

Entry Level Clinical Nutrition Part XIV

Inflammation: Metaflammation

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***Quality of life issues are the
major concerns more than
ever now.***

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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

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 ideas less frequent.

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 march patients with prescriptions on Wal-Mart's \$4 list. And they saw firsthand what Mr. Olguard 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. Olguard said.

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

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 248.

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 enhancements, designed to lure students back to their home states to practice in areas with a shortage of primary care doctors.

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 time to lose.

http://www.nytimes.com/2009/09/09/health/policy/09medschool.html?_r=1&sh=4&sum=4&... 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



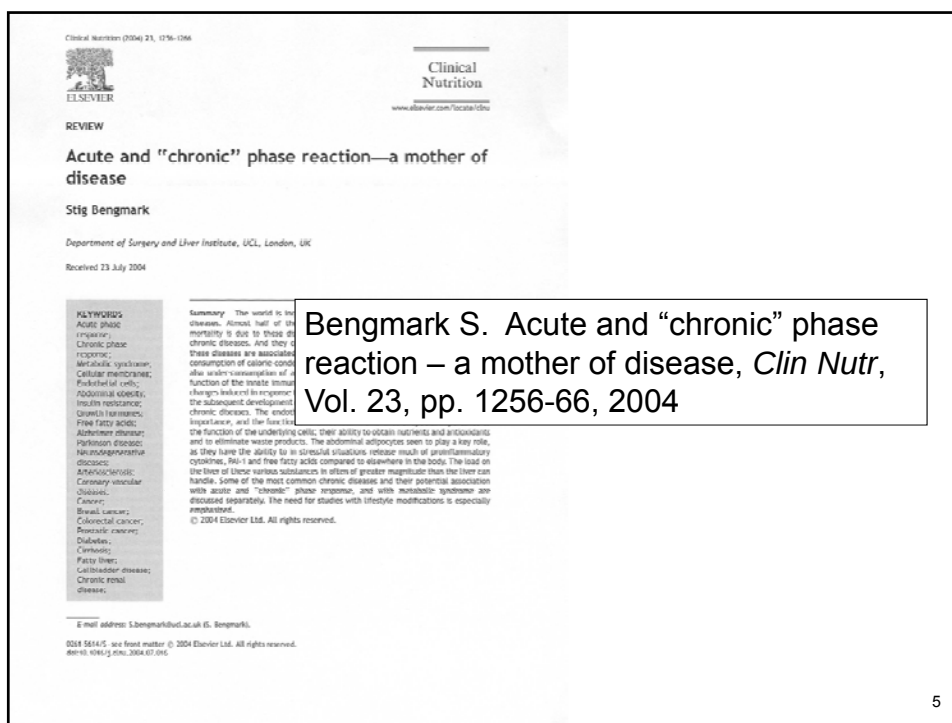
KARGER

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

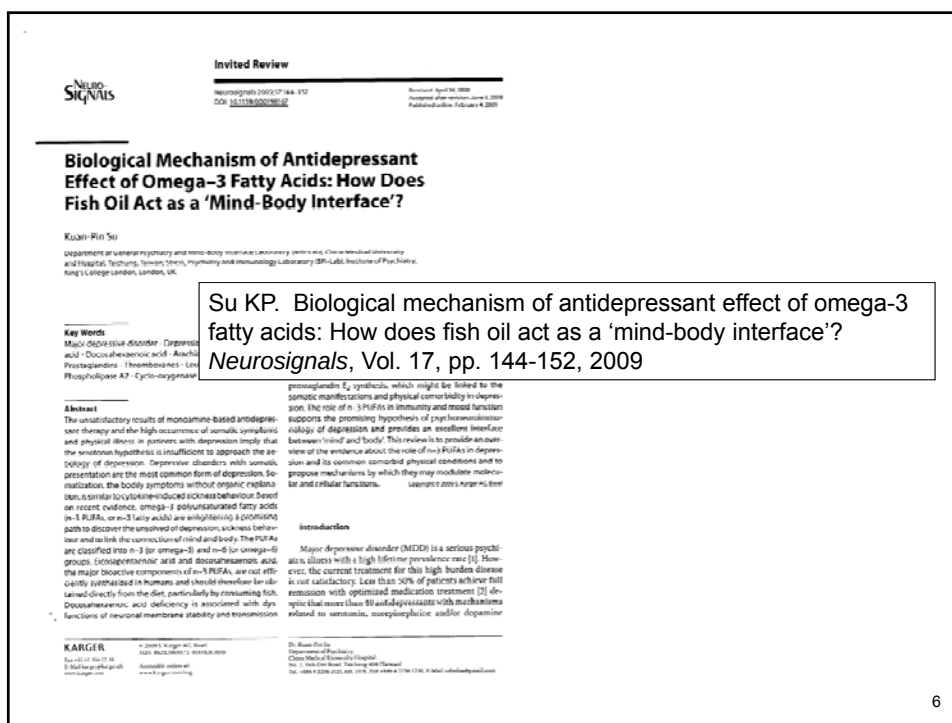
An understanding of the nature of stress is fundamental to the rational design of nutrient mixtures to feed patients whose homeostasis has been altered by one or more stressors.

