial tissue damage primarily stems from excessive shear loading on fragile or vulnerable skin. In contrast, deeper PUs/PIs, known as deep tissue injuries, typically arise from stress concentrations in soft tissues at body regions over sharp or curved bony prominences, or under stiff medical devices in prolonged contact with the skin.

Conclusion:

This review article promotes deeper understanding of the pathophysiology of PUs/PIs, indicating that their primary prevention should focus on alleviating the exposure of cells and tissues to stress concentrations. This goal can be achieved either by reducing the intensity of stress concentrations in soft tissues, or by decreasing the exposure time of soft tissues to such stress concentrations.

Keywords:

Pressure ulcer aetiology, cell and tissue biomechanics, mechanobiology, the vicious cycle of injury, sustained tissue deformations.

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1. Biomechanical pathophysiological understanding is paramount for enhancing awareness

The latest Clinical Practice Guideline on the Prevention and Treatment of Pressure Ulcers/Injuries was published in 2019, summarizing the aetiology of pressure ulcers/injuries (PUs/PIs) with a focus on effects of sustained soft tissue deformations and stresses on cell and tissue viability (Gefen et al., 2019a; Gefen et al., 2022a). Shortly after, in 2020, the first edition of the SECURE[1] Prevention expert panel report, focusing on device-related pressure ulcers/injuries, was published as a Special Issue in the *Journal of Wound Care* (Gefen et al., 2020a). A second edition followed in 2022 (Gefen et al., 2022b). The biomechanical aetiology of PUs/PIs caused by bodyweight forces or by contact forces from a skin-contacting medical device is in fact, the same. The cells and tissues are suffering localized damage resulting from prolonged mechanical loading in various forms such as compression, tension, or shear, typically combined. Soft tissue tolerance to these deformations varies by the tissue type and quality, and is further influenced by factors like microclimate, perfusion, age, health status, and systemic or localized conditions. Key factors in PUs/PIs development include impaired mobility and sensation (Gefen et al., 2022a,b).

Mechanical loads impacting skin and soft tissues include bodyweight forces and external forces from contact with surfaces or devices. These loads have both normal (perpendicular to skin) and shear (parallel to skin) components. Pressure is the normal force per unit area, while shear stress is the shear force per unit area. Friction, related to shear stresses, describes the sliding potential of surfaces, such as skin against a medical device (Shaked and Gefen, 2013; Schwartz et al. 2018a). Tissue response to mechanical loads results in localized tissue strains[2] and stresses, with excessive or prolonged exposure damaging cell structures and hindering transport within tissues (Gefen et al., 2022a,b). This leads to cell death, inflammatory responses, increased interstitial pressures and potentially ischaemic tissue conditions (Gefen, 2018a,b; Gefen & Gershon, 2018). The impact of mechanical loads on cells and tissues depends on anatomical structure, tissue properties, and applied force magnitudes and distributions. Changes in morphology and mechanical properties due to factors like ageing or chronic injury affect tissue response to loading (Gefen, 2014; Gefen 2017). Internal tissue strain/stress responses are irregular, varying across different locations and depending on the specific tissue environment. Normal forces on weight-bearing body parts or from medical devices are likewise non-uniform, with inherent associated shear forces (Reger, 1990; Linder-Ganz et al., 2007, 2008). Imaging techniques like MRI, CT, ultrasound, and finite element (FE) modelling assess internal tissue deformations and predict cell and tissue damage risks. Understanding PU/PI aetiology and effective interventions always rely on knowledge of internal tissue responses to mechanical loads, not just external appearances (Gefen & Levine, 2007; Gefen et al., 2022a,b). Importantly, generic threshold values for cell and tissue damage as function of the cell/tissue strain/stress levels cannot be provided due to the numerous individual factors which affect cell/tissue tolerance to loading and the extent and rate of cell and tissue damage buildup, as will be reviewed in this article (Gefen & Clark, 2019).

Understanding the aetiology of PUs/PIs is paramount for enhancing clinical awareness of this prevalent healthcare issue. By exploring the underlying causes described in this review article, healthcare professionals can develop a more comprehensive understanding, through education and training programs aimed to explain how these wounds develop and progress. This, in turn, empowers clinicians to more easily and quickly identify at-risk patients, apply preventative measures earlier and more effectively, and tailor treatment plans to address the root causes of PUs/PIs at their own

[1] SECURE= **S**kin, **E**ducation, **C**hampion, **U**nderstanding, **R**eport, **E**valuate.

