PRESSURE ULCER AETIOLOGY & BIOMECHANICS

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Declaration of
Financial Interests or Relationships

Speaker Name:

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.
Learning objectives

• At the end of this lecture, students will be able to:
  – Describe the etiology and pathophysiology of pressure ulcer development
  – Distinct between the mechanisms of superficial and deep pressure ulcers
  – Describe microclimate and its effect on skin properties
  – Describe the role of mechanobiology in pressure ulcer development and the primary mechanisms of deformation-induced cell damage
Pressure ulcers (=pressure injuries?)

Category/Stage 1: Changes in skin

Category/Stage 4:
Full thickness skin loss; fat and muscle damage; bone is exposed

* Terminology is evolving as new knowledge accumulates and litigation evolves: the US (NPUAP) have changed to ‘pressure injuries’ (April 2016) consistent with Australia (PPPIA) who were the first. The EPUAP has decided to continue using ‘ulcers’ for now
Populations at risk for pressure ulcers

- Bed/chair-bound patients with impaired mobility/sensation
- Patients post spinal cord injury, brain trauma or stroke
- Patients with degenerative neuromuscular diseases
- Patients who undergo prolonged surgery
- Prosthetic users

Pressure ulcers are difficult to treat, can be painful, isolating and depressing and may also cause death

In the UK alone, pressure ulcers are estimated to cost 1.8-2.6 billion Euros annually to the National Health System (4% of its expenditure)

We sit on our cells, and our cells are therefore distorting and deforming.
Distinct mechanisms of deep versus superficial pressure ulcers

Superficial Pressure Ulcers

Extrinsic
- Moisture and heat

Intrinsic
- Impaired motor-sensory capacities
- Poor nutrition
- Infection

Deep Tissue Injury (DTI)

Extrinsic
- Posture, Time at posture
- Stiffness of the support

Intrinsic
- Impaired motor-sensory capacities
- Muscle atrophy

Progressive necrosis

Deep tissue injury

Superficial pressure ulcers at the buttocks

DTI under the ischial tuberosities
Sustained deformation is the direct cause of cell and tissue death

- Sustained tissue deformations
- Plasma membrane poration
- Cytoskeletal integrity loss
- Cells further distorted
- Interstitial pressure
- Inflammatory edema
- Deformation-induced cell death

Deformation is a cell killer!

References:
- Slomka & Gefen (Annals of Biomedical Engineering 2012)
- Leopold & Gefen (Medical Engineering & Physics 2013)
- Weihs & Gefen (Medical Engineering & Physics 2016)
- Gefen (EWMA Journal 2018)
Etiology and other chapters now put emphasis on internal tissue loads as a primary factor in the injury process.

Deep tissue injury is included in the international classification system.
Why computer modeling?

- Epidemiological studies and clinical trials do not normally reveal the details of injury cascades or mechanisms of action of interventions; they are limited to indicating risk factors or whether there is (statistically significant) efficacy or not.

- Modes of action of medical devices/equipment designed for prevention are particularly difficult to test in clinical settings; studies are costly to run and require large and long follow-ups.

- Computer simulations are complementary to clinical research in providing additional important insights regarding aetiology, and in demonstrating mechanisms of action of potential interventions.

Shoham and Gefen, *Journal of Tissue Viability* 2012
Finite element (FE) computer modeling

- FE modeling is a well-accepted computational method for calculating internal mechanical loads (e.g., deformations and stresses) in structures made of complex shapes and materials.

- FE modeling is used extensively in civil, mechanical and aeronautical engineering, as well as in different fields of bioengineering in order to develop medical devices.

- FE modeling has an enormous potential in advancing the science of pressure ulcer prevention and treatment. The modeling can identify risk factors and at-risk conditions and evaluate the efficacy of devices and interventions.
What do we do at my lab?

In our research of the aetiology of pressure injuries, we study the hypothesis that sustained cell deformations trigger tissue damage due to changes in the mechano-chemical environment of cells.

We also conduct applied research aimed at characterizing risk factors and improving risk assessments and guidelines.

