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BRINGING AMBITION TO LIFE

Overview of Clinical Trials and Practice on Cancer-Cachexia Syndrome

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Faculty Disclosure

	No, nothing to disclose
	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Abbott Nutrition	x							
Dietitian Connection		x						
Nutricia	x							

Overview

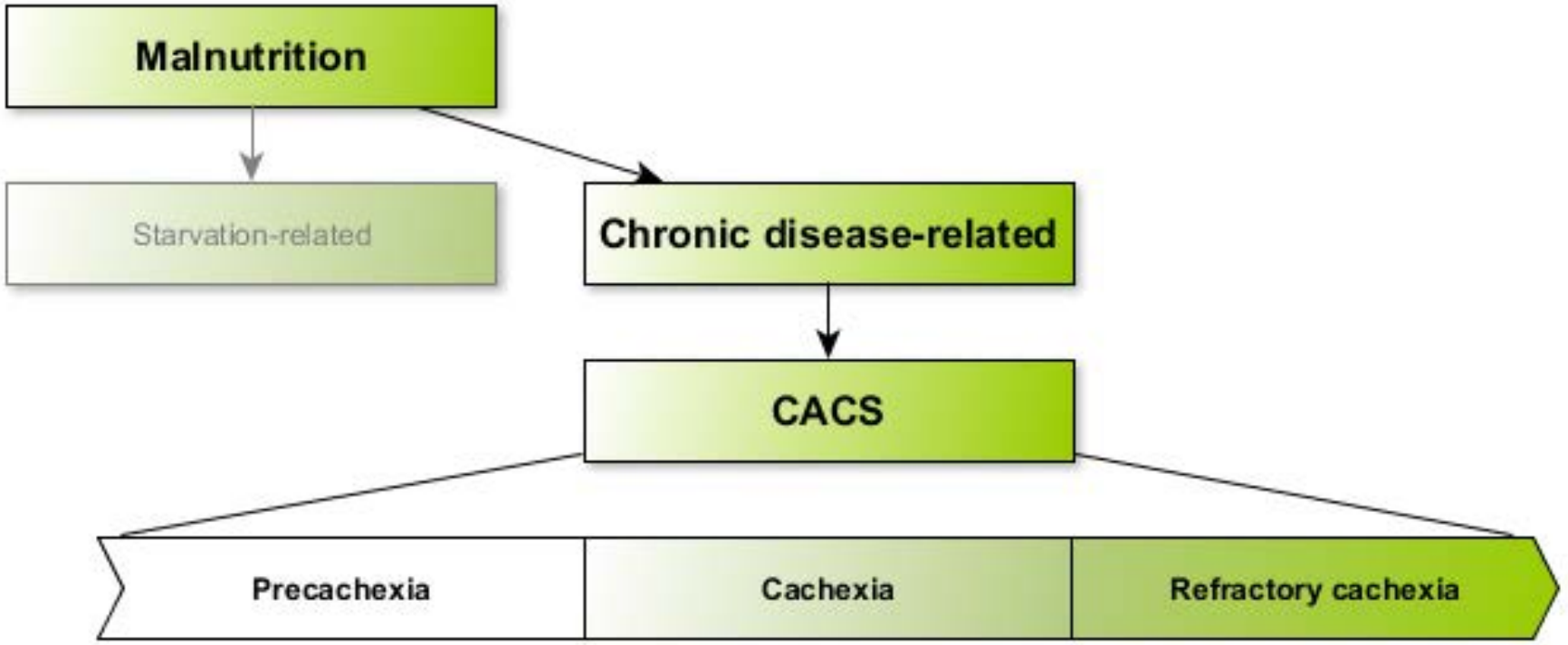
- Cachexia
- Unimodality treatment
- Multimodality treatment
- Nutrition support the cornerstone of cachexia management
- Summary