[2] Strains are engineering metrics to quantify dimensionless (i.e., percentage) deformations that occur in a material element subjected to forces, and are measured as the ratio of the change in size or shape to the original size of the material element.

institution and care environment. Furthermore, enhanced knowledge of PU/PI aetiology fosters critical thinking regarding newly offered wound care equipment and products for which claims are made to have clinical effectiveness in PU/PI prevention (such as in potential presentations by sales representatives). Deeper understanding also drives a proactive and motivated rather than reactive and rote approach to PU/PI prevention, ultimately improving patient outcomes and reducing healthcare costs associated with managing forming and existing PUs/PIs. Therefore, integrating education and training programs on PU/PI aetiology in healthcare settings is crucial for improving patient safety and quality of care, and for promoting better overall clinical outcomes (Gefen et al., 2019b). This article hence promotes deeper understanding of the biomechanical pathophysiology aspects of PUs/PIs, using language accessible to non-technical readers, in order to enhance clinical awareness of the individual susceptibility to deformation-inflicted tissue damage, as discussed further.

2. The responses of skin and deeper soft tissues to sustained mechanical loads and wetness

The primary cause of PUs/PIs is exposure to sustained mechanical loads on soft tissues, often near bony prominences or from medical devices such as ventilation masks or pulse oximeters. These devices, stiffer than skin, cause focal deformations and stress concentrations (Levy et al., 2017a; Lustig et al. 2018). Tissue damage, characterized by cell death, most typically occurs with sustained deformation from bodyweight or external forces (**Figure 1**). The magnitude of internal mechanical load and the duration of application are critical for tissue damage, where both high-magnitude short-term loads and low-magnitude long-term loads can cause irreversible damage (Reswick & Rogers, 1976; Salcido et al., 1994; Breuls et al., 2003a,b; Linder-Ganz et al., 2006; Stekelenburg et al., 2006; Gawlitta et al., 2007a,b; Gefen et al., 2008a). Damage resulting from a brief, intense mechanical load, termed 'impact damage', is not considered to cause PUs/PIs (Gefen et al., 2019a, 2022a). The historical tissue damage threshold by Reswick & Rogers (1976) indicated an inverse relationship between pressure magnitudes and durations but required corrections for extreme loading times. Specifically, high loads can cause immediate microscopic damage, while very low loads extended over time may not lead to damage (Gefen, 2009a,b). Tissue damage thresholds cannot be generically quantified due to individual anatomical and tolerance variabilities (Gefen, 2009a,b; Lachenbruch et al., 2013; Zeevi et al. 2018; Gefen et al., 2020a).

In supported postures such as sitting or lying in bed, the distribution of internal soft tissue stresses near bony prominences (e.g., the ischial tuberosities or sacrum) often exhibits a crater or funnel shape, indicating that the highest soft tissue stresses are concentrated near the most curved ('sharp') bony surface facing the support surface; soft tissue stresses gradually decrease as distance from the bone increases (Linder-Ganz et al., 2007, 2008, 2009). This is because the soft tissues surrounding the bony prominence experience a downward compression force transferred through the bone, creating a depression or indentation in the overlying tissues (resulting from the steep stiffness gradient between the bone and soft tissues), which resembles a crater. This internal soft tissue distortion configuration is causing a risk of deep PU/PI development, as these soft tissues adjacent to the curved bone surfaces and the cells within are subjected to prolonged and concentrated mechanical loading in a localized subdermal tissue region. The soft tissue loading state can intensify again near the surface of the body, depending on the level of the frictional forces acting on the skin and the nature and stiffness of the support surface, which introduces the possibility of a 'sandwich' PU/PI mechanism where the injury concurrently progresses from the bone internally towards the body surface, and from the skin externally into the depth of the tissues (Ohura et al., 2007).

Minimizing interface pressures and shear stresses reduces the PU/PI risk (Brienza et al., 2001; Peko-Cohen et al., 2019; Amrani & Gefen, 2020; Gefen et al., 2020a; Lustig et al., 2020; Peko et al., 2020).

However, pressure measurements alone are not reliable for tissue breakdown risk predictions, as similar pressures may result in different internal tissue loads depending on individual anatomies (Gefen & Levine, 2007; Gefen, 2008a; Sopher & Gefen, 2011; Linder-Ganz et al. 2007, 2008; Brienza et al., 2018). Shear stresses, in combination with pressures, exacerbate the deformation-induced tissue damage (Knight et al., 2001; Linder-Ganz & Gefen, 2007; Shilo & Gefen, 2012). Specifically, sustained shear stresses in soft tissues can lead to capillary distortions in the affected region to an extent that impairs the capillary ability to effectively perfuse the loaded soft tissues. In addition, excessively high shear stresses can damage the endothelial cell lining of the capillaries, compromising their integrity and increasing the vascular permeability, which further contributes to the oedematous-related tissue damage (Figure 1) (Linder-Ganz & Gefen, 2007; Van Damme et al., 2019).

