Research Sheds New Light on What Causes PRESSURE INJURIES

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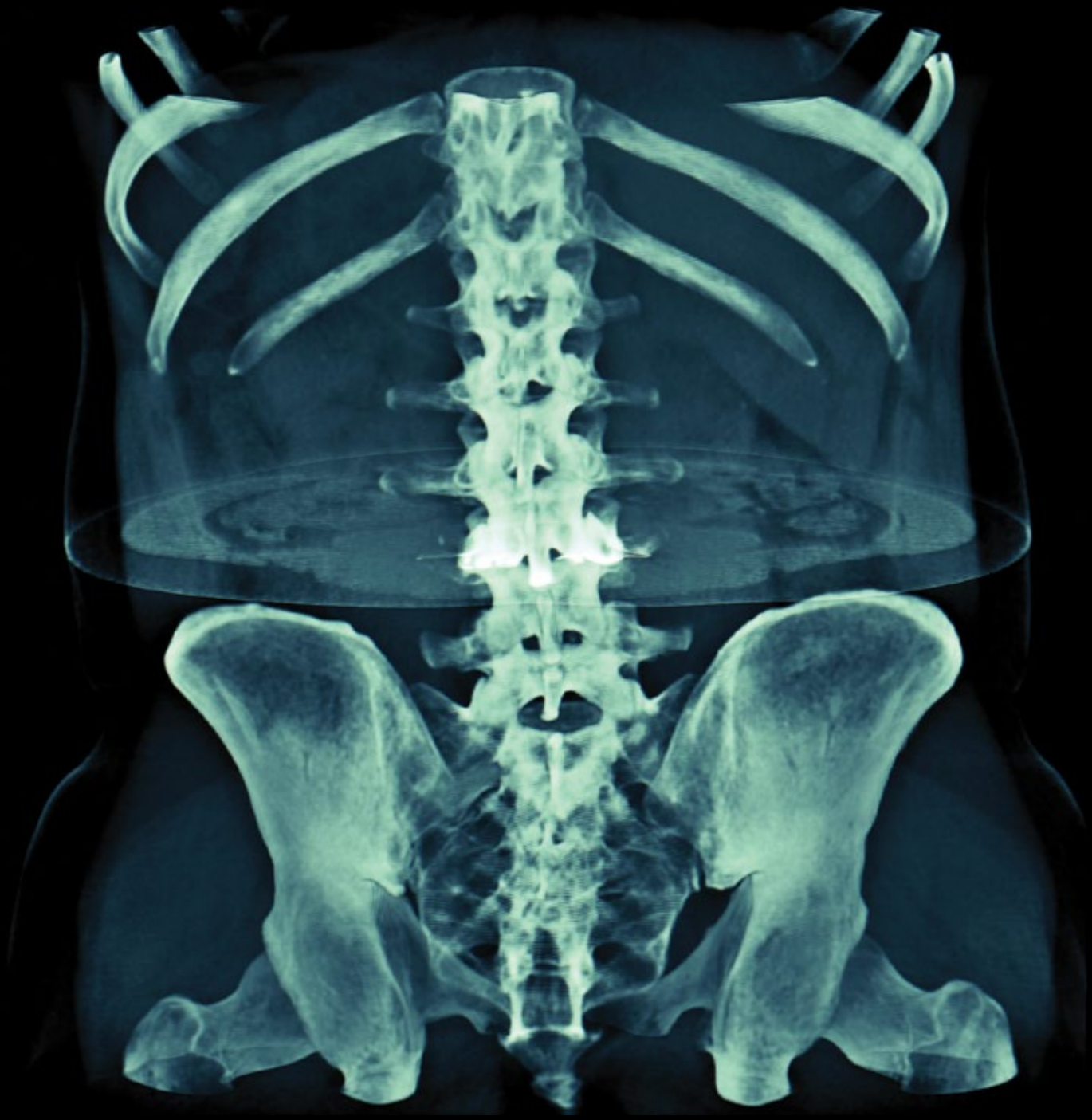

Contemporary evidence suggests that pressure injuries are not solely the consequence of prolonged ischemia but are also caused by soft tissue deformation independent of ischemia.