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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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 ^c
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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Key metabolic imbalances seen with the acute phase response

- Metabolic acidosis
- Loss of lean body mass (sarcopenia)
- Insulin resistance
- Inflamm-aging (Increased innate immunity and decreased adaptive immunity)
- Suboptimal caloric intake and carbohydrate:protein ratio (Refeeding syndrome)
- Gastrointestinal dysfunction/gut atrophy
- Deficiencies of key micronutrients such as zinc, selenium, and vitamin D

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Underlying hypotheses of Entry Level Clinical Nutrition:

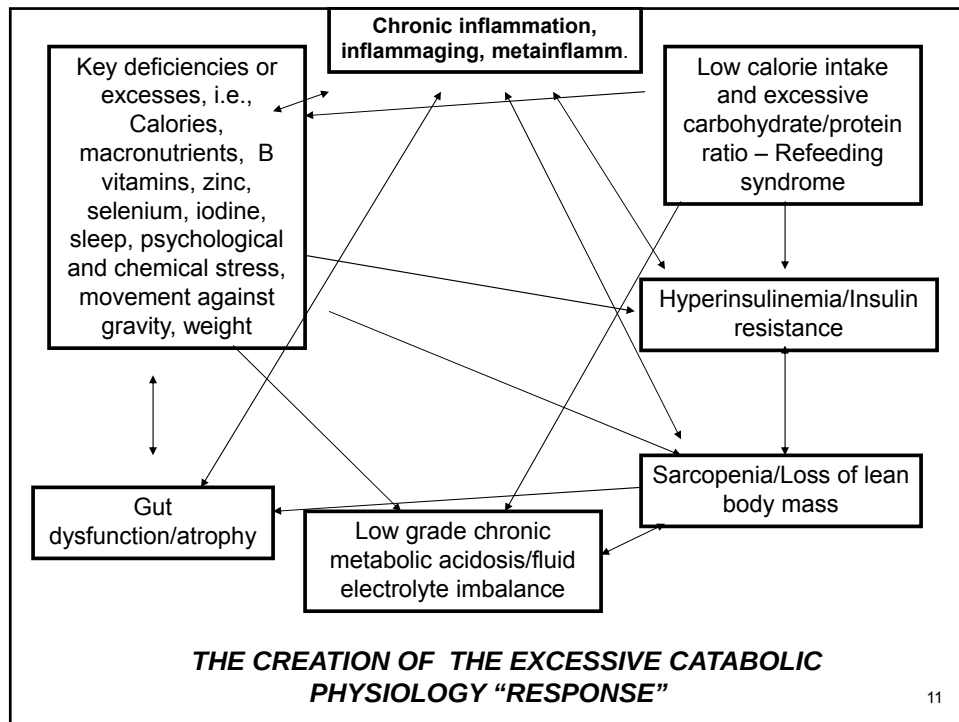
- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

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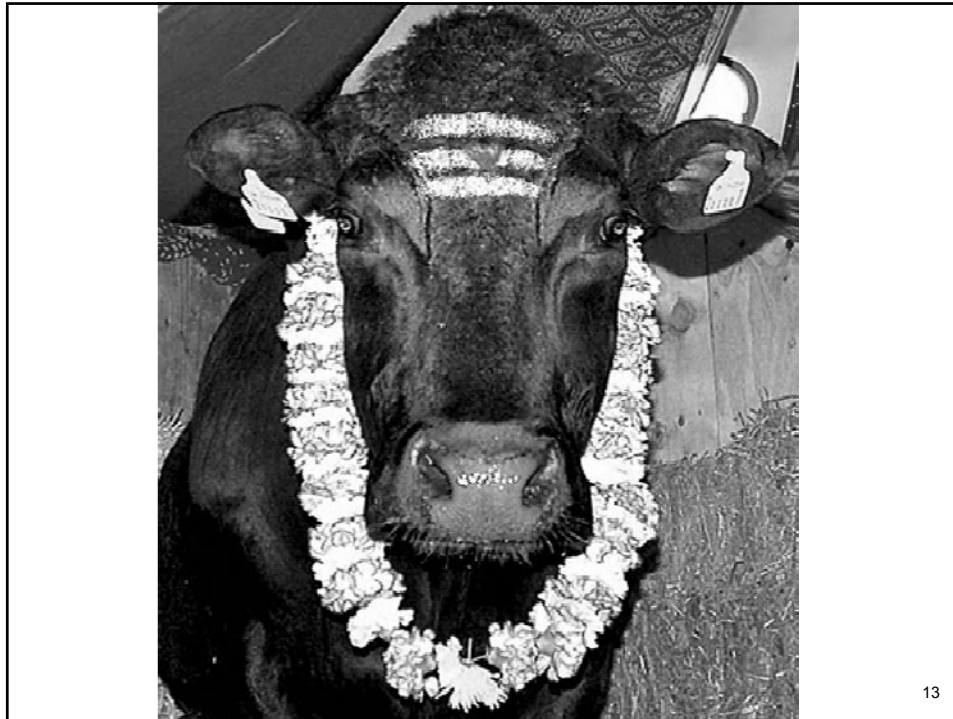
Entry Level Clinical Nutrition:

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

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Inflammation and its
relationship to chronic illness:
Why it matters when
considering vitamin/mineral
supplementation



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VIEWPOINT

Reversals of Established Medical Practices Evidence to Abandon Ship

Vinay Prasad, MD

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John P. A. Ioannidis, MD, DSc

IDEALLY, GOOD MEDICAL PRACTICES ARE REPLACED BY BETTER ONES, based on robust comparative trials in which new interventions outperform older ones and establish

themselves as the new standard of care. But, rarely, some investigators find the courage to test established "truths" with large, rigorous randomized trials. When this happens, empirical evidence suggests that "medical reversals" may be quite common. In an evaluation of 15 trials that were published in a major clinical journal in 2009 and that tested an established clinical practice, 16 (40%) reported results consistent with current beneficial practice, 16 (40%) reported evidence that contradicted current practice and constituted a reversal, and another 3 (20%) were in-

valid. For example, percutaneous coronary intervention performed for stable coronary artery disease and hormone therapy prescribed for postmenopausal women cost billions of dollars and supported the existence of entire specialties for many years. Stable coronary artery disease accounted for 87% of all deaths in the United States at the time of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Strategies (COURAGE) trial.¹ Large, well-designed randomized trials that tested whether these practices improved major patient outcomes revealed that patients were not being helped. Defenders of these therapies argued that the trials were flawed, but the results were consistent across multiple studies.