Stress concentrations at bony prominences can damage deep tissues before superficial damage appears (Todd & Thacker, 1994; Oomens et al., 2003; Linder-Ganz et al., 2004; Gefen et al., 2005; Akins et al., 2016; Linder-Ganz et al., 2007, 2008; Brienza et al., 2018; Amrani & Gefen, 2020; Lustig et al., 2020; Peko et al., 2020). Superficial shear stresses from frictional forces disrupt the skin barrier function, with wetness increasing risks of skin tears and infections (Sopher & Gefen, 2011; Schwartz et al., 2018a; Gefen, 2020a; Gefen & Ousey, 2020). Skin micro-topography changes with sustained pressure and wetness, affecting friction and risk of skin breakdown (Sopher & Gefen, 2011; Shaked & Gefen, 2013; Dobos et al., 2015; Schwartz et al., 2018a; Gefen, 2020a; Gefen et al., 2020a; Gefen & Ousey, 2020). If damage occurs, affected soft tissues may undergo abnormal biomechanical changes, such as localized rigor-mortis in muscles and fibrous scar tissues, contributing to strain/stress concentrations and load inhomogeneity (Gefen et al., 2005; Gefen, 2009c; Sopher et al., 2011; Levy et al. 2013, 2014).

The **microclimate** between the skin and the support surface or any skin-contacting medical device or object plays an important role in the development of superficial PIs. Microclimate refers to the temporal and spatial temperature and humidity of the skin. The characteristics of an optimal microclimate are still a matter of ongoing research, but it is evident that with an increase in temperature and humidity, the skin becomes weaker and more vulnerable to mechanical damage (Gefen, 2011; Kottner et al. 2018; Amrani et al., 2020). Excessively dry skin is also undesirable, as dry skin becomes more brittle and liable to cracking and tears. Wetness of the interface of the skin with any contacting objects therefore dominantly influences the ability of the skin to stay intact when subjected to sustained mechanical loading (Nacht et al., 1981; Gerhardt et al., 2008; Gefen, 2011; Shaked & Gefen, 2013; Schwartz et al., 2018a; Zeevi et al., 2018; Schwartz & Gefen, 2020). The skin also tends to increase in its coefficient of friction (COF) in contact with other surfaces when exposed to warm and moist conditions, likely due to perspiration (Klaassen et al. 2017; Schwartz et al., 2018a). The evaporation of perspiration from the body surface further depends on the local and ambient humidity conditions (Gefen, 2011). The COF value ultimately affects the magnitude of frictional forces acting on the body, and hence the skin and subdermal tissue deformations resulting from any frictional sliding movements between the skin and a support surface, a medical device or other contacting objects (Sopher & Gefen, 2011; Shaked and Gefen, 2013; Schwartz et al. 2018a; Zeevi et al. 2018). Overall, there are strong links between the microclimate conditions and the frictional forces that apply at a certain body region (through the COF), affecting both the surface and the internal soft tissue loading states and therefore the biomechanical conditions of all the cells contained in these tissues (Gefen et al., 2020a; Gefen & Ousey, 2020; Zeevi et al., 2018; Schwartz & Gefen, 2020).

3. Deformation-inflicted soft tissue damage and the individual susceptibility

There are fundamental differences between the aetiology of superficial PUs/PIs affecting skin, versus those PUs/PIs that originate and form in the deeper soft tissues (Kottner et al. 2011). Superficial PUs/PIs are primarily caused by excessive shear exposure at the skin surface whereas deeper PUs/PIs predominantly result from stress concentrations in soft tissues near bony prominences (Gefen 2007a,b, 2008c, 2009c; Agam & Gefen, 2007; Linder-Ganz & Gefen, 2009; Linder-Ganz et al. 2009; Shabshin et al. 2010; Lahmann & Kottner, 2011; Sopher et al. 2011; Shoham & Gefen, 2012; Gefen et al., 2013; Peko Cohen et al. 2018).

