

The Entry Level Clinical
October 2013 Update
Hormesis:

An under appreciated
foundational tenet of Entry
Level Clinical Nutrition

Jeffrey Moss, DDS, CNS, DACBN
jeffmoss@mossnutrition.com

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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 2

With Dr. Jeff Moss

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

The New York Times

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September 9, 2009

Summer of Work Exposes Medical Students to System's Ills

BY KEVIN BAKER

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.

Summer of work exposes medical students to system's ills, *The New York Times*, September 9, 2009

The students learned not only 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 personalities on Wal-Mart's 54 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.

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

Not sure the deal was

"...a tidal wave of chronic illness..."

treatments they can afford early instead of waiting until there's a catastrophic surgery, it's pretty simple.

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=&mc=th&... 9/9/2009



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Nestlé Nutrition Workshop Series
Clinical & Performance Program, Vol. 8

Nutrition and Critical Care

Luc Cynober
Frederick A. Moore

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.”

KARGER



Entry Level Clinical Nutrition Update – Part 2 With Dr. Jeff Moss

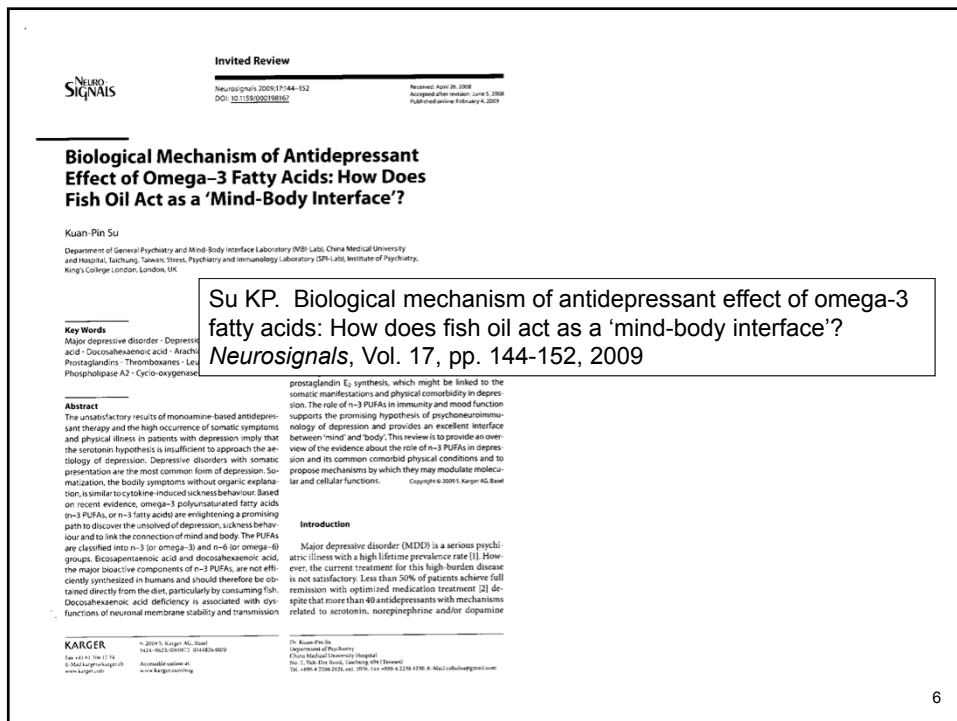
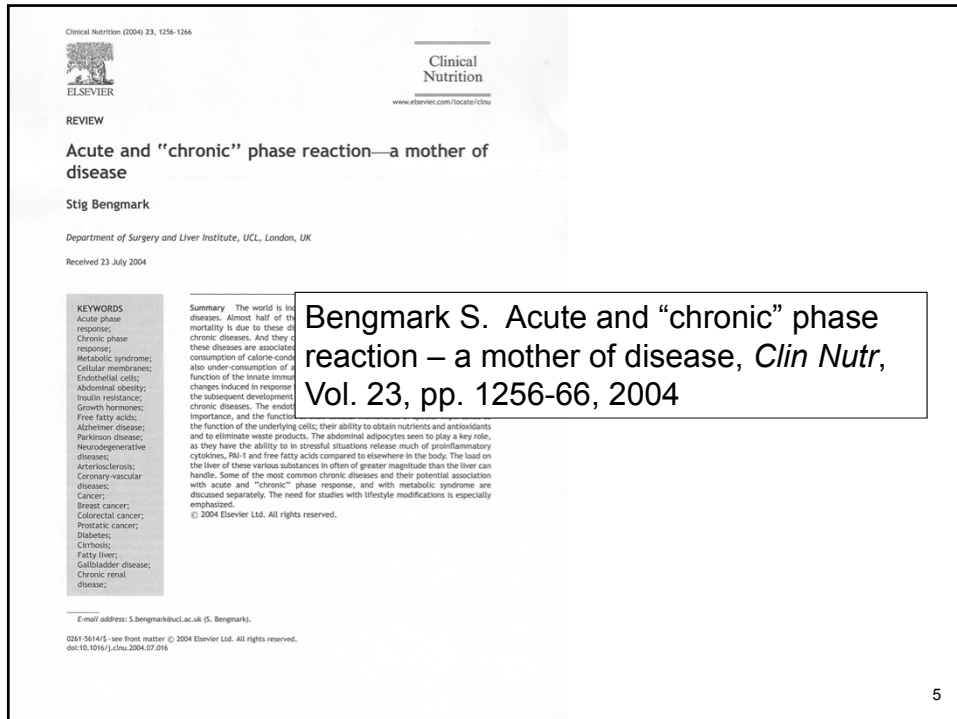


Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

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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Clinical Nutrition 31 (2012) 1002–1007

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journal homepage: <http://www.elsevier.com/locate/clnu>

Opinion paper

The evolutionary benefit of insulin resistance

Maarten R. Soeters^{a,*}, Peter B. Soeters^{b,***}

^a Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

^b Department of Surgery, Maastricht University Medical Center, Maastricht University, The Netherlands

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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, immune activation, growth and cancer, to spare glucose for different biosynthetic purposes such as the production of NADPH, nucleotides in the pentose phosphate pathway and malonate for gluconeogenesis. In these conditions, total glucose available for the biosynthetic acid cycle is actually low and energy demands are largely met by fatty acid and ketone body oxidation.

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

^{***}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 critically ill patients. In this letter, rapid glucose control hypothesizes on the evolutionary importance of insulin resistance.

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.¹ Starvation is accompanied by insulin resistance as shown by targeted inhibition of the action of insulin in oral glucose tolerance tests and clamp 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.2012.05.011

Entry Level Clinical Nutrition Update – Part 2 With Dr. Jeff Moss

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

Jeffrey Moss MD, Account | SIGN OUT

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Original Investigation | September 9, 2013
LESS IS MORE

Intensive Glucose Regulation in Hyperglycemic Acute Coronary Syndrome
Results of the Randomized BIOMARK Study to Identify the Acute Risk of a Coronary Syndrome-2 (BIOMARKS-2) Glucose Trial

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 difference in median extent of myocardial injury measured by myocardial perfusion scintigraphy was not significant (1%).

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.

KEY WORDS: Acute coronary syndrome, Cardiac biomarkers, Cardiology, Diabetes mellitus, Treatment, Endocrinology.

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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

Olivier Bouillanne^{a,b,c,*}, Emmanuel Curis^c, Brigitte Hamon-Vilcot^a, Ioannis Nicolis^c, Pascale Chretien^f, Nathalie Chauvier^a, Jean-Pierre Vincent^a, Luc Cynober^{a,d}, Christian Ausseil^{c,d}

^aService de Geriatrie 2, AP-HP Hôpital Saint-Basile, France

^bService de Geriatrie 4, AP-HP Hôpital Saint-Basile, France

^cService de Nutrition, AP-HP Hôpital Saint-Basile, France

^dLaboratoire de Biologie de la Nutrition, EA 4480, Université Paris Descartes, Paris, France

^eLaboratoire de Biomechanique (IF, Nutrition and 21, 4480), Université Paris Descartes, Faculté de Médecine, France

^fService de Nutrition, AP-HP Hôpital Saint-Basile, France

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

ABSTRACT

Background: Protein pulse feeding is a nutritional strategy that aims to improve protein intake in elderly patients with malnutrition or at-risk of malnutrition. 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: 40 elderly malnourished or at-risk patients in an inpatient rehabilitation unit. All were given a standard diet for 4 weeks. In a pulse diet (PD) group (n = 20), dietary protein was spread over the four daily meals. In a pulse diet (PD) group (n = 20), dietary protein (1.33 g/kg 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 (ASMM), and body cell mass (BCM) index, measured by 3-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 LM, ASMM, and BCM index.

Conclusions: Protein pulse feeding was significantly more efficacious than protein spread feeding in improving LM, ASMM, and BCM index.

Keywords: Protein pulse feeding, Lean mass, Appendicular muscle mass, Body cell mass.

“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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Entry Level Clinical Nutrition Update – Part 2 With Dr. Jeff Moss

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT
Acute Skeletal Muscle Wasting in Critical Illness

Zudin A. Putucheary, MRCP, Jiality Rawal, MRCS, Mark McPhail, PhD, Browne Connolly, BSc, Gaurav Ranjiv, MRCP, Paul Chan, MBBS, Nicholas S. Hopkinson, PhD, Rahul Pathak, PhD, Tracy Dew, MSc, Paul S. Saba, PhD, Cristian Velasco, PhD, John Seymour, PhD, Clifton C. Agre, MSc, Anna Saba, PhD, Maria Limb, PhD, Lindsay M. Edwards, PhD, Kenneth Smith, PhD, Antony Rowlands, PhD, Michael John Barnes, PhD, John Mathew, PhD, Stephen D. R. Harbridge, PhD, Nicholas Hart, PhD, Hugh E. Montgomery, MD

IMPORTANCE Survivors of critical illness demonstrate skeletal muscle wasting with associated functional impairment.

OBJECTIVE To perform a comprehensive prospective characterization of skeletal muscle wasting, defining the pathogenic roles of altered protein synthesis and breakdown.

DESIGN, SETTING, AND PARTICIPANTS Study three critically ill patients (95% male, mean age 60 years).

MAIN OUTCOMES AND MEASURES Muscle loss was determined through serial ultrasound measurement of the rectus femoris cross-sectional area (CSA) on days 1, 3, 7, and 10. In a subset of patients, the fiber CSA area was quantified along with the ratio of protein to DNA on days 1 and 7. Histopathological analysis was performed. In addition, muscle protein synthesis, breakdown rates, and respective signaling pathways were characterized.

