Molecular Mechanisms associated with the Cancer-Cachexia Syndrome

Prof. Dr. Josep M. Argilés
Department of Biochemistry & Molecular Biology
University of Barcelona, Spain

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Cancer cachexia is a devastating, multifactorial and often irreversible syndrome that affects around 50–80% of cancer patients, depending on the tumour type, and that leads to substantial weight loss, primarily from loss of skeletal muscle and body fat.
cachexia is indirectly responsible for the death of at least 20% of all cancer patients

Table 2. The commonest malignancies in which cachexia develops as part of the clinical course.\textsuperscript{6}

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Patients with cachexia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancer</td>
<td>85</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>83</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>61</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>57</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>56</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>54</td>
</tr>
<tr>
<td>Unfavourable non-Hodgkin's lymphoma</td>
<td>48</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>40</td>
</tr>
<tr>
<td>Acute non-lymphocytic leukaemia</td>
<td>39</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>36</td>
</tr>
<tr>
<td>Favourable non-Hodgkin’s lymphoma</td>
<td>31</td>
</tr>
</tbody>
</table>

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Tumor-Related Weight Loss: Outcomes

- ↓ Quality of Life
- ↓ Functional Status
- ↓ Response to Therapy
- ↓ Body Image

- ↑ Hospital Length of Stay
- ↑ Unscheduled Hospitalization
- ↑ Complications/Infections
Cancer and nutrition

↑ Morbidity

↑ Mortality

↓ Quality of life

↑ Sanitary costs

Undernutrition

Cachexia

Cancer
Short Communication
The views and practice of oncologists towards nutritional support in patients receiving chemotherapy

A Spiro¹,²,³, C Baldwin¹,²,³, A Patterson¹, J Thomas¹ and HJN Andreyev¹,²,³
¹Department of Medicine, Imperial College Faculty of Medicine, Chelsea and Westminster Hospital, London, UK; ²The Gastrointestinal Unit, Department of Medicine, Royal Marsden Hospital, Fulham Road, London, SW3 6JJ, UK; ³The Gastrointestinal Unit, Royal Marsden Hospital, Surrey, UK; ⁴Department of Nutrition and Dietetics, King’s College London, London, UK

Table 4: What barriers prevent inclusion of nutrition on oncologist patient care?

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No clear guidelines</td>
<td>80%</td>
</tr>
<tr>
<td>Lack knowledge</td>
<td>70%</td>
</tr>
<tr>
<td>Lack of time</td>
<td>60%</td>
</tr>
<tr>
<td>Unclear responsibility</td>
<td>40%</td>
</tr>
<tr>
<td>Lack RCT evidence</td>
<td>20%</td>
</tr>
<tr>
<td>Low priority</td>
<td>0%</td>
</tr>
</tbody>
</table>
PubMed Analysis:
Cachexia [title] vs Obesity [title]

8743 vs 286327

= 1 : 33
5-year-mortality in Patients aged 50
cachexia (+ CHF/cancer) vs with obesity (no CHF/cancer)

80% vs 4% = 20 : 1

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You cannot treat a disease that you cannot define.
OPINION PAPER

Cachexia: A new definition

William J. Evans*, John E. Morley a, Josep Argilés a, Connie Bales a, Vickie Baracos a, Denis Guttridge a, Aminah Jatoi a, Kamyar Kalantar-Zadeh a, Herbert Lochs a, Giovanni Mantovani a, Daniel Marks a, William E. Mitch a, Maurizio Muc scaritoli a, Armire Najand a, Piotr Ponikowski a, Filippo Rossi Fanelli a, Morrie Schambelan a, Annemie Schols a, Michael Schuster a, David Thomas a, Robert Wolfe a, Stefan D. Anker a

Donald W. Reynolds Institute on Aging, University of Arkansas for Medical Sciences, 4301 W. Markham, Slot 806, Little Rock, AR 72205, USA