The damage cascade in PUs/PIs, illustrated in **Figure 1a**, includes the sequential cell and tissue damage associated with direct deformation (1st factor), damage associated with the inflammatory response (2nd factor), and damage induced by ischaemia (3rd factor) (Gefen et al., 2022a,b). The additive nature of these damages (depicted in **Figure 1b**) highlights the importance of minimization of the exposure to sustained tissue deformations and of early detection of cell and tissue damage for effective PU/PI prevention. In the context of the theoretical framework described in **Figure 1**, the patient-specific internal anatomy, including the sharpness or curvature of bony prominences, the adjacent soft tissue morphologies and the mechanical and thermal properties of these tissues will altogether dictate the state of internal tissue deformations, strains and stresses and the thermodynamic state of the distorted tissues. The individual cell and tissue repair capacity and the transport properties at the cell and tissue scales will further determine the ability of the body to reverse and repair a forming cell and tissue damage. The progression of the damage, along with the progression of healing, will constitute the time for a PU/PI to develop in the individual and the extent and severity to which it will develop.

Cell and tissue death can be caused by either direct mechanical damage, or by biochemical stress associated with lack of supply of essential molecules and impaired clearance of metabolic waste products. In this context, two physiologically-relevant deformation thresholds exist for soft tissues subjected to sustained mechanical loading. One is a lower threshold leading to partial obstruction of the vasculature which may induce ischaemia (Linder-Ganz & Gefen, 2007; Shilo & Gefen, 2012) and/or lymphatic impediments (Gray et al., 2016), and the other is a higher threshold, leading to direct deformation-inflicted damage which causes cell death within short time frames, in the order of minutes (Ceelen et al., 2008; Linder-Ganz et al., 2006; Gefen, 2008b; Gefen et al., 2008a,b; Loerakker et al., 2010, 2011a,b; Oomens, 2010). Ischaemia, as a result of sustained deformations of soft tissues will lead to hypoxia, reduced nutrient supply and impaired removal of metabolic waste products. Deprivation of nutrients and decrease in the pH level towards a more acidic extracellular environment, due to accumulation of metabolic waste products, will eventually lead to cell death and tissue damage, however, cells are able to survive for considerable times, in the order of hours, by shifting to an anaerobic metabolism (Bader et al., 1986; Gawlitta et al., 2007a,b; Linder-Ganz & Gefen, 2007). Prolonged exposure to ischaemic conditions, including an acidic extracellular environment (i.e., low pH), have shown to slow collective cell migration, particularly of fibroblasts, in cell culture models (Topman et al., 2012) which may compromise the body's attempts to repair microscale damage, and hence, contribute to an overall accelerated rate of tissue damage in PIs (Gefen, 2018b; Gefen, 2019). The time duration during which cells and tissues can endure ischaemia without occurrence of irreversible damage differs for the tissue types that are potentially involved in PIs, that is, skeletal muscle, adipose and skin. Muscle tissues are more susceptible to mechanical damage than skin (Salcido et al., 1994; Stekelenburg et al., 2006). Skin is considerably stiffer than muscle or adipose tissues, and therefore, deforms to a lesser extent in most clinically-relevant scenarios. In animal experiments, the first signs of ischaemic damage are found in skeletal muscle after two to four hours of sustained tissue deformations (Bader et al., 1986; Linder-Ganz et al., 2006; Gawlitta et al., 2007a,b; Loerakker et al., 2011a,b).

Sustained skeletal muscle deformations at strains greater than 50% will almost immediately (within minutes) lead to tissue damage at a microscopic scale (Gefen et al., 2008a). At these strain levels, there is a strong correlation between the magnitude of the strain and the amount of damage inflicted to the muscle cells/fibres. This direct deformation-inflicted damage to cells is the result of: (*i*) Loss of integrity and structural support provided to the cell body by the cytoskeleton; (*ii*) Over-stretching of the plasma membrane, which increases when the structural support provided to the membrane by the cytoskeleton diminishes; and (*iii*) Internal signalling pathways related to these excessive cell deformations that cause apoptotic cell death (Breuls et al., 2003a,b; Stekelenburg et al., 2006, 2007, 2008; Slomka & Gefen, 2011, 2012; Leopold & Gefen, 2013; Gefen & Weihs, 2016). Mechanobiology work in the research group of the author, focusing on the cell scale, has further indicated that mechanically stimulating cells, by applying low-level, non-damaging mechanical deformations/strains, accelerates collective cell migration into damage sites in laboratory cell cultures (Toume et al. 2017; Katzengold et al., 2020, 2021). Given that PUs/PIs form when the rate of cell and tissue death is greater than the corresponding rate of tissue regeneration (i.e., through cell proliferation, migration and differentiation), contemporary mechanobiology research has already identified several optimal features of stimuli to promote repair processes, particularly concerning the migration of cells into a damage site at the onset of a micro-scale PU/PI (Toume et al. 2017; Katzengold, 2020,2021).