Not too long ago, the common belief was that pressure injuries (pressure ulcers) were caused by ischemia-related tissue breakdown, occurring when soft tissue was compressed and deformed between bony prominences and supporting surfaces such as seat cushions and mattresses. This understanding resulted in clinical practice guidelines aimed at avoiding long bouts of loading. It was also the impetus for the development of cushions and mattresses that would provide low and even pressure distributions. Contemporary evidence suggests that pressure injuries are not solely the consequence of prolonged ischemia but are also caused by soft tissue deformation independent of ischemia. Clinical practice guidelines must progress as additional sources of tissue damage are identified. As tissue injury can occur from deformation without or prior to the onset of ischemic damage, preventive measures need to consider situations where there is high-loading for shorter periods of time. Practice guidelines should not exclude the possibility of damage that could be caused by bouts of high-loading for a short period of time.

It is important to stress that the new direction of investigation on pressure injury genesis does not negate earlier findings. The ischemia pathway is well known and documented. Nearly 60 years of research has shown ischemia causes tissue breakdown, harking back to Kosiak's study on ischemic ulcers, utilizing dogs as test subjects, that was published in the Archives of Physical Medicine and Rehabilitation[1] in 1959. Confirmatory observations made on human subjects were noted by Reswick and Rogers in the mid-1970's.[2] In their study involving both seated and recumbent patients at Rancho Los Amigos Hospital in California, Reswick and Rogers replicated the etiology of ischemia and pressure injury in human tissue when subjected to load over time (see Figure 1).

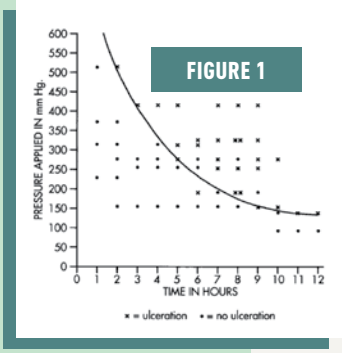

FIGURE 1

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THE ISCHEMIC PATHWAY

Subsequent research in the field has consistently shown that the ischemic pathway to tissue breakdown and ischemic-induced cell death evolves over a relatively long period of time; up to six hours. K. L. McCance explained the fundamentals of the ischemic pathway to tissue breakdown as follows:

- Ischemia is defined as a reduced blood supply to tissue. The process begins with the understanding that adenosine triphosphate (ATP) is the main energy storage and transfer molecule in the cell.

- It has been demonstrated that external forces are the root cause of tissue deformation that can block both blood and lymph vessels.

- The reduced blood and lymphatic flow result in hypoxic conditions within the tissue.

- Lack of an adequate oxygen supply at the cellular level causes a decrease in the mitochondrial phosphorylation, which then causes the supply of ATP to decrease.

- A lack of ATP causes the cell to increase anaerobic metabolism in an attempt to generate sufficient ATP. This also results in an increase in lactate as a byproduct of the ATP conversion process. Once glycogen stores are used up by the cell during anaerobic metabolism, the cell will have insufficient stores of ATP to carry out life-sustaining functions.[3]

This cascading sequence of events continues as the inefficient anaerobic metabolism in the cell causes it to generate waste products that accumulate in areas with impaired lymphatic flow. The subsequent build-up of waste products results in a harmful reduction in pH. Among the most important functions that are disrupted are the sodium/potassium ion pump and the sodium/calcium exchange processes. There is a net flow into the cell of calcium, water and sodium, causing the cell to swell. If the oxygen supply is not restored, these increased concentrations can cause denaturing of essential proteins and DNA. When said conditions persist for an extended period of time (two hours or more), cell injury or death can occur.[3]

Despite knowledge of this repositioning process and adherence to these guidelines, clinical practices such as limiting the amount of time tissue is exposed to deforming forces failed to prevent many pressure injuries and pressure injury incidence and prevalence rates remained high.