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KEYWORDS
Anorexia; Muscle wasting; Inflammation; Involuntary weight loss; Wasting disease

Summary
On December 13th and 14th a group of scientists and clinicians met in Washington, DC, for the cachexia consensus conference. At the present time, there is no widely agreed upon operational definition of cachexia. The lack of a definition accepted by clinician and researchers has limited identification and treatment of cachectic patient as well as the development and approval of potential therapeutic agents. The definition that emerged is: "cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity. While this definition has not been tested in epidemiological or intervention studies, a consensus operational definition provides an opportunity for increased research. © 2008 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.
Multiorgan syndrome
systemic disorder
The Cachexia Pyramid

- **Tumour**
- **Treatment**
- **Food intake**
- **Metabolic abnormalities**
- **Cytokines**
- **Hormones**

**Tumour factors**
- Brain
- Immune system
- Liver
- Skeletal muscle
- Adipose tissue
- Blood
- Gut

**Immobility**
- Quality of life
- Weight loss
- Anemia
- Oedema
- Weakness

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Cachexia is a multifactorial syndrome involving changes in several metabolic pathways, in many tissues and organs:

- Energy balance disorder
- Tumour-driven inflammation
- Muscle wasting and atrophy
  - Adipose tissue wasting
  - Multi-organ syndrome
Cachexia: a problem of energy balance

**ANOREXIA**
- **REDUCED FOOD INTAKE**

**METABOLIC CHANGES**
- **INCREASED ENERGY EXPENDITURE**
BASAL METABOLIC RATE (REE)
DIET-INDUCED THERMOGENESIS (DIT)
PHYSICAL ACTIVITY

Healthy

Cancer
CACHEXIA

FUTILE CYCLE ACTIVITY

ENERGETIC INEFFICIENCY

INCREASED THERMOGENIC ACTIVITY

DECREASED ATP SYNTHESIS
FUTILE CYCLE ACTIVITY
HYPOXIA

HIF-1

GLUCOSE

PYRUVATE

ACETYL-CoA

2 ATP

LACTATE

TUMOUR CELL

GLUCOSE

GLUCOSE

LACTATE

LACTATE

LIVER

- 6 ATP

CORI CYCLE  \( \rightarrow \)  aprox. 300 kcal/day

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DECREASED ATP SYNTHESIS

Mitochondrial dysfunction

Uncoupling
• Altered changes in mitochondrial morphology
• Decreased oxidative capacity
• Disrupted protein synthesis
• Changes in membrane fluidity
• Oxidatively modified mitochondrial proteins
Tumour-driven inflammation
Serum levels of leptin and proinflammatory cytokines in a population of cancer patients according to performance status

Lowest ECOG PS (2 and 3) are associated with highest levels of proinflammatory cytokines (especially IL-6)

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IL-6 and Survival
Advanced cancer patients

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Tocilizumab, a proposed therapy for the cachexia of IL6-expressing lung cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy control groups</th>
<th>Cancer cachexia group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n=10) without MR16-1</td>
<td>Group 2 (n=10) with MR16-1</td>
</tr>
<tr>
<td>Carcass weight (g)</td>
<td>25.9±1.3</td>
<td>26.0±1.5</td>
</tr>
<tr>
<td>Gastrocnemius muscle (mg)</td>
<td>128.1±49.2</td>
<td>115.4±32.2</td>
</tr>
<tr>
<td>Quadriceps muscle (mg)</td>
<td>102.7±46.5</td>
<td>114.2±33.6</td>
</tr>
<tr>
<td>Biceps femoris muscle (mg)</td>
<td>145.4±27.9</td>
<td>174.6±85.3</td>
</tr>
<tr>
<td>Fat tissue around testis (mg)</td>
<td>490.5±80.8</td>
<td>468.4±70.7</td>
</tr>
<tr>
<td>White blood cell (/µL)</td>
<td>4,667±2,317</td>
<td>3,867±1,892</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>32.8±2.5</td>
<td>35.4±1.2**</td>
</tr>
<tr>
<td>Platelet (x10⁶/µL)</td>
<td>54.8±25.7</td>
<td>69.3±20.9</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>87.0±18.2</td>
<td>81.2±28.1</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>311.6±174.9</td>
<td>260.0±40.6</td>
</tr>
</tbody>
</table>