Diffusion of nutrients and clearance of waste products and hormones that regulate tissue metabolism may be hindered by sustained mechanical loading (Gefen, 2008b; Gefen et al., 2008b; Ruschkewitz & Gefen, 2010, 2011). Cell culture, tissue engineering and computational modelling works conducted by the group of the author suggested that localized sustained large tissue deformations in weight-bearing body regions under bony prominences translate to large cellular deformations at the micro-scale, thereby causing distortion of cellular organelles, e.g., considerable stretching of cellular plasma membranes (Slomka et al., 2009; Slomka & Gefen, 2010, 2011; Shoham & Gefen, 2012; Leopold et al., 2011; Leopold & Gefen 2012a,b 2013; Ruschkewitz & Gefen 2010, 2011). The prolonged exposure to large tensional plasma membrane strains may interfere with normal cellular homeostasis, primarily by affecting transport processes through the plasma membrane which becomes more permeable when it is highly stretched. This has been visualized and quantified in cell cultures subjected to physiologically-relevant deformations for periods of 2-3 hours, using biomolecular fluorescent markers (Slomka & Gefen, 2012; Leopold & Gefen, 2013; Gefen & Weihs, 2016). The progression of cell death and tissue necrosis causes gradual local alterations of the mechanical properties of the injured tissues that can, in turn, change the distributions of strains and stresses in forms that are likely to exacerbate the evolving injury, e.g., through development of inflammatory oedema and localized rigor mortis in skeletal muscles (Edsberg et al., 2000; Linder-Ganz & Gefen, 2004; Gefen et al., 2005; Gefen, 2009c; Gefen, 2018a; Gefen, 2020b). Localized inflammatory edema, one of the earliest signs of cell death in PUs/PIs, is detectable via measurement of a biophysical marker called the biocapacitance of tissues (Gefen, 2018a; Gefen & Gershon, 2018; Peko Cohen & Gefen, 2019; Ross & Gefen, 2019; Gefen, 2020b; Peko & Gefen, 2020; Gefen & Ross, 2020). Reperfusion following prolonged ischaemia periods may further escalate the tissue damage as it involves release of damaging oxygen free radicals (Houwing et al., 2000; Peirce et al., 2000; Ikebe et al., 2001; Unal et al., 2001; Reid et al., 2004; Tsuji et al., 2005). The nature of the vicious cycle of PUs/PIs is therefore cumulative: Sustained tissue deformations, localized inflammation and ischaemia are all contributing to the escalation. Exposure to sustained soft tissue deformations is the primary factor and driving force that triggers and progresses inflammatory and ischaemic-reperfusion damage pathways (**Figure 1**).

Importantly, the cell and tissue damage buildup process described in **Figure 1** should be seen as a bioengineering model of the complex PU/PI aetiology, and of course, models are always a

simplification of reality. In the real-world, the deformation-induced, inflammatory-response-related damage and ischaemic damage factors integrate, interact and potentiate each other in a process that is nonlinear and not serial. Accordingly, rather than viewing mechanical loading applied to soft tissues and tissue response as isolated events that occur sequentially, it should be recognized that the aforementioned aetiological factors operate concurrently and may amplify each other during the loading period and following it. For instance, increased mechanical loading on a localized tissue region can lead to simultaneous, excessive cell distortions and compromised tissue perfusion, exacerbating the metabolic dysfunction at the same time when cells start to die due to the direct influence of deformation. Similarly, shear loading acting in tandem with the rise in interstitial tissue pressures can further worsen the tissue damage, by disrupting cell integrity due to mechanical stresses while also concurrently contributing to obstruction of the microvasculature. Furthermore, if decreased tissue perfusion or low oxygenation and resulting ischaemia or hypoxic tissue conditions already exist in a patient who is at-risk for a PU/PI but who did not yet develop a clinical injury, e.g., due to a hemodynamic, vascular or respiratory disease (e.g., pneumonia), these will exacerbate the effects of sustained cell and tissue deformations in a supported posture or under a skin-contacting medical device. The complexity of the PU/PI aetiology stems from the interconnectedness and existence of such synergistic effects between these three primary factors (deformation, inflammation and ischaemia; **Figure 1**), which highlights the importance of considering multiple variables simultaneously when applying preventative measures.