This well documented pathway to ischemic breakdown has led to recommendations in clinical guidelines for periodic unloading and guidance on the duration of safe loading. Despite knowledge of this repositioning process and adherence to these guidelines, clinical practices such as limiting the amount of time tissue is exposed to deforming forces failed to prevent many pressure injuries and pressure injury incidence and prevalence rates remained high. In our recent study on pressure injury among newly injured people with traumatic spinal cord injuries, we found that 37.5 percent of patients developed at least one pressure injury during the time they were in acute and inpatient rehabilitation care.[13]

Faced with the reality that avoiding long bouts of ischemia was not solving the pressure injury problem, researchers confronted the question of what else could be at play in the process of tissue necrosis. Since clinical practice guidelines were based on the long ischemic injury process as the source of pressure injury, and the adherence to the guidelines of periodic unloading did not reduce pressure injury incidence as much as expected, new lines of research focused on testing alternate pathways to tissue breakdown. One of those research efforts aimed to test the hypothesis that tissue deformation caused cell death directly.

TISSUE DEFORMATION

This alternate hypothesis that tissue breakdown results from deformation independent of oxygenation spurred an investigation that began in the early 2000s. The deformation pathway to pressure injury research began with cellular-level studies. The tissue-level investigations undertaken by Cees Oomens' group in the Netherlands, Dan Bader in the United Kingdom, and Amit Gefen in Israel are of particular interest.[4]

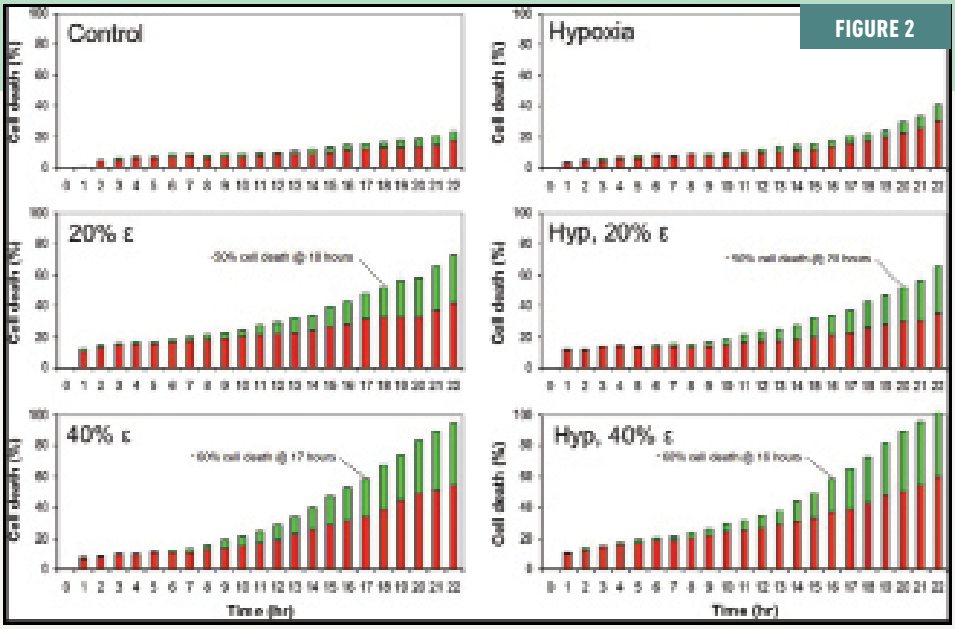

FIGURE 2

One of the questions addressed by Oomens and Bader concerned the interaction of deformation and ischemia with a goal of determining if deformation damage is independent of ischemic damage. An in vitro tissue-level experiment using engineered bio-artificial muscles (BAM) provided initial evidence of veracity to the hypothesis.[4] These BAM consisted of engineered skeletal muscle produced from the culture of murine muscle cells in a collagen gel. The study focused on the assessment of cell viability during compression and ischemia in an in vitro muscle model to determine their relative contributions to damage development.

