How Much Time Does it Take to Get a Pressure Ulcer? Integrated Evidence from Human, Animal, and *In Vitro* Studies

Amit Gefen, PhD

Severe pressure ulcers and deep tissue injury are associated with higher mortality rates, longer hospital stays, and costly treatment. Time is a critical factor in commonly employed measures (eg, pressure redistribution for wheelchair users and patient turning schedules) to prevent pressure ulcers and deep tissue injury. Surprisingly, information regarding the timeframe for pressure ulcer onset, particularly for deep tissue injury onset, is scant. To create a timeframe for the development of pressure ulcers and deep tissue injury, available evidence from the following study types was obtained and reviewed: 1) studies involving patients who underwent surgeries of known duration and subsequently developed a serious pressure ulcer with subcutaneous tissue damage or deep tissue injury; 2) animal studies in which loads were applied on soft tissues of anesthetized animals and tissue viability monitored in real time or using histology post-euthanasia; and 3) in vitro models in cell cultures and tissue-engineered constructs. Findings from the three models indicate that pressure ulcers in subdermal tissues under bony prominences very likely occur between the first hour and 4 to 6 hours after sustained loading. However, research examining these timeframes in sitting patients is not available. Further fundamental research, employing animal and cell culture models, is required to narrow this range further and to correlate the time factor to the extent of tissue damage.

KEYWORDS: pressure ulcer, deep tissue injury, animal model, tissue engineering, injury threshold

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Dr. Gefen is a Senior Lecturer, Department of Biomedical Engineering, Faculty of Engineering, Tel Aviv University, Tel Aviv, Israel. Please address correspondence to: Amit Gefen, PhD, Department of Biomedical Engineering, Faculty of Engineering, Tel Aviv University, Tel Aviv 69978, Israel; email:gefen@eng.tau.ac.il.

Although time is a critical factor in measures taken (eg, pressure redistribution for wheelchair users and patient turning schedules) to minimize the incidence of pressure ulcers (PU), information in the literature is far from definitive. According to current prevention guidelines from the European Pressure Ulcer Advisory Panel (EPUAP) (www.epuap.org), "individuals who are able should be taught to redistribute weight every 15 minutes," but this is qualified by a note that this recommendation is based on expert opinion and few clinical observations. This is just one example of the overall paucity of data on times that are safe/unsafe relevant to positioning. Information is scant regarding the timeline for PU onset and particularly for onset of deep tissue injury (DTI), a condition that places patients at high risk for sepsis, renal failure, and organ system failure.

To create a timeframe for the onset of PUs, a literature review was conducted of available published data involving time to subdermal tissue damage and particularly DTI because it has been reported that pressure-related damage occurs sooner and faster in muscle tissue than in fat and skin.[1,2] Indeed, the US National Pressure Ulcer Advisory Panel (NPUAP) added a new PU category in 2007 – "suspected DTI" — to adopt these changes. Moreover, it has become increasingly accepted in the clinical and basic research communities that PUs very likely start as deep tissue damage; accordingly, the definition of PU should probably be improved to reflect this understanding.[3]

Evidence on the timeframe for PU onset is available as the result of three types of research: 1) studies involving patients who underwent surgeries of known duration and subsequently developed serious PU with subcutaneous tissue damage or DTI; 2) animal studies in which loads were applied on soft tissues of anesthetized animals and tissue viability monitored in real-time or using histology post-euthanasia; and 3) *in vitro* models in cell cultures and tissue-engineered constructs, where predetermined loads were applied to the culture for controlled periods during which cell viability was monitored.[4] This review summarizes data from the above three study types that can be used to develop guidelines and protocols relevant to the timeframe of PU onset. This information is fundamental for clinical prevention of PU and basic research (eg, design of animal studies and tissue engineering models) regarding the etiology of PU. The information was obtained through a search of the literature database included in MEDLINE of articles published from 1966 to 2008 in Hebrew and English, as well as from books.