RESULTS There were significant reductions in the rectus femoris CSA observed at day 10 (-17.7% [95% CI, -25.9% to -8.7%], $P < .001$). In the 28 patients assessed by all 3 measurement methods on days 1 and 7, the rectus femoris CSA decreased by 10.3% (95% CI, -17.7% to -2.9%, $P < .001$).

CONCLUSIONS Muscle protein synthesis was depressed to levels equivalent to the healthy fasted state on day 1, but increased to rates similar to the healthy fed state by day 7; however, the net balance remained catabolic. Importantly, these overall effects occurred despite the administration of enteral nutrition. Unexpectedly, higher protein delivery in the first week was associated with greater muscle wasting.

with multorgan failure compared with single organ failure. These findings may provide insights into skeletal muscle wasting in critical illness.

KEY WORDS muscle wasting, critical illness, protein synthesis, breakdown, ultrasound.

ABBREVIATIONS are listed at the end of this article.

Corresponding Author: Zudin A. Putucheary, MRCP, University College London, 74 Hursley St, Room 443, London WC1E 6EX, England (zudin.putucheary@ucl.ac.uk).

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Original article

Sarcopenia: Prevalence and prognostic significance in hospitalized patients

Salah Gariballa^{a,b,*}, Awad Alessa^a

^aInternal Medicine, Faculty of Medicine, United Arab Emirates University (UAEU), UAE

^bUniversity of Sheffield, UK

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Outcomes
Nutrition
Acute illness

SUMMARY

Background: Sarcopenia is prevalent in older populations with many causes and varying outcomes however information for use in clinical practice is still lacking.

Aims: The aim of this report is to identify the clinical determinants and prognostic significance of sarcopenia in a cohort of hospitalized acutely ill older patients.

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

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1. Introduction

An important challenge of modern medicine is to distinguish physiological changes associated with the process of ageing from an important example of this challenge is sarcopenia, a condition which is prevalent in older populations with many causes and varying outcomes.¹ It is a syndrome characterized by progressive decline in skeletal mass, decreased strength and functional status.

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

which predict outcomes not many data on hospitalized patients are available. Furthermore a valid and reproducible measurement technique of sarcopenia suitable for clinical practice is still a challenge. The aim of this report is to measure the prevalence and prognostic significance of sarcopenia in a cohort of acutely ill older patients.

* Corresponding author. Department of Internal Medicine, Faculty of Medicine and Health Sciences, United Arab Emirates University, PO Box 15666, Al-Ain, UAE. Tel.: +971 37129026; fax: +971 37972905.
E-mail address: s.gariballa@uaeu.ac.ae (S. Gariballa).

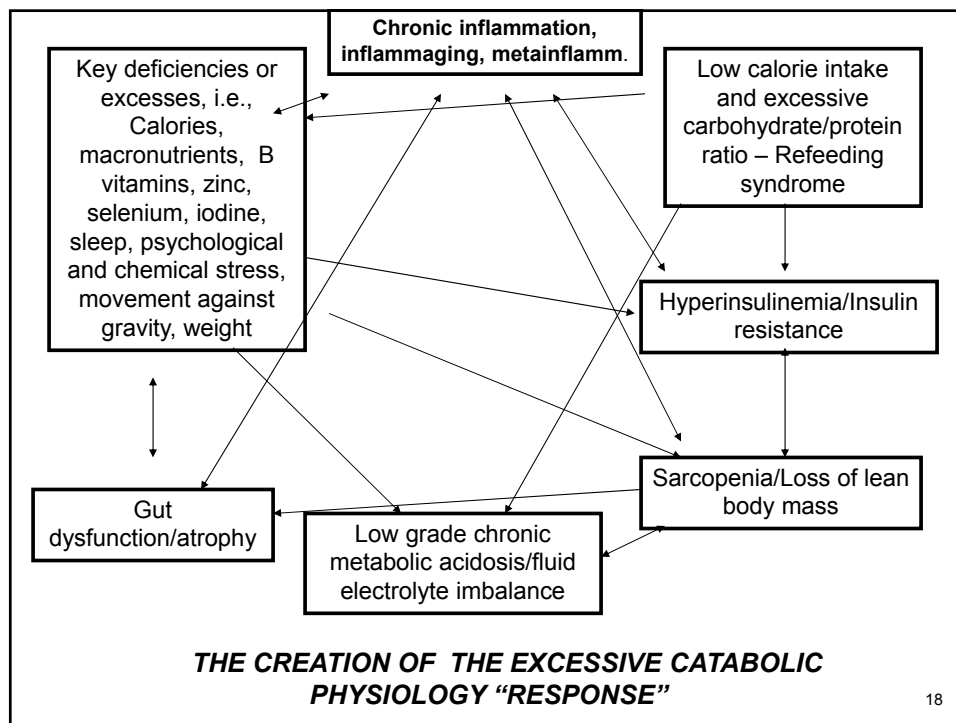
0261-5614/\$ – see front matter © 2013 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.
<http://dx.doi.org/10.1016/j.clnu.2013.01.009>

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Key metabolic imbalances seen with the acute phase response