Oomens and Bader constructed an experimental system on the stage of a microscope to investigate compression at the cellular level.[4] The experiments subjected tissue to three levels of compression — 0, 20 or 40 percent strain — under both hypoxic and normoxic conditions and observed what happened to the cells over time. They monitored cell viability through the use of fluorescent markers for apoptotic and necrotic cell death. The experiments revealed that hypoxia did not result in significant cell death over a 22 hour period but compression could lead to immediate cell death that increased with time. They did not observe any additional effect of hypoxia on cell death.

These data from the study on engineered muscle demonstrated that strain has a greater effect on the rate and extent of cell death compared to hypoxia (see Figure 2). For example, comparing the experimental control condition (see upper left graph in Figure 2) where 'the BAM was provided adequate oxygen (normal oxygen supply condition, normoxic) and was not strained' to the condition where 'the BAM was deprived of oxygen (hypoxic condition) and not strained' demonstrated the potential effects of ischemia. After 22 hours, about twice as many cells died in the hypoxic condition with no strain compared to the normoxic condition (~40 percent versus ~24 percent). The mechanism for the cell death for each 'no strain' condition was largely necrotic. But what was surprising were the results from the conditions where strain was applied to the BAM. For 20 percent strain, (see second row of graphs in Figure 2) the difference between the normoxic condition and the hypoxic condition was relatively small for almost all time points. For example, the mean time to 50 percent cell death was 18 hours for the normoxic condition and a similar 20 hours for the corresponding hypoxic condition. An analogous observation was made for the 40 percent strain conditions (see graphs in row three of Figure 2). In other words, once the artificial muscle was strained, cells die at rates higher than without strain but the results were similar with and without adequate oxygen supply. The implication was clear–when artificial muscles cells were subjected to strain, their survival depended on the amount of strain much more than the oxygen supply. [4]

In an extension of Oomens work and in collaboration with him, Gefen developed an experimental technique to determine the time-dependent, critical compressive strains for necrotic cell death.[5] The goal of such an experiment was to investigate the effects of the various loading parameters, namely strain and time, in order to estimate a critical strain threshold tolerance of muscle cells with a direct correlation to the time it took for cell damage to occur. In the study, BAM were subjected to nonuniform, concentric deformation by means of a half-spherical indenter and observed via confocal microscopy fluorescent

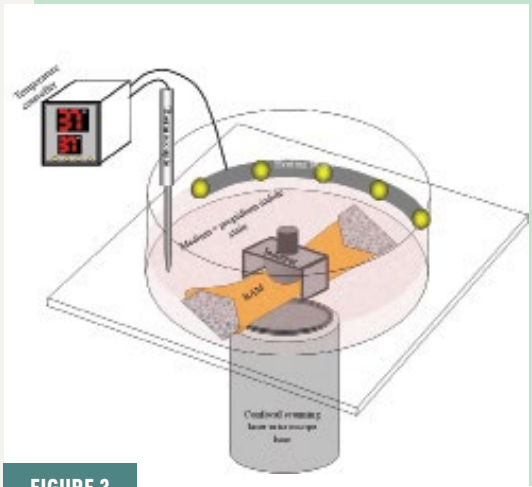

FIGURE 3

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images (see Figure 3). Using the half spherical indenter allowed simultaneous observation of multiple strain levels for each measurement time point. With the indenter lowered into and compressing the tissue, tissue under the apex of the indenter was strained more than tissue under other areas. The magnitude of the strain decreased toward the outer edge as a function of the shape of the indenter.