The mere issuing of a standard of care generates interest because many standards of care are never tested. In another evaluation of trials published in 3 major general medical journals or high-impact, focus specialty journals,² of the 39 randomized controlled trials published in 1990-2007 that found a significant benefit of a clinical intervention, 9 (23%) found effects stronger than those found in subsequent studies and 19 (49%) found results replicated in subsequent studies, but 11 (28%) remained largely unchallenged, with no large trial conducted on the same question.

Many standard reversals involve controversies for which the

appearance probably would not harm patients and might help salvage detailed health budgets. However, it is unlikely that specialists would support trials testing practices that constitute their main source of income. Instead, the research community performs studies of modest incremental value without even knowing whether the basic standards of care are appropriate.

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JAMA, January 4, 2012 • 307(1):37-38 • 37

Prasad V et al. Reversals of established medical practices: Evidence to abandon ship, JAMA, Vol. 307, No. 1, pp. 37-38, January 4, 2012.

"How many established standards of medical care are wrong? It is not known. Medical practice has evolved out of centuries of theorizing, personal experiences, bits of evidence, expert consensus, and diverse conflicts and biases. Rigorous questioning of long-established practices is difficult."

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- “Rarely, some investigators find the courage to test established ‘truths’ with large, rigorous randomized trials.”
- “When this happens, empirical evidence suggests that ‘medical reversals’ may be quite common.”
- “In an evaluation of 35 trials that were published in a major clinical journal in 2009 and that tested an established clinical practice, 16 (46%) reported results consistent with current beneficial practice, 16 (46%) reported evidence that contradicted current practice and constituted reversal, and another 3 (9%) were inconclusive.”

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What reasonably priced
supplement can be
recommended to every patient
that has a reasonable chance of
maintaining or improving quality
of life either now or in the future
with minimal or no diagnosis?

(The “insurance policy” supplement)

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Is it the standard multiple vitamin/mineral supplement?

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Forum

Vitamin/mineral supplements: of questionable benefit for the general population

Donald B. McCormick

In the United States today, there is a multibillion dollar industry in dietary supplements with at least a third sold as vitamin/mineral pills and drinks. Though everyone requires small amounts of these essential micronutrients, and supplements are of benefit to some within the population, the considerable majority of people can fulfill their needs with the intake of healthy diets of mixed foods. In addition, the fortification of some processed foods adds to the amount of essential nutrients, especially those for which there is deemed to be a need in special segments of our population. In spite of this safe and adequate level of intake, there are many who have been led to believe that the frequent ingestion of supplements will be helpful in their efforts to maintain optimal health, live longer, and even prevent or cure non-deficiency diseases. It is the intent of this article to unravel the causes and misconceptions behind this practice and to emphasize that most of the money spent on unnecessary supplementation could be better used for other purposes.

NATURE, OCCUR

There are 13 vitamins that are essential to are therefore defined by us eat. The dis

tion, and nutritional requirements for these micronutrients were detailed during the past century. Understanding at the molecular level has revealed that most vitamins and trace minerals function after metabolic conversion to cofactors within enzyme systems that

tain growth, health, and normal reproductive function, but avoid such excesses as may be deleterious. Most of the peer-reviewed literature on this subject has been summarized in volumes that collate information within periodically updated chapters that are especially appropriate for

McCormick DB. Vitamin/mineral supplements: of questionable benefit for the general population, *Nutr Rev*, Vol. 68, No. 4, pp. 207-213, April 2010

“The continued and important advice for the public is to get their essential micronutrients from foods when possible. The use of supplements should be sparing and best decided in consultation with professionals. The public may additionally benefit from a more careful examination of the excess nutrients consumed in fortified foods, cereals, and vitamin ‘enhanced’ products.”

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- “By categorizing plasma micronutrient results into 6 groups according to increasing CRP concentrations, the current study showed the considerable effect that systemic inflammatory response (SIR) has on their concentrations.”
- “The effect of SIR in lowering plasma selenium and vitamins A, B-6, C and D was apparent with only slightly elevated CRP concentrations.”

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- “In addition, the magnitude of the effect on plasma concentrations of selenium, zinc, and vitamins A, B-6, C, and D was often substantial, particularly with high CRP concentrations.” (>20 mg/L)
- “This makes the interpretation of these micronutrients increasingly difficult as CRP concentrations rise.”
- “The magnitude of the effect was also highly variable, invalidating the possibility of refining interpretation (or identification of deficiency) based on CRP concentrations.”

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Why does SIR have such an impact on plasma micronutrient status?

- “It is likely that the effects of SIR on plasma micronutrient concentrations are, at least in part, mediated by proinflammatory cytokines that suppress hepatic production of many carrier proteins, increase capillary permeability, and promote sequestration of some micronutrients into the liver and other organs.”

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Recommendations

- “We recommend that clinical interpretation of plasma micronutrients only be made when the CRP concentration is known (an indicator of inflammation) or the presence of SIR is excluded.”

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Bio-ecological control of chronic liver disease and encephalopathy

Stig Bengmark

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Bengmark S. Bio-ecological control of chronic liver disease and encephalopathy, *Metab Brain Dis*, Vol. 24, pp. 223-236, 2009.

physical exercise and intake of foods rich in vitamins, antioxidants, fibres, lactic acid bacteria etc. in combination with reduction in intake of refined and processed foods is known to reduce systemic inflammation and prevent chronic diseases. Some lactic acid bacteria, especially *Lb paracasei*, *Lb plantarum* and *pediococcus pentosaceus* have proven effective to reduce inflammation and eliminate encephalopathy. Significant reduction in blood ammonia levels and endotoxin levels were reported in parallel to

“The progress in molecular biology and especially molecular genetics has provided new and important information about the innate immune system and the reactions to both physical and mental stress...Increasing evidence suggest that inflammation precedes and paves the way for subsequent acute and chronic disease and complications to disease—‘*the challenge in critical illness is less the infection than the exuberant inflammatory response*’ – **and the conditions are much the same also in most chronic illnesses.**”

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Does nutrient deficiency still matter?