Ageing leads to considerable physiological changes such as increased connective tissue (including skin) stiffness, making the elderly inherently more susceptible to PUs/PIs. Chronic diseases may further exacerbate this risk, with factors like compromised hemodynamic status impairing tissue perfusion and increasing tissue vulnerability to ischaemic damage. Hyperglycaemia in diabetes hinders the repair capacity of tissues while also impacting tissue stiffness properties through changes to collagen structure and arrangement, leading to stiffer connective tissues that are (like in the ageing patient) less effective in dispersing stress concentrations through deformations. Additionally, poor nutritional status compromises the tissue repair capacities and weakens the protective barrier of the skin. In the context of an overall clinical status, these factors intertwine to increase the susceptibility to PUs/PIs, again highlighting the importance of comprehensive assessment and management strategies tailored to the individual patient in order to effectively mitigate their risk (Gefen, 2019).

4. Future research directions and the expected technological progress in the context of our contemporary etiological understanding

Examples of current PU/PI prevention technologies can be classified into ones that minimize exposure to sustained tissue deformations, versus those which target the biomarkers of early cell damage or death, to prevent progression of the damage. The first category of existing technologies, which concerns minimization of exposure to tissue deformations include support surfaces that enhance body immersion and envelopment and minimize shear (Levy et al. 2015a; Peko-Cohen & Gefen, 2017; Levy et al. 2018; Katzengold & Gefen 2018, 2019; Peko Cohen et al. 2018; Lustig et al., 2020) as well as prophylactic dressings which absorb shear deformations and reduce frictional forces (Levy et al. 2015b; Levy & Gefen, 2016; Gefen et al. 2016; Levy & Gefen, 2017; Levy et al., 2017b; Schwartz et al., 2018b; Burton et al., 2019a,b; Gefen et al., 2019b,c; Peko Cohen et al., 2019; Gefen et al., 2020b,c; Peko et al., 2020; Lustig and Gefen, 2021). The second category of technologies which focuses on biomarkers for early detection and intervention include, for example, biocapacitance measurements using a subepidermal moisture scanner which identifies biophysical changes in tissue properties caused by early inflammation to aid in early detection (Gefen, 2018a; Gefen & Gershon, 2018; Ross & Gefen, 2019; Peko & Gefen, 2019, 2020; Gefen & Ross, 2020; Gefen, 2020b), as well as polymeric

membrane dressings that prophylactically subdue the activity of nociceptive neurons to mitigate the impact and spread of inflammation (Gefen, 2018b,c; Cutting & Gefen, 2019; Schwartz & Gefen, 2020; Amrani et al., 2020; Dabas et al., 2024).

Development of these and other technology-based options to detect and mitigate PI-specific tissue changes caused by exposure to sustained soft tissue deformations, and the resulting inflammation and ischaemia is a timely and feasible endeavour for scientists and biomedical engineers which is anticipated to reduce the burden of PIs going forward. Promising bioengineering innovation is expected to rely more heavily on mechanobiological information (Katzengold et al., 2020) and specifically, on biomarkers, such as those associated with wound odours relating to different pathogens that infect PIs (Ousey et al. 2017). In the near future, we are further expected to witness a growing use of big data, cloud computing and artificial intelligence (AI, e.g., machine learning) to analyse information that is detected automatically from a variety of sensors situated for monitoring the prevention and healing of PIs (Dabas et al., 2023).

5. Summary and conclusions

Sustained mechanical loads acting on soft tissues and leading to localized cell death and tissue damage are the fundamental factor and also, the triggering event in the biomechanical pathophysiology of PUs/PIs. Mechanical loads composed of prolonged compression, tension and shear, acting simultaneously and impacting both bodyweight-bearing soft tissue regions and areas in contact with medical devices, cause tissue strain and stress concentrations that result in deformation-induced cell death followed by inflammation and increased interstitial pressures within tissues, and ultimately, compromise the perfusion and lymphatic function. Understanding internal tissue responses to these sustained loads, assessed through imaging techniques and computer FE modelling, is crucial for effective PU/PI prevention. The research conducted by the author over decades highlights the complex interplay between mechanical forces, tissue response, and individual susceptibility in the development of PUs/PIs. Their work published so far also underscores the importance of minimizing sustained, localized tissue deformations and early detection of damage through advancements in medical technology. Future research directions are focused on developing innovative technologies targeting not only prevention but also early diagnosis and intervention, leveraging the mechanobiological insights and biomarkers. Embracing advancements in big data, cloud computing and AI holds promise for enhancing our understanding and management of PUs/PIs, ultimately reducing their burden on patients and healthcare systems.