Propidium iodide was used to fluorescently stain the development of necrosis in 15 BAMs subjected to strains of up to 80 percent. The lowest strain causing cell death was determined every 15 minutes. Readings were taken at 15-minute intervals for the duration of the 285-minute-long trials. Cell death was noted from fluorescence images of the damage region. The intent of the experiment was to establish a relationship between muscle tissue strain and time to death whereby a critical time-strain-time threshold could be observed beyond which cell death was likely. That is to say it was intended to determine muscle tissue tolerance to strain for a range of loading times. Such a relationship is analogous to the relationship between pressure and time demonstrated by Kosiak's research. The resulting data successfully demonstrated the relationship between direct deformation damage and time.[5]

Gefen's results were significant, showing artificial muscle's tolerance to strain was limited for short loading periods. In fact, observations from the experiment revealed that artificial muscle could not withstand large compressive strains on the order of 75 percent for even 15 minutes. More moderate levels of strain, 40 percent, could be tolerated for nearly 5 hours.[5]

As a result of these BAM tissue-level experiments and a complementary series of cellular-level experiments, the pathway for direct damage from deformation has been described. This deformation pathway to pressure injury begins with pressure and shear force induced deformation. As a result of high strain, cell membrane diffusion properties are altered. Depending upon the severity of the strain and its duration, deformation can cause damage to the cell cytoskeleton followed by cell death. The deformation damage at a relatively high level of strain was shown to occur in less than 15 minutes or up to two hours. Beyond that time, the effects of high-strain deformation and ischemia began to co-mingle and there was not the means to distinguish these as the source of pressure injury.[5]

LIVING TISSUE RESEARCH

The next logical step for this research was to investigate whether the direct deformation damage results would be replicable in tests on living subjects. This work was the natural extension of the in vitro experiments. Using animal model studies with rats, Gefen's and Oomens' groups were able to differentiate deformation damage from ischemic damage. Experimentation on living creatures is more involved than the in vitro experiments performed in a cell

FIGURE 4

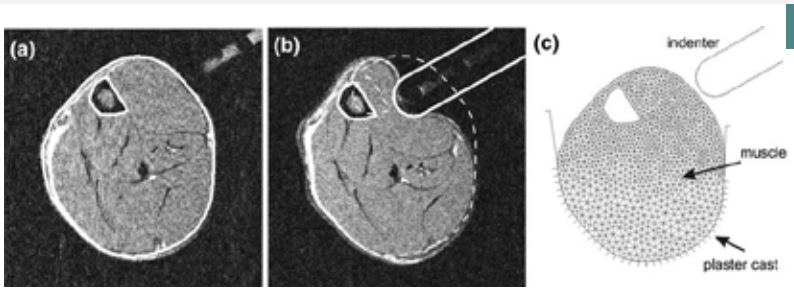

FIGURE 4. (a) Transversal scout image of a cross-section of a rat leg before loading. Contours of leg and tibia were determined (*white lines*) and used for mesh generation. (b) Scout image of the same rat leg during loading. Position of the tibia during loading and angle and depth of indentation were determined (*solid lines*) and used for the essential boundary conditions (contours of leg before loading are shown by *dashed lines*). (c) Resulting FE mesh of the rat leg with indenter and plaster cast modeled as rigid bodies.

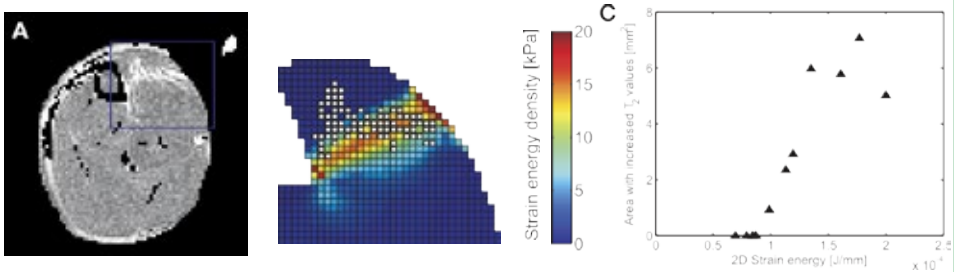

Fig. 1. *A*: T2 map obtained from T2-weighted magnetic resonance images (MRI) of a cross section of a rat leg, indicating that muscle damage [area with increased T2, high-intensity (white) pixels] due to 2-h compression only occurred in a small region of the muscle. *B*: internal strain energy density distribution estimated with finite element (FE) models showed an overlap with the damaged region in the tissue. *C*: total strain energy in the muscle clearly correlated with the amount of tissue damage once a specific threshold value was exceeded [adapted from Loerakker et al. (29)].

