

**Entry Level Clinical Nutrition:
November 2013 Update
Anabolic resistance:
Why it can be more difficult to
increase lean body mass in
aging populations
Part I
Jeffrey Moss, DDS, CNS, DACBN
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***Quality of life issues are the
major concerns more than
ever now.***

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Entry Level Clinical Nutrition Update – Part 3

With Dr. Jeff Moss

Summer of Work Exposes Medical Students to System's Ills - NYTimes.com
Page 1 of 3

September 9, 2009

Summer of Work Exposes Medical Students to System's Ills

By ALVIN BACH

SEATTLE — This summer, medical students from the University of Washington took a long look under the hood of the health care system they are about to inherit, and many returned to campus last week with their eyes wide open and their idealism tempered.

Jacob R. Moore, the executive director of the program, said that the students saw a "tidal wave of chronic disease" — diabetes, hypertension, obesity, depression — that left many questioning how much any one physician could really accomplish.

"I often wondered what we were actually doing to help people," Mr. Olgard said.

Not surprisingly, the students also saw a "tidal wave of chronic illness..."

"You had to be able to deliver babies and suture wounds, but also to order unnecessary tests as protection against lawsuits, to hector specialists into seeing Medicaid patients, to match patients with prescriptions on Wal-Mart's \$4 list. And they saw firsthand what Mr. Olgard called "a tidal wave of chronic disease" — diabetes, hypertension, obesity, depression — that left many questioning how much any one physician could really accomplish.

For 21 years, the University of Washington School of Medicine has dispatched its rising second-year students across the Northwest to provide primary care in rural or underserved areas. The monthlong program is elective, but a record number of students took part this year — 117 from a class of 216.

The school has a cooperative agreement to train medical students from Alaska, Idaho, Montana and Wyoming, none of which has a medical college of its own. The summer program is one of several vehicles, along with loan forgiveness enticements, designed to lure students back to their home states to practice in areas with a shortage of primary care givers.

This year, the students set out as negotiations were intensifying in Washington over wholesale changes to the health care system they will soon be joining. Whether there will be improvements to the system remains to be seen, but few students returned thinking there was little to fix.

http://www.nytimes.com/2009/09/09/health/policy/09medschool.html?_r=1&th=&cmc=th&... 9/9/2009

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Nutrition and Critical Care

Luc Cynober
Frederick A. Moore

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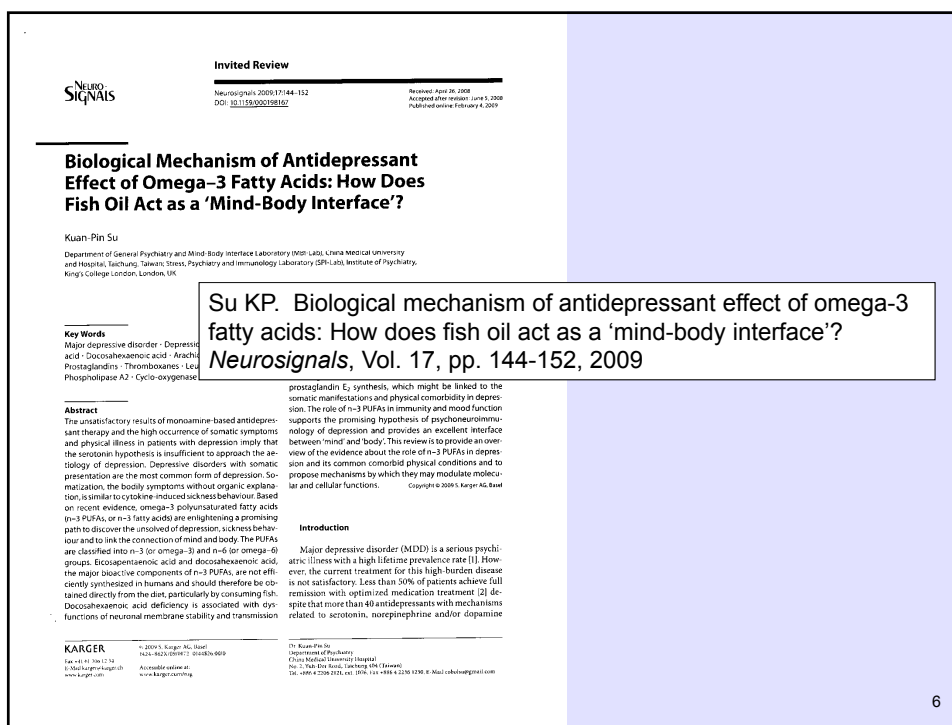
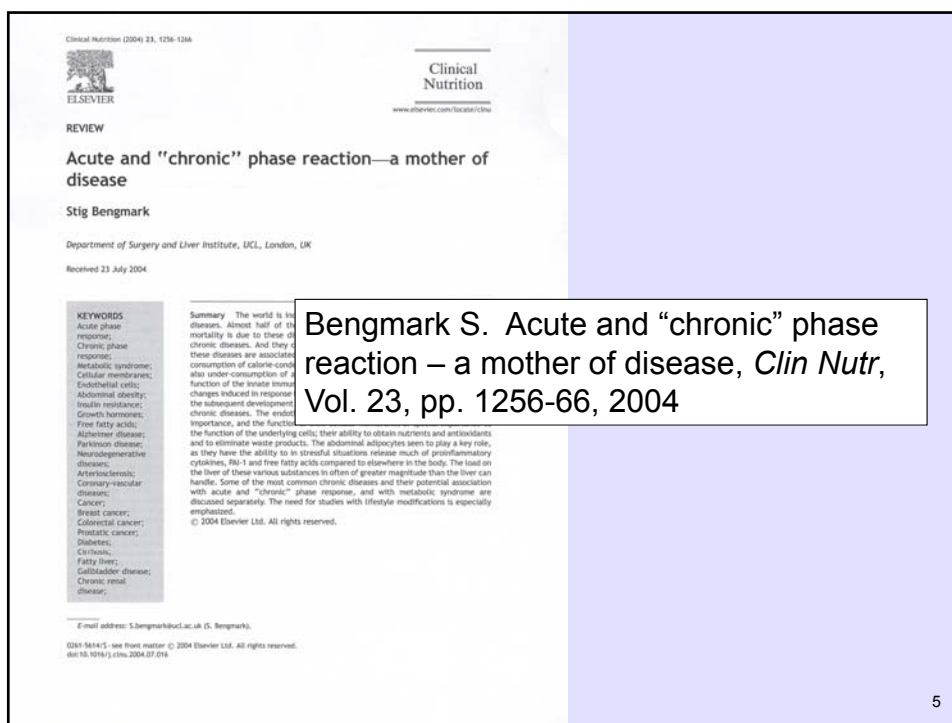
Baracos VE. Overview on metabolic adaptation to stress, pp. 1-13.