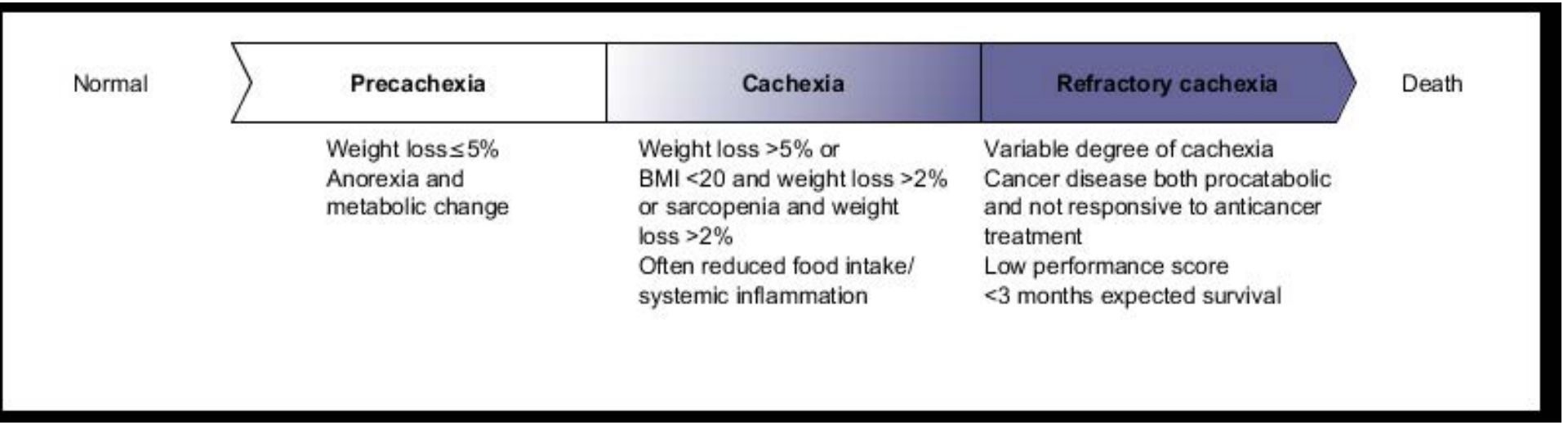
"Do you have anything that you can give me to stop me losing weight?"