Finally, we develop technologies for pressure injury prevention based on understanding the aetiology and risk factors.
Multi-scale approach

- Organ
- Tissue
- Cell
Organ-scale internal tissue loads during sitting determined using subject-specific computational models
Much of our research work focuses on protecting individuals with spinal cord injury from pressure injuries

- Relatively young individuals who are more likely to be involved in car and sports accidents

- Often need to use a wheelchair for mobility for decades

- Are in most cases completely lacking the discomfort/pain ‘alarm’ mechanism that enforces continuous (micro-)movements in healthy

- Undergo dramatic body and tissue changes post the spinal injury which substantially increase their risk for developing pressure injuries

Maggie’s spinal cord injury and her hospitalization which follows, where she develops deep tissue injuries, illustrated in the Oscar winning movie (2005) Million Dollar Baby by Clint Eastwood
Internal tissue loads associated with prolonged sitting: Comparison of spinal cord injury data to healthy

**Intrinsic Risk Factors**  
e.g. internal tissue loads are posture-dependent

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**Fig. 1.** A schematic of the experimental setup for the MRI studies, showing how the angle of lateral back tilt was controlled with respect to neutral. The angle between the spine line (depicted using markers) and a plumb-bob attached to the back of the neck is measured. A photograph of a subject sitting in the MRI during a scan sequence is shown in the upper right frame.
Extrinsic Risk Factors e.g. internal tissue loads are support-dependent

Figure 4.
Tissue deformations (%) of (a) muscle, (b) fat, and (c) effective soft tissue (muscle and fat together) for all support surfaces. *p < 0.03.
Computational modeling employed for evaluating sitting surfaces

Segmentation using Simpleware®

Subject with a spinal cord injury (SCI)
(subject #5 from the Linder-Ganz et al J Biomech (2008) study:
21-years-old male, bodyweight 90 kg
1 year post the SCI (level of spinal injury: T6)

Levy et al. Journal of Tissue Viability 2014
Example: Greater envelopment substantially reduces localized tissue loads during wheelchair sitting

Air-cell-based (ACB) cushion

Flat foam cushion
stiffness= 10 kPa

Levy et al. Journal of Tissue Viability 2014
Microclimate

PRESSURE ULCER PREVENTION
pressure, shear, friction and microclimate in context

a consensus document
Basic concepts: Microclimate from a biomechanics perspective

Wetness increases the static friction coefficient between the skin and support

Wetness also increases skin surface waviness/roughness

In the context of pressure ulcers, microclimate usually refers to skin temperature and moisture conditions at the skin-support surface interface.

Shear loads

Skin morphology changes related to wetness

Perspiration

Changes in mechanical stiffness and strength

Skin damage
Modeling wet skin subjected to shear

- Effects of age on skin architecture and mechanical properties
- Effect of wetness on skin-support friction coefficient, and hence internal skin loads

Fig. 2 Example distributions of mechanical loads in the young skin in the model simulating a combination of compression and shear loading in a wet environment: a maximal shear strains (left panel isometric view, right panel side view); b maximal shear stresses (left panel isometric view, right panel superior view)

Fig. 3 Example distributions of a shear stresses and b contact pressures on the skin surface in the model simulating combined compression and shear loading of young skin in a wet environment. Both distributions are shown from a superior view
*Two different COF were defined between the skin surface and the support, based on experimental studies, where skin samples were rubbed against commercially available hospital fabrics. These COF were 0.42 for dry contact and 0.92 for wet contact.
How do microclimate factors interact with internal mechanical loads in skin and with the tolerance of skin to loading?

Modeling assumptions:

• The rate of production of perspiration depends on ambient and skin temperatures

• The rate of evaporation of perspiration depends on ambient and skin temperatures, but also on the relative humidity

• The rate of drainage of perspiration is a support-dependent property

The accumulated perspiration determines the friction coefficient and hence contact shear stress at the skin-support interface, and also, the shear strength of skin at a certain time point
It is possible to predict which factors need to be controlled in order to prevent skin breakdown.

Figure 2  The calculated dimensionless critical times for skin breakdown versus the skin temperature ($T_s$) for different values of (a) the microclimate parameters of ambient temperature ($T_a$) (left panel) and relative humidity (RH) (right panel), and (b) the interacting parameters of pressure delivered from the support ($P$) (left panel) and permeability to perspiration ($\gamma$) of the materials contacting the skin or being in close proximity to the skin (right panel). The following values were assigned to the model variables in these simulations: $\tau_0^* = 70$ kPa, $P = 7$ kPa$^3$, $\alpha = 2$, $\beta = 1$, and $\gamma = 0.1^3$, $T_a = 35$ °C$^3$ and RH = 0.5$^3$.3 denotes; where not altered as detailed in the specific panel.
The coupling between deformations and heat transfer in weight-bearing tissues

Zeevi et al. *International Wound Journal* 2017
The coupling between deformations and heat transfer in weight-bearing tissues (cont.)

