Overview of Clinical Trials and Practice on Cancer-Cachexia Syndrome

Prof Liz Isenring
Faculty Disclosure

<table>
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<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
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Overview

• Cachexia
• Unimodality treatment
• Multimodality treatment
• Nutrition support the cornerstone of cachexia management
• Summary
“Do you have anything that you can give me to stop me losing weight?”

“My wife nags me because I am not eating and am losing weight”

“"I dread eating with family because they look at what I’m eating - its just not a comfortable environment like it used to be”

“Why am I still losing weight?”
CACS = cancer and anorexia cachexia syndrome
Cachexia
Skeletal muscle and fat mass wasting

- Lipogenesis
- Proteosynthesis
- Energy intake

Lipolysis
Proteolysis
Energy expenditure

Cancer
Inflammation
IL6, TNFα, IL1β, IL8

Catecholamines
Adrenalin, Noradrenalin

ESRD/CKD

COPD

CHF
Treatment Goals of CACS

• Alleviate, manage symptoms

• Reversal of loss of body weight and muscle mass

• Maintain goal body weight and prevent further loss

• At least minimize weight loss & body composition change

• Advantages- may improve tolerance to anti-cancer therapy, symptom management and QoL
Why has research in CACs been slow?

Lack of a consensus definition & important outcomes

Challenges of oncology trials

Limited pharmaceutical funding

Unimodal therapy trials
Pharmacological approaches

- Ace-Inhibitors, ARB’s
- Amino acids (BCAA, Creatine, L-carnitine)
- Beta blockers
- Cannabinoids
- Corticosteroids
- EPA – Fish oil
- Hormones/agonists/antagonists
- Immunological IL-6 antibodies
- Megestrol Acetate
- NSAID’s
- Anabolic steroids-Testosterone
- Macrolides
- Melatonin
- Psychotropics (mirtazipine, olanzapine)
- Thalidomide
- TNF
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<tr>
<th>Evidence</th>
<th>Condition</th>
<th>Weeks</th>
<th>Results</th>
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<td>Level II¹</td>
<td>CHF</td>
<td>8</td>
<td>↔ weight</td>
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<td>↑ physical function</td>
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<td>Level II²</td>
<td>COPD</td>
<td>12</td>
<td>↑ weight</td>
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<td>↑ fat free mass</td>
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<td>Level II⁴</td>
<td>Elderly</td>
<td>8</td>
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<td></td>
<td>↑ QoL</td>
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<td></td>
<td></td>
<td></td>
<td>↑ biochemical parameters</td>
</tr>
<tr>
<td>Level IV⁵</td>
<td>Cancer</td>
<td>8</td>
<td>↔ weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↔ lean body mass</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>↑ strength</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ biochemical parameters</td>
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</table>

Conclusion: Not enough solid evidence for protein supplements in cancer

- HMB, arginine and glutamine:
  - Increase in lean body mass after 4 weeks in advanced solid tumour patients
  - No benefits in lung cancer after 8 weeks
- L-carnitine in pancreatic cancer: increase of BMI and survival
Beta blockers- Anker Coats JCSM 2016

- Espindolol (non-selective blocker, partial β2agonist)
- phase II double blind RCT
- 10mg bid vs 2.5mg bid vs placebo
- Improved weight, fat free mass, handgrip strength
# Fish oil

<table>
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<th>Weak recommendation</th>
<th>In patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished, we suggest to use supplementation with long chain N3 fatty acids to stabilise or improve appetite, food intake, lean body mass &amp; body weight.</th>
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<tbody>
<tr>
<td>Low level evidence</td>
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</table>
Exercise for cancer cachexia in adults: Executive summary of a Cochrane Collaboration systematic review

Antonio Jose Grande1,2*, Valter Silva3 & Matthew Maddocks4

1University of Oxford, Nuffield Department of Population Health Oxford, UK; 2Universidade do Extremo Sul Catarinense Laboratory of evidence-based practice Criciuma, Santa Catarina, Brazil; 3Universidade Federal de Sao Paulo Department of Internal Medicine Sao Paulo, Brazil; 4King’s College London, Guy’s and St Thomas’ Institute Department of Palliative Care, Policy and Rehabilitation London, UK

Abstract

Background Cancer cachexia is a complex syndrome characterized by an ongoing loss of skeletal muscle mass and progressive functional impairment. A proactive management approach is recommended, including physical exercise to maintain function via modulation of muscle metabolism, insulin sensitivity and levels of inflammation. The review aimed to determine the safety, acceptability and effectiveness of exercise in adults with cancer cachexia. Secondary aims, subject to the data availability, were to compare effectiveness according to the characteristics of the study intervention or population.