"An understanding of the nature of stress is fundamental to the rational design of nutrient mixtures to feed patients whose homeostasis has been altered by one or more stressors."

"All stresses may be presumed to be associated with characteristic modifications in the metabolism of lipids, carbohydrates, amino acids, and micronutrients."

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Entry Level Clinical Nutrition Update – Part 3 With Dr. Jeff Moss



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With Dr. Jeff Moss

Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

Symptoms	Prevalence in IFN- α therapy ^a , %	Prevalence in MDD ^b , %
Fatigue/asthenia	39–90	73
Headache	27–67	33 ^e
Gastrointestinal symptoms	50 ^{c, 1}	34–47 ^f
Psychomotor slowing	40 ^c	59–65 ^f
Insomnia	20–39 ^d	63
Irritability	35 ^d	50
Arthralgia	9–36	31 ^e
Musculoskeletal pain	26–32	62–80 ^{g, 2}
Abdominal pain	15–20	21 ^e
Anorexia	13–19	40
Anxiety	13–18 ^d	57
Poor concentration	14 ^d	51

^a [46], unless otherwise specified; ^b [99], unless otherwise specified; ^c [100]; ^d [101]; ^e [102]; ^f [103]; ^g [104].

¹ Nausea, vomiting, bowel problems.

² Result from depressed inpatient population.

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Underlying hypotheses of Entry Level Clinical Nutrition:

- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

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Entry Level Clinical Nutrition:

A new model of functional
medicine that incorporates
allostatic load and the “chronic”
acute phase response

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***This is a relatively easy,
inexpensive way to help
most patients feel better
early on during the course
of therapy no matter what
their “disease” or chief
complaint.***

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A simplified approach to helping patients feel better

- Understanding the true nature of chronic illness: Excessive allostatic load
- Simple, cost effective diagnostic tools
- A simplified, cost effective menu to improve patient quality of life

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Opinion paper
The evolutionary benefit of insulin resistance
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SUMMARY
Insulin resistance is perceived as deleterious, associated with conditions as the metabolic syndrome, type 2 diabetes mellitus and critical illness. However, insulin resistance is evolutionarily well preserved and its persistence suggests that it benefits survival. Insulin resistance is important in various states such as starvation, intense activation, growth and cancer. In spare glucose for different biosynthetic purposes such as the production of NADPH, nucleotides in the pentose phosphate pathway and substrate for anaplerosis. In these conditions, total glucose oxidation by the mitochondria and cycle is actually low and energy demands are largely met by fatty acid and ketone body oxidation.

Soeters MR & Soeters PB. The evolutionary benefit of insulin resistance, *Clin Nutr*, Vol. 31, pp. 1002-1007, 2012.

hypothesis on the evolutionary importance of insulin resistance.

"Insulin resistance" is generally regarded as a deleterious condition associated with the metabolic syndrome, type 2 diabetes mellitus and critical illness; disorders that lead to hyperglycemia. In turn, chronically elevated glucose levels are causing many of the ill effects of these conditions. Consequently, much effort has been invested into treating hyperglycemia on its own; glucose targets have not only been set for patients with type 2 diabetes mellitus, but also for patients with critical illness. In the latter state, glucose control

2. Insulin resistance in starvation
A century ago Benedict demonstrated in his classic work "A study on long term fasting" that the human organism could limit its nitrogen losses during long term starvation. Starvation is accompanied by insulin resistance as shown by targeted inhibition of the action of insulin in well glucose tolerance tests and classic studies