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

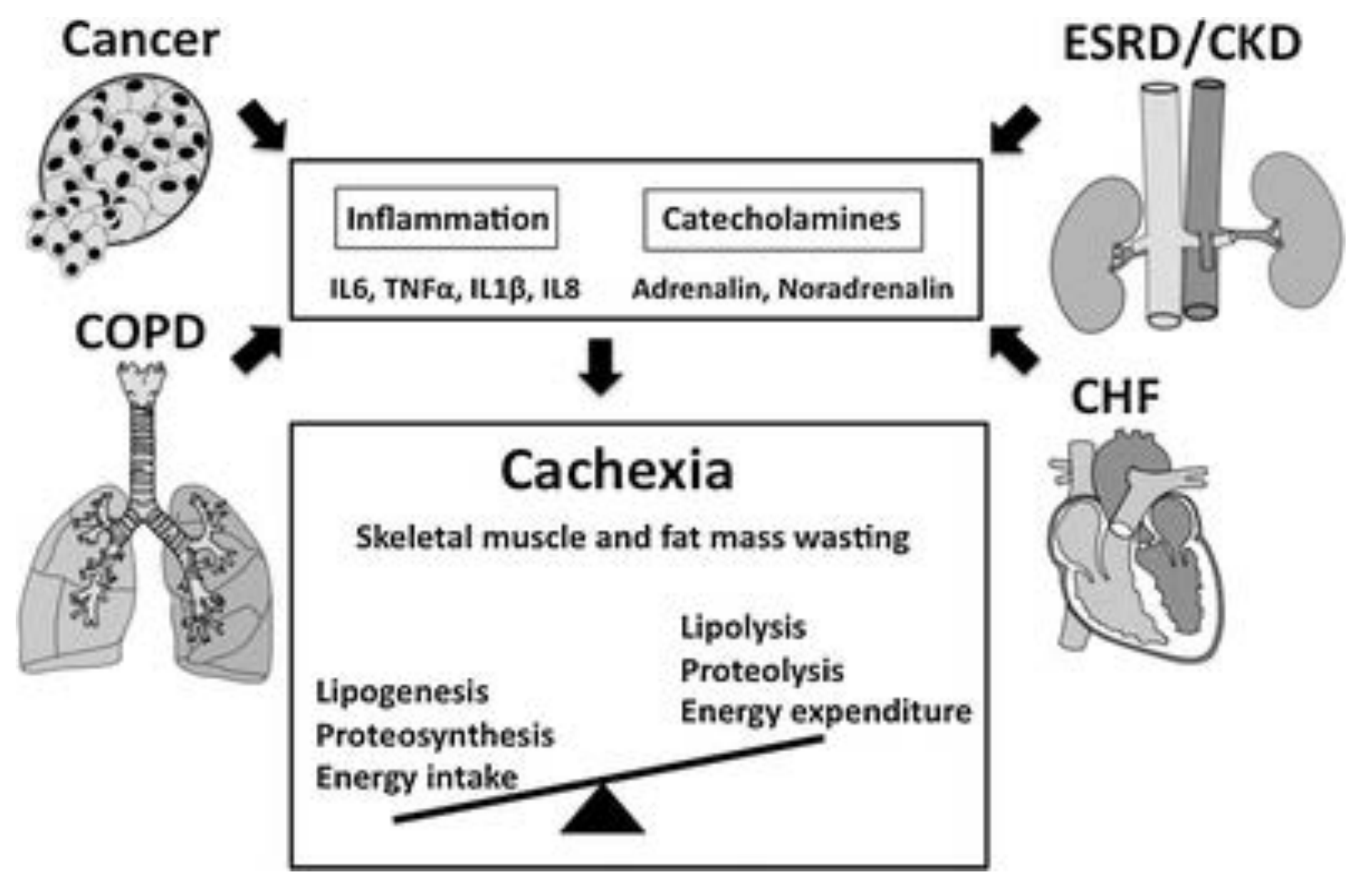
""I dread eating with family because they look at what I'm eating –its just not a comfortable environment like it used to be"

"Why am I still losing weight?"





CACS= cancer and anorexia cachexia syndrome


Cancer
ESRD/CKD
COPD
CHF
Inflammation
Catecholamines
IL6, TNFα, IL1β, IL8
Adrenalin, Noradrenalin
Cachexia
Skeletal muscle and fat mass wasting
Lipolysis
Proteolysis
Energy expenditure
Lipogenesis
Proteosynthesis
Energy intake

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

Evidence	Condition	Weeks	Results
Level II[1]	CHF	8	↔ weight ↑ physical function
Level II[2]	COPD	12	↑ weight ↑ fat free mass ↑ physical activity
Level II[3]	Haemodialysis	12	↑ weight ↑ biochemical parameters
Level II[4]	Elderly	8	↑ strength ↑ QoL ↑ biochemical parameters
Level IV[5]	Cancer	8	↔ weight ↔ lean body mass ↑ strength ↑ biochemical parameters

1. Aquilani *Eur J Heart Fail*, 2008. 10(11): p. 1127-35; 2. Dal Negro *Monaldi Arch Chest Dis*, 2010. 73(1): p. 25-33; 3. Bolasco *Ren Fail*, 2011. 33(1): p. 1-5; 4. Rondanelli *Clin Nutr*, 2011. 30(5): p. 571-7; 5. Madeddu *J Nutr Met*, 2010. 3(2): p. 165-172

REVIEW

Journal of Cachexia, Sarcopenia and Muscle 2017; 8: 25–39
Published online 20 July 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/jcsm.12127

A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia project

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

Mochamat, J Cachexia Sarcopenia Muscle 2016

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

Weak recommendation	In patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished, we suggest to use supplementation with long chain N 3 fatty acids to stabilise or improve appetite, food intake, lean body mass & body weight.
Low level evidence	

Journal of Cachexia, Sarcopenia and Muscle 2015; 6: 208–211
Published online 7 July 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12055