IRB/Ethic/consent statement: Given that this work is solely a literature review, an IRB/Ethics statement and patient consent information are unnecessary.

Reflective questions:

- **How does understanding the biomechanical pathophysiology of pressure ulcers/injuries empower clinicians?**

- **What are the key findings regarding the effects of sustained mechanical loads on skin and soft tissues, as discussed in the contemporary literature?**

- **How do factors such as age, health status, and individual anatomy influence the susceptibility to pressure ulcers/injuries?**

- **What are the current technological advancements aimed at better preventing or treating pressure ulcers/injuries, and how do they align with our current aetiological understanding?**

- **In what ways may emerging bioengineering research directions, including use of big data and artificial intelligence, contribute to management and reduction of pressure ulcers/injuries?**

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Figure captions

Figure 1	A schematic description of the vicious cycle of cell and tissue damage in pressure injuries (a), resulting from sustained mechanical deformations (the triggering event) which inflicts the primary, direct deformation damage (1st damage event: at time point $t_{deformation}$), then leading to secondary inflammatory-oedema related damage (2nd damage event, at time point $t_{inflammatory}$) and finally to tertiary ischaemic damage (3rd damage event, at time point $t_{ischaemic}$). Each of these three damage factors contributes to the cumulative cell and tissue damage which develops in an escalated manner as a result of the added contributions of the above factors (b). Numerical scales cannot be provided due to the individual factors which affect the extent and rate of cell and tissue damage accumulation, as explained in the text. Importantly, the bioengineering model depicted here is, like all models, a simplification of reality. In 'real-world' patients, there are nonlinear and concurrent interactions of factors of cell and tissue deformation events and related direct-deformation-induced damage, inflammatory response to the cell damage and death, and development of ischaemia. This underscores the importance of considering these multiple variables simultaneously when implementing preventative measures.

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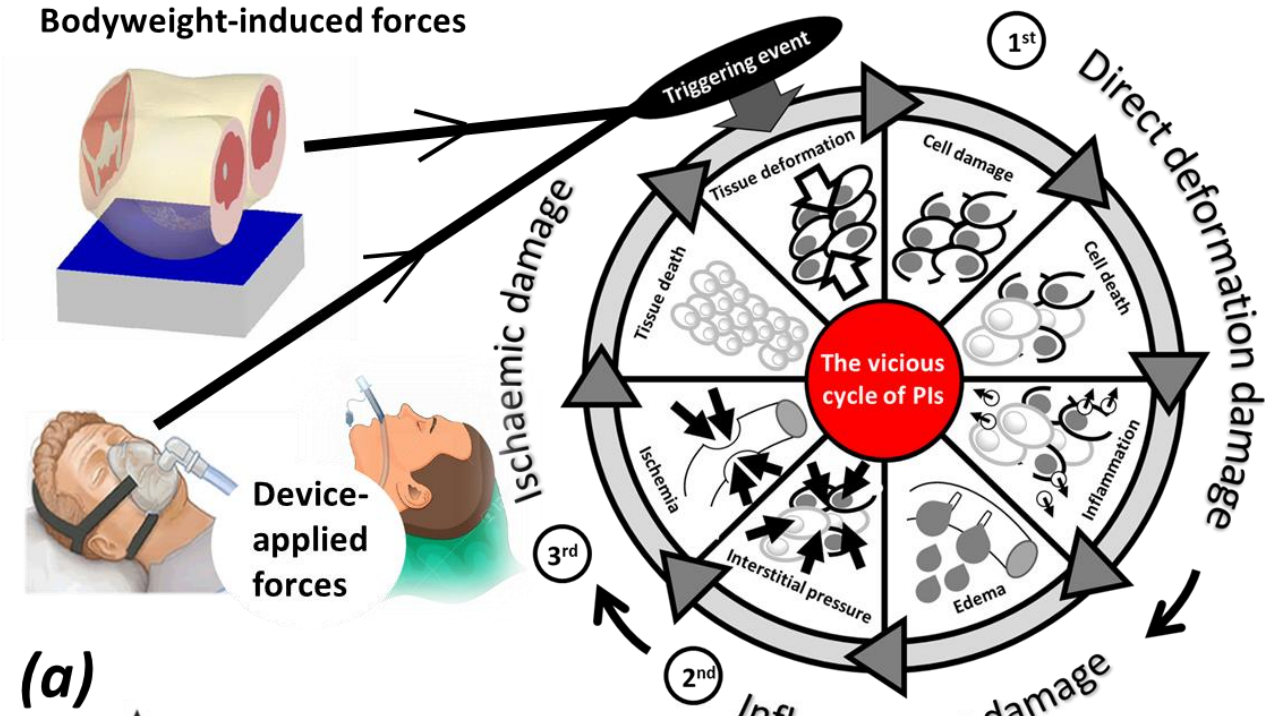