"The bad image of insulin resistance has obscured its potential benefits as an adaptive mechanism. Insulin resistance (or the ability to selectively modulate the cellular/tissue response to insulin) is evolutionarily well preserved in insects, worms, and vertebrates including humans. Having been under so much evolutionary pressure, its persistence suggests that it benefits survival of the species."

doi:10.1016/j.clnu.2012.05.001

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JAMA Network | JAMA Internal Medicine | Intensive Glucose Reg... <http://archinte.jamanetwork.com/article.aspx?articleid=1735896>

Jeffrey Weiss MD, Account | SIGN OUT

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Original Investigation | September 10, 2013

Letter to the Editor

Intensive Glucose Regulation in Hyperglycemic Acute Coronary Syndrome

Results of the Randomized BIOMARKER Study to Identify the Acute Risk of a Coronary Syndrome-2 (BIOMARKER-2) Glucose Trial

ONLINE FIRST

De Mulder M et al. Intensive glucose regulation in hyperglycemic acute coronary syndrome, *JAMA Intern Med*, Published online September 9, 2013.

ABSTRACT

IMPORTANCE: Elevated plasma glucose levels in patients with acute coronary syndrome (ACS) on hospital admission are associated with increased mortality. Clinical trials of glucose regulation have provided inconsistent results with respect to cardiovascular outcomes, perhaps because target glucose levels have been suboptimal.

OBJECTIVE: To evaluate the effect of intensive glucose regulation on mortality in patients with ACS.

DESIGN: Randomized controlled trial.

SETTING: Academic medical center.

PARTICIPANTS: 1000 patients with ACS.

INTERVENTIONS: Intensive glucose regulation vs standard care.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was mortality at 30 days. The secondary outcome was mortality at 1 year. The intensive group had a significantly higher rate of mortality at 30 days (10.5% vs 8.5%, *P* = .004) and at 1 year (18.5% vs 15.5%, *P* = .004).

CONCLUSIONS: Intensive glucose regulation did not reduce infarct size in hyperglycemic patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI), and was associated with harm. Future studies should focus on patients with ACS who have persistently elevated glucose after PCI, and should evaluate alternative strategies for optimizing glycemia.

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Clinical Nutrition

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Randomized control trials

Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: A randomized controlled trial^a

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ABSTRACT

Background: Protein pulse feeding is a nutritional strategy that aims to improve protein intake in elderly patients. The aim of this study was to evaluate the effect of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients.

Methods: A randomized controlled trial was conducted in a geriatric ward. Patients were randomized to receive either protein pulse feeding or standard care. The primary outcome was lean mass at 4 weeks. Secondary outcomes were mortality, morbidity, and quality of life.

Results: Protein pulse feeding significantly increased lean mass at 4 weeks compared to standard care. There was no significant difference in mortality, morbidity, or quality of life.

Conclusion: Protein pulse feeding is an effective nutritional strategy to improve lean mass in malnourished and at-risk hospitalized elderly patients.

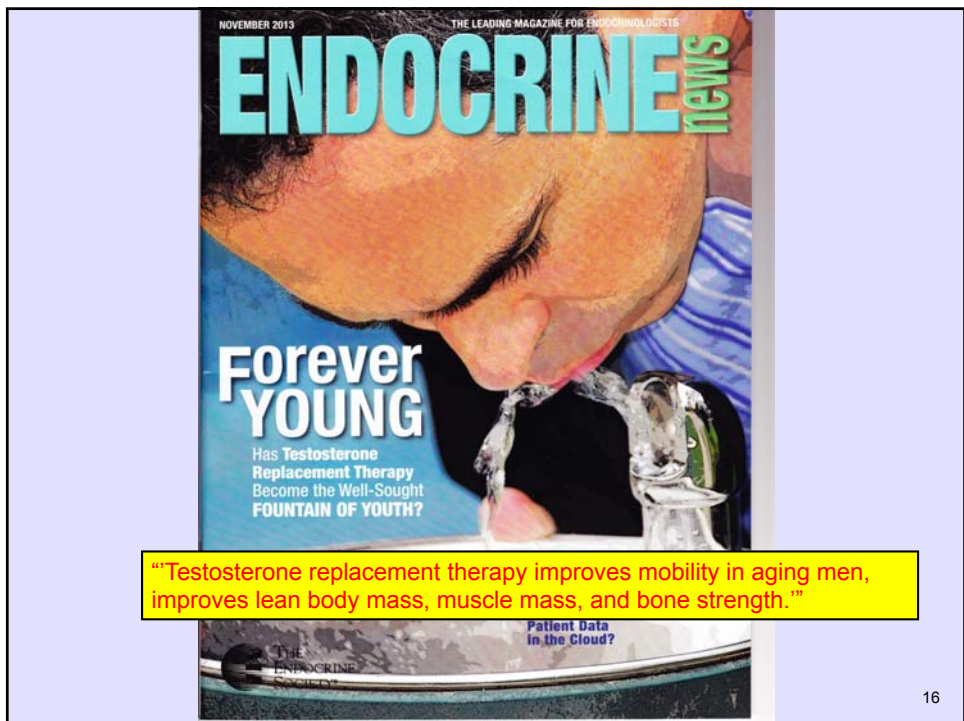
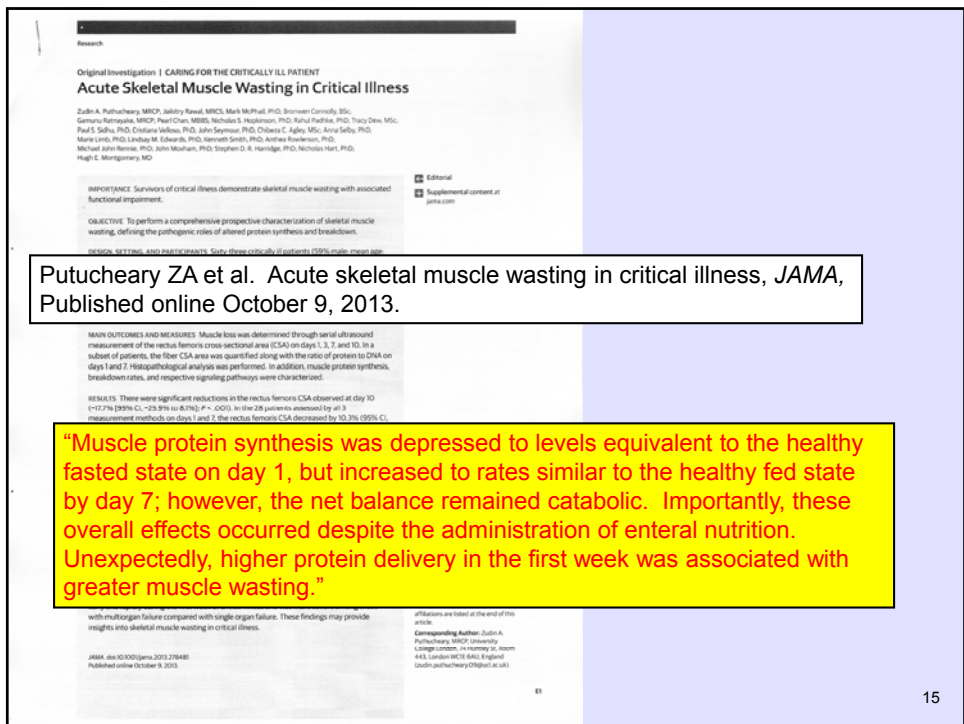
Bouillanne O et al. Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: A randomized controlled trial, *Clin Nutr*, Vol. 32, pp. 186-192, 2013

