

Stress catabolism and protein supplementation in cancer patients

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- 3) Research Associate, Center For Translational Research in Aging And Longevity, Texas A&M University, College Station, Texas, USA



What are the causes of malnutrition and cachexia in cancer patients?

Reduced intake

Catabolic state & anabolic resistance

«Cancer proinflammatory state accelerates muscle catabolism and reduces muscle protein synthesis, leading to muscle loss»

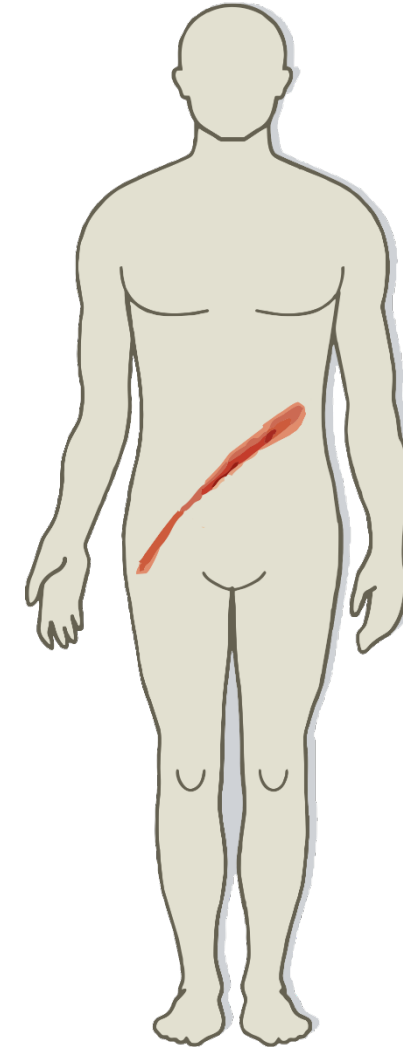
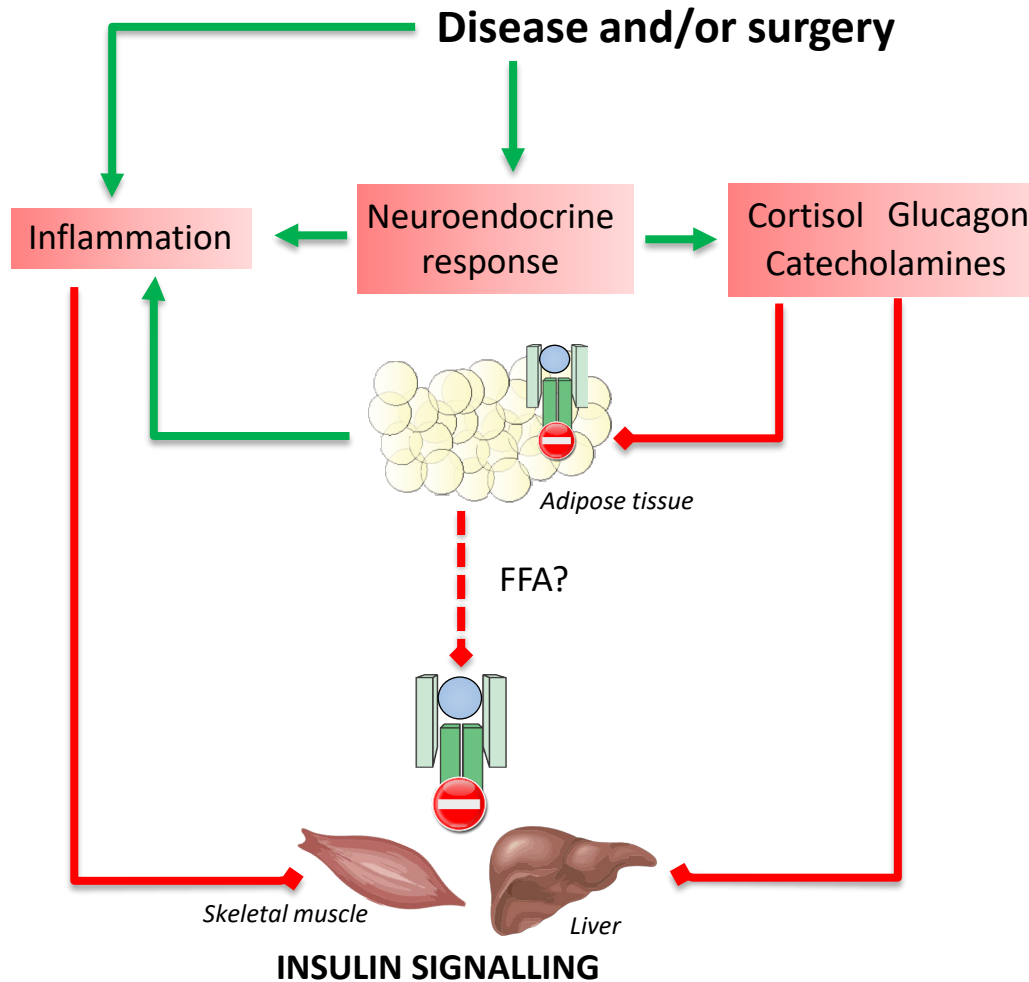
Orsso, C. E. *et al.* Effects of high-protein supplementation during cancer therapy: a systematic review and meta-analysis. *Am. J. Clin. Nutr.* **120**, 1311–1324 (2024).

Agenda

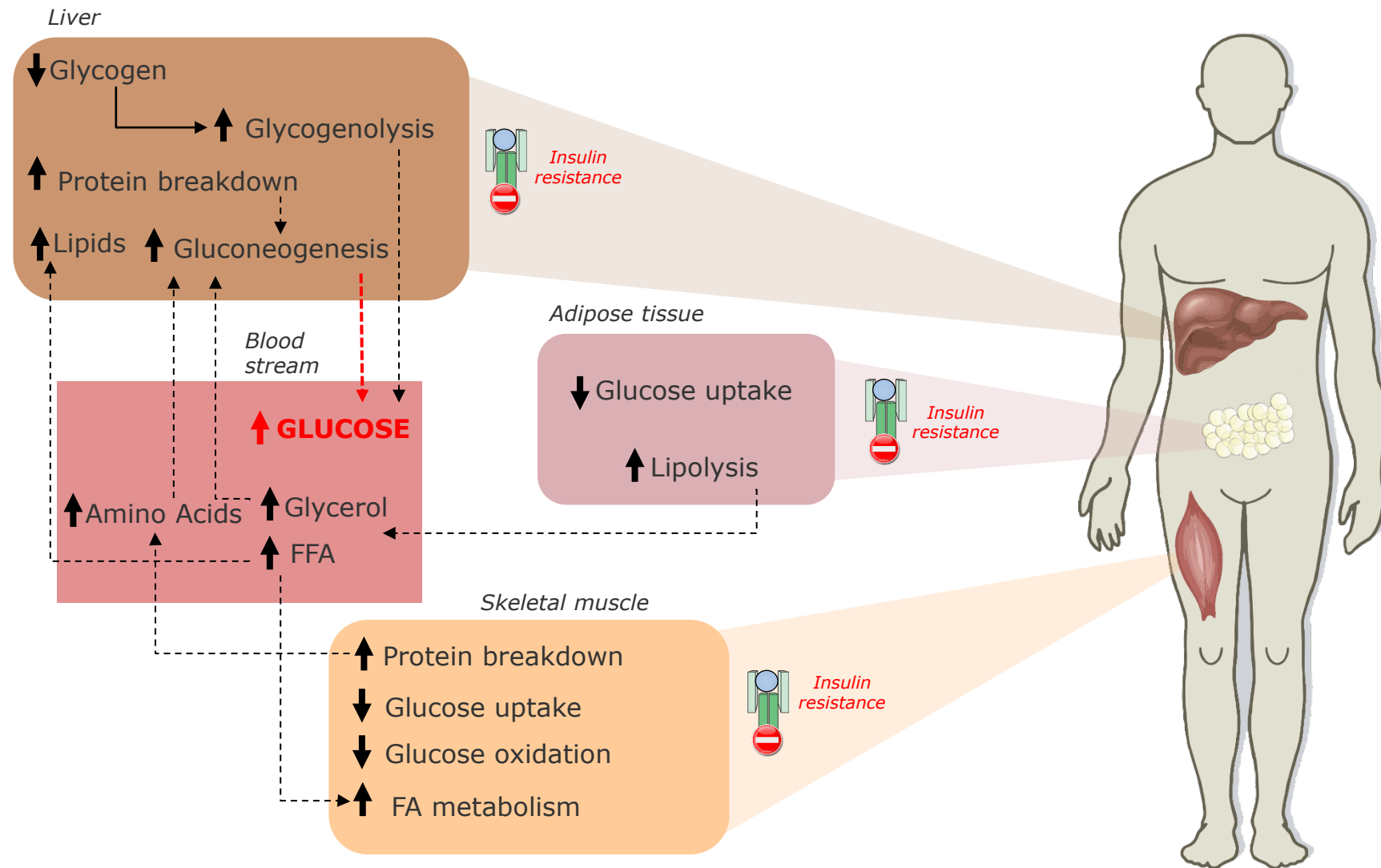
1. Stress catabolism in disease
2. Cancer & protein delivery– What do the guidelines say?
3. Evidence for anabolic resistance in cancer
4. Evidence for increased protein delivery in cancer