Evidence from Clinical Studies

Perhaps the most cited paper about the effect of the time on PU onset, the retrospective study by Reswick and Rogers[5] suggested that external pressures exceeding (approximately) diastolic pressure cause PUs within approximately 6 hours and higher external pressures (approximately four times the systolic pressure) cause PU in less than 1 hour. The data used in their studies were collected from more than 980 medical cases reviewed in the Rancho Los Amigos hospital (Downey, Calif). Because biomechanical studies have found that external pressures when a person is laying down may approach the diastolic pressure under bony prominences[6] and because general anesthetics lower the blood pressure (hypotension), which may compromise perfusion in loaded tissues, patients undergoing prolonged surgeries are considered at high risk for PU development.[7,8] In fact, the appearance of PUs in patients after surgery evoked the idea that they are acute injuries that develop rapidly in excessively/continuously

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KEY POINTS

- The evidence base for frequently used repositioning schedules to help prevent the development of deep pressure ulcers (PU) and deep tissue injury, is limited and was developed many years ago.
- To develop a timeframe for PU onset, the author reviewed and summarized currently available clinical and preclinical data.
- Although data from sitting patients with limited mobility are not available, clinical and preclinical study results suggest that subdermal injury occurs approximately between the first hour and 4 to 6 hours after sustained loading.
- Additional preclinical and clinical research is needed to help narrow this timeframe and help guide clinical practice.

loaded tissues, as opposed to the traditional concept that they are slow-forming, chronic wounds.[9] Therefore, the best evidence for the timeframe during which pressure ulcers appear in humans originates from case studies or clinical trials in which patients were evaluated to rule out existing ulcers, underwent a surgery of known duration, and examined postoperatively to detect a new PU. Not many published studies meet this design but the few papers available[10-14] point to a rather narrow time range.

In the early 1970s, Hicks[10] was one of the first to provide quantitative data for PU incidence among surgical patients. Of the 100 patients who had surgery lasting more than 2 hours, 13 developed PUs. This study concluded that patients should be assessed for PUs postoperatively at body areas in contact with the operating room table and that surgeries lasting longer than 6 hours involve a particular risk for PU development. However, a subsequent study[11] of surgical patients (N = 505) suggests that PUs may occur within substantially shorter timeframes — specifically, skin changes may indicate internal tissue damage in patients who underwent 2.5-hour surgeries on a standard surgical mattress (ie, a mattress with no special foam or gel designs or viscoelastic overlays to reduce PU risk).

Aronovitch[12] reported that out of a cohort of 281 surgical patients hospitalized in the US, nine (~3%) developed a PU related to the surgical event. Six of the nine patients with a PU had at least one comorbidity and were managed with a warming device and eight received three or more anesthetic agents. Also, eight of the patients who developed a PU had been placed on a standard operating room mattress (2-inch foam pad) for the surgical procedure and four were operated in the supine (face up) position. Patients who developed PUs had a 269-minute (4.48-hour) median operating room time (range: 180 to 387 minutes). Aronovitch's study suggests that in patients undergoing surgery, PUs can occur after 3 hours. Also, Aronovitch noted that cardiac and orthopedic surgical procedures performed in the supine position were associated with PUs, which justifies studies that examine the impact of patient position on the operating room table on PU incidence.

In a prospective follow-up study[13] of >4-hour surgery in the Netherlands, 44 out of 208 patients (~21%) developed PUs following surgery on a 2-cm gel mattress. The PUs were observed mainly on the sacrum and heels in patients who were operated in a supine position and mostly on the sternum and chin in patients operated in the prone (face down) position. In a US descriptive study[14] that included patients having >10-hour surgery on a foam surface, 15 out of 33 subjects (~45%) developed a PU. Together, these study data not only provide a timeframe for onset of PUs in patients who are confined to bed for extended periods of time, but also indicate that the incidence of these ulcers markedly increases the longer the patient is laying down.[15,16] It is apparent from the variability in the reported times for PU onset that some individuals can tolerate sustained tissue loading better than others. Likely, this is related to anatomical differences, variations in the mechanical characteristics of tissues, perfusion quality, general health status, the posture sustained, and perhaps interactions of these factors with the biomechanical performances of the specific support surface used. Accordingly, time for onset of PU is not exact but a range of probable times.

Patients who undergo surgery are protected by at least a standard operating room table mattress and in some cases also by gel/foam pads.[11] In this regard, it is interesting to mention statistics relative to the time of sustained position and PU incidence in a cohort of patients who were confined to a bed or wheelchair for reasons other than surgery — eg, due to stroke or sepsis — during hospitalization. In a retrospective study[17] conducted in a large geriatric center in Israel between 1983 and 1992, 128 of the 416 patients (~30%) who were immobile for at least 2 hours and not placed on special support surfaces developed PUs.