Lewis lung carcinoma-bearing mice

Ando et al. (2014) PLOS One 9(7):e102436
Inflammation and survival in cancer

Glasgow Pronostic Score: a *predictor of survival* independent of tumour stage, performance status or treatment

Score 2: patients with elevated C-reactive protein serum levels (>10 mg/L) and hypoalbuminemia (<35 g/L)
Score 1: patients with either elevated C-reactive protein serum levels (>10 mg/L) or hypoalbuminemia (<35 g/L)
Score 0: patients with normal C-reactive protein serum levels and normal albuminemia

Muscle wasting and atrophy
SKELETAL MUSCLE WASTING

INCREASED PROTEOLYSIS

DECREASED AA UPTAKE

INCREASED BCAA OXIDATION

DECREASED PROTEIN SYNTHESIS

DECREASED MUSCLE REGENERATION

INCREASED APOPTOSIS

MITOCHONDRIAL DYSFUNCTION/ SR STRESS
Adipose tissue wasting
Adipose tissue wasting

1. Increased rate of lipolysis

2. Decreased LPL activity

3. Reduced de novo lipogenesis
Cross-talk between adipose tissue and muscle

**Adipose tissue**
- TNF
- IL6
- Leptin
- ADIPONECTIN
- FFA

**Skeletal muscle**
- IL15
- TNF
- IL6

**Adipokines**

**Myokines**

(a) Upper row: Whole body FDG-PET acquired 60 min after intravenous injection of FDG demonstrating intense and extensive FDG uptake in the brown adipose tissue in the supraclavicular and paravertebral regions bilaterally in addition to uptake in the neoplasm. (b) Lower row: Repeat FDG-PET following propranolol intervention on a different day demonstrates there was no FDG uptake in the BAT, though the uptake in the neoplasm persists.
Mechanisms and consequences of WAT browning in cancer cachexia

Multiorgan syndrome
Treating cachexia: elements to be taken into consideration
Drugs in cachexia clinical trials: endpoints

Stimulate food intake
Enhance absorption/Gastric emptying
Preserve LBM
Enhance QoL
Control cancer
Promote health
Cachexia diagnosis & staging

Multidisciplinary team

Multimodal treatment (anabolic + anticatabolic)

- Nutritional counseling
- Nutritional supplements
- Drugs
- Exercise program
Figure 1 Conceptual representation of the definition: cachexia results from adaptation to an underlying illness such as cancer. The illness creates an environment that may be characterized by inflammation, loss of appetite (anorexia), low levels of testosterone and other anabolic hormones, and anemia. Decreased food intake and anorexia result in loss of body and muscle mass. In addition, inflammation, insulin resistance, and low levels of anabolic hormones result in muscle wasting.
The Inverted Pyramid of Cancer Management

Oncologist  Specialist  Surgeon  Radiologist

Psicologist  Nutritionist/Dietitian  Dentist

Nurses  Caregivers

PATIENT

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Efficacy of Multimodal Therapy for Cancer Cachexia

Improved management of cancer cachexia certainly requires a multimodal approach by a multi-disciplinary team and is best commenced earlier rather than later.

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To take home:

Cancer cachexia is an energy balance and multi-organ syndrome

Systemic inflammation, particularly cytokines, drives many of the metabolic changes associated with muscle wasting. Special attention should be given to both muscle and adipose-released cytokines and the intercommunication between the two tissues

The role of adipose tissues –both white and brown– deserves further research and may lead to new therapeutic strategies