Physiology during catabolism in disease



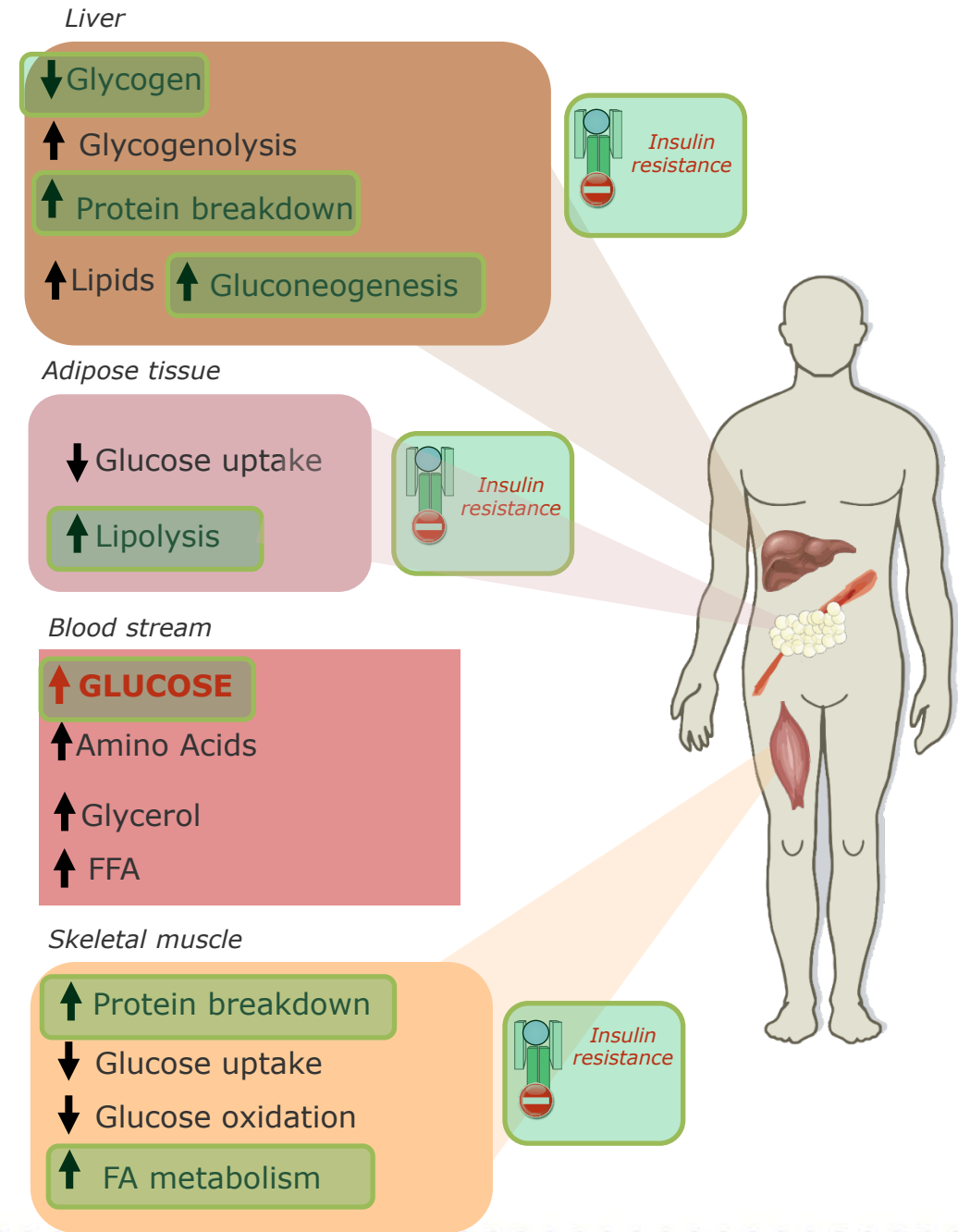
Physiology during catabolism in disease



Physiology during catabolism in disease

METABOLIC CONSEQUENCES:

- Basal metabolic rate can potentially increase
- A multiorgan insulin resistance occurs *that most likely reduces the ability to metabolize administered nutrition*
- Energy storages are emptied
- Muscle tissue is broken down
- There is an availability and a synthesis of glucose.



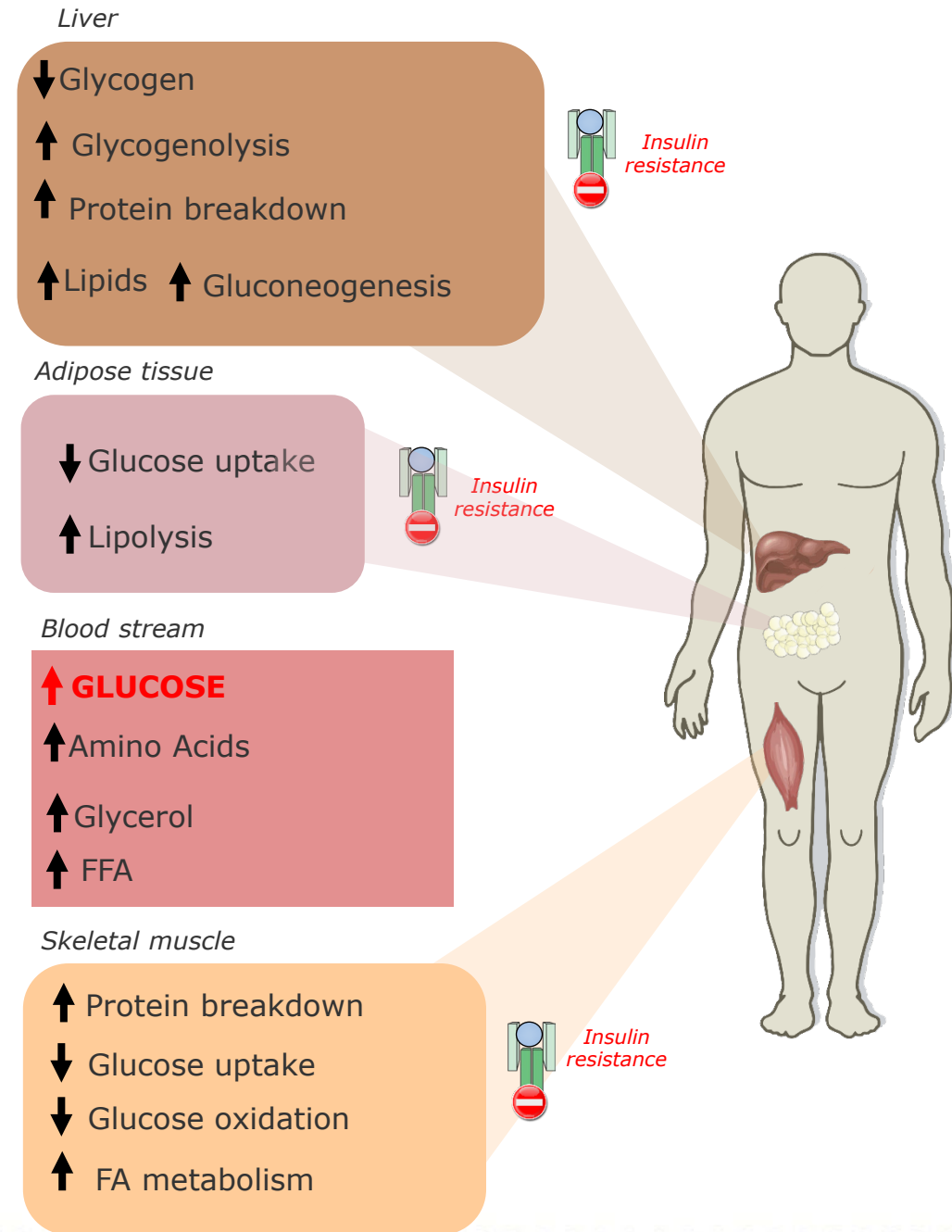
Physiology during catabolism in disease

CLINICAL CONSEQUENCES:

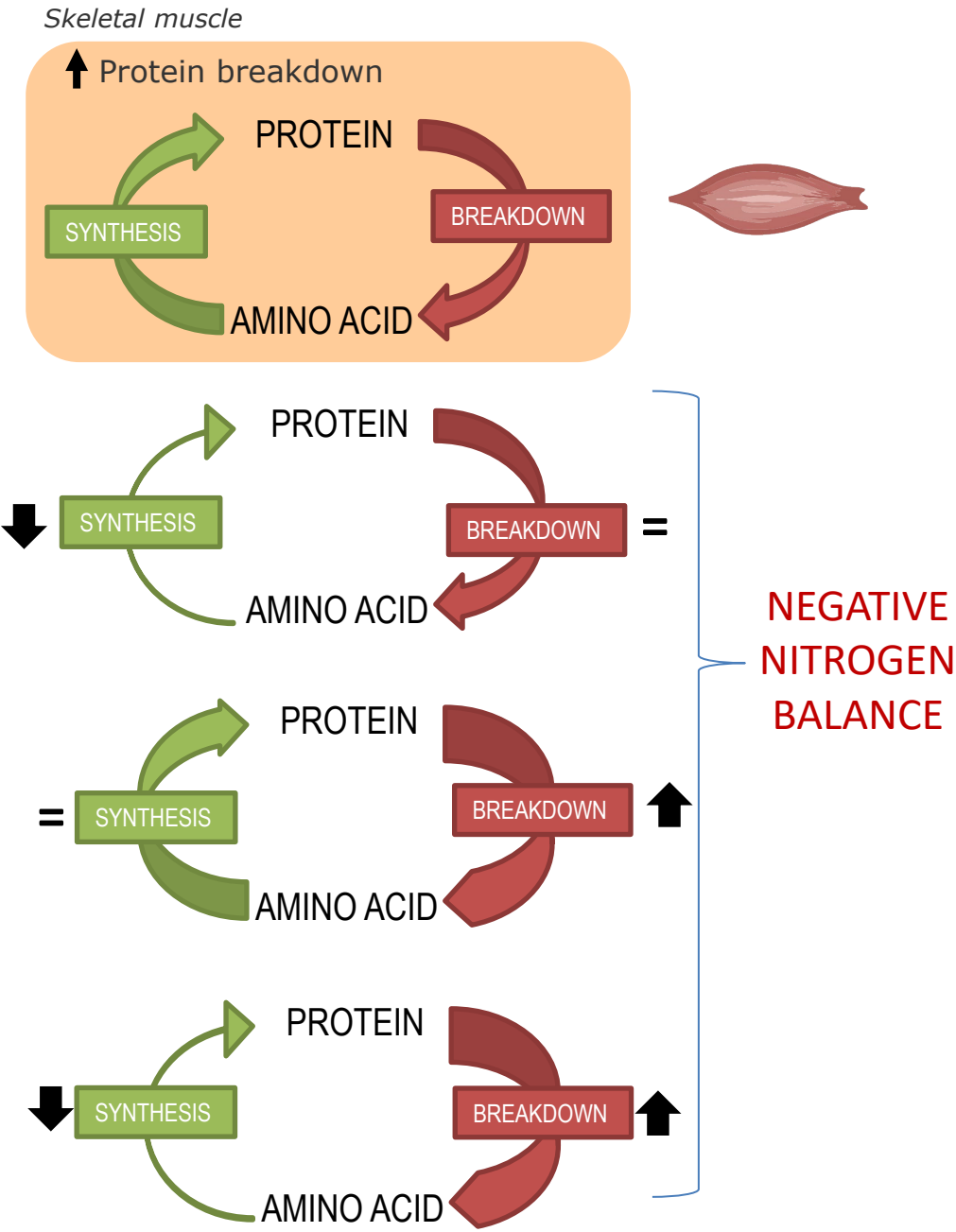
- There are real consequences of catabolism
- There is a lack of substrates available
- There is (often) no negative counterregulation and clinically nutritional support can be beneficial
- If we consider this response something treatable, we should focus on the catabolic response, not necessarily the lack of substrates
- During illness, unmetabolized or unphysiological exogenous nutrition could potentially act as a toxic / damaging agent, rather than an energy source.

	986 mL	1477 mL	1970 mL	2463 mL	Per 1000 mL
Amino acids (g)	50	75	100	125	51
Nitrogen (g)	8	12	16	20	8
Lipids (g)	38	56	75	94	38
Carbohydrates - glucose (anhydrous) (g)	125	187	250	313	127
Electrolytes (mmol)					
Sodium	40	60	80	100	41
Potassium	30	45	60	74	30
Magnesium	5.0	7.5	10	12	5.1
Calcium	2.5	3.8	5.0	6.2	2.5
Phosphate ¹	12	19	25	31	13
Zinc	0.04	0.06	0.08	0.1	0.04
Sulfate	5.0	7.5	10	13	5.1
Chloride	35	52	70	89	36
Acetate	104	157	209	261	106
Energy content					
Total (approx.)	1100 kcal	1600 kcal	2200 kcal	2700 kcal	
4600 kJ					
Non-protein (approx.)	900 kcal	1300 kcal	1800 kcal	2200 kcal	
3800 kJ					

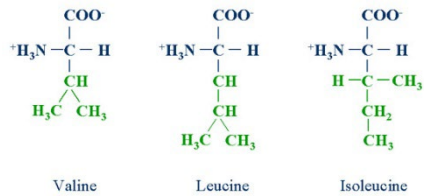
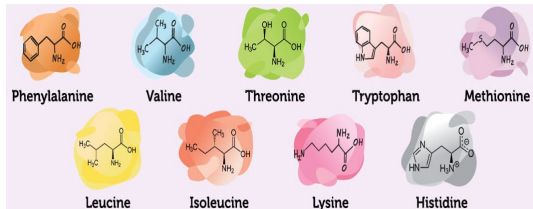
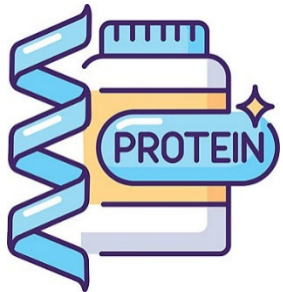
¹ Contribution from both the lipid emulsion and the amino acid solution.



Physiology during catabolism in disease

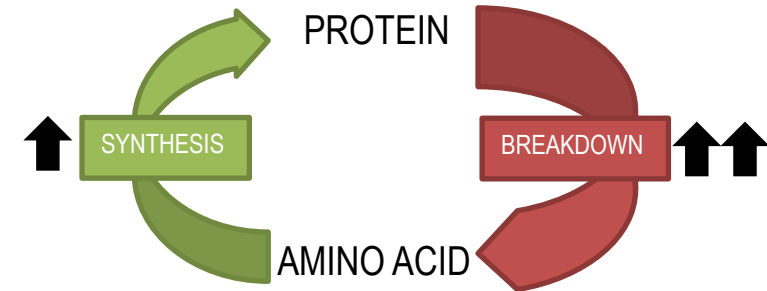
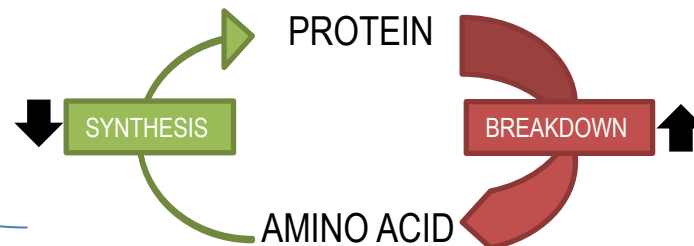
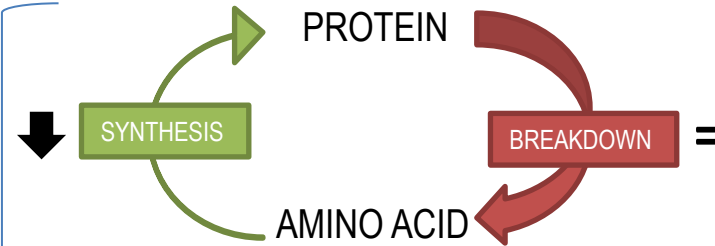
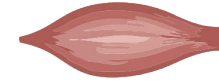
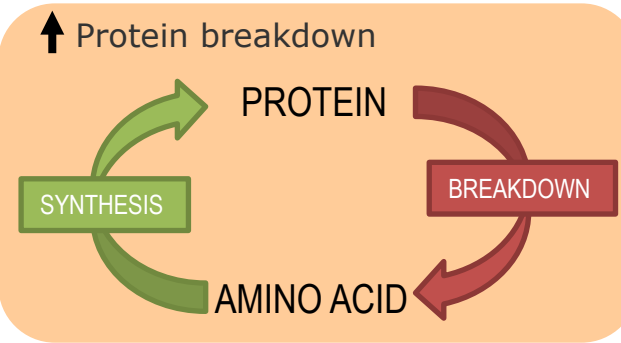


How will different delivery and type of protein affect this balance?



Skeletal muscle

↑ Protein breakdown



NEGATIVE
NITROGEN
BALANCE



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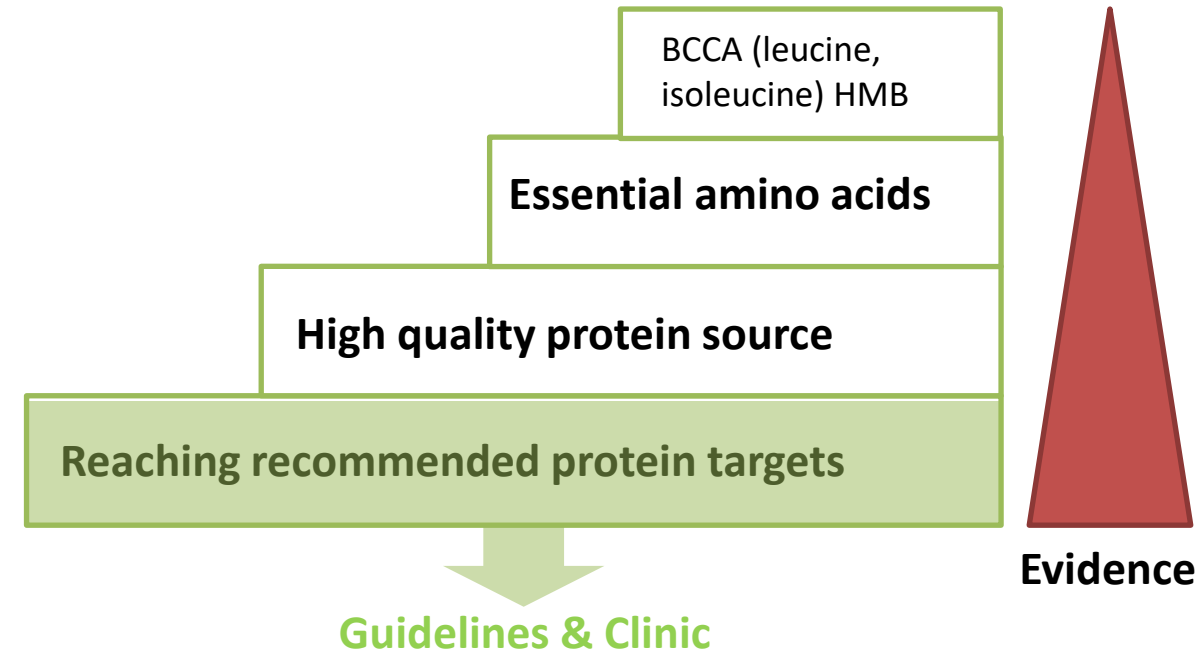
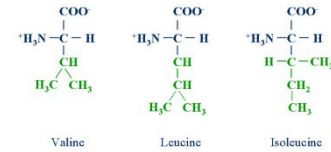
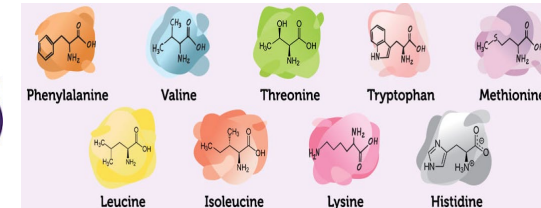
Cancer & protein delivery– What do the guidelines say?