The percentage tissue temperature reduction in the VOI relative to the foam mattress
Organ
Tissue
Cell
Pressure ulcers and deep tissue injury at a tissue-scale

Histopathology data (Phosphotungstic Acid Hematoxylin staining) for muscle tissue of albino rats, which was damaged by compression of 80kPa for 2 hours

Linder-Ganz et al. Journal of Biomechanics 2006
Tolerance of muscle tissue to sustained deformations: Time is a factor

The timecourse of decrease in tolerance cannot be explained by ischemia!
Ischemia does develop however capillary vessels are not fully occluded.

BTW capillaries remain partially open even under extreme (above-physiological) external mechanical loads.

FIGURE 2. Computational modeling of the muscle-fascicle-level finite element (FE) model. (a) Representative hematoxylin and eosin staining of a viable rat skeletal muscle showing muscle fibers, endomysium and capillaries, (b) model geometry segmentation and definition of the region of interest; (c) the FE mesh and loading and boundary conditions.

FIGURE 6. Changes in open-capillary cross-sectional area predicted by the finite element model for different external loading conditions, in terms of the applied external pressure (a), and of the apparent compression strain (b).
Production of tissue-engineered muscles

Isolated myoblast cells (from a C2C12 cell line)

Cell isolation

Concept of producing a BioArtificial Muscle (BAM)

Proliferation

Differentiation to form myotubes

Mechanical stimulation to form parallel myotubes

3D-organized engineered skeletal muscle tissue
Preparation of tissue-engineered muscles

Culture dish preparation:
“House”-like shaped Velcro pieces pinned with 0.1mm pins

Distances between “roofs”
12 mm

Immediately post-molding:
SYLGARD core

Cell/gel mold

1 day post-molding:

3 days post-molding:

7 days post-molding:
BAMs show mature, oriented muscle fibers:

No vasculature included!

Gefen et al. Journal of Biomechanics 2008
Measurement of the lowest deformation level causing cell death

Time-series of propidium iodide fluorescence images

Gefen et al. Journal of Biomechanics 2008
Cell death threshold

- $K + C = 0.57 \pm 0.07$ (engineering strain $77 \pm 7\%$)
- $t_0 = 63 \pm 37\text{ min}$
- $t_0' = 116 \pm 45\text{ min}$
- $t_c = 176 \pm 55\text{ min}$
- $C = 0.42 \pm 0.09$ (engineering strain $52 \pm 9\%$)

Gefen et al. Journal of Biomechanics 2008
Summary so far...

- The time-dependence tissue tolerance should relate to cell-level processes.

- Tolerance is not necessarily ischemia (traditional thinking).
  ** There is no vasculature in tissue-engineered muscles.

- Alternative explanation: tolerance → impaired mass transport @ intracellular or extracellular matrix → cell homeostasis.
Deformation makes the extracellular space denser.

Essential biomolecules come at different shapes and sizes and need to cross the barriers in the extracellular space.

Diffusing biomolecules need to cross barriers.
# Molecular weights of muscle metabolites

<table>
<thead>
<tr>
<th>Nutrients for skeletal muscle cells</th>
<th>Approximate Molecular weight (amu, or Daltons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen ((O_2))</td>
<td>32</td>
</tr>
<tr>
<td>Glycerol ((C_{3}H_{6}O_{3}, \text{taken up during exercise}))</td>
<td>92</td>
</tr>
<tr>
<td>Glucose ((C_{6}H_{12}O_{6}))</td>
<td>180</td>
</tr>
<tr>
<td>Free Fatty Acid (FFA, average formula (C_{17.13}H_{31.66}O_{1}))</td>
<td>254</td>
</tr>
<tr>
<td>Triglycerides (average formula (C_{54.41}H_{99.97}O_{5}))</td>
<td>850</td>
</tr>
<tr>
<td>Glycogen (dendrimer of glucose residues)</td>
<td>1 to 20 million Da = 1000 to 20,000 kDa</td>
</tr>
</tbody>
</table>