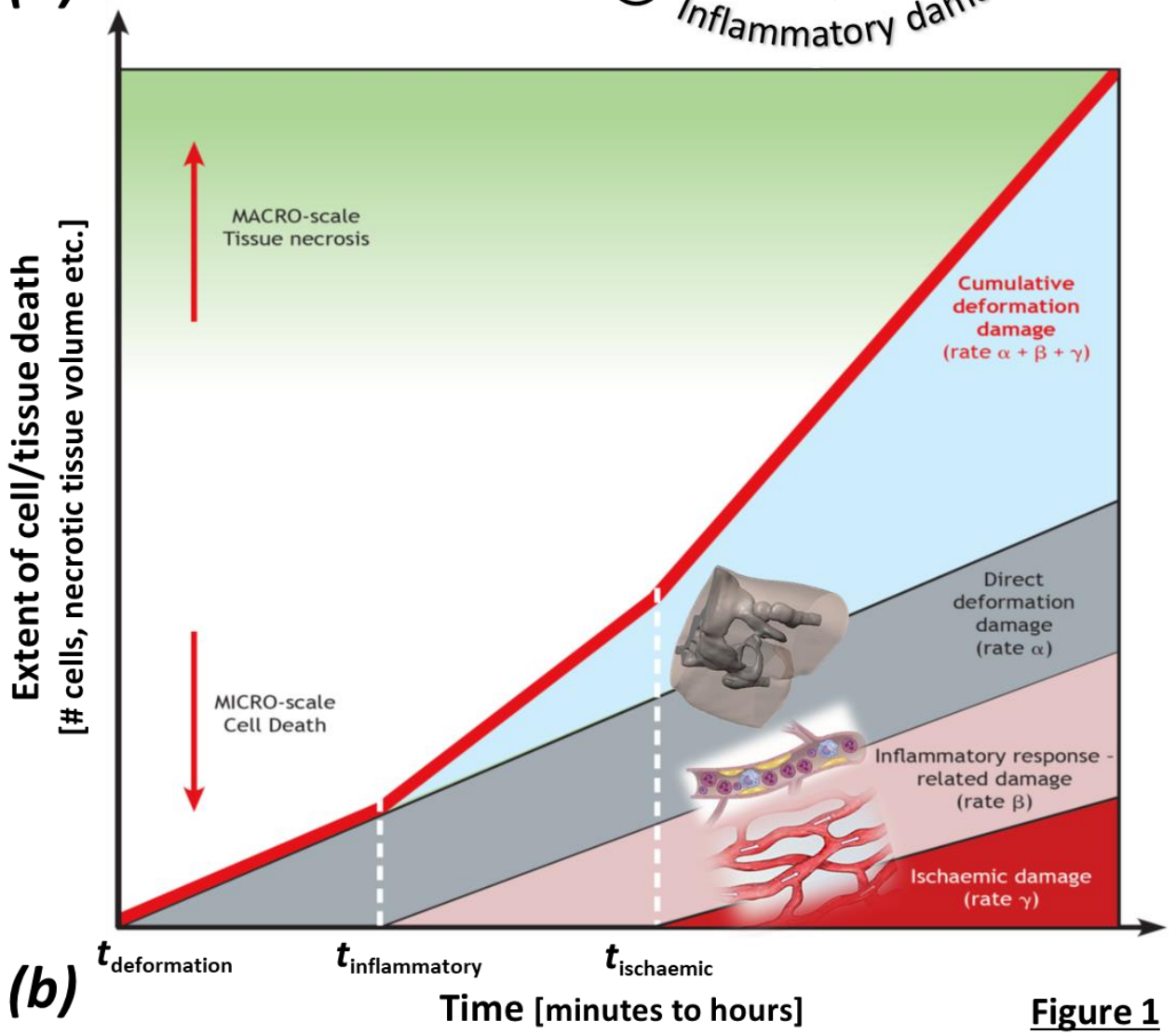

Figure 1