Of course!!

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Original article

Oral citrulline does not affect whole body protein metabolism in healthy human volunteers: Results of a prospective, randomized, double-blind, cross-over study

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“Thibault R et al. Oral citrulline does not affect whole body protein metabolism in healthy human volunteers: Results of a prospective, randomized, double-blind, cross over study, *Clin Nutr*, Vol. 30, pp. 807-811, December 2011.

“Twelve healthy volunteers were included fulfilling the following exclusion criteria: age between 18 and 45 years normal body mass index (BMI), absence of any earlier supplementation with citrulline, glutamine, or ornithine α -ketoglutarate, absence of any treatment with anabolic agents or corticosteroids during the month prior to inclusion in the study, no current artificial feeding, absence of renal, cardiac, respiratory or hepatic insufficiency, or chronic inflammatory disease, fasting blood glucose <6 mmol/L, and for women, the use of oral contraceptive measure, and a negative pregnancy test.”

- “In the current study, a 7-day dietary supplementation with citrulline had no detectable effect on whole body leucine kinetics...”
- “The lack of effect was observed despite an 11-fold rise in plasma citrulline (nearly twice the 6-fold increase observed in our previous study performed in the fed state with the same dose of oral citrulline).”

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- “These findings suggest that enteral citrulline supplementation does not stimulate whole body protein synthesis in the absence of arginine and/or citrulline depletion.”
- “Indeed, until now, the anabolic effect of citrulline has only been documented in animal models associated with citrulline deficiency, such as short bowel syndrome undernutrition and/or dietary protein restriction.”

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Hypothesis:

When does nutrient supplementation work best with chronically ill patients in terms of resolving chief complaints?

- When both deficiency (metabolic and/or absolute) and chronic inflammation and being simultaneously addressed.
- A whole foods diet plus supplemental micronutrients will generally address these issues simultaneously better than just isolated micronutrients.

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Hypothesis:

The standard multi was designed for a different time and a different population

- 70-80 years ago the main health issues were acute illness and lack of dietary variety.
- Less chronic inflammation
- Macronutrient quality and quantity was much better. Lack of micronutrients was a major issue.

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What do we see now?

- Longstanding chronic inflammation is the norm.
- Food fortification has greatly reduced micronutrient deficiency
- Issues with macronutrient quantity, quality, and ratio are epidemic

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What is the best “multi for today’s chronically inflamed, chronically ill patient who won’t improve diet?”

- A whole food based multi – one that contains both nutrients and antiinflammatory factors
- No – I don’t mean one from that company
- That company primarily focuses on food based micronutrients

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What is the best “multi for today’s chronically inflamed, chronically ill patient who won’t improve diet?

- Contains a full complement of high quality macronutrients in the proper quantity and ratio based on both absolute needs induced by poor diet and metabolic needs induced by chronic illness and chronic inflammation
- Contains food based antiinflammatory compounds
- Contains enough micronutrients to address absolute deficiencies caused by poor diet and metabolic deficiencies induced by chronic inflammation and chronic illness.

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What is the place for significant doses of isolated micronutrients?

- As part of an overall, limited range therapeutic program.
- For certain patients based on unique genetic and/or environmental issues

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ORIGINAL ARTICLE

Effects of multivitamin and mineral supplementation on adiposity, energy expenditure and lipid profiles in obese Chinese women

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Li Y et al. Effects of multivitamin and mineral supplementation on adiposity, energy expenditure and lipid profiles in obese Chinese women, *Int J Obes*, Vol. 34, pp. 1070–1077, 2010.

Abstract Multivitamin and mineral supplementation may improve energy expenditure and lipid profiles. Results: A total of 82 subjects completed the study. After 28 weeks, compared with the placebo group, the MVS group had significantly lower BMI, BMI, FM, TC, and LDL-C, significantly higher REE and HDL-C, as well as a borderline significant trend of lower RD ($P=0.030$) and TEE ($P=0.071$). The calcium group also had significantly higher HDL-C and lower LDL-C levels compared with the placebo group. Conclusion: The results suggest that, in obese individuals, multivitamin and mineral supplementation could reduce BMI and improve serum lipid profiles, possibly through increased energy expenditure and fat oxidation. Supplementation of calcium alone (142 mg per day) only improved lipid profiles. *International Journal of Obesity* (2010) 34, 1070–1077. doi:10.1038/sj.ijo.2010.144 published online 9 February 2010

“The results suggest that, in obese individuals, multivitamin and mineral supplementation could reduce body weight and fatness and improve serum lipid profiles, possibly through increased energy expenditure and fat oxidation.”

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Previous studies have shown that vitamins and minerals have an important role in energy and blood lipid metabolism^{1–6} through several mechanisms.^{7–11} Obese individuals are more likely to have either lower blood concentrations or lower bioavailability of minerals and/or vitamins.^{12,13} However, there are limited data on the effect of multivitamin and



Dietary supplementation with multiple micronutrients: No beneficial effects in pediatric cystic fibrosis patients

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Oudshoorn JH et al. Dietary supplementation with multiple micronutrients: No beneficial effects in pediatric cystic fibrosis patients, *J Cystic Fibrosis*, Vol. 6, pp. 35–40, 2007

Abstract Multiple micronutrient supplementation may have beneficial effects on pulmonary function and muscle performance. Methods: A double-blind, randomized, placebo-controlled, crossover trial with a mixture of multiple micronutrients (MLI) was performed in 21 CF patients (11.6±2.5 years) with predominantly mild lung disease. Anthropometric measures, pulmonary function, muscle performance by bicycle ergometry, muscular strength and vitamin A and E were determined. Results: Analysis was performed using the paired Student's *t*-test comparing the change in each parameter during MLI and placebo. Plasma vitamin E and A levels increased during MLI when compared to placebo. However, no significant difference between the effect of the MLI or placebo was observed neither for FEV₁, P_{max}, anthropometry, nor for the parameters for muscle performance. Conclusion: The micronutrient mixture was not superior to placebo with respect to changes in pulmonary function or muscle performance in pediatric CF patients, despite a significant increase in plasma vitamin E concentrations. © 2006 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Keywords: Micronutrients, Children, Cystic Fibrosis