“Aging per se is responsible for gradual loss of skeletal muscle mass (40% from 20 to 80 years of age) and muscle function, termed sarcopenia. Sarcopenia is a major cause of the increased prevalence of disability, falls, morbidity and mortality in elderly people.”

“This study demonstrates for the first time that protein pulse feeding has a positive, clinically relevant effect on lean mass in malnourished and at-risk hospitalized elderly patients.”

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The screenshot shows the title page of a journal article. The journal is 'Clinical Nutrition', Volume 32, Issues 5, October 2013, pages 772-776. The article title is 'Sarcopenia: Prevalence and prognostic significance in hospitalized patients' by Salah Gariballa and Awad Alessa. A yellow box highlights the conclusion: 'Older people with sarcopenia have poor clinical outcome following acute illness compared with those without sarcopenia.' The introduction states that sarcopenia is a condition characterized by progressive decline in skeletal mass, decreased strength and functional status, and is a challenge for modern medicine. The article is available on ScienceDirect.

Gariballa & Alessa A. Sarcopenia: Prevalence and prognostic significance in hospitalized patients, *Clin Nutr*, Vol. 32, No. 5, pp. 772-776, October 2013.

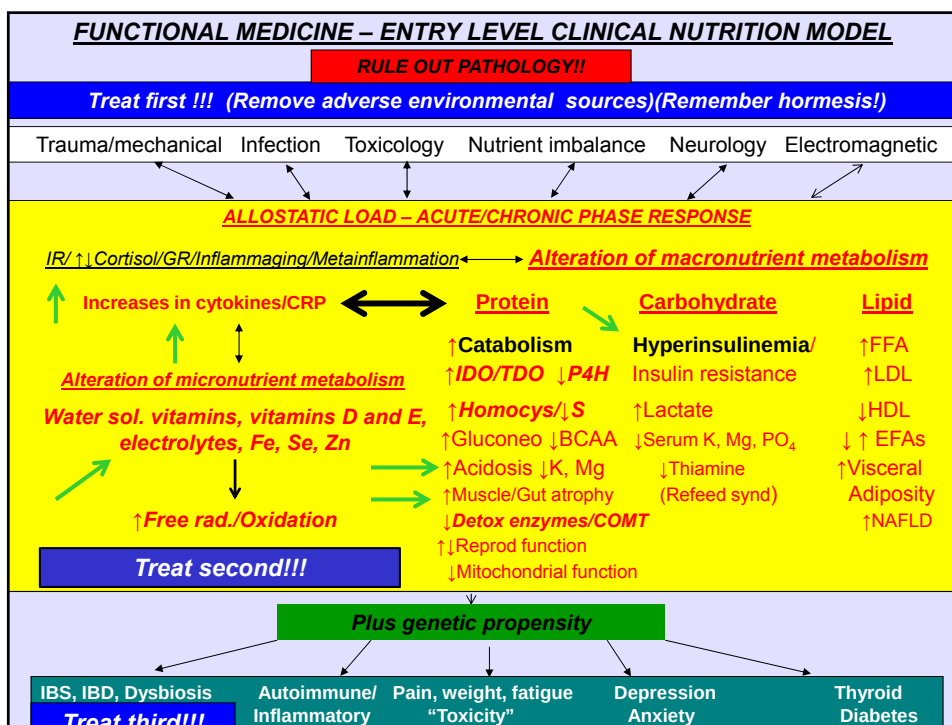
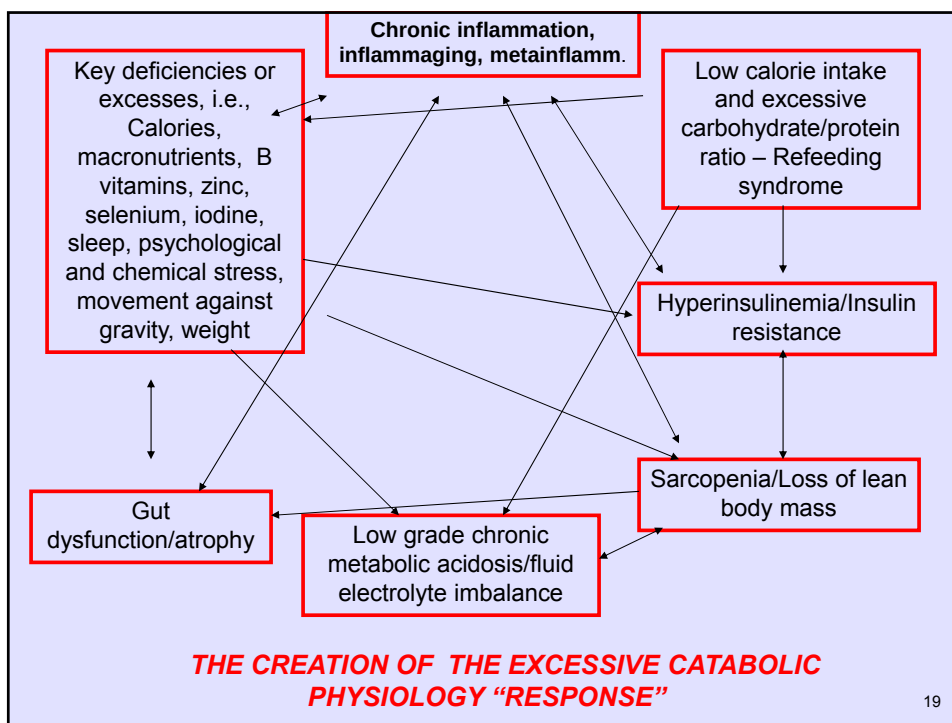
"Older people with sarcopenia have poor clinical outcome following acute illness compared with those without sarcopenia."

Key metabolic imbalances seen with the acute phase response

- Low grade, chronic metabolic acidosis
- Loss of lean body mass (sarcopenia) and its relation to optimal protein intake
- Gastrointestinal dysfunction/gut atrophy
- Inflamm-aging (Increased innate immunity and decreased adaptive immunity)
- Metabolically induced hyperinsulinemia/insulin resistance
- Diet-induced hyperinsulinemia (Refeeding syndrome) and its relation to carbohydrate:protein ratio
- Deficiencies of key micronutrients such as zinc, selenium, and vitamin D