Methods We sought randomised controlled trials (RCTs) in adults meeting international criteria for cancer cachexia, comparing a programme of exercise as a sole or adjunct intervention to usual care or an active control. CENTRAL, MEDLINE, EMBASE, DARE and HTA, ISI Web of Science, LILACS, PEDro, Sciverse SCOPUS, Biosis Previews PreMEDLINE and Open Grey databases were searched up to June 2014. Two authors independently assessed studies for eligibility.

Results We screened 3154 separate titles and abstracts, and reviewed 16 full-texts. Corresponding authors were contacted to determine if samples met cachexia staging criteria. Most authors did not explore this concept. No trial met review eligibility criteria. We were unable to perform a meta-analysis to determine any effects from exercise intervention.

Conclusion Despite a strong rationale for the use of exercise, there is insufficient evidence to determine safety and effectiveness in patients with cancer cachexia. Findings from ongoing studies are awaited. Assessment of cachexia domains, ideally against international criteria, is required for future trials of exercise and supportive care interventions.

Keywords Exercise; Cachexia; Cancer; Human; Physical activity
## Exercise

<table>
<thead>
<tr>
<th>Strong recommendation</th>
<th>We recommend maintenance or increased physical activity in cancer patients to support muscle mass, physical function and metabolic pattern.</th>
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</thead>
<tbody>
<tr>
<td>High level evidence</td>
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</table>

Arends et al 2017
Megestrol acetate for CACs

Ruiz-Garcia Cochrane review 2013
Kouchaki JSCC 2018

Associated with Positive outcomes
Improved appetite
Slight weight gain
Quality of life compared to placebo

Associated with negative outcomes
Edema
Thromboembolism
Death
Ghrelin Clinical Trials

• Weekly Ghrelin for appetite in cancer cachexia n=21
  Double-blind placebo controlled cross-over x 18 days
  *Strasser BJC 2008*

• Daily s.c. Ghrelin for weight loss in GI cancer  n=31
  Double-blind RCT high vs. low dose 8 weeks
  Improved appetite and weight
  No change in tumor markers
  *Lundholm 2010 Cancer*

• Ghrelin during chemo in advanced esophageal cancer n=42
  Randomized Phase II x 1 week
  Improved food intake  and appetite
  *Hiura Cancer 2012*
Ghrelin for the management of cachexia associated with cancer (Review)

Khatib, M.N.a, Shankar, A.H.b, Kirubakaran, R.c, Gaidhane, A.d, Gaidhane, S.e, Simkhada, P.f, Quazi, S.Z.g

aDatta Meghe Institute of Medical Sciences, Division of Evidence Synthesis, School of Epidemiology and Public Health and Department of Physiology, Sawangi Meghe, Wardha, Maharashtra, India
bHarvard University, Department of Nutrition, 655 Huntington Avenue, Building 2, Boston, MA, United States
cChristian Medical College, Cochrane South Asia, Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Carman Block, CMC Campus, Bagayam, Vellore, Tamil Nadu, India

do other domains was unclear or low. We rated the overall quality of the evidence for primary outcomes (food intake, body weight, adverse events) as very low. We downgraded the quality of the evidence due to lack of data, high or unclear risk of bias of the studies and small study size. Authors' conclusions: There is insufficient evidence to be able to support or refute the use of ghrelin in people with cachexia. Adequately powered randomised controlled trials focusing on evaluation of safety and efficacy of ghrelin in people with cancer cachexia is warranted. © 2018 The Cochrane Collaboration.
Ghrelin Agonist Clinical Trials

• Anamorelin for cancer-related cachexia
  2 phase II randomized, double-blind, crossover
  Garcia Lancet Oncol 2015

• Anamorelin multicenter phase III study in NSCLC
  N=979, muscle (p<.0001) and FAACT better  x12 weeks
  No change in hand grip strength
  5% developed hyperglycaemia, 2% diabetes