ESPEN Guideline

ESPEN practical guideline: Clinical Nutrition in cancer

Maurizio Muscaritoli ^{a,*}, Jann Arends ^b, Patrick Bachmann ^c, Vickie Baracos ^d, Nicole Barthelemy ^e, Hartmut Bertz ^b, Federico Bozzetti ^f, Elisabeth Hütterer ^g, Elizabeth Isenring ^h, Stein Kaasa ⁱ, Zeljko Krznaric ^j, Barry Laird ^k, Maria Larsson ^l, Alessandro Laviano ^a, Stefan Mühlebach ^m, Line Oldervoll ⁿ, Paula Ravasco ^o, Tora S. Solheim ^p, Florian Strasser ^q, Marian de van der Schueren ^{r,s}, Jean-Charles Preiser ^t, Stephan C. Bischoff ^u



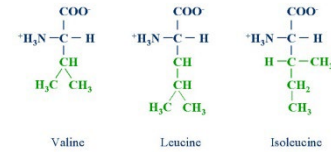
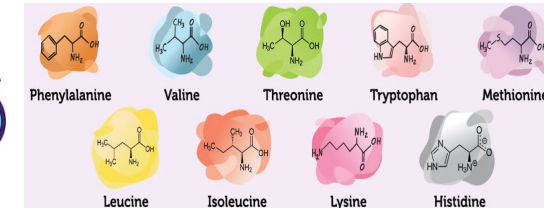
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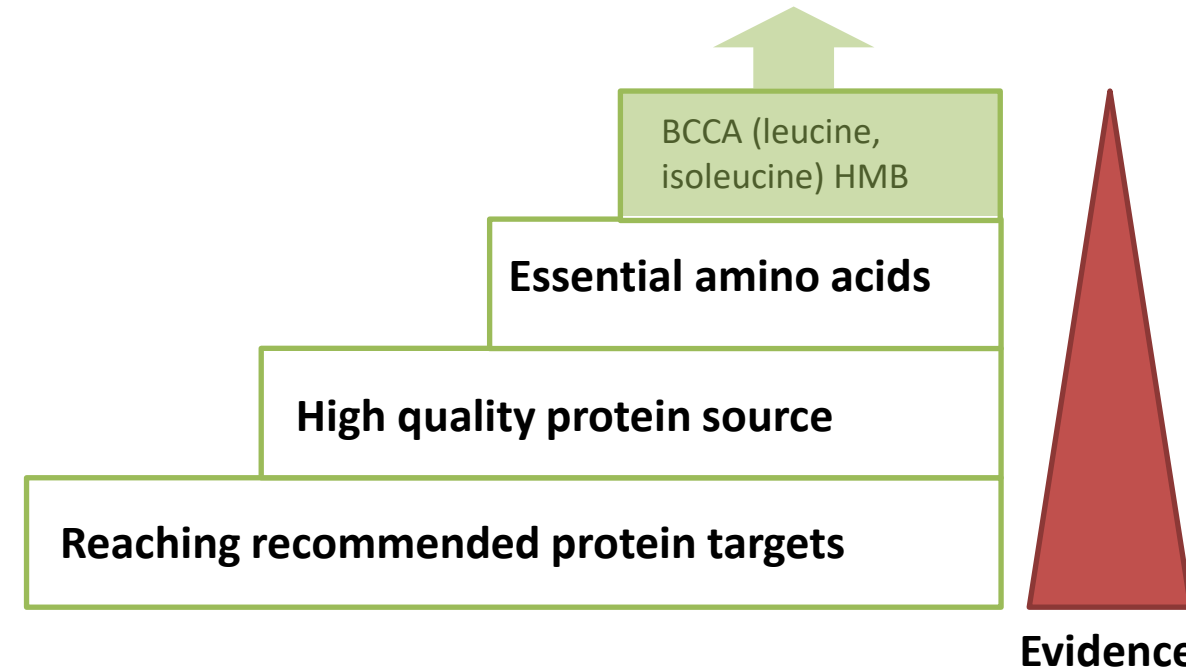
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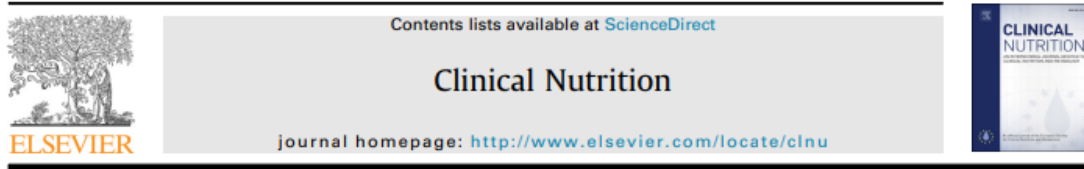


Research



Cancer & protein delivery– What do the guidelines say?

Clinical Nutrition 40 (2021) 2898–2913



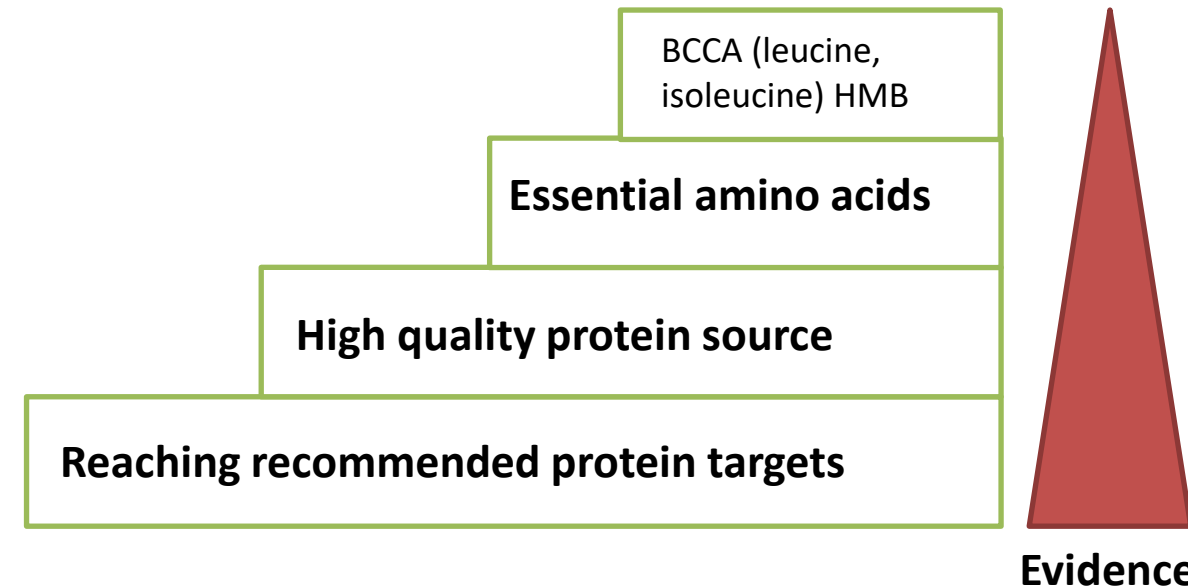
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We recommend that protein intake should be above 1 g/kg/day and, if possible up to 1.5 g/kg/day. (Recommendation B2-2; strength of recommendation strong – Level of evidence moderate – strong consensus)



Cancer and nutrition

- Outcome vs intervention.