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Randomized control trials

Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: A randomized controlled trial¹

Olivier Bouillanne^{4,5,*}, Emmanuel Curi⁶, Brigitte Hamon-Vilot⁴, Ioannis Nicolais⁶, Pascale Chretien¹, Nathalie Schauer⁴, Jean-Pierre Vincent⁴, Luc Cynober^{4,5}, Christian Aussel^{4,5}

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Abstract

Background: Malnutrition is a major cause of increased prevalence of disability, falls, morbidity and mortality in elderly people.^{1,2} Sarcopenia is a major cause of the increased prevalence of disability, falls, morbidity and mortality in elderly people.^{3,4} Malnutrition greatly accelerates sarcopenia in elderly people.^{5,6}

Objective: To evaluate the effect of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients.

Design: Randomized controlled trial.

Setting: Geriatric ward.

Subjects: 40 elderly malnourished or at-risk patients in an intensive rehabilitation unit. All were given a controlled diet for 6 weeks. In a parallel diet (PD) group (n = 20), dietary protein was spread over the day. In a pulse diet (PPD) group (n = 20), 75% of dietary protein (1.1 g/kg body weight on average) was consumed in one meal at noon. The patients were evaluated at admission and at 6 weeks for body composition (lean mass (LM), appendicular skeletal muscle mass (ASM), and body cell mass (BCM) indices, measured by X-ray absorptiometry combined with bioelectrical impedance analysis) (primary outcome), hand grip strength, and activities of daily living (ADL) score.

Results: Protein pulse feeding was significantly more efficacious than protein spread feeding in improving

Bouillanne O et al. Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: A randomized controlled trial, *Clin Nutr*, Vol. 32, pp. 186-192, 2013

“Aging *per se* is responsible for gradual loss of skeletal muscle mass (40% from 20 to 80 years of age) and muscle function, termed sarcopenia. Sarcopenia is a major cause of the increased prevalence of disability, falls, morbidity and mortality in elderly people.”

