“The true cost of inpatient obesity” - impact on inflammatory stress and morbidity.

Professor Bob Grimble, Institute of Human Nutrition, Institute of Developmental Sciences Building, University of Southampton Medical School
One of the first indications that the immune system had a role in mortality from chronic diseases.

Serum albumin is a negative acute phase reactant and is reduced when levels of inflammatory stress become raised.

Phillips et al Lancet 89 1434
The inflammatory response is purposeful, focussed, powerful and dangerous. The perfect response.

"And the lion and the lamb shall lie down together, but the lamb won't get much sleep."  Woody Allen
Normal host response to trauma/infection/burns

Immune system activation

Pro-inflammatory cytokines

T and B cells

Oxidants

Pathogen killing

Tissue damage

Hostile environment
Normal host response to trauma/infection/burns

Immune system activation

Pro-inflammatory cytokines

Oxidants

Pathogen killing

Tissue damage

T and B cells

Immuno-nutrition

Tissue release from host tissues

Glucose

Glutamine

Hostile environment

Appetite loss
Normal host response to trauma/infection/burns

Immune system activation

Pro-inflammatory cytokines

Oxidants

Antiox defence

Pathogen killing

Tissue damage

T and B cells

Immuno-nutrition

Glucose

Nutrient release from host tissues

Glutamine

Sulphur amino acids

Glutathione synthesis

Appetite loss

Hostile environment

Antioxidant defences strengthened
Normal host response to trauma/infection/burns

Immune system activation

Pro-inflammatory cytokines

Feedback systems
IL10, Heat shock proteins

T and B cells

Immuno-nutrition

Oxidants

Antiox defence

Glucose

Tissue damage

Pathogen killing

Antioxidant defences strengthened

Nutrient release from host tissues

Glutamine

Sulphur amino acids

Appetite loss

Hostile environment

Glutathione synthesis

Antioxidant defences strengthened
The inflammatory response is designed so species can combat pathogens and survive injury.

Aggression

Appropriate

Inappropriate
Downside of the inflammatory response.
The lamb gets a little stressed!
Inflammation

Pathogen killing

Inflamatory stimuli pathogens, environmental factors, damaged tissue

Insulin insensitivity

Hyperlipidemia
Inflammation

Pathogen killing

Inflammatory stimuli pathogens, environmental factors, damaged tissue

Diabetes mellitus

Insulin insensitivity

Hyperlipidemia

Atherosclerosis

Mortality and morbidity

Myocardial infarction
The human race is diverse and thus risk factors influencing the inflammatory response are diverse.

What are the key variables which influence the strength and outcome of the response?
Key factors influencing inflammatory stress:-

• Poor anti-oxidant defences
• Polymorphisms (SNP) in cytokine genes
• Obesity
• Gender
• Aging
Key factors influencing inflammatory stress:-

• Poor anti-oxidant defences
• Polymorphisms (SNP) in cytokine genes
• Obesity
• Gender
• Aging
Oxidants and cytokines are partners in crime

Inflammatory cells

Oxidants \rightarrow \text{Cell membrane} \rightarrow \text{Cytokines}

NFkB, IkB
Oxidants and cytokines are partners in crime

- Oxidants
- Inflammatory cells
- Cytokines
- Oxidised cell components
- NFkB
- Cell membrane
- IkB

- Oxidants → Inflammatory cells
- Oxidants → Cytokines
- Cytokines → NFkB
- Oxidised cell components → NFkB
- NFkB → IkB
Oxidants and cytokines are partners in crime

Oxidants

Inflammatory cells

Cytokines

Cell membrane

Oxidised cell components

NFkB

IkB

DNA transcription

Inflammatory mediator production

NFkB

IkB
Oxidants and cytokines are partners in crime.
Key factors influencing inflammatory stress:

• Poor anti-oxidant defences
• Polymorphisms (SNP) in cytokine genes
• Obesity
• Gender
• Aging
Polymorphisms in the promoter region of genes

Single nucleotide base change

From Father

From Mother

Bioactivity of protein produced:
- normal
- increased
- greatly increased
# Cytokine gene polymorphisms associated with altered levels of production

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotype associated with raised inflammatory stress or poor disease outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α -308</td>
<td>TNF2 allele (A)</td>
</tr>
<tr>
<td>LT-α +252</td>
<td>TNFB2:2 (AA)</td>
</tr>
<tr>
<td>IL-1β -511</td>
<td>TT</td>
</tr>
<tr>
<td>IL-6 -174</td>
<td>G allele</td>
</tr>
<tr>
<td>IL-10 -1082</td>
<td>AA</td>
</tr>
</tbody>
</table>
Key factors influencing inflammatory stress:

- Poor anti-oxidant defences
- Polymorphisms (SNP) in cytokine genes
- Obesity
- Gender
- Aging
Say it loud!

I'm fat & I'm proud
AND I AM SUFFERING FROM CHRONIC INFLAMMATION
Adipose tissue becomes an inflammatory site

Wellen & Hotamisligil 2003
JCI 112: 1785
Inflammation

Pathogen killing

Inflammatory stimuli, pathogens, environmental factors, damaged tissue

Diabetes mellitus

Insulin insensitivity

Hyperlipidemia

Atherosclerosis

Mortality and morbidity

Obesity

Myocardial infarction
Effects of a 10-week hypocaloric diet (-600 kcal) on in vitro cytokine production by 400 mg subcutaneous adipose tissue of obese women

*n Value X0.01 for TNF, X0.1 for IL-6

Combined influence of Body Mass Index and LT-α +252 SNP on fasting plasma triglyceride concentrations in healthy men (mmol/l).