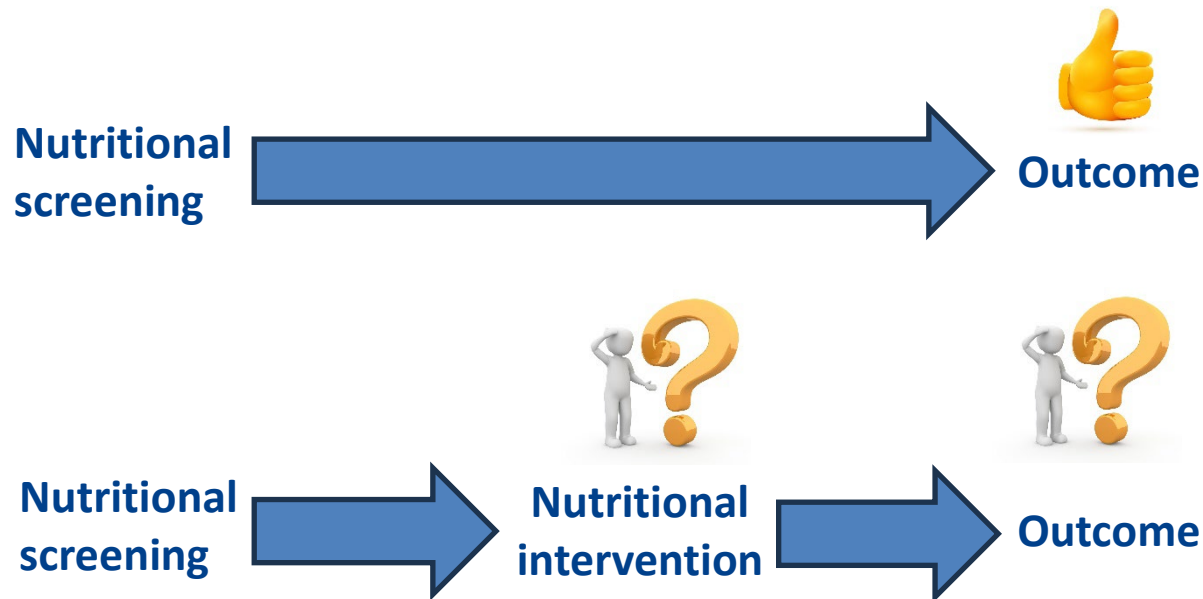
Cancer and nutrition

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Cancer and nutrition

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Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial

Philipp Schuetz, Rebecca Fehr, Valerie Baechli, Martina Geiser, Manuela Deiss, Filomena Gomes, Alexander Kutz, Pascal Tribolet, Thomas Bregenzer, Nina Braun, Claus Hoess, Vojtech Pavlicek, Sarah Schmid, Stefan Bilz, Sarah Sigrist, Michael Brändle, Carmen Benz, Christoph Henzen, Silvia Mattmann, Robert Thomann, Claudia Brand, Jonas Rutishauser, Drahomir Aujesky, Nicolas Rodondi, Jacques Donzé, Zeno Stanga*, Beat Mueller*

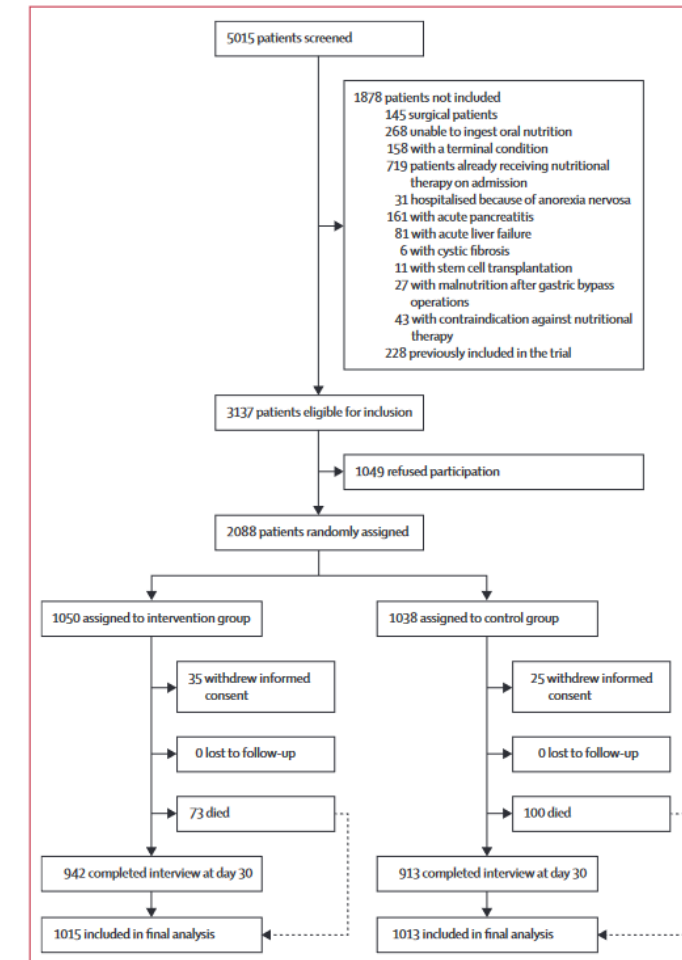


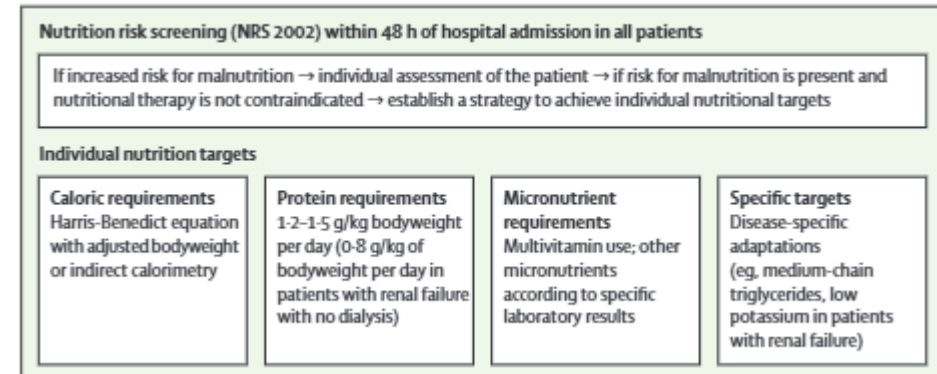
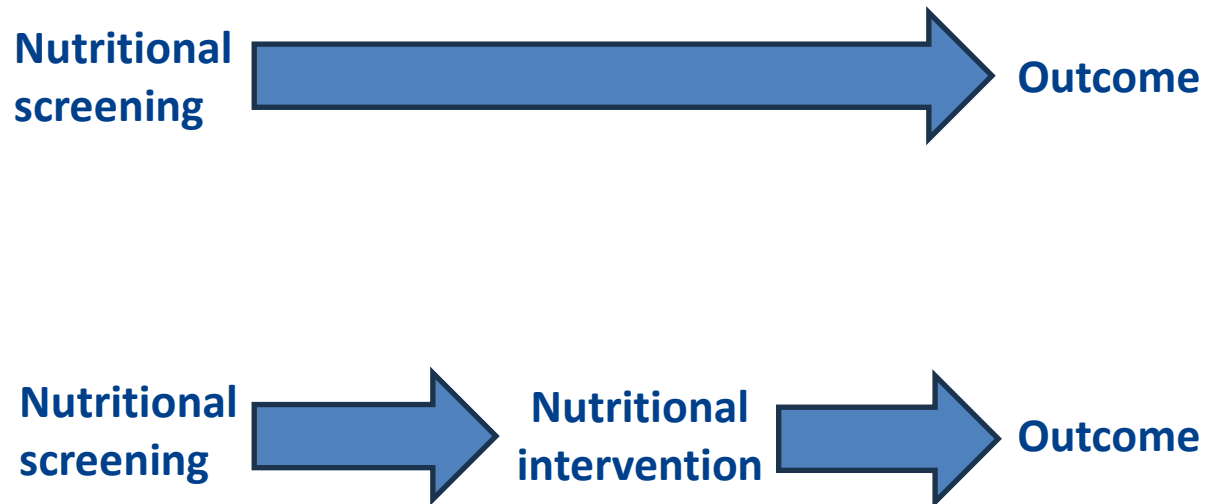
Figure 2: Trial profile

Cancer and nutrition

– Outcome vs intervention.

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	Intervention group (n=1015)	Control group (n=1013)	Odds ratio or coefficient (95% CI)	p value
Outcomes				
Primary outcome				
Adverse outcome within 30 days	232 (23%)	272 (27%)	0.79 (0.64 to 0.97)	0.023
Single components of primary outcome				
All-cause mortality	73 (7%)	100 (10%)	0.65 (0.47 to 0.91)	0.011
Admission to the intensive care unit	23 (2%)	26 (3%)	0.85 (0.48 to 1.51)	0.58
Non-elective hospital readmission	89 (9%)	91 (9%)	0.99 (0.73 to 1.35)	0.96
Major complications				
Any major complication	74 (7%)	76 (8%)	0.95 (0.68 to 1.34)	0.79
Nosocomial infection	40 (4%)	39 (4%)	1.01 (0.63 to 1.59)	0.98
Respiratory failure	14 (1%)	13 (1%)	1.06 (0.49 to 2.28)	0.89
Major cardiovascular event	8 (1%)	7 (1%)	1.11 (0.40 to 3.11)	0.84
Acute kidney failure	32 (3%)	31 (3%)	1.01 (0.61 to 1.69)	0.96
Gastrointestinal events	9 (1%)	15 (1%)	0.57 (0.25 to 1.31)	0.19
Decline in functional status of ≥10%*	35 (4%) of 942	55 (6%) of 913	0.62 (0.40 to 0.96)	0.034
Additional secondary outcomes				
Mean length of stay (days)	9.5 (7.0)	9.6 (6.1)	-0.21 (-0.76 to 0.35)	0.46
Mean Barthel score (points)*	88 (26)	85 (30)	3.26 (0.93 to 5.60)	0.006
Mean EQ-5D VAS (points)†	59 (26)	56 (29)	3.06 (0.53 to 5.59)	<0.0001
Mean EQ-5D index (points)	0.75 (0.32)	0.73 (0.34)	0.13 (0.09 to 0.17)	0.018
Side-effects from nutritional support				
All side-effects	162 (16%)	145 (14%)	1.16 (0.90 to 1.51)	0.26
Gastrointestinal side-effects	43 (4%)	40 (4%)	1.12 (0.68 to 1.83)	0.66
Complications due to enteral feeding or parenteral nutrition	5 (<1%)	3 (<1%)	1.63 (0.38 to 6.95)	0.51
Liver or gall bladder dysfunction	4 (<1%)	7 (1%)	0.54 (0.15 to 1.91)	0.34
Severe hyperglycaemia	48 (5%)	46 (5%)	1.06 (0.69 to 1.61)	0.80
Refeeding syndrome	86 (8%)	73 (7%)	1.21 (0.86 to 1.70)	0.27