FIGURE 5

culture dish and requires different techniques. Loerakker published the results from a seminal study in which magnetic resonance imaging (MRI) was used in combination with finite element modeling (FEM) to monitor the effects of ischemia, deformation and reperfusion on the leg tissue of a live rat.[6] Measures of perfusion and tissue damage were obtained from the MRI while deformation was calculated using FEM. FEM is a mathematical technique for estimating the physical behavior of an object. The method is used extensively in engineering to predict behavior of a physical system when it is subjected to outside influences. By dividing a system into small geometric elements and defining physical characteristics such as their stiffness and interaction with neighboring elements, a virtually unsolvable mathematical problem relating coupled physical relationships can be solved accurately and efficiently. For example, an engineer might use FEM to optimize an airplane wing structure design by changing elements until a satisfactory structure is identified. Loerakker used FEM to calculate stresses and strains in the rat leg muscles so that these parameters could be compared to corresponding MRI observed damage.

Do strains on the order of 40 to 50 percent exist in the clinical situations where a person is sitting on a wheelchair cushion or lying on a mattress? If not, then the forgoing results might not explain observed pressure injury risk. If they do, the forgoing research would add important evidence to the pressure injury risk puzzle.

Figure 4 shows MRI images of the rat leg in the undeformed (see Figure 4a) and deformed (see Figure 4b) states. The corresponding FEM is shown in Figure 4c. Figure 5 shows a result from Loerakker et. al.[5] The MRI image on left, Figure 5a, displays damage in the region where the leg was indented for two hours as high intensity pixels. Figure 5b (center) shows the damage overlapping areas of high strain estimated with the model. As shown in Figure 5c, after a threshold strain was reached, the amount of damaged tissue was proportional to the intensity of strain.

The in vitro and in vivo research described above established that tissue damage can occur for sustained strains on the order of 40 to 50 percent. Do strains on the order of 40-50 percent exist in the clinical situations where a person is sitting on a wheelchair cushion or lying on a mattress? If not, then the forgoing results might not explain observed pressure injury risk. If they do, the forgoing research would add important evidence to the pressure injury risk puzzle. In an effort to answer this question, Linder-Ganz, Gefen, et al., used FEM and MRI to suggest sitting-induced strain does approach the critical levels shown in the earlier experiments.[7] Bone, muscle, fat, and skin properties used in an

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DEFINITIONS

Ischemia
impaired blood supply to tissue

Tissue deformation
a change in shape of tissue from one condition to another

Hypoxic
a condition where tissue cells are deprived of an adequate supply of oxygen

Tissue necrosis
premature death of tissue cells

Normoxic
a condition where tissue cells have adequate oxygen supply for life sustaining function

Apoptotic cell death
normal process programmed cell death in tissue

Perfusion / reperfusion
the flow of blood through the circulatory system (perfusion) and the restarting of flow after a period of no flow (reperfusion)

FEM model were obtained from the literature. The researchers took advantage of what was then a recently introduced open MRI system (Fonar Corporation, Melville, New York) that allowed users to sit in the machine during the imaging process to obtain the geometry for the model. Previous attempts to use MRI and FEM for this purpose were hampered by machines that restricted users to lying in the machine's imaging tube.[14]

The Linder-Ganz study used FEM and MRI to show the stresses (forces) and strains (deformations) in deep tissues when sitting. The non-weight-bearing versus weight-bearing MRI illustrated the high internal stress and strain in muscle near the ischial tuberosity in a seated, able-bodied person.[7] The strain magnitudes recorded were in the same range as the levels demonstrated to cause muscle cell death in the in vivo and in vitro experiments. Linder-Ganz, Gefen, et al., were not the first researchers to show that high deformation could lead to cellular damage, but they were able to isolate the incidence to pre-ischemic conditions. This study was important because it demonstrated that the magnitude of deformation shown to cause direct damage may occur in humans in common situations. In real life, people without additional risk factors don't develop pressure injuries due to deformation while they sit on hard surfaces because compensatory mechanisms such as sensation of pain causes deformation relieving movement before permanent damage occurs and its likely healthy tissue will quickly regenerate and recover from small amounts of damage from deformation.