Exercise for cancer cachexia in adults: Executive summary of a Cochrane Collaboration systematic review

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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

Strong recommendation	We recommend maintenance or increased physical activity in cancer patients to support muscle mass, physical function and metabolic pattern.
High level evidence	

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

Cochrane Database of Systematic Reviews
Volume 2018, Issue 2, 28 February 2018, Article number CD012229

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]

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[b]Harvard University, Department of Nutrition, 655 Huntington Avenue, Building 2, Boston, MA, United States
[c]Christian 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

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 cancer 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

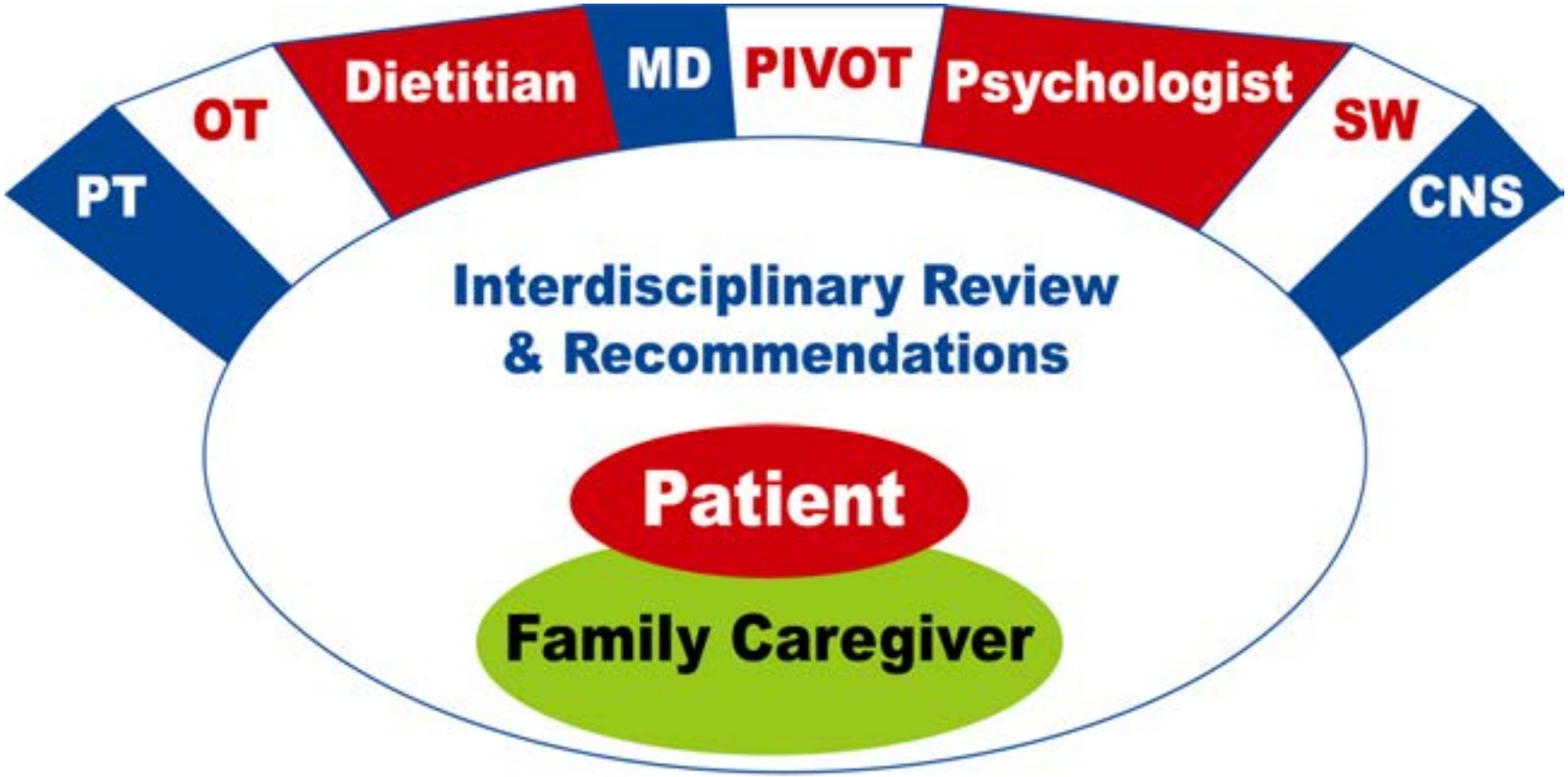
  5% developed hyperglycaemia, 2% diabetes