Data are number of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for predefined prognostic factors (initial nutritional risk screening score and baseline Barthel index) and study centre. *To estimate decline in functional status, we used the Barthel index (scores range from 0 to 100, with higher scores indicating better functional status) and compared initial scores on admission with scores at day 30; only surviving patients were included in this analysis. †To estimate quality of life we used the European Quality of Life 5 Dimensions index (EQ-5D); values range from -0.205 to 1, with higher scores indicating better quality of life) including the visual-analogue scale (EQ-5D VAS; scores range from 0 to 100, with higher scores indicating better health status).

Table 2: Endpoints and adverse events

Cancer and nutrition

– Outcome vs intervention.



Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial

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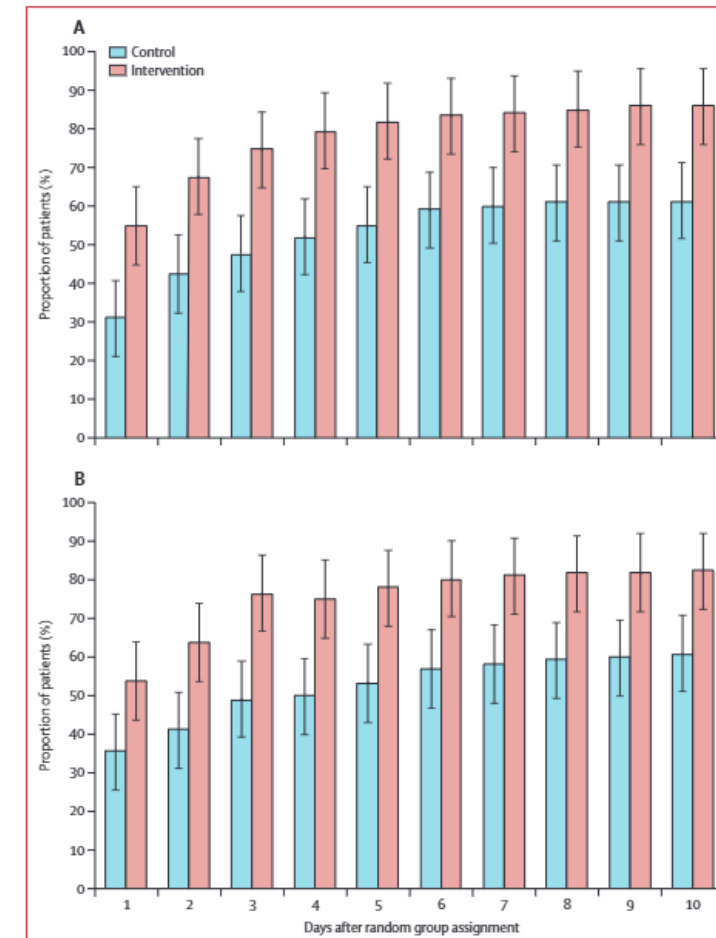


Figure 3: Proportion of patients reaching caloric (A) and protein (B) requirements during the first 10 days after random group assignment

Cancer and nutrition

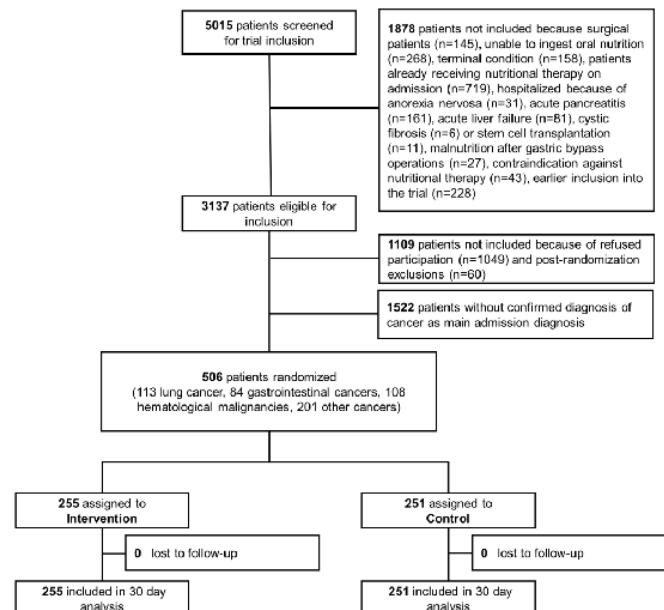
– Outcome vs intervention.

ORIGINAL ARTICLE

Nutritional support during the hospital stay reduces mortality in patients with different types of cancers: secondary analysis of a prospective randomized trial

L. Bargetzi^{1,2†}, C. Brack^{2†}, J. Herrmann^{2†}, A. Bargetzi^{1,2}, L. Hersberger^{1,2}, M. Bargetzi^{2,3}, N. Kaegi-Braun¹, P. Tribolet^{1,4}, F. Gomes^{1,5}, C. Hoess⁶, V. Pavlicek⁶, S. Bilz⁷, S. Sigrist⁷, M. Brändle⁷, C. Henzen⁸, R. Thomann⁹, J. Rutishauser¹⁰, D. Aujesky¹¹, N. Rodondi^{11,12}, J. Donzé^{11,13}, A. Laviano¹⁴, Z. Stanga¹⁵, B. Mueller^{1,2*} & P. Schuetz^{1,2*}

Supplementary Figure 1: Flow chart for patient inclusion



	Control (N = 251)	Intervention group (N = 255)	Type of analysis	Regression analysis (adjusted) (95% CI), P value
Primary outcome				
All-cause mortality within 30 days	50 (19.9)	36 (14.1)	OR	0.57 (0.35-0.94), 0.027
Secondary outcomes				
Clinical outcome				
Combined adverse outcome within 30 days*	93 (37.1)	86 (33.7)	OR	0.81 (0.56-1.19), 0.288
Additional hospital outcomes				
Admission to an intensive care unit within 30 days	6 (2.4)	4 (1.6)	OR	0.62 (0.16-2.5), 0.503
Non-elective hospital readmission within 30 days	22 (8.8)	31 (12.2)	OR	1.53 (0.85-2.75), 0.159
Mean length of index hospital stay (days)	10.4 (6.9)	10.4 (7.8)	HR	1.14 (0.93-1.40), 0.206
Functional outcome				
Decline in functional status of ≥10% from admission to day 30	67 (26.7)	45 (17.6)	OR	0.59 (0.38-0.93), 0.021
Mean Barthel Index score at day 30 (points)	94.72 (10.68)	94.98 (10.21)	Coefficient	0.6 (−1.16 to 2.36), 0.506
Mean EQ-5D Index at day 30 (points)	0.62 (0.39)	0.67 (0.37)	Coefficient	0.08 (0.01-0.15), 0.016
Mean EQ-5D VAS at day 30 (points)	43 (30)	48 (29)	Coefficient	6.16 (0.51-11.8), 0.033
Long-term mortality				
All-cause mortality within 180 days	128 (52.7)	115 (47.3)	HR	0.83 (0.65-1.08), 0.18

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-



What is the evidence of anabolic resistance in cancer?

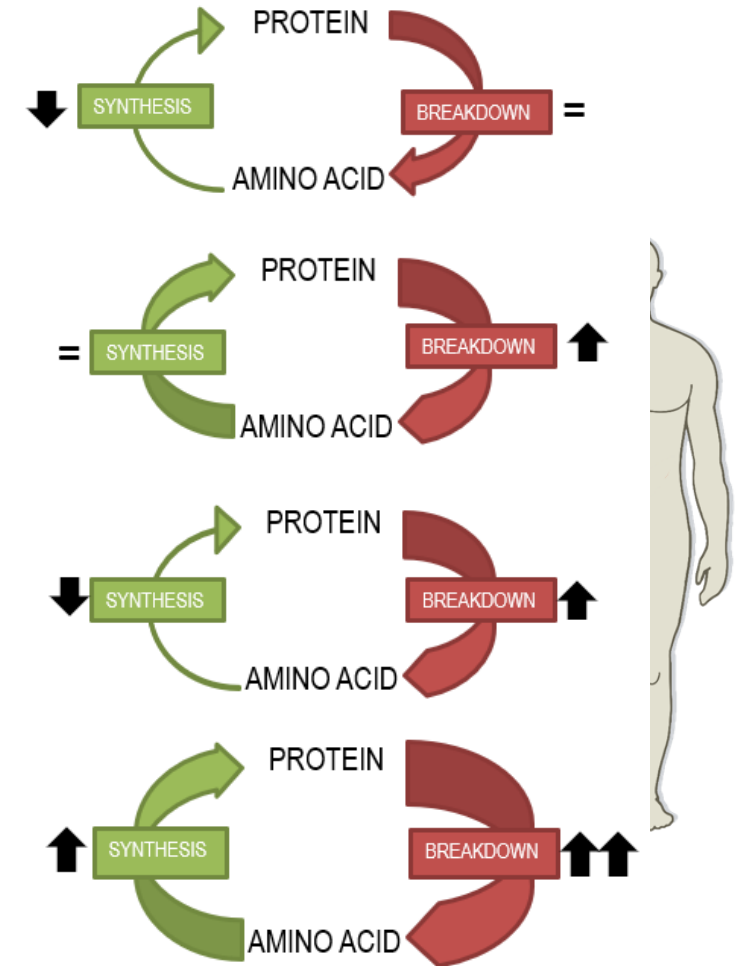
REVIEW



Protein anabolic resistance in cancer: does it really exist?