Vanderwee et al[18] investigated whether alternating patient position on a pressure-redistribution mattress (with 7-cm thick viscoelastic foam overlay) — 4 hours in a supine position and 2 hours in a lateral position — reduced the incidence of PUs in comparison with repositioning every 4 hours. Their specific turning scheme was as follows: semi-Fowler 30°, right-side lateral position 30°, semi-Fowler 30°, and left-side lateral position 30°. Patients in the study group were placed in a semi-Fowler 30° position for 4 hours and in a lateral position 30° for 2 hours; patients in the control group were repositioned at equal 4-hour intervals. Of the

122 patients in their experimental study group, 20 (16.4%) developed a PU (grade 2+, mainly under the sacrum, and less frequently on the ankles and heels), a rate statistically indistinguishable from the 24 (21.2%) of the 113 patients in the control group who were repositioned every 4 hours. Hence, consistent with the other data above from surgical and nonsurgical patients, a considerable number of immobile patients develop PU within 4 hours of confinement to bed.

The times for development of pressure ulcers reported in these clinical studies should be interpreted with some caution. Over the past 40 years, improvements in the technology of support surfaces were introduced concurrent with the accumulation of these data. Patients considered at risk for developing a PU now are usually prescribed high-density foam mattresses rather than a regular spring-form plastic-coated mattress to better distribute body pressures.[19] It is possible that the older data, obtained before the availability of pressure-redistribution mattresses, indicates shorter times for PU onset, but currently no human or animal experimental data are available to support or reject this hypothesis.

Evidence from Animal Models

Results of a meta-analysis of pressure-time combinations causing muscle tissue damage in 174 rats used as models of PU and DTI recently were reported by Linder-Ganz et al.[20] Adopting the concept of Reswick and Rogers,[5] they calculated a pressure-time injury tolerance for skeletal muscle tissue of rats based on histopathology studies of compressed muscle tissue in the literature (including the contributions of Husain[21] and Kosiak[22]). Data collected from the literature were supplemented by similar, complementary studies conducted mainly for muscle tissue that was loaded for periods shorter than 1 hour. To review briefly, rats were anesthetized, the skin above their gracilis muscle was resected, and the muscle was subjected to constant pressures using a spring-derived precalibrated rigid compressor. After the pressure was delivered, the animals were sacrificed and samples from the compressed muscles were harvested for histopathology. Using histological staining (phosphotungstic acid hematoxylin, [PTAH]), the viability of muscle cells and integrity of cross-striation in the muscle were determined for different pressure-time groups. If cell death or loss of cross-striation could be identified in a PTAH-stained specimen under optical microscopy for a certain pressure-time combination, that pressure-time combination was classified as injuring. The researchers found that the critical pressure-time combinations causing muscle tissue damage form a decreasing sigmoid function shape, approximately corresponding to the inverse pressure-time relationship reported by Reswick and Rogers[5] between the first and third hours after exposure to the sustained loading. However, at the extreme times (<1 hour or >3 hours), the pressure-time curve was different than that suggested by Reswick and Rogers — it indicated that at short (<1 hour) and long (3- to 6-hour) exposure to loads, critical loads causing tissue necrosis are nearly time-independent — ie, they are almost constant. The observation that the amount of pressure needed to cause injury decreases significantly at approximately 2 hours post-loading indicates that loaded muscle tissue becomes more vulnerable to PU development and DTI at that time.

The rate studies conducted by Stekelenburg et al[23,24] found that 2 hours of sustained loading is enough to cause DTI. Specifically, continuous loading was applied to the hind limb of anesthetized rats for 2 hours and damage to the tibialis anterior muscle *in vivo* was examined using magnetic resonance imaging (MRI). After the animals were sacrificed, samples were taken for histopathology to verify the MRI findings. These studies showed that compression of the muscle tissue for 2 hours induced elevated T2 values in the loaded muscle regions and location of these increased T2 spots correlated strongly with necrotic muscle regions shown in the histopathology. An additional study by Kwan et al[25] documented the histopathological changes in subcutaneous tissues of rats (around the trochanters) following exposure to sustained external loads delivered in two loading sessions of 6 hours each on two consecutive days. The researchers found progressive degeneration of muscle cells characterized by numerous increases of nuclei occupying the central parts of the muscle fibers. They further reported internalization of peripherally located nuclei, replacement of muscle cells by fibrosis and adipose tissues, and the presence of pyknotic nuclei as well as karyorrhexis. These signs of massive tissue degeneration are believed to indicate that initial tissue damage occurred within much fewer than 6 hours.