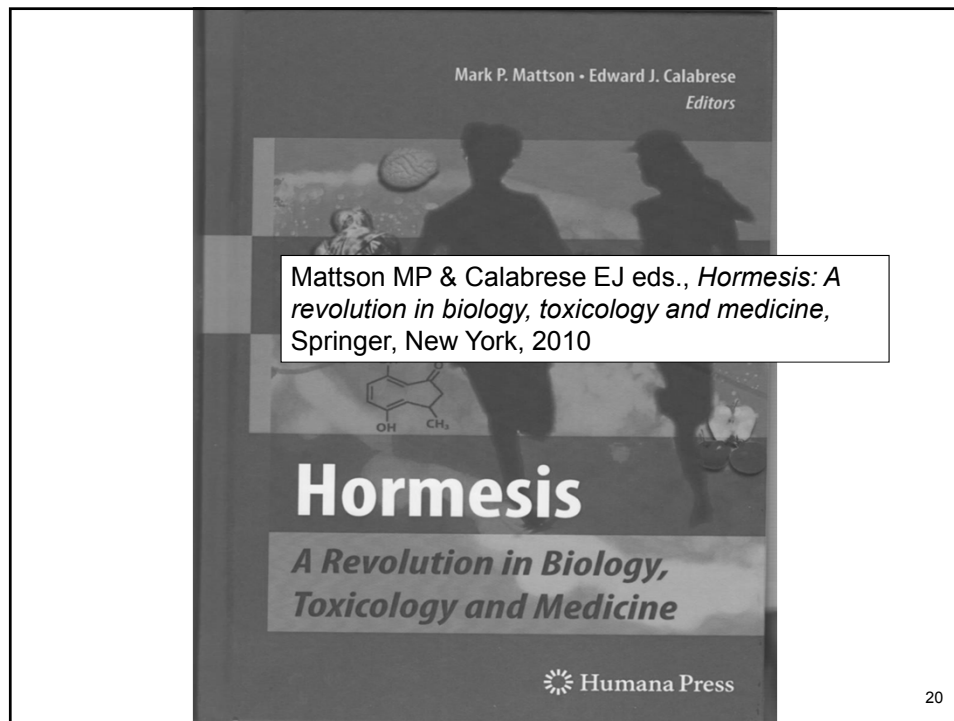
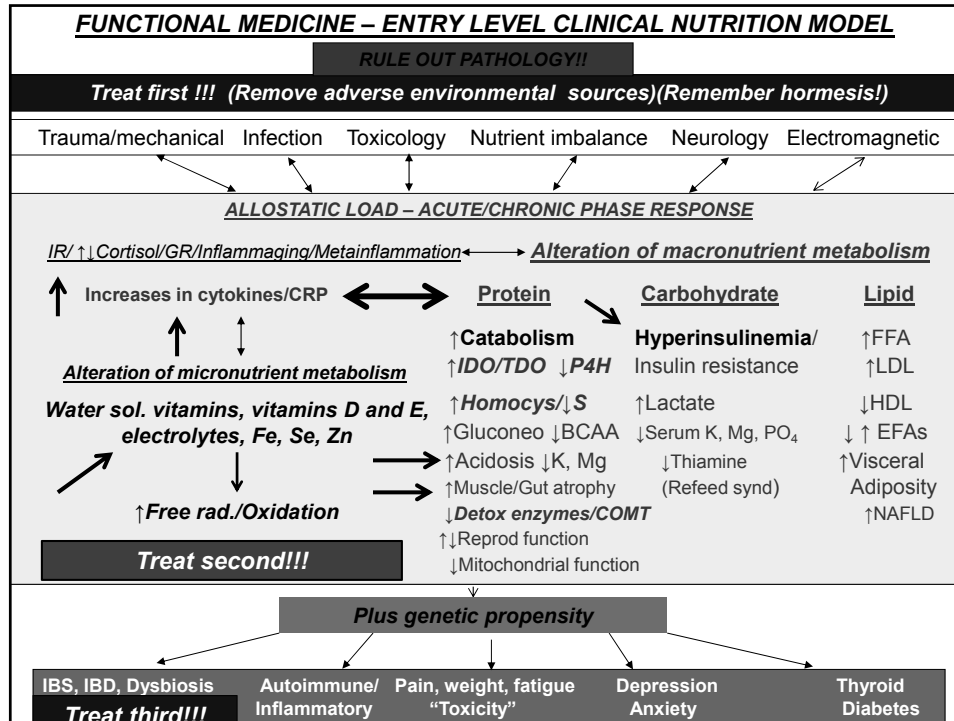
- Low grade, chronic metabolic acidosis
- Loss of lean body mass (sarcopenia) and its relation to optimal protein intake
- Gastrointestinal dysfunction/gut atrophy
- Inflamm-aging (Increased innate immunity and decreased adaptive immunity)
- Metabolically induced hyperinsulinemia/insulin resistance
- 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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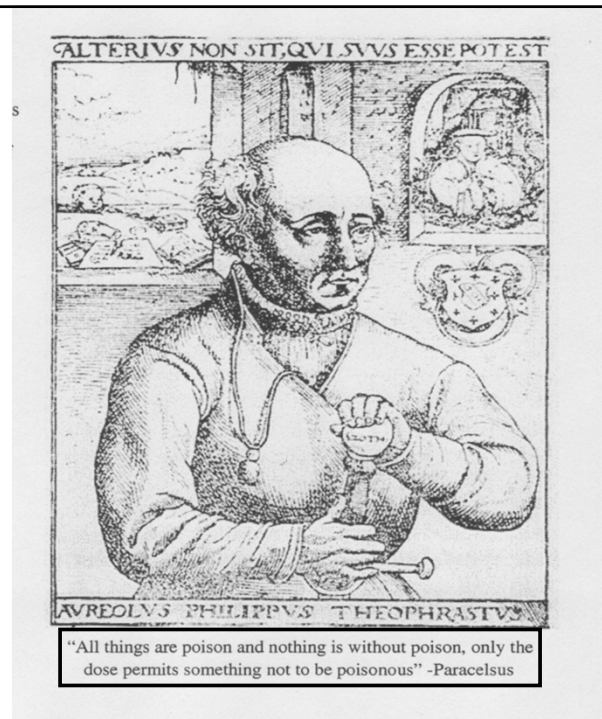
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- “The term *hormesis* is defined as ‘a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces an adaptive effect on the cell or organism.’”

