Hip Fracture – The Final Straw?

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Frailty in the Third Age of Man

Ageing = Increasing frailty of an organism with time that reduces the ability to deal with stress, resulting in increased chance of disease and death.
Ageing and stress

- Risk of physical trauma (Hip-fracture)
  Wood et al 1992; Khasraghi et al 2003
- Emotional stress of caring for a partner
  Kiecolt-Glaser et al 1991; Bauer et al 2000
- Emotional stress of bereavement
- Effect of social isolation
  Keller et al 2003
Immune Function in Healthy Elderly and Hip-fracture patients

Subjects: 35 elderly patients (>65 yrs) with fractured neck of femur; 9 young patients (<33yrs) patients with lower limb fractures; 20 healthy age-matched controls

Infection rates were monitored and neutrophil function assessed at time of trauma and 6 weeks later.

The ratios of serum cortisol:DHEAs were assessed for each group
Infections after Hip-Fracture

- Chest: 15%
- Wound: 12%
- UTI: 10%
- No infection: 63%
Question 1

Why are older people more prone to infections after Trauma (hip-fracture)?
## Age-related increases in infectious diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Change in Elderly subjects</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative sepsis</td>
<td>50% increase in mortality</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial dysentery</td>
<td>3-fold increase in incidence</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>120-fold increase in mortality</td>
<td>2</td>
</tr>
<tr>
<td>GI infections</td>
<td>400-fold increase in mortality</td>
<td>3</td>
</tr>
<tr>
<td>Influenza</td>
<td>160-fold increase in mortality</td>
<td>3</td>
</tr>
</tbody>
</table>

Cells of the immune system
Age and vaccination efficacy

Hainz et al (2005)
Meet the Neutrophil

**OXIDATIVE BURST**
Neutrophils kill microbes by producing reactive oxygen species, demonstrated here with the dye nitroblue tetrazolium (NBT)
Effect of Age on Superoxide generation and phagocytosis

Trauma does not affect neutrophil Phagocytosis

Butcher et al. Aging Cell (2005)
Trauma suppresses neutrophil bactericidal function in the elderly

Butcher et al. Aging Cell (2005)
Superoxide generation was lower in patients who later developed infection

Butcher et al. Aging Cell (2005)
Question 2

Why is stress more of a problem with age?
The Hypothalamic-pituitary-adrenal axis

Hypothalamus → Pituitary (ACTH) → Adrenal → Cortisol

DHEA: Immune enhancer

Immunesuppressor
Adrenal Corticosteroids and Immune Function

• Cortisol
  • Decreased production of pro-inflammatory molecules (IL-1, TNF, GM-CSF, IL-2, IL-3, IL-4, IL-5, IL-8, NO, prostaglandins, leukotrienes)
  • Reduced extravasation of inflammatory cells
  • Induction of apoptosis in lymphocytes and eosinophils
  • Inhibition of neutrophil function

• DHEA/s
  • Increased cytokine production (IL-2, IL-3, IFN-gamma)
  • Increased T cell function (CD8, DTH)
  • Decreased apoptosis of PBMC
  • Increased myelopoiesis and lymphogenesis
DHEAs levels decline with Age - Adrenopause

Cortisol:DHEAS ratio - Young = 0.09; Elderly = 0.17
Cortisol:DHEAs is increased in Elderly hip-fracture patients

<table>
<thead>
<tr>
<th></th>
<th>Young trauma</th>
<th>Elderly trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.087± 0.01</td>
<td>0.562±0.06</td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

[Healthy young = 0.094±0.01; Healthy elderly = 0.176±0.03]
Cortisol:DHEAs is higher in patients who developed infection

Butcher et al. Aging Cell (2005)
Question 3

Can we do anything about this?
DHEAs primes neutrophils superoxide responses

![Graph showing superoxide production in response to different concentrations of DHEAS]
DHEAs counteracts the suppressive effects of Cortisol

Butcher et al. Aging Cell (2005)
Mild trauma: Cortisol increase → Immune system down-regulation
DHEAS increase → Immune system up-regulation

Young

Elderly

Cortisol

DHEAS

Immune downregulation

Infections
Improving immunity after hip fractures in the elderly

- DHEAS supplementation
- Or blocking cortisol
The anti-glucocorticoid also raises DHEAS levels.

![Graph showing DHEAS levels over treatment days for different doses.](image-url)
Older subjects can also raise DHEAS levels

![Graph showing DHEAS levels for different groups and dosages.](image)

- **Legend:**
  - Green bars represent the group of 18 - 30 years old.
  - Grey bars represent the group of > 61 years old.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>18 - 30</th>
<th>&gt; 61</th>
</tr>
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<tbody>
<tr>
<td>Plac</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>150mg</td>
<td>5.0</td>
<td>4.5</td>
</tr>
<tr>
<td>450mg</td>
<td>6.5</td>
<td>5.5</td>
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</table>
"Art is Me, Science is We"

Stephen Butcher
David Radford
David Lascelles
Keqing Wang

Vijay Killampalli
Emin Kaya Alpar
Wiebke Arlt
Jeremy Tomlinson
Healthy Ageing – good genes, good diet….but watch out for slips and trips!