Mariëlle P.K.J. Engelen, Barbara S. van der Meij, and Nicolaas E.P. Deutz

“Cancer patients have a normal anabolic potential”



What is the evidence of anabolic resistance in cancer?

- Smaller clinical isotope studies do not show a clear change in protein turnover, however increased muscle protein breakdown has been suggested more clearly with high oncologic burden.

Biology of Human Tumors

Clinical
Cancer
Research

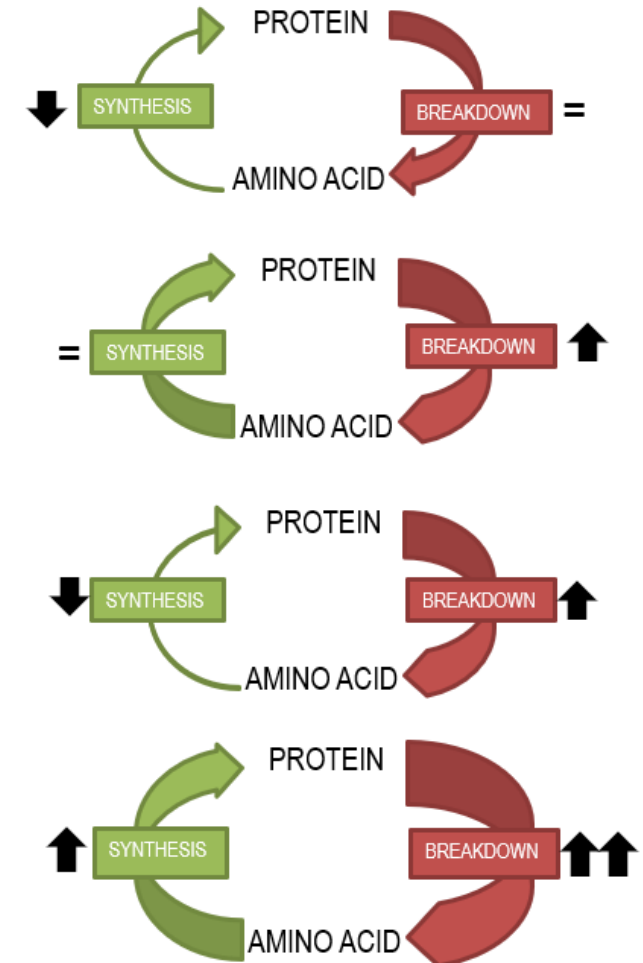
Habitual Myofibrillar Protein Synthesis Is Normal in Patients with Upper GI Cancer Cachexia

Alisdair J. MacDonald¹, Neil Johns¹, Nathan Stephens¹, Carolyn Greig², James A. Ross¹, Alexandra C. Small³, Holger Husi⁴, Kenneth C. H. Fearon¹, and Tom Preston³

Table 3. Skeletal muscle mass (kg), absolute myofibrillar protein synthesis, and absolute myofibrillar protein breakdown (g/day)

	Cancer (n = 10)		Control (n = 7)	
	Median	IQR	Median	IQR
Body weight, kg	71.0	66.8–80	70.4	67.1–80.8
Skeletal muscle mass, kg	20.2	18.6–22.5	19.8	18.9–25.3
Myofibrillar protein synthesis, g/day	41.1	38.2–41.8	37.2	34.0–45.4
Myofibrillar protein breakdown, g/day	42.4	39.1–42.8	37.2	34.0–45.4

NOTE: Patients with cancer with serial CT scans are included (n = 10; comprising 7 weight-losing and 3 weight-stable subjects). Muscle mass was estimated at the time of consuming deuterium oxide. Control subjects (n = 7) were assumed to have stable muscle mass. Protein kinetics were derived from quadriceps biopsy data.



What is the evidence of anabolic resistance in cancer?

- Smaller clinical isotope studies do not show a clear change in protein turnover, however increased muscle protein breakdown has been suggested more clearly with high oncologic burden.

Effect of tumor burden and subsequent surgical resection on skeletal muscle mass and protein turnover in colorectal cancer patients¹⁻⁴

John P Williams, Bethan E Phillips, Kenneth Smith, Philip J Atherton, Debbie Rankin, Anna L Selby, Sarah Liptrot, Jonathan Lund, Mike Larvin, and Michael J Rennie

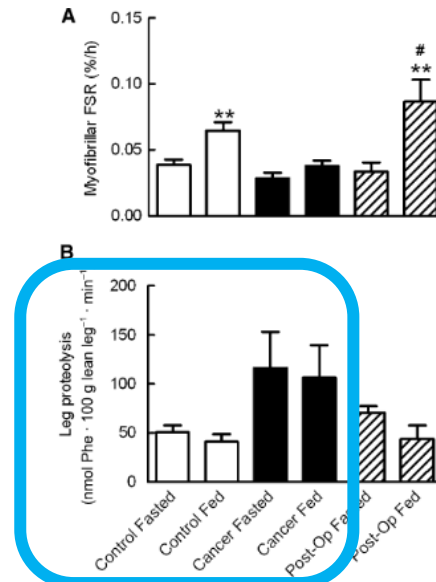
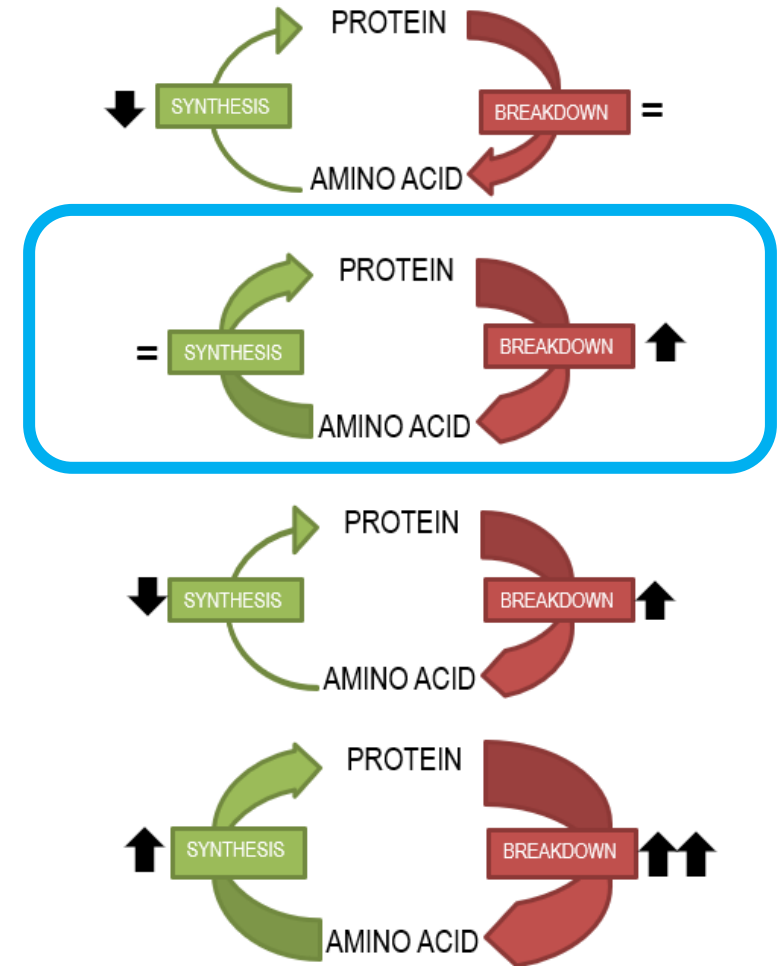
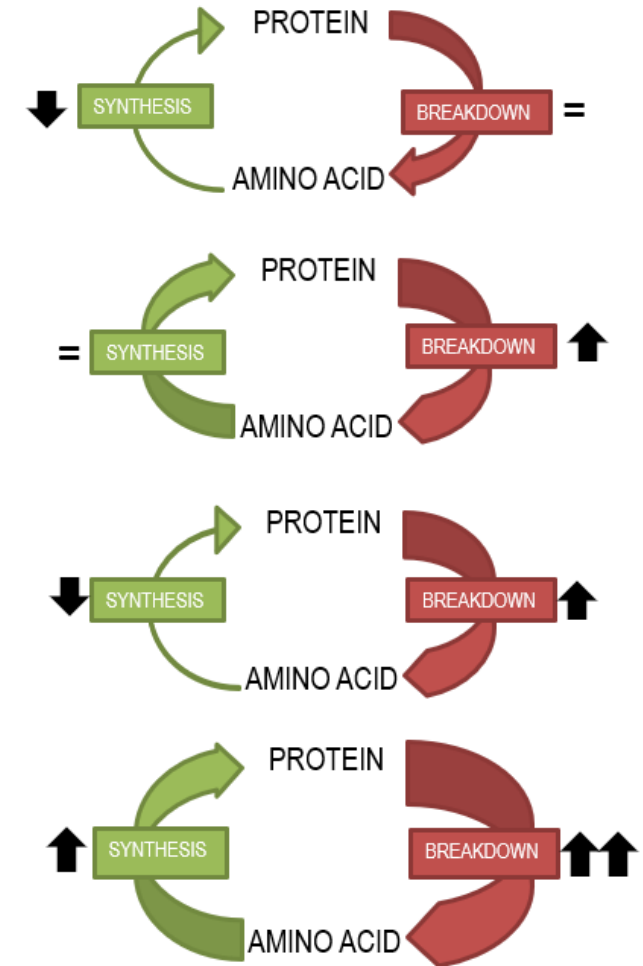


