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 the two lectures, 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
  – List the primary modes of action of protective surfaces
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 therefore distorting and deforming

Shoham et al., Biomech Model Mechanobiol 2016
Distinct mechanisms of deep versus superficial pressure ulcers

Superficial Pressure Ulcers

- Extrinsic: Moisture and heat, Friction properties
- 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

Examples:
- Superficial pressure ulcers at the buttocks
- DTI under the ischial tuberosities

(Black et al., 2005)
Sustained deformation is the direct cause of cell and tissue death
EPUAP-NPUAP-PPPIA
International pressure ulcer guidelines

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 group 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.
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.

Levy and Gefen, OWM 2016
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-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 trunk tilt was controlled with respect to height. The angle between the spine line (depicted using markers) and a plumb-bob attached to the back of the neck (b). A photograph of a subject sitting in the MRI during a scan sequence is shown in the upper right frame.

Fig. 3. Compressive tissue deformations as a function of (a) lateral tilt and (b) anterior tilt.
**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.

Shabshin et al. *Journal of Rehabilitation Research and Development* 2010
Computational modeling employed for evaluating sitting surfaces

Segmentation using Simpleware®

Foam cushions

Air-cell-based (ACB) cushion

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
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.

Skin morphology changes related to wetness.

Changes in mechanical stiffness and strength.

Skin damage.

Shear loads.

Perspiration.
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

![Diagram showing maximal shear strain and stress](image)

**Fig. 1** Finite element model geometries simulating an approximately 3 mm x 3 mm x 1.3 mm-sized young (a) and aged (b) skin samples. Isometric view of the young skin (c) is brought for illustration of the three-dimensional features. Both geometrical model configurations consist of three layers: stratum corneum (SC), epidermis plus upper dermis (subepidermal nonechogenic band, SENO), and deep dermis.

**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.

Figure 1 The model of skin tolerance to superficial pressure ulcers as function of the microclimate factors: (a) Schematic of the skin—clothing—support contact problem. (b) The modeling concept, of seeking the critical time \( t* \) at which the shear stress applied on the skin under the effect of perspiration, \( \tau \), which progressively increases as perspiration accumulates (Eq. 6), exceeds the shear strength of skin, \( \tau_0 \), which continuously decreases, again under the effect of perspiration (Eq. 7).
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: \( r_D^0 = 70 \text{kPa}, P = 7 \text{kPa}^3, \alpha = 2, \beta = 1, \) and \( \gamma = 0.1^3, T_a = 35 \text{°C}^3 \) 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
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
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

Linder-Ganz and Gefen Annals of Biomedical Engineering 2007
Production of tissue-engineered muscles

Isolated myoblast cells (from a C2C12 cell line)

Cell isolation

Proliferation

Concept of producing a BioArtificial Muscle (BAM)

Differentiation to form myotubes

3D-organized engineered skeletal muscle tissue

Mechanical stimulation to form parallel myotubes

Gefen et al. Journal of Biomechanics 2008
Preparation of tissue-engineered muscles

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

Immediately post-molding:
SYLGARD 601

1 day post-molding:
Cell/gel mold

3 days post-molding:
Distance between “roofs” 12 mm

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
Cell death threshold

\[ K+C = 0.57 \pm 0.07 \]  
(Engineering strain 77\%\%)

\[ t_v = 63 \pm 37 \text{ min} \]

\[ t_e = 176 \pm 55 \text{ min} \]

\[ \tilde{z} = 116 \pm 45 \text{ min} \]

(Engineering strain 52\%\%)

Gefen et al. Journal of Biomechanics 2008
• The time-dependence tissue tolerance should relate to cell-level processes

• Tolerance 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.

Gefen et al. Journal of Biomechanics 2008
# 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 (O₂)</td>
<td>32</td>
</tr>
<tr>
<td>Glycerol (C₃H₈O₃, taken up during exercise)</td>
<td>92</td>
</tr>
<tr>
<td>Glucose (C₆H₁₂O₆)</td>
<td>180</td>
</tr>
<tr>
<td>Free Fatty Acid (FFA, average formula C₁₇₋₁₉H₃₁₋₆₆O)</td>
<td>254</td>
</tr>
<tr>
<td>Triglycerides (average formula C₅₄₋₄₁H₉₈₋₉₉O₆)</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**

- Epinephrine (also called adrenaline, limits release and inhibits the effect of insulin): 183
- Glucocorticoid (essential for glycogen breakdown at rest): 382 (Cortisol)
- Insulin (stimulates glucose uptake): 6,000 = 6 kDa
- Leptin (moderates burning of fatty acids): 16,000 = 16 kDa
- Growth hormone (IGF-I, suppresses insulin activity): 22,000 = 22 kDa

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

<table>
<thead>
<tr>
<th></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 (C₃H₆O₃)</td>
<td>90</td>
</tr>
<tr>
<td>Alanine (H₂C₃NO₂)</td>
<td>89</td>
</tr>
<tr>
<td>Glutamine</td>
<td>146</td>
</tr>
</tbody>
</table>


Gefen et al. *Journal of Biomechanics* 2008
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

Temperature [°C]

30 minutes

0 minutes

60 minutes

10 minutes

90 minutes

20 minutes

120 minutes

unloaded limb

External loading location

loaded limb

Linder-Ganz & Gefen, Annals of Biomedical Engineering 2007
Theory of fluorescence recovery after photobleaching
BAM specimens were placed on a confocal microscope stage:

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

- Normalized Diffusion Coefficient 10kD
- Normalized Diffusion Coefficient 20kD
- Normalized Diffusion Coefficient 150kD

$D$ 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%.