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive inherited disorder primarily characterized by chronic pulmonary infection and inflammation [1,2]. Defective active infection neutrophils and macrophages generate reactive oxygen

species (ROS), which are necessary for bacterial killing, but may be harmful when tissue antioxidant capacity is exceeded [3]. Despite routine supplementation with fat soluble vitamins, such as the antioxidants vitamins E and carotenoids, biochemical markers for a disturbed oxidant-antioxidant balance remains present in many CF patients [4–7]. Therefore, several studies concerning micronutrient supplements have been performed in CF patients, using various amounts of α-tocopherol, retinol, ascorbic acid, and carotenoids. These studies have shown beneficial effects on

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Table 1
Composition of the micronutrient mixture ML1

	100 ml		100 ml
Energy value	kcal 80	Protein (casein:whey – 1:1)	g 6.0
			En% 30
		Carbohydrates (lactose, saccharose, organic acids)	g 7.1
			En% 35
		Fat (linoleic acid 0.8)	g 3.1
			En% 35
Minerals:		Vitamins:	
Na	mg 43	A	µg RE ^a 26.7
K	mg 300	D	µg 2.0
Cl	mg 81	C (ascorbic acid)	mg 100
Cu	mg 126	E (α-tocopherol)	mg 215
P	mg 73	B1 (thiamine)	mg 10
Mg	mg 8	B2 (riboflavin)	mg 1.2
		B3 (pantothenate)	mg 1.6
		B5 (niacin)	mg NE ^b 8.0
		B6 (pyridoxine)	mg 2.4
		B11 (folic acid)	µg 240
		B12 (cobalamin)	µg 1.2
		Biotin (vit H)	µg 40
Trace elements:		Others:	
Fe	mg 0.4	Carnitine	mg 1200
Zn	mg 6.0	Choline	mg 40
Cu	mg 0.6	Creatine	mg 1200
Mn	mg 1.2	Taurine	mg 1200
F	mg 0.4	Coenzyme Q10	mg 60
Mo	µg 20		
Se	µg 20		
Cr	µg 13		
I	µg 40		

^a Retinol equivalents.
^b Niacine equivalents.

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Journal of Cystic Fibrosis 10 (2011) 31–36



Original Article

Effect of an antioxidant-rich multivitamin supplement in cystic fibrosis ☆☆☆

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Available online 20 October 2010

Abstract

Sagel SD et al. Effect of an antioxidant-rich multivitamin supplement in cystic fibrosis, *J Cystic Fibrosis*, Vol. 10, pp. 31–36, 2011.

Keywords: Antioxidant; Vitamin; Oxidative stress; Cystic fibrosis

Introduction (CF) is characterized by chronic airway inflammation and oxidative stress. Vitamin A, D, E, and K are essential for maintaining normal lung function and are often deficient in CF. This study evaluated the effect of an antioxidant-rich multivitamin supplement on systemic antioxidant levels, vitamin status, and growth parameters in CF.

“In this study, AquADEKs® increased systemic antioxidant levels, while maintaining vitamin A levels in the normal range, and improved but did not completely normalize vitamin D and K status. Increased β-carotene levels were associated with improved growth parameters.”

This research was supported by the Cystic Fibrosis Foundation, Yonkers, NY, the National Institutes of Health (NIH) (R01HL081161), and the Colorado CFSA grant (13L1RB025798) from NCI/NIH. * Corresponding author. The Children's Hospital, 13121 E. 16th Avenue, B-305, Aurora, CO 80044, United States. Tel.: +1 720 777 4010; fax: +1 720 777 7744. E-mail address: sagel.scott@denver.org (S.D. Sagel).

1969-1965, use three asterisks © 2010 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.
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Table 1
AquADEKS® composition (1 softgel capsule).

Compound	Amount per softgel	% Daily value ^a
Vitamin A (92% β-carotene and 8% palmitate)	18,167 IU	363
Vitamin C (as sodium ascorbate)	75 mg	125
Vitamin D ₃ (as cholecalciferol)	800 IU	200
Vitamin E (as α-tocopherol)	150 IU	500
Vitamin E (other mixed tocopherols)	80 mg	**
Vitamin K ₁ (as phytonadione)	700 mcg	875
Coenzyme Q10	10 mg	**
Thiamin (Vitamin B1)	1.5 mg	100
Riboflavin (Vitamin B2)	1.7 mg	100
Niacin (as niacinamide)	10 mg	50
Vitamin B6 (as pyridoxine hydrochloride)	1.9 mg	95
Folic acid	200 mcg	50
Vitamin B12 (as cyanocobalamin)	12 mcg	200
Biotin	100 mcg	33
Pantothenic acid (as calcium d-pantothenate)	12 mg	120
Zinc (as zinc sulfate)	10 mg	67
Selenium (as selenomethionine)	75 mcg	107