**Hormones that regulate skeletal muscle metabolism**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Approximate Molecular weight (amu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine (also called adrenaline, limits release and inhibits the effect of insulin)</td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid (essential for glycogen breakdown at rest)</td>
<td>362 (Cortisol)</td>
<td></td>
</tr>
<tr>
<td>Insulin (stimulates glucose uptake)</td>
<td>6,000 (= 6 \text{ kDa})</td>
<td></td>
</tr>
<tr>
<td>Leptin (moderates burning of fatty acids)</td>
<td>16,000 (= 16 \text{ kDa})</td>
<td></td>
</tr>
<tr>
<td>Growth hormone (IGF-I, suppresses insulin activity)</td>
<td>22,000 (= 22 \text{ kDa})</td>
<td></td>
</tr>
</tbody>
</table>

**Waste products and metabolic by-products of skeletal muscle cells**

<table>
<thead>
<tr>
<th>Waste product</th>
<th>Approximate Molecular weight (amu/Daltons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon Dioxide</td>
<td>44</td>
</tr>
<tr>
<td>Glycerol</td>
<td>92</td>
</tr>
<tr>
<td>Lactate ((C_{3}H_{6}O_{3}))</td>
<td>90</td>
</tr>
<tr>
<td>Alanine ((H_{2}C_{3}NO_{2}))</td>
<td>89</td>
</tr>
<tr>
<td>Glutamine</td>
<td>146</td>
</tr>
</tbody>
</table>

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The concept of Brownian motion:
Free diffusion accelerates under the effect of heat

\[ D = \frac{k_B T}{6\pi \eta r} \]
Ischemic tissue shows mild temperature drops
Theory of fluorescence recovery after photobleaching

Gefen et al. Journal of Biomechanics 2008
Experimental setup for the FRAP studies

*Temperature at the test chamber was controlled, and kept at the 37°C level
Experimental design of FRAP studies

Baseline

50-60% strain applied

Compare diffusion coefficients $D$

50-60% strain + 3°C temperature drop applied

Gefen et al. Journal of Biomechanics 2008
Diffusion coefficients in unloaded versus loaded bioartificial muscles

$D$ in BAMs were normalized with respect to medium

$D$ of compressed BAMs are consistently ~50% lower than those of uncompressed BAMs

Gefen et al. Journal of Biomechanics 2008
Diffusion coefficients in loaded bioartificial muscles: The effect of a temperature drop

**Diffusion coefficients were normalized with respect to \( D \) of the unloaded BAMs at 37°C

3°C temperature drop on top of deformations significantly reduces diffusivity by additional ~10%
Atrophy of skeletal muscle post spinal cord injury

Human gluteus muscle:
(a) healthy and (b) post spinal cord injury

Rat soleus:
(a) healthy and (b), (c) post spinal cord injury

Wei et al. Molecular Medicine Reports 2016
Multiphysics simulations of glucose transport in muscle tissue

ROI: 320×320µm²

Normal

SCI

Capillary
Muscle cell (fiber)
ECM

Ruschkewitz and Gefen, Comput Methods in Biomech Biomed Eng 2011
There is a critical compression level (~25% for this model) above which large tensional strains start to develop in the walls of the cell, the plasma membrane.
Confocal-microscopy-based 3D cell modeling

Myoblast

Fibroblast
Simulation of a (real) single cell subjected to compression
To look at whether cells also deform in tension when they reside in a compressed extracellular matrix - a condition closer to the *in vivo* state - we test a model of a microscopic construct with embedded cells.

**Source:** BBSRC bioscience for the future, http://www.bbsrc.ac.uk

Slomka et al. *Cellular and Molecular Bioengineering* 2009
Deformed cells in a tissue

(a) Undeformed

(b) 5.7%

(c) 8.6%

(d) 12.9%

(e) 19.4%

(f) 29.2%

(g) 43.8%

(h) 45.3%

Cells clearly elongate (stretch) with an increase in compressive construct deformations

Slomka et al. Cellular and Molecular Bioengineering 2009
Experimental approach for exposing cells to sustained mechanical deformations

(a) Stainless Steel 303
(b) Polycarbonate
(c) Teflon
(d) Clamper

(e) Strip-shaped elastic substrate

$E_{11}$

$E_{22}$

$d$ [mm]

Leopold and Gefen, *Medical Engineering & Physics*, 2012
Uptake of large molecules is deformation-magnitude-dependent as well as molecular-weight-dependent.

Confocal imaging of C2C12 cells subjected to a uniaxial tensile strain of 9% for 3 hours (a) versus control, undeformed cells (b). The left column shows combined morphological staining (actin stress fibers in red; nuclei in purple/blue) and imaging of uptake of a 4kDa Dextran dye (green fluorescence), and the right column shows just the Dextran uptake, for clarity.