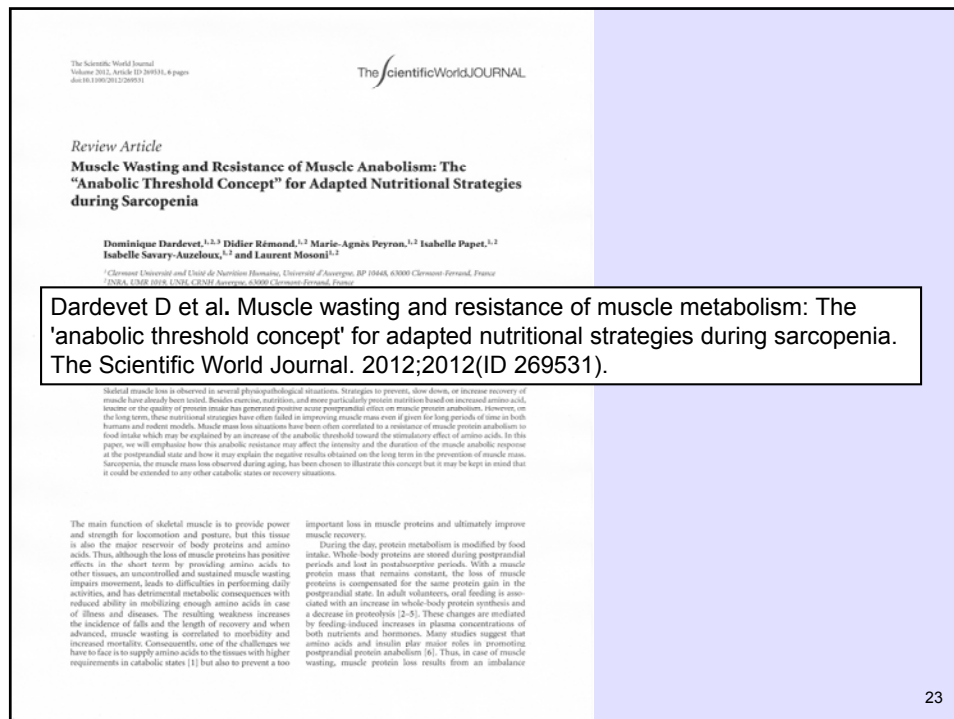
“This study demonstrates for the first time that protein pulse feeding has a positive, clinically relevant effect on lean mass in malnourished and at-risk hospitalized elderly patients.”

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- “Malnutrition greatly accelerates sarcopenia in elderly subjects, in whom it preferentially induces a loss of lean muscle mass, unlike younger, similarly malnourished patients, in whom a loss of fat mass is preferentially induced.”
- “The prevalence of malnutrition in the elderly is between 30% and 78% on hospital admission. It is the most common cause of decreased skeletal muscle mass and strength and secondary immune dysfunction.”

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- **“The main function of skeletal muscle is to provide power and strength for locomotion and posture, but this tissue is also the major reservoir of body proteins and amino acids.”**
- **“Although each muscle wasting situation is characterized by its specific mechanism(s) and pathways leading to muscle loss, an increase of catabolic factors such as glucocorticoids, cytokines, and oxidative stress, often occurs and it is now well established that these factors have potential deleterious effects on the amino acids or insulin signaling pathways involved in the stimulation of muscle anabolism after food intake.”**

“These signaling alterations lead to an ‘anabolic resistance’ of muscle even if the anabolic factor requirements (amino acids e.g.) are theoretically covered, that is, with a normal nutrient availability fitting the recommended dietary protein allowances in healthy subjects.”

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- “This anabolic resistance may be in part explained by an increase of the muscle ‘anabolic threshold’ required to promote maximal anabolism and protein retention.”
- “Because the muscle ‘anabolic threshold’ is higher, the anabolic stimuli (including aminoacidemia) cannot reach anabolic threshold anymore and by consequence, muscle anabolism is reduced with the usual nutrient intake.”

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- **“A possible nutritional therapy is then to increase the intake of anabolic factors (especially amino acids) to reach the new ‘anabolic threshold.’”**
- **“There are several ways to increase amino acid availability to skeletal muscle: increase protein intake, to supplement the diet with one or several free amino acids or to select the protein source on its amino acid composition and physicochemical properties when digested in the digestive tract.”**

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Sarcopenia: Underlying physiology

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- **“Sarcopenia, as other catabolic states, has been found to result from a decreased response and/or sensitivity of protein synthesis and degradation to physiologic concentrations of amino acids.”**
- **“This is related to a defect of the leucine signal to stimulate the mTOR signaling pathway activity.”**

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- **“Choosing free leucine as a supplement over a normal protein diet creates a desynchronization between leucine signal and the rise in all amino acids.”**
- **“Indeed the free leucine is absorbed immediately whereas the other amino acids are released later after gastric emptying and proteolytic digestion in the gut.”**
- **“This nonsynchronization between the stimulation of muscle leucine-associated protein metabolism pathways and the delayed availability of amino acids as substrates can explain that protein anabolism was only stimulated for a very short period of time during the postprandial period and then could not translate into a significant muscle protein accretion.”**

