International Workshop on Cachexia
Cachexia in the Critically Ill

ernährung 2006; Berlin, June 1, 2006
Hill GL et al


Changes in Total Body Protein in various groups of patients
Statement I  Critical illness is characterized by activation of protein catabolism

Statement II  In critical illness activation of protein catabolism is correlated to severity of disease

Statement III  In critical illness severity of disease and activation of protein catabolism is correlated with outcome
One-year outcomes in survivors of the acute respiratory distress syndrome


Change in Weight from Base Line among Patients with ARDS at the Time of Discharge from the ICU and at 3, 6, and 12 Months
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A decade-old dogma in therapy of critical illness

Suppression of protein catabolism will improve prognosis of the critically ill patient ("The search for the magic bullet")
Muscle Cachexia: Current Concepts of Intracellular Mechanisms and Molecular Regulation


Simplified scheme of the ubiquitin-proteasome proteolytic pathway.
Sepsis results in increased activity of the 20S proteasome in skeletal muscle. 20S proteasomes were isolated from muscles of sham-operated (open bars) or septic rats (filled bars)
Novel aspects on the regulation of muscle wasting in sepsis

Hasselgren P-O et al.
Int J Biochem Cell Biol 2005; 37: 2156-68

Increased muscle calcium levels may regulate multiple processes that participate in the development of muscle wasting during sepsis.
Mean total plasma amino acid concentrations before, during (from time 0 to 60 min), and after infusions of an amino acid solution providing 375 mg•kg body wt•60 min•1 in patients with sepsis and in healthy control subjects. The curves are significantly different at all time points, $P < 0.001$.
Changes in protein metabolism in liver and skeletal muscle following trauma complicated by sepsis

Hasselgren PO et al

*J Trauma 1984; 24: 224-229*

Leucine incorporation into hepatic proteins (left) and tyrosine incorporation into muscle proteins (right).
The primary problem in protein catabolism of acutely ill patients is the liver!
Glucose and alanine metabolism in normal volunteers and in patients with sepsis in the basal state and during the infusion of glucose (4mg/kg/min).

*between periods 1 and 2 in the same group ($p < 0.05$).

** from the control value for the corresponding period ($p < 0.05$).
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Statement IV

Activation of protein catabolism in critical illness can not be (completely) suppressed by exogenous nutritional substrates
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A dogma in nutrition therapy of critical illness

Nutrition in the critically ill is not very
important ("wait and see")
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A decade-old dogma in therapy of critical illness

Suppression of protein catabolism will improve prognosis of the critically ill patient ("The search for the magic bullet")
Low Protein Diets Improve Survival from Peritonitis in Guinea Pigs

from Peck MD et al.  

Low Protein Diets Improve Survival from Peritonitis in Guinea Pigs

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Increased Mortality Associated with Growth Hormone Treatment in Critically Ill Adults

Takala et al.  

Numbers of Deaths in the Finnish Study (Panel A) and the Multinational Study (Panel B) According to the Treatment Assignment and Day of Treatment
Creatinine clearances in subjects with sufficient urine flow rates (A) and in subjects who were oliguric, receiving rhIGF-I (filled symbols) or placebo.
Catabolism / nitrogen balance not necessarily an indicator of treatment success or even a primary goal of therapy!
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Statement V

Activation of protein catabolism in critical illness is a physiologic, adaptative response to injury!!

Mere suppression of protein catabolism is ineffective!!

However: Can also be “maladaptative” in hyperinflammatory / hypercatabolic states “septic autoaggression”
Clinical consequences of malnutrition/catabolism

„healthy“ 100%

- Concentration of plasma proteins ↓
- Muscle mass ↓
- Immune response ↓
- Wound healing ↓
- Organ function ↓

Death

Malnutrition + inflammation: 25 % protein loss
Malnutrition: 40% protein loss
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Potential therapeutic approaches

Therapeutic interventions should not be aimed primarily at the reduction of protein catabolism but MUST be focused at the underlying problem; i.e. at mitigating the inflammatory state!!
Short-term bed rest impairs amino acid-induced protein anabolism in humans

Biolo Ch. et al

J Physiol 2004; 558: 369-80

Rates of net leucine deposition (i.e. $R_d$ to protein synthesis minus $R_a$ from proteolysis) into body protein during amino acid infusion in ambulatory and bed rest conditions. *$P < 0.05$
Amino Acid Loss and Plasma Concentrations During Continuous Hemodiafiltration

Frankenfield DC et al. JPN 1993; 17: 551 - 61

Mean losses of individual amino acids in CHD effluent as a function of mean plasma concentrations of each amino acid.
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Potential therapeutic approaches

Nutrition support
- adequate provision of macro- and micronutrients
- specific nutrients (glutamine, arginine, BCAAs, ω-3-FA etc.)
- pharmaconutrients: selenium
- immunonutrition

Hormones and hormone antagonists
- insulin
- HGH, IGF-I, testosterone, anabolic steroids
- anticytokines (TNF-α blockers, etc.)
- anti-glucocorticoids
- β-blockers etc.

Direct catabolism inhibitors
- proteasome blockers, dantrolene, NF-κB-inhibitors, protease inhibitors etc.

Muscle stimulation etc. etc.
Intensive Insulin Treatment in Critically Ill Trauma Patients Normalizes Glucose by Reducing Endogenous Glucose Production

Thorell A et al

*J Endocrinol Metab 2004; 89: 5382-86*

Glucose kinetics in traumatized subjects and healthy controls in the postprandial state (basal), during TPN, and during TPN+I. *, $P < 0.05$ vs. control. Endogenous glucose production (EGP) and whole-body glucose disposal (WGD)

![Glucose kinetics graph](image-url)
Glutamine appearance rate ($R_a$) at baseline (B) and during standard TPN (STPN) or Gln-enriched TPN (GTPN). Significant effects (baseline versus 9 d) ($P < 0.001$) and for DNSgln ($P < 0.05$), (GTPN versus STPN; $P < 0.05$) PDgln, glutamine arising from protein degradation; DNSgln, glutamine arising from de novo synthesis; Infgln, exogenous glutamine.
Does growth hormone allow more efficient nitrogen sparing in postoperative patients requiring parenteral nutrition? A RCT

Sevette A et al.

_Clin Nutr_ 2005; 24: 943-955

Body composition. Values are mean and SEM of the changes in each group on Day 14 compared to the pre-operative values.
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Potential therapeutic approaches

Is it a believe, conviction, a wishful thinking?

Nutrition is the basis of any adequate therapeutic intervention to minimize protein catabolism (and improve prognosis) in the critically ill.
Relationship of BMI to subsequent mortality among seriously ill hospitalized patients


Estimated survival curves by BMI group for four disease classes: coma (top left panel), cancer (top right panel), acute respiratory failure/multiple organ system failure (bottom left panel), and chronic obstructive pulmonary disease/congestive heart failure/cirrhosis (bottom right panel)
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Back to the roots: Nutrition is the future!

Thank you for your attention!