** Daily value not established for these nutrients.

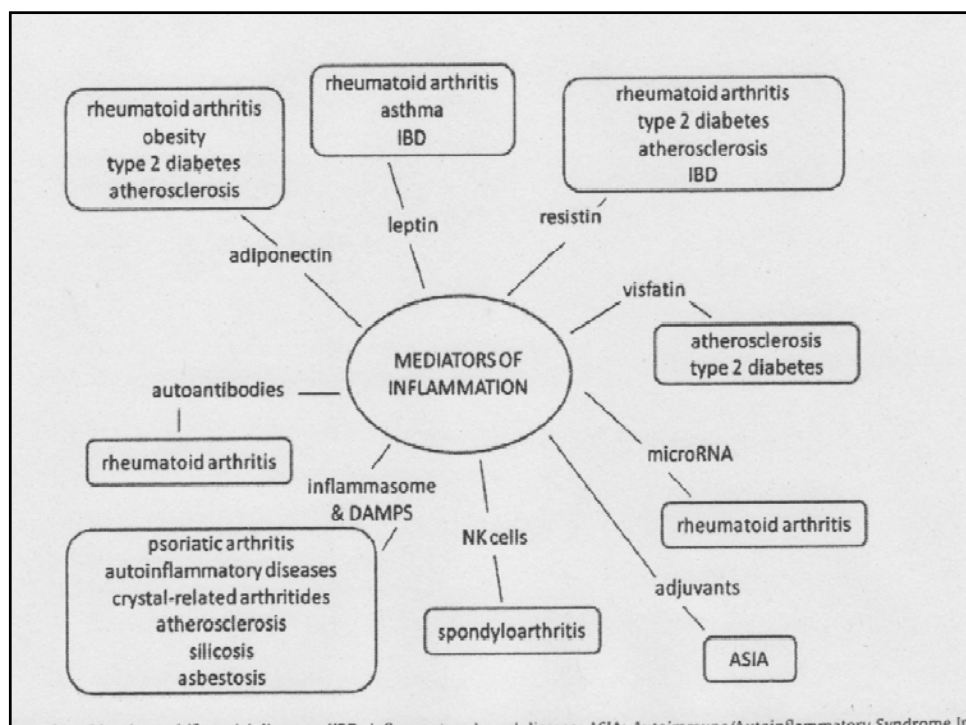
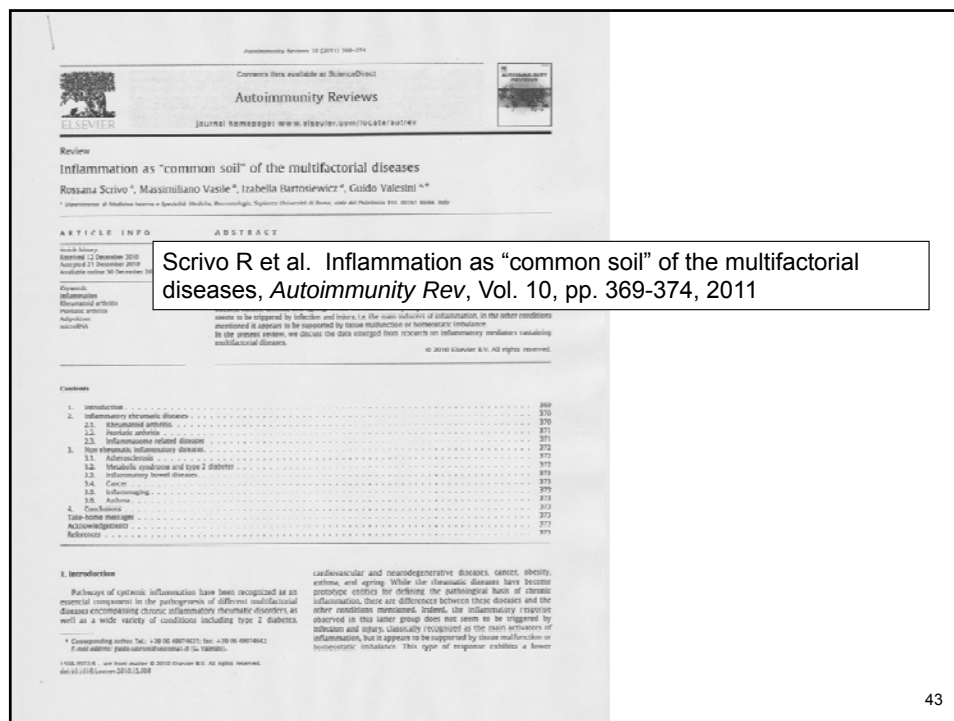
^a Percent daily values based on a 2000 calorie diet.

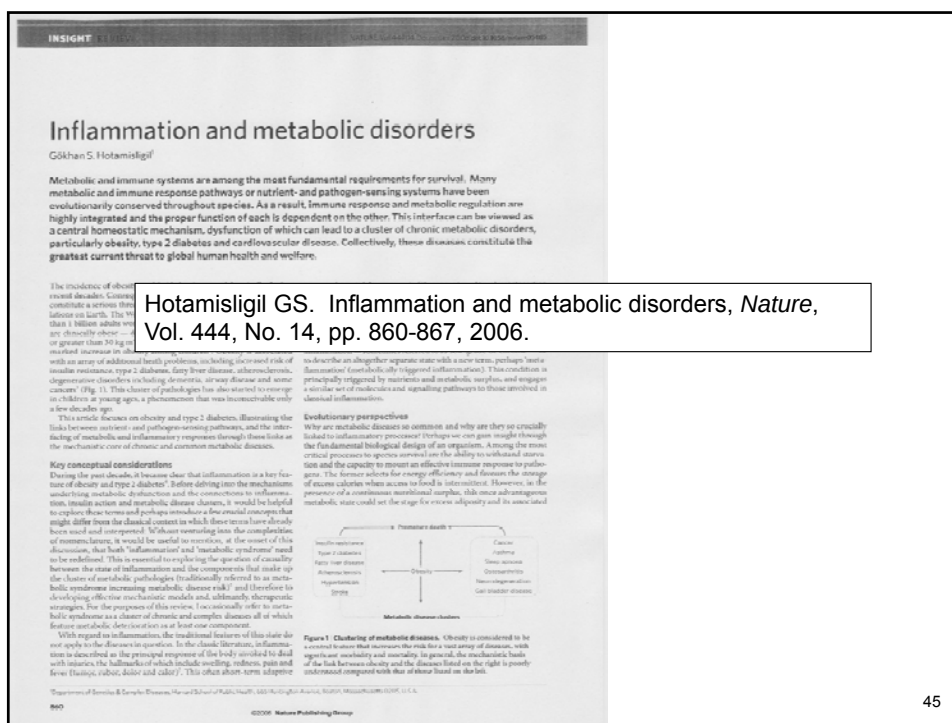
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Inflammation and its relationship with chronic illness:

Metaflammation

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A new way of defining inflammation: Metaflammation

- “With regard to inflammation, the traditional features of this state do not apply to the diseases in question.”
- “In classic literature, inflammation is described as the principal response of the body invoked to deal with injuries, the hallmarks of which include swelling, redness, pain and fever (tumor, rubor, dolor and calor). This often short-term adaptive

A new way of defining inflammation: Metaflammation

- “This often short-term adaptive response is a crucial component of tissue repair and involves integration of many complex signals and distinct cells and organs.”
- “However, the long-term consequences of prolonged inflammation are often not beneficial.”

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A new way of defining inflammation: Metaflammation

- “This certainly seems to be the case in metabolic diseases.”
- “Although many of the same mediators are involved in obesity and diabetes, few, if any, of the classic features of inflammation have been observed.”

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A new way of defining inflammation: Metaflammation

- “Therefore, it would be useful to set out a distinct form of injury response or subclass of inflammation—sometimes referred to as ‘low-grade’ or ‘chronic’—or to describe altogether separate state with a new term, perhaps ‘metaflammation (metabolically triggered inflammation).”

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A new way of defining inflammation: Metaflammation

- “This condition is principally triggered by nutrients and metabolic surplus, and engages a similar set of molecules and signalling pathways to those involved in classical inflammation.”

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A new way of defining inflammation: Metaflammation

- “...it is safe to suggest that the link between inflammatory and metabolic signalling is a delicate balance.”
- “Although there are short-term compensatory and adaptive measures to keep this delicate balance in check, the outcome is often detrimental when one arm overwhelms the other in the long term.”

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A new way of defining inflammation: Metaflammation

- “...it is also clear that metabolic dysfunction can be triggered by chronic excess of nutrients, such as lipids and glucose.”
- “However, in this case, these signals also simultaneously trigger inflammatory responses.”

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A new way of defining inflammation: Metaflammation

- “In this setting of metabolic excess, it is more likely that metabolic signal(s) are triggers for inflammatory responses, which then further disrupt metabolic function, leading to more stress and inflammation, and so on.”

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Obesity and chronic disease: always offender or often just accomplice?

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Obesity: Inflammation? Exaggeration? Liability?

Obesity is known to be a cause of chronic disease, although the exact mechanisms for this are unclear. One view is that the discovery of a form of subclinical, low-grade systemic inflammation, later called ‘metaflammation’ (referring to metabolically triggered inflammation) associated with both obesity and chronic disease, raised hopes of an improved understanding of the causal links between the two, as this form of inflammation is linked with insulin resistance and chronic disease, and obesity seemed to be the driving cause.

However, depending largely on the size of fat storage, obesity can be relatively benign, with little negative impact on health, or metabolically, with apparent links to a range of metabolic and other disorders. Also, a significant proportion of obese individuals suffer none of the dysregulations expected from obesity, and a significant proportion of lean and better has been proposed as the primary cause: there is chronic and metabolic disease such as type 2 diabetes. However, depending largely on the size of fat storage, obesity can be relatively benign, with little negative impact on health, or metabolically, with apparent links to a range of metabolic and other disorders. Also, a significant proportion of obese individuals suffer none of the dysregulations expected from obesity, and a significant proportion of lean

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- “Classical inflammation represents an acute immune reaction to infection or injury.”
- “Metaflammation differs from this in that: (a) it does not involve the classical symptoms of inflammation (tumour, rubor, dolor and calor); (b) it causes only a small rise in immune system markers (i.e. 4-6-fold v. several 100-fold); (c) it results in chronic, rather than acute, allostasis; (d) it has its effects systemically; (e) its antigens are less apparent as foreign agents or microbial organisms (and hence may be better referred to as ‘inducers’); (f) it appears to perpetuate, rather than resolve a disease.”

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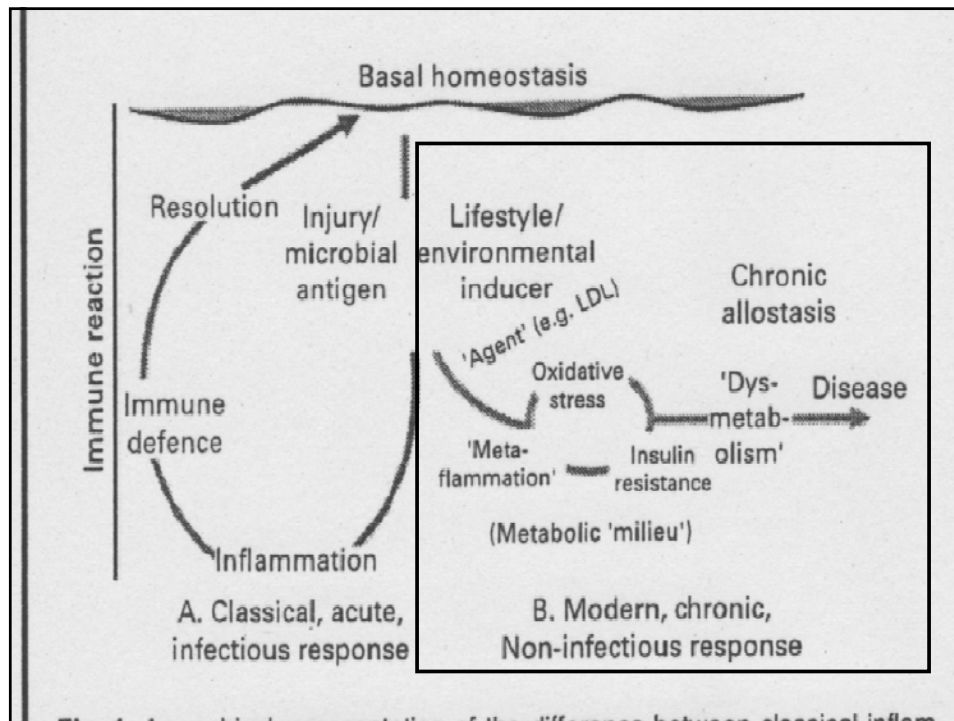