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- “To survive and reproduce in harsh competitive environments, organisms and their cellular components have, through evolution, developed molecular mechanisms to respond adaptively to various hazards or ‘stressors’ that they encounter.”
- “Examples of such stressors include chemicals ingested in food or water (metals, phytochemicals, etc.), increased energy expenditure (running, fighting, cognitive challenges, etc.), and reduced energy availability (food scarcity), among others.”

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- “In most cases, the response of the cell or organism to the stressor exhibits a biphasic dose response, with beneficial/adaptive responses at low doses (improved function, increased resistance to damage and disease) and adverse/destructive effects (dysfunction, molecular damage, or even death) at high doses.”
- “The prevalence of the biphasic (hormetic) dose response characteristic of biological systems merits consideration of hormesis as a fundamental principle of biology.”

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- “Well-known categories of agents that exert biphasic effects on human health are minerals and vitamins.”
- “Selenium, a trace element obtained from the diet, is essential for health because it is necessary for the proper function of at least 30 selenoproteins. However, high levels of selenium are toxic and can even cause death.”

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- “Vitamin D is critical for the growth and health of bones and for wound healing, among other processes, but excessive intake of vitamin D can cause hypercalcemia and associated pathologies in the kidneys and other organs.”
- “Vitamin A is necessary for proper development of multiple organs and for maintenance of the health of the eye and other tissues in the adult; however, excessive intake of vitamin A can cause liver damage, may promote osteoporosis, and may also adversely affect the cardiovascular system.”
- “Iron is essential for red blood cell health and also serves important regulatory functions in other cell types, but excessive iron intake can cause oxidative damage to tissues.”

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What are the dangers of Dihydrogen Monoxide?

Most of these deaths are caused by accidental inhalation of DHMO, but the dangers of dihydrogen monoxide do not end there.

Prolonged exposure to its solid form causes severe tissue damage. Symptoms of DHMO ingestion can include excessive sweating and urination, and possibly a bloated feeling, nausea, vomiting and body electrolyte imbalance. For those who have become dependent, DHMO withdrawal means certain death.

From: www.dhmo.org

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Antioxidants prevent health-promoting effects of physical exercise in humans

Michael Ristow^{1,2}, Kim Larus³, Andreas Oberbach^{2,3}, Nora Klötting⁴, Marc Birringer⁴, Michael Kiehnopf⁵, Michael Stumvoll¹, C. Ronald Kahn⁶, and Matthias Blüher^{2,4}

¹Department of Human Nutrition, Institute of Nutrition, University of Jena, Jena D-07743, Germany; ²German Institute of Human Nutrition, Potsdam-Anhalt D-14558, Germany; ³Department of Medicine, University of Leipzig, Leipzig D-04103, Germany; ⁴Institute of Clinical Chemistry and Laboratory Medicine, University of Jena, Jena D-07743, Germany; ⁵Research Division, Joslin Diabetes Center, Harvard Medical School, Boston, MA 02215

Contributed by C. Ronald Kahn, March 31, 2009 (sent for review March 14, 2009)

Exercise promotes longevity and ameliorates type 2 diabetes mellitus and insulin resistance. However, exercise also increases mitochondrial formation of presumably harmful reactive oxygen species (ROS). Antioxidants are widely used as supplements but whether they affect the health-promoting effects of exercise is unknown. We evaluated the effects of a combination of vitamin C (1900 mg/day) and vitamin E (400 IU/day) on insulin sensitivity as measured by glucose infusion rates (GIR) during a hyperinsulinemic, euglycemic clamp in previously untrained ($n = 19$) and pre-trained ($n = 20$) healthy young men. Before and after a 4 week

intervention of bicycling for 5 h were obtained. Influences of parameters of the absence of 0.001 and not by increased of insulin or proliferator-activated

0.001 for all). Molecular mediators of endogenous ROS defense (superoxide dismutase 1 and 2, glutathione peroxidase) were also induced by exercise, and this effect was blocked by antioxidant supplementation. Consistent with the concept of mitochondrial, exercise-induced oxidative stress ameliorates insulin resistance and causes an adaptive response promoting endogenous antioxidant defense capacity. Supplementation with antioxidants may preclude these health-promoting effects of exercise in humans.

aging | hormones | insulin resistance | oxidative stress | reactive oxygen species