* $p<0.01$ with respect to strain of 3% for the corresponding molecular mass; ** $p<0.05$

Leopold and Gefen, *Medical Engineering & Physics* 2012
The skeleton of the cell (cytoskeleton) breaks down.

Deformation is a cell killer!
**Ischemia**

- Impaired perfusion
- Reduce oxygen
- Change in metabolism
- Accumulation of waste products
- Decrease in pH
- Cell death

**Deformation**

- Deformation of cells
- Disruption of the cytoskeleton
- Cell membrane failure
- Cell permeability increases
- Loss of homeostasis
- Cell death
**Ischemia**

- Impaired perfusion
- Reduce oxygen
- Change in metabolism
- Accumulation of waste products
- Decrease in pH
- Cell death

**Deformation**

- Deformation of cells
- Disruption of the cytoskeleton
- Cell permeability increases
- Loss of homeostasis
- Cell death

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**Deformation is a cell killer!**

- **Up to 6 – 8 hours**
- **Minutes to hours**
Development of cell and tissue damage: The 3 factors

MACRO-scale
Tissue necrosis

Cumulative damage
(rate $\alpha + \beta + \gamma$)

Direct deformation damage
(rate $\alpha$)

Inflammatory response-related damage
(rate $\beta$)

Ischemic damage
(rate $\gamma$)

Micro-scale
Cell death

Extent of cell/tissue death
[# cells, necrotic tissue volume etc.]

Time
[minutes to hours]

$t_{deform}$
$t_{inflam}$
$t_{ischem}$

Gefen EWMA Journal 2018
Cell & tissue damage development: Inter-patient variability

- Extent of tissue damage
  
  Extents and rates of cell and tissue damage are specific to the individual

- Deformation damage rate X2

- Ischemic damage rate X2

- All damage rates are equal

- Time
  
  [dimensionless units]
How is the tissue injury threshold related to damage rates?

The graph shows the relationship between time and the extent of tissue damage. The tissue deformation level decreases over time, reaching irreversible damage levels at specific time points. The graph also illustrates the deformation damage rate at different time points:

- Deformation damage rate X1
- Deformation damage rate X2
- Deformation damage rate X4
- Deformation damage rate X8

The tissue injury threshold is marked on the graph, indicating the point at which irreversible damage occurs.
Some practical implications: Patient characteristics

**Patient B**
- Obesity
- Muscle atrophy

**Patient A**
- Normal body weight
- Normal muscle thickness

Load on muscle tissue vs. Time [Hours]
- Tissue damage
- Injury threshold
- Viable tissue

Time at which injury will likely onset in Patient B < Time at which injury will likely onset in Patient A

[Diagram showing load on muscle tissue and corresponding time frame for injury onset in different patients.]
Some practical implications: Support surface characteristics

Muscle deformation [%]

Time [hours]

Added safe sitting time through greater envelopment

Death of muscle tissue

Viable muscle tissue

No envelopment

Medium envelopment

High envelopment

Cell death tolerance of Gefen et al. (2008)
A holistic approach is needed: Beware of the toilet!

Toilet sitting is a poorly considered at-risk condition: Care facilities can spend millions on sophisticated beds and cushions, or monitoring and diagnostics, but eventually, pressure injuries will still occur if at-risk patients will be left for too long on the toilet.

<table>
<thead>
<tr>
<th>Contoured Toilet Seat</th>
<th>Flat Toilet Seat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>avg</strong></td>
<td><strong>peak press</strong></td>
</tr>
<tr>
<td>mm Hg</td>
<td>mm Hg</td>
</tr>
<tr>
<td>46</td>
<td>≥256</td>
</tr>
<tr>
<td>59.4</td>
<td>≥256</td>
</tr>
</tbody>
</table>

Lustig et al. Journal of Tissue Viability 2017
The field of chronic wound care and prevention in particular rapidly closes the gaps with other fields of medicine (e.g. orthopaedics, cardiovascular) in employing state-of-the-art bioengineering approaches for product design, selection, and evaluation.

Computer modeling facilitates formulation and testing of design concepts using standard, objective, and quantitative measures, which consequently allows rationalized decision-making in either R&D or purchase decision processes.

Multi-disciplinary teams integrating clinical and bioengineering expertise and academia-industry collaboration will continue to push the field forward, for the benefit of patients and families.
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