FIGURE 3. Means (\pm SEMs) of myofibrillar FSR (MPS) (A) and leg proteolysis (MPB) (B) of healthy controls ($n = 8$) and colon cancer patients before and after resection surgery ($n = 13$) in postabsorptive and postprandial conditions. MPS interaction term between feeding and surgery $P = 0.02$; MPB $P = 0.85$. **Compared with the same group in the postabsorptive condition, $P < 0.01$; #compared with preoperative cancer patients in the same condition, $P < 0.05$. Statistical analysis was conducted by using 2-factor ANOVA with Bonferroni's post hoc analysis. FSR, fractional synthetic rate; MPB, muscle protein breakdown; MPS, muscle protein synthesis; Phe, phenylalanine; Post-Op, postoperative.



What is the evidence of anabolic resistance in cancer?

- Smaller clinical isotope studies do not show a clear change in protein turnover, however increased muscle protein breakdown has been suggested more clearly with high oncologic burden.
- For patients receiving surgery and/or more critically ill patients, this could be different.



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What is the evidence of increasing protein in cancer patients?

NONE

What is the evidence of increasing protein in cancer patients?

- Some clinical studies, including RCTs may indicate that increased protein delivery in cancer patients improves outcome, however it remains uncertain.

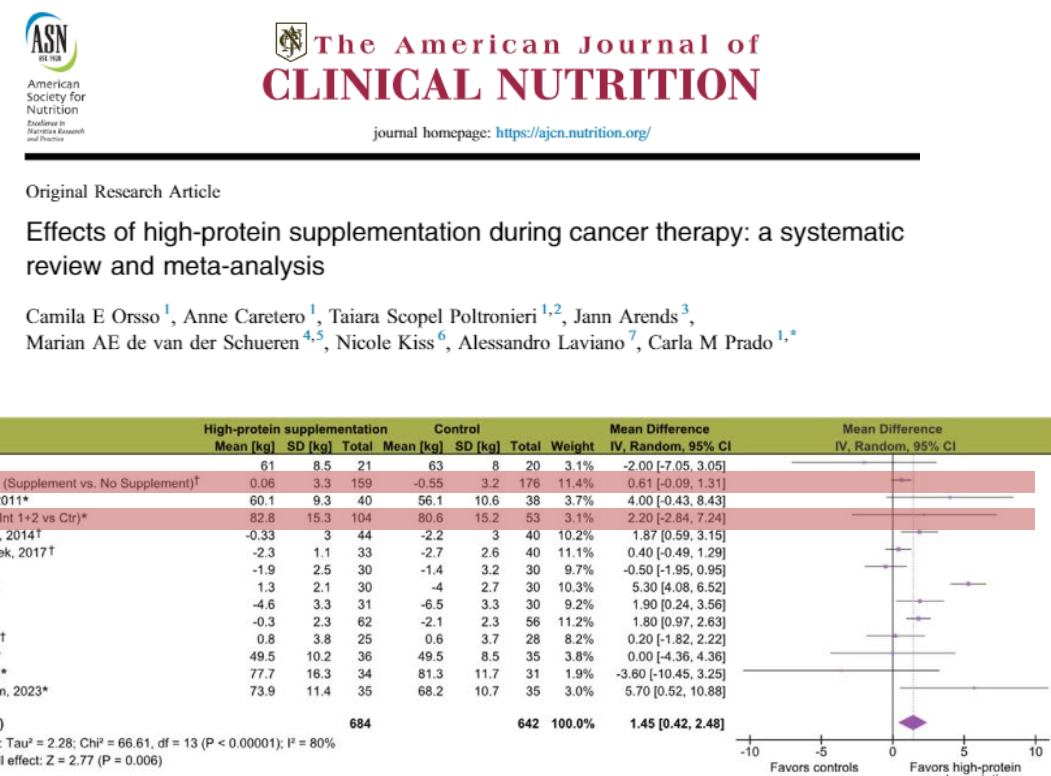
ORIGINAL ARTICLE

Nutritional support during the hospital stay reduces mortality in patients with different types of cancers: secondary analysis of a prospective randomized trial

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What is the evidence of increasing protein in cancer patients?

- Some clinical studies, including RCTs may indicate that increased protein delivery in cancer patients improves outcome, however it remains uncertain.
- No clear study have showed that increased protein delivery improves outcome for cancer patients



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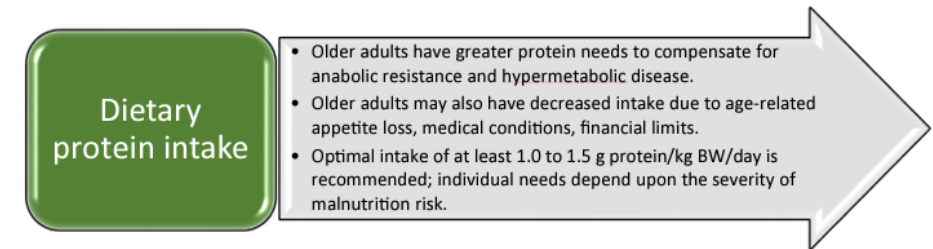
ESPEN Guideline

ESPEN guideline on clinical nutrition and hydration in geriatrics

Dorothee Volkert ^{a,*}, Anne Marie Beck ^b, Tommy Cederholm ^c, Alfonso Cruz-Jentoft ^d, Sabine Goisser ^e, Lee Hooper ^f, Eva Kiesswetter ^a, Marcello Maggio ^{g,h}, Agathe Raynaud-Simon ⁱ, Cornel C. Sieber ^{a,j}, Lubos Sobotka ^k, Dienneke van Asselt ^l, Rainer Wirth ^m, Stephan C. Bischoff ⁿ



“Older person protein intake should be at least 1 g/kg/day”



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- Clinical metabolic studies indicate that high protein could improve protein turnover in cancer patients.



Original article

Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food^{2*}

Nicolaas E.P. Deutz^a, Ahmed Safar^b, Scott Schutzler^a, Robert Memelink^c, Arny Ferrando^a, Horace Spencer^d, Ardy van Helvoort^c, Robert R. Wolfe^{a,*}

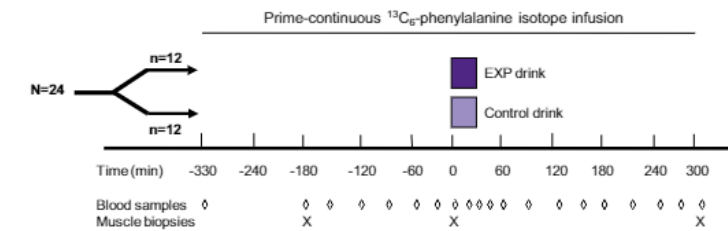
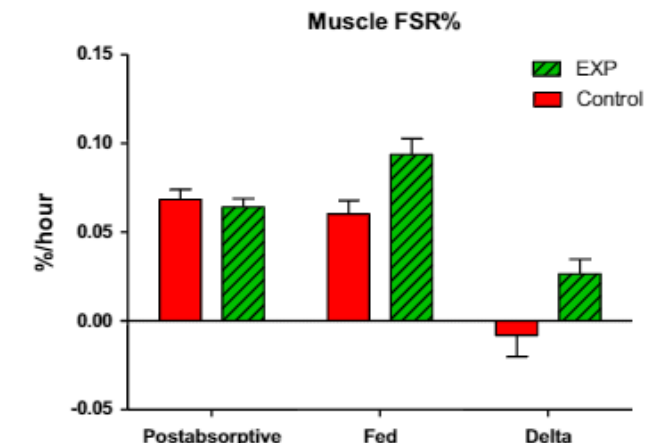


Fig. 1. Study design. Stable isotope infusion was a primed-continuous L-[ring- $^{13}\text{C}_6$]phenylalanine infusion.



Summary

- Although cancer patients' malnutrition and cachexia is partly due to their **catabolic state**, they do not seem to exhibit an **anabolic resistance**, at least to an extent preventing them from benefit from medical nutrition.
- Isotope studies shows a more favorable metabolism administering high protein formulas, suggesting this to be safe and beneficial
- Improved calory intake and protein delivery improves outcome from cancer patients.
- Current recommendation suggests 1-1.5 g/kg/day. This is mostly based on clinical consensus with little evidence, but higher protein intake is most likely beneficial for cancer patients.
- Studies show that cancer patients receive protein considerably lower than the recommended target