Type 2 diabetes mellitus is increasing worldwide at epidemic rates and is associated with both microvascular and macrovascular disease. A common perspective is that insulin resistance is the primary defect in the pathogenesis of type 2 diabetes. The health-promoting effects of physical exercise on insulin resistance involve multiple mechanisms, including enhanced expression of glucose transporters and translocation of glucose transporters to the plasma membrane independent of insulin (10). Exercise, as well as weight loss, has been linked to activation of mitochondrial metabolism, and reduced mitochondrial metabolism has been functionally connected with type 2 diabetes (11). Mitochondria, however, are also the main source of reactive oxygen species (ROS), which are inevitable by-products of oxidative glucose metabolism. Mitochondria are also known to generate free radicals, especially during contraction and physical exercise (12). It has been suggested that ROS may mediate some health-promoting effects, at least in nonprimate model systems (13–17). We here evaluated the possibility that ROS are required for the insulin-sensitizing capabilities of physical exercise in healthy humans and that commonly used antioxidants, such as vitamin

observed between untrained and pre-trained groups. Not surprisingly, pre-trained individuals had a significantly higher fat free mass ($P = 0.03$) and $\dot{V}O_2$ maximum ($P < 0.001$). Half of the previously untrained and previously trained groups were randomly assigned to either antioxidant supplementation as described in Methods or to no supplementation (creating 4 groups of 10 each) (supporting information S1 Fig. S1). All subjects underwent a 4 week exercise training program irrespective of antioxidant supplementation and previous training status. One untrained individual withdrew during the study for personal reasons unrelated to the experimental protocol.

Induction of Oxidative Stress by Short-Term Exercise. It is well-established that physical exercise increases ROS formation in

“Twenty of the 40 subjects enrolled were previously untrained, defined as performing less than 2 hours of exercise (including daily life activities) per week before the study was initiated. The remaining 20 subjects were considered pre-trained, i.e., performed more than 6 hours of exercise per week.”

www.pnas.org/cgi/doi/10.1073/pnas.0803081106

PNAS | May 26, 2009 | vol. 106 | no. 21 | 8665–8670

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- “All 40 subjects were subjected to supervised physical training, which consisted of training sessions on 5 consecutive days of the week for 4 weeks, i.e., 20 sessions in total. Each session included 20 min of biking or running, 45 min of circuit training, and 20 min periods for warming up and cooling down.”
- “Participants in the antioxidant treatment groups ($n = 20$ each, out of which $n = 10$ were untrained and $n = 10$ were pretrained) received 500 mg vitamin C (ascorbic acid, Jenapharm) twice a day and 400 IU vitamin E (RRR-/D- α -tocopherol, Jenapharm) once a day orally.”
- “Physical exercise exerts numerous favorable effects on general health and specifically has been shown to improve glucose metabolism in the insulin-resistant state.”
- “These beneficial effects of physical exercise in insulin resistance involve multiple mechanisms, including enhanced expression of glucose transporters and translocation of glucose transporters to the plasma membrane independent of insulin.”

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- “Exercise, as well as weight loss, has been linked to activation of mitochondrial metabolism, and reduced mitochondrial metabolism has been functionally connected with type 2 diabetes.”
- “Mitochondria, however, are also the main source of reactive oxygen species.”
- “Muscle is also shown to generate free radicals, especially during contraction and physical exercise. It has been suggested that ROS may mediate some health-promoting effects, at least in nonprimate model systems.”
- “We here evaluated the possibility that ROS are required for the insulin-sensitizing capabilities of physical exercise in healthy humans and that commonly used antioxidants, such as vitamin C and E, may abrogate the health-promoting effects of both physical exercise and oxidative stress in humans.”

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Did exercise lead to increased oxidative stress?

- **“To replicate the ROS-inducing capacity of exercise in our specific experimental set-up, we subjected previously untrained individuals to 3 days of exercise with muscle biopsy before and after this short-term intervention.”**
- **“We measured concentrations of thiobarbituric acid-reactive substances (TBARS), a well-established marker of overall oxidative stress reflecting oxidized lipids and thus ROS formation in mammals, within skeletal muscle of these previously untrained individuals in the presence of absence of antioxidant treatment.”**
- **“As expected, we observed a more than 2-fold increase in oxidative stress, as reflected by TBARS levels, following a physical exercise in the absence of antioxidants.”**

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Did the antioxidants reduce TBARS levels?

- **“By contrast, those individuals taking antioxidant supplements showed no significant increase in muscle TBARS levels after exercise resulting in significantly reduced TBARS formation after 3 days of exercise in comparison to untreated individuals.”**

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What about insulin metabolism?

- “As expected, nonsupplemented individuals showed a significant increase in glucose infusion rate, i.e., increased insulin sensitivity after 4 weeks of exercise irrespective of previous training status, confirming previous findings that physical exercise induces an increase in insulin sensitivity.”
- “By contrast, neither previously untrained individuals and pretrained individuals who received antioxidants exhibited significant changes in glucose infusion rates following exercise.”
- “Thus, physical exercise induced an increase in insulin sensitivity only in the absence of antioxidants.”
- “The same impaired effect of exercise on glucose infusion rates seen in the antioxidant-treated group was also apparent in the previously untrained individuals when the supplement-treated individuals were compared to nonsupplemented individuals.”

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“Finally, analysis of all 39 individuals, irrespective of training status, demonstrates a highly significant effect of antioxidant supplementation on the blockage of exercise-induced improvement in glucose infusion rates.”

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What about adiponectin?

- **“Plasma concentrations of the adipocyte-derived secretory protein adiponectin have been shown to be positively correlated with insulin sensitivity in humans and inversely correlated with type 2 diabetes risk.”**
- **“We observe an increase in circulating adiponectin levels following physical exercise in both previously untrained individuals and pretrained individuals.”**
- **“In contrast, previously untrained individuals and pretrained individuals who received antioxidants did not exhibit any significant change in adiponectin levels following exercise when compared to the preintervention state, indicating that the exercise-induced increase in adiponectin levels is blocked by antioxidant supplementation.”**

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What about adiponectin?