  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



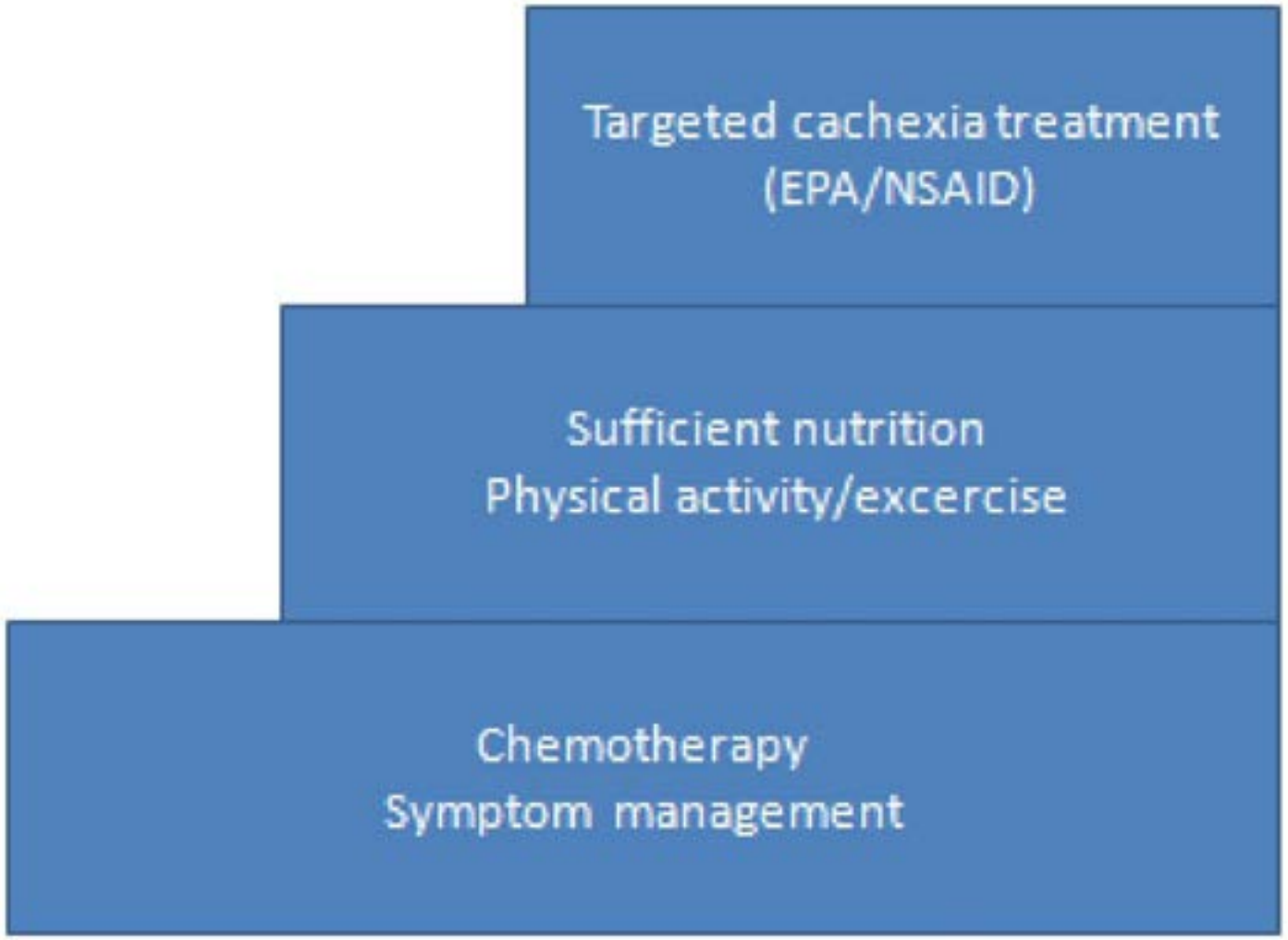
Dr Martin Chasen

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



Tora S Solheim et al. BMJ Support Palliat Care doi: 10.1136/bmjspcare-2017-001440

BMJ Supportive & Palliative Care

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

Strong recommendation	Total energy expenditure , if not measured individually, be assumed to be similar to healthy subjects & generally between 25-30kcal/kg/day
Low level evidence	

Protein requirements

Strong recommendation	Protein intake should be above 1.5g/kg/d
Moderate level evidence	