Certain populations, such as persons with spinal cord injuries and those who are frail and elderly, are known to be at much higher risk of developing pressure injuries than the general population. This high risk can now be explained, at least in part, by considering the nature of how soft tissue deforms under load. High deformation magnitudes have been observed and postulated as the cause for pressure injury consistently over time from Reichel[8] back in the 1950's who observed tissue over the sacrum creasing and folding in response to shear forces from raising the head of hospital bed, to the present day in research by Oomens and Bader, et al.,[9] Brienza and Akins, et al.,[10] and Sonenblum and Sprigle, et al.,[11] For a summary of the research that led to the discovery of the pathophysiology of the deformation pathway, see C. W. J. Oomens, D. L. Bader, S. Loerakker, and F. Baaijens, "Pressure induced deep tissue injury explained."[9]

In addition, the research by Anke Stekelenburg, et al., demonstrated a marked difference in the severity of pressure injury in the deformation pathway versus the ischemia pathway alone. The study showed pressure injury from two hours of deformation resulted in irreversible damage, whereas two hours of ischemia resulted in reversible tissue changes.[12] These results imply that tissue subjected to the combined stress and strain of ischemia and deformation is at risk for irreversible muscle damage.

Understanding the risk of possibly irreversible damage that can be done due to direct deformation will hopefully lead researchers and clinicians to enumerate interventions to help prevent periods of high deformation. In Brienza, 2017, we showed that substantial differences in deformation can result from using different seat cushions. For example, for one participant in the study, the difference in deformation under their ischial tuberosity ranged from 41 to 59 percent based solely on the type of cushion used. Deformation under the ischial tuberosities for one of the control participants (no spinal cord injury) varied from 20 to 47 percent, depending on the cushion used. Another interesting observation from this study was that as tissue was loaded during sitting, much of the muscle tissue deformation observed was the result of muscle tissue displacing and not compressing as the FEM models discussed assumed. In fact, the study showed muscle tissue under the ischial tuberosity in the unloaded condition tended to be displaced laterally and posteriorly when sitting loads are applied. This result suggests that alternative models that more closely predict the tissues' response may be needed to more accurately describe and study tissue response and the pressure injury problem.

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CONCLUSION

... there are two well-defined pathways to tissue damage. The first is via ischemia. In the ischemic pathway, up to six hours is needed to cause cellular damage. The second pathway is via deformation.

The physiology of both ischemic breakdown and deformation breakdown begins with pressure and shear force induced deformation. However, it is acknowledged that these processes do not occur without the interplay of other elements. Other factors shown to have an impact on tissue health are temperature, moisture and a variety of intrinsic factors related to the general well-being of a person including mobility, sensation, age, diseases causing circulatory impairment such as diabetes and smoking.

In summary, there are two well-defined pathways to tissue damage. The first is via ischemia. In the ischemic pathway, up to six hours is needed to cause cellular damage. The second pathway is via deformation. In high-strain situations, damage to cells can occur in minutes to hours. While potentially harmful magnitudes of deformation can occur in typical clinical situations, just as with pressure injuries from ischemia, these forces can be avoided with sufficient preventive measures. Researchers can now combine their knowledge of the ischemic and deformation pathways to tissue damage with clinical observations to develop prevention strategies that specifically address the risk for pressure injuries on both fronts. The goal is to continually advance clinical practice guidelines to reduce the incidence rate of pressure injuries.

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