The data obtained from animal models, while being extremely useful for understanding the etiology of PUs and DTI, need to be treated with reservations. First, marked anatomical and possible physiological differences exist between humans and rodents. Second, data in these studies were obtained from healthy and relatively young rodents; whereas, humans susceptible to ulcer development are commonly elderly individuals with complex chronic comorbidities such as diabetes or cardiovascular diseases.[8,12,18] Third, to produce PUs in the animals, localized loads are applied to the skin[23-25] or muscle[20] using mechanical indentors — an unnatural configuration that probably produces higher local geometrical distortions of tissues and interferes more with the local blood supply when compared with human tissues compressed in natural supported postures. Nevertheless, data obtained in the animal studies[20-25] facilitate understanding of the time course of PU and DTI development, which is impossible to obtain with human subjects for obvious ethical reasons.

Evidence from *In Vitro* Models

The use of tissue engineering model systems to study PUs (and DTI in muscles in particular) is rather new. The practice originated at the Eindhoven University of Technology (the Netherlands) over the last 5 years.[26,27] Specifically, Bruels et al[26] developed an *in vitro* model system of engineered skeletal muscle tissue constructs. The constructs were composed of multilayers of randomly oriented myotubes. Compression of these engineered muscle tissue constructs revealed that most cell death in the deformed constructs occurred between 1 and 4 hours post-loading at clinically relevant tissue deformations (~50%) and that higher deformations led to earlier damage initiation. Gawlitta et al[27] developed a more complex tissue-engineered model system in which muscle cultures produced from murine muscle cells were suspended in collagen gel and allowed to arrange and form longitudinally organized myotubes that more closely mimic the fibered structure of native skeletal muscle. These bioartificial muscles were subjected to compressive