Values mean±SEM

Significant effect of BMI Jonckheere-Terpstra test
(n)= subject s per subgroup

Influence of BMI p=0.003

<table>
<thead>
<tr>
<th>Tertile of BMI</th>
<th>Lowest</th>
<th>Middle</th>
<th>Highest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(21.1±1.4)</td>
<td>(23.8±0.6)</td>
<td>(27.7±2.3)</td>
</tr>
</tbody>
</table>

Normal weight | Overweight
Influence of TNF-α-308 and IL-6 -174 SNPs and being overweight on C-reactive protein concentrations in Peripheral vascular disease patients

![Graph showing the influence of TNF-α-308 and IL-6 -174 SNPs and being overweight on C-reactive protein concentrations in Peripheral vascular disease patients. The graph compares normal weight and overweight patients, with bars indicating the number of patients with different combinations of alleles and weight status. The p-value for the difference between normal weight and overweight patients is 0.036 Mann Whitney.](image-url)
Impact of obesity and overweight status on diseases with an underlying inflammatory aetiology and outcome from operative procedures.
Influence of overweight and obese status on mortality from diseases

- All cause mortality
- Stroke
- Coronary disease
- Type 2 diabetes

(RR increases to 50.7 for BMI ≥ 35 kg/m²)

Morbid Obesity in the Medical ICU:
Ali El-Solh, MD; Pawan Sikka, MD; Erkan Bozkanat, MD; Wafaa Jaafar, MS and Joan Davies, RN * From the Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, James P. Nolan Clinical Research Center, University at Buffalo School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY.

<table>
<thead>
<tr>
<th>Organ Failures</th>
<th>Morbidly Obese Patients</th>
<th>Morbidly Obese Mortality</th>
<th>Nonobese Patients</th>
<th>Nonobese Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19</td>
<td>1 (5)</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>2 (6)</td>
<td>26</td>
<td>1 (4)</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>11 (34)</td>
<td>54</td>
<td>6 (11)</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>15 (65)</td>
<td>25</td>
<td>5 (20)</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>6 (86)</td>
<td>11</td>
<td>7 (64)</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1 (100)</td>
<td>3</td>
<td>3 (100)</td>
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Obesity Is an Independent Risk Factor of Mortality in Severely Injured Blunt Trauma Patients

Angela L. Neville, MD; Carlos V. R. Brown, MD; Janie Weng, BS; Demetrios Demetriades, MD, PhD; George C. Velmahos, MD, PhD

Table 1. Admission Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Obese Group (n = 63)</th>
<th>Nonobese Group (n = 179)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49 ± 18</td>
<td>45 ± 22</td>
<td>.08</td>
</tr>
<tr>
<td>Men, %</td>
<td>63</td>
<td>72</td>
<td>.23</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>98 ± 35</td>
<td>99 ± 27</td>
<td>.99</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>123 ± 36</td>
<td>130 ± 28</td>
<td>.24</td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>11 ± 5</td>
<td>11 ± 5</td>
<td>.34</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>35 ± 7</td>
<td>24 ± 3</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.

Arch Surg. 2004;139:983-987
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Arch Surg. 2004;139:983-987
Obesity is not always a risk factor in all clinical situations in which inflammation is exerting a deleterious effect.
Mediators (adipokines) secreted by adipose tissue

- Adiponectin
- Resistin
- Leptin

Cytokines
- TNF-α
- IL-1α, β
- IL-6
- IL-4, IL-10

Adipsin
Vistatin
Estrogens

Pro-inflammatory
Anti-inflammatory
Unclear effect on inflammation
Interactions between genotype and overweight status and nutrient modulation of the consequences of obesity induced inflammation
Healthful effects of fish oil

- Anti-inflammatory
- Lipid lowering

Herring (Clupea herangus: 30-40 cm)
Influence of combined TNF-α -308 A allele CD36 -3118GG genotype and overweight on ability of fish oil to lower fasting plasma triglycerides in healthy middle aged men.

Change in TGs (mmol/l)

- Overweight: No, No, Yes, Yes
- Genotypes: One, Both, One, Both

<table>
<thead>
<tr>
<th>Nn=</th>
<th>19</th>
<th>7</th>
<th>62</th>
<th>17</th>
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<tbody>
<tr>
<td>0.1</td>
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<tr>
<td>-0.1</td>
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Influence of TNF-α-308 genotype and body weight on the effects of fish oil supplementation on the ratio of LPS stimulated TNF to IL-10 production by monocytes of peripheral vascular disease patients

* Significantly different from overwt patients without TNF-308A allele

Ratio of TNF-α to IL-10 production by monocytes

Raised inflammatory stress

Mann-Whitney

p=0.039

n= 9                        15                      18                     27

Ratio of TNF-α to IL-10 production by monocytes

* Significantly different from overwt patients without TNF-308A allele

n= 9                        15                      18                     27

Ratio of TNF-α to IL-10 production by monocytes
The future- gaining a greater understanding of the influence of phenotype and genotype on the variable impact of immunonutrition on the inflammatory stress caused by obesity.

Thanks for your attention.