- **“Again, as observed for glucose infusion rates, there was a strong effect of antioxidant supplementation on postintervention adiponectin levels for the entire sample irrespective of training status.”**

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What about plasma insulin?

- “Lastly we compared fasting plasma insulin in individuals receiving antioxidants to those receiving no supplementation.”
- “We observed a significant decrease in fasting plasma insulin levels following the exercise intervention in previously untrained and pretrained individuals in the absence of antioxidants, consistent with improved insulin sensitivity.”
- ***“Once again, antioxidant supplementation completely abrogated this effect of exercise.”***

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Why does antioxidant induced ROS improve insulin sensitivity?

- “Based on the evidence derived from the current study, we here propose an essential role for exercise-induced ROS formation in promoting insulin sensitivity in humans. “
- “This induction appears to involve the ROS-dependent transcriptional coactivators PGC1 α and PGC1 β , and the transcription factor PPAR γ and their targets *SOD1*, *SOD2*, and *GPx1*, and, to a reduced extent, *CAT*.”
- ***“Most importantly, these changes in gene expression and the increase in insulin sensitivity following physical exercise are almost completely abrogated by daily ingestion of the commonly used antioxidants vitamin C and vitamin E.”***

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“...oxidative stress can be instrumental in preventing type 2-diabetes.”

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What about all the studies noting that ROS increases insulin resistance?

- “Nevertheless, the published evidence is ambiguous with a number of studies suggesting that exposure to ROS may promote insulin resistance whereas others find the opposite.”
- “In the present study, we find that increased ROS formation efficiently counteracts insulin resistance. Previously published findings in nonprimate models also support this interpretation.”
- “One possible explanation for the apparent conflict between the different studies may be that those studies suggesting an inverse relation between ROS and insulin sensitivity were obtained in models of *continuous* exposure to increased levels of ROS, whereas our current findings and those of other studies may reflect increases in ROS during limited periods of physical exercise only.”

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Conclusions by Ristow et al.

- **“Repeated exposure to sublethal stress has been proposed to culminate in enhanced stress resistance and ultimately increased survival rates due to a process named hormesis.”**
- **“By analogy, for sublethal ROS-dependent processes emanating from the mitochondria, the term ‘mitohormesis’ was recently proposed on a hypothetical basis.”**

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What doesn't kill you makes you stronger!!

- **“In humans, this mitohormetic induction of glucose infusion rates is paralleled by, and may in part be due to, ROS-related induction of PPAR γ , PGC1 α , and PGC1 β , which then secondarily increase expression of ROS-detoxifying enzymes, including *SOD1*, *SOD2*, and *GPx1*.”**
- **“In this way exercise-induced ROS itself could increase endogenous ROS defense capacity in skeletal muscle, producing a mitohormetic state as observed in nematodes and rats.”**

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Entry Level Clinical Nutrition Update – Part 2

With Dr. Jeff Moss



Medical Hypotheses (2006) 66, 832–843

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Sublethal mitochondrial stress with an attendant stoichiometric augmentation of reactive oxygen species may precipitate many of the beneficial alterations in cellular physiology produced by caloric restriction, intermittent fasting, exercise and dietary phytonutrients: “Mitohormesis” for health and vitality

Patrick C. Tapia ^{*,1}

University of Alabama School of Medicine, Medical Student Center, 156 B-100

Tapia PC. Sublethal mitochondrial stress with an attendant stoichiometric augmentation of reactive oxygen species may precipitate many of the beneficial alterations of cellular physiology produced by caloric restriction, intermittent fasting, exercise and dietary phytonutrients: “Mitohormesis” for health and vitality, *Med Hypotheses*, Vol. 66, pp. 832-843, 2006.

triggering elements for a sequence of events that result in benefits ranging from the transiently cytoprotective to organismal-level longevity. With the recent appreciation that reactive oxygen species and reactive nitrogen species function as signaling elements in a interconnected matrix of signal transduction, the entire basis of many widely accepted theories of aging that predominated in the past may need to be reconsidered to facilitate the formulation of an new perspective more correctly informed by the most contemporaneous experimental findings. This perspective, the mitohormesis theory, can be used in many disparate domains of inquiry to potentially explain previous findings, as

* Corresponding author. Tel.: +1 256 259 4218.
E-mail address: ptapia@uab.edu.
¹ Presently in NIH-funded “UAB Summer Research Training Program”.

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Mitohormesis

- **“What the mitohormesis perspective emphasizes is that the mitochondria may generate beneficial signals, among which reactive oxygen species may be found.”**
- **“Furthermore, mitohormesis theory proposes that in cells with reasonably intact physiologies, the specifically oxidative influence on cellular redox balance emanating from mitochondria can be beneficial.”**

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- ***“Furthermore, the mitohormesis perspective emphasizes the potential harm that can be associated with the unfettered reliance upon exogenous antioxidants, as such agents may serve to scramble delicate signal transductive networks in a manner that at the very least may be ineffective and at the very worst may compromise health and lifespan.”***