Gefen et al. Journal of Biomechanics 2008
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
Organ
Tissue
Cell
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

(a) Confocal microscopy images of a myoblast.

(b) Confocal microscopy images of a fibroblast.

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.
Cells clearly elongate (stretch) with an increase in compressive construct deformations.
Experimental approach for exposing cells to sustained mechanical deformations
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; ** $p<0.05$.
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

Cell membrane failure

Cell permeability increases

Disruption of the cytoskeleton

Deformation of cells

Deformation is a cell killer!

Deformation can last up to 6–8 hours

Minutes to hours

Cell death

Decrease in pH

Accumulation of waste products

Disruption of the cytoskeleton

Deformation of cells
Development of cell and tissue damage: The 3 factors
Support surfaces for prevention and treatment

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Declaration of Financial Interests or Relationships

Speaker Name:

My research work on pressure ulcer prevention is supported in part by Molnlycke Health Care (Gothenburg, Sweden)
Effective support systems minimize tissue deformation exposures.
Cell & tissue damage development: Inter-patient variability

Extents and rates of cell and tissue damage are specific to the individual.
How is the tissue injury threshold related to damage rates?

- Extent of tissue damage [dimensionless units]
- Tissue deformation level
- Time

- Deformation damage rate X16
- Deformation damage rate X8
- Deformation damage rate X4
- Deformation damage rate X2
- Deformation damage rate X1

Irreversible damage at time $t_{deform}$ followed by reversal of deformation damage rate. Tissue injury threshold indicated by red curve.

Gefen EWMA Journal 2018
Some practical implications: Patient characteristics

![Diagram showing load on muscle tissue over time for patients A and B, with implications for injury onset.

Patient A: Normal body weight, normal muscle thickness, injury threshold reached at approx. 3 hours.

Patient B: Obesity, muscle atrophy, injury threshold reached at approx. 1 hour, likely onset sooner compared to Patient A.]

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

Gefen, OWM 2008
Some practical implications: Support surface characteristics

- No envelopment
- Medium envelopment
- High envelopment

Death of muscle tissue
Viable muscle tissue

Cell death tolerance of Gefen et al. (2008)

Added safe sitting time through greater envelopment

Muscle deformation [%]

Time [hours]
Maximizing immersion and envelopment dramatically reduces exposure to internal tissue deformations.

Air-cell-based cushion

Flat foam cushion (stiffness = 10 kPa)
Extension of the modeling to three-dimensional anatomies

Analysis of the intensity of tissue deformations (strain energy density)

Brienza et al. Journal of Tissue Viability 2017
Good envelopment should not be on the account of heat trapping: Multiphysics design is needed to consider the MICROCLIMATE conditions

Internal tissue temperatures on different mattresses

Adjustability is a second critically important characteristic of good cushions - body structure and composition are constantly changing.
Scarring in tissues from a history of pressure ulcers is an example scenario for questioning the adjustability of cushions.
The consequences of lack of an adjustability capacity: The example of the contoured foam cushion

Simulating weight loss and gain over a time course post injury (<5 years)

Overweight plus pathoanatomical changes

Right after injury (cushion is fitted to the buttocks’ contours)

-25% fat (catabolic response; weeks to months)

+40% fat and intramuscular fat infiltration

+40% fat and muscle atrophy

Sopher et al. Journal of Biomech Eng 2011

Shoham et al. Advances in Skin & Wound Care 2015
Adaptability is a third important feature: Support surfaces should maintain efficacy regardless of selection of clothing, shoes or pocket contents.
**Durability** is a fourth important feature: Cushions should maintain efficacy over years of exposure to loads, temperatures and fluids.

ISO 16840-6 Wheelchair Seating Part 6: Determination of the Changes in Properties following extended Use – Seat Cushions
Finally, there is the factor of **user interaction** with the support surface: Importance of the rate of delivery of tissue deformations

Levy et al. *Journal of the Mechanical Behavior of Biomedical Materials* 2013
in a nutshell

Safe positioning

Good envelopment with minimal heat trapping
Adjustability
User Interaction
Durability
Adaptability

Gefen OWM 2014
The off-loading concept: the toilet seat as a thought-provoking example for the effects of off-loading on tissue function

A schematic plot of the tc-PO2 signal behavior during the 3 sitting phases

Lustig et al. Journal of Tissue Viability 2017
Off-loading shifts bodyweight loads to somewhere else …

Tissue stress (effective)

Tissue strain (effective)

Off-loading cushion

Air-cell cushion

Peko-Cohen and Gefen *International Wound Journal* 2017
Modeling pressure ulcer risk on positioners

We use engineering testing concepts adopted from the motor vehicle industry e.g. physical phantoms equipped with sensors

Using smart materials with shape memory capacities to optimize envelopment
Combining support surfaces with complementary, prophylactic dressing technologies

Levy & Gefen Ostomy Wound Management 2017
Levy, Schwartz & Gefen International Wound Journal 2017
Schwartz, Gefen et al. Ostomy Wound Management 2018
Peko-Cohen, Gefen et al. Journal of Wound Ostomy Continence Nursing 2018
Discussion

• Understanding the damage cascade at the cell scale facilitates effective interventions.

• Pressure relieving systems should be designed/selected based on: envelopment w/o heat, adjustability, adaptability, durability.

• Bioengineering innovation, employing e.g. computational modeling, smart materials & structures, sensors and importantly state-of-the-art efficacy research, is the way forward.

• 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.
The European Conference on
Controversies in Diabetic Foot Management
2-3 May 2019 | Vienna, Austria

See you at Diabetic Foot Europe 2019

www.diabeticfoot-europe.com

@BiomedSharing
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