Table 1. Lifestyle-related inducers with evidence for a pro- (metaflam-
matory) or anti-inflammatory response in human subjects*

Metaflammatory inducers	
Pro-inflammatory	Anti-inflammatory/neutral
Exercise (excessive)	Exercise/physical activity/CV fitness
Inactivity/low CV fitness	Walking/yoga/resistance, etc
Nutrition	Extensive lifestyle change
Acute nutrient overload	Nutrition
Alcohol (excessive)	Alcohol (moderate)
Energy intake (excessive)	Cocoa/dark chocolate
'Fast' food/Western-style diet	Energy intake (restricted)
Fasting	Mediterranean/varied diet
Fat	Fibre (high intake)
Saturated fat	Fish
Trans fat	Fruits/vegetables
High-fat diet	Garlic
Low n-3/n-6 fatty acids	Herbs and spices
Fructose	Lean game meats
Glucose	Low-GI foods
High glucose/GI foods	Nuts
Glycaemic load	Raisins
Glycaemic status	Tea/green tea
Refined carbohydrate	Vinegar
Salt (excessive)	
Obesity/weight gain	Smoking cessation
Sleep deprivation	Weight loss
Smoking	
Stress	
('burnout')/anxiety/depression	

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Viewpoint

**Should obesity be the main game? Or do we need an
environmental makeover to combat the inflammatory
and chronic disease epidemics?**

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Summary

There is a link between obesity and chronic disease. However, the causal relation-
ship is complicated. Some forms of obesity are associated with low level systemic
inflammation, which is linked to disease. But lifestyle behaviours that may not
necessarily cause obesity (poor diet, inadequate sleep, smoking etc) can indepen-

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- “A possible scenario is that oxidative stress from metabolic overload or an immune reaction resulting from a range of endogenous or exogenous inducers, incites an immune alarm through the production of pro-inflammatory molecules.”
- “This, in turn, causes disruption of insulin receptor signalling leading to the build-up of insulin resistance and, ultimately, to the development of metabolic and other disorders.”

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“With many, if not most factors considered, there appears to be a ‘hormetic’ effect (where hormesis refers to the reverse effects of too little or too much of a substance/activity, compared with a mid-range level).”

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- “In contrast to the large (e.g., hundredfold) acute defensive action of classical inflammation, ‘metaflammation’ is characterized by a small (~3-4 fold), but chronic and systemic rise in proinflammatory markers, many of which have now been identified, that is from C-reactive protein (CRP) at the proximal level, to NF- κ B at the distal transcription level.”

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- “Anti-inflammatory markers indicate the opposing action of antagonising the metaflammatory process.”
- “These are less well known but adiponectin, leptin, and high-density lipoprotein (HDL) are amongst those that have been identified to date.”

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- “Recent findings suggest that while fat stays in the fat cells, for which they are designed, this is not a cause for concern.”
- “Only when lipid intolerant nonadipose organs are not protected from lipid ‘spillover’ during sustained energy surplus does it become a problem.”

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Review

Nutrition in Burns: Galveston Contributions

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Felicia N. Williams, MD¹; Lars-Peter Kamolz, MD, PhD, MSc^{3,4};
and David N. Herndon, MD¹

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Aggressive nutrition support is recommended following severe burn injury. Initially, such injury results in a prolonged and persistent hypermetabolic response mediated by a 10- to 20-fold elevation in caloric, protein, and fat requirements. This review discusses the Galveston contributions to the field of burn nutrition, including the development of the Galveston Nutrition Support System (GNSS) and the Galveston Nutrition Support System (GNSS) and the Galveston Nutrition Support System (GNSS).

Rodriguez NA et al. Nutrition in burns: Galveston contributions, *JPEN*, Vol. 35, No. 6, pp. 704-714, November 2011.

Clinical Relevancy Statement

Provision of nutrition support is an essential component of burn care. Adequate assessment and management can reduce mortality and complications, optimize wound healing, and minimize the deleterious effects of the exaggerated hypermetabolic response; therefore, careful attention must be given to the tools and methods by which we estimate caloric needs. This review allows the reader to possibly change practice in burn nutrition. Furthermore, on the basis of the review data, we believe

that there should be discussion and thought about the ideal intensive care unit nutrition.

Introduction

Severe burn injury is associated with metabolic alterations that persist for up to 2 years postburn.¹ Immediately after injury, patients enter a period of attenuated metabolism and decreased tissue perfusion, also referred to as the “ebb” phase. Shortly after, they enter a phase of hypermetabolic rates and hyperdynamic circulation, known as the “flow” state.² The hypermetabolic phase is coordinated via mediators that initiate a cascade of metabolic alterations that culminate in tissue recovery or cause death. Management of this response can constitute a challenging endeavor to the surgeon, who is faced with the decision to implement myriad strategies that can include confinement of thermoregulation, surgical excision and grafting, exercise, analgesia, anabolic hormones, and neuroendocrine antagonists. The global success of this effort, however, relies on the prompt commencement and maintenance of adequate nutrition support. We present recommendations gained from prospective trials, retrospective analyses, and expert opinions based on Galveston’s contributions that we expect will aid in the nutrition assessment and management of severely burned adult and pediatric patients.

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