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- **“Studies with a synchronized leucine signal and amino acid availability have been performed by using leucine rich proteins that are rapidly digested (whey proteins).”**
- **“With such proteins, leucine availability is increased simultaneously with the other amino acids to reach the increased muscle anabolic threshold.”**
- **“However, as observed for free leucine supplementation, when such dietary proteins were given on the long term in elderly rodents, muscle anabolism was acutely improved but muscle mass remained unchanged.”**

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- **“According to these data, it can be concluded that besides counteracting the muscle anabolic resistance, the duration during which the anabolic resistance is muzzled also plays a critical role in leading to a significant muscle protein accretion.”**
- **“A prolonged stimulation could not be achieved with fast proteins at normal dietary level (even enriched with leucine) since the concentration of amino acids as substrates declines rapidly after their intake.”**

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- **“However, by strongly increasing protein intake, such ideal situations could be nevertheless achieved.”**
- **“The ‘protein pulse feeding’ initially developed by Arnal et al. have shown that, by concentrating 80% of the total daily protein intake in one meal, protein retention was improved in elderly women subjected to such a nutritional strategy.”**
- **“Similarly, when very large amounts of amino acids (wherein leucine formed the highest percentage of the mixture), positive results have been observed.”**

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Will this large protein load pose a risk to kidney function?

- **“The above nutritional strategies discussed raised the problem that the organism has to cope with large amounts of nitrogen to eliminate.”**
- **“This point can be critical with already frail sarcopenic subjects or patients for whom the renal function will be oversolicited whereas it may already be altered.”**

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What's the solution to this problem?

Application of ELCN principles!!

35

- “In order to minimize this deleterious side effect of high protein intake, a strategy to reverse the increase in the ‘anabolic threshold’ would restore the anabolic stimulation during the postprandial period with lower intake of dietary proteins or amino acid supplementation.”
- “This requires the knowledge of the factors involved and responsible in the ‘anabolic threshold’ elevation.”

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- **“The causes can be multiple and specific for each catabolic state.”**
- **“However, most of these muscle loss situations have in common an increase of the inflammatory status.”**
- **“Regarding aging, levels of inflammatory markers, such as interleukin-6 (IL6) and C reactive protein (CRP), increase slightly, and these higher levels are correlated with disability and mortality in humans.”**

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- **“Even if the increase is moderate, higher levels of cytokines and CRP increase the risk of muscle strength loss and are correlated with lower muscle mass in healthy older persons.”**
- **“We have recently shown that the development of a low grade inflammation challenged negatively the anabolic effects of food intake on muscle protein metabolisms and that the pharmacologic prevention of this inflammatory state was able to preserve muscle mass in old rodents.”**

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“A resensitization of muscle protein synthesis to amino acids could also be achieved with other nutrients such as antioxidants.”

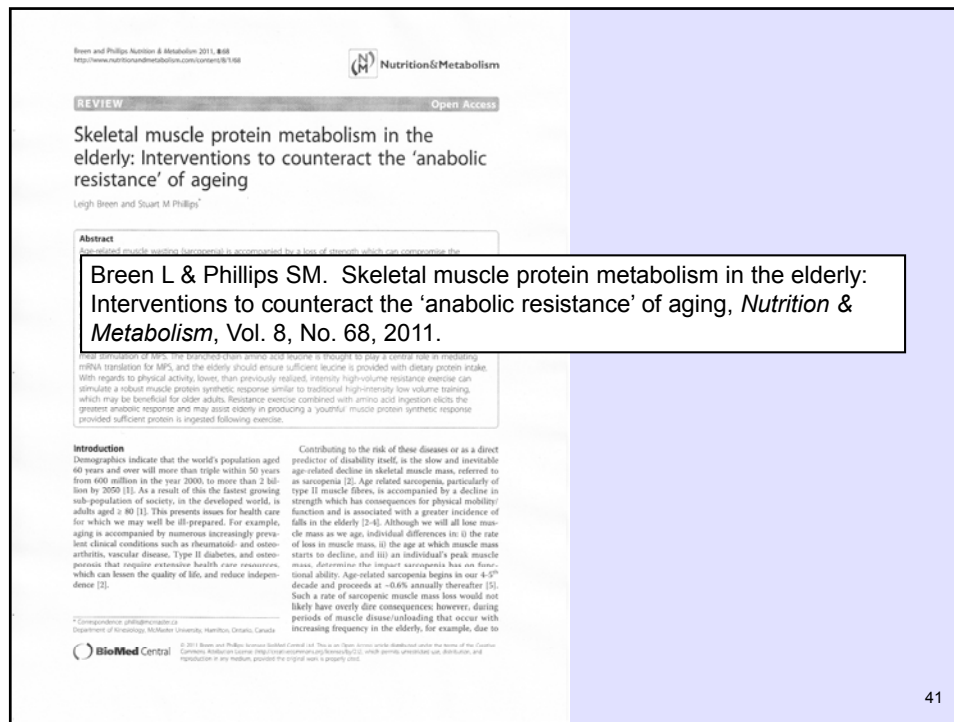
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- “Two strategies can be used (alone or in combination) to deal with this decreased ‘efficient’ postprandial period: (1) by increasing the anabolic signals and particular amino acid availability; however, it is necessary to synchronize the anabolic stimuli with the substrates in order to optimize the incorporation of amino acids into muscle proteins; (2) by increasing the efficiency of the postprandial period with strategies aiming at partially restoring (i.e., decreasing) the muscle ‘anabolic threshold’.”