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Review

Side Effects of Long-Term Glutamine Supplementation

Milan Holecek, MD, PhD, DSc

Abstract

Some people consume chronically glutamine (GLN) in high quantities (~40 g/d), although a number of biochemical pathways and cellular functions may be negatively affected. The following side effects of GLN supplementation are discussed: (1) *alterations in amino acid transport*—as GLN shares the transporters with other amino acids, enhanced GLN intake may impair amino acid distribution among tissues and their absorption in the gut and kidneys; (2) *alterations in GLN metabolism*—GLN supplementation may impair synthesis of endogenous GLN and enhance glutamate and ammonia production; (3) *alterations in ammonia transport*—GLN supplementation may impair ammonia detoxification and negatively affect the role of GLN as the carrier of ammonia among tissues; (4) *abnormalities in aminoacidemia*—increased plasma levels of GLN, glutamate, citrulline, ornithine, arginine, and histidine and decreased levels of valine, leucine, isoleucine, glycine, threonine, serine, and proline are reported; (5) *alterations in immune system*—as GLN has immunomodulating properties, the effect of chronic GLN consumption on the immune system needs to be assessed; (6) *effect on tumor growth*—it should be elucidated whether chronic intake of GLN increases the risk of cancer; (7) *Effect of the withdrawal of GLN supplementation*—due to the adaptive response of the organism to enhanced GLN consumption, the withdrawal of GLN may enhance the risk of health problems resulting from GLN deficiency. It is concluded that enhanced intake of GLN has substantial side effects, and long-term studies should be

Holecek M. Side effects of long-term glutamine supplementation, *JPEN*, Vol. 37, No. 5, pp. 607-616, September 2013

Introduction

Glutamine (GLN) is one of the most abundant amino acids both in the body fluids and in proteins. Most of GLN is produced in skeletal muscle and metabolized in the intestine, liver, and kidney. GLN is known as important energy fuel for rapidly growing cells (especially immune cells, enterocytes, and tumor cells), as a precursor for the synthesis of glucose, proteins, and nucleic acids, and it plays a signaling role in many processes, including activation of amino acid-sensing and

Many healthy people believe that enhanced intake of GLN has no health risk and has beneficial effects, and they consume chronically GLN 1–3 times daily. This is frequent not only among athletes and bodybuilders but also in people who believe that the regular intake of GLN improves memory and immune system. GLN supplementation doses range from 2–40 g/d (high-dose GLN supplementation). This represents 3%–60% of the recommended intake of amino nitrogen. No data in literature explain how long these people have consumed enhanced amounts of GLN. It may often be a couple of years. Annual industrial pro-

“It is concluded that a short-term intake of enhanced amounts of glutamine to compensate for glutamine deficiency is safe despite marked alterations in aminoacidemia in the blood and amino acid distribution among tissues.”

been demonstrated. GLN provision has beneficial effects in intensive care patients, patients with human immunodeficiency virus (HIV), patients with muscle-wasting disorders, cancer patients undergoing chemotherapy, and patients with inflammatory bowel diseases.^{2,3} Reduction of plasma GLN concentration and positive effects of GLN supplementation have been observed also in prolonged strenuous exercise.⁴

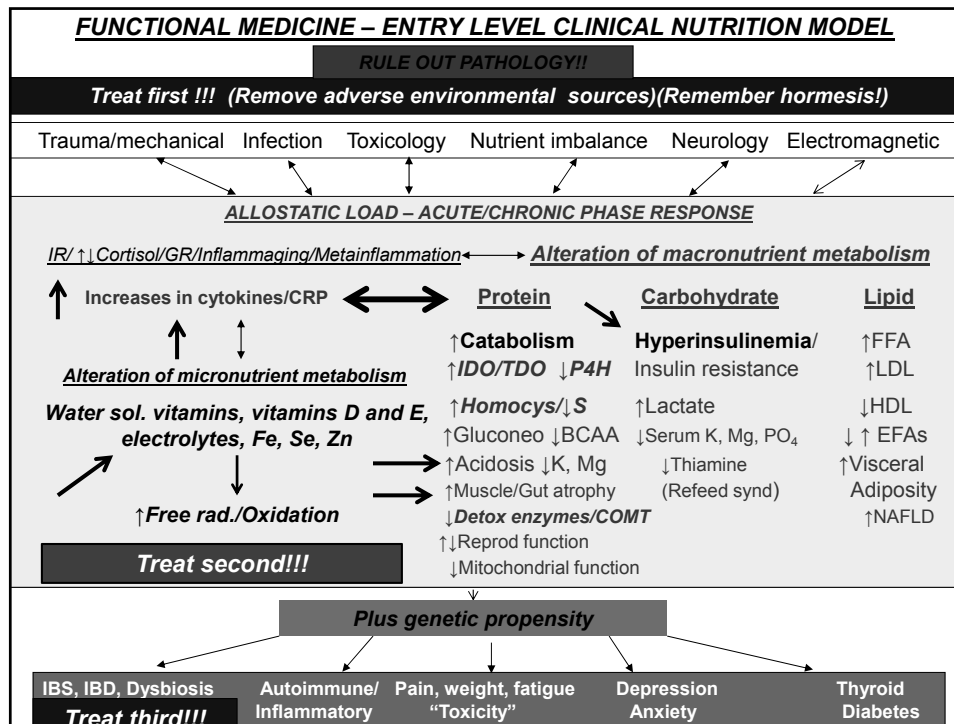
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Corresponding Author:
Milan Holecek, MD, PhD, DSc, Professor of Physiology, Department of Physiology, Charles University in Prague, Faculty of Medicine in Hradec Králové, Selská 870, 500 38 Hradec Králové, Czech Republic.
Email: holecek@lfdk.cz

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Entry Level Clinical Nutrition Update – Part 2
With Dr. Jeff Moss



“All things are poison and
nothing is without poison, only
the dose permits something
not to be poisonous”

Paracelsus

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Thank you!!

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