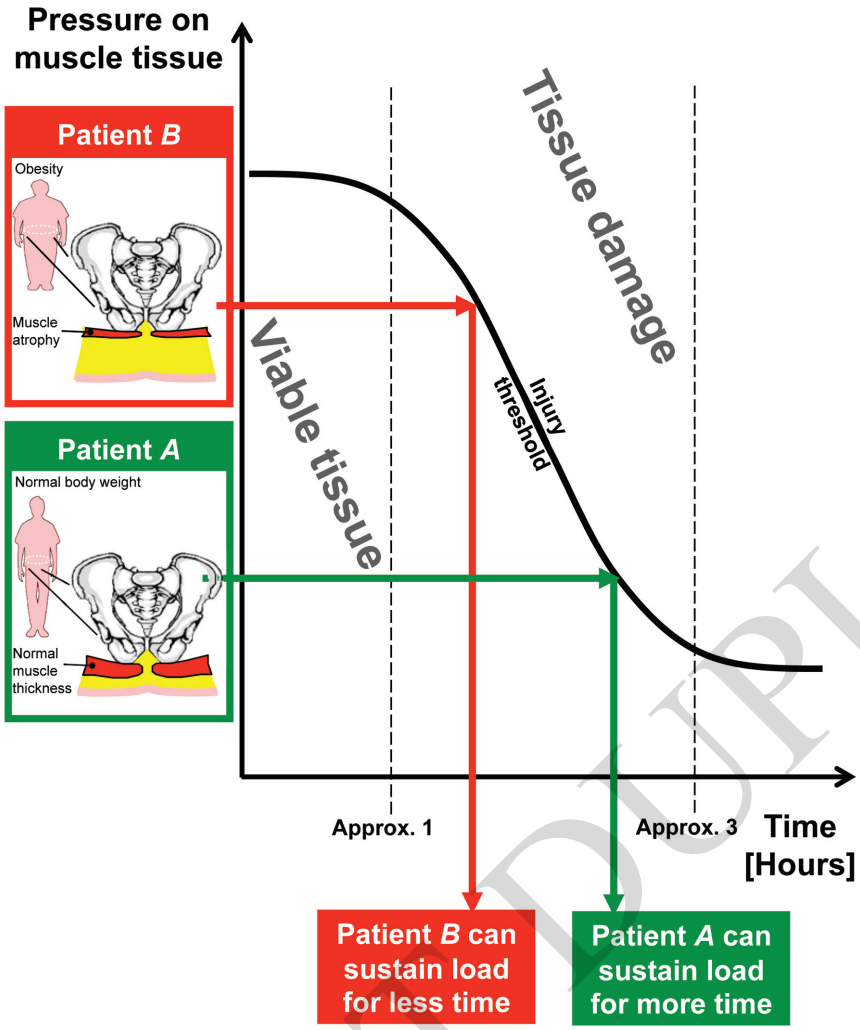

Figure 1. *Suggested effects of the individual anatomy on the time to develop a serious pressure ulcer (PU) or deep tissue injury (DTI), based on the pressure-time injury threshold obtained in animal studies by Linder-Ganz et al.[20] Individuals who are obese and/or have atrophied muscles are expected to develop DTI during a shorter period of time compared to persons with normal bodyweight and normal muscle thickness. Epidemiological studies indicate that an individual with spinal cord injury (SCI) is likely to gain weight and lose muscle tissue over the years post-SCI; therefore, he/she theoretically shifts from the condition of patient A to that of patient B, likely shortening the time for him/her to develop a PU or DTI under sustained loading. The seated buttocks are depicted as an example where internal tissue loads are expected to be higher than when laying down.[34] The theory suggesting that increased bodyweight and loss of muscle mass shorten the time for DTI onset[35] is hypothesized to hold for a supine position as well.*

deformations of up to 40% and cell viability was recorded using a confocal laser scanning microscope that monitored fluorescent markers for apoptotic and necrotic cell death. It was found that after 5 to 6 hours, compressive deformations caused substantial damage in the bioartificial muscles (defined as more than 20% cell death via both apoptotic and necrotic pathways). Most recently, Gefen et al[28] used Gawlitta's[27] tissue-engineered model system to determine the time-dependent critical compressive deformations for necrotic cell death in bioartificial muscles. They used a half-spherical indentor to induce a nonuniform, concentric distribution of deformations in the bioartificial muscle specimens and measured the spread of damage in the muscle cell over time using fluorescence microscopy. Interestingly, the tissue-engineered muscle model system also produced a sigmoid function describing the tissue load tolerance with time parameters similar to those reported in the animal studies of Linder-Ganz et al.[20] Specifically, the same timeframe for loss of muscle tolerance to the sustained loads (1 to 3 hours post-loading) manifested in both studies; this may indicate that loss of structural resistance to loads between 1 and 3 hours is an inherent property of muscle tissue.

As with the human and animal studies, results from cell and tissue culture models must be interpreted with caution. First, cell cultures and tissue-engineered constructs currently lack the true microscopic organization and architecture of native tissue. Also, no interaction with other tissues occurs. For example, the bioartificial muscles of Gawlitta[27] do not contain connective tissue that forms endomysium and perimysium in native muscle. Second, no vasculature is involved and although some factors of ischemia can be simulated by manipulating the medium of the cultures,[27,28] this is a simplification of the real interruption of vascular homeostasis. However, because the

biological variability is relatively small across cultures, these are excellent models for etiological PU research and eliminate the ethical issues involved when conducting animal experiments.

Hypotheses on the Effects of Individual Anatomy on Time for Injury

In a case study collection, obese patients were observed to be at higher risk than nonobese for serious PU and DTI.[29] Apparently, this is surprising, considering the fact that obese individuals tend to have lower interface pressure peaks, as shown in a group of 75 institutionalized elderly where those with the lowest body mass index had the highest peak seat-interface pressures.[30] However, when the fact that interface pressures have been shown to be an unreliable measure of internal tissue loading is considered,[31] this apparent paradox is resolved: the increased vulnerability of the obese patients to PU and DTI is due to their increased bodyweight loading on bony prominences, which in turn induces higher mechanical stress concentrations (ie, high forces per unit area of tissue) in their deep soft tissues. For example, in a study[32] in Israel involving two healthy subjects**,** the addition of 5 kg to the bodyweight of a 27-year-old man (bodyweight 90 kg) and a 26-year-old woman (bodyweight 55 kg) was shown to increase peak muscle and fat tissue deformations ~1.5-fold and their peak mechanical stresses 2.5-fold. Unfortunately, permanent wheelchair users, such as patients with a spinal cord injury (SCI), are more likely to be overweight and obese.[33]