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- “...aging is accompanied by numerous increasingly prevalent clinical conditions such as rheumatoid- and osteoarthritis, vascular disease, Type II diabetes, and osteoporosis that require extensive health care resources, which can lessen the quality of life, and reduce independence.”

- **“Contributing to the risk of these diseases or as a direct predictor of disability itself, is the slow and inevitable age-related decline in skeletal muscle mass, referred to as sarcopenia.”**
- **“Following such periods of disuse, even something as benign as a reduction in daily step counts, can accelerate sarcopenic muscle loss, from which it is more difficult for the elderly to require.”**

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- **“In humans, Toth et al. have shown a strong relationship exists between MPS and circulating concentrations of several markers of immune activation.”**
- **“At the mechanistic level, cytokines, in particular TNF- α , may impair MPS by blunting the phosphorylation of proteins in the mammalian target of rapamycin (mTOR) intracellular signaling pathway; shown to be critical for the regulation of mRNA translation and MPS for muscle hypertrophy.”**

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More on leucine

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- **“The mechanism facilitating the impaired dose-response of MPS to amino acids in the elderly compared with the young is still elusive. However, we and others have hypothesized the existence of a leucine ‘threshold’ that must be surpassed after protein ingestion to stimulate MPS above rest.”**

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- **“This threshold is not absolute and is graded with lower leucine stimulated responses in young persons, whereas the elderly become less sensitive and the threshold becomes higher.”**
- **“The leucine threshold hypothesis is based on a number of recent observations, the most striking of which is that leucine ingestion/infusion results in a phosphorylation of proteins critical for the mTOR pathway.”**

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- **“We postulate that young muscles are more sensitive to the anabolic actions of leucine as ~1 g of orally ingested leucine seems to be sufficient to stimulate MPS above rest.”**
- **“In contrast, our recent observations indicate that the elderly are less sensitive to the anabolic actions of leucine as ~2 g of leucine found in 20 g of whey protein was required to increase MPS rates above rest.”**

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- **“Consistent with the thesis that leucinemia is important in ‘driving’ MPS, the work of Katsanos and colleagues demonstrated that 6.7 g of essential amino acids (EAA) (equivalent to ~15 g whey), increased MPS above rest in the elderly, but only after the leucine content of EAA’s was increased from 26 to 41% (1.7 to 2.8 g).”**

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- **“In line with our hypothesis that younger muscles are more anabolically sensitive, the 26% low leucine treatment in this study was sufficient to increase MPS in the young.”**
- **“Thus, when considering protein feeding strategies that will acutely increase MPS in the elderly, a protein source with high leucine content and rapid digestion kinetics, in order to promote a transient leucinemia ‘spike’ would be an effective option.”**

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Comments on resistance exercise and anabolic resistance by Breen and Phillips

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- “Resistance exercise acutely increases muscle protein synthesis and, when practiced frequently over time, promotes muscle hypertrophy in older adults, although the anabolic response is generally blunted compared with younger adults.”
- “It has been suggested these divergent responses to resistance exercise may be due to the fact that the elderly generally lift a much lower volume of weights than the young. However, we suggest that resistance to the anabolic nature of hypertrophic exercise may be critical in mediating the muscle adaptive remodeling in the elderly.”

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Comments on inflammation fish oil by Breen and Phillips

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- **“Fish-oil-derived omega-3 fatty acids (n-3 polyunsaturated fatty acids) might be a potentially useful therapeutic agent for the treatment and prevention of sarcopenia.”**
- **“Initial studies in animals showed that supplementation with omega-3 fatty acids increased the phosphorylation of anabolic signaling proteins, whole body protein synthesis and attenuated the loss of muscle mass in burned animals.”**

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- **“In elderly humans, Smith et al. showed that 8-weeks of omega-3 fatty acid supplementation augmented hyperinsulinemic-hyperaminoacidemic induced increases in muscle protein synthesis and mTOR signaling, suggesting that omega-3 fatty acids attenuate age-related anabolic resistance.”**

55

- **“Whilst the exact mechanisms by which omega-3 fatty acids act on translational signaling and muscle protein synthesis in the elderly are not entirely clear, the anti-inflammatory properties of omega-3 fatty acids may be a critical factor, particularly in the frail elderly who display elevated levels of inflammation.”**

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- **“On the other hand, recent evidence suggests that fatty acids may have intrinsic muscle protein anabolic properties, as long-chain n-3 polyunsaturated fatty acid supplementation augments hyperinsulinemic-hyperaminoacidemic stimulated muscle protein synthesis in healthy young subjects, in whom inflammation would be expected to be relatively low.”**

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- **“Taken together, these data suggest that fatty acid supplementation alone is insufficient to promote an anabolic response (as basal muscle protein synthesis is not increased).”**
- **“Instead, additional stimuli, such as amino acids, may be required to permit the anabolic effect of fatty acids.”**

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