Nutrition Interventions

Feeding assistance

Nutritionally dense

Family style dining

Dining room environment

Taste & appear ance

Patient & Carer preferences

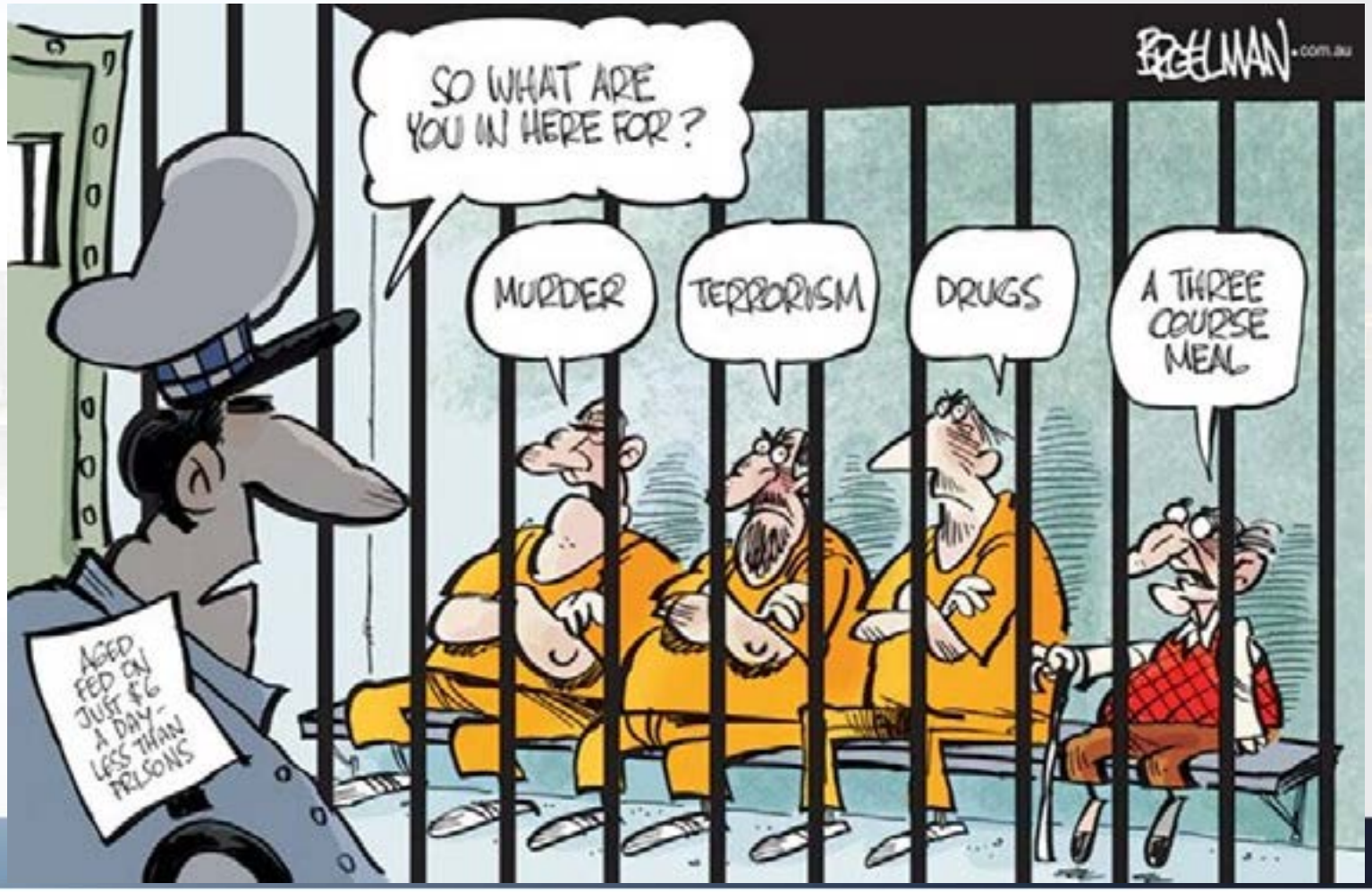
Menu items & selection

Aroma, engagement, gardens, activity

Feeding assistance

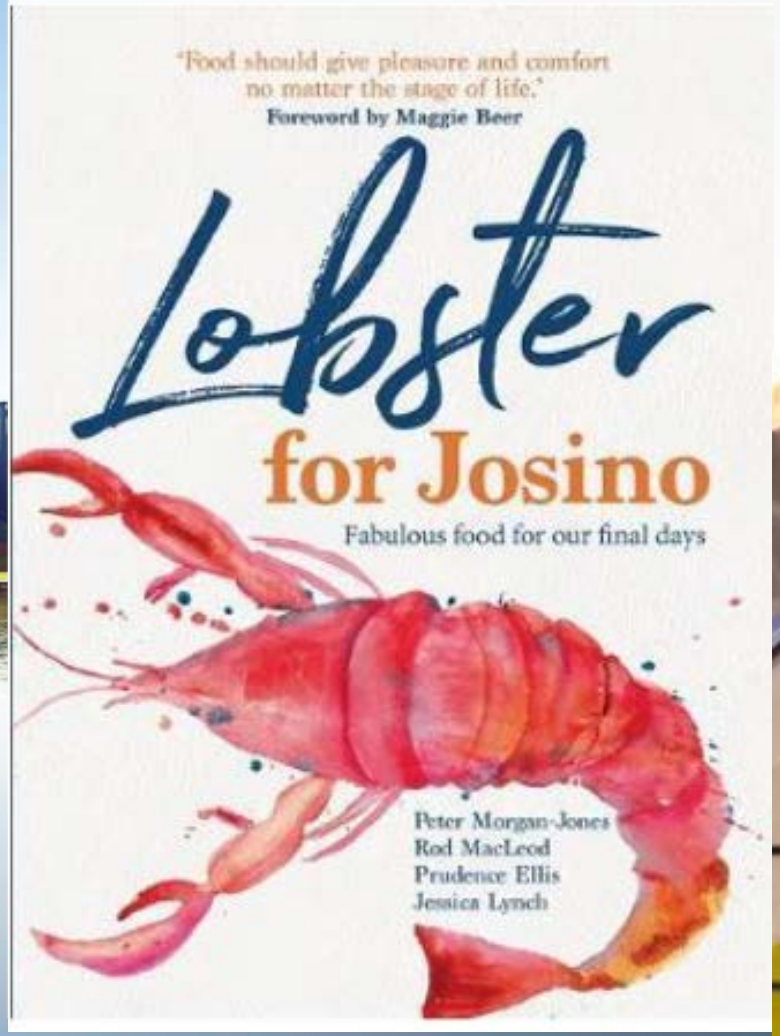
Lantern Project

Dr Cherie Hugo



Pureed meals

Food for our Final Days



Lantern Project

- http://thelanternproject.com.au/

Peter Morgan Jones
http://www.hammond.com.au/shop/palliative-care/lobster-for-josino

Tibor's Kitchen 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

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