Another change that occurs gradually with chronic sitting is loss of muscle mass (atrophy). In a study utilizing MRI measurements and computer models, Linder-Ganz et al[34] showed that (on average) gluteus muscle thickness under the ischial tuberosities in individuals with SCI >1 year post-injury is less than one third the thickness of these muscles in healthy persons. Under sustained bodyweight loading, the thin muscles of paralyzed individuals bear highly elevated mechanical stresses because little natural cushioning is in place to support the loads of the bony prominences that, as mentioned previously, are typically transferring increased bodyweight.[33] In fact, a theoretical study based on engineering mechanics recently showed that mechanical stresses in muscle tissue under the ischial tuberosities increase with a rise in bodyweight or with a decrease in the muscle thickness.[35] Accordingly, based on the load-time injury thresholds of Linder-Ganz et al,[20] severe PUs involving damage to muscle tissue and DTI are expected to develop sooner in patients in whom deep tissue loading is more intense — namely, in patients who are obese, lost substantial muscle mass, or both (see Figure 1).

The issue of internal tissue composition in patients who are at risk of developing PUs and DTI requires additional study in order to gain better understanding of individual susceptibility. In Linder-Ganz et al's study,[34] the authors acquired MRIs of the buttocks of seated individuals to measure the thicknesses of the gluteus muscle and overlying fat under the ischial tuberosities. The ratio of muscle thickness over fat thickness in five subjects

with SCI, excluding one subject who is a professional athlete, ranged between 0 and 1.4. For controls, this ratio ranged between 1.2 and 2.4 (when N = 6), demonstrating substantial loss of muscle mass in the group of patients with SCI. Although no comparable MRI data for obese or cachexic patients are available, it is commonly accepted that from a pathogenetic perspective, muscle and fat masses are strongly interconnected in the individual so the issue of how obesity per se (ie, without SCI) affects muscle mass in individuals susceptible to PU requires further study.

This article presents the point that even when considering bodyweight without accounting for internal tissue composition (ie, muscle/fat distribution), elevated mechanical loads on bony prominences in the obese theoretically increase risk for PU development and DTI. Potential consequences of obesity on internal tissue composition — eg, the replacement of muscle tissue by fat due to a sedentary lifestyle — is an additional bone load risk.

Conclusion

The etiology of PUs and especially DTI is still insufficiently understood. In particular, little methodological work has been performed relevant to timeframes for PU onset and development.[20-27] When considered together, data from the three available model systems — surgical patients, animal models, and *in-vitro* cell culture models — indicate that PUs in subdermal tissues under bony prominences very likely occur approximately between the first hour and 4 to 6 hours after sustained loading. It is important to note that all the relevant clinical data reviewed here, which were used to determine that timeframe, were acquired in studies of patients who have been laying down. Muscle and fat tissue loading under bony prominences during sitting is substantially greater than when the patient is laying down,[34] which, consistent with the schematic model data, theoretically indicates that for certain immobile patients, onset of PU and DTI while sustaining a sitting posture is likely to occur sooner than when laying. Unfortunately, no published studies are available on the timeframe for PU or DTI onset in sitting patients; therefore, studies in this field are needed to expand the current knowledge base. All forms of clinical studies should be useful in this regard, including prospective studies and case studies on wheelchair users with PUs and DTI that document the times of the sustained postures at which the injury occurred, the patient's relevant anatomy, comorbidities, and the type of seating cushion used. Additionally, basic research employing animal and cell culture models is required to further narrow the estimation of the timeframe for PU onset and to correlate the time factor to the extent of tissue damage as well as to the anatomy (eg, thin versus thick muscles), mechanical properties of the affected tissues (eg, spastic versus flaccid muscle), and chronic morbidities (eg, diabetes, cardiovascular disease). - OWM

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