Basic Mechanisms in Cancer Cachexia: more than sarcopenia?

KCH Fearon

Sarcopenia *Max*?

Greig C et al 2010 Clin Nutr
MR image showing loss of muscle mass and fatty infiltration

- Young: 23 yrs
- Old: 80 yrs
- Cancer: 73 yrs

Greig C et al 2010 Clin Nutr

The elephant in the room is...

What about cachexia?

There's more to this than muscle.
Focus for discussion

- Energy metabolism
- Liver metabolism
- Adipose tissue
ENERGY METABOLISM

Negative Energy Balance

INPUT
anorexia
malabsorption

OUTPUT
hypermetabolism
APPR
Measured Resting Energy Expenditure as a % of Predicted Energy Expenditure


Aetiology of hypermetabolism in cancer cachexia

Liver
Glucose
Lactate
Tumour
Cori - cycle

Blood
Glucose
Glycerol
TG
FFA
Fatty AcylCoA
α-Glycerol-P

Adipocyte
Protein

Blood
Fatty acid cycle

Protein Turnover

Amino Acids
Hypermetabolism: Role of UCPs in Brown Fat?

LIVER
## Organ oxygen consumption

<table>
<thead>
<tr>
<th>Organ</th>
<th>O₂ Consumption (ml O₂/min per 100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>3</td>
</tr>
<tr>
<td>Liver*</td>
<td>3</td>
</tr>
<tr>
<td>Kidney</td>
<td>5</td>
</tr>
<tr>
<td>Skin</td>
<td>0.2</td>
</tr>
<tr>
<td>Resting muscle</td>
<td>1</td>
</tr>
<tr>
<td>Contracting muscle</td>
<td>50</td>
</tr>
</tbody>
</table>

* Liver mass=1500g=20% total body oxygen consumption

## FDG-PET-CT
Liver, spleen and tumour growth during last 3 months of life

Cachexia: a viscerally driven syndrome

Change in liver mass will increase REE by 200Kcal/d
Protein Metabolism During Inflammation

- Inflammatory mass
- CYTOKINES
- Amino Acids
- Skeletal Muscle
- Liver
- Acute Phase Proteins
- Urinary nitrogen loss
Cancer Specific Survival in Advanced Cancer (n=772)

The APPR: a double edged sword?

Loss of lean tissue and energy reserves

Circulatory proteins valuable in healing, repair and during infection
Effects of inflammation on post-prandial visceral protein synthesis

Oral Diet → Anabolism in muscle

CYTOKINES → ?

Effects of inflammation on post-prandial visceral protein synthesis

Oral Diet → Anabolism in muscle

CYTOKINES → ?

Albumin synthesis
(Total synthetic rate)

Mean 33% rise
p=0.046

Mean 38% rise
p=0.028

Barber et al 2000, Am J Physiol End Metab, 279, E707-14
### Fibrinogen synthesis

**(Total synthetic rate)**

<table>
<thead>
<tr>
<th></th>
<th>Median and interquartile range.</th>
<th>Cancer patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>Mean 16% rise</td>
<td>g/day</td>
<td>0</td>
</tr>
<tr>
<td>Fed</td>
<td>Mean 74% rise</td>
<td>g/day</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td><strong>NS</strong></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Barber et al, 2000, Am J Physiol End Metab, 279, E707-14

FAT
Body composition in cancer cachexia

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>17.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Non-muscle protein</td>
<td>8.3</td>
<td>8.1</td>
</tr>
<tr>
<td>Muscle protein</td>
<td>2.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Intracellular water</td>
<td>19.1</td>
<td>12.9</td>
</tr>
<tr>
<td>Extracellular water</td>
<td>15.1</td>
<td>17.5</td>
</tr>
<tr>
<td>Minerals</td>
<td>3.0</td>
<td>2.8</td>
</tr>
</tbody>
</table>

LBM (>0.02)

Statistical Significance of Difference: P
- >0.001
- NS
- >0.001
- >0.001
- >0.02

Fearon and Preston, 1990

Cancer Cachexia and Fat–Muscle Physiology
Kenneth C.H. Fearon, M.D.
Intramyocellular lipid droplet accumulation in cancer cachexia

Impact of age-related sarcopenia

Sarcopenia → Frailty → ADL Disability → QoL → Mortality

- (weakness)
- (reserve/resistance)

Strength, balance, depression, comorbidity
Nutrition, vision, cognition, osteoporosis
Social support, poly-pharmacy

Impact of cancer beyond sarcopenia

Sarcopenia → Frailty → ADL Disability → QoL → Mortality

- (weakness)
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PLUS
- Cancer myopenia, chemotherapy myopathy,
  fatigue, anorexia, hypermetabolism
Summary

• Cachexia is multifactorial: it has unique features but can occur in parallel with starvation and sarcopenia of the elderly

• Altered hepatic metabolism and systemic inflammation are key features

• Fat-muscle physiology is likely to be of growing importance

Persons of good sense seldom fall into dispute except lawyers, university men and men of all sorts that have been bred at Edinburgh.

BENJAMIN FRANKLIN 1706 - 1790