  Temel Ann Onc 2014 abst
Multimodal approach

• Multi & interdisciplinary supportive care
• Treatment of secondary causes of Cachexia
• Pharmacotherapy targeting inflammatory and metabolic changes
• Nutritional Counseling
• Physical Therapy & exercise
• Social Support & psychological
Interdisciplinary Care
Planning & Review

Interdisciplinary Review
& Recommendations

Patient

Family Caregiver

Dr Martin Chasen


Discussion

Statistically significant improvements were noted in:

– A number of fatigue domains (General, physican, decreased activity and decreased motivation)
– Nutritional status
– Symptom interference on mood, enjoyment, general activity, walking and work
– Several symptoms
– Endurance, balance and function
– ECOG
Components of optimum cachexia management. EPA, eicosapentaenoic acid; NSAID, non-steroidal anti-inflammatory drugs

- Targeted cachexia treatment (EPA/NSAID)
- Sufficient nutrition
  - Physical activity/exercise
- Chemotherapy
  - Symptom management

MENAC: The Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia trial

MENAC is a large-scale open randomised phase III, multimodal intervention trial.

Primary objective
• To establish whether a multimodal intervention is effective in treating cachexia. This will be assessed after 2 cycles of chemotherapy (study endpoint -between 6 -9 weeks) by measuring weight.

Secondary objectives
• To examine the effect of a multimodal intervention for cancer cachexia on muscle mass, physical performance, performance status, health status, nutritional status, quality of life, toxicity, and hospitalisations.

Patients
• Diagnosis of lung cancer, pancreatic cancer or
• Due to commence anti-cancer therapy

Plans/estimation
• A total of 260 patients will be recruited from out-patient oncology clinics at multiple sites in Europe, Canada and Australia.

Discussion Sat 7.30am Nutrition & Cachexia Study Group meeting
Nutrition-the cornerstone of cachexia management

Box 1
New strategies to update nutritional care in cancer

- Screen each patient's nutritional status early in the course of his or her cancer treatment.
- Identify signs or symptoms of anorexia, cachexia, and sarcopenia as early as possible.
- Measure body cell or muscle mass precisely by sensitive imaging technologies (computed tomography and others) for early detection of malnutrition/sarcopenia.
- Use specific biomarkers to assess severity of cancer-related systemic inflammation, e.g. CRP and albumin.
- Use indirect calorimetry to estimate resting energy expenditure (REE) in order to personalize energy and protein needs.
- Use nutrition and metabolic support as a vital part of cancer care; some new strategies show promise for reducing inflammation and restoring lean body mass.
- Assess physical function routinely to monitor and guide physical rehabilitation.

Arends J, Clin Nutr 2017; 36: 1187-1196
### Energy requirements

<table>
<thead>
<tr>
<th>Strong recommendation</th>
<th>Total energy expenditure, if not measured individually, be assumed to be similar to healthy subjects &amp; generally between 25-30 kcal/kg/day</th>
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<tr>
<td>Low level evidence</td>
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### Protein requirements

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<tr>
<th>Strong recommendation</th>
<th>Protein intake should be above 1.5g/kg/d</th>
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Nutrition Interventions

- Feeding assistance
- Nutritionally dense
- Family style dining
- Taste & appearance
- Patient & Carer preferences
- Feeding assistance
- Aroma, engagement, gardens, activity
- Menu items & selection
- Dining room environment
Lantern Project

Dr Cherie Hugo
Pureed meals
Food for our Final Days

Lobster for Josino
Fabulous food for our final days

Peter Morgan-Jones
Rod MacLeod
Prudence Ellis
Jessica Lynch
Lantern Project


Peter Morgan Jones

Tibor’s Kitchen [https://www.tiborskitchen.com/](https://www.tiborskitchen.com/)
Psycho-social impact of CACS

• For patients & their loved ones
• Help patients cope with body image
• Dry Mouth: Meticulous Oral Care
• Symptom Management
• Encourage family to participate in care
• Acknowledgement / normalising. ? projecting into the future- what to expect.
Summary

- Patients with cancer and their carers have significant nutritional issues & cachexia is under recognised and untreated.
- Several sets of guidelines present best available evidence for nutritional recommendations, less for cachexia specifically.
- Limited evidence for unimodality therapies-multimodal best bet
- Patients should be made aware of challenges and how best to manage
- Multidisciplinary supportive care is recommended
SYDNEY

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bond.edu.au/nutrition